Thromboprophylactic treatment with rivaroxaban or dabigatran compared with enoxaparin or dalteparin in patients undergoing elective hip- or knee replacement surgery

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Background: Due to a high risk of thromboembolism in patients undergoing major orthopaedic surgery it has become standard practice to give thromboprophylactic treatment to these patients. Pharmaceutical interventions with or without addition of mechanical methods are recommended. • This project, commissioned by Helse Bergen HF Ortopedisk klinikk, examined thromboprophylaxis with rivaroxaban or dabigatran compared with low-molecular weight heparins (LMWH, i.e. enoxaparin and dalteparin) with regard to efficacy, safety and cost-effectiveness in patients undergoing elective total hip or knee replacement surgery. • We conducted a systematic review of the literature and made cost-effectiveness analyses based on a model that calculated quality-adjusted life years and life time costs. **Main findings:** • We did not find statistically significant differences between dabigatran and enoxaparin for mortality, pulmonary embolism, deep vein thrombosis or major bleeding. The quality of the evidence ranged from very low to moderate. • For rivaroxaban compared with enoxaparin we found statistically a significant reduction in deep vein thrombosis, *(continued)*

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(continued from page one) but also a trend towards increased risk of major bleeding. For mortality and pulmonary embolism there were no statistically significant differences between treatments. The quality of the evidence ranged from very low to moderate. • Our results indicate a great uncertainty regarding which strategy is the most cost-effective. However, rivaroxaban and enoxaparin had a slightly higher probability of being cost-effective alternatives for patients undergoing total hip or knee replacement, respectively. • The results of our model analysis of the uncertainty surrounding each group of parameters indicated that more research on efficacy data would have the greatest impact on reducing decision uncertainty.

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Norwegian Knowledge Centre for the Health Services
Oslo, June, 2011

Hovedfunn

Det er stor risiko for blodpropp (tromboemboli) hos pasienter som får satt inn hofte- eller kneprotese. Derfor er det vanlig at disse pasientene får tromboseprofylakse for å forebygge blodpropper. Tromboseprofylakse består vanligvis av blodfortynnende legemidler, eventuelt i kombinasjon med ikke-medikamentelle tiltak.

Dette prosjektet ble bestilt av Helse Bergen HF Ortopedisk klinikk. Vi har undersøkt effekt, sikkerhet og kostnadseffektivitet av tromboseprofylakse med rivaroksaban eller dabigatran sammenliknet med enoksaparin hos pasienter som gjennomgår planlagt total hofte- eller kneprotesekirurgi.

Hovedfunnene var:

- Vi fant ingen statistisk signifikante forskjeller mellom dabigatran og enoksaparin med hensyn til dødelighet, lungeemboli (blodpropp i lungene), dyp venetrombose (blodpropp i benene) eller blødninger. Kvaliteten på dokumentasjonen varierte fra veldig lav til moderat.
- For rivaroksaban sammenliknet med enoksaparin fant vi en statistisk signifikant nedgang i forekomst av dyp venetrombose, men også en trend i retning av flere blødninger. For dødelighet og lungeemboli fant vi ikke statistisk signifikante forskjeller mellom behandlingene. Kvaliteten på dokumentasjonen varierte fra veldig lav til moderat.
- Våre resultater viste at det er stor usikkerhet knyttet til hvilken behandling som er mest kostnadseffektiv. Imidlertid hadde rivaroksaban og enoksaparin en noe høyere sannsynlighet enn dabigatran for å være det mest kostnadseffektive alternativet henholdsvis for hoftekirurgi og knekirurgi.
- Usikkerhet i effektestimatene bidrar mest til usikkerheten rundt hvilken behandling som er mest kostnadseffektiv.

3-siders sammendrag

INNLEDNING

Etter kirurgiske inngrep, lang tids sengeleie samt ved noen medisinske tilstander kan uønsket blodlevring finne sted (trombedannelse). Dette kan hindre, eller til og med blokkere blodsirkulasjonen.

Det er stor risiko for blodpropp (tromboemboli) hos pasienter som får satt inn hofte- eller kneprotese. Derfor er det vanlig at disse pasientene får tromboseprofylakse. De får blodfortynnende legemidler, eventuelt i kombinasjon med ikke medikamentelle tiltak. I 2009 ble to nye legemidler beregnet på slike pasienter tilgjengelige i Norge, rivaroksaban og dabigatran. I motsetning til subkutanbehandling med lavmolekylære hepariner (LMWH; eksempelvis enoksaparin og dalteparin), gis de nye legemidlene i tablettform.

I denne rapporten har vi sammenliknet de to nye perorale behandlingsalternativene med LMWH med hensyn på effekt, sikkerhet og kostnadseffektivitet.

METODE

Denne rapporten er laget som en HTA-rapport (metodevurdering). Den består av en systematisk gjennomgang av forskningslitteratur om effekt og sikkerhet og en helseøkonomisk vurdering av de to nye perorale koagulasjonshemmerne sammenliknet med LMWH.

Vi søkte etter systematiske oversikter og randomiserte kontrollerte studier i relevante bibliografiske databaser. Artiklene ble vurdert av to personer uavhengig av hverandre, og data ble kombinert i meta-analyser med hensyn til total dødelighet, dyp venetrombose (DVT), lungeemboli (LE) og blødninger. Dokumentasjonskvaliteten ble vurdert ved bruk av GRADE (Grading of Recommendations, Assessment, Development and Evaluation).

For å vurdere kostnadseffektiviteten til ulike tromboseprofylaksealternativer lagde vi en beslutningsmodell. De to kirurgiske inngrepene, hofte- og kneprotesekirurgi, ble modellert hver for seg for å reflektere forskjeller i underliggende risiko for å utvikle DVT, LE og store blødninger.

Modellen kombinerte to moduler, et beslutningstre for korttidsprofylakse (inntil 90 dager etter inngrepet, akutt fase) og en Markov-modell for langtidskomplikasjoner (inntil pasienten dør eller er 100 år, kronisk fase).

DVT, LE og store blødninger ble modellert i den akutte fasen. Kvalitetsjusterte leveår (QALYs) og kostnader som følge av disse hendelsene ble modellert ut over pasientens levetid. Det ble også behandling av posttrombotisk syndrom (PTS) og nye tilfeller av DVT eller LE. Effektestimater for våre utvalgte endepunkt ble hentet fra den systematiske gjennomgangen av forskningslitteratur tidligere i rapporten. Livskvalitetsdata ble hentet fra publisert litteratur, mens legemiddelpriser er hentet fra Statens legemiddelverk sine listepriser.

Vi utførte en probabilistisk sensitivitetsanalyse, en Monte Carlo simulering med 1000 iterasjoner, for å få et inntrykk av usikkerheten knyttet til resultatene.

RESULTATER

- Vi fant ingen studier som direkte sammenliknet dabigatran med rivaroksaban.
- Vi fant ingen studier som sammenliknet dabigatran eller rivaroksaban med dalteparin.
- Vi fant ingen statistisk signifikante forskjeller mellom dabigatran og enoksaparin med hensyn til dødelighet, LE, DVT eller blødninger. Kvaliteten på dokumentasjonen varierte fra veldig lav til moderat.
- For rivaroksaban sammenliknet med enoksaparin fant vi en statistisk signifikant nedgang i DVT, men også en trend i retning av flere blødninger. For dødelighet og LE fant vi ikke statistisk signifikante forskjeller mellom behandlingene. Kvaliteten på dokumentasjonen varierte fra veldig lav til moderat.
- Ingen av de inkluderte systematiske oversiktene rapporterte data for posttrombotisk syndrom, og heller ikke for våre sekundære endepunkt (varighet av sykehusopphold, reinnleggelser, sykemeldinger, infeksjoner eller livskvalitet).
- Ved å anta en betalingsvilje på NOK 500 000 per vunnet QALY, så var tromboseprofylakse med rivaroksaban ved hofteprotesekirurgi kostnadseffektivt med en sannsynlighet på 38 %.

- Ved å anta en betalingsvilje på NOK 500 000 per vunnet QALY, så var tromboseprofylakse med enoksaparin ved kneprotesekirurgi kostnadseffektivt med en sannsynlighet på 34 %.
- Analyser for å undersøke usikkerhet knyttet til de ulike parametrene i beslutningsmodellen viste at det var effektestimatene som hadde størst påvirkning på usikkerheten.

KONKLUSJON

Dabigatran og rivaroksaban ser ut til å være effektive og godt tolererte antitrombotiske legemidler hos pasienter som får satt inn hofte - eller kneprotese og er sammenliknbare med enoksaparin.

Våre resultater viste at det er stor usikkerhet knyttet til hvilken behandling som er mest kostnadseffektiv. Rivaroksaban og enoksaparin hadde noe høyere sannsyndlighet for å være det mest kostnadseffektive alternativet hos pasienter som får satt inn henholdsvis hofte- eller kneprotese. Analyser for å undersøke usikkerhet knyttet til de ulike parametrene i beslutningsmodellen viste at videre forskning på de kliniske utfallsmålene mest sannsynlig vil redusere usikkerhet i konklusjonen.

Key messages

Due to a high risk of thromboembolism in patients undergoing major orthopaedic surgery it has become standard practice to give thromboprophylactic treatment to these patients. Pharmaceutical interventions with or without addition of mechanical methods are recommended.

This project, commissioned by Helse Bergen HF Ortopedisk klinikk, examined thromboprophylaxis with rivaroxaban or dabigatran compared with low-molecular weight heparins (LMWH, *i.e.* enoxaparin and dalteparin) with regard to efficacy, safety and cost-effectiveness in patients undergoing elective total hip or knee replacement surgery.

We conducted a systematic review of the literature and made cost-effectiveness analyses based on a model that calculated quality-adjusted life years and life time costs.

The main findings were that:

- We did not find statistically significant differences between dabigatran and enoxaparin for mortality, pulmonary embolism, deep vein thrombosis or major bleeding. The quality of the evidence ranged from very low to moderate.
- For rivaroxaban compared with enoxaparin we found statistically a significant reduction in deep vein thrombosis, but also a trend towards increased risk of major bleeding. For mortality and pulmonary embolism there were no statistically significant differences between treatments. The quality of the evidence ranged from very low to moderate.
- Our results indicate a great uncertainty regarding which strategy is the most cost-effective. However, rivaroxaban and enoxaparin had a slightly higher probability of being cost-effective alternatives for patients undergoing total hip or knee replacement, respectively.
- The results of our model analysis of the uncertainty surrounding each group of parameters indicated that more research on efficacy data would have the greatest impact on reducing decision uncertainty.

Executive summary

BACKGROUND

After surgical procedures, long term immobilization or certain medical conditions, such as undesirable blood clot (thrombus) formation may occur. This can slow or even block blood circulation.

Due to a high risk of thromboembolism in patients undergoing major orthopaedic surgery, it has become standard practice to give thromboprophylactic treatment. In general, pharmaceutical interventions with or without addition of mechanical methods are recommended. During 2009 two new pharmaceutical treatment options became available on the Norwegian market: rivaroxaban and dabigatran. Both are given orally, in contrast to low molecular weight heparins (LMWH, *i.e.* enoxaparin and dalteparin), which are given as subcutaneous injections.

In this report we compared LMWH to the new oral treatment options in order to assess the relative efficacy and cost-effectiveness of the different options.

METHODS

This report was conducted as a health technology assessment. It consists of a systematic review of the literature on clinical efficacy and safety as well as a health economic analysis of the new oral anticoagulants compared with LMWH.

We searched for systematic reviews and randomized controlled trials in relevant bibliographic databases. Trials were assessed by two independent reviewers and combined into meta-analyses of four outcomes: overall mortality, deep vein thrombosis (DVT), pulmonary embolism (PE) and bleeding events. The quality of the evidence was evaluated using GRADE (Grading of Recommendations, Assessment, Development and Evaluation).

In order to assess the cost-effectiveness of alternative thromboprophylactic interventions, a decision model was developed. The two surgery types, hip and knee replacement, were modelled separately to reflect differences in the underlying risk of developing DVT, PE and major bleeding.

The model combined two modules; a decision tree for short-term prophylaxis (for a period of 90 days after surgery:, acute phase) and a Markov model for long-term complications (until patients are either dead or 100 years old: chronic phase).

DVT, PE and major bleeding events were modelled for the acute phase. The quality-adjusted life-years (QALYs) and costs arising from these events were modelled over the patient's lifetime, including treatment of post-thrombotic syndrome (PTS) and recurrent VTE. Efficacy estimates were taken from the systematic review part of this report. Quality of life data were extracted from published literature. Costs of medications were based on prices from the Norwegian Medicines Agency.

We performed probabilistic sensitivity analyses, designed as a Monte Carlo simulation with 1 000 iterations, to explore the uncertainty surrounding our results.

RESULTS

- No head-to-head comparison of dabigatran versus rivaroxaban was identified.
- No studies comparing dabigatran or rivaroxaban to dalteparin were identified.
- We did not find statistically significant differences between dabigatran and enoxaparin for the outcomes mortality, PE, DVT or major bleeding. The quality of the evidence ranged from very low to moderate.
- For rivaroxaban compared with enoxaparin we found statistically significant decreases in DVT, but also a trend towards increased risk of major bleeding. For mortality and PE there were no statistically significant differences between treatments. The quality of the evidence ranged from very low to moderate.
- The included systematic reviews did not report on the primary endpoint post-thrombotic syndrome or any of our secondary outcomes (duration of hospital stay, re-submission to hospital, sick-leave, infections, re-operations or quality of life).
- Assuming a willingness to pay of NOK 500 000 per QALY gained, the probability of rivaroxaban as thromboprophylactic treatment after total hip replacement being cost-effective was 38%.
- Assuming the same willingness to pay, the probability of enoxaparin following TKR being cost-effective was 34%.
- The results of our analyses of the uncertainty surrounding different groups of parameters indicated that more research on the input variables is likely to change our base-case results. Efficacy data had the greatest impact on decision uncertainty.

CONCLUSION

Dabigatran and rivaroxaban seem to be well tolerated antithrombotic medicines. Their efficacy and safety in hip and knee replacement surgery are comparable with enoxaparin.

Our results showed that there is a great uncertainty regarding which strategy is the most cost-effective. However, rivaroxaban and enoxaparin had a slightly higher probability of being cost-effective alternatives for patients undergoing either total hip or knee replacement, respectively. The results of our analyses to explore the uncertainty surrounding each group of parameters indicated that more research on efficacy data would have the greatest impact on reducing decision uncertainty.

ABOUT NOKC

Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Directorate for Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

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Glossary and abbreviations

	Explanation
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.
DVT	**Deep vein thrombosis.** Venous thrombosis that occurs in the "deep veins" in the legs, thighs, or pelvis.
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies divided by the difference in effectiveness between these two technologies. $ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$
Markov model	A Markov model is a model that is based on a series of "states" that a patient can occupy at a given point in time. It is a way to represent a changing set of health states over time, where there is a known probability or rate of transition from one health state to another. Markov models are useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once.
Monte Carlo simulation	Monte Carlo simulation is drawing random numbers from each of the input parameter distributions. The end results of the process is a large number (for example, 10 000) of the sets of expected costs and effects that reflect the combined parameter uncertainty in the model.
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money. $NHB = \Delta E - \frac{\Delta C}{\lambda}$
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $NMB = \lambda \cdot \Delta E - \Delta C$
PE	**Pulmonary embolism**. A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries (arteries in the lung).

PSA	**Probabilistic sensitivity analysis** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously.
PTS	**Post-thrombotic syndrome.** Chronic pain, swelling, and occasional ulceration of the skin of the leg that can occur as a consequence of previous deep venous thrombosis.
QALY	**Quality-adjusted life-year(s)** A measure of health outcomes that combines quantity and quality of life. It assigns a weight corresponding to health-related quality of life to each year of life.
RCT	**Randomised controlled trial** An experiment in which investigators use randomisation to allocate participants into the groups that are being compared. Usually allocation is made at the level of individuals, but sometimes it is done at group level e.g. by schools or clinics.
RR	**Relative risk / risk ratio** The ratio of two risks. This denotes the number of times more or less likely an event is to happen in one group compared with another.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. The analysis is repeated using different assumptions to examine the impact on the results. There are different types of sensitivity analyses, such as one-way, multi-way and probabilistic sensitivity analysis.
SR	**Systematic review**. A review in which the search for literature is done systematically to identify all relevant publications for a given research question. In addition, the SR authors may evaluate the included publications for quality/risk of systematic bias and may synthesize data if appropriate.
Statistical significance	Means that the findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 5 out of 100 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
THR	**Total hip replacement**
TKR	**Total knee replacement**
VTE	**Venous thromboembolism.** It includes both DVT and PE. DVT and PE represent different manifestations of the same clinical entity, an entity referred to as venous thromboembolism (VTE).
WTP (λ)	**Willingness to pay**. A pre-specified limit of what society is willing to pay for a given health unit (e.g. QALY or life year). In Norway it is common to use NOK 500 000 per QALY or life year in economic evaluations. Sometimes also called cost-effectiveness threshold.

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Preface

This project was commissioned by Helse Bergen HF Ortopedisk klinikk, who wanted us to examine thromboprophylaxis with rivaroxaban or dabigatran compared to low-molecular weight heparins with regard to efficacy, safety and cost-effectiveness in patients undergoing elective total hip- or knee replacement surgery.

Tove Ringerike was lead reviewer for the clinical evaluation and Vida Hamidi lead the health economic evaluation. Pål Borgen and Ivar Sønbø Kristiansen performed peer review of the report.

The project group consisted of the following employees at Norwegian Knowledge Centre for the Health Services (NOKC)
Tove Ringerike, senior researcher
Vida Hamidi, senior advisor
Gunhild Hagen, advisor
Åsmund Reikvam, senior advisor
Marianne Klemp, research director

We wish to thank Marita Heintz, at The Norwegian Directorate of Health, for performing the systematic literature searches. We also thank Hege Kornør, Ingvil Sæterdal, Vigdis Laurak and Torbjørn Wisløff for constructive comments on the manuscript.

The aim of this report is to support decisions in health care which can lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Gro Jamtvedt *Department director*	Marianne Klemp *Research director*	Tove Ringerike *Lead reviewer, clinical evaluation*	Vida Hamidi *Lead health economist*

Objectives

We have two main objectives in this report:

Objective 1 is to compare efficacy and safety of rivaroxaban or dabigatran to low-molecular weight heparins (LMWH) and to each other if direct comparisons exist in patients undergoing elective total hip- or knee replacement surgery.

Objective 2 is to examine the cost-effectiveness of rivaroxaban or dabigatran compared with low-molecular weight heparins (LMWH).

This report is limited to comparing the two novel oral antithrombotic drugs rivaroxaban and dabigatran with the most commonly used LMWH in Norway (enoxaparin and dalteparin). Even though patients undergoing hip fracture surgery may receive the same antithrombotic drugs, the treatment of these patients is not within the scope of this report. There may be variations in the timing and dose of the antithrombotic drugs used. These variables are described in tables, but it is beyond the scope of this report to explore this issue.

Background

THROMBOPROPHYLACTIC TREATMENT

Blood clotting and formation of thrombus

It is both desirable and important that blood should have the ability to clot implying formation of a thrombus, for example when we get cuts and injuries. However, there must be a balance between the ability to clot and the ability for the blood to circulate through the vessels.

After surgical procedures, long term immobilization or certain medical conditions, unwanted blood clot formation may occur. Several different clotting factors are involved in the cascade leading to formation of the clot, which in turn can slow or even block blood circulation. If this occurs in veins, it is usually called deep vein thrombosis (DVT). However, if the clot shed parts into circulation and these end in the lungs it is called a pulmonary embolism (PE). Collectively DVT and PE are called venous thromboembolism (VTE).

Thromboembolic disease – symptoms and occurrence

Some blood clots are asymptomatic and resolve spontaneously. In other cases the altered or blocked blood circulation may cause local swelling, redness and pain. Prolonged periods with DVT, increased pressure and divertion of blood to other veins can affect the surrounding tissue and the venous valves and hence give long-term symptoms. These symptoms range from mild to severe and include discomfort, pain, swelling, rashes and even skin ulcers (1).

PE may limit the ability of the blood to reach normal oxygen saturation and symptoms include chest pain, shortness of breath and circulatory instability. It may also cause sudden death.

The estimated incidence of thromboembolic disease varies. Based on data from the no prophylaxis arm in a randomized controlled trial it has been estimated that the incidence for DVT was 45% (42% - 48%) in elective hip surgery and 60% (51% - 69%) in elective knee surgery. Corresponding numbers for symptomatic PE was 3% (2%- 5%) for elective hip surgery and not estimable for knee surgery (2).

Given the high incidence of VTE in elective hip- or knee surgery without prophylaxis, it has become standard practice that patients undergoing major orthopaedic surgery receive thromboprophylactic treatment (3;4). Pharmaceutical interventions with or without addition of mechanical methods is recommended. Mobilization as early as possible is also recommended.

Choice of thromboprophylactic treatment

Thromboprophylactic treatment options include both mechanical methods such as compression stockings, intermittent pneumatic compression devices (IPCD) and foot pumps, and pharmacological treatment. The different drugs used in prophylaxis include fondaparinux, low molecular weight heparins (LMWH), dabigatran and rivaroxaban. A short summary of their characteristics' are presented in Table 1. Further description of the interventions can be found in chapter 6.2 in a guideline from NICE (2)

Table 1. Substances and characteristics

Substance	Characteristic
LMWH (e.g dalteparin, enoxaparin)	Binding and accelerating the action of antithrombin, a naturally occurring inhibitor of thrombin and other coagulation enzymes (IX, X, XI and XII)
Fondaparinux	Specific, indirect inhibitor of activated factor Xa
Dabigatran	Direct inhibitor of the enzyme thrombin necessary for the conversion of fibrinogen to fibrin during the coagulation cascade.
Rivaroxaban	Inhibits activated factor X (factor Xa) directly. Inhibition of factor Xa inhibits both thrombin formation and development of thrombi

Data from the Norwegian Arthroplasty Register (5) show that in Norway LMWH (enoxaparin and dalteparin) has been the preferred choice, constituting approx 95% of the use in 2009 (both for hip and knee replacement surgery). Less than 0.5% did not receive any pharmaceutical treatment.

During 2009 two new pharmaceutical treatment options became available in Norway, rivaroxaban and dabigatran. In contrast to LMWH, which is given as subcutanous injections, both are given orally. Enoxaparin, dalteparin, rivaroxaban and dabigatran are given reimbursement from the public health service in Norway (6).

In this report we have compared the most commonly used interventions (LMWH) with the new oral treatment options in order to assess the relative efficacy and cost-effectiveness of the different drug regimes.

Economic burden

DVT and PE are adverse events after major orthopaedic surgery. They may cause readmissions, prolongation of hospital stay or death. In Europe, the annual cost of VTE following major orthopaedic surgery has been estimated at approximately € 4 000 - € 8 265 per patient (38 000- 73 000 Norwegian kroner (NOK); 2010) (7;8). Total costs encompass initial therapy, hospitalisation and follow-up care, including treatment for any subsequent complications such as a further VTE event or PTS. The result of previous studies also showed that the development of VTE almost doubled the costs of inpatient care for patients undergoing major orthopaedic surgery (9;10).

HIP- AND KNEE REPLACEMENT SURGERY IN NORWAY

Hip replacement surgery

According to the Norwegian Arthroplasty Register (5) 137 414 hip replacement operations have been performed in Norway since 1987. In 2009 the number of operations was 8 224, consisting of 7 029 (85.5%) primary operations and 1 195 reoperations. The primary reason for surgery was idiopatic coxarthrosis (66.3%), but sequela after dysplasia and hip fractures contribute additionally (approx. 11% combined). The mean age at operation was 69.4 years and 68.4% were women.

Knee replacement surgery

With regard to knee replacement, 4 859 operations, consisting of 4 425 (91.1%) primary operations and 322 reoperations were performed in 2009. In 90% of the primary operations a total prosthesis was used. The most frequent reason for total prosthesis surgery was idiopatic arthrosis (88.7%), but sequela after meniscus injury, rheumatoid arthritis, sequela after fractures were other reasons for the operations. The mean age at operation was 69.1 years and women contributed 67. 4%

CHOICE OF OUTCOMES IN THIS REPORT

The health outcomes in this report are chosen based on severity, impact on resource use and potential preferences of the patients. The different outcomes are in many ways connected. Our main focus is presented as primary outcomes and are mortality, DVT, PE, bleeding and other adverse events. Avoidance of DVT after surgery may affect the risk of developing PE and long term affliction such as PTS. However, for every medicine there is the possibility of adverse events. These may vary for different medicines, and we will extract data on the frequency of adverse events for the

various pharmaceuticals. Bleeding is a potentially serious adverse event and closely connected to the mechanisms of the antithrombotic drug effect. Therefore this adverse event is extracted specifically.

Both efficacy and adverse effects have impact on outcomes like length of stay in hospital, need for re-operations, re-admissions to hospital, infections and ability to work. Finally quality of life for the patients is reported to supplement the patient perspective. These are therefore included as secondary outcomes.

INTRODUCTION TO HEALTH TECHNOLOGY ASSESSMENTS (HTA)

The basis of a HTA is a systematic review and evaluation of scientific literature on efficacy and safety of different interventions or diagnostics. The HTA also include economic evaluations and a discussion regarding ethical, social, legal and organisational aspects depending on the question under evaluation

This HTA consists of a systematic review of efficacy and safety and an economic evaluation.

INTRODUCTION TO ECONOMIC EVALUATIONS OF HEALTH CARE PROGRAMMES

The basic task of any economic evaluation is to identify, measure, value and compare costs and consequences of different alternatives (11). Hence, results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is calculated as the ratio of the difference in costs between two options over the difference in effectiveness.

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

If incremental costs of an intervention are negative and the incremental effects are positive, an intervention is said to be dominant (more effective and less costly) compared with another intervention. Likewise, positive incremental costs and negative incremental effects results in interventions being dominated (less effective and most costly). In both these circumstances, the ICER is negative and the economic evaluation has a simple conclusion. Otherwise, the ICER is positive and the choice depends on the maximum cost-effectiveness ratio one is willing to accept. The health care sector and society in general, is restricted by scarce resources, economic evaluations are tools to prioritize and maximize benefits within a limited budget. For an economic evaluation to be meaningful in a decision making process, the positive ICER must be judged with regards to a ceiling ratio that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} < \lambda$$

where λ equals WTP, and means that an intervention is considered cost-effective if the ICER is below the ceiling ratio. Because the ICER have poor statistical properties, ICERs are often rearranged to express either net monetary benefit (NMB) or net health benefit (NHB), which yields the following decision rules related to NMB or NHB.

$$NMB : \lambda \cdot \Delta E - \Delta C > 0$$

$$NHB \ : \Delta E - \frac{\Delta C}{\lambda} > 0$$

An intervention can in other words be considered cost-effective if it yields a positive NHB or NMB.

Economic evaluations are often based on decision models (such as decision trees, Markov models etc) that calculate results based on various input parameters. There are always uncertainties related to the values of these parameters, making sensitivity analyses an important feature of any economic evaluation. In short, sensitivity analysis illustrates how much the results vary when model parameters are being changed. Sensitivity analyses can be performed in many ways, with one-way or two-way sensitivity analysis being common approaches. This represents changing, respectively one or two model-parameters at a time while all the other model-parameters are held constant, to see how much impact the variation in these parameters has on the results. One-way sensitivity analyses are often presented as tornado-diagrams, which identify and illustrate the model-parameters that have the highest impact on the results.

Another important kind of sensitivity analysis is referred to as probabilistic sensitivity analysis (PSA), where uncertainties in many model-parameters are taken into account simultaneously. The basic approach in PSA is to assign appropriate probability distributions to the model-parameters, which makes it possible to replace the "fixed" values of the parameters by values generated by random draws from the distributions. Doing this repeatedly, with a definite number of iterations, makes it possible to estimate probabilities of alternatives being cost-effective subject to different ceiling values of WTP. PSA is often presented as scatterplots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane. In addition, a cost-effectiveness acceptability frontier (CEAF) graph shows the probability of cost-effectiveness for the optimal strategy at different WTP's.

PSA may also be used to produce expected value of perfect information (EVPI). This provides information about the societal value of having more accurate information about the input parameters, which subsequently may be used to inform on which parameters it would be most useful to get new and improved data. The ranking of EVPI for different parameters is dependent on the threshold willingness to pay. If EVPI is to be compared between different patient groups, the ranking is also dependent on the number of patients in each group.

In short, making a model probabilistic means that it is possible to estimate the uncertainty in the decisions of implementing alternative interventions, and it also provides a possibility of estimating the value of collecting additional information from new research.

PRIORITY SETTING CRITERIA

According to Norwegian policy documents (12;13), a treatment should be prioritised if the following criteria are met:

1. *The disease is severe;* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.

2. *The treatment is effective;* the patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

3. *The treatment is cost-effective;* the added costs of the treatment should be reasonable compared to the added benefits.

The policy documents mentioned above give no guidance as to what constitutes a ”reasonable” relationship between costs and effectiveness. The Directorate of Health however, has recommended a preliminary estimate of NOK 500 000 per statistical life year in full health (14). However, there exists no academic consensus regarding this threshold value, nor anyubject to a political process, therefore it may be regarded as a tentative suggestion.

Clinical efficacy

METHODS

Literature search

The research librarian planned and executed all systematic searches in collaboration with the project manager and members of the project group. We searched electronic databases for systematic reviews. To ensure that even the most recent publications were identified, we performed a search for newly published randomized controlled trials. We used the same search strategy as for systematic reviews, but used a filter for randomized controlled trials and limited the publication dates to the period from 2009 to September 2010.

The searches were performed 8th July 2010 for systematic reviews and 16th September 2010 for randomized controlled trials. We used Ovid MEDLINE, Ovid EMBASE, The Cochrane Library and CRD databases. We used a combination of keywords and text words relating to the populations and the relevant drugs. The terms used were adapted to the different databases, full search strategies are shown in Appendix 1.

We also handsearched the reference list of included systematic reviews and websites for other published HTA reports (http://www.hta.ac.uk/ and http://www.inahta.org). Finally, pharmacological companies, which have a marketing authorization for one of the pharmaceuticals assessed in this HTA report, were presented with the identified systematic reviews, including which primary studies they were based on, and invited to submit further relevant literature to the scope of this project.

Inclusion criteria

Population:	Patients undergoing elective hip replacement surgery
	Patients undergoing elective knee replacement surgery
Intervention:	Rivaroxaban (Xarelto)
	Dabigatran (Pradaxa)
Comparator:	Rivaroxaban (Xarelto)
	Dabigatran (Pradaxa)
	Enoxaparin (Klexane)

	Dalteparin (Fragmin)
Outcomes:	**Primary**
	Mortality
	Pulmonary embolism (PE)
	Deep venous thrombosis (DVT)
	Post thrombotic syndrome (PTS)
	Bleeding
	Other adverse Events
	Secondary
	Quality of Life
	Duration of hospital stay
	Re-submissions to hospital (totally and cause specific)
	Sick leave / Ability to work
	Infections
	Re-operations
Study design:	Systematic reviews
	Randomized controlled trials
Languages:	No limitations in languages during the search, but we only included articles in English, articles with English abstract or articles in Scandinavian.

Selection of publications

Two persons independently inspected all citations generated by the search to identify potentially relevant publications based on title and/or abstract. Full text versions were obtained for articles appearing to meet the inclusion criteria or in cases where sufficient information was not available to make a decision. Two persons independently assessed whether the publication was relevant or not according to our list of inclusion criteria. Disagreements were resolved by discussion or by consulting a third reviewer.

Publications meeting the predefined inclusion criteria were assessed for quality according to a check list for systematic reviews or for risk of bias for randomized controlled trials (15). All assessments were performed and agreed upon by two persons.

Data analysis

Data were collected from the systematic reviews and presented as they appeared in the reviews. In cases where the systematic review had pooled data into composite endpoints or mixed populations, we extracted data from the identified randomized controlled trials to fit our outcomes and subgroups. We did not check the randomized controlled trials for additional outcomes beyond those reported in the systematic reviews.

When appropriate, we performed meta-analyses using a random effects model. As far as possible our analyses of efficacy are performed according to the principle of "intention-to-treat". Meta-analyses are presented as forest plots.

Grading the quality of evidence

Two reviewers assessed overall confidence in the results for each outcome by using GRADE (Grading of Recommendations, Assessment, Development and Evaluation, www.gradeworkinggroup.org). The method is based on the study design used and involves an evaluation of eight criteria for each outcome. Limitations in any of five criteria may lower the quality: study quality/risk of bias, consistency between trials, directness (in how similar the population, intervention, and outcomes are between the trials and the stated objectives of this report), precision of the estimates and reporting bias. The three criteria to evaluate an increase in quality are: large effect, presence of a dose-response gradient and plausible confounding that would change (lower) the effect.

In performing the evaluation, we used the quality assessments of the randomized controlled trials presented in the systematic review when available or we used a checklist to assess risk of bias ourselves (15). Our assessment is shown in Appendix 4. Finally the overall quality was categorized as high, moderate, low or very low.

GRADE gives the following definition of the different quality of evidence:
High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

RESULTS

Result of literature search

We identified 679 references in the search for systematic reviews. A separate hand search identified an additional two references. Eleven references were found to be potentially relevant and full text copies were reviewed.

To ensure that the most recent publications were identified, we performed a search for randomized controlled trials published after the searches in the systematic re-

views were executed. We identified 228 references. Of these, three met our inclusion criteria, but had already been identified in the included systematic reviews.

Pharmaceutical companies with marketing authorization for the pharmaceuticals included in this HTA were invited to submit additional publications according to our specified criteria and not identified by us. Based on their submission information we identified one open-label comparative study on rivaroxaban. In addition, one study stated as ongoing in the included systematic review was submitted after it was published (RE-NOVATE II).

Finally, three systematic reviews and two randomized controlled trials met the prespecified inclusion criteria. Overview of the identification of documentation is presented in Figure 1. In addition, tables with characteristics of the included references are presented in Appendix 3 and in the following chapters.

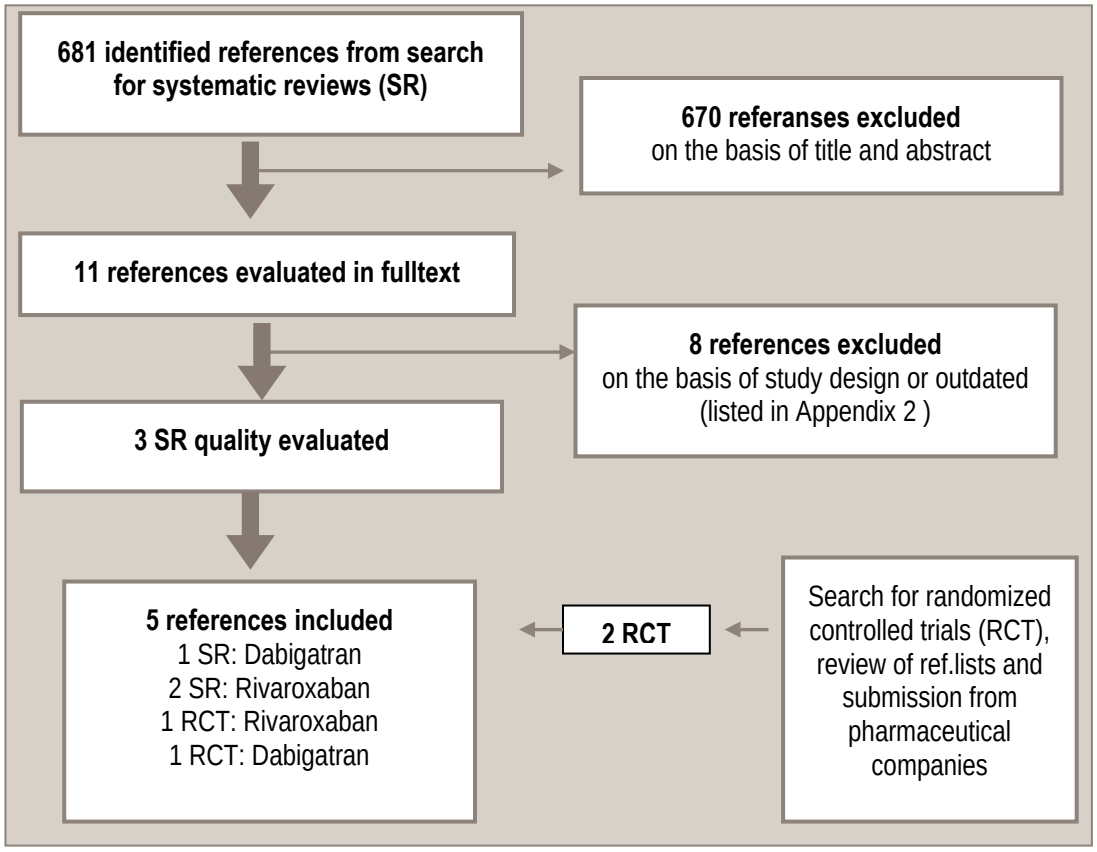


Figure 1. *Flowchart of identification of documentation.*

Description of included systematic reviews/studies

Dabigatran

We included one systematic review of high quality by Salazar and co-workers (4). Their objective was to examine the efficacy and safety of prophylactic anticoagula-

tion with direct thrombin inhibitors (DTIs) versus low molecular weight heparins (LMWH) or vitamin K antagonists in the prevention of VTE in patients undergoing total hip or knee replacement. Their outcome measures were mortality, VTE, bleeding and hepatopathy. They did not report data for post-thrombotic syndrome or any of our secondary outcomes, which are duration of hospital stay, re-submission to hospital, sick-leave, infections, re-operations or quality of life.

The authors only included randomized controlled trial designed to compare prophylactic anticoagulation according to their objective. The authors included 14 studies, of which four used oral dabigatran. All four studies compared dabigatran to enoxaparin and none to dalteparin. We only report data from these four studies, which included at total of 10183 patients. The studies included patients mostly from Europe, Australia, South-Africa and North-America.

Rivaroxaban

For the evaluation of rivaroxaban we found two publications of interest. One was an Evidence review group (ERG) review of a manufacturer's submission to NICE as part of the single technology appraisal (STA) process (16) and the other was a systematic review published as a health technology assessment (HTA) rapid review (3). In the ERG review the search had been evaluated to be adequate but results had been blacked out, as manufacturer's in confidence submission. In the other, the electronic search strategy was limited (but other sources were used as well), studies was listed and described but only briefly evaluated for quality/risk of systematic bias. In neither review had the authors tried to combine the studies into meta-analyses. The reviews reported data on mortality, VTE, PE, DVT, bleeding and adverse events, but not post-thrombotic syndrome or any of our secondary outcomes.

We used data described by Ndegwa and co-workers in the HTA rapid review (3) as far as possible, but retrieved the articles included in full text to finalize a quality assessment and perform meta-analysis. The RECORD 4 study (17) was not published when the HTA was performed, so we retrieved the full text version to extract data from this study. Based on a review of reference lists in publications submitted by the pharmaceutical companies, we identified one further randomized controlled study of rivaroxaban (18). This was also retrieved in full text to extract data. All identified studies compared rivaroxaban to enoxaparin and none to dalteparin.

Efficacy of dabigatran compared to rivaroxaban

We did not identify studies that directly compared dabigatran with rivaroxaban.

Efficacy of dabigatran compared to enoxaparin

We included one systematic review (4), where four studies comparing dabigatran to enoxaparin were included: BISTRO II (19) RE-MOBILIZE (20), RE-MODEL (21) and RE-NOVATE (22). In addition, the ongoing study RE-NOVATE II was finished and published in 2011 and was included in our report (23).

Treatment regimens in the included studies

The doses and treatment duration varied from study to study. In general, dabigatran was tested in several doses with treatment start after surgery, while enoxaparin treatment started the night before surgery. An overview of the treatment regimens used is given in Table 2.

Table 2. Treatment regimens in the included studies comparing dabigatran to enoxaparin.

Study	Type of replacement surgery	Dabigatran Doses used and treatment start	Enoxaparin Doses used and treatment start	Treatment duration Follow-up
BISTRO II (19)	Hip & knee	50 mg bid* 150 mg bid, 225 mg bid or 300 mg Start 1-4 h after surgery	40 mg Start the evening before surgery	7 days Follow-up 4-6 weeks
RE-MOBILIZE (20)	Knee	150 mg, 220 mg Start 6-12 h after surgery	30 mg bid Start 12-24 h after surgery.	12-15 days Follow-up 3 months
RE-MODEL (21)	Knee	150 mg, 220 mg Start 1-4 h after surgery	40 mg Start the evening before surgery	6-10 days Follow-up 2-3 months
RE-NOVATE (22).	Hip	150 mg, 220 mg Start 1-4 h after surgery	40 mg Start the evening before surgery	28-35 days Follow-up 2-3 months
RE-NOVATE II (23)	Hip	220 mg Start 1-4 h after surgery	40 mg Start the evening before surgery	28-35 days Follow-up 2-3 months

*Bid: dosing two times per day

Results of dabigatran compared to enoxaparin

Based on the systematic review by Salazar and colleagues with addition of the newly published RE-NOVATE II study we extracted data and performed meta-analyses. We divided the population into those which underwent total hip surgery and those which underwent total knee surgery. In our presentation it is possible to see the results for each study and within each population of hip or knee surgery (see Figures 2 - 5). Results from all doses used in the study are pooled to get the study estimate.

For the endpoints related to efficacy, PE and DVT, we included treatment with all doses but only treatment duration comparable to the generally recommended treatment duration after hip or knee replacement surgery. These treatment durations are 10-14 days for knee replacement and 30 days for hip replacement. However, for the endpoint related to safety, mortality and bleeding, we included all data, irrespective of treatment time and dose. This was to ensure that all important safety information become easily accessible. As far as possible the extracted data include events in the follow-up (FU) period, when patients still are in the study but no longer take the treatments.

In summary, we did not find statistical significant differences between dabigatran and enoxaparin for any of the outcomes reported. The quality of the documentation ranged from moderate to very low. Overall results are presented in Table 3.

Table 3. Summary of findings for dabigatran vs. enoxaprin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	enoxaparin	**Dabigatran**			
Mortality - hip	**1 per 1000**	**1 per 1000**	**RR 1.17**	5428	
Follow-up: 60-90 days		(0 to 37)	(0.04 to 36.52)	(2 studies)	**very low**[1.2]
Mortality - knee	**3 per 1000**	**3 per 1000**	**RR 1.06**	4652	
Follow-up: 35-90 days		(1 to 9)	(0.36 to 3.12)	(2 studies)	**low**[2.3]
PE - hip	**2 per 1000**	**2 per 1000**	**RR 0.84**	5428	
Follow-up: 60-90 days		(1 to 6)	(0.25 to 2.77)	(2 studies)	**low**[2]
PE - knee	**5 per 1000**	**3 per 1000**	**RR 0.66**	4997	
Follow-up: 35-90 days		(1 to 8)	(0.27 to 1.65)	(3 studies)	**low**[2.3]
DVT - hip	**76 per 1000**	**74 per 1000**	**RR 0.98**	4222	
Follow-up: 60-90 days		(59 to 93)	(0.78 to 1.22)	(2 studies)	**moderate**[4]
DVT - knee	**315 per 1000**	**306 per 1000**	**RR 0.97**	3886	
Follow-up: 35-90 days		(220 to 422)	(0.7 to 1.34)	(3 studies)	**very low**[3.4.5.6]
Major bleeding - hip	**14 per 1000**	**17 per 1000**	**RR 1.24**	6805	
Follow-up: 35-90 days		(12 to 26)	(0.83 to 1.86)	(3 studies)	**moderate**[2.7]
Major bleeding - knee	**14 per 1000**	**12 per 1000**	**RR 0.89**	5292	
Follow-up: 35-90 days		(7 to 24)	(0.47 to 1.69)	(3 studies)	**moderate**[2]

*The basis for the **assumed risk** is the control group of the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.

[1] High lever of heterogeneity.I2=63%. Studies point in different directions.

[2] Low number of events. Wide confidence interval. Downgrade 1 or 2 according to severity.

[3] Includes studies with different enoxaparin dosing. Chose not to downgrade

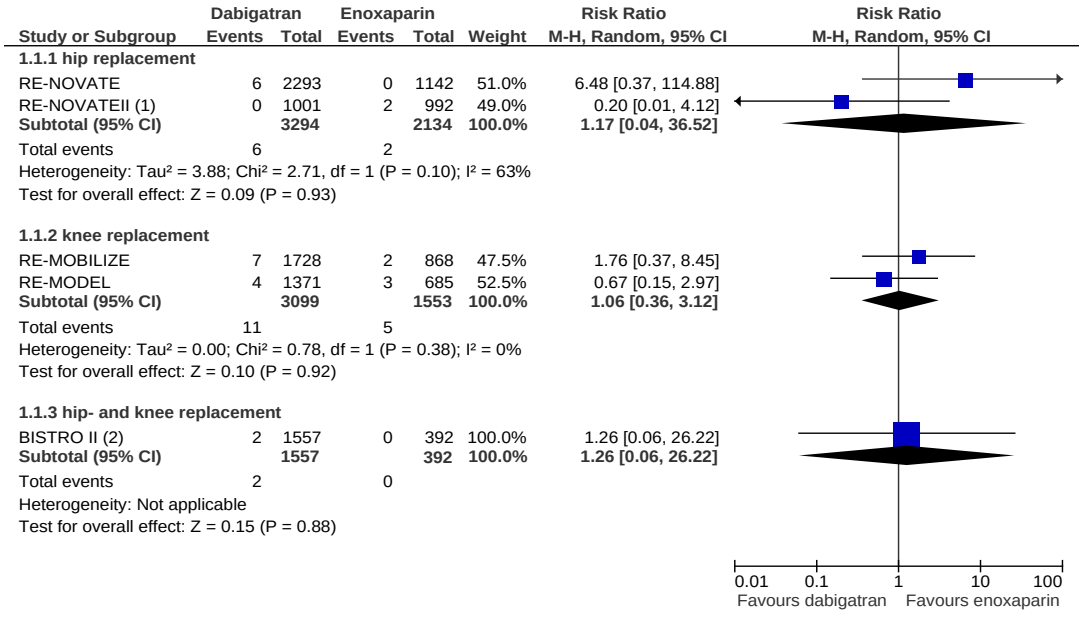
[4] Incomplete outcome data insufficiently addressed. They used mITT which is defined as those with evaluable venography and not as those randomized to treatments.

[5] High lever of heterogeneity I2=90%. Removal of BISTRO II led to I2=79%. Different dabigatran and enoxaparin dosing could possibly explain some of the heterogeneity but probably not all.

[6] Wide confidence interval

[7] Different treatment periods. Chose not to downgrade

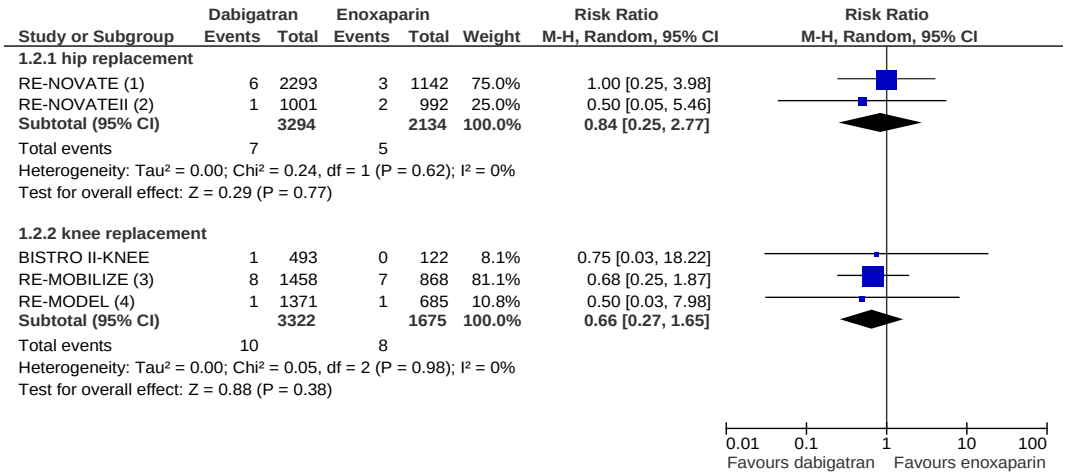
We did not find differences in mortality between treatment with dabigatran and enoxaparin for either hip or knee surgery, relative risks (RR) and 95% confidence interval (CI) 1.17 (0.04 – 36.54) and 1.06 (0.36 – 3.12) respectively. The quality of the documentation was very low and low (Tab 3, Fig 2). We were unable to distinguish whether the deaths in the BISTRO II study related to patients undergoing hip or knee replacement surgery.



(1) 1 of 2 deaths in FU-period
(2) deaths during follow-up, patients wiht active malignancy. Hip or knee not stated.

***Figure 2**. Analysis of mortality – dabigatran vs.enoxaparin.*

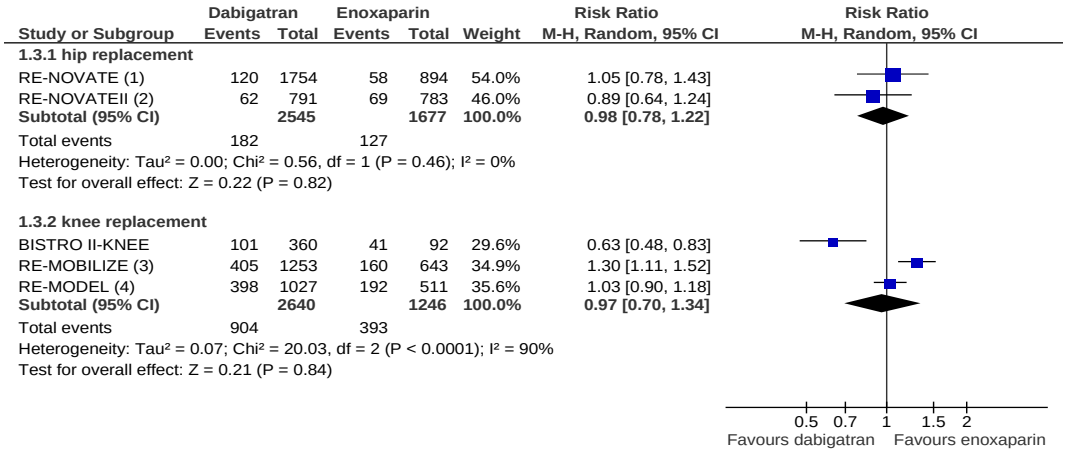
The RR for PE in patients undergoing hip replacement surgery was 0.84 (0.25 – 2.77). We excluded data from the patients undergoing hip surgery in the BISTRO II study due to the short treatment time (the RR was 0.78 (0.03 - 19.01)). The RR was 0.66 (0.27 – 1.65) for patients undergoing total knee replacement surgery. Neither results for hip nor knee replacement surgery was statistically significant and the quality of the documentation was low (Tab 3, Fig 3).



(1) symptomatic PE
(2) symptomatic non-fatal PE
(3) non-fatal PE, including follow-up
(4) symptomatic PE treatment time

***Figure 3**. Analysis of PE – dabigatran vs. enoxaparin*

For DVT, we found RR to be 0.98 (0.78 – 1.22) in patients undergoing hip surgery (moderate quality of the documentation) (Tab 3, Fig 4). As for PE we excluded results from BISTRO II for patients with hip surgery (RR 0.97 (0.67 - 1.40). For patients undergoing total knee surgery, RR was 0.97 (0.70 – 1.34) with very low quality of the documentation. There was high heterogeneity of the knee surgery studies but even with removal of the presumably most different study, the BISTRO II, the heterogeneity was 79% and RR 1.15 (0.92 – 1.45).



(1) asymptomatic dvt + symptomatic dvt + symptomatic "events" during follow-up
(2) Includes 2 symptomatic VTE in each group during follow-up. Included as DVT
(3) including follow-up
(4) asymptomatic dvt + symptomatic dvt + symptomatic "events" during follow-up

***Figure 4.** Analysis of DVT – dabigatran vs.enoxaparin*

For major bleeding RR was 1.24 (0.83 - 1.86) and RR 0.89 (0.47 – 1.69) for hip and knee surgery, respectively. The quality of the documentation was moderate (Tab 3, Fig 5).

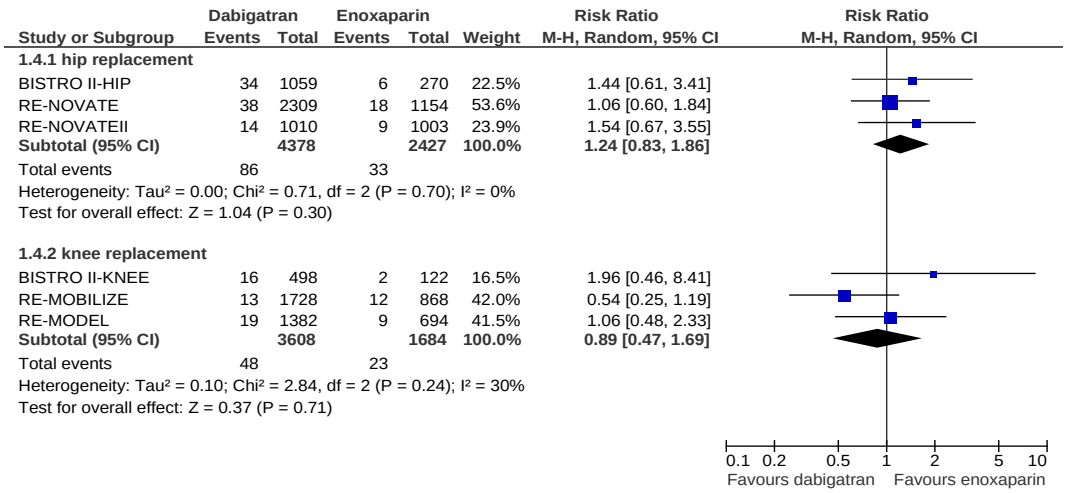


Figure 5. *Analysis of major bleeding – dabigatran vs.enoxaparin*

Additional safety data on minor bleeding and increase in liver enzymes did not indicate any statistical significant differences between treatments for either hip- or knee replacement surgery (Appendix 5).

Efficacy of rivaroxaban compared to enoxaparin

Based on the included systematic reviews and hand search of reference lists, we included four phase II dose-finding studies and four phase III studies (17;18;24-29) for the comparison of rivaroxaban to enoxaparin (Tab.4).

Treatment regimens in the included studies

The drug doses used and treatment duration varied form study to study. In general, rivaroxaban was tested in several doses with treatment start after surgery, while enoxaparin treatment started the night before surgery. An overview is given in Table 4.

Table 4. Treatment regimens in the included studies comparing rivaroxaban to enoxaparin.

Study	Type of replacement surgery	Rivaroxaban Doses used and treatment start	Enoxaparin Doses used and treatment start	Treatment duration Follow-up
Eriksson and co-workers (18)	Hip	2.5 mg bid, 5 mg bid, 10 mg bid, 30 mg , 20 mg bid and 30 mg bid Start 6-8 h after surgery	40 mg Start the evening before surgery	5-9 days Follow-up 30-60 days
ODIXa-HIP (bid) (25)	Hip	2.5 mg, 5 mg, 10 mg, 20 mg or 30 mg, (all bid) Start 6-8 h after surgery	40 mg Start the evening before surgery.	5-9 days Follow-up 30-60 days
ODIXa-HIP (qd) (24)	Hip	5 mg, 10 mg, 20 mg, 30 mg or 40 mg Start 6-8 h after surgery	40 mg Start the evening before surgery	5-9 days Follow-up 30-60 days
RECORD1 (26)	Hip	10 mg Start 6-8 h after surgery	40 mg Start 12 h before surgery and restarted 6-8 h after wound closure	35 days Follow-up 30-35 d after last dose
RECORD2 (27)	Hip	10 mg Start6-8 h after wound closure and continued for 31-39 days	40 mg Start 12 h before surgery and restarted 6-8 h after wound closure	R: 31-39 days E: 10-14 days Follow-up 30-35 days after last dose
ODIXa-KNEE (29)	Knee	2.5 mg, 5 mg, 10 mg, 20 mg or 30 mg (all bid) Start 6-8 h after surgery.	30 mg bid Start 12-24 h after surgery	5-9 days Follow-up 30-60 days
RECORD3 (28)	Knee	10 mg Start 6-8 h after wound closure	40 mg Start 12 h before surgery and restarted 6-8 h after wound closure	10-14 days Follow-up 30-35 days after last dose
RECORD4 (17)	Knee	10 mg Start 6-8 h after wound closure	30 mg bid Start 12-24 h after wound closure	10-14 days Follow-up 30-35 days after last dose

Results of rivaroxaban compared to enoxaparin

Based on the systematic reviews, supplemented with the randomized controlled trials, we extracted data regarding our outcomes of interest. We used the safety population (patients that had received at least one dose of study medication) as basis of the number of participants unless otherwise specified. In our presentation it is possible to see results for each study and within each population of hip or knee surgery (see Figures 6 - 9). Results from all doses used in the study are pooled to get the study estimate.

For the endpoints related to efficacy (PE and DVT) we included treatment with all doses but only treatment duration comparable to the recommended treatment duration after hip or knee replacement surgery. These treatment durations are 10-14 days for knee replacement and 30 days for hip replacement. However, for the endpoints related to safety (mortality and bleeding) we included all data, irrespective of treatment duration and dose. This was to make sure all important safety information become easily accessible. As far as possible the extracted data included events in the follow-up (FU) period, when patients were still in the study but no longer taking the study medication.

In summary, for rivaroxaban compared with enoxaparin we found statistical significant decreases in DVT, but also a trend towards increased risk of major bleeding (only significant for hip replacement). For the endpoints mortality and PE there were too few events to make a conclusion with regard to potential risks or benefits. The quality of the documentation ranged from moderate to very low. The results are presented in Table 5.

Table 5. Summary of findings for rivaroxaban vs. enoxaparin

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	Corresponding risk			
	enoxaparin	**Rivaroxaban**			
mortality - hip	**3 per 1000**	**2 per 1000**	**RR 0.73**	8905	
Follow-up: 35-75 days		(1 to 5)	(0.29 to 1.8)	(5 studies)	**low**[1.2.3]
mortality - knee	**4 per 1000**	**2 per 1000**	**RR 0.62**	6106	
Follow-up: 35-55 days		(1 to 12)	(0.13 to 2.9)	(3 studies)	**low**[3.4]
PE - hip	**1 per 1000**	**1 per 1000**	**RR 1.0**	6890	
Follow-up: 50-75 days		(0 to 15)	(0.07 to 15.28)	(2 studies)	**very low**[2.3.5]
PE - knee	**4 per 1000**	**2 per 1000**	**RR 0.50**	6106	
Follow-up: 35-55 days		(1 to 6)	(0.17 to 1.46)	(3 studies)	**low**[3.4]
DVT - hip	**51 per 1000**	**11 per 1000**	**RR 0.21**	4886	
Follow-up: 50-75 days		(7 to 16)	(0.14 to 0.32)	(2 studies)	**low**[2.6.7]
DVT - knee	**145 per 1000**	**90 per 1000**	**RR 0.62**	3992	
Follow-up: 35-55 days		(74 to 109)	(0.51 to 0.75)	(3 studies)	**moderate**[4.6]

Major bleeding - hip Follow-up: 35-75 days	**2 per 1000**	**4 per 1000** (2 to 9)	**RR 2.23** (1.06 to 4.67)	9064 (5 studies)	**moderate**[2.3]
Major bleeding - knee Follow-up: 35-55 days	**4 per 1000**	**6 per 1000** (3 to 13)	**RR 1.61** (0.8 to 3.24)	6106 (3 studies)	**moderate**[3.4]

*The basis for the **assumed risk** is the control group of the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.**Very low quality:** We are very uncertain about the estimate.

[1] One study open-label. One study without events. Chose not to downgrade

[2] Includes studies with several rivaroxaban doses and/or a study with different treatment duration of rivaroxaban and enoxaparin. Chose not to downgrade.

[3] Low number of events. Wide confidence interval. Downgrade 1 or 2 according to severity.

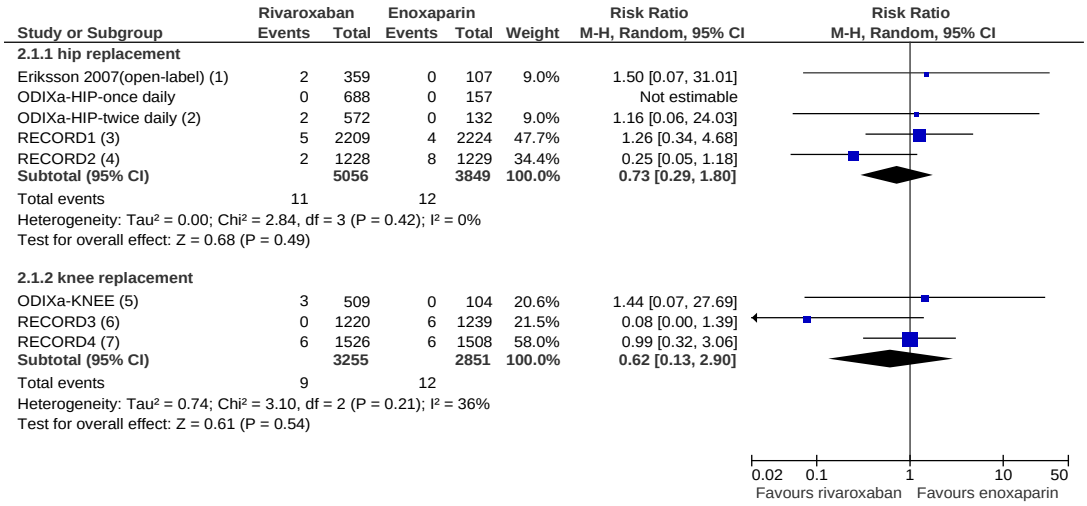
[4] Includes studies with several rivaroxaban doses and/or different dosing of enoxaparin. Chose not to downgrade.

[5] High lever of heterogeneity I2=68%. Possibly explained by shorter enoxaparin treatment time in RECORD2. Studies point in different directions.

[6] Incomplede outcome data insufficiently adressed. They used mITT which is defined as those with evaluable venography, not as those randomized to treatment.

[7] Low number of events

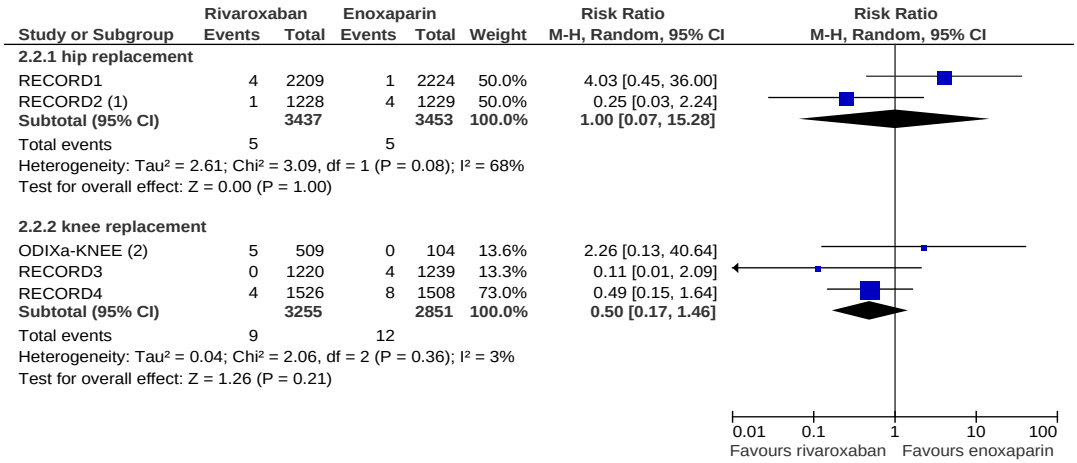
Death is a relatively rare event in these studies and accordingly it is hard to find a precise estimate of the effect of rivaroxaban compared to enoxaparin (low quality of the evidence). At present we found RR 0.73 (0.29 – 1.80) for hip and RR 0.62 (0.13 – 2.90) for knee replacement surgery (Tab 5, Fig 6)



(1) Per protocol population
(2) Deaths during follow-up
(3) includes 1 death during follow-up
(4) 2 deaths in enoxaparin group during follow-up
(5) Deaths occured during follow-up (2 PE+1cardiorespiratory failure)
(6) include 4 in follow-up period
(7) 4 deaths in rivaroxaban and 3 in enoxaparin was in follow-up period

Figure 6. *Analysis of mortality – rivaroxaban vs. enoxaparin*

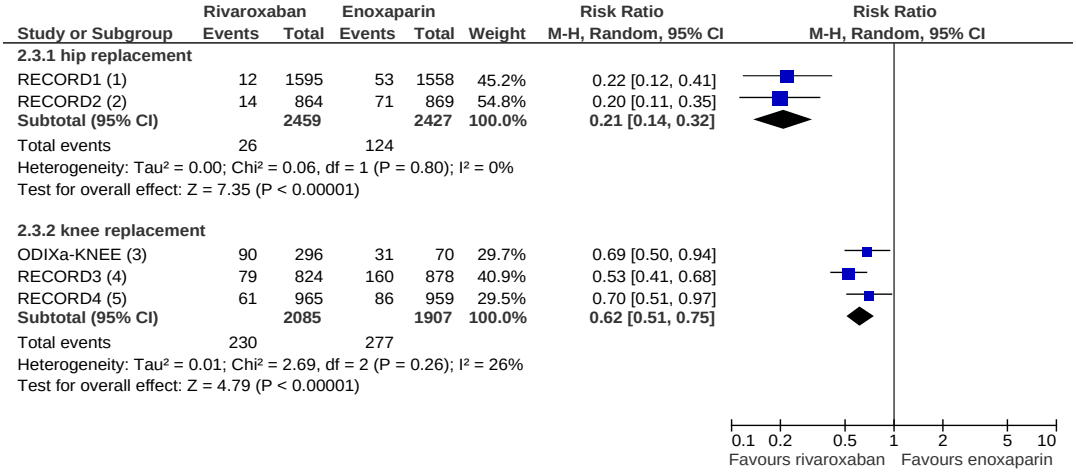
The same limitations as for mortality, low number of events, apply for PE (very low and low quality of the documentation), where we found RR 1.0 (0.07 – 15.28) for patients undergoing total hip replacement surgery. Because of the shorter treatment time, we excluded data from three studies. They were the Eriksson 2007 open label (RR 2.10 (0.11 – 40.34)) and the two ODIXa-HIP studies (RR 1.61 (0.08 – 30.92) once daily dosing and no events in twice daily dosing). For patients undergoing knee replacement surgery we found RR 0.5 (0.17 – 1.46) (Tab 5, Fig 7).



(1) enoxaparin treatment time approx half of rivaroxaban
(2) 2 during treatment and 3 during follow-up (see deaths)

Figure 7. *Analysis of PE – rivaroxaban vs. enoxaparin*

For the outcome of DVT we found RR 0.21 (0.14 – 0.32) for patients undergoing total hip replacement. We excluded the same three studies as for PE. Eriksson 2007 open label (RR 1.03 (0.64 – 1.63)), and the two ODIXa-HIP studies (RR 0.43 (0.28 – 0.64) once daily dosing and RR 0.84 (0.52 – 1.36) twice daily dosing). For patients undergoing knee replacement surgery we found RR 0.62 (0.51 - 0.75). The quality of the evidence was low and moderate (Tab 5, Fig 8). Both results for hip and knee replacement surgery were significant in favour of rivaroxaban.



(1) in modified ITT for efficacy
(2) In modified ITT for efficacy. Enoxaparin treatment time approx half of rivaroxaban
(3) Per protocol population. One additonal dvt during follow-up, group not specified
(4) modified ITT for efficacy analysis
(5) all dvt (asymptomatic+symptomatic) rivaroxaban 55+6; enoxaparin 76+10. mITT for efficacy analysis

Figure 8. *Analysis of DVT – rivaroxaban vs. enoxaparin*

Meta-analysis, with inclusion of all identified studies of major bleeding, showed RR 2.23 (1.06 – 4.67) for hip and RR 1.61 (0.80 – 3.24) for knee replacement surgery. The quality of the evidence was moderate (Tab 5, Fig 9). The result is significant for hip replacement surgery and a trend, although not significant, towards more bleeding for knee replacement surgery.

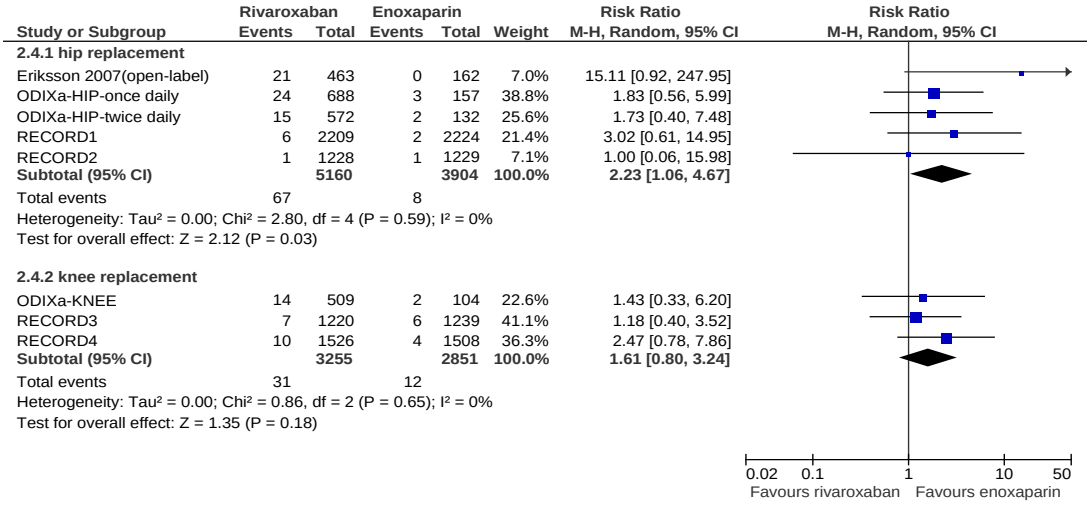


Figure 9. *Analysis for major bleeding – rivaroxaban vs. enoxaparin*

Additional safety data on minor bleeding and increase in liver enzymes did not show any statistically significant differences between treatments for either hip or knee replacement surgery (Appendix 5).

Economic evaluation

METHODS

General

We performed an economic evaluation of the cost-effectiveness of rivaroxaban and dabigatran compared with enoxaparin, for the prophylaxis of VTE in patients undergoing total hip replacement (THR) and total knee replacement surgery (TKR). The analyses were conducted from a healthcare perspective, where relevant costs were expressed in Norwegian kroner (NOK) and effects were expressed in quality adjusted-life-years (QALYs). All future costs and effects were discounted with an annual rate of 4% according to Norwegian guidelines (30).

The results were expressed in incremental cost-effectiveness-ratios (ICERs) and net health benefit (NHB). The conclusions were based the assumption that an intervention can be considered cost-effective if it yields a positive NHB.

We developed a probabilistic decision model, in which the uncertainty in parameters was modelled as probability distributions (Appendix 6). We performed a probabilistic sensitivity analyses, designed as a Monte Carlo simulation, with 10 000 iterations to expressed the uncertainty of our results.

Model structure

In order to assess the cost-effectiveness of alternative thromboprophylactic interventions, a decision model was developed in TreeAge Pro ® 2009. The model was run for 69-year-old women (5) and the patients were followed until death or 100 years of age. The two surgery types, hip- and knee replacement, were modelled separately to reflect differences in the underlying risk of DVT, PE and major bleeding.

The model is divided into two modules; a short-term prophylaxis module (for a period of 90 days after surgery) and a long-term complications module (until patients are either dead or 100 years old). The first module (acute phase) is represented with a decision tree, while a Markov model simulated events occurring over the longer term (chronic phase). A combination structure was chosen in order to incorporate

both the short and the long term effects in terms of increased survival and possible sequela.

DVT (can be symptomatic or asymptomatic [1]), PE and major bleeding events were modelled for the acute phase (the primary VTE risk was assumed to continue for a period of 90 days after surgery (31;32)). The QALYs and costs arising from these events were modelled over the patient's lifetime, including treatment of post-thrombotic syndrome (PTS) and recurrent VTE.

Patients entered the Markov model at the end of the acute phase. The chronic phase model contains three health states "symptom-free patient", "PTS" and "dead". The cycle length of the model was one year, which means that all transitions between the different health states could happen once a year. In each Markov 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. In the model, different health states and associated cost were used for the first year and subsequent years of PTS.

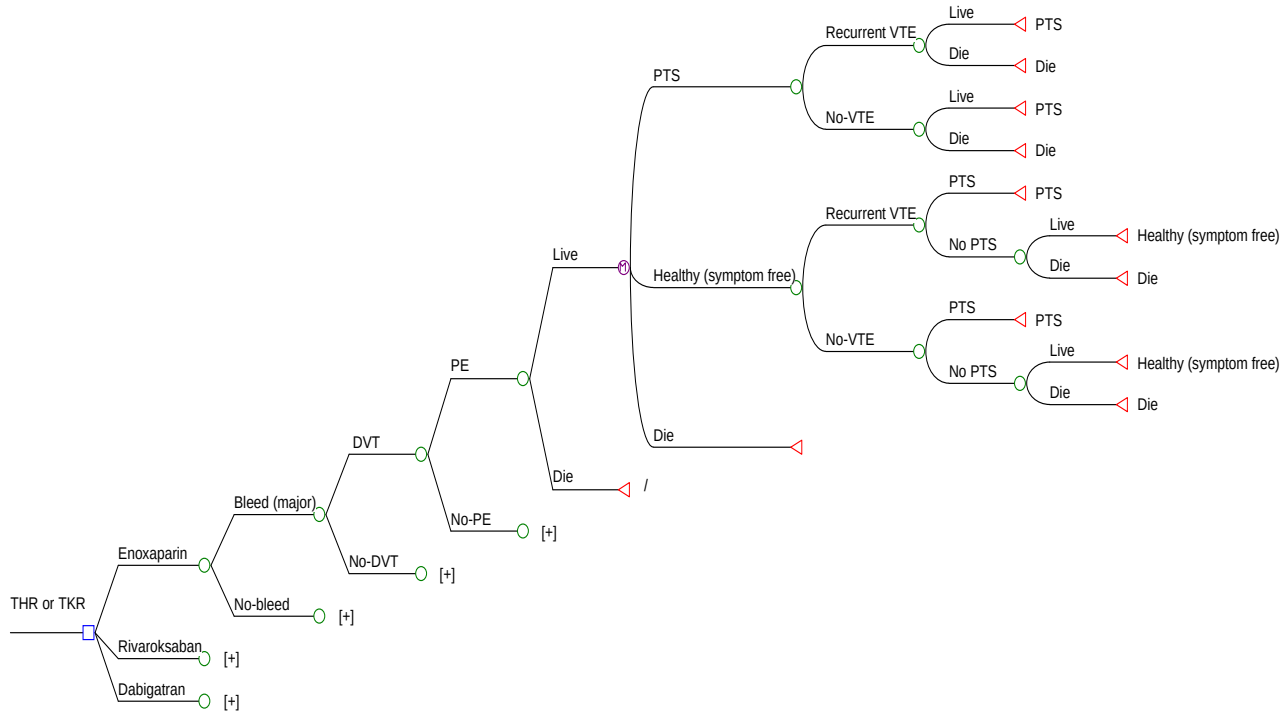


Figure 10. *Model structure (the branches marked with plus signs are similar to their respective opposite branch)*

Model probabilities

The model probabilities are presented in Table 6.

[1] Since diagnostic tests of VTE are not performed systematically in all patients undergoing surgery, patients receive no treatment for asymptomatic VTE events. No costs or utilities are therefore allocated to such events.

The incidence of symptomatic venous thromboembolism (DVT, PE) in patients undergoing THR and TKR are based on a Norwegian study (33). LMWH was given to all patients while hospitalized.

The risk of major bleeding following thromboprophylaxis were taken from a review article that reported major bleeding rates in patients treated with enoxaparin in hip and knee arthroplasty trials (34).

The annual risk of recurrent VTE and developing PTS were estimated from a prospective study of the long-term follow-up of acute VTE over a 5-year follow-up (35). The risk of PTS was assumed to begin after day 90. Patients who had no VTE event in the postsurgical period were assumed to be at the same risk for a VTE event and PTS as the general population (36;37).

For calculating the risk of death in the acute phase, we collected age and gender specific Norwegian all-cause mortality data from Statistics Norway (38). These data were multiplied with relative risk of total death from meta-analyses of the included articles in our systematic review (see Table 3 and 5) for acute phase and the relative risk of death from VTE (35) for the postoperative phase. Death in the postoperative period from all other causes was calculated based on Norwegian all-cause mortality data from Statistics Norway (38).

Table 6. Probabilities used in the model*

Probability	Total hip replacement	Total knee replacement	Source
Major bleeding †	0.017	0.005	Dahl *et al.* 2010 (34)
DVT	0.016	0.016	Bjørnarå *et al.* 2006 (33)
PE	0.011	0.011	Bjørnarå *et al.* 2006 (33)
Developing PTS: year 1	0.180	0.180	Prandoni *et al.* 1997 (35)
Developing PTS: year 2	0.131	0.131	Estimated based on Prandoni *et al.* 1997 (35)
Developing PTS: year 3+	0.068	0.068	Estimated based on Prandoni *et al.* 1997 (35)
Developing recurrent VTE: year 1-2	0.090	0.090	Prandoni *et al.* 1997 (35)
Developing recurrent VTE: year 3+	0.054	0.054	Estimated based on Prandoni *et al.* 1997 (35)

PTS for patients who had no VTE event	0.0008	0.0008	Heit *et al.* 2001 (36)
Recurrent VTE for patients who had no VTE event	0.0014	0.0014	Næss *et al.* 2007 (37)

* The uncertainty in probabilities variables were modelled as probability distributions and presented in Appendix 6.
† Patients treated with enoxaparin.

Clinical efficacy

Efficacy estimates is derived from our systematic review of the literature. Efficacy and grading are based on Tables 3 and 5. We assigned log-normal distributions to the efficacy parameters according to the methodology described by Briggs and co-workers (39).

We incorporated the GRADE assessment into the model by assigning probability distributions related to the quality of the evidence, with a wider distribution for the lower quality documentation. For efficacy estimates based on high quality of the evidence, probability distributions were based on 95% confidence intervals. This is based on the fact that we are confident that the results actually represent the uncertainty they claim. For moderate, low or very low quality results, we have used confidence intervals of respectively 90%, 80% and 70% which reflects that we have less trust in the evidence (Table 7).

Table 7. Efficacy parameters for log-normal distribution

	RR (95% CI)	**Quality of evidence ***	**ln(RR)**	**ln(SE) †**
Dagibatran *vs*. enoxaparin after hip replacement				
Mortality	1.17 (0.04-36.52)	very low	0.157	3.289
PE	0.84 (0.25-2.77)	low	-0.174	0.939
DVT	0.98 (0.78-1.22)	moderate	-0.020	0.136
Major bleeding	1.24 (0.83-1.86)	moderate	0.215	0.245
Dagibatran *vs*. enoxaparin after knee replacement				
Mortality	1.06 (0.36-3.12)	low	0.058	1.042
PE	0.66 (0.27-1.65)	low	-0.416	0.706
DVT	0.97 (0.70-1.34)	very low	-0.030	0.313

Major bleeding	0.89 (0.47-1.69)	moderate	-0.117	0.389
Rivaroxaban *vs*. enoxaparin after hip replacement				
Death	0.73 (0.29-1.80)	low	-0.315	0.712
PE	1.00 (0.07-15.28)	very low	0	2.598
DVT	0.21 (0.14-0.32)	low	-1.561	0.399
Major bleeding	2.23 (1.06-4.67)	moderate	0.802	0.451
Rivaroxaban vs. enoxaparin after knee replacement				
Death	0.62 (0.13-2.90))	low	-0.478	1.211
PE	0.50 (0.17-1.46)	low	-0.693	0.839
DVT	0.62 (0.51-0.75)	moderate	-0.478	0.117
Major bleeding	1.61 (0.80-3.24)	moderate	0.476	0.425

RR: relative risks; PE: pulmonary embolism; DVT: deep venous thrombosis
* For estimates with low or very low quality of the evidence, we assumed that the 95% confidence interval in reality represented a confidence interval of 80% and 70%, respectively.
† Ln (SE) is calculated from the confidence interval and adjusted based on quality of the outcome.

Costs

All costs were measured in 2010 Norwegian Kroner (NOK) and presented in Table 8.

The cost of thromboprophylaxis after hospital discharge is based on maximum pharmacy retails prices (AUP). In-hospital drug costs are calculated based on the prise list that we have received from Drug procurement cooperation (LIS). These prices (LIS-price) are stated in pharmacy purchase prices (AIP), therefore we have converted them into pharmacy retail prices (AUP) by Norwegian Medicine Agency's guidelines for determining the gross profit for a pharmacy (40). Administration cost related to injection of enoxaparin was also included in the model based on the following assumptions: We assumed that 5-13% of patients require nurse assistance during the period after hospital discharge (41;42). Further, we assumed that 65 - 95% of patients discharged to rehabilitation centres (with length of stay ranging from 7 to 14 days) (43). It is most likely that these patients will receive enoxaparin injections in the rehabilitation centres, thus they are not included in the analysis. The estimated costs of all medications and administration for enoxaparin are presented in Appendix 7.

The costs of treating DVT or PE events were based on prices within the Norwegian Diagnosis Related Group (DRG) system (44) which are adjusted for different surgery types depending on the estimates of the average length of stay in hospital (45). For the assessment of the cost of diagnosing DVT or PE, we assumed one physician visit and one diagnostic investigation (for DVT: ultrasound and venography (for 8% of patients (46)) and for PE: spiral computed tomography and chest radiography). The cost of physician visits and diagnostic investigations were obtained from the price list for cost per outpatient clinic consultation and procedure (2010) (47). The cost of treating bleeding was estimated based on prices on the Norwegian DRG system (44).

The cost of PTS were estimated based on the cost of acute and chronic PTS reported by Bjorvatn and Kristiansen (45). We have assumed that the cost of diagnosing PTS is the difference between the cost of acute and chronic PTS, which is used in the Markov model only for the first year.

Table 8. Unit cost estimates per patient by type of procedure in NOK

	Total hip replacement	Total knee replacement	Description/ Source
Dabigatran (inpatient)	23 per day	23 per day	220 mg per day (110 mg on the first day) LOS* THR:7 (5-12) LOS* TKR: 5 (3-10) (48)
Dabigatran (outpatient)	110 mg, 10 capsules: 249 110 mg, 30 capsules: 679	110 mg, 10 capsules: 249 110 mg, 30 capsules: 679	220 mg per day THR:4-6 packages TKR: 1 package
Rivaroxaban (inpatient)	24 per day	24 per day	10 mg per day LOS* THR: 7 (5-12) LOS* TKR: 5 (3-10) (48)
Rivaroxaban (outpatient)	10 mg, 10 tablets: 525 10 mg, 30 tablets: 1 505	10 mg, 10 tablets: 525 10 mg, 30 tablets: 1 505	10 mg per day THR:2-4 packages TKR: 1 package
Enoxaparin (inpatient)	9 per day	9 per day	40 mg per day LOS* THR:7 (5-12) LOS *TKR: 5 (3-10) (48)
Enoxaparin (outpatient)	379 per package	379 per package	40 mg per day THR: 2-4 packages TKR: 1 package
Drug Administration *† **(outpatient)**	250-750 per visit	250-750 per visit	Assumption based on the administration cost of private/municipal nurse visit at home (49;50)
Major bleeding *	24 848	24 848	DRG-categories 174, 175; ISF 2010. Bjorvatn *et al.* 2005 (45)

Treatment DVT * (before discharge)	15 714	16 341	DRG- categories 128; ISF 2010 (44), Bjorvatn *et al.* 2005 (45)
Treatment DVT * (after discharge)	18 132	20 239	DRG- categories 128; ISF 2010 (44), Bjorvatn *et al.* 2005 (45)
Treatment PE * (before discharge)	9 372	16 603	DRG- categories 78; ISF 2010 (44), Bjorvatn *et al.* 2005 (45)
Treatment PE * (after discharge)	49 028	31 471	DRG- categories 78; ISF 2010 (44), Bjorvatn *et al.* 2005 (45)
DVT diagnosis* (post discharge)	2 054	2 054	(47)
PE diagnosis * (post discharge)	3 170	3 170	(47)
PTS diagnosis*	5 668 §	5 668 §	Bjorvatn *et al.* 2005 (45)
PTS treatment * (per year)	7 558 §	7 558 §	Bjorvatn *et al.* 2005 (45)

LOS: length of stay
* The uncertainty in variables were modelled as probability distributions and presented in Appendix 6.
† Related to injection of enoxaparin. Among the patients discharge to their homes, assumed 5-13% required nurse assistance (41;42).
§Costs were adjusted from 2003 to 2010 kroner by using the Norwegian consumer price index (51).

Quality of life

Utility estimates used in the model are summarized in Table 9.

The literature search emphasized a lack of good–quality utility data for this population. Therefore, the utility values are based on different sources which have been adjusted to be used in the model.

The baseline health state value for patients who had THR and TKR without complications and the utility for one year after the operation were taken from Räsänen *et al.* 2007 (52).

Utility value for symptomatic DVT, PE and recurrent VTE were derived from Haentjens *et al.* 2004 (53). The duration of DVT and PE was estimated to 3 months and 6 months, respectively (2;53). These utility values were adjusted based on the values reported by Räsänen and co-workers since no distinction was made between complications following THR and TKR. Utility values for PTS and bleeding were estimated based on values reported by Lenert and co-worker (54) and adjusted for the utilities reported by Räsänen and co-workers (52).

We could not identify reliable data that can show the probable effect of the different methods of administrating the medication on patients' utility, therefore the possible disutility associated with injections is not included in the model.

Table 9. Utility values*

Health state	Value		Utility instrument	Source
	Total hip replacement	Total knee replacement		
No symptomatic thromboembolic event	0.805	0.807	15D	Räsänen *et al.* 2007 (52)
Symptomatic DVT †	0.676	0.678	TTO, 15D	Haentjens *et al.* 2004 (53), Räsänen *et al.* 2007 (52)
PE †	0.612	0.613	TTO, 15D	Haentjens *et al.* 2004 (53), Räsänen *et al.* 2007 (52)
Major bleeding †	0.531	0.532	SG, 15D	Lenert and Soetikno 2007 (54), Räsänen *et al.* 2007 (52)
No VTE event; long-term utility	0.858	0.841	15D	Räsänen *et al.* 2007 (52)
PTS †	0.647	0.735	VAS, 15D	Lenert and Soetikno 2007 (54), Räsänen *et al.* 2007 (52); mean PTS utilities are adjusted for the proportion with mild and severe PTS based on Ashrani *et al.* 2009 (55)
Recurrent VTE †	0.721	0.706	TTO, 15D	Haentjens *et al.* 2004 (53), Räsänen *et al.* 2007 (52)
Death	0	0		

TTO: Time trade-Off; SG: Standard Gamble; VAS: Visual Analogue Scale
* The uncertainty in utility variables were modelled as probability distributions and presented in Appendix 6.
† These utility values were adjusted based on the baseline values reported by Räsänen *and co-workers* (52)

RESULTS

Thromboprophylactic treatment after total hip replacement

The results of the base-case analysis for the THR population are presented in Table 10, where dabigatran and rivaroxaban are each compared with enoxaparin.

The dabigatran strategy decreased both lifetime costs and effectiveness relative to enoxaparin. Comparison of dabigatran with enoxaparin resulted in negative net health benefit (NHB) assuming a willingness to pay of NOK 500 000, and therefore cannot be considered a cost- effective strategy relative to enoxaparin.

Rivaroxaban compared with enoxaparin would yield 0.175 additional QALYs at an additional cost of NOK 8 000. Rivaroxaban in comparison with enoxaparin have positive net health benefits for a willingness to pay of NOK 500 000, hence rivaroxaban can be considered a cost effective strategy compared with enoxaparin.

Table 10. Results of the base-case cost-effectiveness analyses (discounted); dabigatran and rivaroxaban compared with enoxaparin (Total hip replacement)

Strategy	Cost (NOK)	Incremental cost (NOK)	Effect (QALYs)	Incremental effect (QALY)	ICER (NOK/QALY)	NHB
Enoxaparin	4 800		8.029			
Dabigatran	4 200	-610	7.725	-0.304	2 006	-0.302
Rivaroxaban	13 000	8 000	8.204	0.175	4 5 000	0.160

Tornado diagram

To explore the uncertainty of the different costs estimates and outcomes, we used one–way sensitivity analyses. Each parameter estimate was varied, individually, within reasonable bounds in order to investigate the impact on costs or QALYs. We have presented the results of the sensitivity analyses as tornado diagrams that show the top 10 variables that have a large potential impact on the ICER estimates.

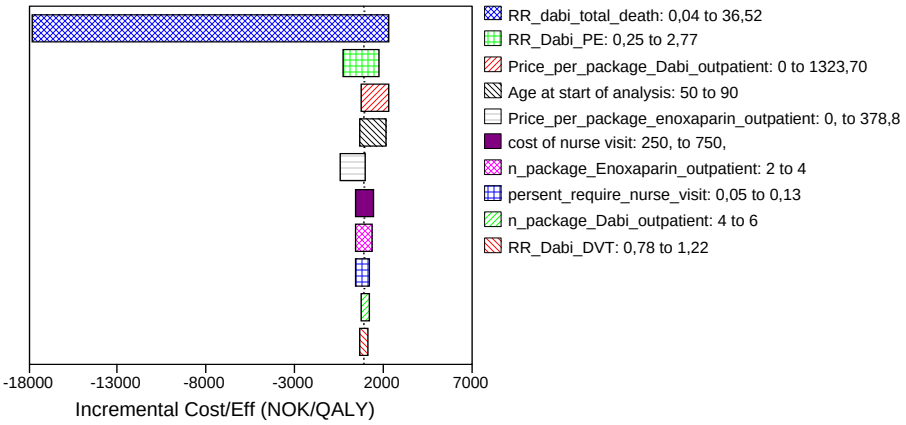


***Figure 11**. The top 10 lists in tornado diagram of dabigatran compared with enoxaparin (Total hip replacement)*

If the comparison analyzed was for dabigatran versus enoxaparin, the results were most sensitive to changes in efficacy data (mortality and PE estimates), thrombo-prophylactic medications' prices, and age at the treatment initiation (Figure 11). It is expected that the new indication of dabigatran will be approved in the near future [1] and thus it is anticipated that the price of dabigatran will be reduced. In that perspective, we have conducted one-way sensitivity analysis to explore the impact of any price reduction (range: NOK 0-1 323) on the results. Based on this analysis and assumed that all other parameters are unchanged, it is unlikely that the conclusion will be different

If the comparison analyzed was for rivaroxaban versus enoxaparin, the results were most sensitive to changes in age at the treatment initiation, the estimation of PE, utility value for mild PTS and cost of treating DVT after hospital discharge (Figure 12).

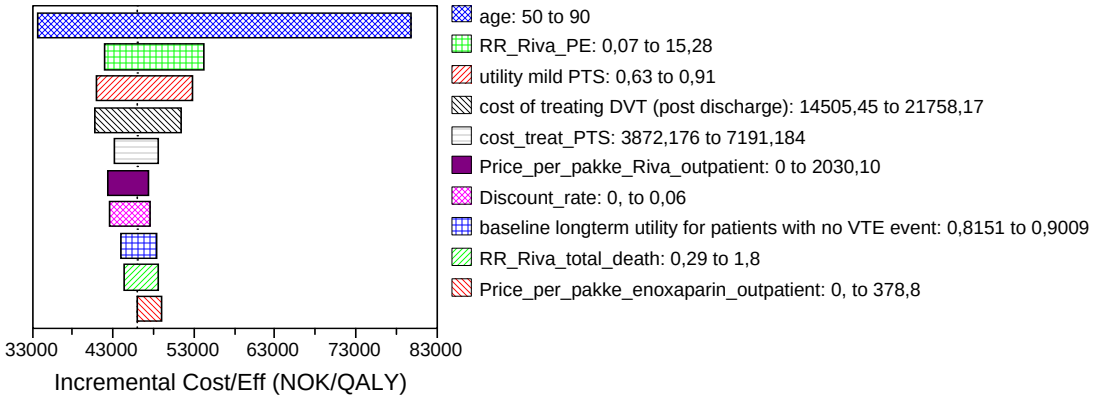


***Figure 12**. The top 10 lists in tornado diagram of rivaroxaban compared with enoxaparin (Total hip replacement)*

[1] Nytt om legemidler nr. 12 - 13. juni 2011 (http://www.legemiddelverket.no).

Probabilistic sensitivity analysis

We performed a Monte Carlo simulation with 10 000 draws from the input distributions. In Figure 13a, enoxaparin is the origo, while the red and blue dots represent the 10 000 simulations of the model results for dabigatran and rivaroxaban, each compared to enoxaparin. In this figure, the dotted line represents one possible threshold for cost-effectiveness (WTP), here set at NOK 500 000 per QALY gained. Figure 13a illustrates that the simulated ICERs are widely spread and indicates a great uncertainty regarding which medicinal products are most likely to be cost-effective.

We also tried varying the willingness to pay from 0 to 1 000 000 (Fig 13b). Figure 13b illustrates the probability of cost-effectiveness for the optimal choice at different levels of WTP. One can observe that rivaroxaban is the optimal strategy as long as the WTP per QALY is more than NOK 80 000. Assuming a WTP per QALY of NOK 500 000, the probability that rivaroxaban was the most cost-effective strategy after THR was 38%. In addition, the figure illustrates that the cheaper drugs (enoxaparin and dabigatran) are more likely to be cost-effective when WTP is low. Dabigatran can be considered the most cost-effective strategy if the WTP per QALY is under NOK 40 000.

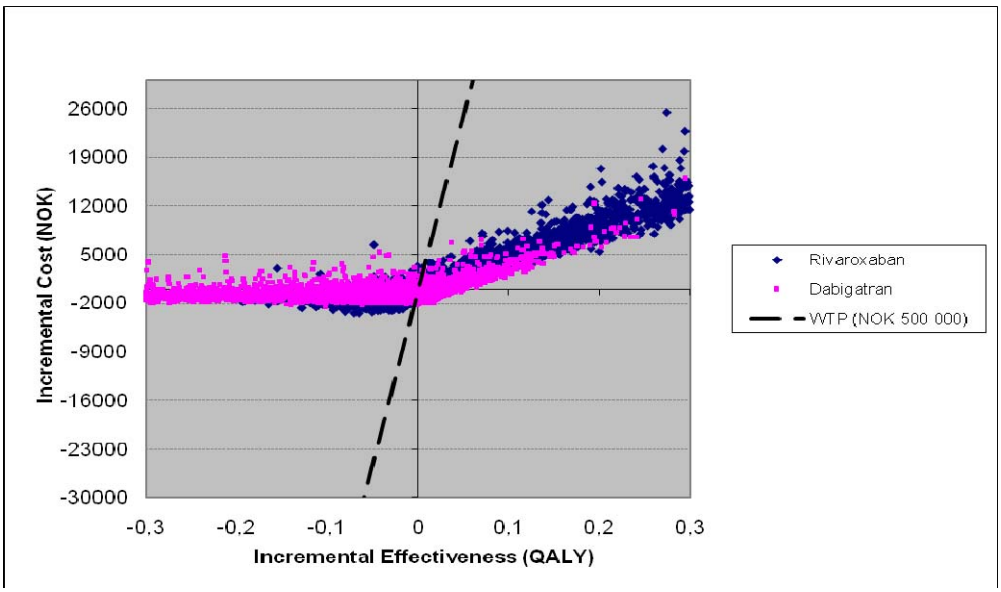


Figure 13a. *Scatter plot of simulations of rivaroxaban and dabigatran compared with enoxaparin after total hip replacement*

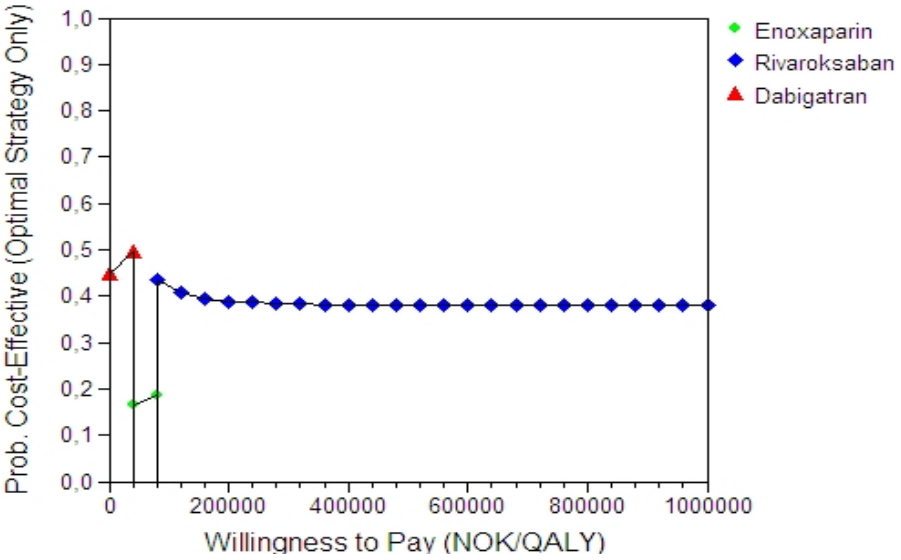


Figure 13b. *Acceptability frontier for total hip replacement*

We also performed an analysis of the expected value of perfect information on all uncertain parameters to explore the uncertainty surrounding specific groups of parameters. The result of these analyses indicated that efficacy and safety parameters have the greatest impact on decision uncertainty and research on these parameters would contribute most to decrease the uncertainty surrounding the results (Figure 14).

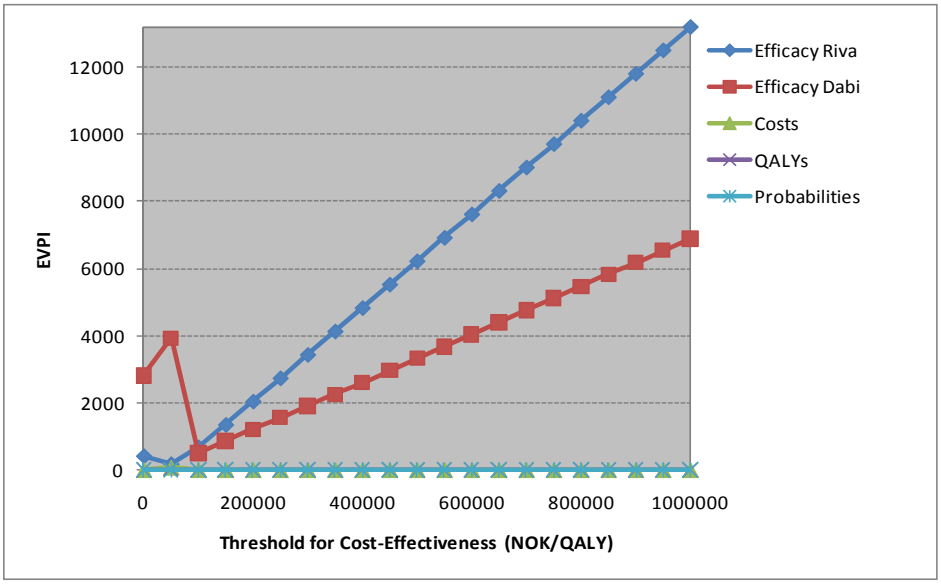


Figure 14. *Expected Value of perfect information for parameters (Total hip replacement)*

Thromboprophylactic treatment after total knee replacement

The base-case cost-effectiveness analysis in a TKR population indicated that dabigatran and rivaroxaban decreased lifetime costs relative to enoxaparin (by NOK 175 and NOK 313, respectively). However the results of our analyses showed that dabigatran and rivaroxaban also resulted in fewer QALYs than the enoxaparin.

Both strategies have negative net health benefit (NHB) compared to enoxaparin assuming a willingness to pay of NOK 500 000, therefore dabigatran and rivaroxaban cannot be considered cost-effective strategies compared to enoxaparin as VTE prophylaxis after TKR.

The base-case results are presented in Table 12.

Table 12. Results of the base-case cost-effectiveness analyses (discounted); dabigatran and rivaroxaban compared with enoxaparin (Total knee replacement)

Strategy	Cost (NOK)	Incremental cost (NOK)	Effect (QALYs)	Incremental effect (QALY)	ICER (NOK/QALY)	NHB
Enoxaparin	3 000		7.867			
Dabigatran	2 900	-175	7.847	-0.020	9 000	-0.019
Rivaroxaban	2 700	-313	7.849	-0.018	17 000	-0.017

Tornado diagram

One-way sensitivity analysis on all model parameters showed that the efficacy parameters (mortality, DVT and PE estimates), age at the treatment initiation, the price of thromboprophylactic medications and the needed amount of drugs had the greatest impact on the comparison results of dabigatran with enoxaparin after knee replacement (Figure 15). It is expected that the new indication of dabigatran will be approved in the near future and thus it is anticipated that the price of dabigatran will be reduced. In that perspective, we have conducted one-way sensitivity analysis to explore the impact of any price reduction (range: NOK 0-497) on the results. Based on this analysis and assumed that all other parameters are unchanged, it is unlikely that the conclusion will be different.

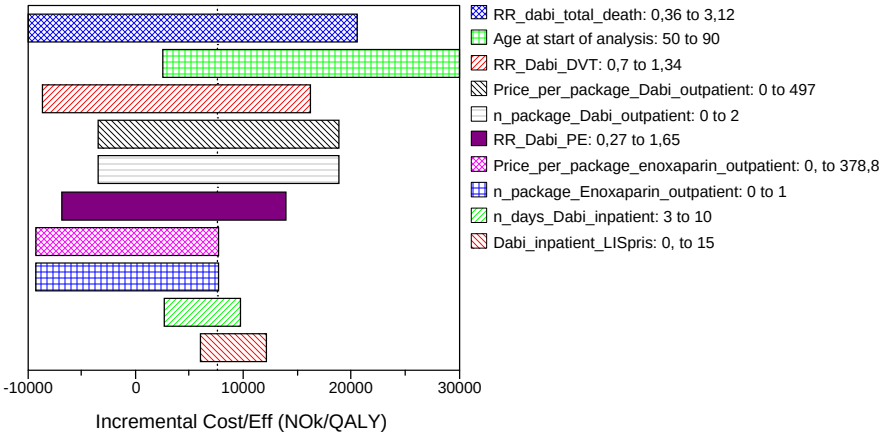


***Figure 15**. The top 10 lists in tornado diagram of dabigatran compared with enoxaparin (Total knee replacement)*

As illustrated in Figure 16, the comparison results of rivaroxaban with enoxaparin were most sensitive to changes in the cost of rivaroxaban, efficacy data (mortality and PE estimates) and the cost of enoxaparin.

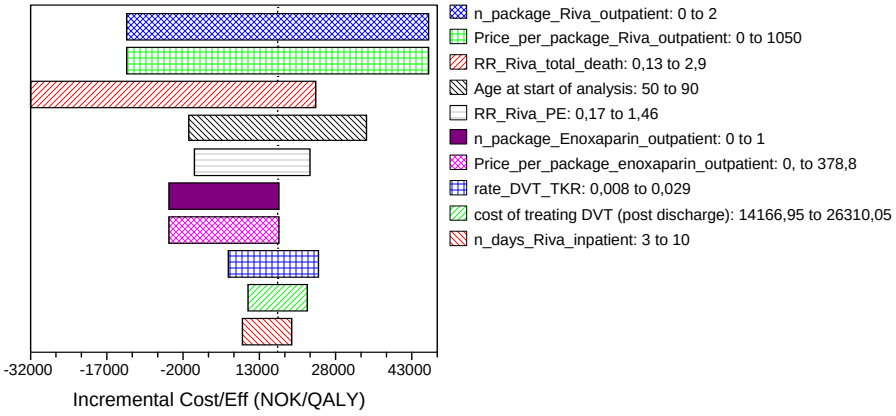


***Figure 16**. The top 10 lists in tornado diagram of rivaroxaban compared with enoxaparin (Total knee replacement)*

Probabilistic sensitivity analysis

Monte Carlo simulations with 10 000 draws from the input distributions are shown in Figure 17a. In this figure, enoxaparin is the origo, while the red and blue dots represent the 10 000 simulations of the model results for dabigatran and rivaroxaban, each compared to enoxaparin. The dotted line represents one possible threshold for cost-effectiveness (WTP), which was set at NOK 500 000 per QALY gained in this analysis. Figure 17a illustrates that the simulated ICERs are widely spread and indicates a considerable uncertainty for what medicinal products that are most likely to be cost-effective.

We also tried varying the willingness to pay from 0 to 1 000 000 (Fig 17b). Figure 19b shows the optimal choice at different levels of WTP. Enoxaparin can be considered the optimal strategy as long as the WTP per QALY is more than NOK 80 000. Although enoxaparin had the highest probability of being cost-effective at a WTP per QALY of NOK 500 000, the probability that enoxaparin was a cost-effective strategy after TKR was only 34%. If WTP per QALY is under NOK 80 000, the probability that rivaroxaban will be the most cost-effective strategy after TKR is between 42 - 57%.

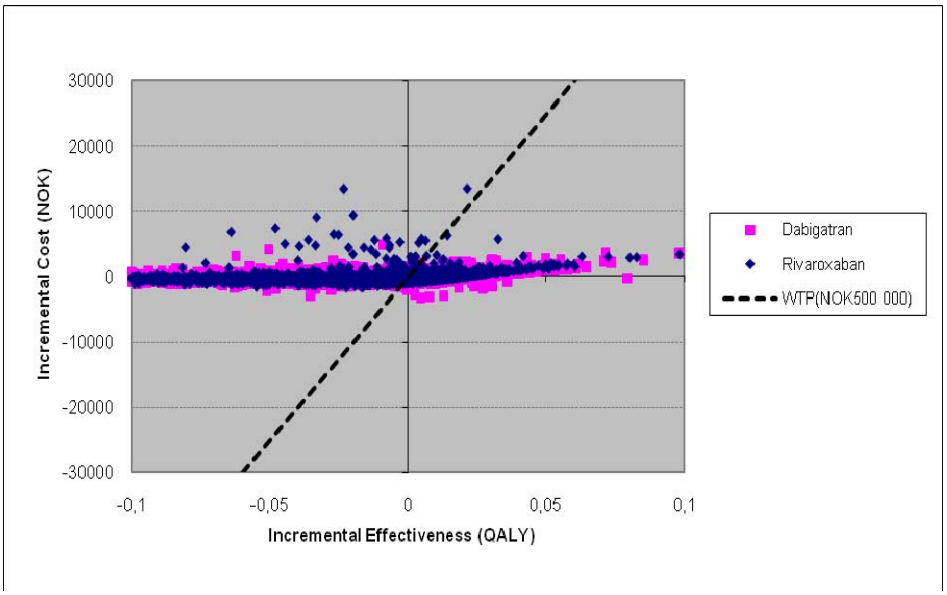


Figure 17a *Scatter plot of simulations of rivaroxaban and dabigatran compared with enoxaparin after total knee replacement*

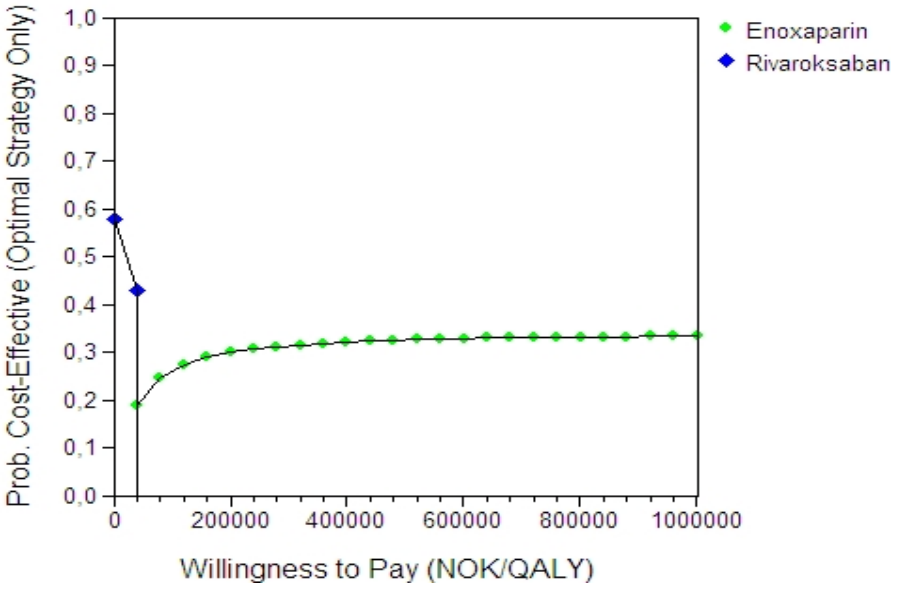


Figure 17b *Acceptability frontier for total knee replacement*

The value of information analysis for TKR indicated the same results as seen for THR. Thus, the efficacy and safety parameters have the greatest impact on decision uncertainty and research on these parameters would contribute most to decrease the uncertainty surrounding the results (Figure 18).

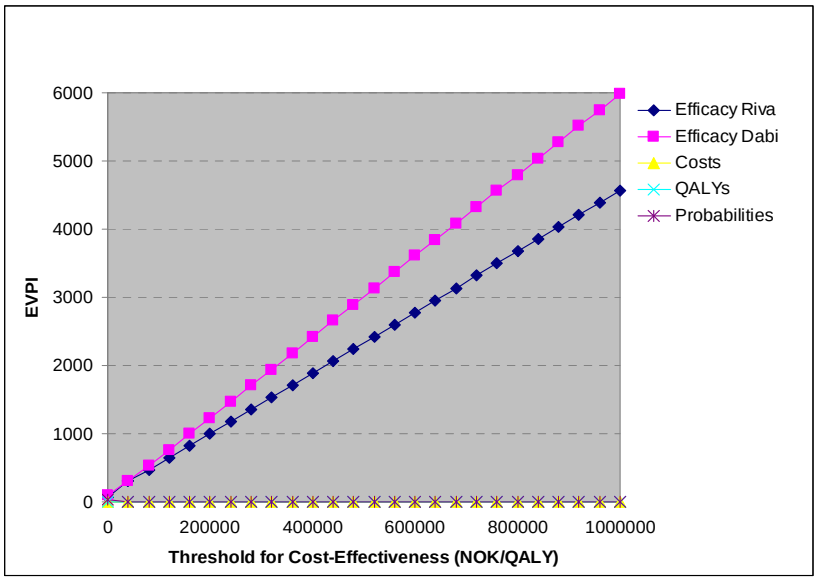


***Figure 18**. Expected Value of perfect information for parameters (Total knee replacement)*

Scenario analyses

As mentioned earlier in this report, we could not identify reliable data that could show the effect of the different methods of administrating the medication on patients' utility. Thus the possible disutility associated with injections was not included in the base-case analyses. Since part of the purpose of the new anticoagulants was the oral administration, we performed scenario analyses to test the assumption of the possible disutility associated with the subcutaneous administration of enoxaparin in our model. We adjusted the baseline health state value with 0.5% (source: Professor Ivar Sønbø Kristiansen) for the duration patients were treated with enoxaparin as thromboprophylaxis after THR and TKR. The correction factor had a very small effect on the results and thus the conclusion was still the same as before. The results of these analyses are showed in Tables 13 and 14.

Table 13. Dabigatran and rivaroxaban compared with enoxaparin; the baseline utility value for enoxaparin adjusted with 0.5% (Total hip replacement)

Strategy	Cost (NOK)	Incremental cost (NOK)	Effect (QALYs)	Incremental effect (QALY)	ICER (NOK/QALY)	NHB
Enoxaparin	4 800		8.028			
Dabigatran	4 200	-618	7.725	-0.303	2 038	-0.302
Rivaroxaban	13 000	8 000	8.205	0.179	45 000	0.161

Table 14. Dabigatran and rivaroxaban compared with enoxaparin; the baseline utility value for enoxaparin adjusted with 0.5% (Total knee replacement)

Strategy	Cost (NOK)	Incremental cost (NOK)	Effect (QALYs)	Incremental effect (QALY)	ICER (NOK/QALY)	NHB
Enoxaparin	3 000		7.869			
Dabigatran	2 800	-181	7.848	-0.021	9 000	-0.019
Rivaroxaban	2 700	-315	7.851	-0.018	18 000	-0.017

In addition, we ran the model for men at the same age as in our base-case scenario for women. These analyses showed the same results for both THR and TKR as the base-case results for women.

Discussion

There is a substantial risk of developing thromboembolic events after orthopaedic surgery, therefore thromboprophylactic treatment is needed. Subcutaneous LMWHs such as enoxaparin have been the primary choice for thrombosis prevention after surgical procedures in Norway. In recent years two new anticoagulants have been approved for use in connection with hip and knee replacement surgery, thus offering an oral treatment that would be less cumbersome for the patients and that would possibly need less health care resources.

In this HTA we have included systematic reviews and additional newly published randomized controlled trials where the oral anticoagulants dabigatran and rivaroxaban were compared to enoxaparin in patients undergoing elective total hip or knee replacement surgery. We evaluated efficacy and safety of the two drugs from clinical trial data, and performed an economic evaluation model to estimate the cost-effectiveness of dabigatran and rivaroxaban in Norway.

SUMMARY OF RESULTS

The main results are:

- No head-to-head comparison of dabigatran versus rivaroxaban was identified.
- No studies comparing dabigatran or rivaroxaban to dalteparin were identified.
- We did not find statistically significant differences between dabigatran and enoxaparin for the outcomes mortality, PE, DVT or major bleeding. The quality of the evidence ranged from very low to moderate.
- For rivaroxaban compared with enoxaparin we found statistically significant decreases in DVT, but also a trend for increased risk of major bleeding. For mortality and PE there were no statistically significant differences between treatments. The quality of the evidence ranged from very low to moderate.
- The included systematic reviews did not report on the primary endpoint post-thrombotic syndrome or any of our secondary outcomes (duration of hospital stay, re-submission to hospital, sick-leave, infections, re-operations or quality of life).
- Our results indicated a great uncertainty regarding which strategy is the most cost-effective. Assuming a willingness to pay of NOK 500 000 per QALY

gained, rivaroxaban following THR had a probability of 38% and enoxaparin following TKR had a probability of 34% of being cost-effective.

- The results of our analyses of the uncertainty surrounding different groups of parameters indicated that more research on the input variables is likely to change our base-case results. Efficacy data had the greatest impact on decision uncertainty.

QUALITY OF DOCUMENTATION/MODEL

The quality of the evidence ranged from moderate to very low. It should be noted, though, that low quality of the evidence does not necessarily mean the same as poorly performed studies. It is a way of saying that further research is likely to have an impact on our confidence in the estimates and that further research is likely to change a given estimate.

In this report we have reported on several rare outcomes, such as mortality, PE and major bleeding, and hence there is likelihood that further research with additional events will change the effect estimates.

For the outcome major bleeding, we downgraded only one step instead of two as we did for mortality and PE, to distinguish from the more severe limitations in the latter. However, the numbers of major bleeding events reported were few, so it could be discussed whether we should have downgraded further. This would have resulted in lower quality of the evidence and hence wider uncertainty in parameter inputs for our health economic analysis.

Often patients recruited to clinical trials are not representative of the total non-selected patient population in question. However, in the setting of orthopaedic surgery the representativeness of the trials seem to be fairly good, illustrated by the fact that the age of the trial patients did not differ much – it was not significantly lower – than the age of the real life patients. The mean age of the latter is 68-70 years according to the Norwegian Arthroplasty Register.

However, awareness should be given to dosing in relation to kidney function, as a substantial proportion of the patients are old, and with increasing age more patients would have reduced glomerular filtration rate (GFR). The clinical trials have not investigated this issue, but the manufacturer of dabigatran advises a lower dose for patients with moderately reduced kidney function and in the elderly over 75 years, whereas similar dose adjustments are not listed for rivaroxaban.

Our cost-effectiveness analyses showed that there is considerable uncertainty around the base-case estimate. Most of the decision uncertainty arises as a result of uncertainty in the effect parameters and it is most reasonable to conduct further research on these parameters.

STRENGTHS AND WEAKNESSES OF THIS REPORT

The use of systematic review versus the ability to find even the most recent information

We have extracted and presented data on efficacy and safety from systematic reviews. Results from systematic reviews are usually deemed to be higher in the hierarchy of evidence as it has collected all studies on a particular topic. To be sure that even the most recent relevant studies became included in our report we specifically searched for the most recent publications. In this way the information presented was very well updated.

A search for trials in the WHO portal for clinical trials displayed several studies using dabigatran and rivaroxaban (http://apps.who.int/trialsearch/ on 17. February 2011). This approach indicated that we had identified all relevant larger randomized controlled trials, thus supporting that our identification method worked well. In addition, the portal identified ongoing observational studies that will provide more data on efficacy and safety in the future. Also studies in other patient populations like atrial fibrillation, acute coronary syndrome, and pediatric patients, as well as studies on an antidote to reverse the anticoagulative effect of these new antithrombotic agents, were identified.

Outcomes of interest and outcomes included in the data

The included systematic reviews did not report on all outcomes that were prespecified in our review protocol. However, our primary outcomes were addressed with the exception of post-thrombotic syndrome. Although we have focused on systematic reviews, we did a quick check of the included randomized controlled trials on which the systematic reviews were based on and did not find our secondary outcomes generally reported. This supports the general understanding of which are the most important endpoints for this research question.

The outcomes under investigation should be considered in more detail. Important endpoints were DVT and PE, collectively called VTE. These conditions are often difficult to diagnose. In all studies the researchers have tried to include both symptomatic events and DVT found only by venography. In a substantial proportion of the trial patients venography was not performed or the interpretation of the venography was inconclusive, hence an incomplete reporting of data. However, the nature and the scale of this problem seem to have been almost similar in all studies. Through sensitivity analyses this weakness was further assessed by some researches, and these analyses indicated that the main conclusions were usually valid (17;22;26-28).

Bleeding seems to be the major safety concern and was reported in numerous different ways in the included randomized controlled trials and in the systematic reviews. They were characterized as major bleeding, minor bleeding, clinically relevant non-major bleeding, volume of blood transfusion, bleeding into a critical organ and several more. We have focused on major bleedings, as they were defined in the studies. This is a serious clinical event, but still happens frequently enough to give an indication with regard to possible differences between treatments. We also estimated minor bleeds (shown in Appendix 5) and noteworthy, although not statistically significant we found a trend towards more minor bleeds in the rivaroxaban group than in the enoxaparin group. This observation confirms the trend found for major bleeding.

Combining data across doses and treatment lengths

It is subject to discussion which data could be combined in a meta-analysis. Each solution comes with at set of advantages and disadvantages. We have combined all events in the studies, for a given outcome, across all doses of dabigatran or rivaroxaban. This is of course debatable, especially with regard to events in the early dose-finding studies. However, doses both higher and lower than the currently recommended doses were incorporated. The uncertainty added by pooling data across doses, may in some way be counteracted by the fact that the number of events increases. We have presented pooled data from each study in addition to the overall estimate across trials, to make it easier for the reader to discover differences between results from the dose-finding studies and the more confirmatory studies. We also combined the enoxaparin data, where a combination of results based on both the European 40 mg once daily and the North-American 30 mg twice daily dosing are presented.

Attention should also be given to the duration of treatment, and it should be noted that in one of the trials of rivaroxaban versus enoxaparin, the former therapy was extended for 31-39 days while enoxaparin was given for 10-14 days (RECORD 2). This study design with a longer rivaroxaban treatment might have favoured rivaroxaban, and a priori one would expect lower frequency of DVT/VTE in the rivaroxaban group than in the enoxaparin group, a finding that in fact was done.

With regard to efficacy and safety of dabigatran versus rivaroxaban, it can be stated that head-to-head comparisons have not been performed. One could try to compare them indirectly, implying an assessment of whether they fared differently in their respective comparisons with enoxaparin. However, such comparisons should be done with caution. Indirect assessment of the presented results indicate that rivaroxaban was somewhat more efficacious than dabigatran for the prevention of VTE, whereas on the other side it carried an increased risk of bleeding. One possible explanation for these observed differences could be a relatively more intensive dosing of rivaroxaban in the clinical trials. The data does not allow us to suggest that one of them has an inherent superior efficacy over the other. Follow-up from clinical

registries and observational studies might shed more light on this relationship in the future.

Limitations in health economic model

Since all models are simplifications of reality, there is always a trade off as to what level of detail is included in the model. It should therefore be considered some limitations associated with our simplistic model and the cost-effectiveness of the thromboprophylactic strategies.

We only included the most common long-term VTE complications (56) (*ie*. PTS and recurrent VTE) in the post-acute phase submodel.

Effect estimates across all doses of pharmaceuticals and treatment lengths have been included in our meta-analyses. It is therefore likely that cost- effectiveness analyses of specific doses or treatment lengths can give other results. The value of information analyses also indicated that efficacy data have the greatest impact on decision uncertainty in our model.

The transition probabilities were based on sources from different countries which could increase the possibility of discrepancy between the data.

The literature search emphasized a lack of good–quality utility data for our study population. The utility values were therefore based on different sources and different instruments, which has been adjusted and applied in the model. In addition, we could not identify reliable data that showed the probable effect of the different methods of administrating the medication on patients' utility. Hence, the possible advantage to patients of taking oral medication is not considered in the base-case results. Moreover, we adjusted the baseline health state value with 0.5% (source: Professor Ivar Sønbø Kristiansen) for the duration patients were treated with enoxaparin as thromboprophylaxis after THR and TKR. The correction factor, however, had a very small effect on the results and the conclusion was still the same as before.

Costs associated with long-term complication from VTE prophylaxis after THR or TKR (*ie*. PTS) used in the model, are mainly calculated based on a Norwegian study (45) adjusted from 2003 to 2010 kroner. The uncertainty around these cost-estimations has however been incorporated into the sensitivity analysis and further explored in the value of perfect information analysis.

Several of the analyses regarding efficacy parameters are based on the meta-analyses of non-significant results. We have in these analyses used efficacy estimates regardless of whether the meta-analysis is statistically significant or not. In health economic evaluation it is a common practice to account for non-significant differences. This is because, effect estimates themselves are considered as the most likely out-

come, and also it is assumed that the probability distributions represent the actual uncertainty.

In the probabilistic sensitivity analysis, we have included results from the grading of the efficacy documentation about the different outcomes based on the grading tool; GRADE. This tool, however, is not designed specifically for the probabilistic sensitivity analysis. It is therefore conceivable that the grading do not fully reflect our confidence in the effect estimates for the various outcomes. For example, sometimes the quality is adjusted down if a confidence interval is non-significant. Therefore, it is possible that our model analyses are underestimating the cost-effectiveness of the new thromboprophylactic treatments.

OUR HEALTH ECONOMIC RESULTS COMPARED TO OTHER REVIEWS OR RESULTS

We have found two cost-effectiveness studies, which compared the costs and effects of prophylaxis with the new oral anticoagulants (rivaroxaban and dabigatran) versus enoxaparin (57;58). These studies were undertaken from the perspective of the healthcare payers. The main results from these studies are presented in the following.

Wolowacz and co-workers (58) in their study which was sponsored by the manufacturer of dabigatran (Boehringer Ingelheim) have made comparison of dabigatran with enoxaparin in patients undergoing THR or TKR. They developed a model which includes a decision-tree and a Markov model component (lifetime analysis). The results indicated that the efficacy was comparable for patients receiving dabigatran and enoxaparin in both the THR and TKR analyses. For both analyses, costs of thromboprophylaxis were higher for enoxaparin compared with dabigatran, therefore dabigatran was dominant (less costly and more effective) compared with enoxaparin. The authors concluded that the probability of cost-effectiveness for dabigatran at a willingness to pay threshold of GBP 20 000 per QALY (approximately NOK 187 000) was 97% in THR and 75% in TKR.

MaCullagh and co-workers (57) developed a decision-tree model with a 180-day post-surgery time horizon. In the THR base-case model, rivaroxaban dominated (less costly and more effective) both enoxaparin and dabigatran. The ICER for dabigatran relative to enoxaparin for patients undergoing THR was € 17 835 per QALY (approximately NOK 153 000; 2010). In the setting of TKR, the base-case analyses showed that, rivaroxaban dominated both dabigatran and enoxaparin and dabigatran also dominated enoxaparin. At a cost-effectiveness threshold of € 45 000 per QALY (approximately NOK 400 000), the probability that rivaroxaban was the most cost-effective strategy after THR was 39%, followed by dabigatran at 32%. The probability that rivaroxaban was the most cost-effective strategy after TKR was 46%, followed by dabigatran at 30%.

Table 12. Summary of cost-effectiveness studies (57;58)

Study	Type of surgery	Time scope	Intervention	Comparator	Cost-effectiveness result (NOK)
Result from long-horizon analysis					
Wolowacz *et al.* 2009 (58)	THR	Lifetime	Dabigatran 220 mg	Enoxaparin 40 mg	Dabigatran dominates
Wolowacz *et al.* 2009 (58)	TKR	Lifetime	Dabigatran 220 mg	Enoxaparin 40 mg	Dabigatran dominates
Result from short-horizon analysis					
McCullagh *et al.* 2009 (57)	THR	180 days	Rivaroxaban 10 mg Dabigatran 220 mg	Enoxaparin 40 mg	Rivaroxaban dominates
McCullagh *et al.* 2009 (57)	TKR	180 days	Rivaroxaban 10 mg Dabigatran 220 mg	Enoxaparin 40 mg	Rivaroxaban dominates

Different assumption for the estimation of efficacy data may be considered as a most important cause of the differences between the results of our study and the two other health economic studies (57;58). We included and combined all relevant studies, across all doses of medicaments and treatment lengths in meta-analyses. While the two other economic evaluations (57;58) were only performed for a 220 mg dose of dabigatran and 40 mg of enoxaparin. Moreover, the results of economic analysis of rivaroxaban compared with enoxaparin for patients undergoing THR in McCullagh and co-workers study (57) was only based on the RECORD 2 study. Rivaroxaban therapy in this study was extended for 31-39 days while enoxaparin was given for 10-14 days, one would therefore expect lower frequency of venous thromboembolism in the rivaroxaban group.

The sensitivity analyses of McCullagh and co-workers study (57) however showed that there is uncertainty associated with their results, where the probability that rivaroxaban or dabigatran could be the most cost-effective strategies compared with enoxaparin was 46% and 30%, respectively.

IMPLICATIONS FOR PRACTICE

Intuitively, a main advantage of the new anticoagulants is the oral administration. It has been hypothesized that the subcutaneous administration of LMWHs after discharge is more cumbersome and might affect patient compliance. However, to our knowledge, the issue has not been addressed in clinical studies and it remains a hypothesis. This problem could be given attention when treatment decisions are made.

At present there is no antidote for the new oral agents. The bleeding risk when acute surgery (re-operations) and spinal aesthesia need to be performed on patients taking these drugs has not been sufficiently addressed. Particular awareness of this problem should be exercised.

Conclusions

CONCLUSIONS

In conclusion, dabigatran and rivaroxaban seem to be well tolerated antithrombotic medicines. Their efficacy and safety in hip and knee replacement surgery are comparable with enoxaparin.

Our results showed that there is a great uncertainty regarding which strategy is the most cost-effective. However, rivaroxaban and enoxaparin had a slightly higher probability of being cost-effective alternatives for patients undergoing total hip or knee replacement, respectively.

The results of our model analyses to explore the uncertainty surrounding each group of parameters indicated that more research on efficacy data would have the greatest impact on reducing decision uncertainty.

NEED FOR FURTHER RESEARCH

There is a fine line between the drug effects – the capability of antithrombotic medicines to prevent VTE – and the concomitantly evoked bleeding risk. Development of new drugs with a more favourable benefit/risk ratio is desirable, and several new anticoagulants are in the pipeline and some have reached clinical evaluation.

Finding optimal doses and treatment duration for the drugs and indications we have investigated should also be a future research topic.

The results of our value of information analysis indicated that further research on efficacy data would have the greatest impact on reducing decision uncertainty.

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Appendices

APPENDIX 1 - SEARCH STRATEGIES

The search strategies were built around the terms used for the population of patients undergoing hip or knee replacement surgery and the relevant pharmaceutical interventions. We used a combination of keywords and text words. Finally, we added a filter for systematic reviews or randomized controlled trials. The terms used were adapted to the different databases. We search Ovid MEDLINE and EMBASE, The Cochrane library and the CRD databases.

Search strategies for systematic reviews

Ovid MEDLINE(R) 1950 to June Week 5 2010

#; Searches

1; Rivaroxaban.rn.

2; Morpholines/

3; Thiophenes/

4; dabigatran etexilate.rn.

5; Benzimidazoles/

6; Pyridines/

7; Anticoagulants/

8; Heparin, Low-Molecular-Weight/

9; Dalteparin/

10; Enoxaparin/

11; Factor Xa/

12; (direct adj (thrombin inhibitors or antithrombins)).tw.

13; (Rivaroxaban or bay 59 7939 or bay 597939 or bay59 7939 or bay597939 or xarelto).tw.

14; (dabigatran or bibr 1048 or bibr1048 or bibr 953 or bibr953 or pradaxa or rendix).tw.

15; (Dalteparin or Kabi 2165 or Kabi2165 or k 2165 or k2165 or FR 860 or FR860 or fragmin or fragmine or low liquemin or Tedelparin).tw.

16; (Enoxaparin or enoxaparin or PK 10,169 or PK10,169 or PK 10169 or PK10169 or EMT 967 or EMT967 or EMT 966 or EMT966 or clexane or klexane or lovenox).tw.

17; (("low molecular" adj1 (heparin or "weight heparin" or "weight fraction")) or LMWH or bm 2123 or bm2123 or choay or depolymerized heparin or ebpm 1 or ebpm 2 or ebpm 3 or ebpm1 or ebpm2 or ebpm3 or ff 1034 or ff1034 or fr 860 or fr860 or gag 869 or heparin lmw 2133 or

nm heparin or "pk 007" or sandoz 5100 or sandoz 6700 or traxyparine).tw.

18; ((anti coagula$ or anticoagula$ or antithrombotic) adj1 (drug? or agent? or therapy or therapies)).tw.

19; ((("blood clotting factor 10a" or "factor xa" or thrombin) adj (inhibitor? or inhibition)) or ((inhibitor? or inhibition) adj "of factor Xa") or ((morpholide or morpholine or morpholinomethyl or oxazolidine or pyridyl or benzimidazole) adj derivative) or (thiophene adj (derivative or compound or series)) or (pyridine adj (derivative or n substituted derivative or series)) or morpholines or benzimidazoles or thiophenes or pyridines).tw.

20; or/1-19

21; Arthroplasty/

22; Arthroplasty, Replacement/

23; Arthroplasty, Replacement, Hip/

24; Arthroplasty, Replacement, Knee/

25; Prosthesis Implantation/

26; "Prostheses and Implants"/

27; exp Joint Prosthesis/

28; (prosthesiology or endoprosthesis or endoprostheses or (prosthetic adj (replacement or substitution or implant? or joint))).tw.

29; ((Joint or hip or "femoral head" or "femur head" or total or knee or orthopedic or Implantation? or "weber huggler" or "mckee ferrar") adj1 (Prosthesis or prostheses)).tw.

30; (arthroplasty or arthroplasties or alloarthroplasty or alloarthroplasties or hemiarthroplasties or hemiarthroplasty or arthroprosthesis or acetabuloplasty or "mac bride acetabulum cup" or "acetabulum plasty" or "hip plasty").tw.

31; ((joint or hip or knee or "femoral head" or "femur head" or (total adj1 (hip or joint or knee))) adj1 (replacement? or reconstruction or artificial)).tw.

32; or/21-31

33; 20 and 32

34; Cost-Benefit Analysis/

35; (cost* adj2 (benefit* or effective* or minim* or utillit*)).tw.

36; cba.tw.

37; cea.tw.

38; cua.tw.

39; Economics, Medical/

40; (health economic? or economic evaluation?).tw.

41; Economics, Pharmaceutical/

42; (pharmac* adj economic?).tw.

43; pharmacoeconomic?.tw.

44; Technology Assessment, Biomedical/

45; technology assessment?.tw.

46; or/34-45

47; 33 and 46

48; limit 33 to "reviews (optimized)"

49; 47 or 48

EMBASE 1980 to 2010 Week 26

#; Searches

1; Rivaroxaban/

2; blood clotting factor 10a inhibitor/

3; morpholine derivative/

4; oxazolidine derivative/

5; thiophene derivative/

6; Xarelto/

7; Dabigatran etexilate/

8; benzimidazole derivative/

9; pyridine derivative/

10; thrombin inhibitor/

11; Dabigatran/

12; low molecular weight heparin/
13; enoxaparin/
14; dalteparin/
15; anticoagulant agent/
16; anticoagulant therapy/
17; (direct adj (thrombin inhibitors or antithrombins)).tw.
18; (Rivaroxaban or bay 59 7939 or bay 597939 or bay59 7939 or bay597939 or xarelto).tw.
19; (dabigatran or bibr 1048 or bibr1048 or bibr 953 or bibr953 or pradaxa or rendix).tw.
20; (Dalteparin or Kabi 2165 or Kabi2165 or k 2165 or k2165 or FR 860 or FR860 or fragmin or fragmine or low liquemin or Tedelparin).tw.
21; (Enoxaparin or enoxaparin or PK 10,169 or PK10,169 or PK 10169 or PK10169 or EMT 967 or EMT967 or EMT 966 or EMT966 or clexane or klexane or lovenox).tw.
22; (("low molecular" adj1 (heparin or "weight heparin" or "weight fraction")) or LMWH or bm 2123 or bm2123 or choay or depolymerized heparin or ebpm 1 or ebpm 2 or ebpm 3 or ebpm1 or ebpm2 or ebpm3 or ff 1034 or ff1034 or fr 860 or fr860 or gag 869 or heparin lmw 2133 or nm heparin or "pk 007" or sandoz 5100 or sandoz 6700 or traxyparine).tw.
23; ((anti coagula$ or anticoagula$ or antithrombotic) adj1 (drug? or agent? or therapy or therapies)).tw.
24; ((("blood clotting factor 10a" or "factor xa" or thrombin) adj (inhibitor? or inhibition)) or ((inhibitor? or inhibition) adj "of factor Xa") or ((morpholide or morpholine or morpholinomethyl or oxazolidine or pyridyl or benzimidazole) adj derivative) or (thiophene adj (derivative or compound or series)) or (pyridine adj (derivative or n substituted derivative or series)) or morpholines or benzimidazoles or thiophenes or pyridines).tw.
25; or/1-24
26; prosthesiology/
27; arthroplasty/
28; exp hip arthroplasty/
29; exp knee arthroplasty/
30; "prostheses and orthoses"/
31; orthopedic prosthesis/
32; endoprosthesis/
33; joint prosthesis/
34; prosthesis/
35; (prosthesiology or endoprosthesis or endoprostheses or (prosthetic adj (replacement or substitution or implant? or joint))).tw.
36; ((Joint or hip or "femoral head" or "femur head" or total or knee or orthopedic or Implantation? or "weber huggler" or "mckee ferrar") adj1 (Prosthesis or prostheses)).tw.
37; (arthroplasty or arthroplasties or alloarthroplasty or alloarthroplasties or hemiarthroplasties or hemiarthroplasty or arthroprosthesis or acetabuloplasty or "mac bride acetabulum cup" or "acetabulum plasty" or "hip plasty").tw.
38; ((joint or hip or knee or "femoral head" or "femur head" or (total adj1 (hip or joint or knee))) adj1 (replacement? or reconstruction or artificial)).tw.
39; or/26-38
40; 25 and 39
41; "Cost Benefit Analysis"/
42; "Cost Effectiveness Analysis"/
43; "Cost Minimization Analysis"/
44; "Cost Utility Analysis"/

45; (cost* adj2 (benefit* or effective* or minim* or utillit*)).tw.
46; cba.tw.
47; cea.tw.
48; cua.tw.
49; Economic Evaluation/
50; Health economics/
51; (health economic? or economic evaluation?).tw.
52; Pharmacoeconomics/
53; (pharmacoeconomic? or (pharmac* adj economic?)).tw.
54; or/41-53
55; 40 and 54
56; limit 40 to "reviews (2 or more terms min difference)"
57; 55 or 56

CRD databases. DARE, NHS EED og HTA

Antall treff: 90 (DARE: 24, NHS EED: 60, HTA: 6)

; Search
1; MeSH Morpholines
2; MeSH Thiophenes
3; MeSH Benzimidazoles
4; MeSH Pyridines
5; MeSH Anticoagulants
6; MeSH Heparin, Low-Molecular-Weight
7; MeSH Dalteparin
8; MeSH Enoxaparin
9; MeSH Factor Xa
10; "direct thrombin inhibitors" OR "direct antithrombins"
11; Rivaroxaban OR "bay 59 7939" OR "bay 597939" OR "bay59 7939" OR bay597939 OR xarelto
12; dabigatran OR "bibr 1048" OR bibr1048 OR "bibr 953" OR bibr953 OR pradaxa OR rendix
13; Dalteparin OR "Kabi 2165" OR Kabi2165 OR "k 2165" OR k2165 OR "FR 860" OR FR860 OR fragmin OR fragmine OR "low liquemin" OR Tedelparin
14; Enoxaparin OR enoxaparin OR "PK 10,169" OR "PK10,169" OR "PK 10169" OR PK10169 OR "EMT 967" OR EMT967 OR "EMT 966" OR EMT966 OR clexane OR klexane OR lovenox
15; "low molecular heparin" OR "low molecular weight heparin" OR "low molecular weight fraction" OR "heparin low molecular" OR "weight fraction low molecular" OR LMWH OR "bm 2123" OR bm2123 OR choay OR "depolymerized heparin" OR "ebpm 1" OR "ebpm 2" OR "ebpm 3" OR ebpm1 OR ebpm2 OR ebpm3 OR "ff 1034" OR ff1034 OR "fr 860" OR fr860 OR "gag 869" OR "heparin lmw 2133" OR "nm heparin" OR "pk 007" OR "sandoz 5100" OR "sandoz 6700" OR traxyparine
16; "anti coagula drug*" OR "anti coagula agent*" OR "anti coagula therapy*" OR "anti coagula therapies*" OR "drug anti coagula*" OR "agent anti coagula*" OR "therapy anti coagula*" OR "therapies anti coagula*" OR "anticoagula drug*" OR "anticoagula agent*" OR "anticoagula therapy*" OR "anticoagula therapies*" OR "drug anticoagula*" OR "agent anticoagula*" OR "therapy" AND anticoagula* AND " OR " AND therapies AND anticoagula* AND " OR " AND antithrombotic* AND drug* AND " OR " AND antithrombotic* AND agent* AND " OR " AND antithrombotic* AND therapy OR "antithrombotic therapies*" OR "drug antithrombotic*" OR "agent antithrombotic*" OR "therapy antithrombotic*" OR "therapies antithrombotic*"

17; "blood clotting factor 10a inhibitor*" OR "blood clotting factor 10a inhibition" OR "factor xa inhibitor*" OR "factor xa inhibition" OR "thrombin inhibitor*" OR "thrombin inhibition" OR "inhibitor of factor Xa*" OR "inhibition of factor Xa" OR "morpholide derivative" OR "morpholine derivative" OR "morpholinomethyl derivative" OR "oxazolidine derivative" OR "pyridyl derivative" OR "benzimidazole derivative" OR "thiophene derivative" OR "thiophene compound" OR "thiophene series" OR "pyridine derivative" OR "pyridine n substituted" OR "pyridine series" OR morpholines OR benzimidazoles OR thiophenes OR pyridines

18; #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

19; MeSH Arthroplasty

20; MeSH Arthroplasty, Replacement

21; MeSH Arthroplasty, Replacement, Hip

22; MeSH Arthroplasty, Replacement, Knee

23; MeSH Prosthesis Implantation

24; MeSH Prostheses and Implants

25; MeSH Joint Prosthesis EXPLODE 1

26; prosthesiology OR endoprosthesis OR endoprostheses OR "prosthetic replacement" OR "prosthetic substitution" OR "prosthetic implant*" OR "prosthetic joint"

27; "prosthesis joint" OR "prosthesis hip" OR "prosthesis femoral head" OR "prosthesis femur head" OR "prosthesis total" OR "prosthesis knee" OR "prosthesis orthopedic" OR "prosthesis implantation*" OR "prosthesis weber huggler" OR "prosthesis mckee ferrar" OR "joint prosthesis" OR "hip prosthesis" OR "femoral head prosthesis" OR "femur head prosthesis" OR "total prosthesis" OR "knee prosthesis" OR "orthopedic prosthesis" OR "implantation prosthesis*" OR "weber huggler prosthesis" OR "mckee ferrar prosthesis"

28; "prostheses joint" OR "prostheses hip" OR "prostheses femoral head" OR "prostheses femur head" OR "prostheses total" OR "prostheses knee" OR "prostheses orthopedic" OR "prostheses implantation*" OR "prostheses weber huggler" OR "prostheses mckee ferrar" OR "joint prostheses" OR "hip prostheses" OR "femoral head prostheses" OR "femur head prostheses" OR "total prostheses" OR "knee prostheses" OR "orthopedic prostheses" OR "implantation prostheses*" OR "weber huggler prostheses" OR "mckee ferrar prostheses"

29; arthroplasty OR arthroplasties OR alloarthroplasty OR alloarthroplasties OR hemiarthroplasties OR hemiarthroplasty OR arthroprosthesis OR acetabuloplasty OR "mac bride acetabulum cup" OR "acetabulum plasty" OR "hip plasty"

30; "joint replacement*" OR "joint reconstruction" OR "joint artificial" OR "hip replacement*" OR "hip reconstruction" OR "hip artificial" OR "knee replacement*" OR "knee reconstruction" OR "knee artificial" OR "femoral head replacement*" OR "femoral head reconstruction" OR "femoral head artificial" OR "femur head replacement*" OR "femur head reconstruction" OR "femur head artificial" OR "hip total replacement*" OR "hip total reconstruction" OR "hip total artificial" OR "joint total replacement*" OR "joint total reconstruction" OR "joint total artificial" OR "knee total replacement*" OR

"knee total reconstruction" OR "knee total artificial"
31; "replacement joint*" OR "reconstruction joint" OR "artificial joint" OR "replacement hip*" OR "reconstruction hip" OR "artificial hip" OR "replacement knee*" OR "reconstruction knee" OR "artificial knee" OR "replacement femoral head*" OR "reconstruction femoral head" OR "artificial femoral head" OR "replacement femur head*" OR "reconstruction femur head" OR "artificial femur head" OR "replacement total hip*" OR "reconstruction total hip" OR "artificial total hip" OR "replacement total joint*" OR "reconstruction total joint" OR "artificial total joint" OR "replacement total knee*" OR "reconstruction total knee" OR "artificial total knee"
32; #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33; #18 AND #32

The Cochrane Library. Cochrane Reviews, Methods Studies

Antall treff: 1 (Cochrane Reviews: 1, Methods Studies: 0)

ID; Search

#1; MeSH descriptor **Morpholines**, this term only
#2; MeSH descriptor **Thiophenes**, this term only
#3; MeSH descriptor **Benzimidazoles**, this term only
#4; MeSH descriptor **Pyridines**, this term only
#5; MeSH descriptor **Anticoagulants**, this term only
#6; MeSH descriptor **Heparin, Low-Molecular-Weight**, this term only
#7; MeSH descriptor **Dalteparin**, this term only
#8; MeSH descriptor **Enoxaparin**, this term only
#9; MeSH descriptor **Factor Xa**, this term only
#10; (direct NEXT (thrombin inhibitors or antithrombins)):ti,ab
#11; (Rivaroxaban or bay 59 7939 or bay 597939 or bay59 7939 or bay597939 or xarelto):ti,ab
#12; (dabigatran or bibr 1048 or bibr1048 or bibr 953 or bibr953 or pradaxa or rendix):ti,ab
#13; (Dalteparin or Kabi 2165 or Kabi2165 or k 2165 or k2165 or FR 860 or FR860 or fragmin or fragmine or low liquemin or Tedelparin):ti,ab
#14; (Enoxaparin or enoxaparin or "PK 10,169" or "PK10,169" or PK 10169 or PK10169 or EMT 967 or EMT967 or EMT 966 or EMT966 or clexane or klexane or lovenox):ti,ab
#15; (("low molecular" NEAR/1 (heparin or "weight heparin" or "weight fraction")) or LMWH or bm 2123 or bm2123 or choay or depolymerized heparin or ebpm 1 or ebpm 2 or ebpm 3 or ebpm1 or ebpm2 or ebpm3 or ff 1034 or ff1034 or fr 860 or fr860 or gag 869 or heparin lmw 2133 or nm heparin or "pk 007" or sandoz 5100 or sandoz 6700 or traxyparine):ti,ab
#16; ((anti coagula* or anticoagula* or antithrombotic) NEAR/1 (drug? or agent? or therapy or therapies)):ti,ab
#17; ((("blood clotting factor 10a" or "factor xa" or thrombin) NEXT (inhibitor? or inhibition)) or ((inhibitor? or inhibition) NEXT "of factor Xa") or ((morpholide or morpholine or morpholinomethyl or oxazolidine or pyridyl or benzimidazole) NEXT derivative) or (thiophene NEXT (derivative or compound or series)) or (pyridine NEXT (derivative or n substi-

tuted derivative or series)) or morpholines or benzimidazoles or thiophenes or pyridines):ti,ab

#18; (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)

#19; MeSH descriptor **Arthroplasty**, this term only

#20; MeSH descriptor **Arthroplasty, Replacement**, this term only

#21; MeSH descriptor **Arthroplasty, Replacement, Hip**, this term only

#22; MeSH descriptor **Arthroplasty, Replacement, Knee**, this term only

#23; MeSH descriptor **Prosthesis Implantation**, this term only

#24; MeSH descriptor **Prostheses and Implants**, this term only

#25; MeSH descriptor **Joint Prosthesis** explode all trees

#26; (prosthesiology or endoprosthesis or endoprostheses or (prosthetic NEXT (replacement or substitution or implant? or joint))):ti,ab

#27; ((Joint or hip or "femoral head" or "femur head" or total or knee or orthopedic or Implantation? or "weber huggler" or "mckee ferrar") NEAR/1 (Prosthesis or prostheses)):ti,ab

#28; (arthroplasty or arthroplasties or alloarthroplasty or alloarthroplasties or hemiarthroplasties or hemiarthroplasty or arthroprosthesis or acetabuloplasty or "mac bride acetabulum cup" or "acetabulum plasty" or "hip plasty"):ti,ab

#29; ((joint or hip or knee or "femoral head" or "femur head" or (total NEAR/1 (hip or joint or knee))) NEAR/1 (replacement? or reconstruction or artificial)):ti,ab

#30; (#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)

#31; (#18 AND #30)

#32; (#18 AND #30) in Cochrane Reviews and Methods Studies

Search strategies for randomized controlled trial

Ovid MEDLINE(R) 1950 to September Week 1 2010

; Search

1; Rivaroxaban.rn.

2; Morpholines/

3; Thiophenes/

4; dabigatran etexilate.rn.

5; Benzimidazoles/

6; Pyridines/

7; Anticoagulants/

8; Heparin, Low-Molecular-Weight/

9; Dalteparin/

10; Enoxaparin/

11; Factor Xa/

12; (direct adj (thrombin inhibitors or antithrombins)).tw.

13; (Rivaroxaban or bay 59 7939 or bay 597939 or bay59 7939 or bay597939 or xarelto).tw.

14; (dabigatran or bibr 1048 or bibr1048 or bibr 953 or bibr953 or pradaxa or rendix).tw.

15; (Dalteparin or Kabi 2165 or Kabi2165 or k 2165 or k2165 or FR 860 or FR860 or fragmin or fragmine or low liquemin or Tedelparin).tw.

16; (Enoxaparin or enoxaparin or PK 10,169 or PK10,169 or PK 10169 or PK10169 or EMT 967 or EMT967 or EMT 966 or EMT966 or clexane or klexane or lovenox).tw.

17; (("low molecular" adj1 (heparin or "weight heparin" or "weight fraction")) or LMWH or bm

2123 or bm2123 or choay or depolymerized heparin or ebpm 1 or ebpm 2 or ebpm 3 or ebpm1 or ebpm2 or ebpm3 or ff 1034 or ff1034 or fr 860 or fr860 or gag 869 or heparin lmw 2133 or nm heparin or "pk 007" or sandoz 5100 or sandoz 6700 or traxyparine).tw.

18; ((anti coagula$ or anticoagula$ or antithrombotic) adj1 (drug? or agent? or therapy or therapies)).tw.

19; ((("blood clotting factor 10a" or "factor xa" or thrombin) adj (inhibitor? or inhibition)) or ((inhibitor? or inhibition) adj "of factor Xa") or ((morpholide or morpholine or morpholinomethyl or oxazolidine or pyridyl or benzimidazole) adj derivative) or (thiophene adj (derivative or compound or series)) or (pyridine adj (derivative or n substituted derivative or series)) or morpholines or benzimidazoles or thiophenes or pyridines).tw.

20; or/1-19

21; Arthroplasty/

22; Arthroplasty, Replacement/

23; Arthroplasty, Replacement, Hip/

24; Arthroplasty, Replacement, Knee/

25; Prosthesis Implantation/

26; "Prostheses and Implants"/

27; exp Joint Prosthesis/

28; (prosthesiology or endoprosthesis or endoprostheses or (prosthetic adj (replacement or substitution or implant? or joint))).tw.

29; ((Joint or hip or "femoral head" or "femur head" or total or knee or orthopedic or Implantation? or "weber huggler" or "mckee ferrar") adj1 (Prosthesis or prostheses)).tw.

30; (arthroplasty or arthroplasties or alloarthroplasty or alloarthroplasties or hemiarthroplasties or hemiarthroplasty or arthroprosthesis or acetabuloplasty or "mac bride acetabulum cup" or "acetabulum plasty" or "hip plasty").tw.

31; ((joint or hip or knee or "femoral head" or "femur head" or (total adj1 (hip or joint or knee))) adj1 (replacement? or reconstruction or artificial)).tw.

32; or/21-31

33; 20 and 32

34; randomized controlled trial.pt.

35; controlled clinical trial.pt.

36; randomized.ab.

37; placebo.ab.

38; drug therapy.fs.

39; randomly.ab.

40; trial.ab.

41; groups.ab.

42; 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41

43; humans.sh.

44; 42 and 43

45; 33 and 44

46; 2009$.ep,ed,dp,yr.

47; 2010$.ep,ed,dp,yr.

48; 2011$.ep,ed,dp,yr.

49; 45 and (46 or 47 or 48)

EMBASE 1980 to 2010 Week 36

; Search

1; Rivaroxaban/

2; blood clotting factor 10a inhibitor/

3; morpholine derivative/

4; oxazolidine derivative/

5; thiophene derivative/

6; Xarelto/

7; Dabigatran etexilate/

8; benzimidazole derivative/

9; pyridine derivative/

10; thrombin inhibitor/

11; Dabigatran/

12; low molecular weight heparin/

13; enoxaparin/

14; dalteparin/

15; anticoagulant agent/

16; anticoagulant therapy/

17; (direct adj (thrombin inhibitors or anti-thrombins)).tw.

18; (Rivaroxaban or bay 59 7939 or bay 597939 or bay59 7939 or bay597939 or xarelto).tw.

19; (dabigatran or bibr 1048 or bibr1048 or bibr 953 or bibr953 or pradaxa or rendix).tw.

20; (Dalteparin or Kabi 2165 or Kabi2165 or k 2165 or k2165 or FR 860 or FR860 or fragmin or fragmine or low liquemin or Tedelparin).tw.

21; (Enoxaparin or enoxaparin or PK 10,169 or PK10,169 or PK 10169 or PK10169 or EMT 967 or EMT967 or EMT 966 or EMT966 or clexane or klexane or lovenox).tw.

22; (("low molecular" adj1 (heparin or "weight heparin" or "weight fraction")) or LMWH or bm 2123 or bm2123 or choay or depolymerized heparin or ebpm 1 or ebpm 2 or ebpm 3 or ebpm1 or ebpm2 or ebpm3 or ff 1034 or ff1034 or fr 860 or fr860 or gag 869 or heparin lmw 2133 or nm heparin or "pk 007" or sandoz 5100 or sandoz 6700 or traxyparine).tw.

23; ((anti coagula$ or anticoagula$ or anti-thrombotic) adj1 (drug? or agent? or therapy or therapies)).tw.

24; ((("blood clotting factor 10a" or "factor xa" or thrombin) adj (inhibitor? or inhibition)) or ((inhibitor? or inhibition) adj "of factor Xa") or ((morpholide or morpholine or morpholi-nomethyl or oxazolidine or pyridyl or ben-zimidazole) adj derivative) or (thiophene adj (derivative or compound or series)) or (pyri-dine adj (derivative or n substituted deriva-tive or series)) or morpholines or benzimida-zoles or thiophenes or pyridines).tw.

25; or/1-24

26; prosthesiology/

27; arthroplasty/

28; exp hip arthroplasty/

29; exp knee arthroplasty/

30; "prostheses and orthoses"/

31; orthopedic prosthesis/

32; endoprosthesis/

33; joint prosthesis/

34; prosthesis/

35; (prosthesiology or endoprosthesis or endo-prostheses or (prosthetic adj (replacement or substitution or implant? or joint))).tw.

36; ((Joint or hip or "femoral head" or "femur head" or total or knee or orthopedic or Im-plantation? or "weber huggler" or "mckee fer-rar") adj1 (Prosthesis or prostheses)).tw.

37; (arthroplasty or arthroplasties or al-loarthroplasty or alloarthroplasties or hemi-arthroplasties or hemiarthroplasty or arthro-prosthesis or acetabuloplasty or "mac bride acetabulum cup" or "acetabulum plasty" or "hip plasty").tw.

38; ((joint or hip or knee or "femoral head" or "femur head" or (total adj1 (hip or joint or knee))) adj1 (replacement? or reconstruction or artificial)).tw.

39; or/26-38

40; 25 and 39

41; Clinical Trial/

42; Randomized Controlled Trial/

43; Randomization/

44; Double Blind Procedure/

45; Single Blind Procedure/

46; Crossover Procedure/

47; PLACEBO/

48; placebo$.tw.

49; randomi?ed controlled trial$.tw.

50; rct.tw.

51; random allocation.tw.

52; randomly allocated.tw.

53; allocated randomly.tw.

54; (allocated adj2 random).tw.

55; single blind$.tw.

56; double blind$.tw.

57; ((treble or triple) adj blind$).tw.

58; Prospective study/

59; or/41-58

60; Case study/

61; case report.tw.

62; Abstract report/

63; Letter/

64; Human/

65; Nonhuman/

66; ANIMAL/

67; Animal Experiment/

68; 65 or 66 or 67

69; 68 not (64 and 68)

70; or/60-63,69

71; 59 not 70

72; 40 and 71

73; 2009$.dd,dp,yr.

74; 2010$.dd,dp,yr.

75; 2011$.dd,dp,yr.

76; 72 and (73 or 74 or 75)

The Cochrane Library. Cochrane Central Register of Controlled Trials (Central)

ID; Search

#1; MeSH descriptor **Morpholines**, this term only

#2; MeSH descriptor **Thiophenes**, this term only

#3; MeSH descriptor **Benzimidazoles**, this term only

#4; MeSH descriptor **Pyridines**, this term only

#5; MeSH descriptor **Anticoagulants**, this term only

#6; MeSH descriptor **Heparin, Low-Molecular-Weight**, this term only

#7; MeSH descriptor **Dalteparin**, this term only

#8; MeSH descriptor **Enoxaparin**, this term only

#9; MeSH descriptor **Factor Xa**, this term only

#10; (direct NEXT (thrombin inhibitors or antithrombins)):ti,ab

#11; (Rivaroxaban or bay 59 7939 or bay 597939 or bay59 7939 or bay597939 or xarelto):ti,ab

#12; (dabigatran or bibr 1048 or bibr1048 or bibr 953 or bibr953 or pradaxa or rendix):ti,ab

#13; (Dalteparin or Kabi 2165 or Kabi2165 or k 2165 or k2165 or FR 860 or FR860 or fragmin or fragmine or low liquemin or Tedelparin):ti,ab

#14; (Enoxaparin or enoxaparin or "PK 10,169" or "PK10,169" or PK 10169 or PK10169 or EMT 967 or EMT967 or EMT 966 or EMT966 or clexane or klexane or lovenox):ti,ab

#15; (("low molecular" NEAR/1 (heparin or "weight heparin" or "weight fraction")) or LMWH or bm 2123 or bm2123 or choay or depolymerized heparin or ebpm 1 or ebpm 2 or ebpm 3 or ebpm1 or ebpm2 or ebpm3 or ff 1034 or ff1034 or fr 860 or fr860 or gag 869 or heparin lmw 2133 or nm heparin or "pk 007" or sandoz 5100 or sandoz 6700 or traxyparine):ti,ab

#16; ((anti coagula* or anticoagula* or antithrombotic) NEAR/1 (drug? or agent? or therapy or therapies)):ti,ab

#17; ((("blood clotting factor 10a" or "factor xa" or thrombin) NEXT (inhibitor? or inhibition)) or ((inhibitor? or inhibition) NEXT "of factor Xa") or ((morpholide or morpholine or morpholinomethyl or oxazolidine or pyridyl or benzimidazole) NEXT derivative) or (thiophene NEXT (derivative or compound or series)) or (pyridine NEXT (derivative or n substituted derivative or series)) or morpholines or benzimidazoles or thiophenes or pyridines):ti,ab

#18; (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)

#19; MeSH descriptor **Arthroplasty**, this term only

#20; MeSH descriptor **Arthroplasty, Replacement**, this term only

#21; MeSH descriptor **Arthroplasty, Replacement, Hip**, this term only

#22; MeSH descriptor **Arthroplasty, Replacement, Knee**, this term only

#23; MeSH descriptor **Prosthesis Implantation**, this term only
#24; MeSH descriptor **Prostheses and Implants**, this term only
#25; MeSH descriptor **Joint Prosthesis** explode all trees
#26; (prosthesiology or endoprosthesis or endoprostheses or (prosthetic NEXT (replacement or substitution or implant? or joint))):ti,ab
#27; ((Joint or hip or "femoral head" or "femur head" or total or knee or orthopedic or Implantation? or "weber huggler" or "mckee ferrar") NEAR/1 (Prosthesis or prostheses)):ti,ab
#28; (arthroplasty or arthroplasties or alloarthroplasty or alloarthroplasties or hemiarthroplasties or hemiarthroplasty or arthroprosthesis or acetabuloplasty or "mac bride acetabulum cup" or "acetabulum plasty" or "hip plasty"):ti,ab
#29; ((joint or hip or knee or "femoral head" or "femur head" or (total NEAR/1 (hip or joint or knee))) NEAR/1 (replacement? or reconstruction or artificial)):ti,ab
#30; (#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)
#31; (#18 AND #30)
#32; (#18 AND #30) in Clinical Trials
#33; (#18 AND #30), in Clincal Trials from 2009 to 2010

CRD databases. NHS EED

; ; Seacrh
#; 1; MeSH Morpholines
#; 2; MeSH Thiophenes
#; 3; MeSH Benzimidazoles
#; 4; MeSH Pyridines
#; 5; MeSH Anticoagulants
#; 6; MeSH Heparin, Low-Molecular-Weight
#; 7; MeSH Dalteparin
#; 8; MeSH Enoxaparin
#; 9; MeSH Factor Xa
#; 10; "direct thrombin inhibitors" OR "direct antithrombins"
#; 11; Rivaroxaban OR "bay 59 7939" OR "bay 597939" OR "bay59 7939" OR bay597939 OR xarelto
#; 12; dabigatran OR "bibr 1048" OR bibr1048 OR "bibr 953" OR bibr953 OR pradaxa OR rendix
#; 13; Dalteparin OR "Kabi 2165" OR Kabi2165 OR "k 2165" OR k2165 OR "FR 860" OR FR860 OR fragmin OR fragmine OR "low liquemin" OR Tedelparin
#; 14; Enoxaparin OR enoxaparin OR "PK 10,169" OR "PK10,169" OR "PK 10169" OR PK10169 OR "EMT 967" OR EMT967 OR "EMT 966" OR EMT966 OR clexane OR klexane OR lovenox
#; 15; "low molecular heparin" OR "low molecular weight heparin" OR "low molecular weight fraction" OR "heparin low molecular" OR "weight fraction low molecular" OR LMWH OR "bm 2123" OR bm2123 OR choay OR "depolymerized heparin" OR "ebpm 1" OR "ebpm 2" OR "ebpm 3" OR ebpm1 OR ebpm2 OR ebpm3 OR "ff 1034" OR ff1034 OR "fr 860" OR fr860 OR "gag 869" OR "heparin lmw 2133" OR "nm heparin" OR "pk 007" OR "sandoz 5100" OR "sandoz 6700" OR traxyparine
#; 16; "anti coagula drug*" OR "anti coagula agent*" OR "anti coagula therapy*" OR "anti coagula therapies*" OR "drug anti coagula*" OR "agent anti coagula*" OR "therapy anti coagula*" OR "therapies anti coagula*" OR "anticoagula drug*" OR "anticoagula agent*" OR "anticoagula therapy*" OR "anticoagula therapies*" OR "drug anticoagula*" OR "agent anticoagula*" OR "therapy" AND anticoagula* AND " OR " AND therapies AND anticoagula* AND " OR " AND antithrombotic* AND drug* AND " OR " AND antithrombotic* AND agent* AND " OR " AND antithrombotic* AND therapy OR "antithrombotic therapies*" OR "drug antithrombotic*" OR "agent antithrombotic*" OR "therapy antithrombotic*" OR "therapies antithrombotic*"
#; 17; "blood clotting factor 10a inhibitor*" OR "blood clotting factor 10a inhibition" OR "factor xa inhibitor*" OR "factor xa inhibition" OR "thrombin

inhibitor*" OR "thrombin inhibition" OR "inhibitor of factor Xa*" OR "inhibition of factor Xa" OR "morpholide derivative" OR "morpholine derivative" OR "morpholinomethyl derivative" OR "oxazolidine derivative" OR "pyridyl derivative" OR "benzimidazole derivative" OR "thiophene derivative" OR "thiophene compound" OR "thiophene series" OR "pyridine derivative" OR "pyridine n substituted" OR "pyridine series" OR morpholines OR benzimidazoles OR thiophenes OR pyridines

#; 18; #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#; 19; MeSH Arthroplasty

#; 20; MeSH Arthroplasty, Replacement

#; 21; MeSH Arthroplasty, Replacement, Hip

#; 22; MeSH Arthroplasty, Replacement, Knee

#; 23; MeSH Prosthesis Implantation

#; 24; MeSH Prostheses and Implants

#; 25; MeSH Joint Prosthesis EXPLODE 1

#; 26; prosthesiology OR endoprosthesis OR endoprostheses OR "prosthetic replacement" OR "prosthetic substitution" OR "prosthetic implant*" OR "prosthetic joint"

#; 27; "prosthesis joint" OR "prosthesis hip" OR "prosthesis femoral head" OR "prosthesis femur head" OR "prosthesis total" OR "prosthesis knee" OR "prosthesis orthopedic" OR "prosthesis implantation*" OR "prosthesis weber huggler" OR "prosthesis mckee ferrar" OR "joint prosthesis" OR "hip prosthesis" OR "femoral head prosthesis" OR "femur head prosthesis" OR "total prosthesis" OR "knee prosthesis" OR "orthopedic prosthesis" OR "implantation prosthesis*" OR "weber huggler prosthesis" OR "mckee ferrar prosthesis"

#; 28; "prostheses joint" OR "prostheses hip" OR "prostheses femoral head" OR "prostheses femur head" OR "prostheses total" OR "prostheses knee" OR "prostheses orthopedic" OR "prostheses implantation*" OR "prostheses weber huggler" OR "prostheses mckee ferrar" OR "joint prostheses" OR "hip prostheses" OR "femoral head prostheses" OR "femur head prostheses" OR "total prostheses" OR "knee prostheses" OR "orthopedic prostheses" OR "implantation prostheses*" OR "weber huggler prostheses" OR "mckee ferrar prostheses"

#; 29; arthroplasty OR arthroplasties OR alloarthroplasty OR alloarthroplasties OR hemiarthroplasties OR hemiarthroplasty OR arthroprosthesis OR acetabuloplasty OR "mac bride acetabulum cup" OR "acetabulum plasty" OR "hip plasty"

#; 30; "joint replacement*" OR "joint reconstruction" OR "joint artificial" OR "hip replacement*" OR "hip reconstruction" OR "hip artificial" OR "knee replacement*" OR "knee reconstruction" OR "knee artificial" OR "femoral head replacement*" OR "femoral head reconstruction" OR "femoral head artificial" OR "femur head replacement*" OR "femur head reconstruction" OR "femur head artificial" OR "hip total replacement*" OR "hip total reconstruction" OR "hip total artificial" OR "joint total replacement*" OR "joint total reconstruction" OR "joint total artificial" OR "knee total replacement*" OR "knee total reconstruction" OR "knee total artificial"

#; 31; "replacement joint*" OR "reconstruction joint" OR "artificial joint" OR "replacement hip*" OR "reconstruction hip" OR "artificial hip" OR "replacement knee*" OR "reconstruction knee" OR "artificial knee" OR "replacement femoral head*" OR "reconstruction femoral head" OR "artificial femoral head" OR "replacement femur head*" OR "reconstruction femur head" OR "artificial femur head" OR "replacement total hip*" OR "reconstruction total hip" OR "artificial total hip" OR "replacement total joint*" OR "reconstruction total joint" OR "artificial total joint" OR "replacement total knee*" OR "reconstruction total knee" OR "artificial total knee"

#; 32; #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31

#; 33; #18 AND #32

#; 34; #18 AND #32 RESTRICT YR 2009 2010

APPENDIX 2 - LIST OF EXCLUDED STUDIES

Studies identified by our literature search

Reference	Description	Reason for exclusion
Holmes, 2009 (59)	Evaluation of manufacturer submission, search, evaluation and health economics	Search performed in February 2008. Outdated: We identified a newer SR covering efficacy and safety of dabigatran.
Hull, 2009 (60)	Focus on different definitions of bleeding	Search only in Medline. Not our focus
Kapoor, 2010 (61)	Cost-effectiveness	Not usable data for efficacy and safety
Melillo, 2010 (62)	Rivaroxaban. Pharmacology, pharmacokinetics, clinical efficacy/safety to inform health care professionals. Acceptable search.	No description of how they identified relevant references or evaluation. Narrative format.
Mitchell, 2010 (63)	LMWH in knee arthroplasty.	Possible limitations in search. Have identified studies relevant for our focus, but data not presented.
Sharrock, 2008 (64)	Death and anticoagulation after THA and TKA	Search only in Medline. Categorization of data unusable for our focus. Outdated.
Wolowacz, 2009 (65)	Efficacy and safety of dabigatran. Meta-analysis	Identification of studies not described.
NHSC, 2006 (66)	Early technology brief on dabigatran	No description of method used to identify literature. No data. Outdated

APPENDIX 3 - CHARACTERISTICS OF INCLUDED STUDIES

PICO for Salazar et al., 2010

Salazar et al., 2010 (4) **Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement.**	
Study design	Systematic review of randomised controlled trials (RCTs

Quality	High
Objective	To examine the efficacy and safety of prophylactic anticoagulation with direct thrombin inhibitors (DTIs) versus LMWH or vitaminK antagonists in the prevention of VTE in patients undergoing THR or TKR.
Patients	Patients who have undergone total hip or knee replacement.
Interventions	Prophylactic anticoagulation with direct thrombin inhibitors
Comparator	Vitamin K antagonists or low molecular weight heparins
Outcomes measured	For efficacy • VTE events (DVT, PE): dichotomous • Mortality events due to VTE: dichotomous For safety • Bleeding events: dichotomous • Hepatopathy events: dichotomous • Mortality events due to bleeding or others: dichotomous • Bleeding volume: continuous
Included studies	14 randomized controlled trials, of which four used oral dabigatran (BISTRO II 2005; RE-MOBILIZE 2009; RE-MODEL 2007; RE-NOVATE 2007)
Notes	Last search performed March 2010.

PICO for Stevenson et al., 2009

Stevenson et al., 2009 (16) **Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal**	
Study design	Systematic review of Phase III studies. Double or single blind RCT
Quality	Medium to high
Objective	Evidence review group (ERG) review of manufacturer's submission to NICE as part of the single technology appraisal (STA) process
Patients	Undergoing elective hip or knee replacement, hip fracture
Interventions	Rivaroxaban
Comparator	Dabigatran, enoxaparin
Outcomes measured	DVT, PE, Safety
Included studies	RECORD 1- 4 (RECORD 4 as abstract only)

	For indirect comparison with dabigatran: RE-NOVATE, RE-MODEL, RE-MOBILIZE
Notes	The search strategy was judged to be effective in identifying relevant literature relating to the question and showed use of relevant search techniques for systematic review and appraisal. Processes and validation of study screening and data extraction appear to be appropriate. Statistical methods were explicitly described for the meta-analyses and indirect comparisons and all relevant analyses were performed, although reporting of the results of these analyses were limited due to the omission of conclusions or plots to aid interpretation. Not possible to use to extract data as most results are blacked out.

PICO for Ndegwa et al., 2009

Ndegwa et al., 2009 (3) **Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety**	
Study design	Systematic review/rapid alert which included Health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials (RCTs)
Quality	Medium to high
Objective	What is the clinical-effectiveness and safety of dabigatran or rivaroxaban compared to low- molecular-weight heparins (LMWH), unfractionated heparin, warfarin, or fondaparinux for thromboprophylaxis after elective total hip replacement, elective total knee replacement, or hip fracture surgery?
Patients	Patients undergoing elective total hip replacement, elective total knee replacement, or hip fracture surgery
Interventions	Thromboprophylaxis using dabigatran or rivaroxaban
Comparator	Thromboprophylaxis using LMWH, unfractionated heparin, warfarin, or fondaparinux
Outcomes measured	All-cause mortality, number of patients withdrawing from trials due to an adverse event, number of patients experiencing at least one adverse event, including symptomatic or asymptomatic DVT, non-fatal pulmonary embolism, myocardial infarction, stroke, major bleeding, minor bleeding, or any other adverse event during the

	treatment phase or the study period.
Included studies	Dabigatran: (BISTRO II) RE-NOVATE, RE-MODEL, RE-MOBILIZE Rivaroxaban: Four phase 2 RCTs and three phase 3 RCTs (RECORD 1.RECORD 2 and RECORD 3 + preliminary results from RECORD 4
Notes	Data is extracted from the studies and presented in tables. They did not perform meta-analysis of these, but have presented a meta-analysis performed by Wolowacz et al., 2009 on dabigatran.

PICO for RE-NOVATE II

Eriksson et al., 2011 (23). Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II)	
Study design	Randomized controlled trial
Objective	Further evaluate the efficacy and safety of dabigatran in the 220 mg dose
Patients	Patients undergoing elective total hip replacement
Interventions	Dabigatran 220 mg daily starting with half a dose 1-4 hours after surgery.
Comparator	Enoxaparin 40 mg daily starting the evening before surgery.
Treatment time and follow-up	Treatment time 28-35 days until mandatory bilateral venography. Follow-up 3 months +/-7 days after surgery
Outcomes measured	Mortality, venographic or symptomatic deep vein thrombosis, pulmonary embolism, bleeding (several categories).
Quality	See risk of bias table
Notes	

APPENDIX 4 - RISK OF BIAS TABLES

Summary of Risk of Bias of included studies on rivaroxaban and *dabigatran*

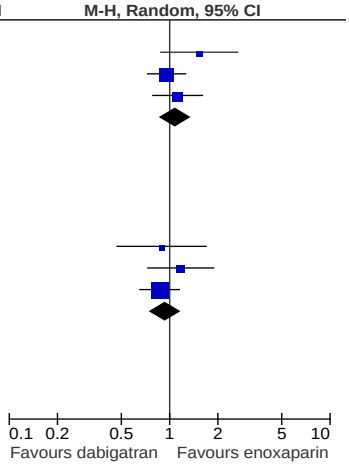
Study → ---------- Entry in RoB ↓	Eriksson, 2007	ODIXa-HIP qd	ODIXa-HIP bid	ODIXa-KNEE	RECORD1	RECORD2	RECORD3	RECORD4	*RE-NOVATE II*
Adequate sequence generation?	+	+	+	+	+	+	+	+	+
Allocation concealment?	+	+	+	+	+	+	+	+	+
Blinding? (participants, personnel, outcome assessors)	-	+	+	+	+	+	+	+	+
Incomplete outcome data adressed?	-	-	-	-	-	-	-	-	+/-
Free of selective reporting?	?	?	?	?	+	?	+	+	?
Free of other bias?	?	?	?	?	?	?	?	?	?

Comment for incomplete data addressed:
The studies operate with several different populations in the analysis. The safety population usually consisted of all randomized patients having received at least one dose of study drug. However, the in the efficacy population participants without or with inconclusive results from the mandatory venography were excluded. This constituted around 25-30% of patients. This may cause a risk for bias of the results.

APPENDIX 5 - META-ANALYSES

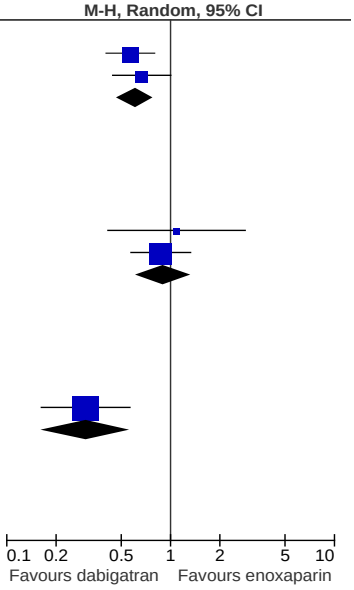
Minor bleeding with dabigatran

Study or Subgroup	Dabigatran Events	Total	Enoxaparin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 hip replacement						
BISTRO II-HIP	84	1059	14	270	15.3%	1.53 [0.88, 2.65]
RE-NOVATE	142	2309	74	1154	51.5%	0.96 [0.73, 1.26]
RE-NOVATEII	61	1010	54	1003	33.3%	1.12 [0.79, 1.60]
Subtotal (95% CI)		**4378**		**2427**	**100.0%**	**1.09 [0.87, 1.36]**
Total events	287		142			
Heterogeneity: Tau² = 0.01; Chi² = 2.32, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.5.2 knee replacement						
BISTRO II-KNEE	40	498	11	122	12.6%	0.89 [0.47, 1.68]
RE-MOBILIZE	56	1728	24	868	23.1%	1.17 [0.73, 1.88]
RE-MODEL	119	1382	69	694	64.3%	0.87 [0.65, 1.15]
Subtotal (95% CI)		**3608**		**1684**	**100.0%**	**0.93 [0.74, 1.17]**
Total events	215		104			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						



Increase in liver enzymes

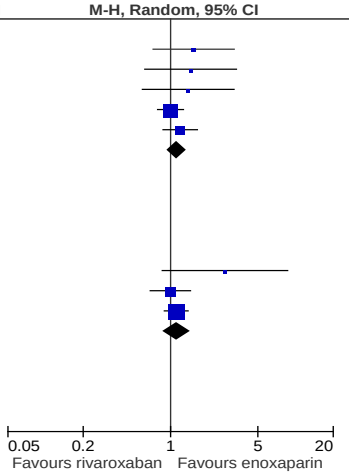
Study or Subgroup	Dabigatran Events	Total	Enoxaparin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 hip replacement						
RE-NOVATE	68	2241	60	1122	59.0%	0.57 [0.40, 0.80]
RE-NOVATEII (1)	37	984	55	975	41.0%	0.67 [0.44, 1.00]
Subtotal (95% CI)		**3225**		**2097**	**100.0%**	**0.61 [0.47, 0.79]**
Total events	105		115			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 3.76 (P = 0.0002)						
1.6.2 knee replacement						
RE-MOBILIZE	13	1728	6	868	15.9%	1.09 [0.42, 2.85]
RE-MODEL	57	1329	33	670	84.1%	0.87 [0.57, 1.32]
Subtotal (95% CI)		**3057**		**1538**	**100.0%**	**0.90 [0.61, 1.32]**
Total events	70		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
1.6.3 hip- and knee replacement						
BISTRO II (2)	15	671	26	352	100.0%	0.30 [0.16, 0.56]
Subtotal (95% CI)		**671**		**352**	**100.0%**	**0.30 [0.16, 0.56]**
Total events	15		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.76 (P = 0.0002)						



(1) >3xULN anytime post baseline
(2) from 5 of 344 to 10 of 327 for dabigatran, hence unclear for the rest of the groups and for hip and knee separately

Minor bleeding with rivaroxaban

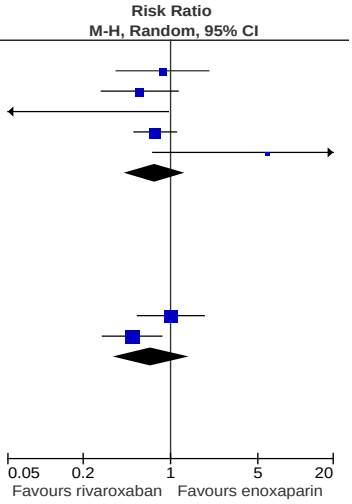
Study or Subgroup	Rivaroxaban Events	Total	Enoxaparin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 hip replacement						
Eriksson 2007(open-label)	35	463	8	162	5.5%	1.53 [0.73, 3.23]
ODIXa-HIP-once daily (1)	38	688	6	157	4.3%	1.45 [0.62, 3.36]
ODIXa-HIP-twice daily (2)	36	572	6	132	4.3%	1.38 [0.60, 3.22]
RECORD1	128	2209	129	2224	54.7%	1.00 [0.79, 1.27]
RECORD2	80	1228	67	1229	31.1%	1.20 [0.87, 1.64]
Subtotal (95% CI)		**5160**		**3904**	**100.0%**	**1.11 [0.94, 1.33]**
Total events	317		216			
Heterogeneity: Tau² = 0.00; Chi² = 2.32, df = 4 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
2.5.2 knee replacement						
ODIXa-KNEE (3)	40	509	3	104	4.6%	2.72 [0.86, 8.64]
RECORD3	53	1220	54	1239	33.2%	1.00 [0.69, 1.44]
RECORD4	155	1526	138	1508	62.2%	1.11 [0.89, 1.38]
Subtotal (95% CI)		**3255**		**2851**	**100.0%**	**1.12 [0.87, 1.44]**
Total events	248		195			
Heterogeneity: Tau² = 0.01; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%						
Test for overall effect: Z = 0.85 (P = 0.39)						



(1) minor bleed
(2) minor bleed
(3) minor bleed

Increase in liver enzymes with rivaroxaban

Study or Subgroup	Rivaroxaban Events	Total	Enoxaparin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 hip replacement						
Eriksson 2007(open-label)	18	453	7	152	23.2%	0.86 [0.37, 2.03]
ODIXa-HIP-once daily	26	642	10	140	27.8%	0.57 [0.28, 1.15]
ODIXa-HIP-twice daily (1)	0	572	2	132	3.3%	0.05 [0.00, 0.96]
RECORD1	43	2128	57	2129	39.5%	0.75 [0.51, 1.12]
RECORD2	6	1101	1	1097	6.3%	5.98 [0.72, 49.57]
Subtotal (95% CI)		**4896**		**3650**	**100.0%**	**0.75 [0.42, 1.32]**
Total events	93		77			
Heterogeneity: Tau² = 0.17; Chi² = 7.67, df = 4 (P = 0.10); I² = 48%						
Test for overall effect: Z = 1.00 (P = 0.32)						
2.6.2 knee replacement						
ODIXa-KNEE	0	0	0	0		Not estimable
RECORD3	20	1150	20	1156	48.0%	1.01 [0.54, 1.86]
RECORD4	19	1471	38	1451	52.0%	0.49 [0.29, 0.85]
Subtotal (95% CI)		**2621**		**2607**	**100.0%**	**0.69 [0.35, 1.39]**
Total events	39		58			
Heterogeneity: Tau² = 0.17; Chi² = 2.89, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 1.03 (P = 0.30)						



(1) and increased bilirudin

APPENDIX 6 – DISTRIBUTIONS USEDIN PROBABILISTIC SENSITIVITY ANALYSIS

Distributions used in PSA (THR)

Name	Parameters/Info
dist_cost_diag_PTS	Gamma, alpha = (7557,86^2)/(1156,815306^2), lambda = 7557,86/(1156,815306^2); Expected value: 7557,86
dist_cost_treat_PTS	Gamma, alpha = (5668,12^2)/(867,5693878^2), lambda = 5668,12/(867,5693878^2); Expected value: 5668,12
dist_cost_PE_inpatient	Gamma, alpha = (9372^2)/(1434,465306^2), lambda = 9372/(1434,465306^2); Expected value: 9372
dist_cost_PE_outpatient	Gamma, alpha = (49028^2)/(7504,233673^2), lambda = 49028/(7504,233673^2); Expected value: 49028
dist_cost_DVT_inpatient	Gamma, alpha = (15714^2)/(2405,158163^2), lambda = 15714/(2405,158163^2); Expected value: 15714
dist_cost_DVT_outpatient	Gamma, alpha = (18132^2)/(2775,277041^2), lambda = 18132/(2775,277041^2); Expected value: 18132
dist_cost_major_bleeding	Gamma, alpha = (24847,5276^2)/(3803,193^2), lambda = 24847,5276/(3803,193^2); Expected value: 24847,5276
dist_price_administration_drug	Gamma, alpha = (500^2)/(127,551^2), lambda = 500/(127,551^2); Expected value: 500
dis_RR_Dabi_bleed	Log-Normal, u (mean of logs) = 0,215111, sigma (std dev of logs) = (Ln(1,86)-Ln(0,83))/(2*GRADE_moderate_quality); Expected value: 1,277867436
dis_RR_Dabi_DVT	Log-Normal, u (mean of logs) = -0,020203, sigma (std dev of logs) = (Ln(1,22)-Ln(0,78))/(2*GRADE_moderate_quality); Expected value: 0,989101187
dis_RR_Dabi_PE	Log-Normal, u (mean of logs) = -0,174353, sigma (std dev of logs) = (Ln(2,77)-Ln(0,25))/(2*GRADE_low_quality); Expected value: 1,304626484
dis_RR_dabi_total_death	Log-Normal, u (mean of logs) = 0,157004, sigma (std dev of logs) = (Ln(36,52)-Ln(0,04))/(2*Grade_ low_quality); Expected value: 40,190914669
dis_RR_Riva_bleed	Log-Normal, u (mean of logs) = 0,802002, sigma (std dev of logs) = (Ln(4,67)-Ln(1,06))/(2*GRADE_moderate_quality); Expected value: 2,468466775
dis_RR_Riva_DVT	Log-Normal, u (mean of logs) = -1,560648, sigma (std dev of logs) = (Ln(0,32)-Ln(0,14))/(2*GRADE_low_quality); Expected value: 0,2212117
dis_RR_Riva_PE	Log-Normal, u (mean of logs) = 0,000000, sigma (std dev of logs) = (Ln(15,28)-Ln(0,07))/(2*GRADE_very_low_quality); Expected value: 29,236776468

dis_RR_Riva_total_death	Log-Normal, u (mean of logs) = -0,314711, sigma (std dev of logs) = (Ln(1,8)-Ln(0,29))/(2*GRADE_low_quality); Expected value: 0,940789461
dis_q_no_VTE_events	Beta, Real-numbered parameters, alpha = 1719,7348, beta = 416,5817; Expected value: 0,805000008
dis_q_longterm_no_event	Beta, Real-numbered parameters, alpha = 757,5916, beta = 125,3823; Expected value: 0,857999993
dis_q_symptomatic_DVT	Beta, Real-numbered parameters, alpha = 270,1745, beta = 51,4618; Expected value: 0,840000025
dis_q_PE	Beta, Real-numbered parameters, alpha = 332,0163, beta = 104,8473; Expected value: 0,759999918
dis_q_recurrent_DVT	Beta, Real-numbered parameters, alpha = 270,1745, beta = 51,4618; Expected value: 0,840000025
dist_q_bleeding	Beta, Real-numbered parameters, alpha = 8, beta = 4; Expected value: 0,666666667
dist_q_PTS	Beta, Real-numbered parameters, alpha = 9, beta = 4; Expected value: 0,692307692
dis_q_severe_PTS	Beta, Real-numbered parameters, alpha = 21,1667, beta = 13,5328; Expected value: 0,610000144
dis_q_mild_PTS	Beta, Real-numbered parameters, alpha = 38,8425, beta = 11,6023; Expected value: 0,770000079
dis_q_mild_PTS	Beta, Real-numbered parameters, alpha = 38,8425, beta = 11,6023; Expected value: 0,770000079
dis_p_bleeding	Beta, Real-numbered parameters, alpha = 3,2856, beta = 231,3985; Expected value: 0,014000096
dis_p_PTS	Beta, Real-numbered parameters, alpha = 314,8294, beta = 1434,2227; Expected value: 0,180000013
dis_p_VTE	Beta, Real-numbered parameters, alpha = 349,5012, beta = 3533,8454; Expected value: 0,090000002
dis_p_recurrent_VTE_no_pre_event	Beta, Real-numbered parameters, alpha = ((0,00143^2)*(1-0,00143)/(0,0001^2)), beta = (0,00143*(1-0,00143)/(0,0001^2))-((0,00143^2)*(1-0,00143)/(0,0001^2)); Expected value: 0,00143
dis_p_PTS_no_pre_events	Beta, Real-numbered parameters, alpha = ((0,000761^2)*(1-0,000761)/(0,00004^2)), beta = (0,000761*(1-0,000761)/(0,00004^2))-((0,000761^2)*(1-0,000761)/(0,00004^2)); Expected value: 0,000761
dist_rate_PE_THR	Beta, Integer parameters only, n = 2512, r = 28; Expected value: 0,011146497
distr_rate_DVT_THR	Beta, Integer parameters only, n = 2512, r = 39; Expected value: 0,015525478
dis_die_recurrent_VTE	Beta, Integer parameters only, n = 130, r = 12; Expected value: 0,092307692

Distributions used in PSA (TKR)

Name	Parameters/Info
dist_cost_diag_PTS	Gamma, alpha = (7557,86^2)/(1156,815306^2), lambda = 7557,86/(1156,815306^2); Expected value: 7557,86
dist_cost_treat_PTS	Gamma, alpha = (5668,12^2)/(867,5693878^2), lambda = 5668,12/(867,5693878^2); Expected value: 5668,12
dist_cost_PE_inpatient	Gamma, alpha = (16603^2)/(2541,260204^2), lambda = 16603/(2541,260204^2); Expected value: 16603
dist_cost_PE_outpatient	Gamma, alpha = (31471^2)/(4816,953061^2), lambda = 31471/(4816,953061^2); Expected value: 31471
dist_cost_DVT_inpatient	Gamma, alpha = (16341^2)/(2501,152041^2), lambda = 16341/(2501,152041^2); Expected value: 16341
dist_cost_DVT_outpatient	Gamma, alpha = (20239^2)/(3097,729592^2), lambda = 20239/(3097,729592^2); Expected value: 20239
dist_cost_major_bleeding	Gamma, alpha = (24847,5276^2)/(3803,193^2), lambda = 24847,5276/(3803,193^2); Expected value: 24847,5276
dist_price_administration_drug	Gamma, alpha = (500^2)/(127,551^2), lambda = 500/(127,551^2); Expected value: 500
dis_RR_Dabi_bleed	Log-Normal, u (mean of logs) = -0,116534, sigma (std dev of logs) = (Ln(1,69)-Ln(0,47))/(2*GRADE_moderate_quality); Expected value: 0,959956765
dis_RR_Dabi_DVT	Log-Normal, u (mean of logs) = -0,030459, sigma (std dev of logs) = (Ln(1,34)-Ln(0,7))/(2*Grade_very_low_quality); Expected value: 1,018780879
dis_RR_Dabi_PE	Log-Normal, u (mean of logs) = -0,415515, sigma (std dev of logs) = (Ln(1,65)-Ln(0,27))/(2*GRADE_low_quality); Expected value: 0,84692469
dis_RR_dabi_total_death	Log-Normal, u (mean of logs) = 0,058269, sigma (std dev of logs) = (Ln(3,12)-Ln(0,36))/(2*Grade_ low_quality); Expected value: 1,511639538
dis_RR_Riva_bleed	Log-Normal, u (mean of logs) = 0,476234, sigma (std dev of logs) = (Ln(3,24)-Ln(0,8))/(2*GRADE_moderate_quality); Expected value: 1,762305448
dis_RR_Riva_DVT	Log-Normal, u (mean of logs) = -0,478036, sigma (std dev of logs) = (Ln(0,75)-Ln(0,51))/(2*Grade_moderate_quality); Expected value: 0,62427506
dis_RR_Riva_PE	Log-Normal, u (mean of logs) = -0,693147, sigma (std dev of logs) = (Ln(1,46)-Ln(0,17))/(2*GRADE_low_quality); Expected value: 0,710914445
dis_RR_Riva_total_death	Log-Normal, u (mean of logs) = -0,478036, sigma (std dev of logs) = (Ln(2,9)-Ln(0,13))/(2*Grade_low_quality); Expected value: 1,291369154
dis_q_no_VTE_events	Beta, Real-numbered parameters, alpha = 1484,2008, beta = 354,9576; Expected value: 0,806999984
dis_q_longterm_no_event	Beta, Real-numbered parameters, alpha = 992,5172, beta = 187,6459; Expected value: 0,841000028
dis_q_symptomatic_DVT	Beta, Real-numbered parameters, alpha = 270,1745, beta = 51,4618; Expected value: 0,840000025
dis_q_PE	Beta, Real-numbered parameters, alpha = 332,0163, beta = 104,8473; Expected value: 0,759999918
dis_q_recurrent_DVT	Beta, Real-numbered parameters, alpha = 270,1745, beta = 51,4618; Expected value: 0,840000025
dist_q_bleeding	Beta, Real-numbered parameters, alpha = 8, beta = 4; Expected value: 0,666666667
dist_q_PTS	Beta, Real-numbered parameters, alpha = 9, beta = 4; Expected value: 0,692307692
dis_q_severe_PTS	Beta, Real-numbered parameters, alpha = 21,1667, beta = 13,5328; Expected value: 0,610000144
dis_q_mild_PTS	Beta, Real-numbered parameters, alpha = 38,8425, beta = 11,6023; Expected value: 0,770000079
dis_q_bleeding	Beta, Real-numbered parameters, alpha = 2,0288, beta = 1,0452; Expected value: 0,659986988

dis_p_bleeding	Beta, Real-numbered parameters, alpha = ((0,009^2)*(1-0,009)/(0,306^2)), beta = (0,009*(1-0,009)/(0,306^2))-((0,009^2)*(1-0,009)/(0,306^2)); Expected value: 0,009
dis_p_PTS	Beta, Real-numbered parameters, alpha = 314,8294, beta = 1434,2227; Expected value: 0,180000013
dis_p_VTE	Beta, Real-numbered parameters, alpha = 349,5012, beta = 3533,8454; Expected value: 0,090000002
dis_p_recurrent_VTE_no_pre_event	Beta, Real-numbered parameters, alpha = ((0,00143^2)*(1-0,00143)/(0,0001^2)), beta = (0,00143*(1-0,00143)/(0,0001^2))-((0,00143^2)*(1-0,00143)/(0,0001^2)); Expected value: 0,00143
dis_p_PTS_no_pre_events	Beta, Real-numbered parameters, alpha = ((0,000761^2)*(1-0,000761)/(0,00004^2)), beta = (0,000761*(1-0,000761)/(0,00004^2))-((0,000761^2)*(1-0,000761)/(0,00004^2)); Expected value: 0,000761
dist_PE_TKR	Beta, Integer parameters only, n = 675, r = 4; Expected value: 0,005925926
dist_DVT_TKR	Beta, Integer parameters only, n = 675, r = 11; Expected value: 0,016296296
dis_die_recurrent_VTE	Beta, Integer parameters only, n = 130, r = 12; Expected value: 0,092307692

APPENDIX 7 - ESTIMATING THE COSTS OF MEDICAMENTS

Costs of medicaments per patient, NOK

	Enoxaparin		**Dabigatran**		**Rivaroxaban**	
	THR	TKR	THR	TKR	THR	TKR
Cost of medicament (inpatient)*	63	45	132	99	168	120
Cost of medicament (outpatient)	1 136.4	378.8	1 176	248.5	1 505	525
Drug administration (outpatient)	850	500	0	0	0	0
Sum	2 049.4	923.8	1 308	347.5	1 673	645

*In-hospital drug costs are calculated based on the prise list

The cost of medicaments was almost similar for all strategies. The main source of difference was associated with cost of administration for enoxaparin.