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.

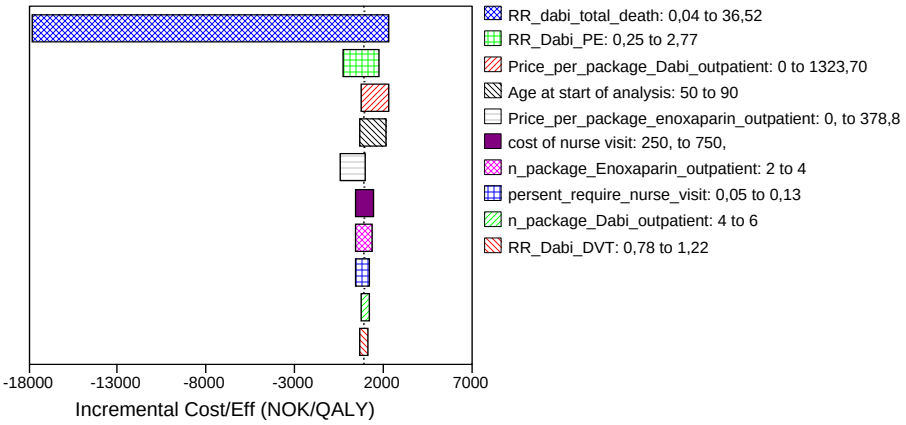


***Figure 11**. The top 10 lists in tornado diagram of dabigatran compared with enoxaparin (Total hip replacement)*

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).

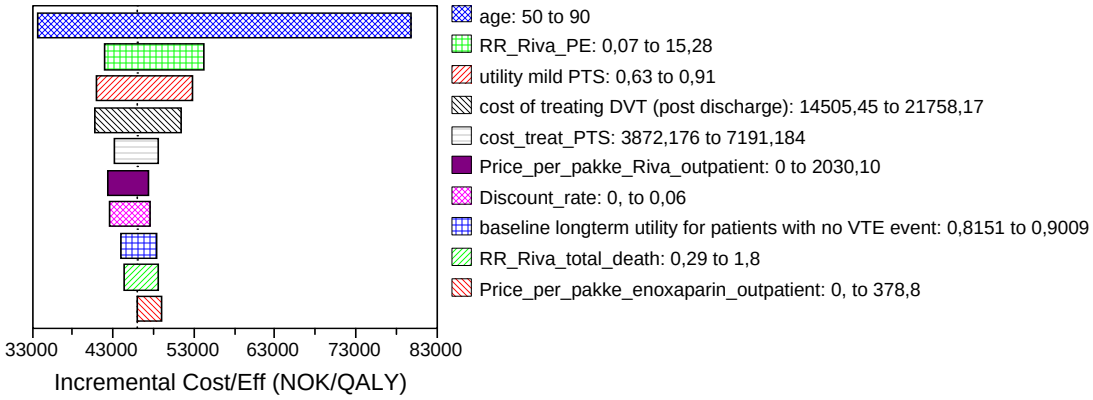


***Figure 12**. The top 10 lists in tornado diagram of rivaroxaban compared with enoxaparin (Total hip replacement)*

[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.

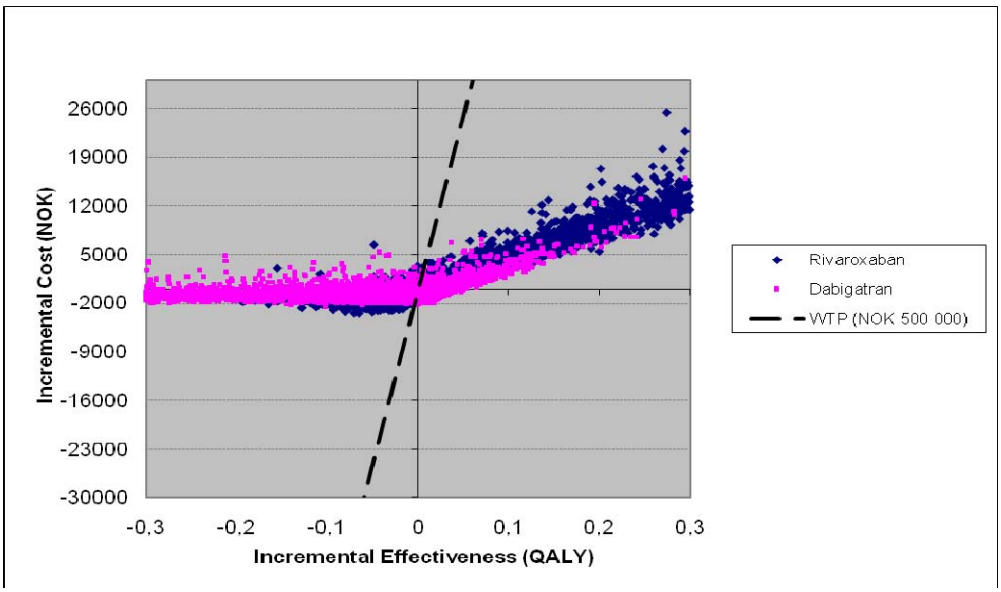


Figure 13a. *Scatter plot of simulations of rivaroxaban and dabigatran compared with enoxaparin after total hip replacement*

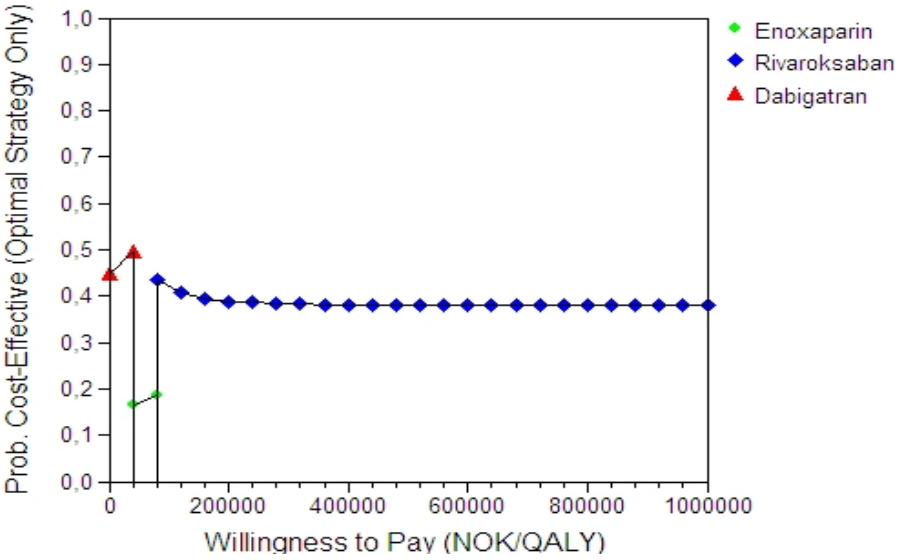


Figure 13b. *Acceptability frontier for total hip replacement*

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).

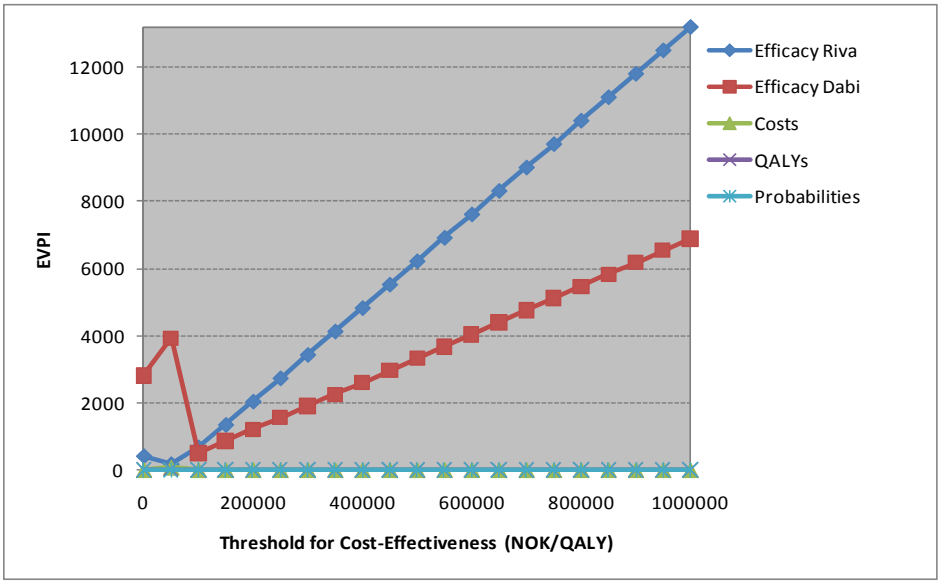


Figure 14. *Expected Value of perfect information for parameters (Total hip replacement)*

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.

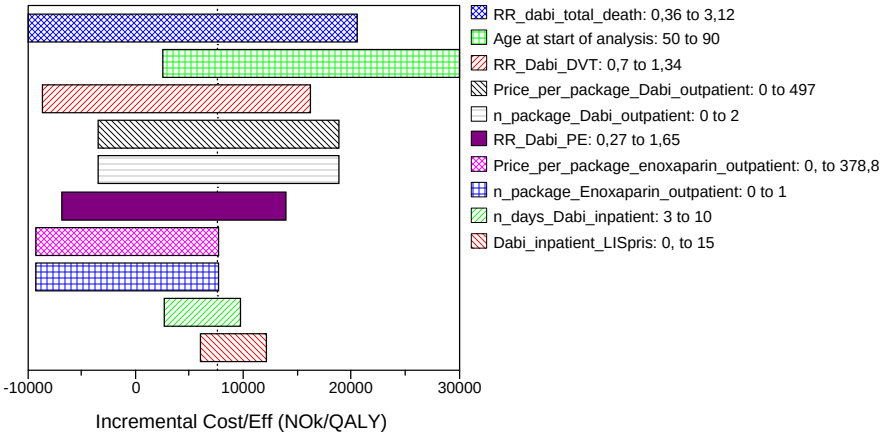


***Figure 15**. The top 10 lists in tornado diagram of dabigatran compared with enoxaparin (Total knee replacement)*

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.

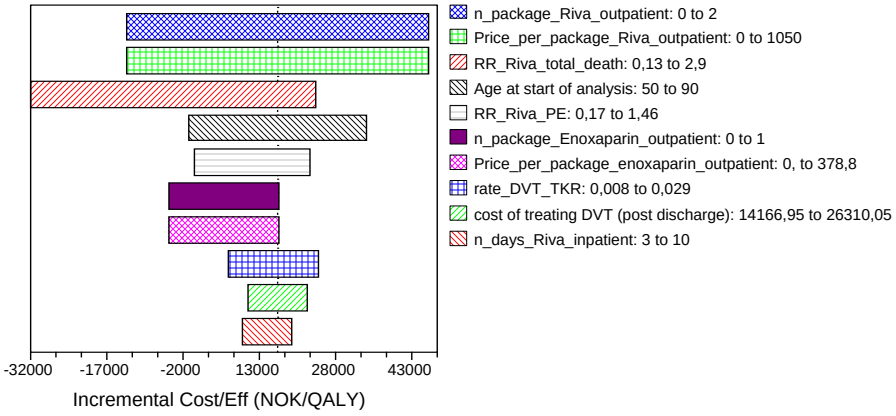


***Figure 16**. The top 10 lists in tornado diagram of rivaroxaban compared with enoxaparin (Total knee replacement)*

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%.

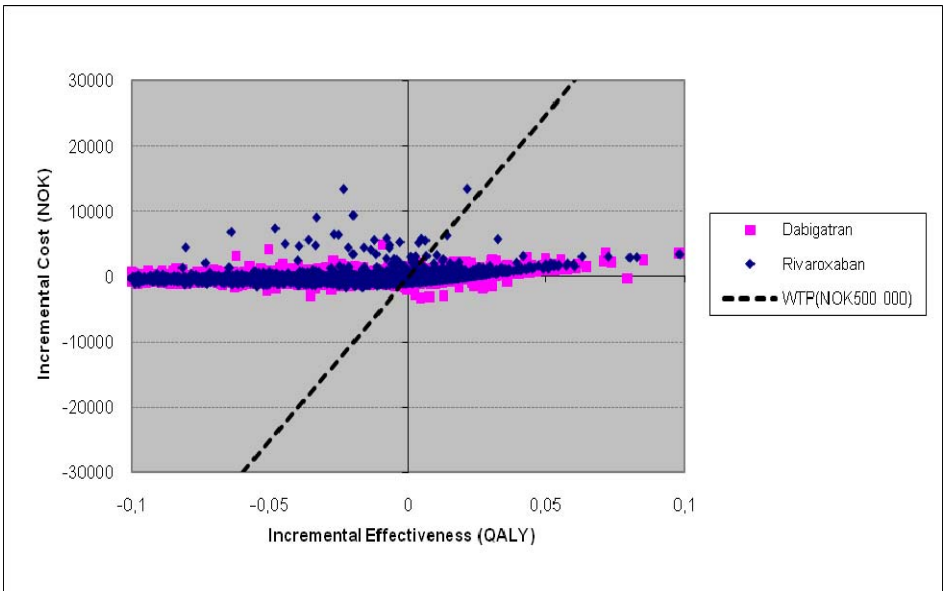


Figure 17a *Scatter plot of simulations of rivaroxaban and dabigatran compared with enoxaparin after total knee replacement*

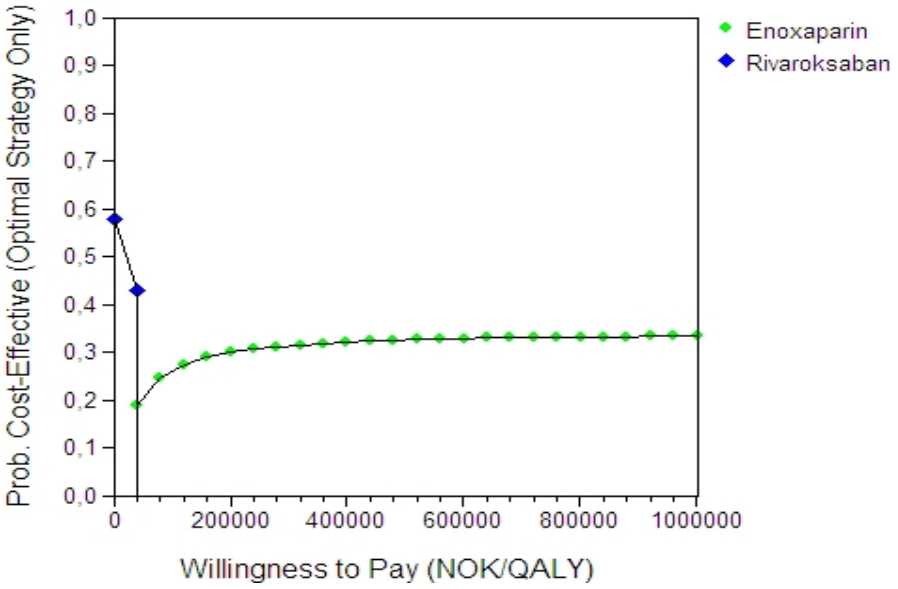


Figure 17b *Acceptability frontier for total knee replacement*

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).

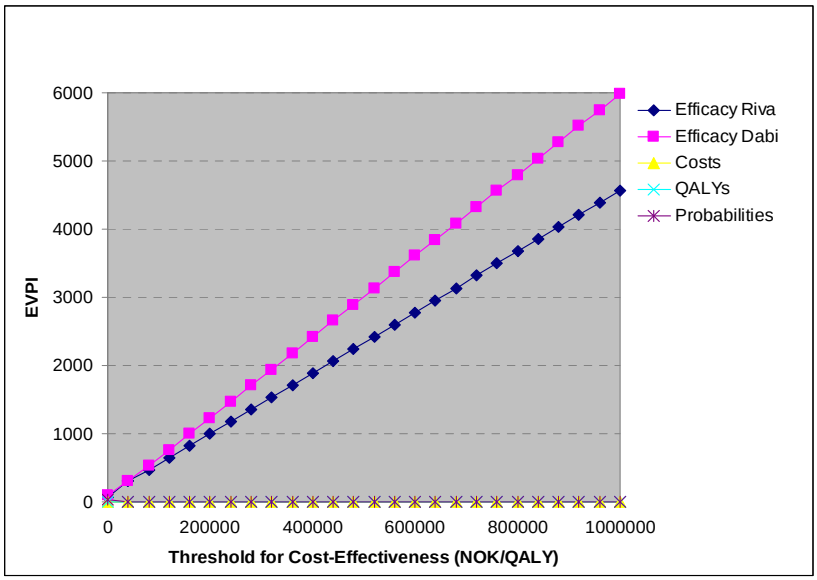


***Figure 18**. Expected Value of perfect information for parameters (Total knee replacement)*

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.

36. Heit JA, Rooke TW, Silverstein MD, Mohr DN, Lohse CM, Petterson TM, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. J Vasc Surg 2001;33(5):1022-7.

37. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007;5(4):692-9.

38. Statistisk sentralbyrå. [http://www.ssb.no]. [oppdatert 2010 ; lest 2011]

39. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. New York: Oxford University Press; 2006.

40. Statens legemiddelverk. Apotekavanse [http://www legemiddelverket no/templates/InterPage_____38823 aspx?filterBy=CopyToGeneral].

41. Offord R, Lloyd AC, Anderson P, Bearne A. Economic evaluation of enoxaparin for the prevention of venous thromboembolism in acutely ill medical patients 1. Pharm World Sci 2004;26(4):214-20.

42. Statens legemiddelverk. Refusjonsrapport-Xarelto (rivaroksaban) som tromboseprofylakse hos pasienter som har gjennomgått elektiv total hodte-eller kneprostesekirurgi. 2010.

43. Prosjektgruppe hofte- og kneopererte. Områdeplan for rehabilitering.: Sørlandet sykehus HF; 2010.

44. Innsatsstyrt finansiering 2010 [http://www helsedirektoratet no/publikasjoner/retningslinjer/regelverk_innsatsstyrt_finansiering_2010_654314]. Oslo: Helsedirektoratet [oppdatert 2010 ; lest 2011]

45. Bjorvatn A, Kristiansen F. Fondaparinux sodium compared with enoxaparin sodium: a cost-effectiveness analysis. Am J Cardiovasc Drugs 2005;5(2):121-30.

46. Pleym k, Sagerup L. Diagnostisering av dyp venetrombose ved kombinasjon av klinikk, D-dimer og ultralyd vener underekstremitet 2007.

47. Forskrift om godtgjørelse av utgifter til helsehjelp som utføres poliklinisk ved statlige helseinstitusjoner og ved helseinstitusjoner som mottar driftstilskudd fra regionale helseforetak. 2010.

48. Nasjonalt Register for Leddproteser. Kneproteser [http://nrlweb ihelse net/for_pasienter/kneproteser htm]. [oppdatert 2011 ; lest 2011]

49. VERBALVEDTAK 4 VEDR. HJEMMETJENESTEN. 2009.

50. NHO SERVICE. HELSE OG OMSORG;Suksessfaktorer for kjøp av helse- og omsorgstjenester. 2009.

51. Statistisk sentralbyrå. Konsumprisindeksen [http://www.ssb no/vis/kpi/kpiregn html]. [oppdatert 2011 ; lest 2011]

52. Rasanen P, Paavolainen P, Sintonen H, Koivisto AM, Blom M, Ryynanen OP, et al. Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. Acta Orthop 2007;78(1):108-15.

53. Haentjens P, De Groote K, Annemans L. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. A cost-utility analysis. Arch Orthop Trauma Surg 2004;124(8):507-17.

54. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc 1997;4(1):49-56.

55. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis 2009;28(4):465-76.

56. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Intern Med 2004;164(1):17-26.

57. McCullagh L, Tilson L, Walsh C, Barry M. A cost-effectiveness model comparing rivaroxaban and dabigatran etexilate with enoxaparin sodium as thromboprophylaxis after total hip and total knee replacement in the irish healthcare setting. Pharmacoeconomics 2009;27(10):829-46.

58. Wolowacz SE, Roskell NS, Maciver F, Beard SM, Robinson PA, Plumb JM, et al. Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism after total knee and hip replacement surgery. Clin Ther 2009;31(1):194-212.

59. Holmes M, Carroll C, Papaioannou D. Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal. Health Technology Assessment (Winchester, England) 2009;13 Suppl 2:55-62.

60. Hull RD, Yusen RD, Bergqvist D. State-of-the-art review: Assessing the safety profiles of new anticoagulants for major orthopedic surgery thromboprophylaxis. Clinical and Applied Thrombosis/Hemostasis 2009;15(4):377-88.

61. Kapoor A, Chuang W, Radhakrishnan N, Smith KJ, Berlowitz D, Segal JB, et al. Cost effectiveness of venous thromboembolism pharmacological prophylaxis in total hip and knee replacement: A systematic review. Pharmacoeconomics 2010;28(7):521-38.

62. Melillo SN, Scanlon JV, Exter BP, Steinberg M, Jarvis CI. Rivaroxaban for thromboprophylaxis in patients undergoing major orthopedic surgery. Annals of Pharmacotherapy 2010;44(6):1061-71.

63. Mitchell M, Williams K, Umscheid CA. Low molecular weight heparins for prevention of venous thromboembolism in total knee arthroplasty patients. 2009.

64. Sharrock NE, Gonzalez D, V, Go G, Lyman S, Salvati EA. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. Clinical Orthopaedics and Related Research 2008;466(3):714-21.

65. Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty: A meta-analysis. Thrombosis and Haemostasis 2009;101(1):77-85.

66. National Horizon Scanning Centre. Dabigatran etexilate for primary deep vein thrombosis prevention post hip and knee surgery: horizon scanning technology briefing. Birmingham: National Horizon Scanning Centre (NHSC) 2006;5.

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*

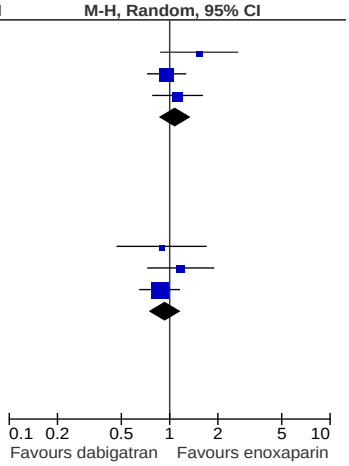
Study → ---------- Entry in RoB ↓	Eriksson, 2007	ODIXa-HIP qd	ODIXa-HIP bid	ODIXa-KNEE	RECORD1	RECORD2	RECORD3	RECORD4	*RE-NOVATE II*
Adequate sequence generation?	+	+	+	+	+	+	+	+	+
Allocation concealment?	+	+	+	+	+	+	+	+	+
Blinding? (participants, personnel, outcome assessors)	-	+	+	+	+	+	+	+	+
Incomplete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

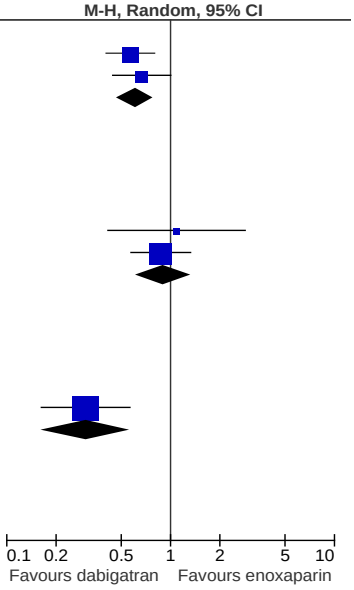
Minor bleeding with dabigatran

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

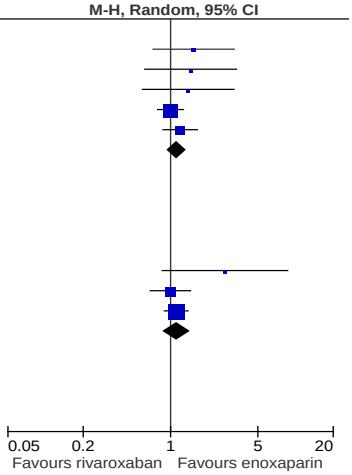
Study or Subgroup	Dabigatran Events	Total	Enoxaparin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 hip replacement						
RE-NOVATE	68	2241	60	1122	59.0%	0.57 [0.40, 0.80]
RE-NOVATEII (1)	37	984	55	975	41.0%	0.67 [0.44, 1.00]
Subtotal (95% CI)		**3225**		**2097**	**100.0%**	**0.61 [0.47, 0.79]**
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

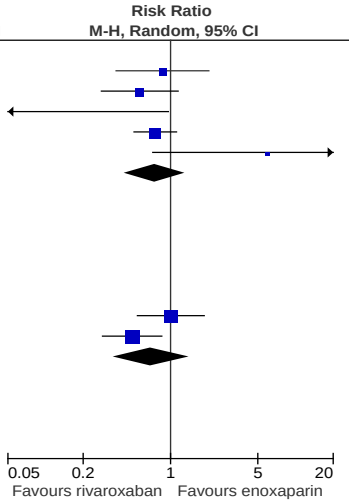
Study or Subgroup	Rivaroxaban Events	Total	Enoxaparin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 hip replacement						
Eriksson 2007(open-label)	35	463	8	162	5.5%	1.53 [0.73, 3.23]
ODIXa-HIP-once daily (1)	38	688	6	157	4.3%	1.45 [0.62, 3.36]
ODIXa-HIP-twice daily (2)	36	572	6	132	4.3%	1.38 [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.