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Cost-Effectiveness of Fondaparinux vs Enoxaparin as Venous Thromboembolism Prophylaxis in Norway

by

Afsane Bjorvatn
Frode Kristiansen

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Afsane Bjorvatn and Frode Kristiansen
May 2003, Bergen

Address for correspondence:
Institute for Research in Economics and Business Administration (SNF)
Breiviksveien 40, NO-5045 Bergen, Norway

Email: Afsane.bjorvatn@snf.no Frode.kristiansen@snf.no

ABSTRACT

Patients undergoing major orthopaedic surgery face considerable risk of venous thromboembolic complications (VTE), which may be fatal, unless they receive prophylactic treatment. Fondaparinux (Arixtra®) is a new antithrombotic agent, which is indicated for prophylaxis of VTE. The report presents a cost-effectiveness analysis of Fondaparinux versus Enoxaparin, which is the most common prophylaxis of VTE. The analysis is based on Norwegian data, which include over 55.000 patients who underwent orthopaedic surgery in the period from 1999 to 2001.

The model estimates expected incidence of VTE and expected costs estimates of VTE-related care for each of the two prophylaxes for different time periods. The results indicate that Fondaprinux is likely to be more effective than Enoxaparin in preventing the incidence of VTE. For long follow-up periods, more precisely, 5 years, Fondaparinux is also likely to represent the lower cost treatment. For hip fracture surgery, Fondaparinux is cost-saving also in the short follow-up time. In addition, the results indicate that Fondaparinux avoids between 3 and 34 VTE-related deaths per 10.000 patients compared to Enoxaparin. Our cost-benefit analysis indicates that Fondaparinux may be the more economical choice. The sensitivity analyses show that our results are robust to changes in the most important parameters. Also in the extreme cases where the Enoxaparin price is reduced by 60% to 100%, Arixtra is still cost-effective alternative after hip fracture surgery in the 5-year follow-up time compared to Enoxaparin.

CONTENTS

1. Background

Different types of venous thromboembolism (VTE) such as deep-vein thrombosis (DVT) and pulmonary embolism (PE) are major causes of morbidity and mortality. Patients undergoing major orthopaedic surgery such as total knee replacement, total hip replacement and hip fracture surgery face considerable risk of venous thromboembolic complications, unless they receive prophylactic treatment. In fact, without prophylaxis the risk of developing DVT is as high as 50%, and the risk of PE is 1-2% (Haake et al, 1989). While DVT is the most common form of VTE, PE has a higher mortality risk. Due to the autopsy routine, especially in elderly patients with chronic conditions, not all incidences of fatal PE are registered. Data from countries where autopsy is common indicate that PE remains a significant problem (Clagett et al., 1998).

The clinical consequences of DVT include acute pain and swelling secondary to the intravenous thrombi, recurrent VTE, and post-thrombotic syndrome i.e. chronic pain, swelling, and ulceration of the legs (Mc Nally et al, 1994; Lowe, 1991). The risk of developing VTE is due to post-operative immobility as well as the effects of surgical trauma on the coagulation system (Clagett et al., 1995). DVT symptoms appear on average 27 days after total hip replacement, 36 days after hip fracture surgery and 17 days after total knee replacement (Dahl, et al., 2000).

1.1 Incidence of orthopaedic surgeries in Norway

During the last 3 years 55.000 major orthopaedic surgeries were performed in Norway, i.e. more than 18.300 surgeries each year[1]. The majority of these operations were due to hip fracture surgery (HFR) (50%) and total hip replacement (THR) (40%), while 10% were due to total knee replacement (TKR). The average age of patients is 77 years for HFR, 72 years for THR and 70 years for TKR. The number of orthopaedic surgeries has been increasing during the last years, predominantly due to increasing age of the population. For more details on incidence of orthopaedic surgeries in Norway, see chapter 3.

[1] Norwegian National Register of Hospital Patients.

1.2 Prophylactic treatment

1.2.1 Current prophylaxis

Prophylactic treatment is recommended in Norway for prevention of VTE in patients who undergo major orthopaedic surgery. The most common prophylactic drugs are either a low-molecular-weight heparin (LMWH) (e.g., Enoxaparin), or Warfarin. The incidence of VTE arising in hospital has remained relatively constant during the last two decades. The lack of improvement in incidence of VTE could reflect an increase in the average population age, an increase in surgical procedures, underutilization of prophylaxis, or prophylaxis failure (Heit, 2002). This implies the need for more effective and safe prophylaxis.

1.2.2 Fondaparinux

Fondaparinux (Arixtra®) belongs to a new class of synthetic antithrombotic agents that are specific inhibitors of factor Xa. Fondaparinux prevents clot formation and is indicated for prophylaxis of VTE in patients undergoing orthopaedic surgeries[2,3].

Four clinical Phase III clinical trials have compared Fondaparinux with Enoxaparin in reducing the risk of VTE after major orthopaedic surgery: Turpie et al. (2002) “the Ephesus study”; Lassen et al. (2002) “the Pentathlon 2000 study”; Bauer et al. (2001) ”the Pentamaks study” and Eriksson et al. (2001) “the Penthifra study”. In all four trials, patients in Fondaparinux group received injections of 2,5 mg postoperatively. In Pentathlon 2000 and Pentamaks, patients treated with Enoxaparin received postoperative injections of 30 mg twice daily (US practice), while in Ephesus and Penthifra 40 mg Enoxaparin was given once daily (European practice), starting preoperatively.

Ephesus and Pentathlon 2000 were conducted for THR. The outcome from Pentathlon 2000 was that Fondaparinux was as effective as Enoxaparin in reducing risk of VTE. In the Ephesus study Fondaparinux was found to be more effective.

Pentamaks and Penthifra compare Fondaparinux with Enoxaparin in patients undergoing major knee surgery and hip fracture surgery, respectively. The outcome of these studies was that Fondaparinux lowered the risk of VTE by at least 55% compared to Enoxaparin.

[2] Fondaparinux is contraindicated in patients weighing less than 50 kg.
[3] Further clinical investigations are being carried out to extend the use of Fondaparinux (Arixtra®) for preventing DVT in abdominal surgery and treatment, and for the treatment of unstable coronary disease.

Turpie et al. (2002) present a meta-analysis of data from the four Phase III clinical trials mentioned above. These four studies enrolled 7344 patients over age 18, from North America, Australia and Europe. The analysis showed that Fondaparinux reduced the incidence of VTE by day 11 by over 50%.

Lundkvist et al. (2002) analyse the cost-effectiveness of Fondaparinux (Arixtra®) based on an international simulation model with Swedish unit costs. The analyses compared the costs and effects of prophylaxis with Fondaparinux and Enoxaparin. The results showed that overall Fondaparinux was cost saving and more effective than Enoxaparin. The sensitivity analyses showed that the results were fairly stable and thus confirmed the robustness of the model.

Posnett, et al. (2002) is a UK analysis that evaluates the cost-effectiveness of Fondaparinux relative to Enoxaparin over a period of five years post-surgery. The study concludes that using Fondaparinux in UK could reduce costs by £3.8 million per year relative to Enoxaparin.

1.3 Aim of the study

Fondaparinux (Arixtra®) has already been launched in Norway[4] (ATC-code B01AX05), but it is not yet included in the Norwegian reimbursement system.

Since January 2002 cost-effectiveness analyses are compulsory for all new medicines in Norway. The outcome of cost-effectiveness analysis is important for negotiations between manufacturers and the authorities, concerning price and reimbursement decisions. Our study presents a Norwegian cost-effectiveness analysis of Fondaparinux versus Enoxaparin based on an international model. The analysis is based on Norwegian data, provided by *Norwegian Register of Hospital Patients*, which include over 50.000 patients who underwent orthopaedic surgery in the period from 1999 to 2001. We would like to emphasize that our study is a cost-effectiveness/benefit analysis and does not aim at discussing subjects such as improved life quality or increased productivity for patients who avoid VTE by receiving Arixtra®.

[4] June 2002.

2. The Arixtra model

It is important to study the cost and effectiveness of new prophylactic drugs in order to find their place in the treatment praxis. Therefore a model of the outcomes and costs of prophylaxis in major orthopaedic surgery has been developed and used to examine the cost-effectiveness of Fondaparinux versus Enoxaparin (Posnett, 2002).

This chapter is a summary of the Arixtra model presented in "Arixtra® Health Economic Model – A model of cost effectiveness of fondparinux versus Enoxaparin – Executive summary, 2002". The model analyses the outcomes and costs of prophylaxis in patients undergoing three major orthopaedic surgeries: total hip replacement (THR), total knee replacement (TKR) and hip-fracture repair (HFR). Patients are assumed to receive one of two prophylaxes: Fondaparinux or Enoxaparin.

2.1 Model structure

The design of the model is based in part on an earlier decision-analytic model of the outcomes, clinical management, and costs of VTE and PE that was developed by Oster and colleagues in the mid-1980's (Oster, et al., 1987). The model has been updated to reflect changes in the understanding of the natural history of VTE as well as patterns of clinical management.

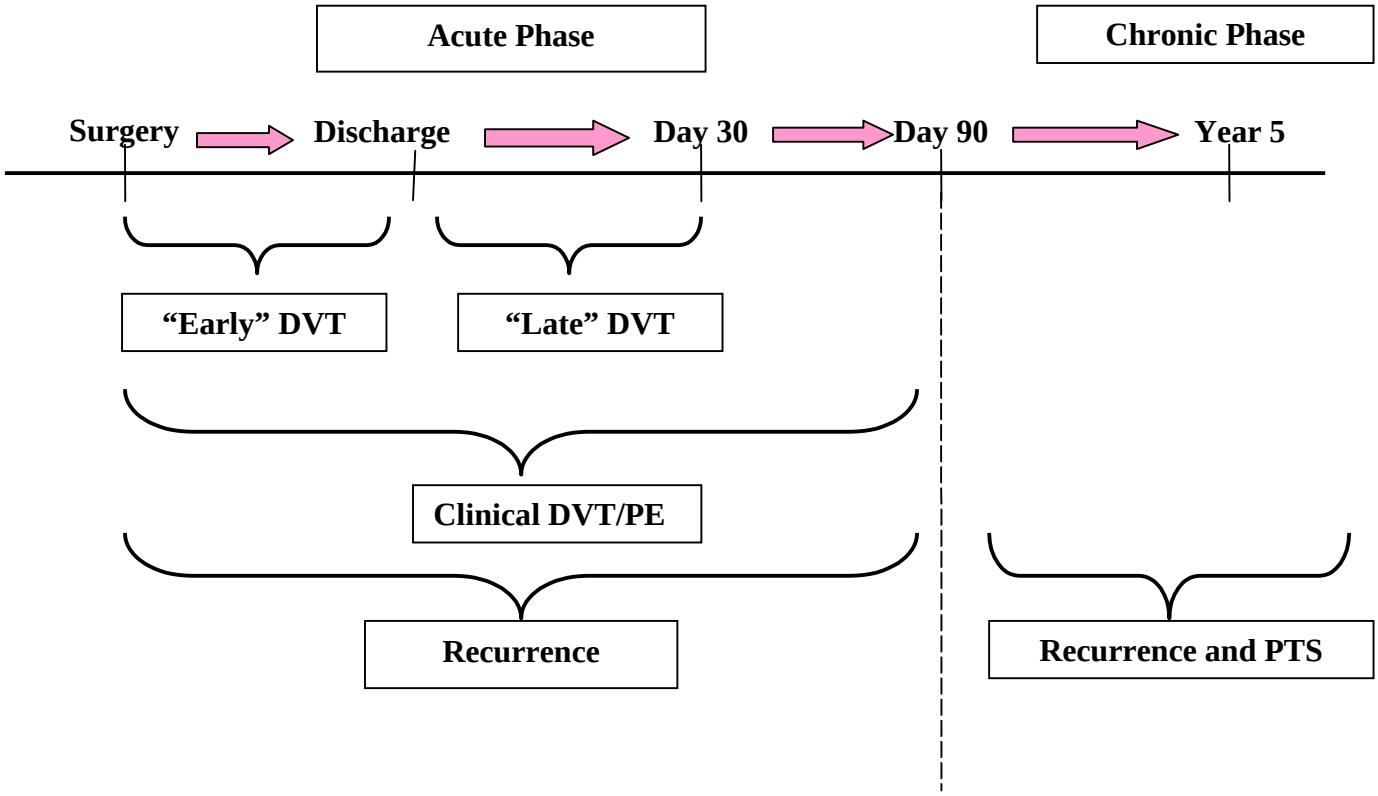
In the original model, patients were assumed to be at risk of developing VTE only during the in-hospital period. In the updated model, VTE risk is assumed to continue for a period of 90 days following surgery. Some patients are therefore assumed to develop VTE after hospital discharge. The following events are accounted for in the model: patients may or may not develop VTE while they are hospitalised, which may be clinically apparent (symptomatic) or remain silent. In line with daily clinical practice, detection of DVT is based on clinical diagnosis alone (i.e. patients would not routinely be screened). The model also accounts for those patients who are wrongly suspected clinically of having a DVT (i.e. false positive). Patients with detected (and confirmed) DVT are assumed to undergo treatment for DVT, but to remain at risk of long-term complications (recurrences or post-thrombotic syndrome (PTS)). Patients with undetected (silent, or asymptomatic), and hence untreated DVT, are also assumed to be at risk of long term complications (post-thrombotic syndrome); moreover some of them will develop PE. A similar reasoning also applies to PE, i.e, a patient may develop a

clinical PE and then is assumed to undergo treatment for PE but to remain at risk for long-term complications.

In addition, the model considers the risk of fatality, whether PE related or not, and reflects the risk of major haemorrhage during either prophylaxis or treatment of DVT or PE. Finally, the model also accounts for the fact that patients may develop DVT later, i.e. *after* they are discharged from hospital, and are then subjected to the same risks as described above.

The model discriminates between two distinct periods: an *acute phase*, which begins with surgery and ends 90 days thereafter; and a chronic phase, which begins on day 91 and ends five years after the initial surgical procedure (see figure 2.1).

Figure 2.1 Possible outcomes according to timing



In the acute phase, patients are assumed to be at risk of developing "early" DVT during the period of initial hospitalisation, and "late" DVT between hospital discharge and day 30. Patients with early or late DVT are assumed possibly to present with clinical DVT or PE any time thereafter prior to day 90. During the chronic phase, patients are assumed to be at risk of

selected long-term complications based on outcomes during the acute phase (i.e, risk of recurrent VTE and/or PTS).

2.2 Estimation of model probabilities

Analyses are conducted separately for hypothetical cohorts of 10.000 THR, TKR, and HFR patients receiving prophylaxis alternatively with Fondaparinux or Enoxaparin. The model timeframe is five years, but results after different follow-up times could be estimated.

2.2.1 Risk of DVT: Enoxaparin vs. Fondaparinux

Patients are assumed to be at risk of developing thrombi during two periods: prior to hospital discharge (early DVT), and between hospital discharge and day 30 following surgery (late DVT).

Enoxaparin

The risk of early DVT for a patient receiving Enoxaparin was estimated using data on the rate of *venographic* DVT from the four Fondaparinux Phase III trials, as follows: 9,04%, 27,15%, and 18,78% for THR, TKR, and HFR respectively (Bauer et al., 2001; Eriksson et al., 2001; Lassen, 2002).

The risk of late DVT with Enoxaparin (19,3%) was estimated using data from a randomized trial of post-discharge prophylaxis with enoxaparin among 179 THR patients who had negative findings on venography at hospital discharge (Planes, 1996).

Fondaparinux

The risk of early DVT for a patient receiving Fondaparinux was estimated by applying relative risk to the probabilities for Enoxaparin: Compared with Enoxaparin, Fondaparinux was assumed to reduce the risk of early DVT in the model by 54%, based on the global relative risk reduction across all four of the Fondaparinux Phase III clinical trials, see chapter 1.

The risk of late DVT for patients receiving Fondaparinux is assumed to be identical to that of Enoxaparin.

2.2.2 Risk of prophylaxis-related major hemorrhage: Enoxaparin vs. Fondaparinux

Prophylaxis-related hemorrhage was assumed to occur only during the inpatient period, as data from the Phase III trials suggest that 80% of these events occurred during the first four days of hospitalization.

The risk of major hemorrhage (2,6%) for patients receiving Enoxaparin, was based on pooled data from the Fondaparinux Phase III trials where a dose of 40 mg Enoxaparin was given 12 hours preoperatively. The risk of major hemorrhage with Fondaparinux was assumed to be 2,8% for Fondaparinux based on observed rates from clinical trials in patients treated as per labeling recommendations (source: European labeling).

Detailed comments on risk estimations of DVT, treatment-related major hemorrhage and other post-operative events in the model are presented in appendix 1.

2.3 Estimation of resource use and costs

Estimates of VTE-related resource use and associated costs in the model are country dependant parameters and include estimates for:

- Prophylaxis: including cost of drug, administration and monitoring.
- Confirmation and Treatment of clinical VTE: because clinical VTE can occur during hospitalization as well as after hospital discharge, confirmation and treatment are estimated separately for VTE occurring in each of these settings.
- Suspected but unconfirmed DVT and PE: costs of tests and physician visits.
- Major Hemorrhage.
- Post thrombotic syndrome (PTS).

2.4 Measures and sensitivity analysis

Model results are calculated for multiple time periods including surgery to hospital discharge, hospital discharge to day 30, day 31 to day 90, day 91 to year 1, and year 2 to year 5.

The model allows conducting analysis separately for patients undergoing each type of procedure (THR, TKR, and HFR), as well as for the combined population of major

orthopaedic surgery patients, in which results are weighted by the distribution of THR, TKR, and HFR admissions.

In addition to base case analyses, a variety of sensitivity analyses will also be conducted to explore the robustness of the findings with respect to changes in selected model parameters, e.g. relative risk of early and late DVT applied to Fondaparinux versus Enoxaparin, risks of PTS and recurrence costs of VTE (DVT/PE) and so on.

3. Estimation of resource use and unit costs

3.1 Analysis of data from national inpatient care statistics

3.1.1 Selection of units (stays in hospital)

Units were selected from the complete files of the Norwegian National Register of Hospital Patients (NPR). In these files each record represents a single completed stay in hospital for a single patient. We will refer to these analysis units both as stays and as patients.

A total of 54.988 patients undergoing THR, TKR or HFR in the years 1999, 2000 and 2001 were identified by operation codes: NFBxx for total hip replacement, NGBxx for total knee replacement or NFJxx for hip fracture repair (Table 3.1). Due to changes in both operation codes and ICD-standards from 1999, patients in previous years were not included. (From January 1. 1999, ICD-10 replaced ICD-9 in Norwegian registers. Simultaneously the Norwegian version of the NOMESCO Nordic Classification of Surgical Procedures was implemented).

Of the total number of identified patients, 50.640 had one of the relevant operation codes registered as their first procedure (operation code1). The other 4.348 patients underwent different treatments before THR, TKR or HFR were performed.

In addition to patients with relevant operation code 1, we selected a subset of patients with relevant operation code 2. These 1.568 patients had removal of hip or knee implants (NFUxx) registered as operation code 1, and constituted 46,7% of all patients with a relevant operation code 2. The next largest category with relevant operation code 2 (13,5%) was patients who had EKG performed before THR, TKR or HFR. These and other patients with relevant operation code 2, (in total 2.658) were not selected for the analyses (Table 3.1). This choice is in accordance with the clinical studies of treatments with Fondaparinux (Bauer et al., 2001; Eriksson et al., 2001). The purpose is to exclude patients with multiple traumas affecting more than one organ system. However, our approach is crude compared to the detailed criteria applied and documented in the clinical studies.

As in the clinical studies, 756 patients under 18 years, and 8 patients registered as “out-patients” were also excluded from further analysis. In all, 11 patients with DVT, PE or bleeding as main diagnoses were also excluded.

As a result of these reductions, the net number of patients has been reduced to 51.555. Therefore, the mix of procedures in the sample was 40,1% THR, 10,7% TKR and 49,2% HFR (Table 3.2).

The average ages of patients in the sample were 71,62 years for THR, 69,73 years for TKR and 78,78 years for HFR[5]. The fractions of female patients in the sample were 72% for THR, 70% for TKR and 71% for HFR.

Table 3.1 Selection of units (stays in hospital) for analysis

	1999	**2000**	**2001**	**Total**
Total THR, TKR or HFR	17451	18144	19393	54988
- Operation code 2 or higher (and operation code 1 not equal NFUxx)	-927	-924	-807	-2658
- Age less than 18 years	-234	-255	-267	-756
- DVT, PE or bleeding as main diagnosis	-8	-1	-2	-11
- Outpatients	-4	-1	-3	-8
Net selected patients	16278	16963	18314	51555

Table 3.2 Distribution of units (stays in hospital) for analysis, by Operation code 1 (or Op.code 2 for patients with NFU (<u>Removal</u> of hip or knee implants) as Op.code 1)

	1999	**2000**	**2001**	**Total**
THR (operation code NFBxx) for: Total hip replacement	6352 39,0%	6800 40,1%	7545 41,2%	20697 40,1%
TKR (operation code NGBxx)for Total knee replacement	1504 9,2%	1844 10,9%	2160 11,8%	5508 10,7%
HFR (operation code NFJxx) for: Hip fracture repair.	8422 51,8%	8319 49,0%	8609 47,0%	25350 49,2%
Total	16286 100,0%	16964 100,0%	18316 100,0%	51555 100,0%

[5] In the <u>total</u> population of 54.988, the average ages of patients were 71,59 years for THR, 69,58 years for TKR and 76,53 years for HFR.

In the sample we found that 511 patients had a secondary diagnosis of PE, DVT or Bleeding in hospital. PE was indicated by ICD-code I26, DVT by ICD-code I80, Bleeding-1 by ICD-codes T81.0, I60, I61, I62, RO4, R58, K62.5 or K92.2. Bleeding-1 is in terms of the Arixtra-model: *prophylaxis related* and given a fairly wide definition. An alternative indicator, narrower in scope, Bleeding-2 may be only ICD-codes K62.5 or K92.2, related with gastrointestinal bleeding. This indicator would be more *treatment related* (related to anticoagulation treatment of DVT or PE).

For patients with more than one of the above secondary diagnoses, we chose the most serious, that is PE over DVT, and DVT over Bleeding. Table 3.3 shows that PE is least frequent (24,7%), while 29,7% suffer from DVT and Bleeding-1 occurs among 45,6% of the patients with these selected secondary diagnoses.

Table 3.3 Secondary diagnosis of PE, DVT or bleeding in hospital per year.

	1999	**2000**	**2001**	**Total**
PE, Pulmonary embolism	44 26,7%	36 24,8%	46 22,9%	126 24,7%
DVT, Deep-vein thrombosis	50 30,3%	47 32,4%	55 27,4%	152 29,7%
Bleeding-1	71 43,0%	62 42,8%	100 49,8%	233 45,6%
Total	165 100,0%	145 100,0%	201 100,0%	511 100,0%

Table 3.4 Secondary diagnosis of PE, DVT or bleeding in hospital per operation

	THR (NFB)	**HFR (NFJ)**	**TKR (NGB)**	**Total**
PE, Pulmonary embolism	51 24,2 %	62 25,8%	13 21,7%	126 24,7%
DVT, Deep-vein thrombosis	73 34,6%	42 17,5%	37 61,7%	152 29,7%
Bleeding-1	87 41,2%	136 56,7%	10 16,7%	233 45,6%
Total	211 100,0%	240 100,0%	60 100,0%	511 100,0%

Table 3.4 indicates that a secondary diagnosis of DVT is the most common complication after TKR, while Bleeding-1 is relatively more frequent after THR or HFR.

In Table 3.5, it is apparent that the secondary diagnoses (under current medical conditions) are only present in hospital during 1% of the stays in the sample.

Table 3.5 Secondary diagnosis of PE, DVT or bleeding in hospital as fractions of total performed operations

	THR (NFB)	**HFR (NFJ)**	**TKR (NGB)**	**Total**
No relevant secondary diagnosis	20486 99,0%	25110 99,1%	5448 98,9%	51044 99,0%
PE, Pulmonary embolism	51 0,2%	62 0,2%	13 0,2%	126 0,2%
DVT, Deep-vein thrombosis	73 0,4%	42 0,2%	37 0,7%	152 0,3%
Bleeding-1	87 0,4%	136 0,5%	10 0,2%	233 0,5%
Total	20697 100,0%	25360 100,0%	5508 100,0%	51555 100,0%

Patients **readmitted** after major surgery (THR, TKR or HFR) with a main diagnosis of either PE, DVT or bleeding were identified from the complete patient files. For modelling purposes only patients readmitted within 90 days after surgery are of interest. In the Norwegian files of hospital stays, patients are not identifiable across years. In terms of event history analysis (Blossfeld and Rohwer, 1995), this implies a *right censoring* of the patient distributions: We were forced to exclude surgeries performed after October 2 in each year, because we could not identify all relevant cases of readmitted patients following these surgeries[6].

In Table 3.6 the right censoring of patient distributions must be considered. The frequencies of readmitted patients should be related to surgeries performed in the first (365-90) days of each year, or about 76% of the 51.555 surgeries listed in Table 3.2.

[6] This argument applies as far as frequencies of readmitted patients are concerned, but may not be relevant when mean LOS for readmitted patients are in question.

Table 3.6 Number of patients readmitted to hospital within 90 days with diagnosis of PE, DVT or bleeding by performed operation. (For first 365-90 days in each year).

	THR (NFB)	**HFR (NFJ)**	**TKR (NGB)**	**Total**
PE, Pulmonary embolism	35 31,8%	50 22,6%	6 30,0%	91 25,9%
DVT, Deep-vein thrombosis	53 48,2%	86 38,9%	7 35,0%	146 41,6%
Bleeding-1	22 20,0%	85 38,5%	7 35,0%	114 32,5%
Total	110 100,0%	221 100,0%	20 100,0%	351 100,0%

In table 3.7 the relative frequency of patients readmitted within 90 days after discharge from hospital is listed by performed surgery.

Table 3.7 Fraction of patients readmitted to hospital within 90 days with diagnosis of PE, DVT or bleeding by performed operation. (For first 365-90 days in each year).

	THR (NFB)	**HFR (NFJ)**	**TKR (NGB)**	**Total**
PE, Pulmonary embolism	0,23%	0,25%	0,15%	0,23%
DVT, Deep-vein thrombosis	0,34%	0,43%	0,17%	0,37%
Bleeding-1	0,14%	0,43%	0,17%	0,29%
Total	0,71%	1,11%	0,50%	0,89%

3.1.2 Length of stay

The design of the analysis was based on the LOS-study reported in the Swedish analysis of the Arixtra Model (Lundkvist, Jönsson and Jönsson, 2002). As in the Swedish analysis a log-linear regression model was constructed to predict the effect on length of stay in hospital. A log-linear model, also in the analysis of Norwegian data, had favourable normality of residuals compared to a completely linear model.

The presence of PE, DVT or bleeding was represented as explanatory dummy variables in the model. The model also included age (continuous, years - 18) and sex (dummy, male =1) of the patients as explanatory variables.

Table 3.8 shows the average LOS in hospital, by procedure. First, for patients without incidence of PE, DVT or bleeding, second for patients with these complications. LOS is presented as both a regular arithmetic mean and as a trimmed mean, the arithmetic mean calculated when the largest 5% and the smallest 5% of the cases have been eliminated. Eliminating extreme cases from the computation of the mean results in a better estimate of central tendency, especially when the data are non-normal.

Table 3.8 Average length of stay by procedure and in case of PE, DVT and bleeding

Average LOS (standard deviation)	**Total knee replacement**	**Total hip replacement**	**Hip fracture repair**
With no secondary diagnosis	12,44 (6,366)	12,54 (7,828)	10,74 (11,035)
PE	20,08 (20,65)	16,51 (9,758)	16,39 (13,009)
DVT	18,35 (11,121)	18,34 (11,957)	20,17 (17,691)
Bleeding-1	13,60 (5,602)	25,18 (19,460)	17,32 (14,183)
Total	12,50 (6,500)	12,62 (7,987)	10,81 (11,03)
5% trimmed mean of LOS			
With no secondary diagnosis	11,92	11,68	9,35
PE	17,36	15,99	15,20
DVT	17,06	16,76	18,25
Bleeding-1	13,72	23,13	16,00
Total	11,95	11,73	9,40

The average length of stay for HFR patients (10,8 days) is short compared to the LOS of the other procedures, TKR (12,5) or THR (12,6). In Sweden average LOS for HFR patients is reported as 14,6 days, which is considerably longer than Swedish LOS for TKR (9,3) or THR (9,8). The increasing use of 'patient hotels', in which patients may stay in transition from hospital treatment to own home, has been suggested as an explanation of shorter LOS after HFR in Norway. Although this service probably is relevant for HFR patients, the Norwegian data set does not include indicators of patient hotel use, and concerning time of discharge the status of patient staying in hotels in 1999 – 2001 may vary between hospitals. One of the largest Norwegian hospitals has offered patient hotel services since 1998. In the data set this hospital shows an average LOS for HFR of 17,8 days, which does not indicate use of 'patient hotels' as an explanation of shorter LOS.

What certainly separates HFR from the other procedures is a higher rate of patient mortality in hospital. As many as 819 (3,2%) of Norwegian HFR patients died in hospital in 1999 – 2001. For TKR the mortality rate was only 0,1% and for THR 0,9%. With secondary diagnosis of PE, the mortality rate after HFR was as high as 29%. This figure not only suggests the potential for improvements in PE treatment. It also implies estimation problems as far as LOS is concerned[7]. When the mortality rate is this high, a secondary diagnosis of PE may lead to shorter as well as longer LOS.

Table 3.9 shows results from the regression on Ln of LOS for the total sample of 51 555 patients. Table 3.10, 3.11 and 3.12 present separately the results from the regression on Ln of LOS for patients undergoing surgery of THR, TKR or HFR, performed on separate samples.

In the total sample, all explanatory variables were found highly significant. In the smallest sample (of TKR patients), the effects of bleeding on LOS are not significant. Surprisingly age (defined as age of patient – 18), is negative in the regression against the total sample (in table 3.8). This may be due to distortion from the distribution of patient age within the hip fracture repair sample, as against LOS for HFR, age (years - 18) is negative but not significant.

Table 3.9 Results from regression model (total sample)

Ln of length of stay	**Number of observations**	**Coefficient**	**Standard error**	**P>:t: Sig.**	**95% Confid. interval**
Age (years - 18)	51555	-,004	,000	,000	-,004 to -,003
Sex	51555	-,063	,007	,000	-,077 to -,048
PE in hospital	126	,365	,067	,000	,235 to ,496
DVT in hospital	152	,500	,061	,000	,381 to ,620
Bleeding-1 in hospital	233	,505	,049	,000	,409 to ,601
Constant		2,439	,016	,000	2,708 to 2,470

[7] This could also be considered as a case of *right censoring* of the patient distribution (section 3.1.1).

Table 3.10 Results from regression model: Total knee replacement (TKR)

Ln of length of stay	**Number of observations**	**Coefficient**	**Standard error**	**P>:t: Sig.**	**95% Confid. interval**
Age (years - 18)	5508	,007	,001	,000	,006 to ,008
Sex	5508	-,071	,015	,000	-,100 to -,043
PE in hospital	13	,279	,136	,040	,013 to ,546
DVT in hospital	37	,375	,081	,000	,217 to ,534
Bleeding-1 in hospital*)	10	,055	,155	,724	-,249 to ,358
Constant		2,069	,036	,000	1,999 to 2,139

Table 3.11 Results from regression model: Total hip replacement (THR)

Ln of length of stay	**Number of observations**	**Coefficient**	**Standard error**	**P>:t: Sig.**	**95% Confid. interval**
Age (years - 18)	20697	,002	,000	,000	,002 to ,003
Sex	20697	-,017	,008	,029	-,032 to -,002
PE in hospital	51	,156	,069	,024	,020 to ,292
DVT in hospital	73	,357	,058	,000	,243 to ,470
Bleeding-1 in hospital	87	,565	,053	,000	,461 to ,669
Constant		2,284	,017	,000	2,251 to 2,318

Table 3.12 Results from regression model: Hip fracture repair (HFR)

Ln of length of stay	**Number of observations**	**Coefficient**	**Standard error**	**P>:t: Sig.**	**95% Confid. interval**
Age (years - 18)*)	25350	-,000	,000	,898	-,001 to ,001
Sex	25350	-,042	,013	,001	-,067 to -,017
PE in hospital	62	,524	,114	,000	,301 to ,748
DVT in hospital	42	,553	,138	,000	,282 to ,824
Bleeding-1 in hospital	136	,525	,077	,000	,374 to ,676
Constant		2,006	,029	,000	1,949 to 2,063

3.1.3 Additional days

Because the model is log-linear the coefficients must be converted to show the effect of specific variables on additional days in hospital. Conversion was performed by multiplying the coefficients of secondary diagnoses with the sample's mean value of LOS.

Table 3.13 Additional days in hospital after PE, DVT and bleeding.

Additional days from log-lin regression	**Total knee replacement**	**Total hip replacement**	**Hip fracture repair**
PE	3,49	1,97	5,66
DVT	4,69	4,51	5,98
Bleeding-1	1,16	7,13	5,68

The results presented in Table 3.13, may be compared to the mean and trimmed mean of LOS for patients, in Table 3.8. Estimated LOS for PE after THR (1,97 days) is exceptionally low[8], but also estimated LOS for PE after TKR seems low. Bleeding-1 after TKR (only 1,16 days) is based on the value of the mean differences, as the regression coefficient was not significant. On the whole, the estimated values are lower than the differences between calculated means.

3.1.4 Readmitted patients

The length of stays for patients readmitted after major surgery (THR, TKR or HFR) with a main diagnosis of either PE, DVT or bleeding were analysed separately. In the previous section the problem of right censoring by year for patient distributions is explained. In Table 3.14 mean LOS by diagnoses for readmitted patients are presented.

Table 3.14 Mean LOS for patients readmitted to hospital within 90 days with diagnosis of PE, DVT or bleeding by performed operation

	THR (NFB)	**HFR (NFJ)**	**TKR (NGB)**	**Total mean**
PE, Pulmonary embolism	11,17	9,60	7,17	10,04
DVT, Deep-vein thrombosis	5,25	5,77	5,86	5,58
Bleeding-1	7,91	5,54	8,57	6,18
Total	7,66	6,55	7,20	6,93

[8] The mortality rate in this group of patients is 19%, which is high but still 10% lower than for PE after HFR.

As in the Swedish study we chose not to perform estimation of LOS for readmitted patients by regression analysis. The smaller number of observations (see Table 3.6) makes regression on LOS of readmitted patients less reliable.

3.2 Costs of procedures and treatments

3.2.1 Identifying DRG-groups

Cost estimates for inpatients were based on current prices within the Norwegian DRG-system, where patients are classified in one DRG-group only, per stay in hospital. A DRG-group may be a diagnosis or a procedure. In the DRG system mean costs for stays has been calculated for every group, and are used as a key in hospital founding/financing from central government.

The method for DRG cost calculations in Norway is ***top-down*****:** The total operational costs of hospitals are decomposed into cost units, and cost units are attributed to specific DRGs by applying keys that reflect historical use of resources and length of stay within each DRG (Ministry of Health, 2001). The Norwegian top-down approach is in contrast to the ***bottom-up*** method used in other countries, like Sweden and Finland. In the bottom-up system, all actual use of resources is registered on the single hospital patient level. Cost information on this level is currently not collected in Norway. The Norwegian guidelines for pharmacoeconomic analysis for drug reimbursement applications recommend official DRG-price as cost input to analysis of hospital stays (Norwegian Medicine Agency, 2002).

The relevant DRG-categories for procedures were identified by listing occurrences of actually applied categories by patients undergoing surgery of THR, TKR or HFR, in the total sample. (Table 3.15). For THR and TKR, almost all occurrences are within the DRG-category 209. For HFR, the pair of DRG-categories 210/211 covers nearly 95% of all stays.

Table 3.15 Identifying DRG-categories by surgery procedure.

Main Norwegian DRG-categories applied (Labels in English from US 2001-DRG)	**2002-cost (NOK)**	**THR**	**TKR**	**HFR**
209 Major joint & limb reattachm. proc. of lower extremity	106529	99,2%	97,3%	1,3%
210 Hip & femur procedures ex. major joint age >17 with complications	69450	-	-	38,9%
211 Hip & femur procedures ex. major joint age >17 without complications	45613	-	-	55,5%
236 Fractures of hip & pelvis	27662	-	-	1,2%
245 Bone diseases & specific arthropathies without complications	16185	-	2,1%	-
Other DRG-categories (< 1% frequency)		0,8%	0,6%	3,1%
Total		100% (20697)	100% (5508)	100% (25350)

In Table 3.16 we have identified the relevant DRG-categories for PE, DVT and Bleeding-1 by listing occurrences of actually applied categories by patients with either of these diagnoses as main diagnosis in the total file of Norwegian hospital stays 1999 – 2001. The total file of hospital stays was used because in the sample file PE, DVT and Bleeding-1 are only present as secondary diagnoses. (In the sample file it is the procedures THR, TKR or HFR that are associated with the main diagnosis of the stay).

While the diagnoses of PE and DVT are fairly concentrated within a small number of DRG-categories, Bleeding-1 is harder to classify. This is a consequence of Bleeding-1 being a less homogenous group, encompassing a larger number of diagnoses and ICD-10 codes.

Table 3.16 Identifying DRG-categories by "secondary diagnosis"

Main Norwegian DRG-categories applied (Labels in English from US 2001-DRG)	**2002-cost (NOK)**	**PE**	**DVT**	**Bleeding-1**
1 Craniotomy age >17 except for trauma	94170	-	-	5,5%
14 Specific cerebrovascular disorders except tia	37374	-	-	40,0%
66 Epistaxis	12654	-	-	11,2%
78 Pulmonary embolism	44731	88,9%	-	-
99 Respiratory signs & symptoms w cc	21188	-	-	1,4%
100 Respiratory signs & symptoms w/o cc	9711	-	-	2,1%
128 Deep vein thrombophlebitis	26485	-	86,0%	-
130 Peripheral vascular disorders w cc	31488	-	2,8%	-
131 Peripheral vascular disorders w/o cc	18834	-	10,2%	-
144 Other circulatory system diagnoses w cc	34431	4,6%	-	-
145 Other circulatory system diagnoses w/o cc	21188	3,8%	-	-
174 G.i. hemorrhage w cc	30605	-	-	8,4%
175 G.i. hemorrhage w/o cc	18245	-	-	13,6%
442 Other o.r. procedures for injuries w cc	82693	-	-	2,0%
452 Complications of treatment w cc	27368	-	-	3,8%
453 Complications of treatment w/o cc	12654	-	-	7,7%
Other DRG-categories (< 1% frequency)		2,7%	1,0%	4,3%
Total		100% 5394	100% 8050	100% 20466

3.2.2 Assigning cost to procedures and treatments

Table 3.15 and 3.16 above are the basis for assigning cost-figures to operational procedures and diagnoses. Therefore, we have a choice of (at least) two approaches:

1. Select one DRG-category per procedure or diagnosis as "the correct" or "most representative". This approach implies that other, less frequent DRG-categories actually applied for this procedure or diagnosis, have been applied mistakenly. Therefore, the cost of "the correct" DRG-group is selected.

2. Compose a weighted cost-figure, based on the costs and occurrences of all the listed DRG-groups per procedure or diagnosis. The cost associated with each DRG-group is in this approach weighted by its frequency of occurrence (the percent figures in Tables 3.15 and 3.16). This method is better suited to capture the spread across DRG-groups within the set of diagnoses labelled “Bleeding-1” (*prophylaxis* related).

In the Swedish Arixtra-study, cost of Bleeding-2 caused by *treatment* of DVT or PE was based on the Swedish DRG nr 175, “bleeding in gastrointestinal tract” which was considered the DRG closest to “general major hemorrhage”. The cost of bleeding in gastrointestinal tract was also believed to be a relevant estimation of the cost of general major hemorrhage since it has been seen that gastrointestinal bleeding is the most common type of bleeding among patients with anticoagulation treatment.

In the Norwegian case we find a very heterogeneous set of ICD-10 codes, and resulting DRGs for Bleeding-1 *(prophylaxis* related) in Table 3.16, not suited as basis for cost indication. Based on medical advice we chose Norwegian DRGs nr 174 and 175, as better indicators of both Bleeding-1 and Bleeding-2 (treatment related).

3.2.3 Conclusion

For the purpose of this study, we have chosen to apply a combination of the two approaches above when assigning cost-figures to operational procedures and diagnoses. The assignments thus are based on the most frequent DRG applied, except when the most frequent is part of a DRG-pair. In the Norwegian system of DRGs the only difference between code 210 and 211 is that 210 is used for patients with complications/multiple diagnosis. Also DRGs 174 and 175 are parts of a pair, with DRG 174 as the DRG for patients suffering complications.

1. The cost of DRG 209 is chosen for THR og TKR
2. The weigthed mean from costs of DRG-pair 210 and 211 is chosen for HFR
3. The cost of DRG 78 is chosen for PE
4. The cost of DRG 128 is chosen for DVT
5. The weigthed mean from costs of DRG-pair 174 and 175 is chosen for Bleeding (both prophylaxis related and treatment related).

Table 3.17 Costs of treatment in hospital. DRG assigned to operations and secondary diagnosis.

	DRG	**2002-cost (NOK)**	**Mean LOS**	**Cost per mean day**
Total hip replacement	209 (100%)	106 529	13,15	8101
Total knee replacement	209 (100%)	106 529	13,15	8101
Hip fracture repair.	210 (41,2%) and 211 (58,8%)	55 434	10,94	5067
PE	78 (100%)	44 731	9,18	4873
DVT	128 (100%)	26 485	5,44	4869
Bleeding Prophylaxis & Treatment	174 (38,2%) and 175 (61,8%)	22 967	4,93	4659

3.3 Prophylaxis and costs of drugs

3.3.1 Prophylaxis

The most common prophylaxis for prevention of VTE after orthopaedic surgeries (TKR, THR and HFR) in Norway is Dalteparin (Fragmin®). Prophylaxis with Enoxaparin (Klexane®) counts for around 20% (personal communication).

Both prophylaxes start 12 hours preoperatively with a daily dose of 5000 IU Dalteparin or 40 mg (0,4 ml) Enoxaparin. In acute cases, usually HFR surgery, patients receive a half dose of Dalteparin or Enoxaprin right before the surgery. The duration of both prophylaxes during the hospitalization time is 7 days. In some cases, where the probability of thromboembolism is considered to be very high, patients receive a dose of 500-1000 ml Dextran (Macrodex®) on the operation day.

3.3.2 Costs of drugs

In our model, we assume prophylaxis with Enoxaparin and Fondaparinux starting preoperatively. Consistent with Norwegian practice, we assume a daily dose of 40 mg Enoxaparin for 7 days. The costs of both drugs are based on wholesale prices in Norway[9]. The cost of one dose of 40 mg Enoxaparin was estimated to 41,99 NOK. The total cost of 7 days of Enoxaparin treatment was estimated to 293,93 NOK. The cost of 2,5 mg (0,5 ml pre-filled syringe; 5 mg/ml) Fondaparinux was estimated to 111,8 NOK, and 782,60 NOK for 7 days treatment.

3.4 Length of stay

The lengths of stays for the three procedures were calculated from the sample taken from the Norwegian national register of hospital patients. The data in Table 3.8 shows that patients (ages 18 and up) with THR on average stayed 12,6 days in hospital, patients with TKR stayed 12,5 days and patients with HFR stayed 10,8 days.

3.5 Confirmation and treatment of VTE

Clinical VTE (DVT/PE) after orthopaedic surgery can occur prior to or after hospital discharge. In the model, we estimate the costs of confirmation and treatment separately for DVT and PE occurring before (inpatient) and after hospital discharge (outpatient). We assume that patients developing VTE during the initial hospitalisation time have to spend additional days in hospital. Patients who develop VTE after hospital discharge are assumed to readmit to the hospital for treatment.

Patients who develop VTE are assumed to require: one physician visit for assessment of DVT or PE, drug treatment, and 10 INR tests (PT tests are not very common in Norway)[10]. The following costs were estimated for use in the model; one extra day at hospital, 3556 NOK; physician visit, 1191 NOK; and INR test, 22 NOK. The cost of one extra day at hospital was estimated based on the average net cost per hospitalisation day for DVT and PE, i.e., exclusive of physician, drug and test costs. The costs of all other procedures, diagnostic

[9] Based on the price list for 2002, by the Norwegian Medicine Agency.
[10] Personal communication with physician.

investigations and tests mentioned in this chapter and chapter 3.6 and 3.7, were obtained from the price list for cost per outpatient clinic consultation and procedure by the Ministry of Health (2002), and information provided from The National Insurance Services[11]. Some diagnostic tests were not specified in the price list. These costs were provided by personal communication with one of the hospitals in Norway[12]. The costs mentioned above are used in calculations in chapter 4.

All estimates of resource use and unit cost for confirmation and treatment of DVT and PE are presented in Table 3.18 and 3.19.

3.5.1 Confirm/Treat DVT in hospital

The additional length of stay for patients undergoing TKR, THR or HFR and also having a secondary diagnosis of DVT (ICD-10 code I80) was calculated from the regression model (summarized in Table 3.13). The extra length of stay was estimated to 4,69 days after TKR, 4,51 after THR and 5,98 days after HFR.

According to the Norwegian practice, DVT is treated with either Dalteparin og Enoxaparin for 5 days, supplemented by Warfarin for 90 days (Personal communication). We assumed treatment with Enoxaparin, which requires 1 mg per kg (depending on patient's weight) times 2. Therefore, a daily dose for a patient with a weight of 75 kg is 150 mg Enoxaparin for 5 days, followed by Warfarin for 3 months. The Warfarin dose depends on individual test results and varies between different patients. We consider a dose of 7,5 mg Warfarin to be the normal dose (2,5 mg three times a day).

The cost of 150 mg Enoxaparin was estimated to 117,60 NOK per day, amounting to 588 NOK for 5 days. The cost of 7,5 mg of Warfarin was estimated to 2,36 NOK per day, and 212,40 NOK for 90 days. As mentioned earlier, we assume that patients required one physician visit and 10 INR-test during the treatment period.

[11] The price list indicates reimbursement rates paid by The National Insurance Services. These rates cover 50% of the total costs. The Regional Health Authorities cover the rest. The relevant rates listed in the price list are therefore multiplied by two. Note: Physician consultations only qualify for reimbursements from The National Insurance Services.
[12] Rikshospitalet in Oslo.

The additional hospital days for patients suffering from DVT after TKR, THR and HFR was 4,69, 4,51 and 5,98 days respectively. The total cost of confirmition and treatment of DVT in hospital was estimated to 18.880 NOK for TKR, 18.232 NOK for THR and 23.469 for HFR.

3.5.2 Confirm/Treat DVT after discharge (readmitted patients)

The total incidence of DVT after discharge in our sample was about 0,4%, while the estimated incidence of DVT after discharge in the model was about 2,5%. Some of this difference may be due to missing diagnoses and some that patients having a DVT after discharge are treated as outpatients. No information of the distribution of outpatients and in-hospital patients was available.

The average length of stay for patients readmitted with a diagnosis of DVT (ICD-10 code I80) within 90 days after discharge was calculated to 5,86 days after TKR, 5,25 after THR and 5,77 days after HFR (Table 3.14). The total cost of confirmation and treatment of DVT for these patients was estimated to 23.050 NOK for TKR, 20.880 NOK for THR and 22.730 for HFR.

3.5.3 Confirm/Treat PE in hospital

The additional length of stay for patients undergoing TKR, THR or HFR and also having a secondary diagnosis of PE (ICD-10 code I26) was calculated from the regression model (summarized in Table 3.13). The extra length of stay was estimated to 3,49 days after TKR, 1,97 days after THR and 5,66 days after HFR.

According to the Norwegian practice, PE is treated with either Dalteparin og Enoxaparin, followed by Warfarin. We assume treatment with Enoxaparin with a daily dose of 150 mg Enoxaparin (for a person with a weight of 75 kg) for 5 days, and 7,5 mg Warfarin for 6 months.

The cost of 150 mg Enoxaparin is estimated to 117,60 NOK, and 588 NOK for 5 days. The cost of 7,5 mg of Warfarin is estimated to 2,36 NOK, and 424,80 NOK for 180 days. In addition, we assume one physician visit and 10 INR tests during the treatment period. The total cost of confirmition and treatment of PE in hospital is estimated to 14.825 NOK for TKR, 9.425 NOK for THR and 22.567 for HFR.

3.5.4 Confirm/Treat PE after discharge (readmitted patients)

The total incidence of PE after discharge in our sample was about 0,25 %, while the expected incidence of PE after discharge is about 0,9%.

The average length of stay for patients readmitted with a diagnosis of PE (ICD-10 code I26) within 90 days after discharge was calculated to 7,17 days after TKR, 11,17 days after THR and 9,60 days after HFR (Table 3.14). The total cost of confirmation and treatment of PE after hospital discharge was estimated to 27.920 NOK, 42.144 NOK and 36.562 NOK for TKR, THR and HFR respectively.

3.6 Suspected but unconfirmed DVT and PE

3.6.1 Suspected but unconfirmed DVT

In this case, we assume that patients receive ultrasound or venography investigation, in addition to one physician visit. The average cost of these procedures is estimated to 1.627 NOK. The total cost of suspected but unconfirmed DVT is therefore estimated to 2.818 NOK, see table 3.18 and 3.19.

3.6.2 Suspected but unconfirmed PE

There are several diagnostic methods for investigation of PE such as spiral-CT (Computed tomography), DSA (Digital Subtraction Angiography), and so on. We assume one physician visit and one spiral-CT which is the most common method for confirming PE. The cost of spiral-CT is 872 NOK. The total cost of suspected but unconfirmed PE is estimated to 2063 NOK.

3.7 Major hemorrhage

3.7.1 Bleeding 1 – prophylaxis related

Cost of bleeding caused by prophylaxis was based on a weighted average of DRG nr 174 and DRG 175, i.e, “Bleeding in gastrointestinal tract with complications” and “Bleeding in

gastrointestinal tract without complications". These DRGs were closest to "general major hemorrhage". Gastrointestinal bleeding is the most common type of bleeding among patients receiving anticoagulation treatment (personal communication), and therefore assumed to be a relevant cost estimation of "general major hemorrhage".

The additional hospital days (in original stay) for patients suffering from bleeding (ICD-codes T81.0, I60, I61, I62, RO4, R58, K62.5 or K92.2) after THR, TKR and HFR was 1,16, 7,13 and 5,68 respectively[13]. Additional length of stay for the entire sample was calculated to 5,92 days[14]. The total cost was estimated to 21.052 NOK.

3.7.2 Bleeding 2 – treatment related

Gastrointestinal bleeding is the most common type of bleeding among patients with anticoagulation treatment and also among patients treated for DVT or PE (personal communication). Cost of bleeding caused by treatment of DVT or PE was based on a weighted average of DRG nr 174 and 175.

From the available data, files identifying and separating patients with treatment related to bleeding is not possible with any certainty. What we do is to calculate mean hospital days for readmitted patients suffering from bleeding, whether this is related to treatment of DVT/PE or not.

The average length of stay for patients readmitted with a diagnosis of bleeding within 90 days after discharge was calculated to 8,57 days after TKR, 7,91 after THR and 5,54 days after HFR[15] (Tabel 3.14). Additional length of stay for the entire sample based on readmissions for Bleeding-2 (ICD-10, K625 and K922), was 4,67 days. The additional days for Bleeding-2 are less than the case for Bleeding-1. The total cost was estimated to 16.607 NOK.

[13] The cost of treating major hemorrhage/bleeding was estimated to 4.125 NOK for TKR, 25.355 NOK for THR and 20.181 NOK for HFR.

[14] Additional LOS for the entire sample (N = 51.555) was calculated based on mean LOS = 11,72 days, coefficient = 0,505.

[15] The cost was estimated to 30.475, 28.128 and 19.700 NOK after TKR, THR and HFR respectively.

3.8 Post thrombotic syndrome

3.8.1 Post thrombotic syndrome – acute

The cost of post thrombotic syndrome (PTS) is based on a Swedish study of cost of long-term complications of DVT (Bergqvist et al., 1997). The study includes the costs of treating cellulites, chronic venous insufficiency, varicose veins and venous ulcer. This definition is compatible with the PTS risk assumptions in the Arixtra-model. The distribution of the costs between acute and chronic was also based on the international assumption that 25 % of PTS-related costs would be accrued at the time of initial diagnosis, and that the remaining costs would be distributed evenly over time. This means that the cost of acute PTS (the first quarter) was estimated to 7.860 NOK[16].

3.8.2 Post thrombotic syndrome – chronic

The cost of chronic PTS was, as mentioned above, based on an evenly distribution of 75 % of the total cost of PTS. This means that the cost per quarter was estimated to 1241 NOK.

[16] Costs were converted from Swedish kroner by using average exchange rates from January to September 2002.

Table 3.18 Resource-use estimates for the analyses, by type of procedure

	Total knee replacement	**Total hip replacement**	**Hip fracture repair**
Prophylaxis			
Enoxaparin (days)	7	7	7
Arixtra (days)	7	7	7
Confirm/Treat DVT, before discharge			
Additional hospital days*	**4,69**	**4,51**	**5,98**
Physician visits	1	1	1
Enoxaparin (days)	5	5	5
Warfarin (days)	90	90	90
INR tests	10	10	10
Confirm/Treat DVT, after discharge Inpatient (readmitted)			
Hospital days	**5,86**	**5,25**	**5,77**
Physician visits	1	1	1
Enoxaparin (days)	5	5	5
Warfarin (days)	90	90	90
INR tests	10	10	10
Confirm/Treat PE, before discharge			
Additional hospital days*	**3,49**	**1,97**	**5,66**
Physician visits	1	1	1
Enoxaparin (days)	5	5	5
Warfarin (days)	180	180	180
INR tests	10	10	10
Confirm/Treat PE, after discharge			
Hospital days	**7,17**	**11,17**	**9,60**
Physician visits	1	1	1
Enoxaparin (days)	5	5	5
Warfarin (days)	180	180	180
INR tests	10	10	10
Suspected DVT			
Physician visits	1	1	1
Ultrasound or venography	1	1	1
Suspected PE			
Physician visits	1	1	1
Spiral-DT	1	1	1
Bleeding – prophylaxis-related**			
Additional hosp. days – entire sample	**5,92**	**5,92**	**5,92**
Bleeding – treatment-related**			
Additional hosp. days – entire sample	**4,67**	**4,67**	**4,67**

* The additional hospital days are based on results from the regression analysis.

** Based on estimated additional days for the entire sample.

Table 3.19 Unit cost estimates used in analyses by type of procedure

	Total knee replacement	Total hip replacement	Hip fracture repair
	Unit costs per patient, NOK		
Prophylaxis:			
Fondaparinux (7 days)	782,60	782,60	782,60
Enoxaparin (7 days)	293,93	293,93	293,93
Confirm/Treat DVT, before discharge	18880	18232	23469
Confirm/Treat DVT, after discharge	23050	20880	22730
Confirm/Treat PE, before discharge	14825	9425	22567
Confirm/Treat PE, after discharge	27920	42144	36562
Suspected DVT	2818	2818	2818
Suspected PE	2063	2063	2063
Bleeding, prophylaxis-related*	21052	21052	21052
Bleeding, treatment-related*	16607	16607	16607
Post thrombotic syndrome - acute (per quarter)	7860	7860	7860
Post thrombotic syndrome – chronic (per quarter)	1241	1241	1241

* Based on estimated additional days for the entire sample.

4. The results

Analyses were conducted separetely for hypothetical cohorts of 10000 patients undergoing TKR, THR and HFR. The model results were calculated for multiple time periods: from surgery to hospital discharge, day 30, day 90, year 1 and year 5.

Cost outcomes

Unit costs presented in Table 3.19 were used in simulations of the Arixtra model. The results from these simulations are presented in Table 4.1 and 4.2 for TKR, THR, HFR, and for the combined population of patients after major orthopedic surgery. In the latter case, the results were weighted by the distribution of TKR, THR and HFR procedures in our sample, i.e. 40,1%, 10,7% and 49,2% respectively.

Table 4.1 Cost outcomes from the analyses: VTE-related costs per patient

		Follow-up time				
	Treatment	**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 621	1 890	2 104	2 288	2 872
	Enoxaparin	1 283	1 643	1 902	2 195	3 129
	Difference	337	247	202	93	-256
	% Difference/Enoxaparin	26 %	15 %	11 %	4 %	-8 %
THR	Arixtra	1 518	1 898	2 212	2 391	2 962
	Enoxaparin	1 065	1 599	2 003	2 226	2 936
	Difference	453	299	209	165	26
	% Difference/Enoxaparin	43 %	19 %	10 %	7 %	1 %
HFR	Arixtra	1 595	2 213	2 671	2 867	3 467
	Enoxaparin	1 246	2 119	2 697	2 966	3 787
	Difference	349	94	-26	-99	-320
	% Difference/Enoxaparin	28 %	4 %	-1 %	-3 %	-8 %
Combined	Arixtra	1 564	2 048	2 421	2 609	3 196
	Enoxaparin	1 170	1 851	2 324	2 577	3 365
	Difference	393	197	97	32	-170
	% Difference/Enoxaparin	34 %	11 %	4 %	1 %	-5 %

Table 4.1 shows that at discharge, and up to 30 days, Arixtra (Fondaparinux) is the higher cost treatment. For instance, among patients undergoing TKR, VTE-related costs per patient at

hospital discharge are estimated to 1.621 NOK for Arixtra and 1.283 for Enoxaparin, which indicates 26% higher cost for Arixtra.

The longer is the follow-up time, the smaller is the cost disadvantage of Arixtra relative to Enoxaparin. Indeed, for the 5-year follow-up scenario, Arixtra is cost saving for both TKR, HFR and the combined population, and only slightly more expensive than Enoxaparin for THR. For HFR, Arixtra is the lower-cost alternative from day 90 onward.

Clinical Outcomes

Arixtra is the more efficient drug in terms of preventing VTE-events. Table 4.2 reports the estimated difference in VTE-events between the two drugs. We have already concluded that for long follow-up time periods, Arixtra is the more cost effective drug. Therefore, when bringing in the issue of effectiveness in preventing VTE, we focus on shorter follow-up periods, up to 90 days. We see that in a cohort of 10.000 patients undergoing TKR, THR, HFR and major orthopaedic surgery (combined population), Arixtra is expected to avoid respectively 80, 33, 51 and 47 DVT-events more than Enoxaparin prior to hospital discharge. Corresponding figures for PE-events avoided, are 34, 19, 28 and 25. Also during the follow-up time (30 days and 90 days after surgery) Arixtra is expected to be more effective than Enoxaparin. For instance, at day 90 Arixtra is expected to avoid 124, 84, 132 and 113 DVT-events, and 53, 51, 84 and 67 PE-events more than Enoxaparin.

Table 4.2 Clinical outcomes: Number of clinical VTE-events per 10000 patients

			Follow-up time		
	Event	**Treatment**	**Inpatient**	**Day 0-30**	**Day 0-90**
TKR	**DVT**	Arixtra	67	114	149
		Enoxaparin	147	223	273
		Difference	-80	-109	-124
	PE	Arixtra	29	50	66
		Enoxaparin	63	96	119
		Difference	-34	-46	-53
THR	**DVT**	Arixtra	29	112	184
		Enoxaparin	62	180	271
		Difference	-33	-68	-87
	PE	Arixtra	16	40	58
		Enoxaparin	35	80	109
		Difference	-19	-40	-51
HFR	**DVT**	Arixtra	43	195	314
		Enoxaparin	94	302	446
		Difference	-51	-107	-132
	PE	Arixtra	25	69	97
		Enoxaparin	53	134	181
		Difference	-28	-65	-84
Combined	**DVT**	Arixtra	40	153	244
		Enoxaparin	87	245	357
		Difference	-47	-92	-113
	PE	Arixtra	22	55	78
		Enoxaparin	47	108	145
		Difference	-25	-53	-67

Table 4.3 Clinical outcomes: Number of VTE-related deaths per 10000 patients

		Follow-up time				
		Inpatient	**Day 0-30**	**Day 0-90**	**Year 1**	**Year 5**
TKR	Arixtra	14	16	19	18	18
	Enoxaparin	26	30	34	35	35
	Difference	-12	-14	-15	-17	-17
THR	Arixtra	4	10	14	13	14
	Enoxaparin	7	16	22	21	23
	Difference	-3	-6	-8	-8	-9
HFR	Arixtra	12	36	51	50	50
	Enoxaparin	23	63	84	83	84
	Difference	-11	-27	-33	-33	-34
Combined	Arixtra	9	24	32	32	32
	Enoxaparin	17	41	54	54	54
	Difference	-8	-17	-22	-22	-22

Table 4.3 presents number of VTE-related deaths for different procedures and time periods. In general, Arixtra avoids between 3 and 34 deaths per 10.000 patients compared to Enoxaparin.

Clearly, in cases where Arixtra is the more cost-efficient (lower cost) alternative, the cost-effectiveness analysis is trivial: Arixtra is both cheaper and more effective in preventing VTE, and should be the preferred drug. As we have seen, this conclusion is true only when a very long follow-up time is required. For shorter follow-up time spans, Arixtra is the medication with higher cost, and we have to consider its effectiveness in preventing VTE in order to reach a conclusion in the cost-benefit analysis.

Costs per avoided VTE-event

To calculate the cost per avoided VTE-event, we divide the total cost difference between Arixtra and Enoxaparin by the total number of avoided events. For instance, for TKR we know from Table 4.1 that at discharge, the added medication cost of treatment with Arixtra (cost difference) is 343 NOK per patient, which for 10.000 patients amounts to 3.43 million NOK. From Table 4.2 we know that the reduction in DVT-events for inpatients is estimated at 80. The incremental cost for each of these avoided cases is equal to 3.43 million NOK divided by 80. Hence, the cost per avoided DVT-event is 42.125 NOK, see Table 4.4. Similarly for the other categories.

Table 4.4 Cost per avoided VTE-event, NOK

		Discharge	Day 30	Day 90
DVT	**TKR**	42 125	22 661	16 290
	THR	137 273	43 971	24 023
	HFR	68 431	8 785	-1 970
	Combined	83 617	21 413	8 584
PE	**TKR**	99 118	53 696	38 113
	THR	238 421	74 750	40 980
	HFR	124 643	14 462	-3 095
	Combined	157 200	37 170	14 478
VTE	**TKR**	29 561	15 935	11 412
	THR	87 115	27 685	15 145
	HFR	44 177	4 921	-1 204
	Combined	54 583	13 586	5 389

Net costs per avoided VTE-event

Avoiding VTE-events saves money. We have information on hospitalisation costs of DVT and PE, see Table 3.19. To calculate net cost per avoided VTE-event, we subtract the saving of hospitalisation costs from the costs reported in Table 4.4. For instance, the cost saving from each avoided case of TKR is 18.880 NOK. Hence, the net cost per avoided case, where we take in to account saved hospitalisation costs, is $42.125 - 18.880 = 23.425$ NOK. Similarly for the other categories[17].

Table 4.5 reports the net costs per avoided event. A negative number implies that our cost-benefit analysis is in favour of Arixtra. A positive number implies that use of Arixtra involves added costs, and that these added costs must be weighed against benefits not included in our study, such as improved life quality and productivity of those who avoid VTE.

[17] Example, VTE-case: (23245 + 84293) – (18880 + 14825) = 73833.

Table 4.5 Net cost per avoided VTE-event, NOK

		Discharge	Day 30	Day 90
DVT	**TKR**	23 245	-389	-6 760
	THR	119 041	23 091	3 143
	HFR	44 962	-13 945	-24 700
PE	**TKR**	84 293	25 776	10 193
	THR	228 996	32 606	-1 164
	HFR	102 076	-22 100	-39 657
VTE	**TKR**	73 833	-25 584	-47 536
	THR	320 380	-7 327	-61 045
	HFR	101 002	-95 337	-123 649

We note from Table 4.5 that the cost per avoided VTE-event is reduced as the follow-up time increases. There are three reasons for this. First, as we have noted from Table 4.1, the added medication costs from using Arixtra go down as the time period increases. Second, allowing for a longer time span means more clinical VTE-events, as is evident from Table 4.2. Third, the cost of VTE treatment is higher for readmissions than for inpatients, as shown in Table 3.19. The first argument says that the added costs of using Arixtra goes down, while the second and third arguments imply that the benefits of using the more effective drug goes up.

As is evident from Table 4.5, while at discharge the net cost per avoided VTE-event is always positive, at day 30 and day 90 the added net cost is negative for DVT-events following TKR and for both DVT and PE-events following HFR. At day 90, the net cost is also negative for PE-events following THR. As emphasised before, our cost-benefit analysis would in these cases clearly be in favour of Arixtra. For the cases with positive costs per avoided event, the added costs must be weighed against benefits not included in the present study.

Note in particular the high added net costs of THR, at discharge approximately 119.000 NOK for DVT and approximately 229.000 NOK for PE. This is due to the fact that the reduction in number of VTE-events by using Arixtra in the THR case is not so large; 33 more avoided cases of DVT and 19 of PE compared to Enoxaparin, according to Table 4.2. Moreover, the

treatment of these cases is also not so expensive, as is evident from Table 3.19. These observations explain why there the benefits of Arixtra are relatively modest, and therefore why the cost per avoided case is so high.

5. Sensitivity analyses

Sensitivity analyses are usually conducted for the key parameters in the analysis. By changing the value of key parameters, one can test how these changes could have an effect on the study results. We conducted several sensitivity analyses in order to test the validity of our results. All sensitivity analyses were performed for TKR, THR, HFR and combined population of major orthopaedic surgery patients.

The model results were based on 3% discount rate. The results from sensitivity analysis with 0% and 5% discount rates are presented in Table 4.6. In another sensitivity analysis, we changed the additional hospital days in case of treatment-related bleeding from 4,67 days[18] (see table 3.18) to 6,18 days which is the mean length of stay for the entire sample, see table 4.7. We also changed the price of Enoxaparin in another sensitivity analysis. The reason for this, was based on the fact that prophylaxis with Enoxaparin is not as common as Dalteparin (Fragmin®) in Norway, see chapter 3.3. The price of one dose of Dalteparin is almost 10% higher than Enoxaparin. By adding 10% to the cost of Enoxaparin, it would be as if we compare Dalteparin with Fondaparinux (Arixtra), given that Dalteparin has the same probabilities in preventing VTE as Enoxaparin, see Table 4.8. We experimented also with a 10% to 50% reduction in the price of Arixtra and Enoxaparin. The results from these analyses are presented in Table 4.9 to 4.13.

In addition to sensitivity analysis for discount rates, additional hospitalisation days and Arixtra prices, we have carried out similar tests for reductions in the costs of Enoxaparin with 10% to 50%, see Table 4.14 to 4.19, and even more extreme cases where Enoxaparin price is reduced by 60% to 100%, see table 4.20

The general impression from sensitivity analysis is that the results are robust to changes in important parameters. For instance, changing the discount rate from 3% to 0% or 5% has only a marginal impact on VTE-related costs, and then only in a 5-year time perspective. Sensitivity analysis on length of stay had a very small effect on costs compared to base case. Similarly, a 10% change in the price of Enoxaparin or Arixtra had very modest affects on the treatment costs. For instance, with a 10% reduction in the price of Arixtra, with a 90-day follow-up time, it is still the case that HFR is the only category for which Arixtra is the more

[18] Based on results from the regression analysis.

cost-effective drug[19]. By day 90, Arixtra was more cost effective than Enoxaparin in all cases. Table 4.9 to 4.13 analyse the results of larger reductions in the price of Arixtra relative to the base case.

Table 4.20 shows the results from extreme sensitivity analyses conducted on Enoxaparin price by reductions from 60% to 100%. Only the results from 5-year follow-up time are presented here. As evident from the table, it is still the case that Arixtra is cost saving compared to Enoxaparin when the Enoxaparin price is reduced up to 80% in the case of TKR, and when reduced by 100% in the case of HFR.

Table 4.6 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Discount rate 0%	Discount rate 5%
		Year 5	**Year 5**
TKR	Arixtra	2 917	2 845
	Enoxaparin	3 200	3 085
	Difference	-283	-240
	% Difference/Enoxaparin	-9 %	-8 %
THR	Arixtra	3 006	2 936
	Enoxaparin	2 991	2 903
	Difference	15	32
	% Difference/Enoxaparin	1 %	1 %
HFR	Arixtra	3 512	3 439
	Enoxaparin	3 849	3 749
	Difference	-336	-310
	% Difference/Enoxaparin	-9 %	-8 %
Combined	Arixtra	3 241	3 169
	Enoxaparin	3 426	3 329
	Difference	-185	-160
	% Difference/Enoxaparin	-5 %	-5 %

[19] The cost reduction is, however, sufficiently large to change the sign of the net cost per avoided VTE-events in a couple of cases. Both price changes reduced the net cost per avoided DVT following TKR by day 30. By changing the price of Enoxaprin, net cost per avoided PE following THR was also reduced by day 90. The 10% reduction in price of Arixtra had however much larger effect.

Table 4.7 Results from sensitivity analyses, VTE-related costs per patient, NOK Treatment-related bleeding, additional hospital days 6,18 days

		Follow-up time				
		Discharge	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 622	1 892	2 107	2 290	2 875
	Enoxaparin	1 286	1 647	1 907	2 200	3 134
	Difference	336	245	200	91	-259
	% Difference/Enoxaparin	26 %	15 %	10 %	4 %	-8 %
THR	Arixtra	1 518	1 900	2 214	2 394	2 965
	Enoxaparin	1 066	1 602	2 007	2 230	2 941
	Difference	452	298	207	163	24
	% Difference/Enoxaparin	42 %	19 %	10 %	7 %	1 %
HFR	Arixtra	1 596	2 216	2 676	2 872	3 472
	Enoxaparin	1 248	2 124	2 705	2 974	3 794
	Difference	348	92	-29	-101	-322
	% Difference/Enoxaparin	28 %	4 %	-1 %	-3 %	-8 %
Combined	Arixtra	1 564	2 050	2 425	2 613	3 200
	Enoxaparin	1 172	1 855	2 330	2 583	3 372
	Difference	393	195	95	30	-172
	% Difference/Enoxaparin	34 %	11 %	4 %	1 %	-5 %

Table 4.8 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Enoxaparin +10%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 621	1 890	2 104	2 288	2 872
	Enoxaparin	1 313	1 673	1 931	2 224	3 158
	Difference	308	217	173	63	-286
	% Difference/Enoxaparin	23 %	13 %	9 %	3 %	-9 %
THR	Arixtra	1 518	1 898	2 212	2 391	2 962
	Enoxaparin	1 095	1 629	2 032	2 255	2 966
	Difference	423	270	179	136	-3
	% Difference/Enoxaparin	39 %	17 %	9 %	6 %	0 %
HFR	Arixtra	1 595	2 213	2 671	2 867	3 467
	Enoxaparin	1 275	2 148	2 727	2 995	3 816
	Difference	320	64	-56	-128	-349
	% Difference/Enoxaparin	25 %	3 %	-2 %	-4 %	-9 %
Combined	Arixtra	1 564	2 048	2 421	2 609	3 196
	Enoxaparin	1 200	1 880	2 353	2 606	3 395
	Difference	364	168	68	3	-199
	% Difference/Enoxaparin	30 %	9 %	3 %	0 %	-6 %

Table 4.9 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Arixtra price –10%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 542	1 812	2 026	2 209	2 794
	Enoxaparin	1 283	1 643	1 902	2 195	3 129
	Difference	259	168	124	15	-334
	% Difference/Enoxaparin	20 %	10 %	7 %	1 %	-11 %
THR	Arixtra	1 440	1 820	2 133	2 312	2 884
	Enoxaparin	1 065	1 599	2 003	2 226	2 936
	Difference	374	221	131	87	-52
	% Difference/Enoxaparin	35 %	14 %	7 %	4 %	-2 %
HFR	Arixtra	1 517	2 135	2 593	2 789	3 389
	Enoxaparin	1 246	2 119	2 697	2 966	3 787
	Difference	271	15	-105	-177	-398
	% Difference/Enoxaparin	22 %	1 %	-4 %	-6 %	-11 %
Combined	Arixtra	1 485	1 970	2 343	2 531	3 118
	Enoxaparin	1 170	1 851	2 324	2 577	3 365
	Difference	315	119	19	-46	-248
	% Difference/Enoxaparin	27 %	6 %	1 %	-2 %	-7 %

Table 4.10 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Arixtra price –20%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 464	1 734	1 948	2 131	2 716
	Enoxaparin	1 283	1 643	1 902	2 195	3 129
	Difference	181	90	46	-64	-413
	% Difference/Enoxaparin	14 %	5 %	2 %	-3 %	-13 %
THR	Arixtra	1 361	1 742	2 055	2 234	2 806
	Enoxaparin	1 065	1 599	2 003	2 226	2 936
	Difference	296	143	52	8	-131
	% Difference/Enoxaparin	28 %	9 %	3 %	0 %	-4 %
HFR	Arixtra	1 439	2 056	2 515	2 711	3 310
	Enoxaparin	1 246	2 119	2 697	2 966	3 787
	Difference	193	-63	-183	-255	-476
	% Difference/Enoxaparin	15 %	-3 %	-7 %	-9 %	-13 %
Combined	Arixtra	1 407	1 891	2 265	2 453	3 039
	Enoxaparin	1 170	1 851	2 324	2 577	3 365
	Difference	237	40	-59	-124	-326
	% Difference/Enoxaparin	20 %	2 %	-3 %	-5 %	-10 %

Table 4.11 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Arixtra price –30%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 386	1 655	1 870	2 053	2 638
	Enoxaparin	1 283	1 643	1 902	2 195	3 129
	Difference	103	12	-33	-142	-491
	% Difference/Enoxaparin	8 %	1 %	-2 %	-6 %	-16 %
THR	Arixtra	1 283	1 664	1 977	2 156	2 727
	Enoxaparin	1 065	1 599	2 003	2 226	2 936
	Difference	218	65	-26	-70	-209
	% Difference/Enoxaparin	20 %	4 %	-1 %	-3 %	-7 %
HFR	Arixtra	1 360	1 978	2 436	2 632	3 232
	Enoxaparin	1 246	2 119	2 697	2 966	3 787
	Difference	115	-141	-261	-334	-554
	% Difference/Enoxaparin	9 %	-7 %	-10 %	-11 %	-15 %
Combined	Arixtra	1 329	1 813	2 186	2 374	2 961
	Enoxaparin	1 170	1 851	2 324	2 577	3 365
	Difference	159	-38	-138	-203	-404
	% Difference/Enoxaparin	14 %	-2 %	-6 %	-8 %	-12 %

Table 4.12 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Arixtra price –40%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 308	1 577	1 791	1 974	2 559
	Enoxaparin	1 283	1 643	1 902	2 195	3 129
	Difference	24	-66	-111	-220	-569
	% Difference/Enoxaparin	2 %	-4 %	-6 %	-10 %	-18 %
THR	Arixtra	1 205	1 585	1 899	2 078	2 649
	Enoxaparin	1 065	1 599	2 003	2 226	2 936
	Difference	140	-14	-104	-148	-287
	% Difference/Enoxaparin	13 %	-1 %	-5 %	-7 %	-10 %
HFR	Arixtra	1 282	1 900	2 358	2 554	3 154
	Enoxaparin	1 246	2 119	2 697	2 966	3 787
	Difference	36	-219	-339	-412	-633
	% Difference/Enoxaparin	3 %	-10 %	-13 %	-14 %	-17 %
Combined	Arixtra	1 251	1 735	2 108	2 296	2 883
	Enoxaparin	1 170	1 851	2 324	2 577	3 365
	Difference	80	-116	-216	-281	-483
	% Difference/Enoxaparin	7 %	-6 %	-9 %	-11 %	-14 %

Table 4.13 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Arixtra price –50%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 229	1 499	1 713	1 896	2 481
	Enoxaparin	1 283	1 643	1 902	2 195	3 129
	Difference	-54	-145	-189	-299	-647
	% Difference/Enoxaparin	-4 %	-9 %	-10 %	-14 %	-21 %
THR	Arixtra	1 127	1 507	1 820	1 999	2 571
	Enoxaparin	1 065	1 599	2 003	2 226	2 936
	Difference	61	-92	-183	-226	-365
	% Difference/Enoxaparin	6 %	-6 %	-9 %	-10 %	-12 %
HFR	Arixtra	1 204	1 821	2 280	2 476	3 076
	Enoxaparin	1 246	2 119	2 697	2 966	3 787
	Difference	-42	-298	-418	-490	-711
	% Difference/Enoxaparin	-3 %	-14 %	-15 %	-17 %	-19 %
Combined	Arixtra	1 172	1 657	2 030	2 218	2 805
	Enoxaparin	1 170	1 851	2 324	2 577	3 365
	Difference	2	-194	-294	-359	-561
	% Difference/Enoxaparin	0 %	-11 %	-13 %	-14 %	-17 %

Table 4.14 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Enoxaparin -10%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 621	1 890	2 104	2 288	2 872
	Enoxaparin	1 254	1 614	1 873	2 165	3 099
	Difference	367	276	232	122	-227
	% Difference/Enoxaparin	29 %	17 %	12 %	6 %	-7 %
THR	Arixtra	1 518	1 898	2 212	2 391	2 962
	Enoxaparin	1 036	1 570	1 973	2 196	2 907
	Difference	482	329	238	194	55
	% Difference/Enoxaparin	47 %	21 %	12 %	9 %	2 %
HFR	Arixtra	1 595	2 213	2 671	2 867	3 467
	Enoxaparin	1 216	2 090	2 668	2 937	3 757
	Difference	379	123	3	-69	-290
	% Difference/Enoxaparin	31 %	6 %	0 %	-2 %	-8 %
Combined	Arixtra	1 564	2 048	2 421	2 609	3 196
	Enoxaparin	1 141	1 822	2 295	2 547	3 336
	Difference	423	226	127	62	-140
	% Difference/Enoxaparin	37 %	12 %	6 %	2 %	-4 %

Table 4.15 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Enoxaparin -20%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 621	1 890	2 104	2 288	2 872
	Enoxaparin	1 224	1 585	1 843	2 136	3 070
	Difference	396	306	261	152	-197
	% Difference/Enoxaparin	32 %	19 %	14 %	7 %	-6 %
THR	Arixtra	1 518	1 898	2 212	2 391	2 962
	Enoxaparin	1 006	1 540	1 944	2 167	2 877
	Difference	512	358	268	224	85
	% Difference/Enoxaparin	51 %	23 %	14 %	10 %	3 %
HFR	Arixtra	1 595	2 213	2 671	2 867	3 467
	Enoxaparin	1 187	2 060	2 639	2 907	3 728
	Difference	408	152	32	-40	-261
	% Difference/Enoxaparin	34 %	7 %	1 %	-1 %	-7 %
Combined	Arixtra	1 564	2 048	2 421	2 609	3 196
	Enoxaparin	1 111	1 792	2 265	2 518	3 307
	Difference	452	256	156	91	-111
	% Difference/Enoxaparin	41 %	14 %	7 %	4 %	-3 %

Table 4.16 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Enoxaparin -30%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 621	1 890	2 104	2 288	2 872
	Enoxaparin	1 195	1 555	1 814	2 107	3 040
	Difference	426	335	290	181	-168
	% Difference/Enoxaparin	36 %	22 %	16 %	9 %	-6 %
THR	Arixtra	1 518	1 898	2 212	2 391	2 962
	Enoxaparin	977	1 511	1 915	2 137	2 848
	Difference	541	388	297	253	114
	% Difference/Enoxaparin	55 %	26 %	16 %	12 %	4 %
HFR	Arixtra	1 595	2 213	2 671	2 867	3 467
	Enoxaparin	1 158	2 031	2 609	2 878	3 698
	Difference	438	182	62	-11	-231
	% Difference/Enoxaparin	38 %	9 %	2 %	0 %	-6 %
Combined	Arixtra	1 564	2 048	2 421	2 609	3 196
	Enoxaparin	1 082	1 763	2 236	2 489	3 277
	Difference	482	285	185	120	-81
	% Difference/Enoxaparin	45 %	16 %	8 %	5 %	-2 %

Table 4.18

Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Enoxaparin -40%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 621	1 890	2 104	2 288	2 872
	Enoxaparin	1 166	1 526	1 785	2 077	3 011
	Difference	455	364	320	210	-139
	% Difference/Enoxaparin	39 %	24 %	18 %	10 %	-5 %
THR	Arixtra	1 518	1 898	2 212	2 391	2 962
	Enoxaparin	948	1 482	1 885	2 108	2 819
	Difference	570	417	326	283	144
	% Difference/Enoxaparin	60 %	28 %	17 %	13 %	5 %
HFR	Arixtra	1 595	2 213	2 671	2 867	3 467
	Enoxaparin	1 128	2 002	2 580	2 848	3 669
	Difference	467	211	91	19	-202
	% Difference/Enoxaparin	41 %	11 %	4 %	1 %	-6 %
Combined	Arixtra	1 564	2 048	2 421	2 609	3 196
	Enoxaparin	1 053	1 733	2 206	2 459	3 248
	Difference	511	315	215	150	-52
	% Difference/Enoxaparin	49 %	18 %	10 %	6 %	-2 %

Table 4.19 Results from sensitivity analyses, VTE-related costs per patient, NOK

		Follow-up time				
Enoxaparin -50%		**Discharge**	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	Arixtra	1 621	1 890	2 104	2 288	2 872
	Enoxaparin	1 136	1 496	1 755	2 048	2 982
	Difference	484	394	349	240	-109
	% Difference/Enoxaparin	43 %	26 %	20 %	12 %	-4 %
THR	Arixtra	1 518	1 898	2 212	2 391	2 962
	Enoxaparin	918	1 452	1 856	2 079	2 789
	Difference	600	446	356	312	173
	% Difference/Enoxaparin	65 %	31 %	19 %	15 %	6 %
HFR	Arixtra	1 595	2 213	2 671	2 867	3 467
	Enoxaparin	1 099	1 972	2 550	2 819	3 640
	Difference	496	241	121	48	-173
	% Difference/Enoxaparin	45 %	12 %	5 %	2 %	-5 %
Combined	Arixtra	1 564	2 048	2 421	2 609	3 196
	Enoxaparin	1 023	1 704	2 177	2 430	3 219
	Difference	540	344	244	179	-23
	% Difference/Enoxaparin	53 %	20 %	11 %	7 %	-1 %

Table 4.20 Results from sensitivity analyses, VTE-related costs per patient

Sensitivity on Enoxaparin price		**YEAR 5**				
		-60%	**-70%**	**-80%**	**-90%**	**-100%**
TKR	Arixtra	2 872	2 872	2 872	2 872	2 872
	Enoxaparin	2 952	2 923	2 893	2 864	2 835
	Difference	-80	-50	-21	8	38
	% Difference/Enoxaparin	-3 %	-2 %	-1 %	0 %	1 %
THR	Arixtra	2 962	2 962	2 962	2 962	2 962
	Enoxaparin	2 760	2 730	2 701	2 672	2 642
	Difference	202	232	261	290	320
	% Difference/Enoxaparin	7 %	8 %	10 %	11 %	12 %
HFR	Arixtra	3 467	3 467	3 467	3 467	3 467
	Enoxaparin	3 610	3 581	3 551	3 522	3 493
	Difference	-143	-114	-85	-55	-26
	% Difference/Enoxaparin	-4 %	-3 %	-2 %	-2 %	-1 %
Combined	Arixtra	3 196	3 196	3 196	3 196	3 196
	Enoxaparin	3 189	3 160	3 130	3 101	3 072
	Difference	7	36	66	95	124
	% Difference/Enoxaparin	0 %	1 %	2 %	3 %	4 %

6. Discussion and conclusion

Our analyses were based on statistics from Norwegian National Register of Hospital patients, which included 55.000 major orthopaedic surgery patients from 1999 to 2001. Of these patients, 51.555 were included in our analysis. Our analyses were based on Norwegian unit costs. It was assumed that these patients received prophylaxis either with Fondaparinux or Enoxaparin. The model conducted estimates of expected incidence of VTE and expected costs estimates of VTE-related care for each of the two prophylaxes. The results were calculated for multiple time periods: from surgery to hospital discharge, day 30, day 90, year 1 and year 5.

Our results indicate that Fondaprinux (Arixtra) is likely to be more effective than Enoxaparin in preventing the incidence of VTE (DVT and PE) in all time periods. For long follow-up periods, more precisely, 5 years, Arixtra is also likely to represent the lower cost treatment. For HFR, Arixtra is cost-saving from day 90 onward.

As mentioned above, for shorter follow-up periods and, indeed, treatment of inpatients, Arixtra is the higher cost treatment. On the other hand, our results show that Arixtra is more effective than Enoxaparin in reducing VTE-events. We also find that Arixtra avoids between 3 and 34 VTE-related deaths per 10.000 patients compared to Enoxaparin. The question is then whether the benefits of a more effective drug, such as improved life quality or increased productivity for the patients who avoid VTE by taking Arixtra rather than Enoxaparin, can defend the higher costs involved. Our analysis does not give an answer to that question. However, we calculate the cost per avoided VTE-event so that we can have an idea of how large the other benefits must be in order to make Arixtra the better choice.

The cost-benefit analysis shows that for inpatients it is almost always the case that Arixtra is less economical than Enoxaparin. The reason is that there are then fewer cases of VTE, that treatment of VTE is less costly than for outpatients, and finally that the short time period makes Arixtra relatively more expensive than Enoxaparin. When use of Arixtra significantly reduces the events of VTE, and the costs of treating the relevant form of VTE is relatively high, our cost-benefit analysis shows that Arixtra may be the more economical choice. This is for instance the case for DVT following TKR and the case for DVT and PE (VTE-events) following HFR for follow-up periods of 30 days or more. In these cases, the cost-benefit analysis is clearly in favour of Arixtra.

The sensitivity analyses show that our results are robust to changes in the most important parameters. Both quantitatively and qualitatively speaking, very little changes. Sensitivity analyses conducted on reduction of Enoxaparin up to 50% show that it is still the case that Arixtra is the more cost-effective alternative the 5-year follow-up time compared to Enoxaparin. Also in the extreme cases where the Enoxaparin price is reduced by 60% to 100%, Arixtra is still cost-effective compared to Enoxaparin in the cases of TKR and HFR. Clearly, reductions in the price of Arixtra up to 50% make this drug more attractive (cost-effective) than Enoxaparin in a broader set of cases.

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Appendix 1: Estimation of model probabilities

This appendix is a based on estimating of model probabilities used in the Arixtra model presented in "Arixtra® Health Economic Model – A model of cost effectiveness of fondparinux versus enoxaparin, 2002".

A. Enoxaparin

The risk for a patient receiving enoxaparin to develop DVT prior to hospital discharge, (ie *early* DVT*)* was estimated using data on the rate of *venographic* DVT from the four fondaparinux Phase III trials, as follows: 9.04%, 27.15%, and 18.78% for THR, TKR, and HFR respectively (Bauer, 2001; Eriksson, 2001; Lassen, 2002).

The probabilities that patients would then develop *clinically* detected and confirmed DVT and PE were estimated using literature data from clinical trials or cohort studies in which the prophylaxes of interest were used and symptomatic events were tracked for three or more months following surgery (THR or TKR) (LeClerc, 1998, Colwell, 1999).

No such published data exist to estimate the rate of clinical events for patients undergoing HFR. Nonetheless, one might expect such event rates to be higher among HFR patients due to their advanced age, comorbid conditions, and the traumatic nature of their injury. Indeed, data from literature show an incidence of fatal PE between 3 and 6 times higher and suggest an at least twice incidence for total (fatal and non fatal PE) (Eriksson, 2001; Lubinus, 2001; PEP trial, 2000;Lanssen, 2002; Turpie, 2002). Also, a ratio HF/THR of 1.7 is found from either a review of literature, or results from fondaparinux phase III trials when looking at venographic proximal DVT rates which have been shown to correlate with the incidence of symptomatic events (Geerts, 2001). A similar ratio is also found in the PEP trial (2000). It was therefore assumed that the incidence of symptomatic events in patients with HFR is increased by 70% compared with THR.

The risk of *late* DVT with enoxaparin (19.3%) was estimated using data from a randomized trial of post-discharge prophylaxis with enoxaparin among 179 THR patients who had negative findings on venography at hospital discharge (Planes, 1996).

Probabilities described herein are for the entire 90-day period; DVT/PE rates for enoxaparin (and similarly fondaparinux) are then apportioned to the three periods of the acute phase (i.e.,

surgery to hospital discharge, discharge to day 30, and day 31 to day 90) based on the temporal pattern of events from White et al (White, 1998). In particular, findings from this study suggest that nearly two-thirds of clinical events following TKR occur during hospitalization versus only about 20% following THR (this study was not used to estimate event rates because of its reliance on ICD-9-CM codes for case identification and an absence of detailed information on thromboprophylaxis).

B. Fondaparinux

The risk for a patient receiving Fondaparinux to develop DVT prior to hospital discharge, (ie *early* DVT*)* was estimated by applying relative risk to the probabilities for enoxaparin: compared with enoxaparin, Fondaparinux was assumed to reduce the risk of *early* DVT by 54%, based on the global relative risk reduction across Fondaparinux Phase III clinical trials[20].

As for the risk of *late* DVT, and in the absence of long term follow up data, it is assumed to be identical to that of enoxaparin.

The risk of major haemorrhage for a patient receiving Fondaparinux compared to Enoxaparin was estimated based on observed rates in patients treated at recommended dose during clinical trials (2.8 % Fondaparinux, versus 2.6% Enoxaparin[1]).

No data are available that would allow to estimate the probabilities that patients receiving Fondaparinux would develop *clinically* detected and confirmed DVT and PE. The rate of transformation from venographic DVTs into clinical events (ie contingent probability) is thus calculated based on Enoxaparin rates as estimated above, and subsequently applied to the Fondaparinux arm.

C. Risk of Prophylaxis-Related Hemorrhage

For patients receiving Enoxaparin, assumed rate of major hemorrhage (2.6%) was based on pooled data on the occurrence of major hemorrhage to day 11 of follow-up, from the Fondaparinux Phase III trials where Enoxaparin 40mg od was given starting 12 hours preoperatively.

[20] Source: European labelling

D. Suspected but Unconfirmed Clinical DVT & PE

The rates of suspected but unconfirmed DVT and PE (respectively 10% and 2%, based on Phase III trials) were assumed not to differ by type of procedure or prophylaxis.

E. Risk of Treatment-Related Hemorrhage

The risk of major hemorrhage related to treatment of clinical DVT or PE (2.24%) was estimated using pooled data from English-language reports of randomized clinical trials of heparin, LMWH, and/or warfarin that involved at least three months of follow-up (Hull, 1982; Lagerstedt, 1985; Pini, 1994; Das, 1996; Prandoni, 1992; Lopaciuk, 1999; Monreal, 1994).

F. Risk of Recurrent VTE

The risk of recurrent VTE was estimated using data from a Swedish report of a long-term follow-up study of 738 patients with objectively verified symptomatic DVT (Hansson, 2000).

The cumulative incidence of recurrence in this study over five years of follow-up was reported to be 21.5%; however, the relative risk of recurrence among patients undergoing orthopedic surgery was only 0.21. The overall cumulative incidence of recurrent VTE was multiplied by this relative risk to obtain an estimate of absolute risk in the population of interest (4.5%).

In the model, it was necessary to apportion this estimate between the acute and chronic phases, as the risk of recurrence is assumed to begin immediately after an initial DVT or PE.

Note: Because no information was available from this follow-up study on the incidence of recurrence during the first 90 days (the typical period of VTE treatment) versus later, data from the above-described treatment trials as well as a large randomized trial of short- versus long-term oral anticoagulation (Schulman, 1995) were used to estimate the risk of recurrence during treatment (2.6%). This risk was adjusted to reflect the experience of an orthopaedic surgery cohort using the above-noted relative risk of 0.21, yielding an estimated risk of recurrence of 0.6% during the acute phase (i.e., first 90 days) of the model; the remaining risk (3.9%) was distributed throughout the chronic phase according to the temporal pattern observed in the long-term recurrence study (i.e., quarterly risks of 0.31%, 0.275%, and 0.155% for one, two, and three or more years following surgery respectively).

G. Risk of Post-Thrombotic Syndrome

The risk of PTS was assumed to begin as of the start of the chronic phase of the model (i.e., day 91). This risk was estimated separately for patients assumed to develop clinical DVT or PE within 90 days of surgery versus those assumed to have developed subclinical DVT only during this period.

Among the former, cumulative risks of PTS over one, two, and five years (17.3%, 22.8%, and 28.0% respectively) were obtained from a prospective cohort study (n=355) of the long-term clinical course of acute VTE in Italy (Prandoni, 1996).

Data do not exist on the incidence of PTS among patients with untreated subclinical DVT; two retrospective studies have been published, however, that report the incidence of PTS among orthopedic surgery patients with venographically detected DVT (Ginsberg, 2000; Siragusa, 1997).

While study entry criteria and the definition of PTS used in these studies were quite similar, findings with respect to PTS incidence were not (4% and 24% respectively). The pooled incidence from these two studies (12%) was used for basecase estimate, assuming that cumulative incidence would follow the same pattern as that among patients experiencing clinical VTE.

H. Mortality

The risk of death among THR and TKR patients who develop PE (14.5%) was estimated using an average case-fatality rate based on the large studies by LeClerc and Colwell as well as two additional studies of VTE incidence in large samples (these studies were not used to estimate other model probabilities because the prophylaxes of interest in this analysis were not employed) (LeClerc, 1998; Colwell, 1999; Heit, 2000; Pellegrini, 1996.

Because literature-based estimates were not available for HFR, data from the Fondaparinux Phase III clinical trial in HFR were used to estimate the risk of fatal PE (68.2%) among these patients (Eriksson, 2001).

The risk of death following hemorrhage (0.63%) was calculated using the percentage of patients with major bleeding from the Fondaparinux Phase III clinical trials whose bleeding was seemed to be the cause of death after adjudication.

Mortality from all other causes among patients undergoing THR and TKR was assumed to be identical to that of the general population for persons aged 65-69 years, and we based our estimate (2% annually) on US statistics data (unpublished data, National Vital Statistics System, National Center for Health Statistics, 2001). A much higher rate of mortality was expected for patients undergoing HFR, however, as they are typically older (mean age: 80 years) and more severely ill than those undergoing elective procedures. Mortality risks among HFR patients were estimated using data from a retrospective study of Medicare beneficiaries with hip fractures (Lu-Yao, 1994); resulting estimates were 1.6%, 5.4%, and 6.0% for the periods between surgery and hospital discharge, hospital discharge to day 30, and day 31 to day 90; it was 10% annually thereafter.