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Extended Prophylaxis with Fondaparinux versus Enoxaparin against Venous Thromboembolism

by

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The research at Institute for Research in Economics and Business Administration (SNF) covers a wide range of topics such as policy decisions at micro and national level, pharmaceutical economics and health economics.

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ABSTRACT

Patients undergoing major orthopaedic surgery face considerable risk of venous thromboembolic complications (VTE). Fondaparinux (Arixtra®) is a new antithrombotic agent, which is indicated for VTE prophylaxis. This paper presents cost-effectiveness analysis of fondaparinux and enoxaparin, the most common prophylaxis of VTE. The model used in the analysis is a "core" model that examines the cost-effectiveness of extended prophylaxis with fondaparinux from one week to four weeks in patients undergoing hip fracture surgery (HFS) and total hip replacement (THR). The model estimates the expected incidence of VTE (deep vein thrombosis and pulmonary embolism) and VTE-related deaths, treatment costs per patient, incremental cost per VTE-event avoided and cost per death avoided for each of the two prophylaxes for different periods. In addition, the model measures cost per life-year gained. The analysis is based on Norwegian data, which include about 50,000 patients who underwent HFS and THR in the period from 1999 to 2001. All cost estimates in the model are based on the Norwegian unit costs. The results are calculated for multiple time periods: from surgery to day 30, day 90, year 1 and year 5.

The results from clinical outcomes show that in general, fondaparinux is the more effective drug in terms of preventing VTE-events both compared to the scenario with no extended prophylaxis after surgery, and compared to extended prophylaxis with enoxaparin in all time periods. For instance, by day 30 Fondaparinux is expected to prevent between 142 and 204 VTE-events per 10,000 patients after THR and HFS respectively compared to enoxaparin. For the 90 days follow-up time, the corresponding figures are 217 and 273 avoided VTE-events per 10,000 patients compared to enoxaparin.

Fondaparinux is also more cost-effective in terms of preventing VTE-events compared to enoxaparin. By day 90, incremental cost per avoided VTE after THR and HFS is estimated to approximately NOK 72,000 and 41,000 respectively. The economic gains of avoided VTE-events for the society are cost savings related to hospitalisation of patients with VTE. For the 90 days follow-up time, the net cost per avoided VTE following THR is NOK 45,268, and NOK 9,752 after HFS. Over a period of 5 years, cost per death avoided following HFS is expected to be approximately NOK 50,000, while cost per life year gained is around NOK 6,000.

The sensitivity analysis confirmed the robustness of the main results. The results were however sensitive to price reductions of fondaparinux.

1. Introduction

1.1 Background

Venous thromboembolism (VTE) complications such as deep-vein thrombosis (DVT) and pulmonary embolism (PE) are major causes of morbidity and mortality. Patients undergoing major orthopaedic surgery face considerable risk of VTE, unless they receive prophylactic treatment. In fact, without prophylaxis the risk of developing DVT within 7-14 days after major orthopaedic surgery is over 50% in patients undergoing hip replacement, 60% in patients undergoing hip fracture surgery and 80% in patients undergoing knee replacement surgery (Geerts et al., 2001). The risk of developing PE is 7-11% after major orthopaedic surgery (Geerts et al., 2001). Moreover, within 4-5 weeks after discharge from the hospital, about 10-20% of these patients may develop an acute DVT and 6% may develop a PE (Geerts et al., 2001). While DVT is the most common form of VTE, PE has a higher mortality risk.

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). Despite the routine prophylactic treatment after major surgery, patients are still at risk of VTE complications. VTE can be symptomatic or clinically silent. In fact, the incidence of DVT is silent in a majority of patients. 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., 1997). The clinical diagnosis is not always reliable in detecting DVT, and commonly available non-invasive tests are not sensitive enough for diagnosis of all asymptomatic DVT. Undetected and hence untreated VTE will put the patient at risk for later complications. As the risk of VTE persists up to 3 months after surgery, patients at high risk for postoperative VTE may benefit from extended prophylaxis (e.g, an additional 3 weeks after the first 7 to 10 days) (Kearon, 2003).

1.2 Prophylaxis against VTE

The most common prophylactic drugs for prevention of VTE in patients who undergo major orthopaedic surgery are low-molecular-weight heparins (e.g., enoxaparin) (Finsen 2002). Despite current prophylaxis regimens, venography-proven VTE remains significant in patients receiving low-molecular-weight heparin; up to 16% with elective hip replacement, 27% with

hip fracture surgery, and 31% with knee replacement surgery (Geerts et al., (2001). Fondaparinux (Arixtra®) belongs to a new class of synthetic antithrombotic agents that prevents clot formation and is indicated for prophylaxis of VTE in patients undergoing orthopaedic surgeries. Fondaparinux was launched in Norway in June 2002 (ATC-code B01AX05).

1.2.1 Efficacy of fondaparinux

Four Phase III clinical trials have compared fondaparinux with enoxaparin in reducing the risk of VTE after major orthopaedic surgery: Turpie et al. (2002a); Lassen et al. (2002); Bauer et al. (2001) and Eriksson et al. (2001). Turpie et al. (2002b) 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% (95% CI, 45,8 to 63,1%; $P<0.001$) compared to enoxaparin.

Recent clinical trials indicate that extending prophylaxis with fondaparinux from one to four weeks after hip fracture surgery reduced the risk of VTE by 96% and was well tolerated (Eriksson, et al., 2003).

1.2.2 Cost-effectiveness of fondaparinux

Cost-effectiveness of fondaparinux for short-term duration (one week) prophylaxis has been studied in several countries. These analyses compared the costs and effects of prophylaxis with fondaparinux versus enoxaparin. Posnett, et al. (2002) is based on data from United Kingdom. The study concludes that using fondaparinux in UK could reduce costs by £3.8 million per year relative to enoxaparin over a period of five years post-surgery. Lundkvist et al. (2003) analyse the cost-effectiveness of fondaparinux based on Swedish unit costs. The results showed that fondaparinux was cost saving and more effective than enoxaparin after TKR and HFS and had costs per prevented VTE of about €239 after THR. Bjorvatn and Kristiansen (2003) analyse the cost-effectiveness of fondaparinux based on Norwegian unit costs. The analysis included 55,000 patients who underwent major orthopaedic surgery from 1999 to 2001. The results showed the cost-effectiveness of fondaparinux per avoided VTE-event from day 30 onward compared to enoxaparin. In all studies mentioned above, fondaparinux was found to be more effective than enoxaparin in preventing VTE-events.

1.3 Aim of the study

The incidence of hip fracture in Norway is high and increasing (Falch et al., 1993). During the years 1999, 2000 and 2001, a total of 54,988 major orthopaedic surgeries were performed in Norway[1]. The majority of these operations were due to hip fracture surgery (HFS) (50%) and total hip replacement (THR) (40%). Therefore, determining the most cost-effective thromboprophylaxis is important.

The objective of this study is to present a cost-effectiveness analysis of extended prophylaxis with fondaparinux (Arixtra®) versus enoxaparin after hip fracture surgery and total hip replacement. The model used in the analysis estimates the incidence of clinical VTE and VTE-related deaths, treatment costs per patient, cost per VTE-event avoided and cost per death avoided. In addition, the model measures cost per life-year gained. The study does not discuss subjects such as improved life quality or increased productivity for patients who avoid VTE by receiving fondaparinux. Data used in the analysis are provided by the *Norwegian Register of Hospital Patients (NPR),* which include about 50,000 patients who underwent HFS and THR in the period from 1999 to 2001. Further, all estimates of unit costs in the model are based on costs within the *Norwegian Diagnosis Related Group (DRG)* and other relevant costs.

2. Method

The study is based on an simulation model that has been developed in order to examine the cost-effectiveness of extending prophylaxis with fondaparinux from one week to four weeks in patients undergoing HFS and THR, and/or to compare the cost-effectiveness of extending prophylaxis fondaparinux versus enoxaparin.

Costs of VTE-related care (DVT and PE) during both inpatient and outpatient period, post-thrombotic syndrome (PTS) and major haemorrhage are incorporated in the model. The model can be run for a hypothetical cohort of patients undergoing either surgical procedure over various time periods up to 5 years following surgery. The main outcomes of the model are the incidence of clinical VTE and VTE-related deaths, and treatment costs per patient. In

[1] Norwegian National Register of Hospital Patients.

addition, incremental cost per VTE-event avoided, cost per death avoided and incremental cost per life-year saved are calculated.

2.1 Model structure

The model analyses the clinical outcomes and costs of extending VTE prophylaxis in patients undergoing HFS and THR. The structure of the model is close to the model developed for estimating the cost-effectiveness of short-term duration prophylaxis with fondaparinux versus enoxaparin (Gordois et al. 2003; Sullivan et al. 2002). An underlying assumption of the model is that patients undergoing HFS or THR are at risk of DVT and PE, and that either short-term duration or extended duration prophylaxis with fondaparinux or enoxaparin reduces the risk of VTE. In the model, patients are considered to be at risk of clinical VTE events (initial DVT or PE, and subsequent recurrences) during the first 90-day time period. For the day 90 to year 5 time period, patients are assumed to be at risk for recurrent VTE events (either fatal or non-fatal) and post-thrombotic syndrome (PTS). Those who have experienced a clinically detected and confirmed DVT and PE are assumed to be at risk of recurrent VTE and PTS. Those with subclinical DVT only are assumed to be at risk of PTS.

The decision tree model contains two decision nodes: choice of prophylaxis and choice of extending prophylaxis. The decision tree model can be divided into four major time frames: the initial 7-day period which corresponds to the short-term duration prophylaxis, the day 7 – day 30 time frame which corresponds to the extended duration prophylaxis, day 30 – day 90, when patient is still at risk of clinical VTE, and the day 90 – year 5 period which includes the chronic phase. The possible outcomes at each node are listed below.

1. **Day 7**

   - Symptomatic (clinical) VTE events (DVT, fatal and non-fatal PE)
   - Bleeding events (major bleedings)

2. **Day 30**

   - Venographically detected (sub-clinical) DVT
   - Symptomatic (clinical) VTE events (DVT, fatal and non-fatal PE)
   - False-positive VTE events
   - Bleeding events (major bleedings)

3. **Day 90**

    - Symptomatic (clinical) VTE events (DVT, fatal and non-fatal PE)
    - False-positive VTE events
    - Recurrent VTE (fatal and non-fatal)

4. **Year 1 - Year 5 (follow-up time frame)**

    - Recurrent VTE (fatal and non-fatal)
    - Post-thrombotic syndrome (PTS)

2.2 Estimation of model probabilities

Event probabilities in the model were derived from fondaparinux Phase III trial data (Lassen, 2002; Turpie, 2002; Eriksson, 2001), Pentifra Plus trial data (Eriksson, 2003) and data in published literature sources. Estimation of the underlying probabilities in the model is described in further details in Appendix A. See also Tables 1 to 3 in Appendix A for all model probabilities.

2.3 Estimation of resource use and costs

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

- Prophylaxis: including cost of drug, administration and monitoring.
- Confirmation and treatment of clinical DVT and PE, while inpatient and after discharge.
- Suspected but unconfirmed DVT and PE, while inpatient and after discharge; costs of tests and physician visits.
- Major Hemorrhage: bleeding index ≥ 2 [2] and clinically relevant.
- Post thrombotic syndrome (PTS): acute and chronic phase.

[2] Number of units of packed red blood cells or whole blood transfused, *plus* [prebleeding *minus* postbleeding hemoglobin values in g/dl]

2.4 Measures

The model can be run for hypothetical cohorts of either 1,000 or 10,000 patients. Model results are calculated for multiple time points (Day 30, Day 90, Year 1 and Year 5). The model generates estimates of the expected incidence of symptomatic VTE events (DVT and PE), recurrent VTE, and PTS, as well as the expected number of VTE-related deaths. The model also generates estimates of the expected costs of VTE-related care for THR and HFS, cost per VTE event avoided, cost per death avoided and incremental cost per life-year saved.

3. Estimation of resource use and unit costs used in the analysis

3.1 Analysis of data

Data in the analysis were selected from the complete files of the *Norwegian National Register of Hospital Patients (NPR),* where each record represents a single completed stay in hospital for a single patient. The sample contains data for the years 1999, 2000, and 2001. During these years a total of 54,988 major orthopaedic surgeries were performed in Norway. Patients were identified by operation codes: NFBxx for total hip replacement, NGBxx for total knee replacement or NFJxx for hip fracture repair. The majority of these operations were due to HFS (50%) and THR (40%), while 10% were due to total knee replacement (Bjorvatn and Kristiansen, 2003).

The focus in this study is on patients who underwent HFS and THR. Of the total number of 54,988 identified patients, those who had undergone TKR, and those who had undergone other major surgeries before THR and HFS, patients under age of 18 and patients with DVT, PE or bleeding as *main* diagnosis were excluded from the analysis. Hence, 46,047 were selected for the analysis. Table 3.1 shows the distribution of patients who underwent THR and HFS in the years 1999, 2000 and 2001. The average ages of patients in the sample were 71.62 years for THR and 78.78 years for HFS.

Table 3.1 Distribution of patients (hospital stays)

	1999	**2000**	**2001**	**Total**
Total hip replacement	6,352	6,800	7,545	20,697
Hip fracture surgery	8,422	8,319	8,609	25,350
Total	14,774	15,119	16,154	46,047

Secondary diagnosis of PE, DVT or Bleeding in hospita were identified by ICD-10 codes. PE was indicated by ICD-code I26, DVT by ICD-code I80, Bleeding by ICD-codes T81.0, I60,

I61, I62, RO4, R58, K62.5 or K92.2. Bleeding is in terms of the fondaparinux-model: *prophylaxis related* and given a fairly wide definition[3].

Table 3.2 shows the total number of hospital stays (patients) and average length of stay for patients who underwent THR or HFS from 1999 to 2001. In addition, the Table presents the total number of patients and average length of stay for those who had a secondary diagnosis of DVT, PE or bleeding during their initial stay in hospital (inpatient period). For instance, 51 and 62 patients were treated for a secondary diagnosis of PE after THR and HFS respectively, while 73 and 42 patients were treated for a secondary diagnosis of DVT after THR and HFS.

Length of stay

The length of stays in hospital for the two procedures in the sample was as follows; Patients with THR stayed on average 12,62 days in hospital, while patients with HFS stayed 10,81 days, see table 3.2.

Table 3.2 Hospital stays from 1999 to 2001; Inpatient period

	Total hip replacement	**Hip fracture surgery**
Total number of patients	**20,697**	**25,350**
No secondary diagnosis	20,486	25,110
Secondary diagnosis of PE	51	62
Secondary diagnosis of DVT	73	42
Secondary diagnosis of Bleeding	87	136
Average length of stay (days)	**12.62**	**10.81**
No secondary diagnosis	12.54	10.74
Additional days by s.d. of PE	1.97	5.66
Additional days by s.d. of DVT	4.51	5.98
Additional days by s.d. of Bleeding	7.13	5.68

s.d: Secondary diagnosis
Source: Bjorvatn & Kristiansen (2003).

Table 3.3 presents the number of hospital stays (patients) and average length of stay for patients who underwent THR or HFS and readmitted the hospital with a secondary diagnosis of DVT, PE or bleeding within 90 days. For instance, after THR and HFS, 35 and 50 patients

[3] An alternative indicator, narrower in scope, 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).

readmitted the hospital with a secondary diagnosis of PE respectively. The average length of hospital stay for these patients was 11.17 and 9.6 days respectively.

Table 3.3 Hospital stays from 1999 to 2001; Readmissions with secondary diagnosis within 90 days

	Total hip replacement	Hip fracture surgery
Total number of patients	**110**	**221**
PE	35	50
DVT	53	86
Bleeding	22	85
Average length of stay (days)		
PE	11.17	9.60
DVT	5.25	5.77
Bleeding	7.91	5.54

Source: Bjorvatn & Kristiansen (2003).

3.2 Estimation of other parameters used in the analysis

Estimation of life expectancy

Table 3.4 presents the expected additional life years for men and women in Norway. The average life expectancy of patients undergoing THR and HFS is assumed to be the same as in the general population matched for the age and sex of the patients in the sample.

Table 3.4 Expected additional life years in Norway

Age	Men	Women
69	13.41	16.59
70	12.74	15.77
71	12.06	14.99
72	11.42	14.25
73	10.77	13.49
74	10.17	12.76
75	9.58	12.03
76	9	11.34
77	8.46	10.66
78	7.94	9.97
79	7.42	9.34

Source: Norwegian population statistics 2002, *Statistics Norway*.

In calculating the expected additional life years among undergoing THR and HFS, the population data in the sample have been weighted by patients' age and sex. As indicated in

Table 3.5, the average age of THR patients in the sample is 71.62 years, where 72% of the patients are female. The expected additional life years for THR patients weighted by age and sex is calculated to 13.73 years. Hence, the average life expectancy for THR patients in the model was set to 85.35 years. HFS is associated with substantial morbidity and should be reduced by 25% compared with the general population matched for age and sex with the studied cohort (Braitwait, 2003). For HFS patients, the expected additional life years is calculated to 8.91 years. A reduction by 25% will change the expected additional life years to 6.68. Therefore, the life expectancy for HFS patients was set to 85.46 years.

Table 3.5 Expected additional life years by type of surgery

Surgery	Age (mean years)	Female patients	Expected additional life years
THR	71.62	72%	13.73
HFS	78.78	71%	6.68

In the model, we assumed that 25% of the patients require assistance from a nurse for the injection of fondaparinux or enoxaparin after discharge from the hospital. All estimates of the parameters used in the model are presented in Table 3.7.

Table 3.6 Parameter estimates for the analyses, by type of procedure

	Total hip replacement	Hip fracture surgery
Length of initial prophylaxis (days)	7	7
Length of extended prophylaxis (days)	21	21
Length of inpatient stay (days)	12.62	10.81
Average age of patients (years)	71.62	78.78
Average life expectancy (years)	85.35	85.46
Outpatient visit by nurse (%)	25%	25%

3.3 Costs of procedures and treatments

Prophylaxis costs

In the model, we assume prophylaxis with enoxaparin (Klexane) and fondaparinux (Arixtra) for 7 days while inpatient, and extended prophylaxis for 21 days. The costs of both drugs are

based on wholesale prices in Norway[4]. The cost of one dose dose of 40 mg enoxaparin is NOK 42.87. The cost of 2,5 mg (0,5 ml single-dose, prefilled syringe; 5 mg/ml) fondaparinux is NOK 108,59.

Administration costs by nurse

The cost of injection of fondaparinux or enoxaparin after discharge from hospital was set to NOK 35 (Personal communication with health care centre).

Costs of procedures

The relevant DRG-categories were identified by listing occurrences of actually applied categories by patients undergoing surgery of THR and HFS, in the total sample. For THR, almost all occurrences are within the DRG-category 209. For HFS, the pair of DRG-categories 210/211 covers nearly 95% of all stays (Table 3.7). For more details, see Bjorvatn and Kristiansen (2003).

Table 3.7 DRG-categories assigned to operations and secondary diagnosis.

	DRG-category	**Description**
THR	209 (100%)	Major joint & limb reattachm. proc. of lower extremity
HFS	210 (41,2%) and 211 (58,8%)	210: Hip & femur procedures ex. major joint, age >17 with complications (cc); 211: Hip & femur procedures ex. major joint, age >17 without cc
PE	78 (100%)	Pulmonary embolism
DVT	128 (100%)	Deep vein thrombophlebitis
Bleeding	174 (38,2%) and 175 (61,8%)	174: Gastrointestinal hemorrhage with cc 175: Gastrointestinal hem. without cc

Cost estimates for inpatients were based on current prices within the *Norwegian Diagnosis Related Group* (DRG) system, where patients are classified in one group only, per stay in hospital[5]. The method for DRG cost calculations in Norway is *top-down.* The total operational

[4] Based on the price list provided by the Norwegian Medicine Agency.
[5] The Norwegian guidelines for pharmacoeconomic analysis for drug reimbursement applications recommend official DRG-prices as cost inputs to analysis of hospital stays (Norwegian Medicine Agency, 2002).

costs of hospitals are decomposed into cost units, and cost units are attributed to specific DRGs by applying keys that reflect the historical use of resources and length of stay within each DRG. The total DRG rate for DVT or PE includes diagnosis and treatment according to standard medical practice, follow-up visits and INR monitoring[6].

Costs were estimated separately following each surgical procedure depending on the estimates of length of stay in hospital from our analyses For the assessment of suspected but unconfirmed DVT and PE, we assumed one physician visit and one diagnostic investigation; venography or ultrasound for DVT and spiral computed tomography for PE (personal communication). The costs of physician visits and diagnostic investigations were obtained from the price list for cost per outpatient clinic consultation and procedure provided by *The Norwegian Ministry of Health*, and information provided from *The National Insurance Services*.

The weighted mean from costs of DRG-pair 174 and 175 was chosen for both prophylaxis and treatment-related bleeding. The costs of treatment of post-thrombotic syndrome were estimated from a Swedish study of long-term consequences of VTE (Bergkvist et al., 1997).

Table 3.8 presents unit cost estimates used in the analysis by each procedure. For more details on estimates of resource use and unit costs for confirmation and treatment of DVT and PE, major bleeding and PTS used in this analysis, see the study of cost-effectiveness analysis of short-term prophylaxis with fondaparinux versus enoxaparin by Bjorvatn and Kristiansen (2003).

[6] PT tests are not very common in Norway (Personal communication with physician).

Table 3.8 Unit cost estimates used in analyses by type of procedure, per patient, NOK

		Total hip replacement	Hip fracture Surgery
Prophylaxis per day	Arixtra	108.59	108.59
	Enoxaparin	42.87	42.87
Injection by nurse, outpatient	Arixtra/ Enoxaparin	35	35
DVT	Confirmed inpatient	18,232	23,469
	Confirmed post discharge	20,880	22,730
	Suspected inpatient	1,628*	1,628*
	Suspected post discharge	2,818	2,818
PE	Confirmed inpatient	9,425	22,567
	Confirmed post discharge	42,144	36,562
	Suspected inpatient	933**	933**
	Suspected post discharge	2,063	2,063
Major Bleeding	Bleeding index ≥ 2***	21,052	21,052
	Clinically relevant	16,607	16,607
Post thrombotic syndrome	Acute (first quarter)	7,860	7,860
Post thrombotic syndrome	Chronic (per quarter)	1,241	1,241

* Ultrasound or venography, ** Spiral-DT, ***Prophylaxis related.
Source: Bjorvatn & Kristiansen (2003).

4. The results

All analyses are conducted separetely for hypothetical cohorts of 10,000 patients undergoing THR and HFS. The model results are calculated for multiple time periods: from surgery to day 30, day 90, year 1 and year 5. Costs are discounted at 3% per year. The objective of this study is to compare the cost-effectiveness of extended prophylaxis with fondaparinux versus enoxaparin. The results are presented in section 4.2. However, section 4.1 presents the clinical outcomes of extended prophylaxis with fondaparinux versus no extended prophylaxis.

4.1 Extended prophylaxis with fondaparinux (Arixtra) versus no extended prohpylaxis

Table 4.1 presents the clinical outcomes of extended prophylaxis with fondaparinux for 3 weeks versus no extended prohpylaxis. The follow-up time is 30 days and 90 days after surgery. As we see, for 30 days follow-up time period extending prophylaxis with fondaparinux prevents 223 and 240 cases of VTE-events per 10,000 patients after THR and HFS respectively. When the follow-up time increases to 90 days, fondaparinux prevents 330 and 343 VTE-events after THR and HFS per 10,000 patients respectively.

Table 4.1 ***Number of clinical VTE-events per 10,000 patients***

		DVT	Non fatal PE	Fatal PE	Total
		30 days follow-up time			
THR	Arixtra extended	48	17	3	**68**
	No extended prophylaxis	207	71	12	**291**
	Difference	159	55	9	**223**
HFS	Arixtra extended	37	22	39	**98**
	No extended prophylaxis	127	75	136	**339**
	Difference	90	53	97	**240**
		90 days follow-up time			
THR	Arixtra extended	52	18	3	**72**
	No extended prophylaxis	287	99	17	**403**
	Difference	236	81	14	**330**
HFS	Arixtra extended	38	23	41	**102**
	No extended prophylaxis	167	100	178	**445**
	Difference	129	77	137	**343**

4.2 Extended prophylaxis with fondaparinux (Arixtra) versus enoxaparin

4.2.1 Clinical outcomes

Table 4.2 presents the number of VTE-events for different procedures and time periods. The follow-up time is 30 days and 90 days after surgery. For the 30 days follow-up time, fondaparinux is expected to prevent 101 DVT, 35 non-fatal PE and 6 fatal PE or deaths per 10,000 patients after THR. After HFS, fondaparinux is expected to prevent 77 DVT, 45 PE and 82 deaths per 10,000 patients compared to enoxaparin. Hence in total, fondaparinux prevents 142 VTE-events after THR and 204 VTE-events after HFS per 10,000 patients compared to enoxaparin. For the 90 days follow-up time, the corresponding figures are 217 and 273 VTE-events in total per 10,000 patients.

Table 4.2 ***Number of clinical VTE-events per 10,000 patients***

		DVT	Non fatal PE	Fatal PE	Total
		30 days follow-up time			
THR	Arixtra extended	48	17	3	**68**
	Enoxaparin extended	150	51	9	**210**
	Difference	101	35	6	**142**
HFS	Arixtra extended	37	22	39	**98**
	Enoxaparin extended	113	68	122	**302**
	Difference	77	45	82	**204**
		90 days follow-up time			
THR	Arixtra extended	52	18	3	**72**
	Enoxaparin extended	206	71	12	**289**
	Difference	155	53	9	**217**
HFS	Arixtra extended	38	23	41	**102**
	Enoxaparin extended	141	84	150	**376**
	Difference	103	61	110	**273**

4.2.2 VTE-related cost outcomes

Table 4.3 presents costs per patient for VTE-related care at different time periods for fondaparinux and enoxaparin. When the follow-up time increases, the incremental cost of fondaparinux relative to Enoxaparin decreases. For example, the cost difference between the

two drugs at 30 days follow-up time is NOK 1,321 after HFS, while at 5 years follow-up time this difference is expected to be NOK 552. A detailed cost outcome for different VTE-events is presented in Appendix B.

Table 4.3 VTE-related costs per patient, NOK

		30 days	90 days	1 year	5 years
THR	Arixtra extended	4,555	4,674	4,688	4,737
	Enoxaparin extended	2,793	3,107	3,194	3,496
	Difference	1,762	1,567	1,494	1,241
HFS	Arixtra extended	4,514	4,619	4,634	4,685
	Enoxaparin extended	3,192	3,495	3,635	4,132
	Difference	1,321	1,124	998	552

4.2.3 Incremental cost-effectiveness

Table 4.4 presents the incremental cost-effectiveness ratios. The results are presented as cost per clinical VTE avoided, cost per death avoided and cost per life year gained. For instance, the incremental cost effectiveness ratio per avoided VTE-event is the additional cost associated with treating with Arixtra rather than enoxaparin, divided by the number of avoided VTE-events.

Table 4.4 Incremental cost-effectiveness ratios per patient, NOK

		30 days	90 days	1 year	5 years
THR	Cost per VTE avoided	123,891	72,230	-	-
	Cost per death avoided	2,955,208	1,729,339	1,639,281	1,335,367
	Cost per Life Year Gained	258,072	151,019	143,155	118,868
HFS	Cost per VTE avoided	64,724	41,099	-	-
	Cost per death avoided	160,860	102,600	90,993	50,065
	Cost per Life Year Gained	20,237	12,908	11,448	6,331

Cost per avoided VTE-event

As mentioned earlier, fondaparinux is more effective in preventing VTE-events than enoxaparin. For example, at the 90 days time period, fondaparinux prevents an additional 273 VTE-events per 10,000 patients after HFS (Table 4.1). The difference in treatment costs by fondaparinux compared to enoxaparin is NOK 1,124 per patient (Table 4.2). Hence, the cost per avoided VTE after HFS is approximately NOK 41,000 at the 90 days time period.

Cost per death avoided and cost per life year gained

As we see from Table 4.4, the cost per death avoided and cost per life year gained decrease when the follow up time increases. Over a period of 5 years, the cost per death avoided following HFS is expected to be approximately NOK 50,000 while cost per life year gained is around NOK 6,000.

4.2.4 Net cost per avoided VTE-event

The cost per avoided VTE must be compared to the cost of treating each VTE-event. The net costs of avoided VTE-events are therefore costs per avoided VTE-event, reported in Table 4.4, minus hospitalisation costs, see Table 3.8.

Table 4.5 presents net costs per avoided DVT and PE after THR and HFS. For instance, from Table 4.4 we see that the cost per avoided VTE after HFS is NOK 64,724 for 30 days follow up time. From Table 3.8 we see that the hospitalisation cost in this case is NOK 22,730 for DVT and 36,562 in case of PE. Hence, the net cost per avoided case, is $64{,}724 - 22{,}730 = 41{,}994$ NOK in case of DVT and $64{,}724 - 36{,}562 = 28{,}162$ NOK in case of PE after 30 days. We also calculate the net cost per avoided VTE-event, measured as a weighted average of number of DVT and PE cases. As we see from Table 4.2 fondaparinux avoids 204 cases of VTE after HFS by day 30, of which 77 cases (37,75%) are DVT, and 127 (62,25%) are PE cases. Hence, the weighted net cost per avoided VTE is $64{,}724 - (37{,}75\% * 22{,}730) + (62{,}25\% * 36{,}562) = 33{,}384$ NOK. Similarly for the other categories.

Table 4.5 Net cost per avoided VTE-event, NOK

	Event	Day 30	Day 90
THR	DVT	103,011	51,350
	PE	81,747	30,086
	VTE (weighted average)	96,866	45,268
HFS	DVT	41,994	18,369
	PE	28,162	4,537
	VTE (weighted average)	33,384	9,752

The net cost per avoided DVT, PE and VTE following THR is NOK 51,350, 30,086 and 45,268 respectively for 90 days follow-up time. The corresponding costs after HFS is NOK 18,369 for DVT, NOK 4,537 for PE and NOK 9,752 for VTE. These costs must be weighed against benefits not included in the present study, such as the personal utility of the people who stay healthy because of the treatment by fondaparinux.

5. Sensitivity analyses

Several sensitivity analyses were conducted in order to test the validity of the results. The analyses were performed on discount rates and on fondaparinux price, both for THR and HFS patients.

Discount rates

According to the Norwegian guidelines for pharmacoeconomics analysis, we varied the discount rate between 0% to 8%. Table 5.1 and Table 5.2 present the results of the sensitivity analysis on different discount rates. The results of the sensitivity analysis in case of VTE-related costs per patient are presented only for the 5 years follow-up time, since there was no change in the results for 30 days, 90 days and 1 year time period. As we see, changing the discount rates from 0% to 8% had an effect on cost per life year gained, and had a marginal effect on cost per avoided death in 5 years time period.

Table 5.1 Results of the sensitivity analysis on discount rate; VTE-related cost outcomes per patient, NOK, 5 years

		0%	2%	4%	6%	8%
THR	Arixtra extended	4,740	4,738	4,735	4,733	4,731
	Enoxaparin extended	3,519	3,503	3,489	3,475	3,463
	Difference	1,221	1,235	1,247	1,258	1,269
HFS	Arixtra extended	4,688	4,686	4,683	4,681	4,679
	Enoxaparin extended	4,171	4,145	4,121	4,098	4,078
	Difference	518	541	563	583	601

Table 5.2 Results of the sensitivity analysis on discount rate; Incremental cost-effectiveness ratios per patient, NOK

	Disc. rate		30 days	90 days	1 year	5 years
THR	0%	Cost per VTE avoided	123,891	72,230	-	-
		Cost per death avoided	2,955,208	1,729,339	1,639,281	1,314,401
		Cost per Life Year Gained	215,237	125,953	119,394	97,582
	2%	Cost per VTE avoided	123,891	72,230	-	-
		Cost per death avoided	2,955,208	1,729,339	1,639,281	1,328,652
		Cost per Life Year Gained	243,434	142,454	135,035	111,562
	4%	Cost per VTE avoided	123,891	72,230	-	-
		Cost per death avoided	2,955,208	1,729,339	1,639,281	1,341,825
		Cost per Life Year Gained	273,036	159,776	151,456	126,369
	6%	Cost per VTE avoided	123,891	72,230	-	-
		Cost per death avoided	2,955,208	1,729,339	1,639,281	1,354,024
		Cost per Life Year Gained	303,843	177,804	168,545	141,906
	8%	Cost per VTE avoided	123,891	72,230	-	-
		Cost per death avoided	2,955,208	1,729,339	1,639,281	1,365,343
		Cost per Life Year Gained	335,648	196,415	186,187	158,070
HFS	0%	Cost per VTE avoided	64,724	41,099	-	-
		Cost per death avoided	160,860	102,600	90,993	46,940
		Cost per Life Year Gained	18,054	11,515	10,212	5,295
	2%	Cost per VTE avoided	64,724	41,099	-	-
		Cost per death avoided	160,860	102,600	90,993	49,064
		Cost per Life Year Gained	19,501	12,438	11,031	5,978
	4%	Cost per VTE avoided	64,724	41,099	-	-
		Cost per death avoided	160,860	102,600	90,993	51,027
		Cost per Life Year Gained	20,981	13,382	11,868	6,689
	6%	Cost per VTE avoided	64,724	41,099	-	-
		Cost per death avoided	160,860	102,600	90,993	52,844
		Cost per Life Year Gained	22,487	14,343	12,720	7,425
	8%	Cost per VTE avoided	64,724	41,099	-	-
		Cost per death avoided	160,860	102,600	90,993	54,530
		Cost per Life Year Gained	24,016	15,318	13,585	8,183

Arixtra price

Tables 5.3-5.5 present the results of the sensitivity analysis on Arixtra price, where the price reduction varies from 10% up to 20%. For instance, at the 5 years time period, a 20% reduction in the price of fondaparinux makes fondaparinux cost saving after HFS compared to enoxaparin. Table 5.5 presents the net costs per avoided VTE-event. By day 90 after only a 10% price reduction is enough to make fondaparinux more economical compared to enoxaparin.

Table 5.3 Results of the sensitivity analysis on Arixtra price; VTE-related costs per patient, NOK

Procedure			30 days	90 days	1 year	5 years
THR	Arixtra –10%	Arixtra extended	4,252	4,371	4,385	4,434
		Enoxaparin extended	2,793	3,107	3,194	3,496
		Difference	**1,459**	**1,264**	**1,192**	**938**
	Arixtra –20%	Arixtra extended	3,949	4,069	4,082	4,131
		Enoxaparin extended	2,793	3,107	3,194	3,496
		Difference	**1,156**	**962**	**889**	**635**
HFS	Arixtra –10%	Arixtra extended	4,212	4,317	4,331	4,382
		Enoxaparin extended	3,192	3,495	3,635	4,132
		Difference	**1,019**	**822**	**696**	**250**
	Arixtra –20%	Arixtra extended	3,910	4,015	4,029	4,080
		Enoxaparin extended	3,192	3,495	3,635	4,132
		Difference	**717**	**520**	**394**	**-52**

Table 5.4 Results of the sensitivity analysis on Arixtra price; Incremental cost-effectiveness ratios per patient, NOK

			30 days	90 days	1 year	5 years
THR	Arixtra –10%	Cost per VTE avoided	102,596	58,273	-	-
		Cost per death avoided	2,447,251	1,395,190	1,307,092	1,009,475
		Cost per Life Year Gained	213,713	121,839	114,146	89,859
	Arixtra –20%	Cost per VTE avoided	81,301	44,317	-	-
		Cost per death avoided	1,939,294	1,061,042	97,4902	683,582
		Cost per Life Year Gained	169,354	92,659	85,136	60,849
HFS	Arixtra –10%	Cost per VTE avoided	49,925	30,050	-	-
		Cost per death avoided	124,080	75,017	63,453	22,664
		Cost per Life Year Gained	15,610	9,438	7,983	2,866
	Arixtra –20%	Cost per VTE avoided	35,126	19,001	-	-
		Cost per death avoided	87,301	47,434	35,912	-4,737
		Cost per Life Year Gained	10,983	5,968	4,518	-599

Table 5.5 Results of the sensitivity analysis on Arixtra price; Net cost per avoided VTE-event, NOK

		Event	Day 30	Day 90
THR	Arixtra –10%	DVT	81,716	37,393
		PE	60,452	16,129
		VTE (weighted average)	75,571	31,311
	Arixtra –20%	DVT	60,421	23,437
		PE	39,157	2,173
		VTE (weighted average)	54,276	17,355
HFS	Arixtra –10%	DVT	27,195	7,320
		PE	13,363	-6,512
		VTE (weighted average)	18,585	-1,297
	Arixtra –20%	DVT	12,396	-3,729
		PE	-1,436	-17,561
		VTE (weighted average)	3,786	-12,346

6. Discussion and conclusion

Our analyses were based on statistics from *Norwegian National Register of Hospital Patients (NPR),* which included 50,000 patients who underwent HFS and THR from 1999 to 2001. Of these patients, over 46,000 were selected in the analysis. All cost estimates in the model were based on the Norwegian unit costs, i.e. DRG-costs for hospital stays and other relevant costs.

The model used in the analysis is a "core" model that has been developed to examine the cost-effectiveness of extended prophylaxis with fondaparinux (Arixtra®) from one week to four weeks in patients undergoing hip fracture surgery and total hip replacement. In the model, we assume that patients receive prophylaxis either with fondaparinux or enoxaparin. The model conducts estimates of expected incidence of clinical VTE and VTE-related deaths, and expected costs estimates of VTE-related care. In addition, cost per VTE-event avoided, cost per death avoided and cost per life-year saved are calculated in the model. The results are calculated for multiple time periods: from surgery to day 30, day 90, year 1 and year 5. The analysis has also been conducted for the scenario where patients recieve no extended prophylaxis after hospital discharge.

The results from the clinical outcomes show that in general, fondaparinux is the more effective drug in terms of preventing VTE-events both compared to the scenario with no extended prophylaxis after surgery, and compared to extended prophylaxis with enoxaparin in all time periods. For instance, by day 30 fondaparinux is expected to prevent between 142 and 204 VTE-events per 10,000 patients after THR and HFS respectively compared to enoxaparin. For the 90 days follow-up time, the corresponding figures are 217 and 273 avoided VTE-events per 10,000 patients compared to enoxaparin. In Norway, around 16.700 THR and HFS operations are performed every year. This means that extended prophylaxis with fondaparinux avoids 363 VTE-events after THR and 456 VTE-events after HFS compared to enoxaparin. Hence, in total 820 VTE-events are avoided per year.

Fondaparinux is more cost-effective in terms of preventing VTE-events compared to enoxaparin. When the follow-up time increases, the incremental cost of fondaparinux relative to enoxaparin decreases. For example, the cost difference between the two drugs at 30 days follow-up time is NOK 1,321 after HFS, while at 5 years follow-up time this difference is expected to be NOK 552.

By day 90, cost per avoided VTE after THR and HFS is estimated to approximately NOK 72,000 and 41,000 respectively. The economic gains of avoided VTE-events for the society are cost savings related to hospitalisation of patients with VTE. Net costs of avoided VTE-events are therefore costs per avoided VTE-event minus hospitalisation costs. For 90 days follow-up time, the net cost per avoided VTE-event following THR is NOK 45,268, while the corresponding cost after HFS is NOK 9,752. These costs must be weighed against benefits not included in the present study, such as the personal utility of the people who stay healthy because of the treatment by fondaparinux.

We estimated cost per death avoided and cost per life year gained by using fondaparinux rather than enoxaparin. Over a period of 5 years, cost per death avoided following HFS is expected to be approximately NOK 50,000, while cost per life year gained is around NOK 6,000.

The results have shown that the costs per avoided VTE-event, net costs, cost per death avoided and cost per life year gained are higher after THR than HFS. There could be several reasons for why this is the case. First, fondaparinux avoids more VTE-events, especially fatal PE, after HFS compared to THR. Second, the length of stay in hospital by readmissions is higher among THR patients than HFS. Finally, THR patients have higher additional life expectancy than HFS patients.

The sensitivity analysis conducted on discount rates confirmed the robustness of our results. Changing the discount rates from 0% to 8% has a marginal effect on VTE-related costs, cost per avoided death and cost per life year gained. The results are however sensitive to price reductions of Aixtra. Finally, the cost-benefit analysis shows that a 10% price reduction reduces the net costs per avoided VTE after HFS, and it makes fondaparinux more economical (cost saving) compared to enoxaparin.

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Appendix A: Estimation of model probabilities

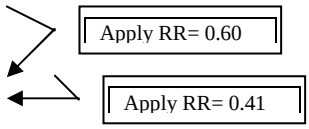
This appendix is a summary of estimation of the model probabilities used in the fondaparinux long-term prophylaxis model presented in "Cost-effectiveness of extending prophylaxis with fondparinux against venous thromboembolism in patients undergoing hip fracture surgery and total hip replacement (2003)".

Risk of Subclinical DVT

Patients are assumed to be at risk of developing a thrombus through Day 30 following surgery. The rate of subclinical DVT at Day 30 was based on the rate of venographically detected DVT from several different trials and published meta-analyses. Rates of subclinical DVT and PE at Day 30 were available from extended prophylaxis trial data for HFS patients using fondaparinux (Penthifra *Plus*, Eriksson 2003). Rates were available from the literature for THR patients using LMWH/heparin (Eikelboom, 2001). In cases where the subclinical rate was not available, an estimate was constructed using relative risks on known subclinical rates, ie assuming that the relative benefit of extending prophylaxis with a given drug will be the same in either the HFS or THR population.

- **Estimation of subclinical DVT rates at day 30 in patients undergoing HFS:**

Prophylaxis	All VTE	Clinical VTE	Subclinical DVT
Fondaparinux 7-day	35%	2.73%	32.27%
Fondaparinux 28-day	1.44%	0.31%	1.14%
Enoxaparin 7-day			53.38%
Enoxaparin 28-day			22.10%



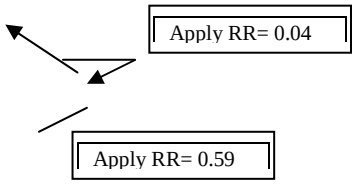
Among HFS patients receiving short-term duration prophylaxis with fondaparinux, the rate of subclinical DVT at Day 30 (32.3%) was obtained by subtracting the rate of symptomatic events (2.7%) from the all VTE rate (35%). The rate of subclinical DVT for extended prophylaxis (1.1%) was obtained similarly (Eriksson 2003).

For HFS patients receiving short term duration prophylaxis with enoxaparin, the rate of subclinical DVT at day 30 (53.4%) was estimated by adjusting the corresponding rate for HFS patients receiving short term duration fondaparinux prophylaxis (32.3%) , using the relative risk ratio of VTE for fondaparinux versus enoxaparin in HFS patients at Day 30 (RR= 0.60) (Gordois, 2003). The rate of subclinical DVT at day 30 among HFS patients

receiving extended duration prophylaxis with enoxaparin was calculated by multiplying the rate of subclinical DVT calculated above by the relative risk of subclinical DVT for short term duration enoxaparin versus extended enoxaparin (RR= 0.41) (Eikelboom 2001), ie assuming that the benefit of extending prophylaxis with enoxaparin that was observed in patients undergoing total hip replacement would be the same in patients undergoing surgery for hip fracture.

- **Estimation of subclinical DVT rates at day 30 in patients undergoing THR:**

Prophylaxis	All VTE	Clinical VTE	Subclinical DVT
Fondaparinux 7-day			10.95%
Fondaparinux 28-day			0.45%
Enoxaparin 7-day			18.60%
Enoxaparin 28-day			7.70%



Among THR patients receiving enoxaparin, the rate of subclinical DVT at Day 30 was based on data from a meta-analysis of extended prophylaxis for THR patients using LMWH /heparin (Eikelboom 2001). The rate of subclinical DVT at Day 30 for the short-term duration prophylaxis group was 18.6% versus 7.7% for the extended duration prophylaxis group.

For THR patients receiving short term duration prophylaxis with fondaparinux, the rate of subclinical DVT at day 30 (10.9%) was similarly estimated by adjusting the rate of subclinical DVT for patients receiving short term duration prophylaxis with enoxaparin (18.6%) using the relative risk of VTE for fondaparinux versus enoxaparin in THR patients at Day 30 (0.59) as estimated by Gordois when both drugs were administered for a median duration of 7-days (Gordois, 2003). For THR patients receiving extended duration prophylaxis with fondaparinux, the rate of subclinical DVT at Day 30 (0.45 %) was calculated by multiplying the estimated rate of subclinical DVT at Day 30 for THR patients receiving short term duration prophylaxis described above (10.9%) by the relative risk of all VTE [7] for fondaparinux short term duration prophylaxis versus extended prophylaxis among HFS patients (0.04) (Eriksson, 2003) ie assuming that the benefit of extending prophylaxis with fondaparinux that was observed in patients undergoing surgery for hip fracture would be the same in patients undergoing total hip replacement.

[7] Conservative proxy for the relative risk for subclinical DVT

Risk of clinical VTE

Clinical VTE at Day 7:

The rate of clinically symptomatic VTE at day 7 was based on published trial data.

For HFS patients, the rate for fondaparinux of 0.68% is from the PenthifraPlus trial data; this compares to the rate of 1.56% for enoxaparin (LMWH), which was derived by adjusting this rate using the relative risk of all VTE at Day 11 for enoxaparin versus fondaparinux ((0.44) when both drugs were administered for a median duration of 7-days in patients undergoing hip fracture surgery (Eriksson 2001).

For THR patients, the rate for enoxaparin (0.69%) has been estimated from the literature, using the studies included in the meta-analysis published by Eikelboom, for which such rates were available (Eikelboom, 2001, Bergqvist 1996, Dahl 1997, Lassen 1998, Manganelli 1998, Heit 2000). The rate for fondaparinux (0.39%) was then derived by adjusting this rate using the relative risk of all VTE at Day 11 for enoxaparin versus fondaparinux (0.57) when both drugs were administered for a median duration of 7-days in patients undergoing total hip replacement (Lassen 2002, Turpie 2002).

Clinical VTE Day 7-Day 30:

The rates of clinical VTE for HFS patients receiving fondaparinux and THR patients receiving enoxaparin were taken directly from extended prophylaxis trial data. For the rates of clinical VTE for HFS patients receiving enoxaparin and THR patients receiving fondaparinux, an estimate was constructed similarly as above using relative risks on known clinical rates, ie assuming that the relative benefit of extending prophylaxis with a given drug will be the same in either the HFS or THR population

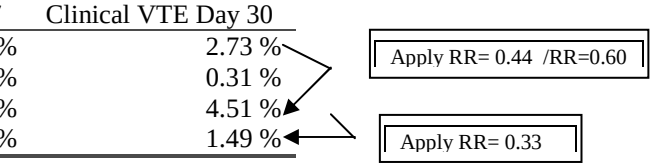
Among HFS patients receiving fondaparinux, the rate of clinical DVT at Day 30 was 2.7% for short term duration prophylaxis and 0.3% for extended prophylaxis (Eriksson 2003).

For HFS patients receiving short term duration prophylaxis with enoxaparin, the rate of clinical VTE at day 30 (4.5%) was estimated by adjusting the rate of symptomatic VTE at Day 30 for HFS patients receiving short term duration fondaparinux prophylaxis (2.7%) by using the relative risk ratio of VTE for fondaparinux versus enoxaparin in HFS patients at Day 30 (0.60) (Gordois, 2003). The rate of clinical VTE for HFS patients receiving extended

duration prophylaxis with enoxaparin (1.5%) was estimated by adjusting the rate for the short term group (4.5%) by the relative risk for symptomatic VTE (0.33) for short-term duration enoxaparin versus extended enoxaparin (Eikelboom 2001).

Estimation of clinical event rates up to day 30 in HFS:

Prophylaxis	Clinical VTE Day 7	Clinical VTE Day 30
Fondaparinux 7-day	0.68 %	2.73 %
Fondaparinux 28-day	0.68 %	0.31 %
Enoxaparin 7-day	1.56 %	4.51 %
Enoxaparin 28-day	1.56 %	1.49 %

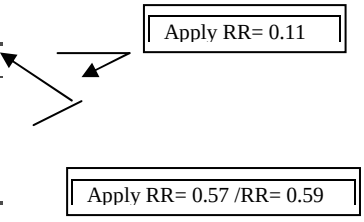


Among THR patients receiving enoxaparin, the rate of clinical DVT at Day 30 was based on data from the meta-analysis of extended prophylaxis using heparin (Eikelboom 2001). The rate of clinical DVT at Day 30 for the short term duration prophylaxis group was 4.3% versus 1.4% for the extended duration prophylaxis group.

Among the THR population, the rate of clinical VTE at day 30 for patients on short term duration fondaparinux prophylaxis (2.5%) was derived by multiplying the rate of clinical VTE at Day 30 among THR patients in the short term duration enoxaparin group (4.3%) by the relative risk of VTE for fondaparinux versus enoxaparin in THR patients at Day 30 (0.59) as estimated by Gordois when both drugs were administered for a median duration of 7-days (Gordois, 2003). Then, the rate of clinical VTE in the extended duration group (0.28%) was estimated by multiplying the rate for the short term duration group described above (2.5%) by the relative risk of symptomatic VTE for fondaparinux short term duration prophylaxis versus extended prophylaxis (0.11) among HFS patients (Eriksson, 2003).

Estimation of clinical event rates up to day 30 in THR:

Prophylaxis	Clinical VTE Day 7	Clinical VTE Day 30
Fondaparinux 7-day	0.39 %	2.52 %
Fondaparinux 28-day	0.39 %	0.28 %
Enoxaparin 7-day	0.69 %	4.29 %
Enoxaparin 28-day	0.69 %	1.42 %



Clinical VTE Day 30-Day 90

The study of the temporal pattern of VTE events conducted by White et al. was used to calculate the ratio of the number of clinical events from day 60-day 90 over the number of clinical events from day 7 to day 30 (White, 1998). Data for patients receiving no extended

prophylaxis were extrapolated to the day30- day 90 time period by applying this ratio to the actual rate of clinical events reported from day 7- day 30. A contingent probability was then constructed to calculate the probability of a clinical VTE at day 90, given the probability of a subclinical VTE at day 30. This probability was then used to estimate the clinical rates at day 90. A similar approach was made for both HFS and THR and a contingent probability was thus calculated separately for the HFS and THR patient populations.

Risk to develop clinical symptomatic VTE after day 30 (contingent probability):

	HFS	THR
All VTE at Day 30	0,35000	0,18600
Clinical DVT at Day 30	0,02727	0,0429
Clinical DVT rate at Day 90	0,01251	0,01968
Total DVT/PE contingent probability	*0,0388*	*0,1058*

Proportion of Clinical DVT/PE

Due to the limited number of individual events (DVT or PE) reported, the event rates have been combined into a clinical VTE rate. In order to assess the individual consequences of DVT and PE, the clinical VTE rate was proportioned between DVT and PE based on the following ratios, calculated using larger populations (It is assumed to differ only by type of orthopedic surgery and was not considered to be dependent on type of prophylaxis). In the HFS patient population, the proportion of VTE that was allotted to DVT was 37.5% versus 62.5% for PE (Eriksson 2001, Eriksson 2003). In the THR patient population, the proportion was 71.3% for DVT and 28.7% for PE (Colwell 1999, Leclerc 1998).

Major Bleeding

The risks of major haemorrhage (defined as 1/ fatal bleeding, bleeding in a critical organ, bleeding leading to re-operation and 2/ overt bleeding associated with a bleeding index>2[8]) following prophylaxis were taken from trial data of short-term prophylaxis enoxaparin versus fondaparinux (Lassen 2002, Turpie 2002, Eriksson 2001) as well as trial data of extended duration prophylaxis (Eriksson 2003). The model assumed no difference between active groups in the extended phase of prophylaxis (see table 2).

[8] Number of units of packed red blood cells or whole blood transfused, *plus* [prebleeding *minus* postbleeding hemoglobin values in g/dl]

False-Positive Clinical DVT & PE

A false-positive rate was applied to the decision tree model to assess patients incorrectly suspected of having a DVT (10%) or PE (2%). Rates are modal values taken from the literature (Davies 2000, Devlin 1998, Drummond 1994, Hawkins 1997, Hillson 1990, Levin 1998, Levin 2001, Lloyd 1997, Lloyd 2001, Menzin 1995, Nicolaides 1999, O'Brien 1994, Oster 1987a, Oster 1987b, Pechevis 2000, Szuchs 1999). The false-positive rates were assumed to be the same for both surgery groups and type of prophylaxis.

Risk of Recurrent VTE

The risk of recurrent VTE was calculated using data from a long-term follow-up study of patients with objectively verified symptomatic DVT (Prandoni 1996). The incidence over five years of recurrence for the overall population was 21.5%, while the relative risk of recurrence for patients who had undergone major orthopedic surgery was 0.21. In order to estimate the risk of recurrence in the THR and HFS populations, the overall incidence was multiplied by the relative risk to get the estimate of 4.5%.

Since the above study did not report the recurrence rate for the first 90 days following a VTE, data from other treatment trials were used to estimate the risk of recurrence during treatment (2.6%) (Hull 1982a, Hull. 1982 b, Lagerstedt 1985, Pini 1994, Schulman 1995, Das1996). This rate was also adjusted using the relative risk of 0.21 from above; this resulted in a recurrence rate of 0.6% for the first 90 days and 3.9% for the period from day 90 to year 5. The latter recurrence rate was apportioned according to the temporal pattern observed in the long-term recurrence study (Prandoni 1996).

Risk of Post-Thrombotic Syndrome

The probability of developing PTS for patients who had a clinical VTE during first 90 days (28% at 5 years) was based on data from a prospective study of the long-term clinical course of acute VTE over one, two and five years (Prandoni 1996). Among patients who had only a subclinical VTE, the risk of PTS (12%) was based on the weighted average incidence of PTS among orthopedic surgery patients with venographically detected DVT in two retrospective studies (Ginsberg 2000, Siragusa 1997). In all cases, the risk of PTS was assumed to begin after day 90 (see table 3).

Mortality

The model accounts for the risk of fatal PE, and also for deaths from all other causes. The risk of *fatal PE* was assumed to differ only by type of orthopedic surgery and was not considered to be dependent on type of prophylaxis. For THR patients having a PE, the risk of fatal PE (14.5%) was estimated using four large studies of VTE incidence (Pelligrini, LeClerc 1998, Colwell 1999, Heit 2000). Since literature-based estimates were not available for HFS, the PE fatality rate from the Pentifra and Penthifra Plus trial was used to estimate the risk of fatal PE in this group (64%) (Eriksson 2001, Eriksson 2003).

Life expectancy

For THR patients, life expectancy was assumed to be the same as in the general population matched for age and sex with the studied cohort (source: national statistics). Hip fracture is associated with substantial mortality and morbidity, and was reported to result in a 25% reduction in life expectancy (Braithwaite, 2003) and survival was adjusted in the HFS patients accordingly.

Tables

Table 1. Prophylaxis dependent VTE- related probabilities

Table 1.1 VTE-related probabilities / HFS

Type of prophylaxis	HFS	Reference(s)
Enoxaparin		
Day 1-Day 7		
Symptomatic VTE	0.0156	Calculation
Extended Prophylaxis		
Symptomatic VTE before Day 30	0.0149	Calculation
Subclinical VTE - Day 7-Day 30	0.2210	
Risk to develop Symptomatic DVT - Day 30-Day 90	0.0388	Calculation
No Extended Prophylaxis		
Symptomatic VTE before Day 30	0.0451	Calculation
Subclinical VTE - Day 7-Day 30	0.5338	Calculation
Risk to develop Symptomatic DVT - Day 30-Day 90	0.0388	Calculation
Fondaparinux		
Day 1-Day 7		
Symptomatic VTE	0.0068	Eriksson 2003
Extended Prophylaxis		
Symptomatic VTE before Day 30	0.0031	Eriksson 2003
Subclinical VTE - Day 7-Day 30	0.0114	Eriksson 2003
Risk to develop Symptomatic DVT - Day 30-Day 90	0.0388	Calculation
No Extended Prophylaxis		
Clinical Symptomatic VTE before Day 30	0.0273	Eriksson 2003
Subclinical VTE - Day 7-Day 30	0.3227	Eriksson 2003
Risk to develop Symptomatic DVT - Day 30-Day 90	0.0388	Calculation

Table 1.2 VTE-related probabilities / THR

Type of prophylaxis	THR	Reference(s)
Enoxaparin		
Day 1-Day 7		
Symptomatic VTE	0.0069	Bergqvist 1996, Dahl 1997, Lassen 1998, Manganelli 1998, Heit 2000 (from Eikelboom 2001)
Extended Prophylaxis		
Symptomatic VTE before Day 30	0.0142	Eikelboom 2001
Subclinical VTE - Day 7-Day 30	0.0770	Eikelboom 2001
Risk to develop Symptomatic DVT - Day 30-Day 90	0.1058	Calculation
No Extended Prophylaxis		
Symptomatic VTE before Day 30	0.0429	Eikelboom 2001
Subclinical VTE - Day 7-Day 30	0.1860	Eikelboom 2001
Risk to develop Symptomatic DVT - Day 30-Day 90	0.1058	Calculation
Fondaparinux		
Day 1-Day 7		
Symptomatic VTE	0.0039	Calculation
Extended Prophylaxis		
Symptomatic VTE before Day 30	0.0028	Calculation
Subclinical VTE - Day 7-Day 30	0.0045	Calculation
Risk to develop Symptomatic DVT - Day 30-Day 90	0.1058	Calculation
No Extended Prophylaxis		
Clinical Symptomatic VTE before Day 30	0.0252	Calculation
Subclinical VTE - Day 7-Day 30	0.1095	Calculation
Risk to develop Symptomatic DVT - Day 30-Day 90	0.1058	Calculation

Table 2. Probabilities of major bleeding

Bleeding index >2[1]				**Other Major Bleeding[2]**			
		Fondaparinux	**Enoxaparin**			**Fondaparinux**	**Enoxaparin**
	7-day	extended	extended		7-day	extended	extended
HFS				HFS			
Day 1-7	0,018	0,018	0,019	Day 1-7	0,004	0,004	0,004
Day 8-30	0	0,018	0,018	Day 8-30	0,006	0,006	0,006
THR				THR			
Day 1-7	0,026	0,026	0,016	Day 1-7	0,003	0,003	0,003
Day 8-30	0	0,018	0,018	Day 8-30	0,006	0,006	0,006

Sources: Lassen 2002, Turpie 2002, Eriksson 2001, Eriksson 2003

[1] overt bleeding associated with a bleeding index>2[9]

[2] fatal bleeding, bleeding in a critical organ, bleeding leading to re-operation

Table 3. Other probabilities

	Type of procedure		
Parameter	**HFS**	**THR**	**Reference(s)**
False-positive DVT	0.10	0.10	Davies 2000, Devlin 1998, Drummond 1994, Hawkins 1997, Hillson 1990, Levin 1998, Levin 2001, Lloyd 1997, Lloyd 2001, Menzin 1995, Nicolaides 199, O'Brien 1994, Oster 1987a, Oster 1987b, Pechevis 2000, Szuchs 1999
False-positive PE	0.02	0.02	Same as above
Death			
Due to fatal PE	0.64	0.0145	Leclerc 1998, Colwell 1999, Heit 2000, Pelligrini 1996Eriksson 2001, Eriksson, 2003
Due to recurrent VTE	0.1231	0.0279	Prandoni 1996
All other causes:			According to national statistics
Post-thrombotic syndrome			
Patients with clinical DVT or PE			
Day 90 to Year 1	0.1730	0.1730	Prandoni 1996
Year 2	0.0550	0.0550	Prandoni 1996
Year 3 +	0.0173	0.0173	Prandoni 1996
Patients with subclinical DVT			
Day 90 to Year 1	0.0722	0.0722	Ginsberg 2000, Siragusa 1997
Year 2	0.0229	0.0229	Ginsberg 2000, Siragusa 1997
Year 3 +	0.0072	0.0072	Ginsberg 2000, Siragusa 1997
Recurrent VTE			
Day 1- day 30	0.0018	0.0018	Hansson 2000
Day 31-Day 90	0.0036	0.0036	Hansson 2000
Chronic phase (day 91- year 5)	0.0397	0.0397	Hansson 2000

[9] Number of units of packed red blood cells or whole blood transfused, *plus* [prebleeding *minus* postbleeding hemoglobin values in g/dl]

Appendix B. Detailed cost outcomes after THR and HFS

Table 1. THR –Cost outcomes per patient, NOK

	Day 30	Day 90	Year 1	Year 5
ARIXTRA extended				
Prophylaxis	3162	3162	3162	3162
Major bleeding	1089	1089	1089	1089
Suspected not confirmed VTE	174	280	280	280
Clinical DVT	92	99	99	99
Clinical PE	38	43	43	43
Recurrences	0	1	2	7
PTS	0	0	12	56
TOTAL	4555	4674	4688	4737
ENOXAPARIN extended				
Prophylaxis	1320	1320	1320	1320
Major bleeding	868	868	868	868
Suspected not confirmed VTE	159	256	256	256
Clinical DVT	292	411	411	411
Clinical PE	154	250	250	250
Recurrences	0	3	9	29
PTS	0	0	81	363
TOTAL	2793	3107	3194	3496

Table 1. HFS –Cost outcomes per patient, NOK

	Day 30	Day 90	Year 1	Year 5
ARIXTRA extended				
Prophylaxis	3171	3171	3171	3171
Major bleeding	919	919	919	919
Suspected not confirmed VTE	178	270	270	270
Clinical DVT	86	89	89	89
Clinical PE	160	169	169	169
Recurrences	0	1	2	6
PTS	0	0	13	61
TOTAL	4514	4619	4634	4685
ENOXAPARIN extended				
Prophylaxis	1326	1326	1326	1326
Major bleeding	934	934	934	934
Suspected not confirmed VTE	137	209	209	209
Clinical DVT	263	325	325	325
Clinical PE	532	699	699	699
Recurrences	0	2	7	21
PTS	0	0	135	619
TOTAL	3192	3495	3635	4132