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Prophylaxis with Fondaparinux versus Enoxaparin against Venous Thromboembolism after Major Orthopaedic Surgery

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.

CONTENTS

ABSTRACT

Objective: 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 report presents cost-effectiveness analysis of fondaparinux compared with enoxaparin, the most common prophylaxis of VTE. The cost-effectiveness of short-term duration (one week) prophylaxis as well as prolonged prophylaxis (four weeks) with fondaparinux versus enoxaparin are examined here.

Methods: The models used in the analyses are developed to simulate the impact of prophylaxis with fondaparinux compared with enoxaparin after major orthopaedic surgery. The short-term model examines the cost-effectiveness of fondaparinux in patients undergoing total knee replacement, total hip replacement and hip fracture surgery. The second model examines the impact of extended prophylaxis following hip fracture surgery, and extrapolates the results in patients undergoing total hip replacement.

Data: The analysis is based on Norwegian data, which include about 55.000 patients who underwent major orthopaedic surgery in the period from 1999 to 2001. All cost estimates in the models are based on the Norwegian unit costs.

Results: The results from clinical outcomes show that in general, fondaparinux compared with enoxaparin is the more effective drug in terms of preventing VTE-events (deep vein thrombosis, fatal and not fatal pulmonary embolism). By day 90 after surgery, fondaparinux is expected to avoid additional 194 VTE-events after total knee replacement, 146 events after total hip replacement and 249 events after hip fracture surgery per 10.000 patients compared to enoxaparin. Extended prophylaxis with fondaparinux prevents 217 and 273 VTE-events per 10.000 patients following total hip replacement and hip fracture surgery respectively compared to enoxaparin at 90 days follow-up time.

Short-term prophylaxis with fondaparinux is also more cost-effective than enoxaparin. From day 30 onward, fondaparinux is cost saving after major orthopaedic surgeries. Fondaparinux is also highly cost saving with respect to incremental costs per VTE avoided, VTE-related deaths avoided and costs per life-year gained. However, in the case of extended prophylaxis, fondaparinux is the higher cost alternative relative to enoxaparin, but the cost difference decreases over time. The sensitivity analyses confirmed the robustness of the main results.

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. 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). 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 50%-60% in patients undergoing major orthopaedic surgery, while the risk of developing PE is 7-11% (Geerts et al., 2001). While DVT is the most common form of VTE, PE has a higher mortality risk.

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 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%), while 10% were due to total knee replacement (TKR).

The prevalence of VTE is high in patients undergoing major orthopaedic surgery (Geerts et al., (2001). In Norway, the most common prophylactic drugs for prevention of VTE after

[1] Norwegian National Register of Hospital Patients.

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). Given the large number of major orthopaedic surgeries in Norway and costs related to treatment of VTE, determining the most cost-effective prophylaxis against thromboembolism is an important issue.

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. The objective of this study is to present cost-effectiveness analyses of short-term and long-term duration prophylaxis with fondaparinux versus enoxaparin after major orthopaedic surgery. The short-term prophylaxis refers to the prophylaxis during the inpatient period (e.g. 1 week), while the long-term duration refers to extended prophylaxis after the discharge from the hospital (e.g. additional 3-4 weeks). The outcome of the cost-effectiveness analysis is important for the health authorities concerning price and reimbursement decisions, and for physicians at hospitals concerning inclusion of this new drug in treatment praxis.

The study is based on international simulation models developed for determining the costs and effects of fondaparinux versus enoxaparin. The study provides estimates of the incidence of clinical VTE and VTE-related deaths, treatment costs per patient, incremental cost per VTE-event avoided, cost per death avoided and 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 55.000 major orthopaedic surgery patients. Further, all estimates of unit costs in the model are based on costs within the *Norwegian Diagnosis Related Group (DRG)* and other relevant costs for year 2004.

1.3 Fondaparinux as prophylaxis against VTE

Fondaparinux is indicated for prophylaxis of VTE in patients undergoing orthopaedic surgeries and was launched in Norway in June 2002 (ATC-code B01AX05). The following

sections present a literature overview over Phase III clinical trials of fondaparinux and its pharmacoeconomic evaluations compared with enoxaparin.

1.3.1 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. (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 2,5mg postoperatively. In Pentathlon 2000 and Pentamaks, patients treated with Enoxaparin received postoperative injections of 30mg twice daily (US practice), while in Ephesus and Penthifra 40mg enoxaparin was given once daily (European practice), starting preoperatively. Ephesus and Pentathlon 2000 were conducted for total hip replacement. 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.

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. There were no differences between fondaparinux and enoxaparin in rates of fatal bleeding, bleeding in a critical organ or bleeding leading to reoperation. The incidence of major bleeding (bleeding index of ≥ 2)[2] was 1% higher with fondaparinux compared with enoxaparin (2,7% vs 1,7%; P=0.008). A *post hoc* analysis showed that the bleeding risk was related to the timing of the first dose. The bleeding risk was highest when fondaparinux was administered within the first 6 hours postoperatively. However, when fondaparinux was injected after the first 6 hours postoperatively, there was no difference in bleeding rates between fondaparinux and enoxaparin.

[2] Bleeding index of ≥ 2 is defined as the number of units of packed red blood cells or whole blood transfused plus the pre-bleeding minus post-bleeding hemoglobin values (g/dL).

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% (95% CI, 87,2% to 99,7%; P<0,001). Extended prophylaxis was associated with a lower incidence of proximal, total or distal DVT and fewer symptomatic VTEs than prophylaxis for one week (Eriksson, et al., 2003). Fondaparinux was generally well tolerated and there was no significant increase in the incidence of bleeding events with prolonged prophylaxis compared with standard duration (short-term) prophylaxis.

1.3.2 Cost-effectiveness studies of fondaparinux

Short-term duration prophylaxis

Pharmacoeconomic studies of fondaparinux prophylaxis have been performed in several countries. These studies were undertaken from the perspective of the healthcare payers, and compared the costs and effects of prophylaxis with fondaparinux versus enoxaparin. The main results from some of these studies are presented in the following. In all studies mentioned here, fondaparinux was found to be more effective than enoxaparin in preventing VTE-events.

Gordois et al. (2003) is based on data from United Kingdom. The study concludes that using fondaparinux in UK reduces costs by £27 per patient 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 and 2005) 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. Recently, several non-European studies have been published, concluding the cost-effectiveness of fondaparinux compared with enoxaparin; two US-studies by Sullivan et al. (2004) and Wade et al. (2004), and a Canadian-study by Dranitsaris, et al. (2004).

Extended duration prophylaxis

The cost-effectiveness of extended prophylaxis (28 days) with fondaparinux after hip fracture surgery has been studied in the US (Sullivan and Kwong, 2003a; 2003b). These studies

concluded that extended prophylaxis with fondaparinux instead of enoxaparin would avoid 204 VTE-events (including 82 deaths) per 10.000 patients by day 30 after surgery, and 278 VTE-events (including 111 deaths) per 10.000 patients by day 90 after hip fracture surgery. Further, fondaparinux was found to be cost saving compared to enoxaparin from day 90 onward.

2. Method

The study is based on simulation models that have been developed in order to examine the cost-effectiveness of fondaparinux compared with enoxaparin for both short-term and extended duration prophylaxis. The short-term model examines the cost-effectiveness of fondaparinux in patients undergoing total knee replacement, total hip replacement and hip fracture surgery. The second model examines the impact of extended prophylaxis following hip fracture surgery, and extrapolates the results in patients undergoing total hip replacement.

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 models. The models 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 models are the incidence of clinical VTE and VTE-related deaths, and treatment costs per patient. In addition, the extended duration model estimates the incremental cost per VTE-event avoided, incremental cost per death avoided and incremental cost per life-year gained. In order to make comparisons between the results of the short-term and extended duration analyses, we also provide own estimates of the incremental costs per VTE-event avoided, death avoided and incremental cost per life-year gained for the short-term prophylaxis.

2.1 Model structure

The design of the main 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 in the mid-1980's (Oster, et al., 1987). In the original model, patients were assumed to be at risk of developing VTE only during the inpatient period. In the fondaparinux 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 short-term duration model estimates the clinical outcomes and costs of VTE prophylaxis in patients undergoing hip fracture surgery, and total knee and hip replacement, developed by Gordois et al. (2003) and Sullivan et al. (2002). The structure of the extended duration model is close to the short-term duration model. This model estimates the clinical outcomes and costs of extending VTE prophylaxis in patients undergoing hip fracture surgery, and extrapolates the results in patients undergoing total hip replacement.

An underlying assumption of the models is that patients undergoing either orthopaedic surgery 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 models, patients are considered to be at risk of clinical VTE events for a period of 90 days following surgery. From day 90 and up to 5 years after surgery, patients are assumed to be at risk for recurrent VTE events (fatal or non-fatal) and post-thrombotic syndrome (PTS). Patients with 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. Finally, 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.

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 to day 30 time frame which corresponds to the extended duration prophylaxis, day 30 to day 90, when patient is still at risk of clinical VTE, and the day 90 to year 5 period which includes the chronic phase. The possible outcomes at each node are as follows.

1. **Day 7**
    - Symptomatic (clinical) VTE events (DVT, fatal and non-fatal PE)
    - Bleeding events (major bleedings)

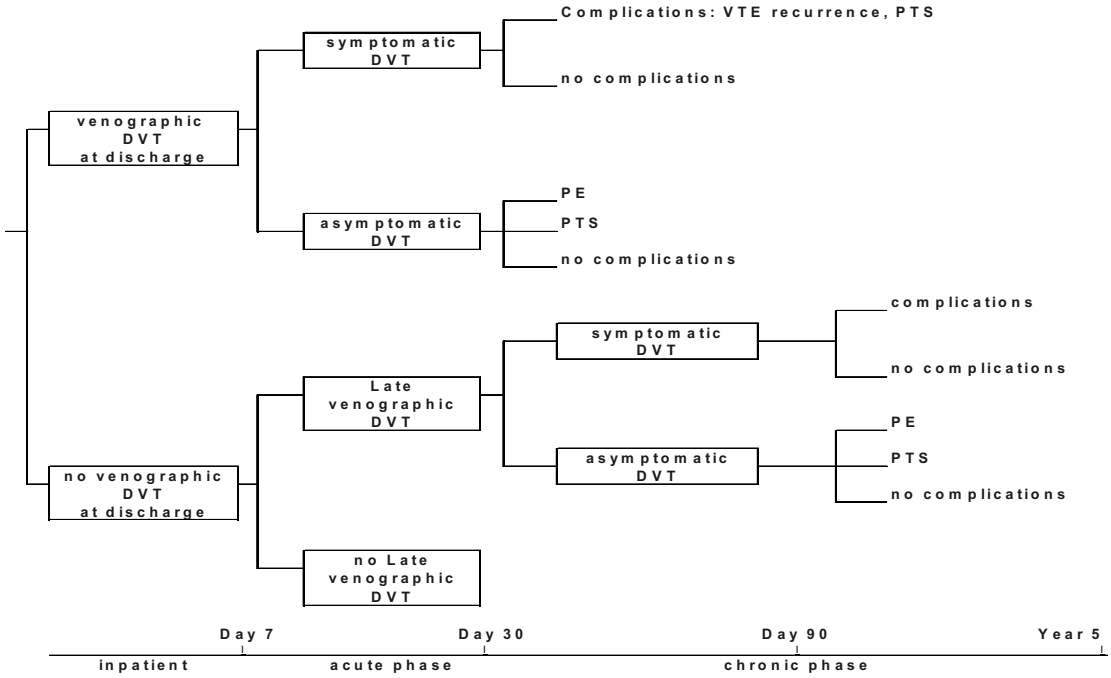
2. **Day 30**
    - Venographically detected (sub-clinical) DVT
    - Symptomatic (clinical) VTE events (DVT, fatal and non-fatal PE)
    - False-positive VTE events
    - Bleeding events (major bleedings)

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

Figure 1 illustrates the graphic representation of the model.

Figure 1: Graphic representation of the model



Source: Policy Analysis Inc (2003)

2.2 Estimation of model probabilities

Event probabilities in the models are derived from fondaparinux Phase III trial data (Eriksson, 2001; Bauer, 2001; Lassen, 2002; Turpie, 2002; Eriksson, 2003) and data in published literature sources. For details on model probabilities see Gordois et al. (2003) and Sullivan et al. (2004). Estimation of the underlying probabilities in the extended duration 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 models 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 [3] (prophylaxis related) and clinically relevant.
- Post thrombotic syndrome (PTS): acute and chronic phase.

2.4 Measures

The models can be run for hypothetical cohorts of either 1.000 or 10.000 patients. Model results are calculated for multiple time points including surgery to hospital discharge, Day 30, Day 90, Year 1 and Year 5 after sugery. The models generate estimates of the expected incidence of symptomatic VTE events (DVT and PE), as well as the expected number of VTE-related deaths. The short-term duration model estimates the expected costs of VTE-related care for TKR, THR, and HFS, while the extended duration model generates estimates of the expected costs of VTE-related care for THR and HFS, incremental cost per VTE event avoided, incremental cost per death avoided and incremental cost per life-year gained.

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

3. Estimation of resource use and unit costs used in the analysis[4]

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 surgery. The majority of these operations were due to HFS (50%) and THR (40%), while 10% were due to total knee replacement.

In the sample, patients who had undergone other major surgeries before TKR, THR and HFS, patients under age of 18 and patients with DVT, PE or bleeding as *main* diagnosis were excluded from the analysis. Further, patients with multiple traumas affecting more than one organ system, or who were under 18 years of age, were excluded, resulting in a sample of 51.555 patients. The distribution of procedures in the sample was 10.7% TKR, 40.1% THR, and 49.2% HFS.

Table 3.1 shows the distribution of patients who underwent TKR, THR and HFS in the years 1999, 2000 and 2001. The average ages of patients in the sample were 69.73 years for TKR, 71.62 years for THR and 78.78 years for HFS.

Table 3.1 Distribution of patients (hospital stays)

	1999	**2000**	**2001**	**Total**
Total knee replacement	1 504	1 844	2 160	5 508
Total hip replacement	6 352	6 800	7 545	20 697
Hip fracture surgery	8 422	8 319	8 609	25 350
Total	16 286	16 964	18 316	51 555

Source: Bjorvatn and Kristiansen (2003)

[4] Section 3.1 is based on the analysis of data presented in SNF-report no 13/03 by Bjorvatn and Kristiansen (2003).

Secondary diagnoses of PE, DVT or bleeding in hospital were identified by ICD-10 codes. PE was indicated by ICD-code I26, DVT by ICD-code I80 and 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. 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).

Table 3.2 shows the total number of hospital stays (patients) and average length of stay for patients who underwent major orthopaedic surgery 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, 13, 51 and 62 patients were treated for a secondary diagnosis of PE after TKR, THR and HFS respectively, while 37, 73 and 42 patients were treated for a secondary diagnosis of DVT after TKR, THR and HFS.

Length of stay during initial hospitalisation

A log-linear regression model was constructed to predict the effect on length of stay during hospitalization. The incidences of PE, DVT or bleeding were represented as explanatory dummy variables in the regression model. The model also included age and sex of the patients as explanatory variables.

The length of stays in hospital for the three procedures in the sample was as follows; Patients with TKR stayed on average 12.5 days in hospital, while patients with THR and HFS stayed on average 12.62 and 10.81 days in hospital, respectively, see Table 3.2.

During the inpatient period, 37 patients developed DVT after TKR, while 73 and 42 patients developed DVT following THR and HFS respectively. The additional length of stay for these patients was estimated to 4.69 days after TKR, 4.51 days after THR and 5.98 days after HFS.

The number of patients who developed a secondary diagnosis of PE is 13 after TKR, 51 after THR and 62 after HFS. The estimated additional length of stay for these patients was 3.49 days after TKR, 1.97 days after THR and 5.66 days after HFS. The additional length of stay LOS for prophylaxis-related bleeding for the entire sample was estimated at 5.92 days.

Table 3.2 Hospital stays from 1999 to 2001; Inpatient period

	Total knee replacement	Total hip replacement	Hip fracture surgery
Total number of patients	**5 508**	**20 697**	**25 350**
No secondary diagnosis	5 448	20 486	25 110
Secondary diagnosis of DVT	37	73	42
Secondary diagnosis of PE	13	51	62
Secondary diagnosis of Bleeding	10	87	136
Average length of stay (days)	**12.5**	**12.62**	**10.81**
No secondary diagnosis	12.44	12.54	10.74
Extra days by s.d. of DVT	4.69	4.51	5.98
Extra days by s.d. of PE	3.49	1.97	5.66
Extra days, s.d. of Bleeding, prophylaxis related [1]	5.92	5.92	5.92
Extra days, s.d. Bleeding	4.67	4.67	4.67

s.d: Secondary diagnosis
[1] For model simulation purposes, length of stay for the entire sample is applied.
Source: Bjorvatn & Kristiansen (2003).

Length of stay after initial hospitalisation (readmissions)

The length of stays for patients readmitted with a main diagnosis of PE, DVT or bleeding was calculated separately, as mean days. Table 3.3 presents the number of hospital stays (patients) and average length of stay for patients who underwent TKR, THR or HFS and readmitted the hospital with a secondary diagnosis of DVT, PE or bleeding within 90 days. For instance, number of readmitted patients with a secondary diagnosis of DVT was 7 following TKR, 53 following THR and 86 following HFS. The mean LOS for readmitted patients with DVT was 5.86 days following TKR, 5.25 days following THR and 5.77 days following HFS.

After TKR, THR and HFS, 6, 35 and 50 patients readmitted the hospital with a secondary diagnosis of PE respectively. The average length of hospital stay for these patients was 7.17, 11.17 and 9.6 days respectively.

Separate estimates of additional length of stay related to bleeding caused by treatment of DVT or PE were not justified by the available data. For modelling purposes, however, separate mean calculations were made for patients readmitted within 90 days. For readmissions with treatment-related bleeding, mean length of stay for the entire sample was 4.67 days.

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

	Total knee replacement	Total hip replacement	Hip fracture surgery
Total number of patients	**20**	**110**	**221**
DVT	7	53	86
PE	6	35	50
Bleeding	7	22	85
Average length of stay (days)			
DVT	5.86	5.25	5.77
PE	7.17	11.17	9.60
Bleeding, treatment-related[1]	4.67	4.67	4.67

[1] For model simulation purposes, length of stay for the entire sample is applied.
Source: Bjorvatn & Kristiansen (2003).

3.2 Estimation of other parameters used in the analysis

Estimation of life expectancy

In the analysis, we will provide estimates of costs per life-year gained for patients. Therefore, it is necessary to calculate estimates of the additional life years for patients undergoing major orthopaedic surgeries. Table 3.4 presents the expected additional life years for the general population (men and women) in Norway. The age category shown in the Table is from 69 to 79 years.

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	9.00	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 the model, the average life expectancy of patients undergoing major orthopaedic surgery patients is assumed to be the same as in the general population matched for the age and sex of the patients in the sample. In calculating the expected additional life years among patients undergoing THR, TKR and HFS, we have weighted the population data in the sample 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 among 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. The same reasoning applies for TKR patients. Hip fracture surgery 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
TKR	69.73	70%	15.07
THR	71.62	72%	13.73
HFS	78.78	71%	6.68

Duration of prophylaxis

In the model, we assume 7 days of prophylaxis during the inpatient period. Fondaparinux is indicated for extended duration prophylaxis following total hip replacement and hip fracture surgery. Fondaparinux can be administered for a period of 31 days in total. Therefore, we assume extended prophylaxis for 24 days (i.e. after hospital discharge). Further, we assume 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 3.6.

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

	Total knee replacement	**Total hip replacement**	**Hip fracture surgery**
Length of initial prophylaxis (days)	7	7	7
Length of extended prophylaxis (days)	Not relevant	24	24
Length of inpatient stay (days)	12.5	12.62	10.81
Average age of patients (years)	69.73	71.62	78.78
Average life expectancy (years)	84.40	85.35	85.46
Outpatient visit by nurse (%)	Not relevant	25%	25%

3.3 Costs of procedures and treatments

Costs of procedures

In the analysis, estimates of costs for inpatients were based on current prices for year 2004 within the *Norwegian Diagnosis Related Group* (DRG) system. In this system, 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 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 relevant DRG-categories for DVT, PE and bleeding were identified by listing occurrences of actually applied categories by patients with one of these diagnoses as the main diagnosis, in the total sample. For bleeding, the pair of DRG-categories 174 and 175 covered 38.2% and 61.8% of all stays respectively. The actual treatment costs in hospital for DVT, PE and bleeding based on DRG-prices, average length of stay per DRG and average costs per day per DRG are provided in Table 3.7. The results from the estimates of additional length of stay in hospital by secondary diagnosis showed variations in hospitalisation time among patients undergoing different surgical procedures. The average costs per day, together with the estimates of length of stay were used in estimating costs of treatment of DVT and PE after each surgical procedure.

[5] The Norwegian guidelines for pharmacoeconomic analysis for drug reimbursement applications recommend official DRG-prices as cost inputs to analysis of hospital stays (Norwegian Medicines Agency, 2002).

Table 3.7 DRG-categories and total costs of treatment in hospital

	DRG-category	Description	2004-cost, NOK	Mean LOS	Average cost per day, NOK
DVT	128	Deep vein thrombophlebitis	27 098	5.44	4 981
PE	78	Pulmonary embolism	46 243	9.18	5 037
Bleeding	174 (38.2%), 175 (61.8%)	174: Gastrointestinal hemorrhage with complications 175: Gastroin. hem. without compl.	22 033	4.93	4 469

DRG: Diagnosis-related groups
LOS: Length of stay

The total DRG rate for DVT or PE includes diagnosis and treatment according to standard medical practice, follow-up visits and INR monitoring (Dahl and Pleil, 2003). Costs were estimated separately following each surgical procedure depending on the estimates of length of stay in hospital.

For the treatment of DVT and PE, we assumed one physician visit, drug treatment and 10 INR tests[6] (personal communication with physician). 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 visit, drug costs and test costs. 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*.

According to the Norwegian practice, DVT/PE is treated with either dalteparin og enoxaparin, supplemented by warfarin (Personal communication). For treatment of DVT and PE, we assumed enoxaparin administration for 5 days, followed by warfarin for 90 days in case of DVT, and 180 days in case of PE. The dose of enoxaparin was set to 150mg[7]. The warfarin dose depends on individual test results and varies between different patients. We consider a dose of 7,5mg warfarin to be the normal dose (2,5mg three times a day). The cost of 150mg enoxaparin is NOK41 per day[8] (LIS price). The cost of 7,5mg of warfarin is NOK2.36 per day.

[6] PT tests are not very common in Norway (Personal communication with physician).
[7] 1mg per kg (depending on patient's weight) times 2. Therefore, a daily dose for a patient with a weight of 75kg is 150mg.
[8] The price is based on a package of 10x1ml syringes (150mg).

For the assessment DVT after initial hospital stay, we assumed one physician visit and one diagnostic investigation; venography or ultrasound for DVT, and spiral computed tomography for PE (personal communication). For the assessment of suspected DVT while inpatient, we assumed only diagnostic investigations.

There are several diagnostic methods for investigation of PE such as spiral-CT (Computed tomography), DSA (Digital Subtraction Angiography), and so on. We assumed one physician visit and one spiral-CT, which is the most common method for confirming PE after initial hospital stay. For the assessment of suspected PE during the inpatient period, we assumed only diagnostic investigations.

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 (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 assumption that 25% of PTS-related costs would be accrued at the time of initial diagnosis, while the remaining costs would be distributed evenly over time. Costs were converted from Swedish kroner by using average exchange rates for year 2004.

Prophylaxis costs

In the model, we assume prophylaxis with enoxaparin (Klexane®) and fondaparinux (Arixtra®) for 7 days while inpatient, and extended prophylaxis for 24 days. The costs of both drugs are based on wholesale prices in Norway (LIS price and consumer price)[9].

The cost of one dose of 40mg enoxaparin once daily is NOK8 for the inpatient period (LIS price), and NOK 44.5 for the outpatient period (consumer price). The former price is based on a package of 50x0.4ml syringes, while the latter is based on a package of 10x0.4ml syringes. Enoxaparin is also available in packages containing 10 syringes, at NOK13.50 per unit. We have also conducted a sensitivity analysis based on this price in section 5.

[9] Based on the price list provided by the manufacturer and The Norwegian Medicines Agency.

The cost of 2.5mg (0.5ml single-dose, 5mg/ml) fondaparinux once daily is NOK40.64 for the inpatient period (LIS price), and NOK108.59 for the outpatient period (consumer price). These prices are based on a package of 20x0.5ml syringes.

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). Table 3.8 presents all unit cost estimates used in the analysis for each surgical procedure.

Table 3.8 Unit cost estimates used in analyses by type of procedure, per patient, 2004 prices, NOK

		Total knee replacement	Total hip replacement	Hip fracture Surgery
Fondaparinux per day	Inpatient	40.64	40.64	40.64
Fondaparinux per day	Outpatient	108.59	108.59	108.59
Enoxaparin per day	Inpatient	8	8	8
Enoxaparin per day	Outpatient	44.50	44.50	44.50
Injection by nurse, Fondaparinux/Enoxaparin	Outpatient	Not relevant	35	35
Treatment DVT	Inpatient	19 374	18 693	24 205
Treatment DVT	Post discharge	23 763	21 480	23 426
Suspected DVT	Inpatient [1]	1 628	1 628	1 628
Suspected DVT	Post discharge[2]	2 818	2 818	2 818
Treatment PE	Inpatient	15 291	9 521	23 562
Treatment PE	Post discharge	29 282	44 479	38 514
Suspected PE	Inpatient[3]	872	872	872
Suspected PE	Post discharge[4]	2 063	2 063	2 063
Major Bleeding	Prophylaxis-related	22 033	22 033	22 033
Major Bleeding	Clinically relevant	22 033	22 033	22 033
Post thrombotic syndrome	Acute (first quarter)	8 739	8 739	8 739
Post thrombotic syndrome	Chronic (per quarter)	1 380	1 380	1 380

[1] Ultrasound or venography
[2] Physician visit and Ultrasound or venography
[3] Spiral-DT
[4] Physician visit and Spiral-DT.

4. The results

All analyses are conducted separetely for cohorts of 10.000 patients undergoing total knee and hip replacement, and hip fracture surgery. The model results are calculated for multiple time periods from surgery to hospital discharge, day 30, day 90, year 1 and year 5 after surgery. In section 4.1, the clinical outcomes and VTE-related cost outcomes of short-term (7 days) prophylaxis with fondaparinux versus enoxaparin are presented, while in section 4.2, the clinical outcomes and VTE-related cost outcomes of extended prophylaxis (24 days) with fondaparinux and enoxaparin are presented.

4.1 Short-term prophylaxis (1 week)

4.1.1 Clinical outcomes

Table 4.1 presents the clinical outcomes of prophylaxis with fondaparinux versus enoxaparin for short-term prophylaxis. In a cohort of 10.000 patients undergoing TKR, THR, HFS, fondaparinux (Arixtra) is expected to avoid respectively 80, 33 and 51 DVT-events more than enoxaparin prior to hospital discharge. The corresponding figures for PE-events avoided, are 34, 19 and 28. Finally, Arixtra prevents additional 12 deaths (fatal PE) after TKR, 3 deaths after THR and 11 deaths after HFS per 10.000 patients compared to enoxaparin.

At longer follow-up times (30 days and 90 days after surgery) Arixtra is also expected to be more effective than enoxaparin. For instance, at day 90 following, Arixtra is expected to avoid additional 124, 87 and 132 DVT-events, and 53, 51 and 84 PE-events per 10.000 patients following TKR, THR and HFS respectively compared to enoxaparin. Finally, using fondaparinux avoids 17 more deaths after TKR, 8 more deaths after THR and 33 more deaths after HFS per 10.000 patients compared to enoxaparin.

Table 4.1 ***Short-term prophylaxis: Number of clinical VTE-events per 10.000 patients***

		DVT	Non fatal PE	Fatal PE	Total
Inpatient/Discharge					
TKR	Arixtra	67	29	14	**110**
	Enoxaparin	147	63	26	**236**
	Difference	-80	-34	-12	**-126**
THR	Arixtra	29	16	4	**49**
	Enoxaparin	62	35	7	**104**
	Difference	-33	-19	-3	**-55**
HFS	Arixtra	43	25	12	**80**
	Enoxaparin	94	53	23	**170**
	Difference	-51	-28	-11	**-90**
30 days follow-up time					
TKR	Arixtra	114	50	16	**180**
	Enoxaparin	223	96	30	**349**
	Difference	-109	-46	-14	**-169**
THR	Arixtra	112	40	10	**162**
	Enoxaparin	180	80	16	**276**
	Difference	-68	-40	-6	**-114**
HFS	Arixtra	195	69	36	**300**
	Enoxaparin	302	134	63	**499**
	Difference	-107	-65	-27	**-199**
90 days follow-up time					
TKR	Arixtra	149	66	18	**233**
	Enoxaparin	273	119	35	**427**
	Difference	-124	-53	-17	**-194**
THR	Arixtra	184	58	14	**256**
	Enoxaparin	271	109	22	**402**
	Difference	-87	-51	-8	**-146**
HFS	Arixtra	314	97	51	**461**
	Enoxaparin	446	181	84	**711**
	Difference	-132	-84	-33	**-249**

Figures are rounded.

4.1.2 Cost outcomes

In this section, treatment costs per patient, incremental costs per VTE avoided, costs per death avoided and costs per life-year gained are presented for different surgical procedures and at different time periods for short-term duration prophylaxis (7 days) with fondaparinux and enoxaparin. Costs are discounted at 3% per year.

VTE-related cost outcomes

Unit costs presented in Table 3.8 were used in simulations of the model. The results from the analysis of short-term prophylaxis with fondaparinux compared with enoxaparin are presented in Table 4.2. The results are reported for the three surgical procedures and different time periods. In the table, a negative number implies cost savings by fondaparinux, while a positive number implies that prophylaxis with fondaparinux involves added costs.

Table 4.2 ***Short-term prophylaxis:*** **VTE-related costs per patient, NOK**

			Follow-up time			
Procedure	**Treatment**	**Discharge**	**30 days**	**90 days**	**1 year**	**5 years**
TKR	Arixtra	1 081	1 357	1 577	1 780	2 428
	Enoxaparin	1 056	1 428	1 694	2 018	3 052
	Difference	25	-70	-117	-238	-624
THR	Arixtra	974	1 366	1 689	1 887	2 521
	Enoxaparin	826	1 379	1 797	2 044	2 830
	Difference	148	-13	-108	-156	-310
HFR	Arixtra	1 061	1 700	2 174	2 391	3 056
	Enoxaparin	1 023	1 930	2 530	2 827	3 736
	Difference	38	-230	-356	-436	-680

Figures may not sum because of rounding.

Table 4.2 shows that at discharge fondaparinux (Arixtra) is the higher cost treatment after the three surgical procedures. For instance, among patients undergoing TKR, VTE-related costs per patient at hospital discharge are estimated to NOK1.081 for Arixtra and NOK1.056 for enoxaparin, which indicates added medication costs of NOK25 by using Arixtra. The longer is the follow-up time, the smaller is the cost disadvantage of Arixtra relative to enoxaparin. Indeed, from day 30 onward, Arxitra is cost saving after the three surgical procedures. For

example, by day 30, Arixtra is cost saving by NOK70 after TKR, NOK13 after THR and NOK230 after HFS compared with enoxaparin.

Incremental cost-effectiveness ratios

Table 4.3 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 by using fondaparinux. In the Table, negative numbers indicate cost savings by using fondaparinux.

Table 4.3 Short-term prophylaxis: Incremental cost-effectiveness ratios per patient, NOK

		Follow-up time			
Procedure		**30 days**	**90 days**	**1 year**	**5 years**
TKR	Cost per VTE avoided	-4 142	-6 031	-	-
	Cost per death avoided	-50 000	-68 824	-140 000	-367 059
	Cost per Life Year Gained	-3 318	-4 567	-9 290	-24 357
THR	Cost per VTE avoided	-1 140	-7 397	-	-
	Cost per death avoided	-21 667	-135 000	-195 000	-387 500
	Cost per Life Year Gained	-1 578	-9 832	-14 202	-28 223
HFS	Cost per VTE avoided	-11 588	-14 297	-	-
	Cost per death avoided	-85 185	-107 879	-132 121	-206 061
	Cost per Life Year Gained	-12 752	-16 150	-19 779	-30 847

Figures are rounded.

The incremental cost effectiveness ratio per avoided VTE-event is the additional cost associated with treating with fondaparinux rather than enoxaparin, divided by the total number of avoided VTE-events. For instance, with TKR the cost savings of treatment with fondaparinux (cost difference) is NOK70 per patient at day 30, which for 10.000 patients amounts to NOK700.000 (Table 4.2), while the total number of avoided VTE-events is 169 (Table 4.1). Hence, the incremental cost savings per avoided VTE-event is NOK4.142 at day 30. By day 90, the cost savings increase to NOK6.031. The same reasoning applies for the other procedures. As evident from the Table, fondaparinux is also cost saving after total hip replacement and hip fracture surgery. In general, the cost savings per avoided VTE-event by using fondaparinux increase over time.

We calculated costs per death avoided by dividing the total cost difference between fondaparinux and enoxaparin by the difference in the total number of VTE-related deaths avoided. By day 30, fondaparinux avoids additional 14 deaths after TKR and 6 deaths after THR per 10.000 patients compared to enoxaparin. Hence, by day 30, cost savings per death avoided is NOK50.000 following TKR and NOK21.667 following THR. Further, the number of deaths avoided with fondaparinux is greatest in HFS patients, where 27 more deaths are avoided. In case of HFS, fondaparinux reduces costs per death avoided by NOK85.185 by day 30. As evident from the Table, cost savings by using Arixtra instead of enoxaparin increase over time.

Finally, we calculated cost per life-year gained. As we see, using fondaparinux indicates significant cost savings already by day 30, with benefits increasing over time. For example, cost savings per life-year gained after TKR by day 30 are NOK3.318, while over a period of 5 years these savings increase to NOK24.357.

4.2 Extended prophylaxis (24 days)

4.2.1 Clinical outcomes

For the extended prophylaxis, the results are shown for 30 days and 90 days after surgery in Table 4.4. For the 30 days follow-up time, fondaparinux is expected to prevent 101 DVT, 35 non-fatal PE and 6 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 avoided VTE-events in total per 10.000 patients.

Table 4.4 ***Extended prophylaxis: 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**

Figures may not sum because of rounding.

4.2.2 Cost outcomes

In this section, treatment costs per patient, incremental costs per VTE avoided, costs per death avoided and costs per life-year gained are presented for different surgical procedures and at different time periods for extended duration prophylaxis with fondaparinux and enoxaparin. Costs are discounted at 3% per year.

VTE-related cost outcomes

Unit costs estimates presented in Table 3.8 were used in simulations of the model. The results from these simulations are presented in Table 4.5 for the three surgical procedures. In the tables, a negative number implies cost savings by fondaparinux, while a positive number implies that prophylaxis with fondaparinux involves added costs.

Table 4.5 Extended prophylaxis: VTE-related costs per patient, NOK

		Follow-up time			
Procedure		**30 days**	**90 days**	**1 year**	**5 years**
THR	Arixtra extended	4 162	4 282	4 297	4 351
	Enoxaparin extended	2 692	3 015	3 111	3 446
	Difference	1 469	1 266	1 186	905
HFS	Arixtra extended	4 247	4 353	4 369	4 426
	Enoxaparin extended	3 196	3 510	3 665	4 217
	Difference	1 051	843	704	208

Figures may not sum because of roundings.

Table 4.5 presents costs per patient for VTE-related care at different time periods for fondaparinux and enoxaparin. As we see, fondaparinux is the higher cost treatment alternative compared with enoxaparin. However, when the follow-up time increases, the cost difference between the two drugs decreases. For example, the cost difference between the two drugs at 30 days follow-up time is NOK1.469 after total hip replacement, while at 5 years follow-up time this difference is expected to be NOK905. For hip fracture surgery, the cost difference between the drugs is NOK1.051 at discharge, and NOK208 at 5 years follow-up time.

Incremental cost-effectiveness ratios

Table 4.6 presents the incremental cost-effectiveness ratios for extended prophylaxis with fondaparinux versus enoxaparin.

Table 4.6 Incremental cost-effectiveness ratios per patient, NOK

Procedure		30 days	90 days	1 year	5 years
THR	Cost per VTE avoided	103 328	58 372	-	-
	Cost per death avoided	2 464 731	1 397 550	1 300 885	974 014
	Cost per Life Year Gained	179 514	101 788	94 748	72 311
HFS	Cost per VTE avoided	51 485	30 838	-	-
	Cost per death avoided	127 958	76 983	64 159	18 904
	Cost per Life Year Gained	19 155	11 524	9 605	2 844

Extended prophylaxis with fondaparinux is more effective in preventing VTE-events than enoxaparin. For example, at the 30 days time period, extended prophylaxis with fondaparinux prevents an additional 142 VTE-events per 10.000 patients after total hip replacement (Table 4.4). The difference in treatment costs by fondaparinux compared to enoxaparin is NOK1.469 per patient (Table 4.5). Hence, the incremental cost per avoided VTE after THR is NOK103.328 at the 30 days time period[10]. At day 90, the cost per avoided VTE is NOK NOK58.372.

At day 30, fondaparinux prevents an additional 204 VTE-events per 10.000 patients after hip fracture surgery compared to enoxaparin. In this case, the cost difference between fondaparinux compared to enoxaparin is NOK1.051 per patient. Therefore, the cost per avoided VTE after HFS is NOK51.485 at day 30. For the 90 days follow-up time, the incremental cost per avoided VTE is NOK30.838.

As we see from Table 4.6, the cost per death avoided and cost per life-year gained decrease when the follow up time increases. Over a period of 5 years, cost per death avoided following HFS is expected to be NOK18.904, while cost per life-year gained is only NOK2.844.

[10] Please notice that costs presented in Table 4.5, as well as number of avoided VTE-events, are rounded.

5. Sensitivity analyses

Several sensitivity analyses were conducted in order to test the validity of the results. The analyses were performed on enoxaparin price (inpatient) and on fondaparinux price for outpatient treatment.

5.1 Short-term prophylaxis

Enoxaparin price (NOK13.50 per day)

In the main analysis, the price of enoxaparin is set to NOK8 per unit (inpatient period). This price is based on a package of 50 syringes of 40mg enoxaparin at NOK400 (LIS price). Enoxaparin is also available at NOK135 for 10x40mg syringes, with a unit price at NOK13,50. A sensitivity analysis was conducted in order to test the impact of this price on our results.

Results

Table 5.1 presents the results of the sensitivity analysis for the short-term prophylaxis. Please notice that in the Table, only the cost difference between fondaparinux and enoxaparin for each surgical procedure is reported. A negative number implies cost savings by fondaparinux, while a positive number implies that prophylaxis with fondaparinux involves adde costs.

Table 5.1 Sensitivity analysis:
VTE-related cost difference between fondaparinux and enoxaparin, per patient, NOK

Short-term prophylaxis		**Follow-up time**				
		Discharge	**Day 30**	**Day 90**	**Year 1**	**Year 5**
TKR	***Base case (enoxaparin, NOK8)***	***25***	***-70***	***-117***	***-238***	***-624***
	Enoxaparin price: NOK13.50	-14	-109	-156	-277	-662
THR	***Base case (enoxaparin, NOK8)***	***148***	***-13***	***-108***	***-156***	***-310***
	Enoxaparin price: NOK13.50	*109*	*-52*	*-147*	*-195*	*-348*
HFS	***Base case (enoxaparin, NOK8)***	***38***	***-230***	***-356***	***-436***	***-680***
	Enoxaparin price: NOK13.50	-1	-269	-394	-474	-718

The results from the sensitivity analysis show that when enoxaparin price is increased to NOK13,50 fondaparinux becomes cost saving after total knee replacement and cost neutral after total hip replacement already at discharge. From day 30 onward, it is also cost saving after total hip replacement. For example, in the main analysis (base case) at discharge, fondaparinux had added costs of NOK25 after TKR, while in the sensitivity analysis cost savings of NOK14 are achieved by using fondaparinux. By day 30, cost savings with fondaparinux relative to enoxaparin increase to NOK109 after TKR, NOK52 after THR and NOK269 after HFS.

5.2 Extended prophylaxis

Enoxaparin price (NOK13.50 per day)

In the main analysis, the price of enoxaparin is set to NOK8 per unit (inpatient period) based on a package of 50 syringes of 40mg enoxaparin at NOK400. Enoxaparin is also available at NOK135 for 10x40mg syringes, with a unit price at NOK13.50. We conducted a sensitivity analysis was conducted in order to test the impact of this price on the results from the main analysis.

Fondaparinux price, outpatient

For the short-term prophylaxis, fondaparinux was cost saving already at discharge following total knee replacement and cost neutral following hip fracture surgery. For the extended prophylaxis, fondaparinux had higher medication costs relative to enoxaparin. The higher medication costs with fondaparinux relative to enoxaparin might be due to the price of outpatient prophylaxis with fondaparinux. This price, which is paid by patients after hospital discharge, is considerably higher than the inpatient price of fondaparinux (NOK108.59 [11] vs NOK40.64 [12]). In order to test the impact of lower prices for outpatient prophylaxis with fondaparinux, we reduce this price by 10% to 20%.

Results

Table 5.2 presents the results of the sensitivity analyses on enoxaparin price (inpatient). and on fondaparinux price (outpatient) for the extended prophylaxis with fondaparinux and

[11] Wholesale price; package of 20x0.5ml syringes.
[12] LIS price

enoxaparin. Please notice that in the Table, the results of the different sensitivity analyses are only reported for the cost difference between fondaparinux and enoxaparin.

Table 5.2 Sensitivity analyses:
VTE-related cost difference between fondaparinux and enoxaparin, per patient, NOK

Extended prophylaxis		**Follow-up time**				
		Discharge	**Day 30**	**Day 90**	**Year 1**	**Year 5**
THR	***Base case (enoxaparin, NOK8)***	**-**	***1 469***	***1 266***	***1 186***	***905***
	Enoxaparin price: NOK13.50	-	1 400	1 197	1 117	836
	Fondaparinux price, outpatient: -10%	-	1 954	1 663	1 543	1 129
	Fondaparinux price, outpatient: -20%	-	1 073	870	789	508
HFS	***Base case (enoxaparin, NOK8)***	**-**	***1 051***	***843***	***704***	***208***
	Enoxaparin price: NOK13.50	-	992	784	645	149
	Fondaparinux price, outpatient: -10%	-	834	626	487	-9
	Fondaparinux price, outpatient: -20%	-	617	409	269	-226

A price increase of enoxaparin to NOK13,50 reduces the cost difference between enoxaprin and fondaparinux. For example, following TKR at day 30 the cost difference between the two drugs is NOK1.469 in the main analysis (base case), while after the price increase this difference is reduced to NOK1.400. However, enoxaparin is still the lower cost treatment alternative compared with fondaparinux.

Changing the price of outpatient treatment with fondaparinux has a positive impact on the cost difference between the two drugs especially after hip fracture surgery. A 10% reduction in the price of fondaparinux, makes fondaparinux cost saving by NOK9 compared to enoxaparin over a period of 5 years, while a 20% price reduction results in cost savings with fondaparinux by NOK226.

6. Discussion

Our analyses were based on statistics from *Norwegian National Register of Hospital Patients (NPR)*, which included 55.000 patients who underwent major orthopaedic surgery from 1999 to 2001. Of these patients, 51.555 were selected in the analysis. The main model used in the analysis is a "core" model that has been developed to examine the cost-effectiveness of prophylaxis with fondaparinux versus enoxaparin in patients undergoing major orthopaedic surgery. All cost estimates in the model were based on the Norwegian unit costs, i.e. DRG-costs for hospital stays and other relevant costs for year 2004.

Short-term prophylaxis

The results from the clinical outcomes indicate that in general, fondaparinux is the more effective drug in terms of preventing VTE-events both for the short-term prophylaxis compared to enoxaparin in all time periods. Compared with enoxaparin, short-term prophylaxis with fondaparinux is expected to avoid additional 194 DVT-events per 10.000 patients following total knee replacement, 146 events following total hip replacement and 249 events following hip fracture surgery by day 90 after surgery. These figures include 17 deaths after total knee replacement, 8 deaths after total hip replacement and 33 deaths after hip fracture surgery.

In Norway, around 18.330 major orthopaedic surgeries are performed every year. Of these surgeries, 10% are total knee replacements, 40% total hip replacements and 50% hip fracture surgeries. This means that using fondaparinux instead of enoxaparin after these surgeries would prevent additional 371 VTE-events, including 39 deaths (fatal PE) per year in Norway[13].

The results from our analysis indicate that short-term prophylaxis with fondaparinux is more cost-effective in terms of preventing VTE-events compared to enoxaparin. From day 30 onward, fondaparinux is cost saving after the three orthopaedic surgeries. Fondaparinux is also highly cost saving with respect to incremental costs per VTE avoided, VTE-related deaths avoided and costs per life-year gained, with benefits growing over time.

[13] Based on the distribution of the three surgeries in our data set.

Extended prophylaxis

Compared to enoxaparin, extended prophylaxis with fondaparinux is expected to prevent additional 217 VTE-events (including 9 deaths) per 10.000 patients after total hip replacement, and additional 273 VTE-events (including 110 deaths) after hip fracture surgery by day 90.

Of the total number of 18.330 major orthopaedic surgeries performed every year in Norway, 16.500 surgeries are hip replacements and hip fracture surgeries. Extended prophylaxis with fondaparinux would avoid additional 409 VTE-events, including 107 deaths, per year compared to enoxaparin after total hip replacement and hip fracture surgery.

In the case of extended prophylaxis, fondaparinux is the higher cost alternative relative to enoxaparin, but the cost difference decreases over time. For example, the cost difference between the two drugs at 30 days follow-up time is NOK1.051 after hip fracture surgery, while at 5 years follow-up time this difference is expected to be NOK208.

Our results show that the costs per avoided VTE-event, cost per death avoided and cost per life-year gained are higher after total hip replacement than hip fracture surgery. For instance, by day 90, the incremental cost per avoided VTE-event is estimated to approximately NOK58.400 after total hip replacement and NOK30.800 after hip fracture surgery. Over a period of 5 years, the incremental cost per death avoided following total hip replacement is expected to be around NOK974.000, while the incremental cost per life-year gained is around NOK72.300. The incremental cost per death avoided following hip fracture surgery is expected to be around NOK18.900, while cost per life-year gained is only NOK2.800. There could be several reasons for why these costs are higher after total hip replacement. First, fondaparinux avoids more VTE-events, especially fatal PE, after hip fracture surgery compared to total hip replacement. Second, the length of stay in hospital by readmissions is higher among patients with total hip replacement than hip fracture surgery.

New therapies usually involve higher costs than current therapies. This is also the case for extended prophylaxis with fondaparinux. Health authorities or hospitals have limited budgets and have to consider the effectiveness of the new therapies relative to the higher costs involved. In US, costs per death avoided or life-year gained below $50.000-60.000 are considered “acceptable” for the value of a life-year gained (e.g. Owens, 1998; Kanis et al., 2002). A recent study in Norway suggests GDP per capita (approximately NOK350.000) as a

measure for the value of one additional life-year gained (Kristiansen, 2003). Given these values, fondaparinux is clearly cost-effective. As seen above, the incremental cost per life-year gained with fondaparinux after hip fracture surgery is only NOK19.000 at day 30 and NOK2.800 five years after surgery. The same reasoning applies for total hip replacement.

Study perspective

In the end, this study is undertaken from the perspective of healthcare payers in Norway and does not consider the societal perspective. The economic gains of avoided VTE-events for the society (that is cost savings related to hospitalisation of patients with VTE), and benefits such as utility of the people who stay healthy because of the treatment by fondaparinux are not included in the present study.

7. Conclusion

In conclusion, short-term prophylaxis with fondaparinux is more effective than enoxaparin in preventing VTE-events after total knee and hip replacement, and hip fracture surgery. Extended prophylaxis with fondaparinux demonstrates even greater efficacy in preventing VTE-events. Finally, using fondaparinux instead of enoxaparin is a cost-effective strategy. Short-term prophylaxis with fondaparinux is also highly cost saving with respect to incremental costs per VTE-event avoided, VTE-related deaths avoided and costs per life-year gained, with benefits growing over time.

The sensitivity analysis conducted on enoxaparin price confirmed the robustness of our results. However, for the extended prophylaxis, the results were sensitive to price reductions of outpatient prophylaxis with fondaparinux.

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Appendix A: Estimation of model probabilities

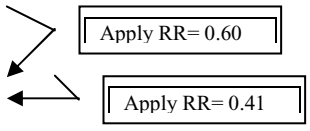
This appendix is a summary of estimation of the model probabilities used in the fondaparinux extended prophylaxis model presented in "Cost-effectiveness of extending prophylaxis with fondparinux against venous thromboembolism in patients undergoing hip fracture surgery and total hip replacement (2003)".

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%



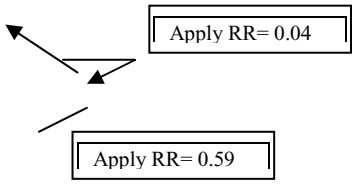
Among HFS patients receiving short-term duration prophylaxis with fondaparinux, the rate of subclinical DVT at Day 30 (32.3%) was obtained by subtracting the rate of symptomatic events (2.7%) from the all VTE rate (35%). The rate of subclinical DVT for extended prophylaxis (1.1%) was obtained similarly (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 [14] 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.

[14] 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 %

Apply RR= 0.44 /RR=0.60

Apply RR= 0.33

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 %

Apply RR= 0.11

Apply RR= 0.57 /RR= 0.59

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[15]) 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).

[15] 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 1.1 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	
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
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
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
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[16]
[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

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