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Original article

Economic evaluation of dabigatran etexilate for the primary prevention of venous tromboembolic events following major orthopedic surgery in the Netherlands

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Abstract

Objectives:
Dabigatran etexilate is a new oral direct thrombin inhibitor for prophylaxis of venous thromboembolism (VTE) in patients who have elective surgery for total hip replacement (THR) or total knee replacement (TKR). Among the advantages of dabigatran etexilate over subcutaneous prophylaxis with Low Molecular Weight Heparin (LMWH) are reduced resource uses for (i) teaching patients to self-inject; (ii) home-care visits for subcutaneous administration; and (iii) absence of heparin-induced thrombocytopenia (HIT). Based on the demonstrated non-inferiority, the aim of this study was to conduct a cost-minimization analysis of oral dabigatran etexilate vs subcutaneous low-molecular weight heparin (LMWH) and fondaparinux from the Dutch healthcare perspective.

Methods:
A retrospective cohort study was conducted to measure resource use associated with subcutaneous prophylaxis. Results of this study were used in the model to elucidate specific advantages of dabigatran etexilate, next to reduced needs for self-inject teaching and lack of Heparin-Induced Thrombocytopenia. Drug and other resource utilization data were combined with local unit costs. Probabilistic sensitivity analysis was performed to account for uncertainty around relevant parameters included.

Results:
Home-care visits for subcutaneous administration problems were needed in 9.9% (95% CI = 6.4–13.4) and 9.6% (95% CI = 5.8–13.4) of THR and TKR patients, respectively. Based on costs for 1000 patients treated with dabigatran etexilate vs LMWHs, per patient cost-savings with dabigatran etexilate were estimated at €30.68 (95% CI = 2.01–65.52) and €23.19 (95% CI = 0.69–48.48) for THR and TKR, respectively. The probability that dabigatran etexilate would be cost-saving was estimated at 98.3% and 97.9% for THR and TKR, respectively. These cost-savings were even higher when including fondaparinux in the analysis, with per patient cost-savings of €69.87 (43.42–106.10) and €18.33 (1.63–41.26) for THR and TKR, respectively. Separate calculations for dabigatran etexilate vs nadroparin and dalteparin in THR resulted in probabilities of achieving cost-savings with dabigatran etexilate of 36.2% and 100%, respectively. For TKR these probabilities were estimated at 54.3% and 100%, respectively.

Conclusions:
Thromboprophylaxis with dabigatran etexilate is cost-saving in patients undergoing THR and TKR from the Dutch healthcare perspective, compared to subcutaneous LMWHs.

Introduction

Patients undergoing major orthopedic surgery are at elevated risk of venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and pulmonary embolism (PE). Due to a period of immobilization, the risk of VTE persists for up to 3 months after orthopedic surgery. The incidence of thromboembolic complications among patients not receiving thromboprophylaxis after orthopedic surgery was previously estimated at 40–60% (DVT), 2–5% (non-fatal PE) and 0.1% (fatal PE)[1,2]. Primary prevention with thromboprophylactic treatment around orthopedic surgery reduces the risk of non-symptomatic and symptomatic VTE considerably[1,3,4]. International guidelines recommend thromboprophylaxis for patients undergoing total hip replacement (THR) or total knee replacement (TKR) with low molecular weight heparins (LMWHs), fondaparinux, or vitamin K antagonists (VKAs)[1,5,6]. From national and international surveys it seems that most orthopedic patients receive thromboprophylactic therapy with LMWHs[7–10]. In particular, data from an observational study showed that, of adults who have undergone THR and TKR surgery, 65–80% receive LMWHs in the Netherlands[9,10]. It is recommended in Dutch guidelines to administer LMWHs for a period of 4–6 weeks after THR and TKR surgery[6]. The therapeutic complexity related to the subcutaneous route of administration of anticoagulants may lead to reluctance of patients to self-administer in the home-setting following discharge from hospital or even it is impossible for them to do so. This may lead to inaccurate dosing, low therapy compliance, and, therefore, lower effectiveness of subcutaneous thromboprophylaxis to reduce the risk of VTE in daily practice[11–15].

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim, Ingelheim, Germany) is a novel oral direct thrombin inhibitor for prophylaxis of VTE for adult patients who have undergone elective THR or TKR surgery. Phase III clinical studies—RE-NOVATE and RE-MODEL—have demonstrated non-inferiority for dabigatran etexilate vs enoxaparin, a low-molecular weight heparin (LMWH) in patients who have undergone THR or TKR surgery[16–18]. Oral dabigatran etexilate was found to be as effective as the subcutaneous LMWH enoxaparin in reducing the risk of VTE and VTE-related mortality[18]. Also, safety of dabigatran etexilate and LMWHs was comparable with a similar bleeding profile for both these types of agents[18].

Oral anticoagulants are recognized as more patient-friendly in daily practice. In particular, the new oral thromboprophylactic agents like dabigatran etexilate, rivaroxaban, and apixapan have potential advantages over parenteral prophylaxis with LMWHs or fondaparinux, given the absence of possible problems with subcutaneous administration for the former. However, drug costs for, for example, dabigatran exceed those of the LMWHs. Yet, downstream savings might be expected related to the advantages of the new thromboprophylactic agents. In the Netherlands, advantages of these oral direct thrombin inhibitors for VTE prophylaxis include (but may not be limited to) reduced resource use for (i) teaching patients to self-inject, (ii) home-care visits for parenteral administration by nurses due to self-administration problems, and (iii) absence of heparin-induced thrombocytopenia (HIT)[19,20].

Yet, only scarce information is available on the occurrence of problems with self-administration of subcutaneous antithrombotics at home. In particular, on the involvement of homecare visits by a nurse to solve these problems, no hard data exist. Several studies indicate that such problems occur in 7.5–44% of the patients administering LMWHs or fondaparinux at home[9,10,12–15].

This study was designed to quantify the potential administration problems with subcutaneous thromboprophylaxis by measuring the prevalence of such problems among patients that have undergone THR or TKR. Furthermore, based the demonstrated non-inferiority and data on the prevalence of administration problems, we conducted a cost-minimization analysis of oral dabigatran etexilate vs parenteral LMWHs and fondaparinux from the Dutch healthcare perspective.

Methods

Patient interview on administration problems

The occurrence of administration problems with subcutaneous administration of thromboprophylaxis was evaluated among 687 Dutch patients who had undergone THR or TKR surgery by a retrospective telephone interview. The research was conducted in two regional Dutch hospitals (De Tjongerschans, Heerenveen; Antonius Ziekenhuis, Sneek) and one teaching hospital (Medisch Centrum Leeuwarden) in 2008. Approval was received from the Medical Ethical Review Committee 'RTPO'. Patients who had undergone THR or TKR surgery in 2008 (February–December in Heerenveen, May and June in Sneek, and September–December in Leeuwarden) received an informative letter in which the research was introduced. After oral informed consent, patients were interviewed using a structured questionnaire. Next to patient characteristics, several questions were asked to measure healthcare resource use (e.g. type of surgery, hospital stay, instruction for administration), potential problems related to self-administration of subcutaneous administration in the home-setting, and patients' preferences for subcutaneous and/or oral thromboprophylaxis.

Cost-minimization analysis

A cost-minimization analysis was conducted to compare oral dabigatran etexilate with subcutaneous thromboprophylaxis formulations. Dutch drug-utilization patterns and healthcare resource data were combined with local unit costs to calculate the healthcare cost of thromboprophylaxis with dabigatran etexilate, LMWH, and fondaparinux formulations. In particular, potential advantages of dabigatran etexilate over LMWHs and fondaparinux could be quantified relating to: (i) resource use incurred giving patients and/or relatives instructions for self-administration of LMWHs or fondaparinux; (ii) homecare for the administration of LMWHs or fondaparinux following discharge from hospital; and (iii) heparin-induced thrombocytopenia (HIT)[19,20].

The base-case cost-minimization analysis reflects the comparative costs and potential savings for oral vs subcutaneous thromboprophylaxis using a mix of LMWHs reflecting actual use. Within the healthcare perspective used, Dutch cost data for drugs and healthcare resource use were derived from a previous Dutch observational study[9,10], and the patient interview designed specifically for this analysis (see above). All analyses were conducted separately for both THR and TKR surgery populations. All costs were expressed in 2010 values, without discounting, as all costs are incurred within a maximum period of 10 weeks within the same financial year[21,22].

Scenario analysis, deterministic and probabilistic sensitivity analysis

Various scenario analyses were conducted based on the different possible comparator treatment options or combinations of these comparator therapies. In the absence of data on various aspects, in probabilistic sensitivity analysis distributions were generally chosen to follow the symmetric triangular distribution, with plausible minima and maxima (see below and Appendix). The probability of administration problems for both the THR and TKR analyses were assumed to follow a Beta distribution[23]. For the occurrence of HIT, a specific study was available, enabling the specification of a Beta distribution with observed mean and estimated standard error[20]. Next to varying all relevant parameters at once (multivariate), a univariate probabilistic approach was elaborated to identify the importance of each individual parameter, separately. For this purpose, subsequently each relevant parameter was allowed to vary over its specified distribution, with all other parameters kept at their respective expected values (2000 iterations per parameter). All analyses were done in Excel (MicroSoft), using @Risk add-in (Palisade, Athica, NY, USA) to perform probabilistic analyses.

Dutch population data

Dutch treatment guidelines recommend extended prophylaxis after discharge up to 6 and 4 weeks in THR and TKR, respectively[6]. Based on an average hospital length of stay of 8 days for THR as well as for TKR[9,10], total treatment periods were assumed to be 50 and 36 days for THR and TKR, respectively[24,25]. In probabilistic sensitivity analysis, symmetric triangular distributions were used (THR: minimum at 2 weeks, maximum at 10 weeks; TKR: minimum at 2 week, maximum at 6 weeks)[15].

Data on inpatient days and drug-utilization from July 2005–July 2006 were available for further analysis (source: PHARMO Utrecht, a specific report on the data is available on request). To adequately reflect the patient population who had undergone elective THR or TKR, all admissions for hip and knee fractures were excluded[9,10]. From these data, the percentage distribution of specific LMWHs and fondaparinux used in Dutch current practice was estimated (enoxaparin is not routinely used in the Netherlands). We assumed that the clinical trial results for dabigatran etexilate vs enoxaparin are also valid vs other types of LMWHs (and fondaparinux)[26]. In particular, we analyzed two options for the comparator: the LMWH mix and the LMWH/fondaparinux mix from the daily practice observations in the PHARMO-data (for exact percentage distributions see below). The latter LMWH/fondaparinux comparator for dabigatran etexilate may be considered to most closely reflect the Dutch real-life situation, and the LMWH mix may be considered the preferred comparator in most guidelines.

Costing

Prior to discharge from hospital, THR and TKR patients are instructed on self-administration of subcutaneous VTE prophylaxis to ensure that patients use the correct injection technique, to prevent needle-stick injuries, and to early identify patients who are unable, unwilling, or highly reluctant to inject themselves. Costs for such an instruction were based on an assumed 30 minutes of nursing time in the hospital, according to instruction protocols (in probabilistic sensitivity analysis: symmetric triangular distribution with minimum 20 and maximum 40 minutes). Given the hourly costs[22], the costs for half an hour of instruction were estimated at €15.52 per patient.

Table 1 shows the unit costs for the different types of home care after hospital discharge, using estimated time investments and guideline unit prices[22]. We considered two options for those patients with parenteral self-administration problems at home. In particular: (i) we conservatively assumed that these patients would require standard domiciliary care anyhow for other health reasons, and we inserted only the extra costs for a visit by a trained nurse (for subcutaneous administration) over a visit not

requiring a trained nurse as savings for dabigatran etexilate (€9.95 per day; difference between standard price for domicillary care (€6.24) and domiciliary care by trained nurse (€16.19)); and (ii) we assumed a maximal approach considering that these patients would have no reason for follow-up visits for reasons other than the administration of thromboprophylaxis and the full €16.19 per day (standard price for domiciliary car by trained nurse) was included as savings for patients receiving dabigatran etexilate. In the threshold analysis, both the conservative and maximal approach were elaborated. In the base case, it was assumed that the two options occurred 50–50 in practice. In probabilistic sensitivity analysis a symmetric triangular distribution was used for this distribution (minimum: 25%; maximum: 75%).

In the Netherlands, dalteparin and nadroparin are the LMWHs that are mostly used following elective orthopedic surgery (Table 2). Additionally, 28.2% and 12.5% of patients undergoing THR and TKR use fondaparinux. Based on the Z-index ('Taxe' reflecting the official Dutch pricelist), daily costs for dabigatran etexilate were assumed at €4.41 (both 150 mg and 220 mg), €3.45 for dalteparin (5000 units), €2.30 for nadroparin (3800 units), and €7.66 for fondaparinux (2.5 mg)[27]. These daily costs and mentioned percentages translate into cost estimates for 50 days use after THR and 36 days use after TKR, as shown in Table 3[9,10,27].

Costs related to HIT were based on an 0.8% incidence of HIT among LMWH users in the Netherlands, as reported by ten Berg *et al.*[28], which is in line with data found in international studies[20,29,30]. In probabilistic sensitivity analysis, a Beta distribution was assumed with parameters α and β at 14 and 1640, respectively[30]. Costs for HIT were assumed to amount to €3110 in 2010 and were not assumed for fondaparinux (i.e. the LMWH/fondaparinux mix)[31].

Table 1. Unit costs for different types of homecare[22], based on normative durations of visits and inclusive travel costs, difference shown for whether a (trained) nurse is involved or not (homekeeping help only).

Type	Costs per unit of time
Regular homecare	€6.24 for 10 minutes
Nurse	€16.19 for 15 minutes

Source: 'OP Normtijden 2008/zorgactiviteiten packet' 2008 and personal communication 'thuiszorg' (homecare) in the Netherlands.

Table 2. Percentage distribution for LMWH used in the Netherlands[9,10], used in the LMWH mix comparator with and without fondaparinux.

	THR	TKR
LMWH mix		
Dalteparin	62.8%	50.9%
Nadroparin	37.2%	49.1%
LMWH mix including fondaparinux		
Dalteparin	45.1%	44.5%
Nadroparin	26.8%	43.0%
Fondaparinux	28.2%	12.5%

Results

Administration problems

Six hundred and eighty-seven patients (response rate 87.4%) were interviewed. Patient characteristics are presented in Table 4. A total of 511 (74.4%) of these patients used subcutaneous thromboprophylaxis at home, with the remainder primarily using vitamin K antagonists. Of the interviewed patients, 48.8% reported administration problems varying from local pain, bruises, and itches. Almost 60% of all THR and TKR patients would prefer oral over subcutaneous thromboprophylaxis, if efficacy and safety would be comparable. Home-care visits for subcutaneous administration problems were required by 9.9% (95% CI = 6.4–13.4) and 9.6% (95% CI = 5.8–13.4) of THR

Table 3. Per-person costs for prophylaxis following THR (50 days) or TKR (36 days)[6,9,10].

Agent	Costs of prophylaxis THR (in €)	Costs of prophylaxis TKR (in €)
Dabigatran etexilate	221	159
Dalteparin	173	124
Nadroparin	115	83
LMWH mix	151	104
LMWH/fondaparinux mix	217	125

Table 4. Patient characteristics, homecare needs, and average duration of hospitalization.

Characteristics	Hip replacement *n* (%)	Knee replacement *n* (%)
Number of patients	372 (100)	315 (100)
Gender		
Male	114 (30.6)	109 (34.6)
Female	258 (69.4)	206 (65.4)
Age (year)		
40–49	7 (1.9)	2 (0.6)
50–59	55 (14.8)	54 (17.1)
60–69	119 (32.0)	114 (36.2)
70–79	147 (39.5)	101 (32.1)
≥80	42 (11.3)	44 (14.0)
Unknown	2 (0.5)	0 (0)
Average (SD)	69 (9)	69 (9)
Homecare		
Before surgery	29 (7.8)	22 (7.0)
After surgery	221 (59.4)	158 (50.2)
Duration hospital admission		
Average number of days	8; SD = 6	7; SD = 4

n, number of patients, SD, standard deviation.

and TKR patients, respectively[30]. As mentioned above, homecare visits for subcutaneous administration problems can be sub-divided in patients that solely require homecare for administration and patients that require homecare for administration next to other help (Table 5).

Cost-minimization analysis

Table 6 reports the costs for separate cost components and different comparator scenarios in the base case. For both THR and TKR, costs for treatment with dabigatran etexilate exceed costs of treatment in other comparator treatment scenarios. Relevant cost offsets are estimated for all three other components: instruction, homecare, and HIT. In general, total costs for the different treatment scenarios were lower for dabigatran etexilate, which means that future dabigatran etexilate use could result in cost-savings. Dabigatran etexilate does not appear to offer cost-savings vs nadroparin, however the additional costs are low.

Sensitivity analysis

Table 7 shows the per-patient cost-savings for dabigatran etexilate vs the other therapeutic strategies including probabilistic results on 95% confidence intervals and the probabilities of achieving cost-savings with dabigatran etexilate. Per patient cost-savings with dabigatran etexilate vs the observed mix for LMWHs are estimated at €30.68 (95% CI = 2.01–65.52) and €23.19 (95% CI = 0.69–48.48) for THR and TKR patients, respectively. Furthermore, the probability that dabigatran etexilate would be cost-saving is 98.3% and 97.9% for THR and TKR, respectively. If costs of HIT are excluded from the analysis, these cost-savings are lower and turn in low additional costs for dabigatran etexilate for TKR patients (€3.14; 95% CI = − 20.92–19.17). Cost-savings are higher when including fondaparinux alongside the observed mix of LMWHs, with per patient cost-savings varying between €18.33 (95% CI = 1.63–41.26) for TKR patients and €69.87 (95% CI = 43.42–106.10) for THR patients, if using dabigatran etexilate. The probabilities of achieving cost-savings with dabigatran etexilate vs the LMWH/fondaparinux mix strategy are close to or even 100%.

Separate calculations for dabigatran etexilate vs nadroparin and dalteparin in THR result in probabilities of achieving cost-savings with dabigatran etexilate of 36.2% and 100%, respectively. These figures are essentially similar for TKR. Exclusion of costs for HIT results in overall slightly less favorable findings for dabigatran etexilate compared to the different LMWHs (dalteparin and nadroparin). Yet, the probability of achieving cost-savings reduces dramatically with dabigatan etexilate vs nadroparin, approaching 0%.

Results presented in Figures 1 and 2 show limited variation around the mean estimate for dabigatran etexilate vs the LMWH mix. In particular, the percentage requiring homecare, occurrence of HIT, and costs related to these aspects resulted in the largest confidence intervals for the per-patient cost-savings. However, all variations in

Table 5. Proportion of patients requiring homecare for parenteral administration problems.

	THR (%; 95% CI)	TKR (%; 95% CI)
Homecare for subcutaneous administration	9.9 (6.4–13.4)	9.2 (5.4–12.9)
Solely for subcutaneous administration	6.4 (3.5–9.2)	6.1 (3.0–9.2)
For subcutaneous administration and other help	3.5 (1.4–5.7)	3.1 (0.8–5.3)

Table 6. Costs for 1000 patients treated with respective medications for THR and TKR (in €).

Cost components	Dabigatran etexilate	Dalteparin	Nadroparin	LMWH mix	LMWH/fondaparinux mix
THR					
Prophylaxis (extended)	220,500	172,500	115,000	151,110	216,624
Self-administration instruction	0	15,518	15,518	15,518	15,518
Homecare	0	58,225	58,225	58,225	58,225
HIT	0	26,324	26,324	26,324	18,901
Total excluding HIT	220,500	246,243	188,743	224,853	290,366
Total including HIT	220,500	272,567	215,067	251,177	NA
TKR					
Prophylaxis (extended)	157,760	124,200	82,800	103,873	125,343
Self-administration instruction	0	15,518	15,518	15,518	15,518
Homecare	0	36,232	36,232	36,232	36,232
HIT	0	26,324	26,324	26,324	23,034
Total excluding HIT	158,760	175,950	134,550	155,623	177,093
Total including HIT	158,760	202,274	160,874	181,947	NA

NA, not appilicable (no HIT assumed for the mix including fondaparinux).

Table 7. Per-patient cost-savings of dabigatran etexilate vs LMWHs, LMWH mix, and LMWH/fondaparinux mix.

	Comparator (dabigatran etexilate vs)	Per-patient cost-savings (95% CI)	Probability of achieving cost-savings
THR excl HIT	Dalteparin	€25.74 (9.64–59.59)	98.1%
	Nadroparin	−€31.76 (−59.55–0.71)*	2.7%
	LMWH mix	€4.35 (−20.88–36.79)	59.4%
	LMWH/fondaparinux mix	€69.87 (43.42–106.10)	100%
THR incl HIT	Dalteparin	€52.07 (23.75–87.38)	100%
	Nadroparin	−€5.43 (−36.16–28.96)*	36.2%
	LMWH mix	€30.68 (2.01–65.52)	98.3%
	LMWH/fondaparinux mix	NA	NA
TKR excl HIT	Dalteparin	€17.19 (0.43–40.02)	97.9%
	Nadroparin	−€24.21 (−43.49–−1.64)*	1.9%
	LMWH mix	−€3.14 (−20.92–19.17)*	34.2%
	LMWH/fondaparinux mix	€18.33 (1.63–41.26)	98.7%
TKR incl HIT	Dalteparin	€43.51 (21.49–69.66)	100%
	Nadroparin	€2.11 (−21.84–27.84)	54.3%
	LMWH mix	€23.19 (0.69–48.48)	97.9%
	LMWH/fondaparinux mix	NA	NA

*Negative cost-savings indicate costs.

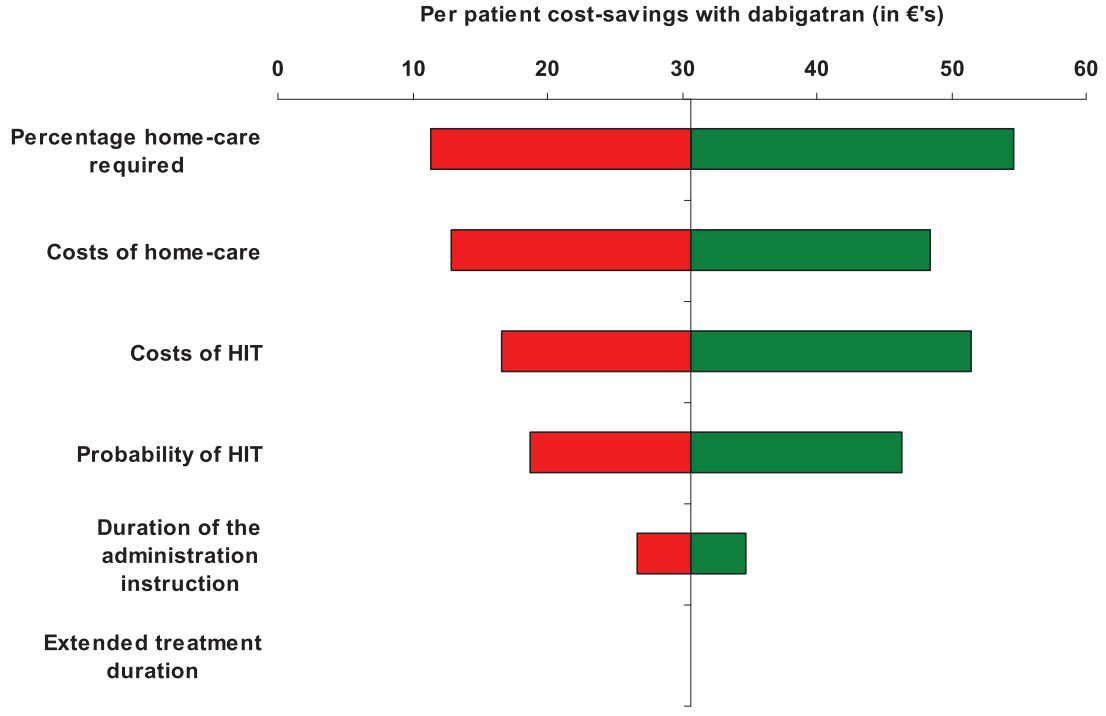

Figure 1. Tornado-diagram for THR showing the mean and 95% confidence limits following from univariate probabilistic sensitivity analysis.

individual parameter assumptions did not result in incremental costs.

Discussion

The current analysis highlights the potential for cost-savings with dabigatran etexilate as VTE prophylaxis following orthopedic surgery vs subcutaneous thromboprophylxis with either LMWH or fondaparinux. The higher acquisiton cost of dabigatran etexilate is generally offset by the costs for homecare, HIT, and related healthcare resource use associated with LMWHs. Probabilistic sensitivity analysis resulted in high probabilities of achieving cost-savings with dabigatran etexilate. Results were estimated to be most sensitive to the percentage of patients experiencing administration problems, occurrence of HIT, and to the costs related to these aspects. Results were,

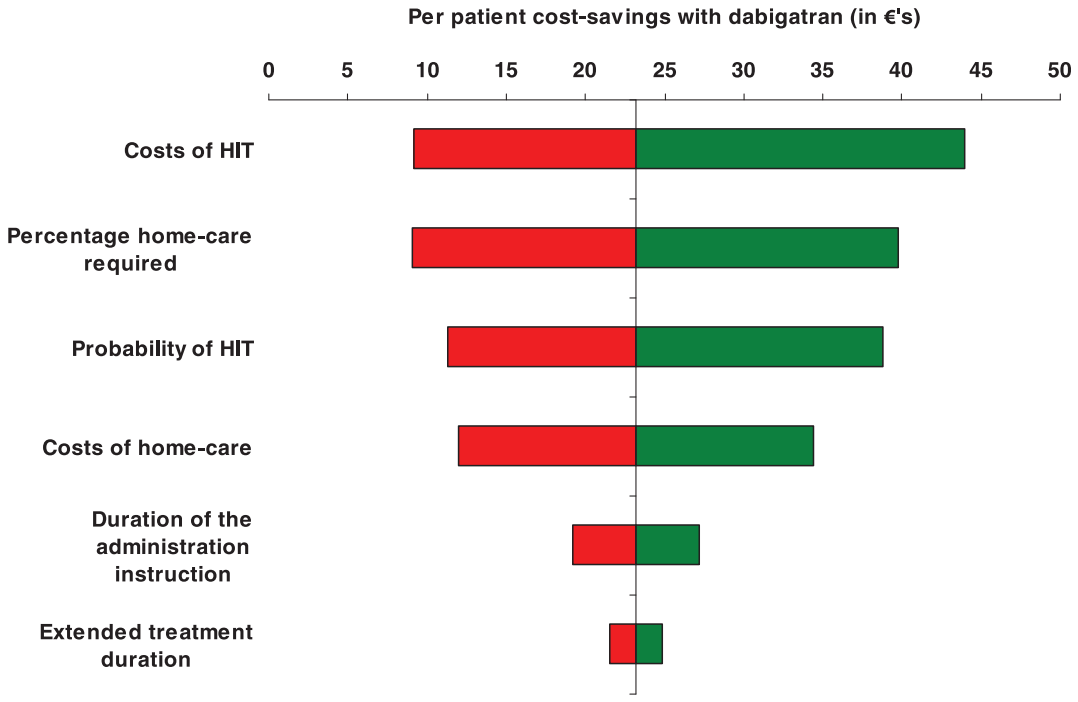

Figure 2. Tornado-diagram for TKR showing the mean and 95% confidence limits following from univariate probabilistic sensitivity analysis.

for example, less sensitive to exact durations of treatment and training.

In the presence of non-inferiority studies for oral dabigatran etexilate, we designed a cost-minimization framework to analyze the health economics of dabigatran etexilate as compared to its subcutaneous comparators. We note that our cost-minimization framework was limited and conservative in the sense that some potential further benefits of the oral formulation over the subcutaneous administration were not included. For example, needle-stick injuries and sharps disposal will be absent for the oral formulation, whereas it does occur in real-life settings with subcutaneous administrations[14]. Additionally, the hospital nursing staff will need less time for administering oral dabigatran etexilate than for parenteral formulations. Besides, platelet monitoring for HIT and potential differences in the occurrence of VTE assuming poor adherence to thromboprophylaxis following discharge from the hospital could be other potential cost drivers for the subcutaneous LMWH or oral dabigatran as well. Finally, we note that some other economic evaluations have inserted superior point estimates of dabigatran etexilate over LMWHs into their models, as suggested in the clinical trials[32]. The presented approach has been successful for achieving reimbursement in the Netherlands and has been acknowledged in a quality assessment of these type of studies in the context of evidence-based medicine and reimbursement in the Netherlands[33,34].

We generally aimed at following a conservative approach in our analysis, for example, excluding the risk for HIT in the full LMWH/fondaparinux mix. Yet, in the absence of information on discounts we applied list prices for LMWHs and fondaparinux. In practice, discount may be provided to hospitals and could worsen our estimated cost-effectiveness. Notably, in addition to the advantages modeled, an oral administration route can be expected to result in further inpatient (as well as outpatient) cost-savings due to reduced nursing-time for administration of oral medication, and also the absence of risk for needle-stick injuries and sharps disposal. Furthermore, recent evidence might support limited adherence next to limited convenience with self-administration of LMWHs[12,13,15,35,36]. Observational studies among THR and TKR patients have shown that ~35–40% of patients have problems with self-administration of subcutaneous prophylaxis, which ultimately leads to a situation where 7.5–37.5% of patients are completely or partially non-compliant, thereby reducing the effectiveness of VTE prophylaxis and posing risks for DVTs[12,13,15]. The UK's National Institute for Health and Clinical Excellence (NICE) estimated the risk of developing DVT following orthopedic surgery in the absence of (effective) thromboprophylaxis to be as high as 44% for patients having THR and 27% for patients having TKR, highlighting the importance of compliance to anti-thrombotic therapy in general[36]. Also, we note that our findings from the patient interviews that

almost 60% of all THR and TKR patients would prefer oral over subcutaneous thromboprophylaxis, if efficacy and safety would be comparable, might still under-estimate the real preference. In particular, coping mechanisms with the current administration form might play a role here. Finally, we limited our scope on those costs related to HITs actually occurring and preventable with dabigatran, whereas also just suspected HITs already generate costs. Additionally, averted HIT in general not only provides cost savings, but also reduces (though relatively rare) devastating complications[37]. For the specific Dutch setting, our cost-minimization approach was relevant and appropriate. Whether the same applies to other countries depends on various factors inclusive of the relative costs of the different drugs involved and the specific levels of costs for home in individual countries. Transferability to other countries of our results may therefore be limited.

Conclusion

We conclude that—based on our conservatively designed cost-minimization analysis—thromboprophylaxis with dabigatran etexilate is likely to be cost-saving in patients undergoing THR and TKR compared to its subcutaneous comparators if considered from the Dutch healthcare perspective.

Transparency

Declaration of funding

This research was supported by a grant from Boehringer Ingelheim (Alkmaar, Netherlands). All stages of the research were discussed with employees of Boehringer Ingelheim. One of the co-authors is from Boehringer Ingelheim.

Declaration of financial/other relationships

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Appendix: Parameter distributions

The distributional assumptions for all parameters included are listed below. In the absence of any information on distributional properties, triangular distributions were specified with plausible minima and maxima.

Parameter	Distribution
Specific for THR	
Percentage homecare required:	
• administration only	Beta ($\alpha_1 = 17.94$; $\alpha_2 = 236.06$)
• administration additional to other help	Beta ($\alpha_1 = 9.96$; $\alpha_2 = 271.04$)
Treatment duration (in days)	Triang (ll = 22; ml = 50; ul = 78)
Specific for TKR	
Percentage homecare required:	
• administration only	Beta ($\alpha_1 = 13.94$; $\alpha_2 = 214.06$)
• administration additional to other help	Beta ($\alpha_1 = 6.97$; $\alpha_2 = 221.03$)
Treatment duration (in days)	Triang (ll = 22; ml = 36; ul = 50)
Other	
Costs of homecare (based on time in minutes):	
• administration only	Triang (ll = 7.5; ml = 15; ul = 22)
• administration additional to other help	Triang (ll = 5; ml = 10; ul = 15)
Duration of administration instruction (in minutes)	Triang (ll = 20; ml = 30; ul = 40)
Costs of HIT	Triang (ll = 1555; ml = 3110; ul = 4665)
Probability of HIT	Beta ($\alpha_1 = 14$; $\alpha_2 = 1640$)

ll, lower limit; ml, most likely value; ul, upper limit.

