Economic Evaluation of Dabigatran Etexilate for the Prevention of Venous Thromboembolism After Total Knee and Hip Replacement Surgery

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ABSTRACT

Objective: This was an evaluation of the cost-effectiveness of oral dabigatran etexilate compared with subcutaneous low-molecular-weight heparin (enoxaparin) for the prevention of venous thromboembolism (VTE) after total knee replacement (TKR) and total hip replacement (THR) surgery from the perspective of the UK National Health Service.

Methods: Dabigatran etexilate (220 mg once daily) was compared with enoxaparin (40 mg once daily) in patients undergoing TKR (duration of prophylaxis, 6–10 days) and THR (duration of prophylaxis, 28–35 days). The 10-week acute postsurgical phase was modeled using a decision tree. A Markov process (1-year cycle length) was used to model long-term events (recurrent VTE, postthrombotic syndrome, and consequences of intracranial hemorrhage) for patients' remaining lifetimes. Relative risks for VTE and bleeding events were derived from 2 Phase III studies that compared dabigatran etexilate with enoxaparin 40 mg once daily. The probabilities of long-term events were estimated using data from published longitudinal studies.

Results: Rates of VTE and bleeding events did not differ significantly between dabigatran etexilate and enoxaparin. Dabigatran etexilate was less costly than enoxaparin in TKR and substantially less costly in THR, primarily due to differences in administration costs. The cost of prophylaxis for THR patients, including drugs and administration costs, was estimated at £137 for dabigatran etexilate and £237 for enoxaparin (£7 for nursing time during the hospital stay, £91 for nurse home visits for administration after hospital discharge, and an additional £2 in drug costs). At a willingness-to-pay threshold of £20,000 per quality-adjusted life-year, the probability of cost-effectiveness for dabigatran etexilate was 75% in TKR and 97% in THR. These results were robust across a range of sensitivity analyses.

Conclusion: From the perspective of the UK National Health Service, thromboprophylaxis with dabigatran etexilate was cost-saving compared with enoxaparin 40 mg once daily, with comparable efficacy and safety profiles. (*Clin Ther.* 2009;31:194–212) © 2009 Excerpta Medica Inc.

Key words: thromboembolism, primary prevention, total hip replacement, total knee replacement, model, economics.

INTRODUCTION

Patients undergoing orthopedic surgery are at considerable risk for development of deep-vein thrombosis (DVT) and pulmonary embolism (PE),[1] collectively known as venous thromboembolism (VTE). In the longer term, thromboembolic events may recur and may result in chronic venous insufficiency in the lower

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extremity, producing chronic pain, venous ulceration, swelling, and skin changes in the affected leg, collectively known as postthrombotic syndrome (PTS).[2]

The majority of patients undergoing orthopedic surgery receive some kind of thromboprophylaxis, most commonly low-molecular-weight heparin (LMWH).[3,4] Recent guidelines recommend prophylaxis for most patients undergoing total knee replacement (TKR) and extended prophylaxis for those undergoing total hip replacement (THR).[5,6] However, the subcutaneous route of administration of LMWH may act as a barrier to implementation of the more effective extended prophylactic regimens[7,8]; therefore, many patients (30%–40%) may not receive continued anticoagulant prophylaxis after their discharge from the hospital.[9] Current trends toward shorter lengths of hospital stay may lead to increasingly fewer patients receiving prophylaxis for the guideline-recommended durations.[5,6] There is a clear need for new, effective interventions that do not present barriers related to administration after hospital discharge.

Dabigatran etexilate* is a new direct thrombin inhibitor that is approved for the primary prevention of VTE events in adults who have undergone elective TKR or THR.[10] It is administered orally at a fixed dose of 220 mg once daily and has no specific monitoring requirements.[11] Three Phase III trials have investigated the safety profile and efficacy of dabigatran etexilate compared with those of the LMWH enoxaparin after TKR (RE-MODEL[12] and RE-MOBILIZE[13]) and THR (RE-NOVATE[14]). The objective of the present analysis was to estimate the cost-effectiveness of dabigatran etexilate compared with LMWH, the most commonly used intervention in the United Kingdom, from the perspective of the UK National Health Service. A cost-utility framework was selected, as this enables the benefits and adverse effects of prophylaxis to be evaluated in terms of a single measure—the quality-adjusted life-year (QALY). A cost-effectiveness analysis also was performed to estimate the incremental cost per VTE avoided and cost per life-year gained.

MATERIALS AND METHODS

Decision Model

To estimate the differences in costs and outcomes between alternative prophylactic interventions, the analysis was designed to capture acute and recurrent VTE events, their long-term consequences (ie, PTS), prophylaxis-related adverse events (ie, bleeding, heparin-induced thrombocytopenia [HIT]), and deaths associated with VTE and adverse events. A modeling approach was necessary to capture events occurring beyond the ends of the trial periods (6-week follow-up for TKR, 10-week follow-up for THR) and to incorporate external evidence as necessary (eg, to estimate the long-term risk of PTS).

The model structure was devised based on the findings of a systematic review of economic evaluations of VTE prophylaxis after TKR or THR.[15] The structure was similar to that of the model described by Botteman et al[16] and included a decision tree and a Markov model component. The decision tree modeled events occurring within the initial 10-week period (the acute phase) (**Figure 1A**). Adverse events were modeled simultaneously in such a way that all patients were at risk for major and minor bleeding events and HIT (**Figure 1B**). The Markov component simulated events occurring over the longer term (the chronic phase) (**Figure 1C**).

The primary end point of the Phase III dabigatran etexilate trials was total VTE (defined as the composite of venographic and/or symptomatic DVT and symptomatic PE) and all-cause mortality. This end point was applied as the primary efficacy measure in the model and was used to estimate the probability of VTE. A VTE could be DVT (proximal or distal) or PE only and could be symptomatic or asymptomatic. PE could be fatal before symptoms emerged (ie, immediately fatal). Symptomatic events could be detected while the patient was in the hospital after surgery (possibly resulting in an increased length of stay) or could be detected after discharge and require readmission or outpatient treatment. Patients could present with symptoms of VTE that were not subsequently confirmed (ie, false-positive events), resulting in costs associated with diagnostic procedures but having no effect on the outcomes. Patients also could die after surgery from causes unrelated to VTE (ie, other post-surgical death).

Major bleeding events were categorized in the model as intracranial, gastrointestinal, surgical site, or other so that costs and outcomes could be assigned appropriately. Patients with an intracranial hemorrhage could recover, die, or be permanently disabled. Patients with other types of major bleeding or HIT could recover or die. Patients with minor bleeding events were assumed to recover.

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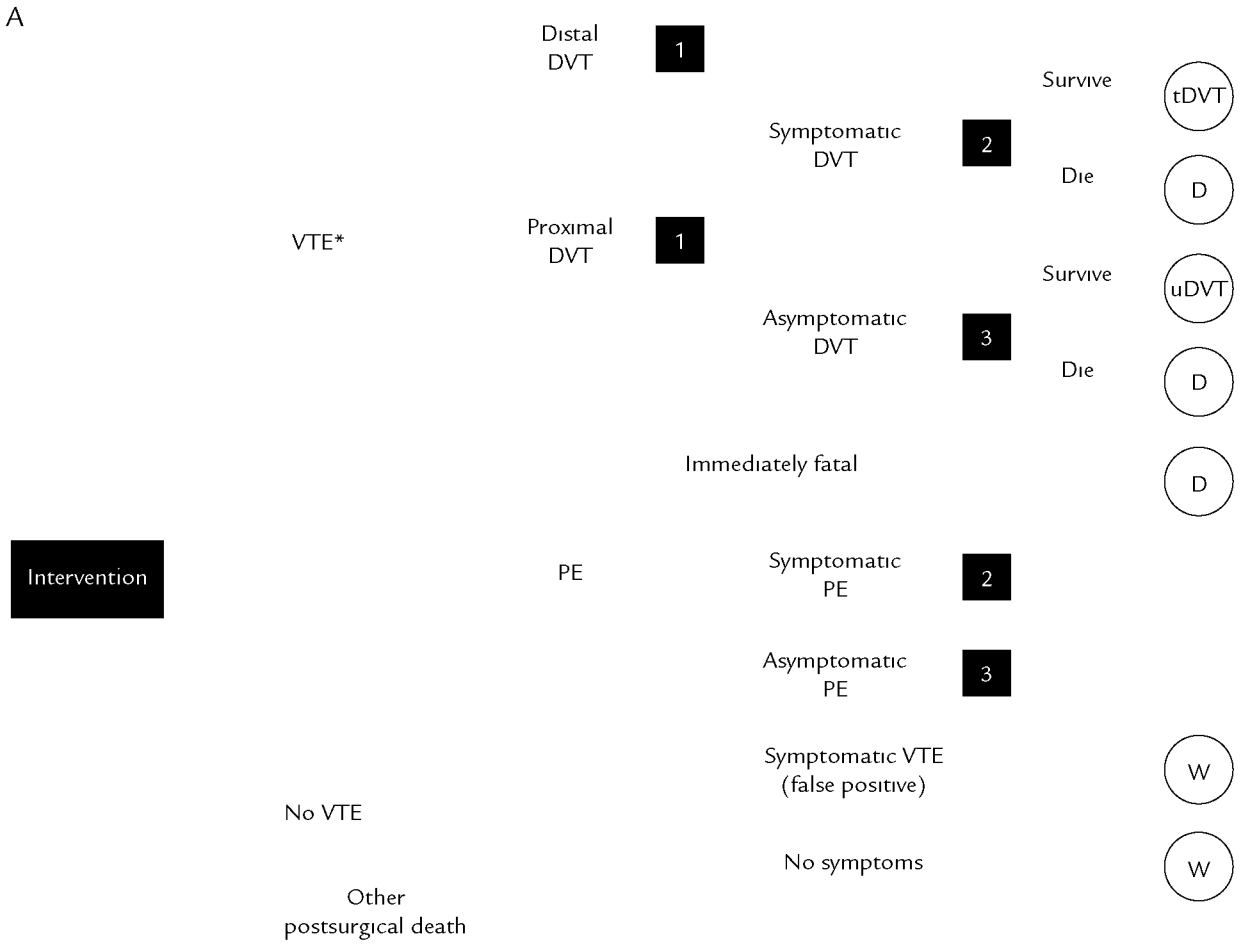

Figure 1. Diagram of the model structure. (A) Decision-tree model for venous thromboembolism (VTE) events (10-week acute phase).

(continued)

At the end of the acute phase, patients could enter the Markov model in 1 of 5 health states. All patients who had no VTE event, including those who recovered from a bleeding event, entered the model in the "well" state. Patients who had an asymptomatic VTE that was, therefore, not treated entered the model in the "untreated VTE" state. Patients who had recovered from a VTE that was symptomatic and treated entered the model in the "treated VTE" state. Patients who were permanently disabled after intracranial hemorrhage remained in the "disabled" state, and patients who had a fatal VTE, fatal bleeding event, or other postsurgical death remained in the "dead" state. The "treated VTE" and "untreated VTE" states actually represent 3 health states—"proximal DVT," "distal DVT," and "PE"—but were simplified in the figure.

In each Markov cycle (cycle length, 1 year), patients could develop symptoms of recurrent VTE (DVT or PE) or PTS (mild to moderate or severe at the time of diagnosis) or could die from other causes. To allow for differences in diagnostic and/or treatment patterns and associated costs in the first year, separate health states were used for the first and subsequent years of PTS. To simplify transitions for which there were

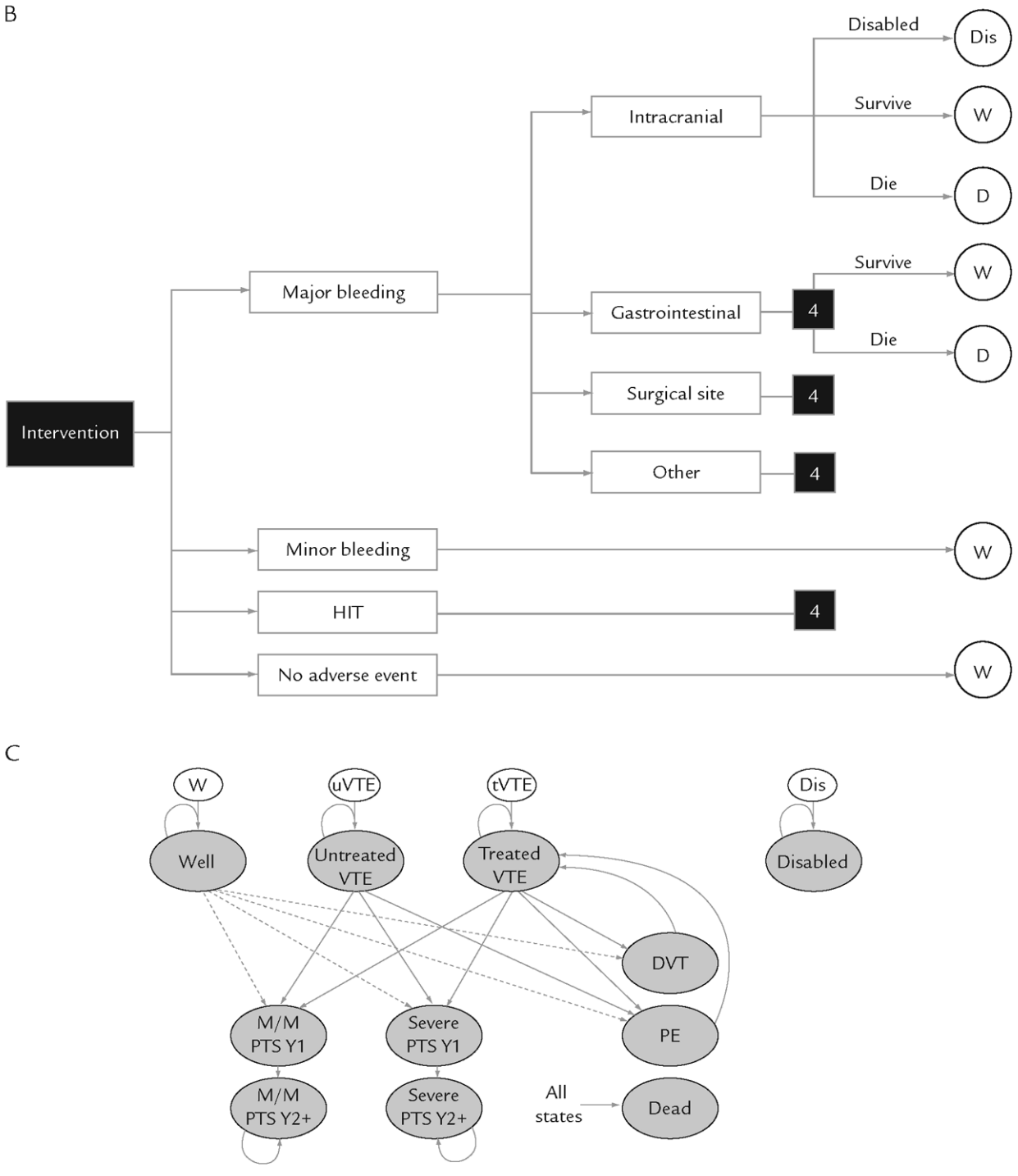

Figure 1 (continued). Diagram of the model structure. (B) decision-tree model for adverse events (10-week acute phase); and (C) Markov model (chronic phase). *Primary end point of the dabigatran etexilate trials (total VTE and all-cause mortality). DVT = deep-vein thrombosis; t = treated; D = died; u = untreated; PE = pulmonary embolism; W = well; Dis = disabled after intracranial hemorrhage; HIT = heparin-induced thrombocytopenia; M/M = mild to moderate; PTS = postthrombotic syndrome; Y = year.

scarce data,[16] patients did not transition between the "mild to moderate PTS" and "severe PTS" states; rather, costs and utility weights for each state represented the average for this group of patients for the remainder of their lifetimes. Thus, a proportion of patients in the "severe PTS" state could have an open ulcer at diagnosis that healed and then recurred. Once patients entered a PTS state, they could experience a recurrent VTE event or remain in this state until death or the end of the simulation.

The time horizon of the analysis was chosen to encompass the maximum lifetime of patients undergoing TKR or THR (60 years from the time of surgery, based on a minimum age at surgery of 40 years[4] and a maximum age of 100 years).

Patient Population

The 2 surgery types were modeled separately to reflect differences in the underlying risk of VTE, age and sex distribution, and duration of VTE prophylaxis. The mean age of patients entering the model was 70 years for TKR patients and 68 years for THR patients; the proportion of male patients was 43% for TKR patients and 40% for THR patients, as reported by the National Joint Registry for England and Wales.[4] Subgroup analyses were performed by age, sex, and risk factors for VTE (eg, previous VTE[17]).

Interventions

The interventions analyzed were dabigatran etexilate given at the approved dose of 220 mg once daily, with a half-dose on day 1, initiated 1 to 4 hours after surgery,[18] and enoxaparin sodium* given at 40 mg once daily (the approved dose in patients undergoing orthopedic surgery in the United Kingdom[19]), initiated 12 hours before surgery. The durations of prophylaxis were those investigated in 2 of the Phase III trials of dabigatran etexilate (**Table I**).[12,14] The third Phase III trial (RE-MOBILIZE[13]) was not included in the primary analyses because the dose of enoxaparin used was 30 mg BID, a strength and regimen that are not approved or available in the United Kingdom.

Event Probabilities

In the base-case analysis, probabilities of all acute VTE events were linked to the primary end point of the Phase III trials of dabigatran etexilate—total VTE and all-cause mortality. For enoxaparin, the probabilities of VTE (total VTE and all-cause mortality), major bleeding, and minor bleeding were calculated based on the incidence of events in the TKR trial (RE-MODEL[12]) and the THR trial (RE-NOVATE[14]) (**Table I**). For dabigatran etexilate, probabilities were calculated by applying the relative risk for each end point to the probabilities in the enoxaparin arm.

The probability of each type of VTE event within the primary end point (asymptomatic and symptomatic proximal/distal DVT, symptomatic PE, or fatal) and the types and consequences of adverse events were assumed to be the same for both interventions (**Table II**). These data were identified from the published literature by means of a systematic review.[15] The probability of HIT for dabigatran etexilate was taken from the Phase III trials[12,14] and for enoxaparin from a published meta-analysis[25] (**Table I**).

Time-dependent probabilities of recurrent VTE and PTS were estimated from Weibull functions fitted to longitudinal follow-up data from 16 published studies (**Figure 2**).[47–62] Two further distributions were fitted to the data from the studies reporting the highest and lowest incidence estimates to derive high and low distributions. These values were assumed to represent the upper and lower 95% CIs of the distribution and were used to estimate an SE for the Weibull scale parameter (as the CI width ÷ 2 × 1.96). The scale parameters (λ) were sampled in the probabilistic analysis from normal distributions defined by the mean and estimated SE; the shape (γ) parameters were assumed to be constant. The range of reported estimates was very large for PTS, which is likely due to differences in the definition of PTS between studies. The study by Prandoni et al,[50] which was also used by Botteman et al,[16] was selected for the central estimate.

Because the incidence of recurrent VTE has been reported to be lower for females than for males,[51] this value was adjusted by sex in the subgroup analysis, using a relative risk of 3.6 for males versus females. The incidence of PTS after distal DVT, which has been reported to be lower than that of PTS after proximal DVT,[63] was reduced in the model using a relative risk of 4.0 for proximal DVT versus distal DVT. Twenty-three percent of PTS cases were assumed to be severe at diagnosis, based on the mean of data from 8 studies.[48,50,54,55,57,58,60,61] Patients who had no VTE event in the postsurgical period were assumed to be at

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Table I. Intervention-specific input parameters: Cost of prophylaxis, efficacy, and safety.

Cost of Prophylaxis	Dabigatran Etexilate 220 mg Once Daily		Enoxaparin 40 mg Once Daily		Distribution for Probabilistic Sensitivity Analysis
	TKR	THR	TKR	THR	
No. of days of prophylaxis, mean (SD)	7.7 (1.3)[a]	33.0 (5.2)[b]	7.6 (1.4)[a]	33.2 (5.1)[b]	Normal
Drug cost per day, £[c]	4.20[d]	4.20[d]	4.20[e]	4.20[e]	Fixed
Administration cost per day, £					
Inpatient	0	0	0.82[f]	0.82[f]	Fixed
Outpatient	–	0	–	25.10[g]	

Efficacy	RR, Dabigatran Etexilate vs Enoxaparin (95% CI)		Incidence, % (n/N)		Distribution for Probabilistic Sensitivity Analysis
	TKR	THR	TKR	THR	
Total VTE and all-cause mortality	0.97[a] (0.82–1.13)	0.90[b] (0.63–1.29)	37.7[a] (193/512)	6.7[b] (60/897)	RR, log-normal; incidence, β

Safety	RR, Dabigatran Etexilate vs Enoxaparin (95% CI)		Incidence, % (n/N)		Distribution for Probabilistic Sensitivity Analysis
	TKR	THR	TKR	THR	
Major bleeding event	1.14[a] (0.46–2.78)	1.29[b] (0.70–2.37)	1.3[a] (9/694)	1.6[b] (18/1154)	RR, log-normal; incidence, β
Minor bleeding event[h]	0.96[a] (0.75–1.24)	1.04[b] (0.82–1.33)	15.3[a] (106/694)	9.9[b] (114/1154)	RR, log-normal; incidence, β
Incidence of HIT, % (95% CI)	0[a]	0[b]	0.2[i] (0.1–0.4)	0.2[i] (0.1–0.4)	Normal

TKR = total knee replacement; THR = total hip replacement; RR = relative risk; VTE = venous thromboembolism; HIT = heparin-induced thrombocytopenia.

[a] Sources: references 12 and 20.

[b] Sources: references 14 and 20.

[c] Source: reference 21.

[d] Cost: two 110-mg tablets per day, except on day 1, when it was one 110-mg tablet (£2.10).[21]

[e] Dose: 40-mg prefilled syringe.[19,21]

[f] Cost: 2.14 minutes of nurse time[22] at £0.38 per minute.[23]

[g] Estimate for patients unable to self-administer subcutaneous injections (13% of patients[24]; 1 district nurse visit per day at £25.10[23]). For patients able to self-administer (87% of patients[24]), a one-time cost was attributed for 30 minutes of nurse time for training in self-administration[17] at £11.50.[23]

[h] Combined end point for clinically relevant and minor bleeding.

[i] Source: reference 25.

Table II. Other model parameters.

Parameter	Proximal DVT	Distal DVT	PE	Sources (References)
VTE events, non–intervention-specific probability				
Type of event	0.310	0.591[a]	0.098	Calculated from 17
Symptomatic event	0.40	0.05	0.29	26, 27
Event detected before discharge	0.53[b]	0.53[b]	0.53[b]	28
Symptomatic event not confirmed	0.13	0.13	0.10	27, 29, 30
Mortality, non–intervention-specific probability				
Immediately fatal	–	–	0.11	27
Death during treatment	0.03	0.03	0.14	26, 31
Asymptomatic, untreated event	0.05[c]	0.05[c]	0.30	27
Costs of events detected before discharge, £				
Diagnosis[d]	95	95	142	Calculated from 17, 32
Treatment[e]	1627	1565	2511	Calculated from Hospital Episode Statistics,[e] 17, 32
Costs of events detected after discharge, £				
Diagnosis[f]	213	213	288	Calculated from 17, 32
Treatment of admitted patients[g]	1390	1328	1729	Calculated from 17, 32, 33
Treated on outpatient basis (38% of DVTs)[h]	463	401	–	
Utility weights				
Period of inpatient stay (utility = 0), d	4.9	4.9	5.7	Hospital Episode Statistics[e]
Treatment period after discharge (decrement of 0.08 applied), wk	26	12	26	17, 34

Major Bleeding Events	Intracranial	Surgical Site	Gastrointestinal	Other	Sources (References)
Site of bleeding event,[i] probability	0.01	0.36	0.10	0.53	Calculated from 17
Mortality, probability	0.44	0.008	0.008	0.008	35, 36
Survivor permanently disabled, probability	0.65	–	–	–	37
Costs, £					
Acute care[j]	7268	2355	2355	1027	32, 38, 39
Long-term care	5953	–	–	–	32, 38, 39
Utility decrement	0.10 for period of hospitalization (5.4 d)				32, 40

(continued)

Table II (continued).

Other Events	PTS: Minor Bleeding	PTS: HIT	PTS: Mild to Moderate	PTS: Severe	Sources (References)
Mortality, probability	0	0.23	–	–	Minor bleeding, assumption; HIT, 41
Costs, £					
Year 1	89	293	541	2461	42, 43; minor bleeding, assumption
Year 2+	–	–	220	602	
Utility decrement	0	0	0.02	0.07	44; minor bleeding and HIT, assumption

DVT = deep-vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism; PTS = postthrombotic syndrome; HIT = heparin-induced thrombocytopenia.

[a] The remaining 0.1% was death from other causes recorded during the trial.

[b] Data for total knee replacement; the estimate for total hip replacement was 24%.

[c] The relative risk of death for untreated versus treated PE events reported by Oster et al[27] was applied to DVT patients.

[d] DVT: Doppler ultrasound[17]; PE: computed tomography pulmonary angiogram, chest radiograph, and electrocardiogram.[17]

[e] Personal communication from the Hospital Episode Statistics Service Team, Northgate Information Solutions, Hemel Hempstead, United Kingdom, April 2007. Increased length of stay for DVT and PE estimated from UK Hospital Episode Statistics (2005–2006) for a total of 97,582 discharge episodes: 52,344 episodes of total knee replacement (*Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th Revision* [*OPCS-4*] codes W40.1, W41.1, and W42.1[45]) and 45,238 episodes of total hip replacement (*OPCS-4* codes W37.1, W38.1, and W39.1[45]), of which 317 had a diagnosis of DVT (but no PE) and 282 had a diagnosis of PE (*International Statistical Classification of Diseases and Related Health Problems, 10th Revision* [*ICD-10*] codes I80.1 and I80.2 for DVT and I26.0 and I26.9 for PE[46]). Total cost included the incremental length of stay (4.9 days for DVT, 5.7 days for PE), 7 injections of low-molecular-weight heparin, 6 months of warfarin therapy, graduated compression stockings, 7 anticoagulation clinic visits (5% of patients requiring ambulance transport), and 2 full blood counts.[17] Patients treated for distal DVT (5% of all distal DVTs[17]) received the same treatment, but only 3 months of warfarin therapy and 5 anticoagulation clinic visits.[17]

[f] Outpatient visit for DVT; accident and emergency department visit for PE plus diagnostics (see note d).

[g] National Health Services reference cost for a PE or DVT admission[32] (weighted average of elective and nonelective inpatient Healthcare Resource Groups E20 and E21 for DVT and Healthcare Resource Groups D10 and D11 for PE) plus 6 months of warfarin therapy (3 months for distal DVT) and 7 anticoagulation clinic visits (5 for distal DVT).

[h] Five injections of low-molecular-weight heparin, 3 months of warfarin therapy, graduated compression stockings, 5 anticoagulation clinic visits, 8 district nurse visits, and a full blood count.[17] The percentage of patients treated on an outpatient basis was taken from Davies et al.[33]

[i] Probabilities for the type of major bleeding event were sampled in the probabilistic analysis from a β distribution defined by the number of patients experiencing an event of that type and the number experiencing another type of major bleeding event.

[j] The cost of acute care for intracranial bleeding was sampled in the probabilistic analysis from a normal distribution (CIs were symmetrical about the mean estimate) defined by the mean and SE.

the same risk for a VTE event and PTS as the general population.[16,64]

Death in the postoperative period from causes other than VTE or bleeding events was included in the analysis to account for the cost of prophylaxis in this group of patients in whom the benefit of prophylaxis cannot be realized. The probability in both prophylaxis cohorts was 0.4%, taken from the National Joint Registry for England and Wales.[4] Death from other causes in the long term was governed by time-dependent probabilities estimated from age- and sex-specific mortality rates for the United Kingdom,[65] which were adjusted for the age and sex distribution of the starting population and for the aging of patients in each model cycle.

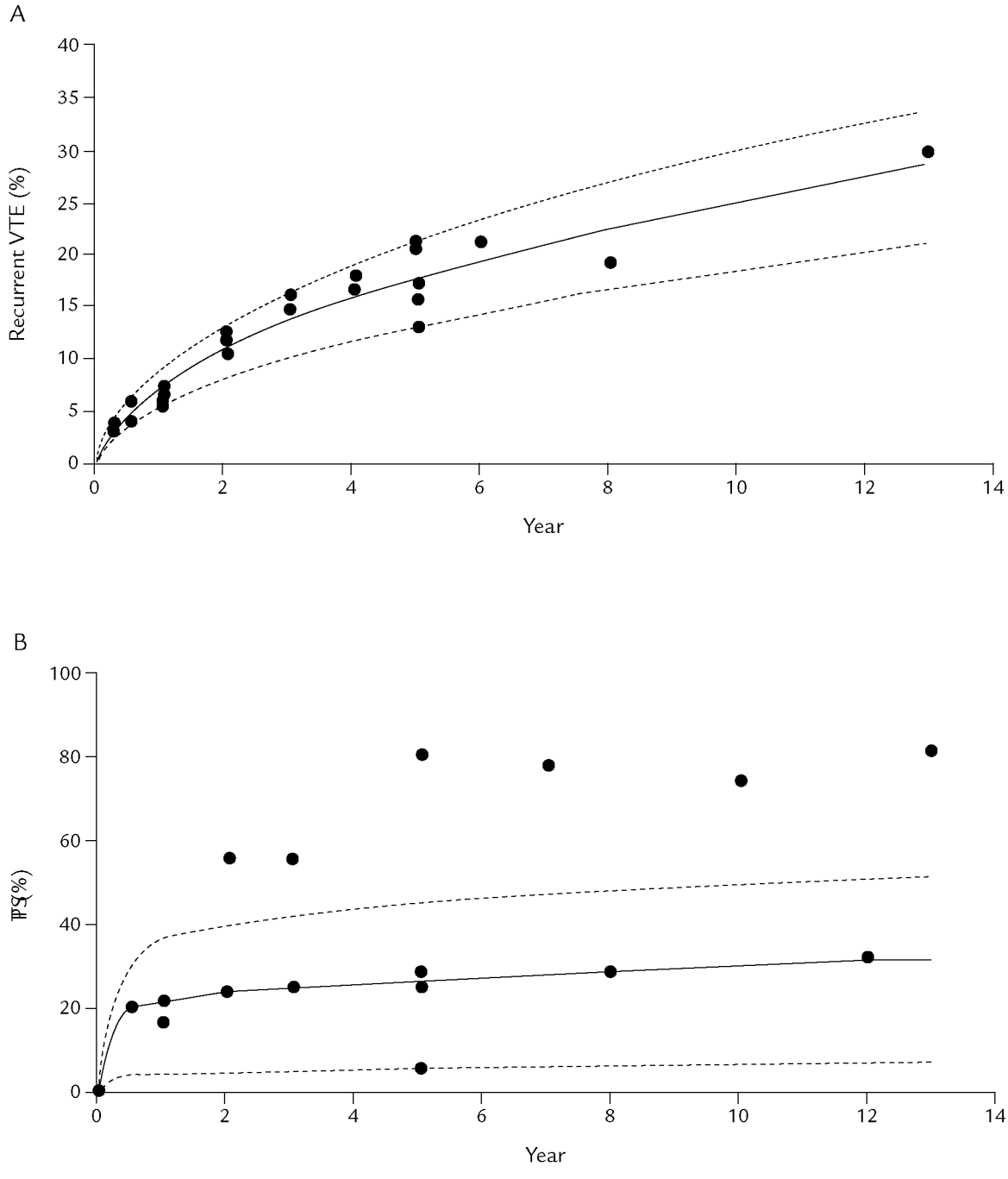

Figure 2. Estimation of the probabilities of recurrent venous thromboembolism (VTE) and postthrombotic syndrome (PTS). Cumulative incidence of (A) recurrent VTE and (B) PTS from published longitudinal follow-up studies.[47-62]

Resource Use and Cost Estimates

The cost year of the analysis was 2008; unit costs not available for 2008 were inflated using the Hospital and Community Health Services Pay and Prices Index.[23] Drug acquisition costs assumed the mean durations of prophylaxis in the TKR and THR trials (**Table I**). Nursing time for injection of LMWH during hospitalization (2.14 minutes per injection) was taken from an economic analysis by Offord et al.[22] For prophylaxis after hospital discharge, THR patients who were able to self-administer medication were assumed to require 30 minutes of nurse time for instruction during their hospital stay. Thirteen percent of patients were assumed to be unable or unwilling to self-administer medication[24] and to require 1 district nurse visit per injection. No administration costs were assumed for dabigatran etexilate.

The costs of managing VTE and adverse events are summarized in **Table II**. Patients with symptoms of DVT were assumed to undergo Doppler ultrasound investigation,[17] and those with symptoms of PE were assumed to undergo a computed tomography pulmonary angiogram, chest radiography, and an electrocardiogram.[17]

The increased length of stay for confirmed cases of DVT and PE detected before discharge was estimated from UK Hospital Episode Statistics (HES) for 2005–2006 (personal communication, HES Service Team, Northgate Information Solutions, Hemel Hempstead, United Kingdom, April 2007). Because VTE occurs more frequently in older TKR and THR patients,[5] who are likely to have longer-than-average hospital stays, inpatient episodes were grouped by age (0–59, 60–69, and ≥70 years), sex, and surgery type, and the length of stay for patients with and without VTE was compared within each group. A weighted average of the incremental mean length of stay was calculated for the overall population (4.9 days for DVT, 5.7 days for PE). The cost associated with the additional length of stay was estimated using a per diem cost (general ward).[66] Ten percent of PE patients were assumed to receive care in the intensive care unit.[17] Other resource use for VTE treatment (**Table II**) was based on an economic analysis conducted by the UK National Collaborating Centre for Acute Care,[17] which underpinned recent guidelines for thromboprophylaxis issued by the National Institute for Health and Clinical Excellence (NICE).[6]

Patients first presenting with symptoms of VTE after discharge were assumed to have an outpatient visit for a suspected DVT or an accident and emergency department visit for a suspected PE, as well as undergoing the diagnostic tests described previously. Sixty-two percent of patients with confirmed DVT and all patients with confirmed PE were assumed to be readmitted[33] and were assigned the mean National Health Service reference cost for a DVT or PE admission.[32] Resource use after hospital discharge or for DVT patients treated on an outpatient basis was based on the National Collaborating Centre for Acute Care analysis.[17]

The cost associated with the diagnosis and management of PTS was derived from an analysis of the economic burden of the long-term complications of DVT after THR surgery in the United States.[43]

The cost of major bleeding events was based on UK National Health Service reference costs for inpatient admissions.[32] The cost of acute care for intracranial bleeding was based on a retrospective study involving 38 patients with a major bleeding event associated with warfarin treatment in the United Kingdom.[38] The cost of long-term care was based on a study of resource-use data from 457 stroke patients treated in the United Kingdom,[39] adjusted for the disability level expected after intracranial bleeding.[37] For minor bleeding events, the proportion of patients requiring medical attention was estimated from the proportion of all patients with minor bleeding considered clinically relevant in the dabigatran etexilate trials (38%).[20] Resource use for clinically relevant minor bleeding was estimated as 2 outpatient visits, based on clinical opinion. Other minor bleeding events were assumed to result in negligible costs. Resource utilization for HIT was based on a published economic analysis.[42]

Utility Estimates

For VTE events, the assumed utility decrement was equal to the duration of hospitalization for the event,[16,17] plus a decrement of 0.08 for the duration of treatment after discharge. Both decrements were based on a study that involved 121 DVT patients receiving warfarin treatment and used the EuroQol EQ-5D to estimate utility weights (**Table II**).[34] Utility estimates for PTS were taken from a study that enrolled 30 healthy volunteers and 30 physicians and used standard gamble methods.[44]

For major bleeding events, a utility decrement of 0.1 was assumed for the duration of hospital stay, based on a study that involved 54 patients with atrial

fibrillation receiving warfarin treatment and used standard gamble methods.[40] For patients with long-term disability after an intracranial bleeding event, a utility decrement of 0.5 was applied to the remainder of their lifetime (based on the mean of 109 published decrements for stroke). Minor bleeding and nonfatal HIT were assumed to have a negligible effect on health-related quality of life. This simplifying assumption was expected to be conservative for dabigatran etexilate, as HIT can result in necrosis and amputation, and may occur in patients receiving enoxaparin but not those receiving dabigatran etexilate.

To model the impact of aging, a utility weight that decreased over time was attributed to all surviving patients. Age- and sex-specific utility weights for the general population were taken from a national survey conducted in England using the EuroQol EQ-5D.[67]

Analysis

Costs and outcomes were discounted at 3.5% per annum (varied from 0% to 6% in the sensitivity analysis).[68]

Uncertainty in the estimated incremental cost-effectiveness ratios was explored by univariate and probabilistic sensitivity analyses. In the probabilistic analysis, key model parameters were sampled from parametric distributions to generate 1000 estimates of the costs and effects in each arm, from which the probabilistic mean incremental cost-effectiveness ratios and 95% CIs were estimated. Parameters were sampled from appropriate statistical distributions for each parameter type (**Table I**).[69]

In addition to the cost-effectiveness analysis, a cost-minimization analysis was performed to estimate cost differences if the incidence of VTE and bleeding events was assumed to be equivalent for the 2 interventions.

In the univariate sensitivity analysis, the relative risks for dabigatran etexilate versus enoxaparin were applied from 2 meta-analyses, one of the 2 European studies (RE-MODEL and RE-NOVATE) and the other of all 3 dabigatran etexilate trials.[20] Subgroup analyses were performed by age, sex, and risk factors for VTE (general anesthesia, body mass index ≥30 kg/m^2, previous VTE, cancer, use of oral contraceptives, use of hormone replacement therapy, and varicose veins). Differences between these subpopulations were propagated through the model by adjusting the underlying risk of VTE[17] and differences in life expectancy (using age- and sex-specific probabilities of all-cause mortality[65]). An exploratory analysis was performed to compare the cost-effectiveness of extended dabigatran etexilate use (33 days) versus enoxaparin for the duration of the hospital stay (7.6 days[66]) by adjusting the treatment effects observed in the RE-NOVATE trial[14] for the difference in efficacy and safety between LMWH given during the inpatient stay only and LMWH given for an extended period after discharge. The relative risks for VTE and major bleeding were taken from a large network meta-analysis.[17] The relative risks for minor bleeding were taken from a supplementary analysis of the same trial set.[20]

Model Validation

The model was designed to comply with the NICE reference case for economic analyses,[68] and its structure and parameters were reviewed and validated by 2 of the authors (G.D. and I.J.B.), who are practicing clinical experts in the United Kingdom. Quality control of model programming and verification of all input data against the original sources were performed according to a prespecified test plan by health economists who were not involved in model development.

RESULTS

The results of the base-case analysis are presented in **Table III**. The outcomes were comparable for patients receiving dabigatran etexilate and enoxaparin in both the TKR and THR analyses, although the incidence of VTE events was slightly lower for dabigatran etexilate than for enoxaparin and the incidence of bleeding events was slightly higher. In both the TKR and THR analyses, the incidence of HIT was 0% for dabigatran etexilate and 0.2% for enoxaparin. Overall, mean estimated QALYs were slightly higher in the dabigatran etexilate cohort, but the differences were small, reflecting the similar efficacy and safety profiles of the 2 interventions in the RE-MODEL[12] and RE-NOVATE[14] trials.

In patients undergoing TKR, the cost of prophylaxis was slightly higher for enoxaparin relative to dabigatran etexilate due to the cost of nursing time for administration of subcutaneous injections during the inpatient stay. The slightly lower drug cost for dabigatran etexilate was due to the half-dose given on the first day of prophylaxis. The cost of VTE events was slightly lower for dabigatran etexilate than for enoxaparin, and the cost of adverse events was slightly higher. Overall, mean total expected lifetime costs were

Table III. Base-case results for total knee replacement (TKR) and total hip replacement (THR).*

	TKR			THR		
Variable	Dabigatran Etexilate	Enoxaparin	Incremental	Dabigatran Etexilate	Enoxaparin	Incremental
Estimated outcomes						
Symptomatic VTE, %	16.0	16.3	−0.4	5.9	6.1	−0.2
Nonfatal proximal DVT	9.8	10.0	−0.2	3.7	3.9	−0.1
Nonfatal distal DVT	2.3	2.4	−0.1	0.9	0.9	0
Nonfatal PE	2.1	2.2	0	0.9	0.9	0
VTE-related death	1.7	1.7	0	0.4	0.4	0
PTS, %	8.4	8.5	−0.1	4.8	4.9	−0.1
Major bleeding, %	1.5	1.3	0.2	2.0	1.6	0.5
Minor bleeding, %	14.7	15.3	−0.6	10.3	9.9	0.4
HIT, %	0	0.2	−0.2	0	0.2	−0.2
Mean no. of life-years per patient	10.261	10.252	0.009	11.242	11.234	0.008
Mean no. of QALYs per patient	7.647	7.639	0.007	8.432	8.426	0.006
Estimated costs, 2008 £						
Prophylaxis (total)	30	38	−8	137	237	−101
Drug	30	32	−2	137	139	−3
Administration in hospital	0	6	−6	0	7	−7
Administration after discharge	0	0	0	0	91	−91
VTE events	531	543	−12	220	227	−7
Adverse events	25	22	3	35	28	7
Management of other acute events	1	1	0	0	0	0
Total	589	606	−17	392	493	−101

Cost-Effectiveness Variable	TKR	THR
Incremental cost per VTE avoided	Dabigatran etexilate dominant	Dabigatran etexilate dominant
Incremental cost per LYS	Dabigatran etexilate dominant	Dabigatran etexilate dominant
Incremental cost per QALY	Dabigatran etexilate dominant	Dabigatran etexilate dominant
Probability of cost-effectiveness, %		
£20,000 per QALY	75	97
£30,000 per QALY	75	96

VTE = venous thromboembolism; DVT = deep-vein thrombosis; PE = pulmonary embolism; PTS = postthrombotic syndrome; HIT = heparin-induced thrombocytopenia; QALYs = quality-adjusted life-years; LYS = life-year saved.
*Numbers may not sum precisely due to rounding.

slightly lower in the dabigatran etexilate arm (**Table III**); therefore, dabigatran etexilate was dominant over enoxaparin.

In patients undergoing THR, the cost of prophylaxis was substantially higher for enoxaparin compared with dabigatran etexilate, primarily due to the cost of administration after hospital discharge. Again, the cost of VTE events was slightly lower for dabigatran etexilate relative to enoxaparin, and the cost of adverse events was slightly higher. Overall, the total expected lifetime costs were substantially lower in the dabigatran etexilate arm (**Table III**); again, dabigatran etexilate was dominant over enoxaparin.

The results of the probabilistic sensitivity analysis are presented in **Figure 3**. In TKR patients, dabigatran etexilate was dominant over enoxaparin in ~66% of simulations and was dominated by enoxaparin in ~25% of simulations. The probability of cost-effectiveness at the UK willingness-to-pay threshold of £20,000 per QALY[68] was 75% (**Table III**). In THR patients, dabigatran etexilate was dominant in the majority of simulations; the probability of cost-effectiveness at the threshold of £20,000 per QALY was 97%.

Results of the cost-minimization and univariate sensitivity analyses are presented in **Table IV**. In the cost-minimization analysis, dabigatran was cost-saving in both TKR and THR patients. If the cost of LMWH was altered to reflect the mean for the various LMWH agents available in the United Kingdom (enoxaparin, dalteparin, tinzaparin, and bemiparin), the incremental cost was reduced, but the overall findings were not affected.

The results were sensitive to the sources of the efficacy and safety data that were applied. The results of the meta-analysis of the 2 trials that compared dabigatran etexilate with enoxaparin 40 mg once daily[20] were similar to those of the base-case analysis. When data from the meta-analysis of all 3 dabigatran etexilate trials were used,[20] the results for THR patients were largely unchanged; in TKR patients, however, dabigatran etexilate was no longer dominant but was dominated. Although the results were sensitive to the efficacy data applied, differences in outcomes between the 2 interventions were small, reflecting the similarity in efficacy and safety profiles in the clinical trials.

If all THR patients were assumed to be willing and able to self-administer LMWH, the total costs for dabigatran etexilate were still slightly lower than those for enoxaparin due to the cost associated with nurse time for LMWH injections during the inpatient stay and the time for training patients to administer LMWH after discharge. Alteration of the time horizon and discount rates had little effect on the results. Cost savings were greater in males than in females, as the risk of recurrent VTE is higher for males.[51] In the youngest age group (<60 years), cost savings were slightly lower because the underlying risk of VTE is lower[17]; in the oldest age group (>70 years), cost savings were also slightly lower because shorter life expectancy resulted in lower long-term benefits. In the group at highest risk for recurrent VTE (those with a previous VTE event),[17] cost savings were increased, as a slight reduction in VTE risk with dabigatran etexilate resulted in a greater reduction in the absolute number of VTE events in this high-risk population compared with that in populations at lower risk.

Although extended LMWH prophylaxis is recommended for the majority of THR patients,[6] most patients (30%–40%) do not in fact continue anticoagulant prophylaxis after hospital discharge.[9] In the exploratory analysis comparing extended prophylaxis with dabigatran etexilate (33 days) with enoxaparin given only for the duration of the hospital stay (7.6 days), dabigatran etexilate was cost-effective compared with enoxaparin. Prophylaxis costs were higher for dabigatran etexilate than for enoxaparin (£137 vs £38, respectively), and bleeding events were slightly more frequent (major bleeding: 2.0% vs 1.3%; minor bleeding: 10.3% vs 9.3%). However, the estimated incidence of symptomatic VTE events over patients' lifetimes was substantially lower for dabigatran etexilate than for enoxaparin (5.9% vs 8.6%). Overall, a mean of 0.04 QALY per patient was gained in the dabigatran etexilate cohort compared with the enoxaparin cohort, and total costs were £24 higher. The incremental cost per QALY was estimated at £754.

DISCUSSION

LMWH is the most widely used[4] and recommended[5,6] prophylactic intervention in patients undergoing TKR and THR in the United Kingdom. Dabigatran etexilate has been reported to have comparable efficacy to LMWH with a similar safety profile.[12–14,20] The study results suggest that from the perspective of the UK National Health Service, dabigatran etexilate was cost-effective compared with the dose of enoxaparin approved for use in patients undergoing orthopedic surgery in the United Kingdom (40 mg once daily). In

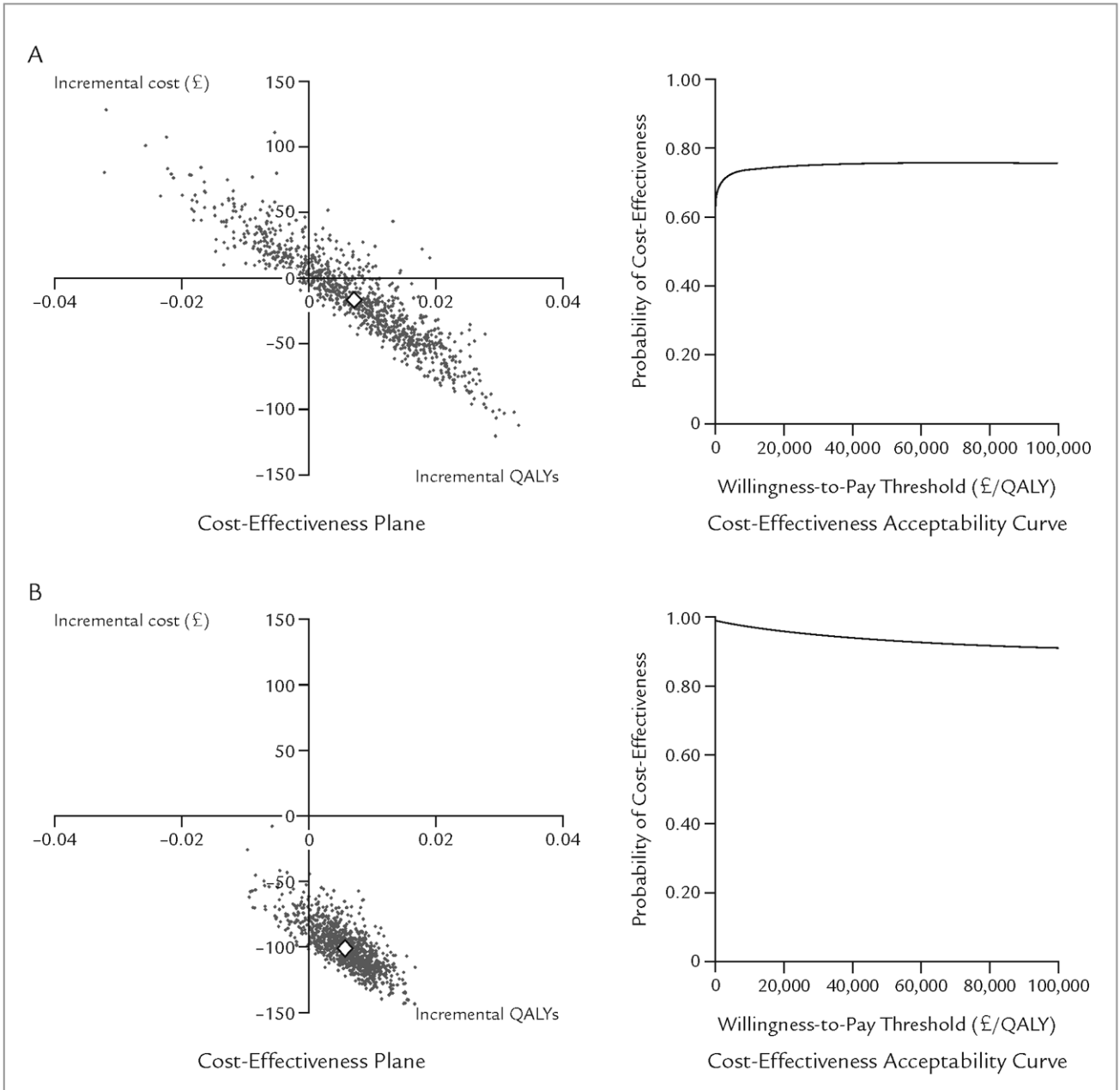

Figure 3. Results of the probabilistic analysis for dabigatran etexilate versus enoxaparin in (A) total knee replacement and (B) total hip replacement. The white diamonds in the cost-effectiveness planes represent the deterministic mean incremental costs and quality-adjusted life-year (QALY) estimates.

TKR patients, costs and outcomes were similar for the 2 interventions; modest cost savings may be expected with dabigatran etexilate as a result of its oral route of administration. In THR patients, in whom extended prophylaxis is recommended,[6] the estimated cost savings were more substantial. When enoxaparin use was limited to the duration of the inpatient stay, extended prophylaxis with dabigatran etexilate was associated with a clear benefit in terms of VTE events avoided (and thus QALYs) and was cost-effective. The findings were consistent across age groups and sexes, as well as in those at high risk for VTE.

Table IV. Sensitivity analysis results for dabigatran etexilate versus enoxaparin in total knee replacement (TKR) and total hip replacement (THR).

Variable	TKR	THR
Base case	Dominant (-£17)	Dominant (-£101)
Cost-minimization analysis (all VTE and bleeding outcomes assumed to be equivalent)	Cost saving (-£8)	Cost saving (-£112)
Mean cost of LMWH (based on mean use of licensed agents in the United Kingdom*)	Dominant (-£16)	Dominant (-£95)
Meta-analysis of the RE-MODEL and RE-NOVATE trials[20]	Dominant (-£23)	Dominant (-£99)
Meta-analysis of all 3 Phase III trials of dabigatran etexilate[20]	Dominated (-0.003 QALYs; +£10)	Dominant (-£99)
Proportion of patients unable or unwilling to self-administer LMWH after hospital discharge set to zero	Not applicable	Dominant (-£21)
Time horizon reduced to 10 wk	Dominant (-£9)	Dominant (-£96)
Discount rate 0% for costs and outcomes	Dominant (-£19)	Dominant (-£102)
Discount rate 6% for costs and outcomes	Dominant (-£16)	Dominant (-£100)
Males only	Dominant (-£22)	Dominant (-£104)
Females only	Dominant (-£12)	Dominant (-£97)
Age <60 y	Dominant (-£13)	Dominant (-£97)
Age 60–69 y	Dominant (-£18)	Dominant (-£101)
Age ≥70 y	Dominant (-£16)	Dominant (-£100)
High-risk patients	Dominant (-£29)	Dominant (-£123)

VTE = venous thromboembolism; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year.
*The analysis assumed that 80% of patients received enoxaparin, 20% received dalteparin, and 20% received tinzaparin at a daily cost of £4.20, £2.82, and £3.83, respectively.[21]

The analysis included a substantial amount of modeling to estimate the occurrence and impact of symptomatic VTE events and adverse events, as well as the long-term impact of recurrent VTE and PTS. Although systematic searches were performed and the model structure and parameters were validated by clinical experts, as in any model, uncertainty in the parameters is propagated into the results. In addition, certain assumptions were necessary to perform the analyses. The event probabilities estimated from the trial data reflected the probability of having at least 1 event of that type, and it was not possible to reflect, for example, >1 DVT occurring in an individual patient during the trial period. When a single patient had >1 event (eg, DVT and PTS), the impact of the events was assumed to be additive (ie, the cost of managing a patient with DVT and PTS was identical to the sum of the cost of each individual event).

The analyses were most sensitive to the efficacy data applied, reflecting the fact that the 2 interventions have similar safety and efficacy profiles and drug acquisition costs.[70] Because dabigatran etexilate has been reported to be statistically noninferior in efficacy to enoxaparin 40 mg once daily[12,14] with a similar safety profile, the study analyses, at their simplest, compared the costs of the 2 interventions that were unaffected by uncertainty in other parameters. The simple cost-minimization analysis indicated that da-

bigatran etexilate was expected to be cost-saving compared with enoxaparin 40 mg once daily. As the drug acquisition costs were essentially equivalent, the key uncertainty lay in the costs associated with administration of enoxaparin. However, under any plausible set of assumptions in which the duration of prophylaxis is equivalent, the total cost of dabigatran etexilate prophylaxis would be expected to be lower than that of enoxaparin.

This analysis did not include costs associated with platelet monitoring for HIT, needle-stick injuries, or sharps disposal. Neither did it include any utility benefits that might be associated with the oral route of administration and avoidance of daily subcutaneous injections. For these reasons, the benefits of dabigatran etexilate may have been underestimated.[70]

Finally, because this analysis was performed from the perspective of the UK National Health Service, the results may not be generalizable to other health systems. This is likely to be particularly pertinent to jurisdictions that differ substantially from the United Kingdom in terms of the proportion of patients receiving assistance for enoxaparin administration or the cost of this assistance, or in terms of the proportion of resources committed to monitoring for HIT. In addition, no analyses were performed in which dabigatran etexilate was compared with enoxaparin 30 mg BID, which is not approved or available in the United Kingdom but may be used in other countries. In the Phase III trial comparing these regimens (RE-MOBILIZE[13]), dabigatran etexilate did not satisfy the criterion for noninferiority. However, the incidence of major bleeding was lower with dabigatran etexilate (0.6% vs 1.4%, respectively), and the cost of the higher enoxaparin dose and twice-daily administration also needs to be taken into account. Country-specific analyses are needed to evaluate the overall balance of costs and outcomes for this comparison.

Dabigatran etexilate prophylaxis appears to offer important practical benefits over LMWH prophylaxis. The oral route of administration removes the need to train patients in self-administration or, for those who are unwilling or unable to self-inject, the need for additional health care contacts to administer LMWH after hospital discharge. Both are recognized barriers to wider use of extended prophylaxis. Also avoided are the costs of platelet monitoring for HIT, needle-stick injuries, and sharps disposal. In addition, patients may prefer an oral medication to subcutaneous injection, which may potentially improve compliance.

CONCLUSION

In this analysis from the perspective of the UK National Health Service, thromboprophylaxis with dabigatran etexilate was cost-saving compared with enoxaparin 40 mg once daily, with comparable efficacy and safety profiles.

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