Cost-effectiveness of Dabigatran Etexilate 150 mg for the Prevention of Venous Thromboembolism in Patients Aged Over 75 Years Undergoing Total Hip or Knee Arthroplasty

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INTRODUCTION

- Orthopaedic surgery patients are at considerable risk of developing deep-vein thrombosis (DVT) in their lower limbs and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE).[1]
- Consequently, most patients receive thromboprophylaxis, most commonly a low-molecular-weight heparin (LMWH).[2]
- Elderly patients represent a special population for thromboprophylaxis. In individuals older than 30 years, a natural decline in glomerular filtration rate is observed,[3] which may lead to a reduced rate of anticoagulant clearance and potentially an increased rate of bleeding.[4,5]
- Dabigatran etexilate (DBG, Pradaxa®) is a new reversible oral direct thrombin inhibitor[6] that is approved at a standard fixed dose of 220 mg once daily (od), and at a lower dose of 150 mg od for patients older than 75 years.[7]
- A recent economic analysis for the United Kingdom (UK) has demonstrated that DBG 220 mg od is cost-saving when compared with the commonly used subcutaneous LMWH, enoxaparin sodium (Clexane®, sanofi-aventis, Paris, France) 40 mg od, with comparable efficacy and safety.[8]
- This analysis investigates the cost-effectiveness of DBG 150 mg od compared with enoxaparin 40 mg od.* for the prevention of VTE in the subset of patients older than 75 years undergoing total knee arthroplasty (TKA) or total hip arthroplasty (THA) from the perspective of the UK National Health Service. *No dosage adjustments are necessary for enoxaparin in elderly patients, provided creatinine clearance exceeds 30 mL/min.[9]

METHODS

Interventions

- DBG was investigated at 150 mg od, with the first dose (a half-dose) given 1 to 4 hours post-surgery.[7] Enoxaparin was investigated at the UK-licensed dose of 40 mg od starting 12 hours pre-surgery. The duration of prophylaxis was as investigated in the phase 3 trials comparing these agents (Table 1).

Table 1. Interventions Investigated

	DBG 150 mg od (oral)		Enoxaparin 40 mg od (sc injection)	
Duration of prophylaxis, mean days (standard deviation)	Total	Out-patient[a]	Total	Out-patient[a]
TKA patients[10]	7.8 (1.3)	0.0	7.6 (1.4)	0.0
THA patients[11]	33.1 (5.1)	21.8	33.2 (5.1)	21.9
Drug cost per day[12]	£4.20 (2 x 75 mg tablet)[b]		£4.20 (40 mg pre-filled syringe)	
Cost per in-patient administration	–		£0.82[c]	
Cost of out-patient administration				
Patients unable or unwilling to self-administer sc injections	–		£25.10 per day[d]; 13% of patients[13]	
Patients able and willing to self-administer sc injections	–		£11.50 per patient[e]; 87% of patients[13]	

sc = subcutaneous.

[a] Days out-patient prophylaxis calculated using mean length of hospital stay for patients aged > 75 years (13.5 days for TKA and 11.3 days for THA patients, UK Hospital Episode Statistics[14]).

[b] Half-dose (1 x 75 mg tablet) on day of surgery = £2.10.

[c] 2.14 minutes of nurse time[15] at £23.00 per hour.[16]

[d] 1 district nurse visit per day[17] for administration of sc injections at £25.10 per visit.[16]

[e] 30 minutes of nurse time for training in self-administration[17] at £23.00 per hour.[16]

Analysis Structure

- A published model[8] was adapted for the analysis. TKA and THA patients entered the model at the time of their surgeries. Acute events occurring during the first 10 weeks post-surgery were modelled using a decision tree. Longer-term events were modelled via a Markov model with a cycle length of 1 year. The time horizon was expected remaining lifetime (up to 60 years). Costs and outcomes were discounted at 3.5% per annum (varied from 0% to 6% in sensitivity analyses).

Efficacy and Safety Data

- Data were taken from sub-group analyses[18] of the two phase 3 trials that compared DBG with the UK-licensed enoxaparin dose for patients older than 75 years[17] (RE-MODEL[10] and RE-NOVATE[11]). The trials' primary end-point (total VTE and all-cause mortality) was used to estimate the probability of VTE. In order to reflect differential underlying risks of events in TKA and THA patients, probabilities of VTE, major bleeding, and minor bleeding for enoxaparin were estimated separately for TKA and THA patients based on the incidences in the individual trials. Probabilities for DBG were estimated by applying the relative risk (RR) for DBG versus enoxaparin to the risk in the enoxaparin arm (Table 2). In order to maximise the statistical power of the analysis, RRs were estimated by meta-analysis of data for patients older than 75 years from both trials.

Table 2. Efficacy and Safety Data for Patients Older Than 75 Years

End-point	Probability for Enoxaparin 40 mg bid		RR of DBG 150 mg od vs. Enoxaparin 40 mg bid (95% CI)[a]
	TKA	THA	
Total VTE and all-cause mortality	0.404	0.158	0.81 (0.60, 1.11)
Major bleeding	0.020	0.038	0.48 (0.15, 1.54)
Minor bleeding[b]	0.192	0.146	0.86 (0.59, 1.26)

bid = twice a day; CI = confidence interval.

[a] Estimated by meta-analysis of data from RE-MODEL and RE-NOVATE for patients aged > 75 years.

[b] Clinically relevant or minor non-major bleeding.

Model Probabilities

- The conditional probability of each type of VTE event within the primary end-point (proximal DVT, distal DVT, PE, asymptomatic, symptomatic, or fatal) were taken from the published literature and assumed to be the same for both interventions.[8] Time-dependent probabilities for recurrent VTE and post-thrombotic syndrome (PTS) were estimated from Weibull functions fitted to longitudinal follow-up data from 16 published studies.[8]

Costs

- Drug acquisition costs assumed the mean administration duration observed in the trials (Table 1). Administration costs for enoxaparin assumed that 13% of THA patients would be unable or unwilling to self-administer and therefore would require home nursing visits after hospital discharge, based on estimates for fondaparinux, another parenteral anticoagulant.[13] (The use of these estimates for fondaparinux may have resulted in an underestimate of the cost of nurse visits for LMWH administration, as fondaparinux is easier to administer than LMWH. In addition, the fondaparinux estimates were for a younger population on average, and older patients are less likely to be able and willing to self-administer.) Cost estimates for DVT, PE, and bleeding events were derived from UK Hospital Episode Statistics, National Reference Costs, and estimates prepared for the National Institute for Health and Clinical Excellence (NICE).[8] Costs for heparin-induced thrombocytopenia (HIT) and PTS were from the published literature.[8] The cost year of the analysis was 2008.

Utilities

- For VTE events, a utility decrement equal to the duration of hospitalisation for the event was assumed,[19] plus a decrement of 0.08 for the duration of post-discharge warfarin treatment.[20] For major bleeding events, a utility decrement of 0.10 for the duration of hospital stay was assumed.[21] Estimates for PTS[22] and long-term disability from intracranial haemorrhage[8] were from the published literature.

Sensitivity Analysis

- Probabilistic sensitivity analysis was performed. The mean treatment duration was sampled from a normal distribution, incidence estimates for enoxaparin from a beta distribution, and RRs from a normal distribution on the log scale.
- Further (univariate) sensitivity analyses were performed using alternative estimates for the risk of VTE and bleeding (based on the full evaluable population of each trial rather than the subgroup aged > 75 years); alternative RRs (from each individual trial rather than from the meta-analysis), varying the drug price (to reflect other LMWHs used in the UK), varying the proportion of patients unable to self-administer LMWH, and varying the time horizon of the analysis and discount rates.
- Subgroup analyses were performed for males, females and patients with an additional risk factor for VTE (previous history of VTE, general anaesthesia, body mass index ≥ 30, cancer, use of oral contraceptives, use of hormone replacement therapy, and varicose veins).

RESULTS

- DBG was less costly than enoxaparin in TKA and significantly less so in THA (Table 3).
- Symptomatic VTE and bleeding rates were lower for DBG than for enoxaparin, and mean total expected quality-adjusted life-years (QALYs) were higher (differences not significant).
- The probability of cost-effectiveness was 91% in TKA and 99% in THA at a willingness-to-pay threshold of £20,000 per QALY (Figure 1).
- DBG was dominant, or cost-saving with equivalent outcomes (incremental QALYs < 0.001), in all univariate sensitivity analyses and subgroup analyses.

Figure 1a. Probabilistic Results: Patients Older Than 75 Years Undergoing TKA

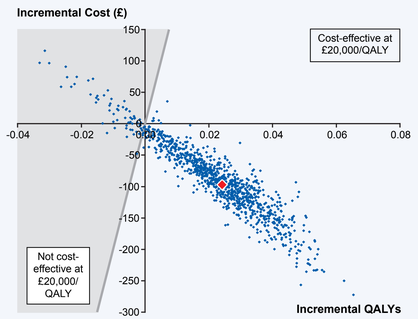

Figure 1b. Probabilistic Results: Patients Older Than 75 Years Undergoing Total Hip Arthroplasty

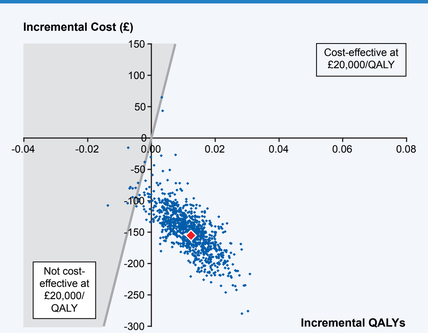

Table 3. Base-Case Results for Patients Older Than 75 Years Undergoing TKA or THA

	TKA			THA		
	DBG	Enoxaparin	Incremental	DBG	Enoxaparin	Incremental
Estimated outcomes						
Symptomatic VTE	13.2%	15.7%	–2.5%	6.8%	7.7%	–1.0%
PTS	7.3%	8.2%	–0.9%	4.9%	5.3%	–0.4%
Major bleed	1.0%	2.0%	–1.0%	1.8%	3.8%	–2.0%
Minor bleed	16.5%	19.2%	–2.7%	12.5%	14.6%	–2.0%
HIT	0.0%	0.2%	–0.2%	0.0%	0.2%	–0.2%
Mean life-years per patient (95% CI)	8.256 (8.206, 8.292)	8.225 (8.195, 8.257)	0.031 (–0.009, 0.060)	8.388 (8.360, 8.406)	8.372 (8.347, 8.393)	0.016 (0.000, 0.030)
Mean QALYs (per patient) (95% CI)	6.016 (5.976, 6.046)	5.992 (5.964, 6.019)	0.024 (–0.007, 0.048)	6.088 (6.065, 6.103)	6.076 (6.055, 6.092)	0.012 (0.000, 0.024)
Estimated costs per patient (£)[a]						
Prophylaxis (drug and administration)	31	38	–7	137	230	–93
VTE events	426	497	–71	238	265	–27
Adverse events	17	35	–19	31	66	–35
Management of other acute events	1	1	0	1	1	0
Total cost (95% CIs)	475 (327, 661)	572 (398, 753)	–97 (–195, 19)	410 (340, 538)	565 (478, 671)	–155 (–216, –78)
Cost-effectiveness estimates						
Incremental cost per QALY	DBG is dominant			DBG is dominant		
Probability of cost-effectiveness at £20,000 per QALY	91%			99%		

[a] 2008 values.

Numbers in the table may not sum precisely due to rounding.

DISCUSSION

- The validity of the model adapted for this analysis has been discussed in detail previously.[8]
- The limitations in available efficacy and safety data for patients older than 75 years must be recognised. Data were from post-hoc subgroup analyses for which sample sizes were small. An imbalance of confounding factors between treatment groups cannot be ruled out. However, uncertainty resulting from the small sample sizes was fully reflected in the probabilistic analysis.
- Utility benefits from the avoidance of daily sc injections were not included in this analysis, which may have resulted in underestimation of the benefits of DBG.[23]
- Costs associated with platelet monitoring, needle stick injuries, and sharps disposal were not included, which may have resulted in underestimation of the total cost of enoxaparin prophylaxis.
- The oral route of administration for DBG is likely to be preferred by patients and may overcome the barriers that may have limited the implementation of extended prophylaxis.

CONCLUSIONS

- Thromboprophylaxis with DBG 150 mg od in patients older than 75 years is cost-saving compared with enoxaparin 40 mg od, with comparable efficacy and safety.
- The probability of cost-effectiveness at a threshold of £20,000 per QALY was very high. Therefore, despite the small sample sizes, it is reasonable to conclude that DBG is cost-effective at the threshold applied by NICE.
- Findings were consistent across different gender groups, as well as in higher-risk patients.

ABBREVIATIONS BOX

bid	twice a day
CI	confidence interval
DBG	dabigatran etexilate (Pradaxa®)
DVT	deep vein thrombosis
HIT	heparin-induced thrombocytopenia
LMWH	low-molecular-weight heparin
NICE	National Institute for Health and Clinical Excellence
od	once daily
PE	pulmonary embolism
PTS	post-thrombotic syndrome
QALY	quality-adjusted life-year
RR	relative risk
sc	subcutaneous
SD	standard deviation
THA	total hip arthroplasty
TKA	total knee arthroplasty
UK	United Kingdom
VTE	venous thromboembolism

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