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REVIEW ARTICLE

Thromboprophylaxis with dabigatran etexilate in patients over seventy-five years of age with moderate renal impairment undergoing or knee replacement

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Abstract
Purpose Prospective, double-blind studies in orthopaedic patients have been conducted using the direct thrombin inhibitor dabigatran etexilate (hereafter referred to as dabigatran), with two doses investigated and approved for adults (220 mg and 150 mg once daily) to prevent venous thromboembolism (VTE). The European Medicines Agency decided that in major joint orthopaedic surgery, the lower dose should be used in elderly patients (aged over 75 years) and those with reduced renal function (creatinine clearance between 30 and 50 ml/min). Our objective was to understand the efficacy and bleeding data for the lower dose in this subpopulation.

Methods We extracted and analysed data from the elderly or from moderately renally impaired patients (*n* 632 of = 5,539) from the orthopaedic clinical development programme of dabigatran.

Results Dabigatran 150 mg once daily was as effective as the standard European enoxaparin regimen, with numerically fewer major bleeding events. Rates of major VTE were 4.3% vs 6.4% of patients, respectively. Major bleeding events occurred in four (1.3%) vs 11 (3.3%), which shows a trend towards lower bleeding with dabigatran 150 mg [odds ratio (OR) 0.40; 95% confidence interval (CI) 0.13–1.25; p=0.110]. Mean volume of blood loss was 395 vs 417 ml, and transfused units were 2.4 vs 2.5,

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respectively. Other safety parameters, including the incidence of wound infections and complications, were similar for 150 mg once daily dabigatran and enoxaparin.
Conclusion For patients at higher risk of bleeding, dabigatran 150 mg once daily is as effective as enoxaparin following major orthopaedic surgery and is associated with a favourable bleeding rate.

Introduction

Major joint replacement is a suitable model for the development of antithrombotic drugs due to the high frequency of silent deep vein thrombosis (DVT). In addition, it is easy to observe and quantify any effects on bleeding rate [1]. As a result, trials in orthopaedic surgery are frequently used to assess the efficacy and safety of new anticoagulant compounds before other indications are explored [2, 3]. As the main route of elimination for many anticoagulants is via the kidney, patients with impaired renal function receiving thromboprophylaxis may experience increased surgical bleeding [4, 5], which may have a detrimental effect on clinical and functional outcome. Age also influences bleeding risk. Older patients have more comorbidities and an increased risk of venous and arterial thromboembolic complications and death compared with younger patients [6–8]. At the same time, there is an inverse relationship between renal function and age [9]. A lower antihaemostatic dosing regimen than that used in younger healthy adults appears to be particularly pertinent for these patients.

Several prospective, double-blind studies in orthopaedic surgery patients have been conducted with the oral direct thrombin inhibitor dabigatran etexilate (hereafter referred to as dabigatran), with two dosage regimens investigated [10–13]. These two dosages [220 mg and 150 mg once daily (qd)] have been approved for preventing venous thrombosis in major joint replacement in adult patients. European approval was based on the first two studies comparing postoperatively initiated dabigatran with preoperatively initiated enoxaparin 40 mg qd [10, 11]. The European Medicines Agency (EMA) recommends dabigatran 150 mg qd as the appropriate dose for certain subsets of patients undergoing total hip or knee replacement. For those over 75 years or with moderately reduced renal function [creatinine clearance (CrCl) between 30 and 50 ml/min], the recommended dose is 150 mg qd. For patients concomitantly taking dabigatran with strong P-glycoprotein inhibitors (i.e., amiodarone, quinidine or verapamil), dosing should also be reduced to 150 mg qd and the medicines should be taken at the same time. In patients with moderate renal impairment and concomitantly treated with dabigatran and verapamil, further dose reduction to 75 mg qd should be considered. Finally, dabigatran is contraindicated in patients with severe renal impairment (CrCl <30 ml/min) [14]. To further support the scientific rationale behind the dosing decision in elderly patients and patients with moderately impaired renal function, we extracted and pooled data from the large database for the prospective, double-blind trial programme conducted in joint replacement patients [10, 11].

Patients and methods

The data source comprised information on 5,539 joint replacement patients [10, 11]. All studies were conducted in a prospective, double-blind, randomised, multicentre fashion, mainly in Europe. Two dosing regimens of dabigatran were studied in the trial programme: 150 mg qd and 220 mg qd, starting with a half dose one to four hours after surgery. Enoxaparin 40 mg qd commencing 12 hours before surgery was the comparator. Treatment duration ranged from six to ten up to 28–35 days. Aspirin up to 160 mg, selective cyclo-oxygenase-2 inhibitors and elastic compression stockings were permitted concomitantly. Efficacy and safety outcome data from patients who received 150 mg qd dabigatran orally were compared with data from patients who received injections of enoxaparin 40 mg qd. Information was extracted from the database for all patients over 75 years and/or with moderately reduced renal function (CrCl ≥30 and <50 ml/min). Secondly, analyses were conducted on the separate subpopulations who were over 75 years of age and those who had moderate renal impairment.

Radiological DVT detection

The trials used mandatory bilateral venography to quantify the prevalence of DVT within 24 hours of the last oral dose. Venograms were judged to be evaluable for major venous thromboembolism (VTE) if they permitted complete visualisation of all proximal deep veins in both legs. DVT was diagnosed when a constant intraluminal filling defect was seen on at least two images. In addition, all patients with a confirmed symptomatic proximal DVT, pulmonary embolism (PE) or VTE-related death were included in the analysis population for major VTE (*vide infra*). All patients were followed up for three months after study end to detect late side effects [10, 11].

Outcome measures

The efficacy endpoint used in this analysis was major VTE during the treatment period (from first administration of study drug until three days after final administration) defined as the composite of proximal DVT detected on

bilateral venography, any symptomatic DVT or PE, and deaths in which VTE could not be excluded as the cause (assessed by an independent adjudication committee) [15]. The principal safety outcomes were major bleeding events (MBE), which included surgical-site bleeds, and clinically relevant nonmajor bleeding events (CRBE) from presurgery randomisation onwards, i.e. for the complete treatment period, including bleeds during and after surgery. Since there is no standardisation of bleeding outcomes used in orthopaedic clinical trials, it is necessary to describe the criteria used in our trial programme [16, 17]. MBE were defined as fatal bleeds; clinically overt bleeds associated with a greater than 20 g/l fall in haemoglobin or leading to transfusion of more than two units of packed cells or whole blood; bleeding into a critical organ (retroperitoneal, intracranial, intraocular or central nervous system); bleeding requiring treatment cessation; bleeding leading to reoperation. CRBE comprised the following: spontaneous skin haematoma greater than 25 cm^2, wound haematomas greater than 100 cm^2, spontaneous nose bleed lasting for over five minutes, macroscopic haematuria (spontaneous or lasting for more than 24 hours if associated with an intervention), spontaneous rectal bleeding, gingival bleeding for more than five minutes and any other bleeding event considered as clinically relevant by the investigator. All bleeding events were adjudicated by an independent expert committee blinded to treatment allocations and were categorised as a MBE, CRBE, minor bleeding event or no bleeding event [10, 11, 15, 18]. In this study, we also present the composite of MBE and CRBE, as this was seen as the most informative and relevant bleeding definition for understanding the bleeding profile of drugs used in this investigational setting. In addition, blood loss during surgery, drainage volume postsurgery and sites of MBE and CRBE events, as reported by the investigators, were determined. Other reported parameters are overall systemic infection rates, wound infection rates, rates of other wound complications (including impaired healing), number of patients who withdrew prematurely and associated reasons for premature discontinuation.

Statistics

Event rates are expressed as numbers and percentages. Odds ratios (OR), with 95% confidence intervals (CI) and p values (two-sided), were generated for comparisons between dabigatran and enoxaparin. An OR over one indicates a lower risk with dabigatran compared with enoxaparin. In addition, the χ^2- and Fisher's exact tests were used to compare treatment groups. A p value <0.05 was considered to be significant on a descriptive level. All statistical calculations were performed using SAS (Statistical Analysis Software 8.2, SAS Institute Inc., Cary, NC, USA).

Results

We identified 632 out of 5,539 patients (11.4%) older than 75 years or who had moderate renal impairment (CrCl between 30 and 50 ml/min) and were treated with either 150 mg qd dabigatran or 40 mg enoxaparin (Fig. 1). No differences were found in baseline characteristics between these two treatment arms (Table 1). Within this main group, there were 563 patients who were over75 years, and of those, 155 (27.5%) also had moderate renal impairment; there were 224 patients who had moderate renal impairment, and of those, 155 (69.2%) were also over 75 years.

Patient discontinuations

A total of 93/632 patients (14.7%) prematurely discontinued treatment, and proportions were similar between 150 mg qd dabigatran (14.3%) and 40 mg enoxaparin (15.1%) arms (Fig. 1). Wound infection or discharge was not given as a reason for discontinuation. The rates of discontinuation due to drug noncompliance were low in both arms.

Efficacy outcomes

A total of 465/632 patients (73.6%) were available for efficacy outcome (evaluable venograms, *vide supra*; 167 had incomplete data). Compared with enoxaparin, the rate of major VTE was similar with 150 mg qd dabigatran (Fig. 2).

When patients over 75 years (n=421 available for efficacy) and patients with moderate renal impairment (CrCl between 30 and 50 ml/min; n=159 evaluable for efficacy) were analysed separately, in both cases the rates of major VTE or VTE-related death were again similar (though numerically lower) in the 150 mg qd dabigatran group compared with the 40 mg qd enoxaparin group (Table 2).

Bleeding events

Data on blood loss, drainage volume and bleeding site (as reported by the investigator) are presented in Table 3. No significant differences were seen between the two treatment arms in blood loss or drainage volume, and there were numerically fewer investigator-reported MBE with 150 mg qd dabigatran than with enoxaparin.

All 632 patients with a higher risk of bleeding and treated with 150 mg qd dabigatran or 40 mg enoxaparin were analysed for MBE and CRBE (safety analyses). MBE rates in the 150-mg qd dabigatran group were numerically lower than in the 40-mg qd enoxaparin group, although the difference was not statistically significant (p=0.11) (Fig. 3). Two of the four MBE in the dabigatran group started before

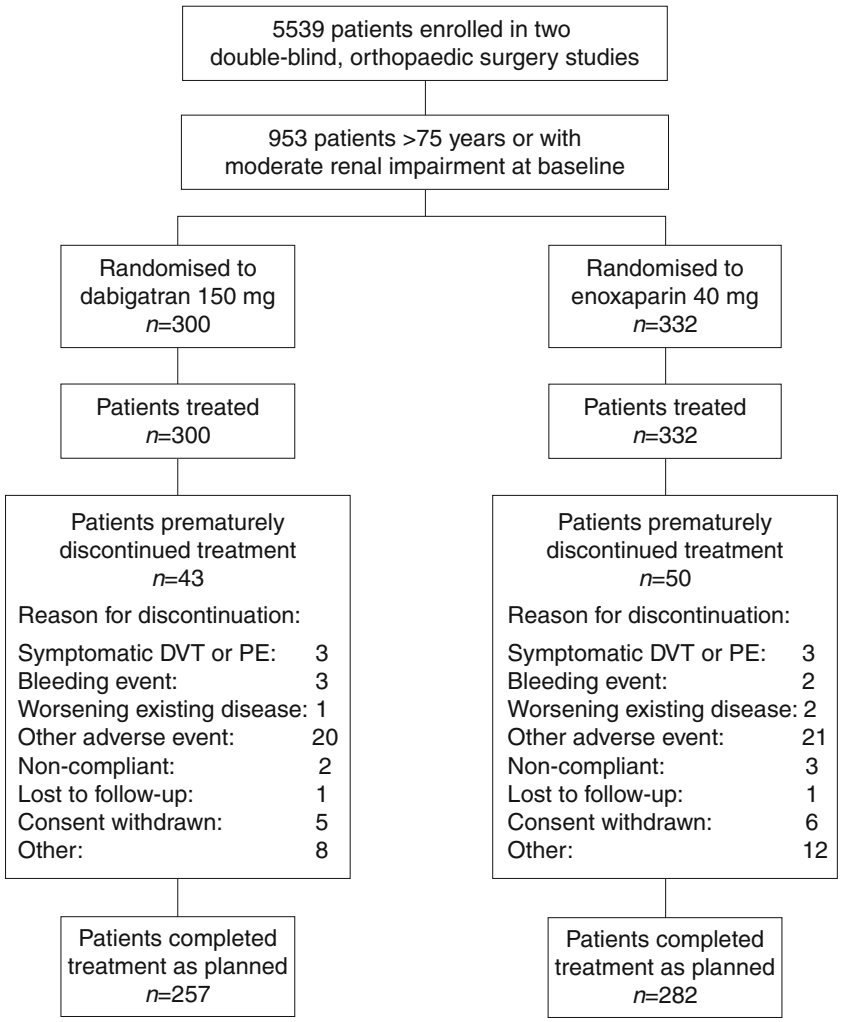

Fig. 1 Randomisation and flow of patients at higher risk of bleeding (aged >75 years or with moderate renal impairment). Patients with a baseline creatinine clearance <30 ml/min were excluded. *Noncompliant* patients who did not comply with protocol

Table 1 Baseline characteristics of patients at higher risk of bleeding (aged >75 years or with moderate renal impairment[a]) by treatment arm

Characteristic	150 mg qd dabigatran	40 mg qd enoxaparin
Number of patients	300	332
Female gender [*n* (%)]	221 (73.7)	242 (72.9)
Mean age (years)[b]	78.4±3.7	78.0±3.9
Age>75 years [*n* (%)]	271 (90.3)	292 (88.0)
Mean body mass index (kg/m^2)[b]	27.3±4.2	26.8±4.2
CrCl ml/min		
Median	57.4	56.4
Min	30.2	30.9
Max	119.1	126.0
<50 ml/min CrCl [*n* (%)]	96 (32.0)	128 (38.6)

CrCl creatinine clearance

[a] Patients with a baseline creatinine clearance <30 ml/min were excluded

[b] Mean±standard deviation

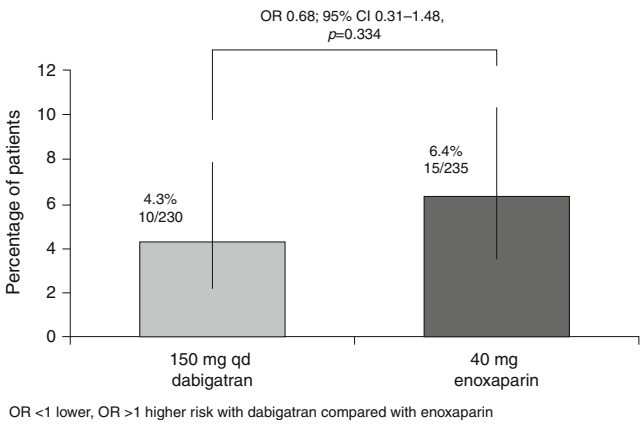

Fig. 2 Comparison between 150 mg qd dabigatran and 40 mg qd enoxaparin for major venous thromboembolism, a prespecified efficacy endpoint for the dabigatran trials, in patients at higher risk of bleeding (aged >75 years, or with moderate renal impairment). Patients with a baseline creatinine clearance <30 ml/min were

Table 2 Comparison of 150 mg qd dabigatran with enoxaparin for major venous thromboembolism (VTE) (efficacy outcome) and rates of major bleeding events (safety outcome) in patients aged >75 years and, separately, for patients with moderate renal impairment

	150 mg qd dabigatran	40 mg qd enoxaparin	Odds ratio (95% confidence interval) *p* value
Aged >75 years			
Major VTE [*n* (%)]	10/213 (4.7)	12/208 (5.8)	0.81 (0.36–1.84) $p=0.613$
Major bleeding [*n* (%)]	4/271 (1.5)	2/292 (2.7)	0.54 (0.16–1.77) $p=0.321$
Moderate renal impairment			
Major VTE [*n* (%)]	3/70 (4.3)	8/89 (9.0)	0.48 (0.13–1.73) $p=0.271$
Major bleeding [*n* (%)]	0/96 (0.0)	6/128 (4.7)	$p=0.039$[a]

Odds ratio <1 lower, odds ratio >1 higher risk with dabigatran etexilate compared with enoxaparin

[a] Odds ratio could not be calculated, as the event ratio is 0; hence, *p* value is given

the first postoperative dose. MBE and CRBE rates were 24/300 (8.0%) with dabigatran and 31/332 (9.3%) with enoxaparin (OR 0.86; 95% CI 0.51–1.43; $p=0.572$).

For patients over 75 years old, MBE rates were similar between treatment groups. For patients with moderate renal impairment, no MBE were reported in the 150 mg qd

Table 3 Data on blood loss, drainage, sites of major bleeding events (*MBE*) and clinically relevant nonmajor bleeding events (*CRBE*) (investigator-reported), and transfusions in patients at higher risk of bleeding (aged >75 years or with moderate renal impairment[a])

	150 mg qd dabigatran	40 mg qd enoxaparin
Number of patients treated and operated upon (%)	299 (100)	326 (100)
Number of patients with blood loss data >0 ml during surgery (%)	248 (82.9)	256 (78.5)
Mean blood loss during surgery (ml)	395	417
95% CI of mean	363–427	379–455
Number of patients with drainage volume >0 ml postoperatively, i.e. before and from first oral dose (%)	237 (79.3)	272 (83.4)
Mean drainage volume postoperatively (ml)	685	717
95% CI of mean	630–739	659–775
Number of patients with drainage volume >0 ml from first oral dose (%)	230 (76.9)	269 (82.5)
Mean drainage volume from first oral dose (ml)	437	443
95% CI of mean	399–476	405–482
No. of patients treated (%)	300 (100)	332 (100)
No. of patients with MBE (%)	4 (1.3)	11 (3.3)
Surgical site	4	11
Intracranial	0	0
Retroperitoneal	0	0
Intraoccular	0	0
Intraspinal	0	0
Other	0	0
No. of patients with CRBE (%)	21 (7.0)	21 (6.3)
No. patients with MBE or CRBE (%)	24 (8.0)	31 (9.3)
Total number of MBE or CRBE events[b]	25	34
Surgical site	19	25
Intracranial	0	0
Retroperitoneal	0	0
Intraoccular	0	0
Intraspinal	0	0
Other	6	9
No. patients with at least one nonautologous transfusion (%)	102 (34.1)	123 (37.7)
Units of nonautologous transfusions per person[c]	2.4±1.1	2.5±1.3

CI confidence interval

[a] Patients with a baseline creatinine clearance <30 ml/min were excluded

[b] Some patients had more than one bleeding event

[c] Mean±standard deviation

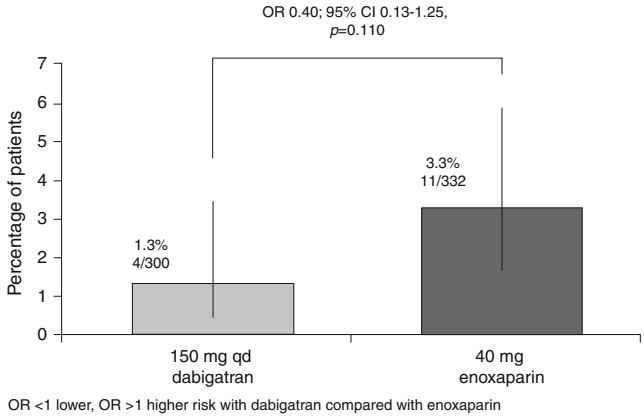

Fig. 3 Comparison between 150 mg qd dabigatran and 40 mg qd enoxaparin for rates of major bleeding events (safety outcome) in patients at higher risk of bleeding (aged >75 years or with moderate renal impairment). Patients with a baseline creatinine clearance <30 ml/min were excluded

dabigatran group (0%) compared with 4.7% in the 40 mg qd enoxaparin group (p=0.04) (Table 2).

Infection rates and wound complications

There were no statistically significant differences in wound complications, including infections, abscesses and delayed healing (Table 4).

Discussion

Surgical bleeding may adversely affect the clinical outcome following major orthopaedic surgery and is a serious concern for orthopaedic surgeons [19, 20]. It is a particular problem in elderly patients with reduced renal function in whom standard doses of antithrombotic drugs can increase bleeding [4, 5]. A recent international survey emphasised physicians' concerns about bleeding risk in patients undergoing orthopaedic surgery, with the majority of respondents favouring the development of new anticoagulants that offered a reduced bleeding risk whilst maintaining similar VTE prevention compared with existing agents [19]. In this study, we found that a lower than standard dose (150 mg qd instead of 220 mg qd) of postoperatively administered dabigatran was as effective as preoperatively injected 40 mg qd enoxaparin for VTE prevention (major VTE or VTE-related death: 4.3% vs 6.4%, respectively) and was associated with numerically lower rates of bleeding (MBE 1.3% vs 3.3%; MBE/CRBE: 8.0% vs 9.3%, respectively). These bleeding rates appear to compare favourably with those observed in placebo-treated patients following hip replacement [21]. However, it is difficult to directly compare bleeding rates between trials because of the different definitions used [16, 17]. The reduction in bleeding found in our study in the elderly and/or moderately renally impaired patients was not statistically significant but showed a trend towards lower bleeding with the lower dose. Given the limited number of patients over 75 years or with moderate renal impairment in the database, we did not have power to show statistically significant differences. However, based on a power of 80%, approximately 2 × 975=1,950 patients would need to have been evaluated to enable conclusions that reached statistical significance based on our MBE findings (Fig. 3).

Although the subgroup of patients with moderate renal impairment was smaller and the statistical significance should be interpreted with caution, there were fewer major bleeding events when these patients were treated with 150 mg qd dabigatran compared with enoxaparin (p=0.04).

Even with the relatively few patients we traced in the database, results of this study support the view of the EMA of using a lower dose of dabigatran for patients at higher risk of bleeding. In the same type of orthopaedic population, reduced plasma clearance, and hence increased risk of bleeding with the standard dose of fondaparinux (2.5 mg) in certain fragile patient groups, resulted in the EMA recommending a lower fondaparinux dose (1.5 mg) in patients with a CrCl 20–50 ml/min [22]. Furthermore, a

Table 4 Infections and wound complications in patients at higher risk of bleeding (aged >75 years or with moderate renal impairment[a])

	150 mg qd dabigatran	40 mg qd enoxaparin
Number of patients (%)	300 (100)	332 (100)
Infections and infestations (%)	21 (7.0)	25 (7.5)
Wound infection (%)	3 (1.0)	4 (1.2)
Postoperative wound infection (%)	1 (0.3)	0
Wound abscess (%)	0	0
Wound complications (%)	5 (1.7)	5 (1.5)
Postoperative wound complications (%)	2 (0.7)	2 (0.6)
Impaired healing (%)	3 (1.0)	0
Wound inflammation (%)	0	0
Postprocedural complication (%)	0	0
Wound decomposition (%)	0	0

Patients with more than one event may be counted in more than one category

[a]Patients with a baseline creatinine clearance<30 ml/min were excluded

recent report suggests that 1.5 mg fondaparinux administered to patients with moderate renal impairment offers a similar predicted exposure as does 2.5 mg in patients with normal renal function [23]. Although the low-molecular-weight heparin dalteparin does not seem to increase bleeding in patients with severe renal impairment [23], the principal impression from available data suggests an increased risk of bleeding even in these patient groups [22, 24–27]. The medicinal authorities have applied a similar approach to dabigatran by approving two doses for VTE prophylaxis in patients undergoing major joint replacement: a higher dose (220 mg qd) for healthy adults and a lower dose (150 mg qd) for elderly patients and those with reduced renal function (CrCl ≥30 to <50 ml/min). This strategy is supported by the findings in this study that daily administration of 150 mg dabigatran is at least as safe as preoperative injections of the standard European dose of enoxaparin these patients. Furthermore, a recent international clinical guideline committee noted that renal function should be considered and that lower than standard doses of anticoagulant therapy should be prescribed [7]. This view is supported by a recent comment by van Thiel et al. that additional studies with lower drug doses be undertaken if there is concern over bleeding with new antithrombotic agents [28].

No difference was seen in surgical-site bleeding during surgery or in drainage volume after surgery. As dabigatran was not administered until one to four hours after surgery and did not trigger any additional perioperative bleeding compared with enoxaparin, this indicates that dabigatran can be administered safely without any increase in the risk of wound bleeding. There was also no difference between treatments in the number of patients receiving transfusions or in units transfused per person, and there were few postoperative clinical bleeding events at the surgical site or elsewhere (Table 3).

The rate of other wound complications, such as infections, abscesses and healing disturbances, were few and equally distributed, indicating that the studied doses of dabigatran and enoxaparin do not interfere with the inflammatory healing process. This is in line with earlier enoxaparin studies in which there were no higher rates of wound complications compared with placebo-treated patients [29, 30]. The low wound infection rate was similar to a study of enoxaparin and fondaparinux (0.7%) [31], and no correlation between wound infection and postoperative anticoagulation therapy following joint replacement was reported in two other studies [32, 33]. Of particular concern to orthopaedic surgeons is the impact of anticoagulant treatment on wound healing. In this study, there was no significant difference in the rate of impaired wound healing. Similar results (no difference) were found in a pilot study of wound healing comparing fondaparinux with enoxaparin in patients undergoing knee replacement surgery [34].

In summary, for patients at higher risk of bleeding (i.e. over 75 years or with moderate renal impairment), 150 mg qd dabigatran is as effective as enoxaparin for preventing VTE following elective total hip or knee replacement surgery. In addition, 150 mg qd dabigatran is associated with numerically less bleeding events (including wound bleeding) and a comparable safety profile to enoxaparin.

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Conflict of interest OED has been a scientific consultant to AstraZeneca, Bayer/Johnson & Johnson, Boehringer Ingelheim, BMS, GSK, Pfizer and sanofi-aventis. AAK has been a scientific consultant to Boehringer Ingelheim and given presentations on behalf of the company. NR has been a scientific consultant to AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, BMS, GSK, Janssen, Pfizer, and sanofi-aventis. BIE has been a scientific consultant to Astellas, Bayer, Boehringer Ingelheim, BMS and Takeda. HN and AC are employees of Boehringer Ingelheim.

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