

ARTICLE

# Direct Oral Anticoagulants Vs. Enoxaparin for Prevention of Venous Thromboembolism Following Orthopedic Surgery: A Dose–Response Meta-analysis

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We carried out a dose–response model-based meta-analysis to assess venous thromboembolism (VTE) and bleeding with factor Xa (FXa) inhibitors (apixaban, edoxaban, rivaroxaban) and a thrombin inhibitor (dabigatran) compared with European (EU) (40 mg q.d.) and North American (NA) (30 mg Q12H) dose regimens of a low molecular weight heparin (enoxaparin) following orthopedic surgery. Statistically significant differences in both VTE and bleeding outcomes were found between the NA and EU doses of enoxaparin, with odds ratios (95% confidence interval) for the NA vs. EU dose of 0.73 (0.71–0.76) and 1.20 (1.14–1.29) for total VTE and major bleeding, respectively. At approved doses, estimated odds ratios vs. both doses of enoxaparin for the three FXa inhibitors (range: 0.35–0.75 for VTE; 0.76–1.09 for bleeding) compared with those for dabigatran (range: 0.66–1.21 for VTE; 1.10–1.38 for bleeding) suggested generally greater efficacy and less bleeding for the FXa inhibitors.

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## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Conventional meta-analyses of the efficacy and safety of direct-acting oral anticoagulants (DOACs) compared to prior standard of care for the prevention of venous thromboembolism following orthopedic surgery have generally failed to consider the dose of the comparator, resulting in potentially biased estimates of comparative efficacy and safety.

### WHAT QUESTION DID THIS STUDY ADDRESS?

✓ We conducted a model-based meta-analysis to estimate efficacy and safety dose–response relationships and therapeutic index of individual DOACs relative to both the European and North American dose regimens of the comparator, enoxaparin.

### WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The results indicate that there is a difference in efficacy and safety between the two regimens of enoxaparin and that estimates of relative effect for the DOACs vs. enoxaparin are dependent on both the DOAC and enoxaparin doses.

### HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

✓ The use of dose–response model-based meta-analyses in clinical pharmacology can better inform dose selection and designs of efficacy and safety studies, resulting in more efficient clinical development.

A number of new anticoagulants have been approved in one or more regions worldwide for the prevention of venous thromboembolism (VTE) following total hip replacement (THR) and total knee replacement (TKR) surgery, including direct factor Xa (FXa) inhibitors and direct thrombin inhibitors. The clinical trials for this indication have generally included a comparison with a low-molecular-weight heparin (LMWH), usually enoxaparin. Because of the regional differences in the approved dosing regimen of enoxaparin (40 mg once daily (q.d.) initiated 9 to 15 h prior to surgery in Europe; 30 mg every 12 h (Q12H) initiated 12 to 24 h following surgery in North America; or 20 mg twice daily (b.i.d.) initiated 24

to 36 h after surgery in Japan), the clinical development programs for new anticoagulants have generally included multiple studies to provide comparisons with different doses of enoxaparin in both THR and TKR surgery patients.

The availability of different regimens of comparators complicates an integrated assessment of the overall efficacy and safety of new agents relative to the current standard of care, as well as indirect comparisons among the new agents, but this factor has not always been considered in published meta-analyses for single<sup>1–7</sup> or multiple<sup>8–18</sup> agents. Dose regimen of the comparator has been acknowledged as a potential source of heterogeneity for a number of

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previous analyses.<sup>1–3,5,6,10–14,18</sup> These analyses have generally evaluated the dose regimen of the comparator in a sensitivity assessment that did not support separate comparisons by dose regimen. Notable exceptions have included three analyses that evaluated outcomes compared only with the 40 mg q.d. regimen of enoxaparin,<sup>6,10,12</sup> and two recent analyses that included indirect comparisons of the 40 mg q.d. and 30 mg Q12H regimens of enoxaparin and estimates of efficacy and safety of other anticoagulants relative to each regimen.<sup>19,20</sup>

We have taken a different approach to evaluate the comparative efficacy and safety of anticoagulants for the prevention of VTE following THR and TKR surgery, by conducting a dose–response model-based meta-analysis. When compared with traditional meta-analyses of study-level data, the major distinction of this approach is that functional relationships consistent with the underlying pharmacology of these agents are used to account for the impact of dose. This allows more data to be included (e.g., results of all doses in phase II dose-finding studies), and permits comparisons of various doses of drugs. In addition, the impact of explanatory factors on dose–response relationships can be assessed to provide insight on patient, disease, and treatment characteristics that may impact relative effects.

A previous article has described the use of this model-based meta-analysis to explore differences in the therapeutic index between anticoagulant drug classes.<sup>21</sup> The key findings of the previous analysis were: i) for a given end point, the shape of the dose–response relationship was the same for all anticoagulant drugs and drug classes, and ii) the therapeutic index for direct FXa inhibitors relative to enoxaparin was greater than that for other classes of anticoagulants.

This article describes an extension of that analysis to assess the impact of dose on the efficacy and safety of recently approved direct FXa inhibitors (apixaban, edoxaban, and rivaroxaban) and a direct thrombin inhibitor (dabigatran) compared to that of the European and North American marketed regimens of the LMWH, enoxaparin.

## METHODS

### Data set

As described previously,<sup>21</sup> an extensive systematic literature search was conducted in Medline to identify randomized, controlled trials of anticoagulants for the prevention of VTE in THR and TKR surgery. The original search was conducted in 2009 and updated in April 2014. The only changes to the search terms were the addition of TAK442 as a treatment of interest and the inclusion of alternate names for some treatments. The primary literature data sources were supplemented with data from the US Food and Drug Administration and the European Medicines Agency websites, and published abstracts/presentations from scientific meetings. Reference lists of published studies and meta-analyses were reviewed to identify any additional sources. Briefly, randomized, placebo- and active-controlled trials in which at least 75% of the patients underwent THR or TKR surgery and reported on one of the anticoagulants of interest were included. Major VTE (composite of proximal deep vein thrombosis (DVT), clinical pulmonary embolism (PE) ± all-cause or VTE-related death), total VTE (composite of distal DVT

and major VTE), and clinical PE were the efficacy end points of interest. Only trials that used mandatory venography for VTE assessment and confirmed clinical PE by an objective methodology were included. Major bleeding, major bleeding plus clinically relevant nonmajor bleeding (hereafter referred to as clinically relevant bleeding), and total bleeding were the safety end points of interest. Criteria for major bleeding were generally consistent with the definition of major bleeding used by the International Society on Thrombosis and Haemostasis<sup>22</sup> adapted for the surgical population. Acute, clinically overt bleeding that did not meet the criteria for major bleeding was classified as clinically relevant nonmajor bleeding.

From the 476 sources identified in the literature search, 98 trials met the criteria for inclusion in the analysis, of which 89 were included in the original analysis and are listed in the online Supplementary Information for the previous paper.<sup>21</sup> **Table S1** provides a summary of included and excluded sources. The new data sources identified since our prior analysis are provided in **Table S2** in the online **Supplementary Material**. When only abstracts were available for the analysis, and full articles later became available, those articles are referenced in the **Supplementary Material**. Apart from detailed information on end points, drug, and dose, information on covariates related to treatment (regimen, time of treatment start relative to surgery, treatment duration), patient population characteristics (age, weight, sex, type of anesthesia, type of surgery (hip vs. knee)), trial characteristics (year of trial start, method of venography (unilateral vs. bilateral), and primary geographic location (Asia, Australia, Europe, or North America)) were extracted. A summary of the information available for each drug included in the analysis has either been published previously<sup>21</sup> or is included in **Table S2** in the online **Supplementary Material** for the newly included trials.

### Analysis methodology

A detailed description of the analysis methodology was presented previously.<sup>21</sup> Briefly, the probability of a patient having an event for end point (k) in a treatment arm (j) of a trial (i) ( $P(event)_{kij}$ ) was modeled as a function of a placebo response for that end point in that trial ( $E_{0,ki}$ ) and a dose–response relationship for the treatment effect for that end point ( $g(x)_k$ ) that includes covariates ( $X_{ij}$ ) and trial-specific model parameters ( $\theta_i$ ), according to the following general structure:

$$P(event)_{kij} = f\{E_{0,ki} - g(Drug_{ij}, Dose_{ij}, X_{ij}, \theta_i)_k\}$$

The function  $f\{x\}$  is the inverse logit transformation to constrain probabilities between 0 and 1. The trial-specific placebo response (i.e., mean event rate in each trial) accounted for the trial-to-trial variability in overall event incidence. Additional random between-trial heterogeneity in the relative effect between arms was accounted for by the trial-specific model parameters, which were assumed to be normally or log-normally distributed. The correlation between multiple observations within one arm was accounted for by assuming a compound symmetry structure for all observations within one arm within a trial.

The dose–response relationship for the efficacy end points was best described by a sigmoid  $E_{\max}$  model:

$$g(x) = \frac{E_{\max} \cdot Dose^n}{Dose^n + ED_{50}^n},$$

where  $E_{\max}$ ,  $ED_{50}$ , and  $n$  are the maximal effect, the dose to achieve 50% of maximal effect (potency), and the steepness of the dose–response relationship, respectively. The dose–response relationship for the three bleeding end points was best described by a linear model:

$$g(x) = \frac{Dose}{ED_{\text{bid}}},$$

where  $ED_{\text{bid}}$  represents the dose that yields a change in the log of the odds ratio of 1. Different  $ED_{50}$  and  $ED_{\text{bid}}$  values were estimated for each drug.

For analysis purposes, a “trial” was defined as every unique trial or every unique stratum (THR or TKR surgery) within a trial. The three efficacy end points (total VTE, major VTE, and PE) were analyzed jointly in the model for efficacy, and the three bleeding end points (major, clinically relevant, and total bleeding) were analyzed jointly in the model for safety. Only results for total VTE, major VTE, major bleeding, and clinically relevant bleeding are reported here. The models allowed for differences in dose–response relationships between end points for drugs and drug classes. Enoxaparin was treated as a separate class from the other LMWHs because it was the reference treatment against which other treatments were compared.

After accounting for drug and dose, no additional random heterogeneity in the treatment response (i.e., the difference between control and active treatment) could be discerned, based on a log-likelihood ratio test at an acceptance  $P$ -value of 0.01. However, estimates of the trial-specific placebo response for total VTE, but not major VTE, were found to be dependent on type of surgery (higher for TKR than for THR) and primary geographic location (possibly due to differences in adjudication). No impact of covariates on the parameters of the dose–response relationship was detected; in particular, no impact of dose regimen was found, and the dose–response relationship was therefore expressed in terms of total daily dose.

Estimates of odds ratios for efficacy and bleeding of approved doses of the oral anticoagulants (apixaban 2.5 mg b.i.d., edoxaban 30 mg q.d., rivaroxaban 10 mg q.d., and dabigatran 220 mg q.d.) vs. 40 mg q.d. and 30 mg Q12H regimens of enoxaparin were obtained, and 95% confidence intervals (CIs) were approximated using the variance matrix of the parameter estimates. The results of the efficacy and bleeding analyses were also used to estimate the therapeutic index for each oral anticoagulant compared with that for enoxaparin.

The therapeutic index was defined as the ratio of the model estimates of potency (bleeding ( $ED_{\text{bid}}$ )/efficacy ( $ED_{50,\text{vte}}$ )) for a particular drug,<sup>21</sup> as an indication of the separation of doses resulting in specific measures of efficacy and bleeding. In the calculation of the therapeutic index, major bleeding was used as the reference point for bleeding and major VTE was

used as the reference point for efficacy. The relative therapeutic index was defined as the therapeutic index relative to that of enoxaparin. If a drug had a relative therapeutic index greater than 1.0, this represented the potential to choose a dose resulting in better efficacy without increased bleeding or in similar efficacy with lower bleeding relative to the comparator. If a drug had a relative therapeutic index less than 1.0, this indicated that there was no dose that would have an advantage over the comparator agent for efficacy without more bleeding or for bleeding without lower efficacy.

## RESULTS

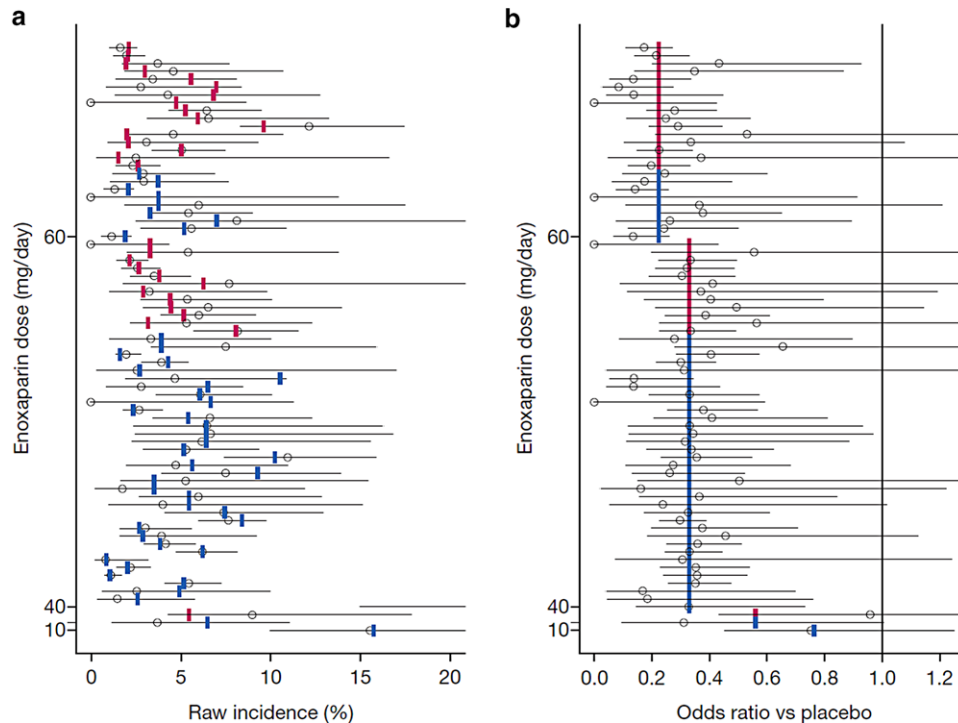
### Estimated efficacy and bleeding dose–response relationships for enoxaparin

**Figure 1** shows the observed and predicted major VTE results for enoxaparin in all active- and placebo-controlled trials of this drug included in the analysis. Panel a shows the observed raw incidence (95% CI) sorted by enoxaparin daily dose on the y-axis and type of surgery within dose (the blue and red lines indicate the model predictions for THR and TKR surgery, respectively), illustrating the considerable trial-to-trial variability in absolute incidence of total VTE and the ability of the dose–response model to predict the outcomes across all trials. Panel b shows the results expressed as odds ratio vs. the estimated placebo response for each trial, illustrating that the odds ratio is not subject to the same variability as raw incidence, and clearly showing the efficacy of enoxaparin 40 mg q.d. when compared with placebo and the additional efficacy with enoxaparin 30 mg Q12H. **Figure 2** shows similar plots for major bleeding. These plots demonstrate that the model provides a good description of the observed data for enoxaparin, and that the incidence of bleeding increases with increasing enoxaparin dose. For both the major VTE and major bleeding end points, there was no significant difference in the estimates of odds ratios of enoxaparin vs. control between THR and TKR surgery. This suggests that the type of surgery does not impact the relative effectiveness of treatments.

Model-based estimates of odds ratios for total VTE, major VTE, and all bleeding end points for each dose of enoxaparin vs. placebo and for a comparison of the two doses of enoxaparin, are presented in **Table 1**. Both enoxaparin 40 mg q.d. and 30 mg Q12H regimens are predicted to provide a substantial, statistically significant (upper bound of the 95% CI <1.0) risk reduction for total and major VTE compared with placebo, and enoxaparin 30 mg Q12H is predicted to provide a statistically significantly greater reduction compared with enoxaparin 40 mg q.d. Both enoxaparin 40 mg q.d. and 30 mg Q12H regimens are predicted to result in a statistically significant (lower bound of 95% CI >1.0) increased incidence of total and major bleeding (point estimate <twofold) compared with placebo, and enoxaparin 30 mg Q12H is predicted to result in a statistically significant increased incidence of bleeding compared with enoxaparin 40 mg q.d.

### Predicted and observed efficacy and bleeding dose–response relationships for apixaban, edoxaban, rivaroxaban, and dabigatran

**Figure 3** shows the observed odds ratios for the approved doses of apixaban, rivaroxaban, edoxaban, and dabigatran



**Figure 1** Observed and estimated incidence (%) of major VTE for enoxaparin in all active- and placebo-controlled trials included in the analysis. Symbols and horizontal lines represent observed incidence and 95% CI for each unique treatment group, and vertical lines represent model-based estimates for THR (blue) and TKR (red). Note that the dose (y) axis is not linear and the axis labels serve to group the studies by dose (10, 20, 40, and 60 mg per day). Panel **a** shows model-based estimates and observations of absolute incidence for each dose in each individual trial. Panel **b** shows the model-estimated and observed odds ratio vs. the predicted placebo response for each trial. CI, confidence interval; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

vs. control for total and major VTE in all trials included in the analysis in which the approved doses were evaluated. Data from other doses of these drugs were included in the analysis but are not shown in this figure. The estimated odds ratios from the efficacy analysis are shown by the vertical lines. The figure shows that there is good agreement between the observed and model-estimated odds ratio vs. control. Similarly, **Figure 4** shows that the bleeding analysis provides estimates of the odds ratios vs. control for major and clinically relevant bleeding that are in good agreement with the observed values. The model-estimated odds ratios for approved doses of apixaban, edoxaban, rivaroxaban, and dabigatran vs. both the 40 mg q.d. and 30 mg Q12H regimens of enoxaparin for efficacy and bleeding end points are shown in **Table 2**. The models predict different responses relative to the two doses of enoxaparin for each drug, with a lower odds ratio for efficacy vs. enoxaparin 40 mg q.d. than vs. enoxaparin 30 mg Q12H, and a higher odds ratio for bleeding vs. enoxaparin 40 mg q.d. than vs. enoxaparin 30 mg Q12H.

### Relative therapeutic index

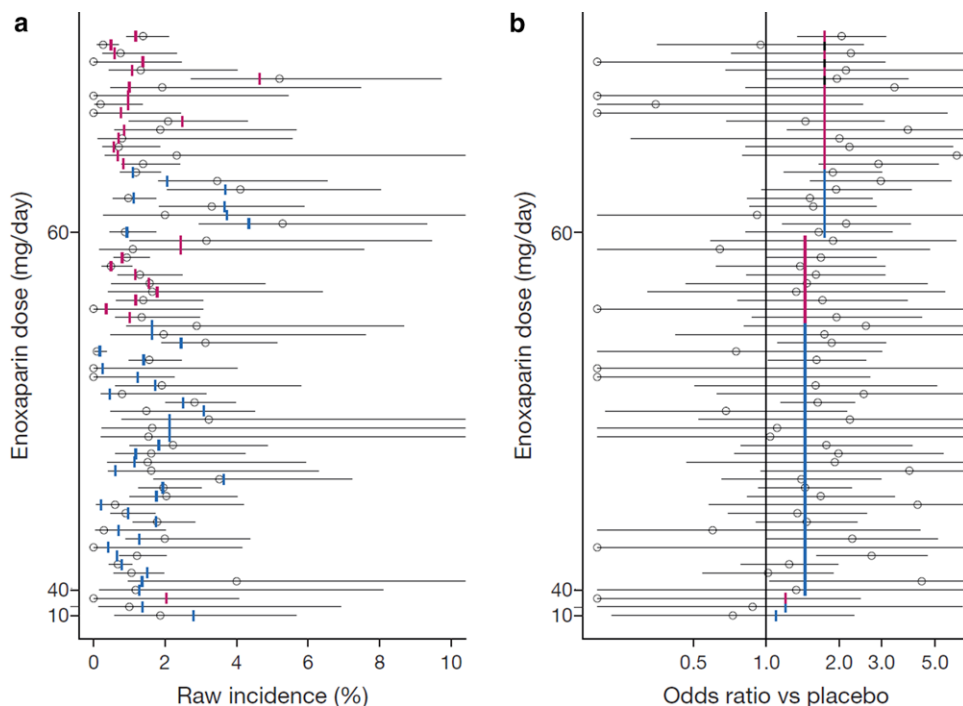
The estimated relative therapeutic index values (95% CI) for apixaban, edoxaban, rivaroxaban, and dabigatran vs. enoxaparin were 2.73 (1.33–5.74), 2.48 (0.86–7.41), 2.46 (1.46–4.13), and 0.83 (0.54–1.26), respectively. The results show that apixaban and rivaroxaban are predicted to have a significantly greater therapeutic index than enoxaparin. The

relative therapeutic index estimate for edoxaban was similar to those for apixaban and rivaroxaban; however, the comparison was not significantly different. The relative therapeutic index estimate for dabigatran was not significantly different from enoxaparin, with a point estimate close to 1.0.

The therapeutic index of the newer anticoagulants vs. enoxaparin was explored further by plotting the predicted dose–response relationship of odds ratio vs. enoxaparin for efficacy and bleeding end points for apixaban, edoxaban, rivaroxaban, and dabigatran (**Figure 5**). The dose range over which both efficacy and bleeding were predicted to be favorable compared with both doses of enoxaparin (odds ratio <1.0) is 3.7 to 6.8 mg/day for apixaban, 15 to 25 mg/day for edoxaban, and 5.0 to 8.2 mg/day for rivaroxaban. Among the FXa inhibitors, apixaban was the only agent that had its approved dose within this dose range. For dabigatran, there was no dose that would be expected to perform better than either dose of enoxaparin with respect to both efficacy and bleeding, as the point where the predicted dose–response relationships for efficacy and bleeding end points cross was not below an odds ratio of 1.0.

### DISCUSSION

As part of a model-informed drug development strategy,<sup>23,24</sup> a model-based meta-analysis was carried out to evaluate the dose–response relationships for efficacy end points (major VTE and total VTE) and safety end points (major, clinically



**Figure 2** Observed and estimated incidence (%) of major bleeding for enoxaparin in all active- and placebo-controlled trials included in the analysis. Symbols and horizontal lines represent observed incidence and 95% CI for each unique treatment group, and vertical lines represent model-based estimates for THR (blue) and TKR (red). Note that the dose (y) axis is not linear and the axis labels serve to group the studies by dose (10, 20, 40, and 60, mg per day). Panel **a** shows model-based estimates and observations of absolute incidence for each dose in each individual trial. Panel **b** shows the model-estimated and observed odds ratio vs. the predicted placebo response for each trial. CI, confidence interval; THR, total hip replacement; TKR, total knee replacement.

relevant, and total bleeding) of anticoagulants used for the prevention of VTE following THR and TKR surgery. A similar analysis was previously used to compare the various classes of anticoagulants and demonstrated that the therapeutic index relative to enoxaparin was greater for direct FXa inhibitors than for other classes of anticoagulants.<sup>21</sup> While those results have contributed to a mechanistic

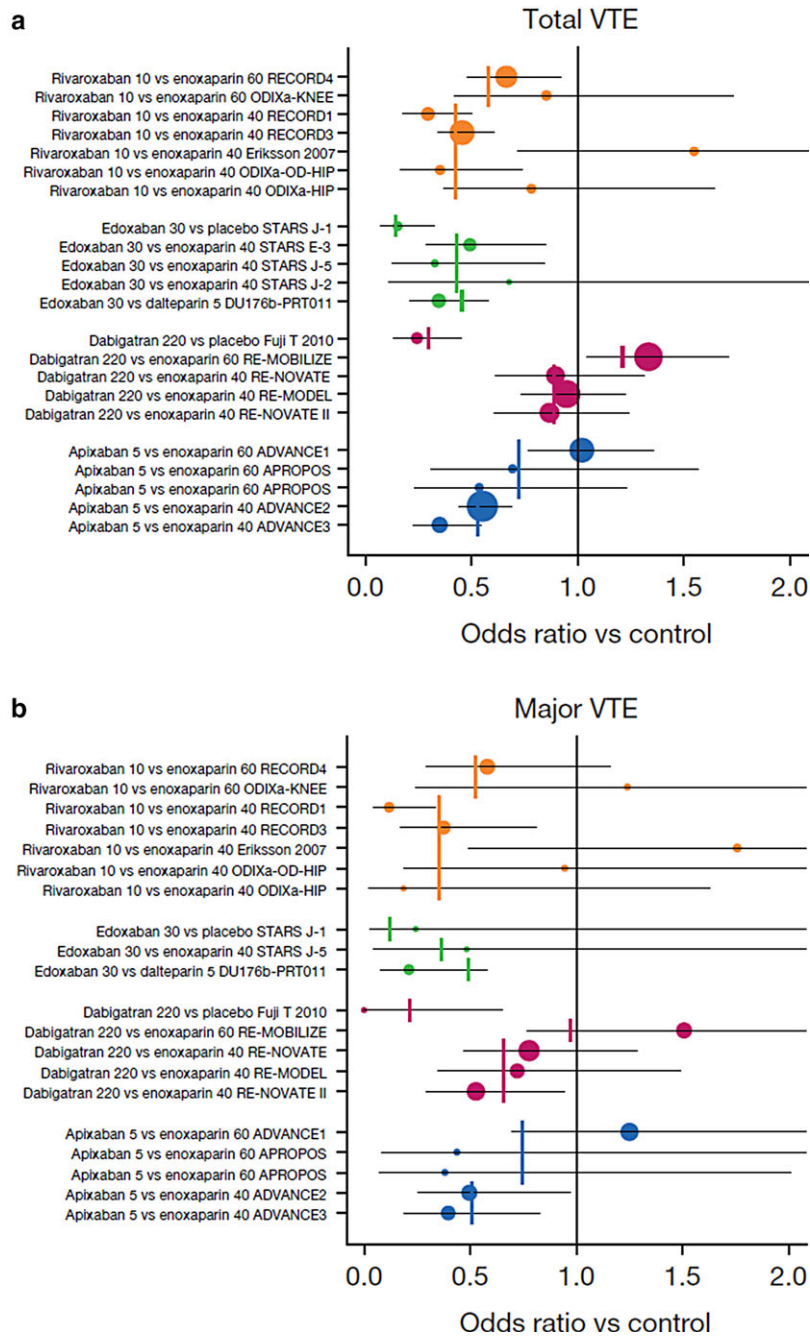
understanding of differences in clinical outcomes, the choice of dose for an individual anticoagulant determines the ultimate clinical benefit/risk profile. With this in mind, the present analysis focused on the dose–response relationships of the direct oral anticoagulants and enoxaparin to provide estimates of relative treatment effects at the approved doses.

**Table 1** Dose–response model-estimated odds ratio (95% CI) of efficacy and bleeding end points for 40 mg q.d. enoxaparin vs. placebo, 30 mg Q12H enoxaparin vs. placebo, and 30 mg Q12H enoxaparin vs. 40 mg q.d. enoxaparin

Comparison	End point	Odds ratio (95% CI)
Enoxaparin 40 mg q.d. vs. placebo	Total VTE	0.33 (0.28–0.39)
	Major VTE	0.33 (0.25–0.42)
	Major bleeding	1.45 (1.31–1.66)
	Clinically relevant bleeding	1.31 (1.21–1.46)
	Total bleeding	1.24 (1.17–1.34)
Enoxaparin 30 mg Q12H vs. placebo	Total VTE	0.24 (0.21–0.29)
	Major VTE	0.22 (0.17–0.30)
	Major bleeding	1.74 (1.49–2.14)
	Clinically relevant bleeding	1.49 (1.33–1.76)
	Total Bleeding	1.38 (1.26–1.54)
Enoxaparin 30 mg Q12H vs. 40 mg q.d.	Total VTE	0.73 (0.71–0.76)
	Major VTE	0.68 (0.64–0.72)
	Major bleeding	1.20 (1.14–1.29)
	Clinically relevant bleeding	1.14 (1.10–1.21)
	Total bleeding	1.11 (1.08–1.16)

CI, confidence interval; Q12H, every 12 h; q.d., once daily; VTE, venous thromboembolism.

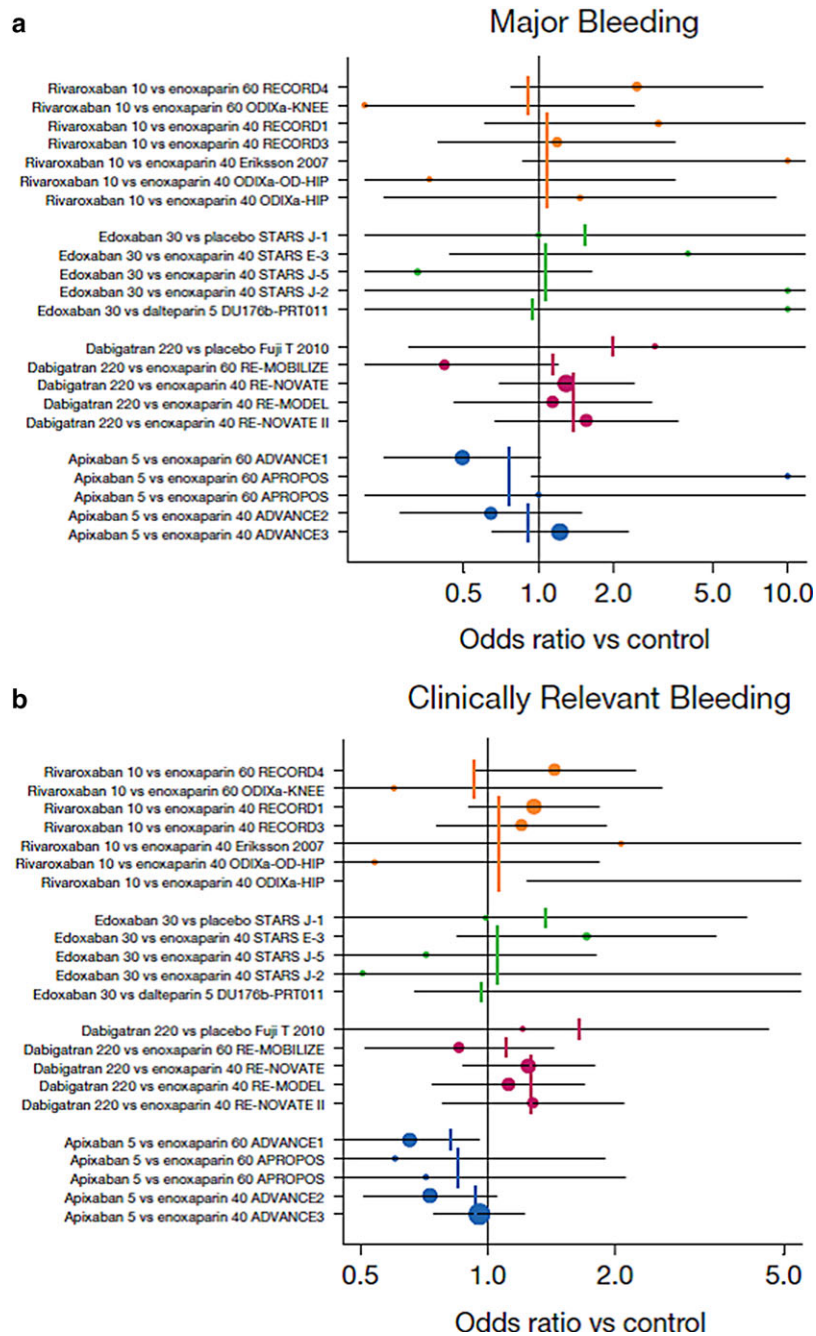




**Figure 3** Observed and estimated odds ratio vs. control for major VTE (panel a) and total VTE (panel b) for all trials that evaluated apixaban, edoxaban, rivaroxaban, and dabigatran at their approved doses. The symbols represent the observed odds ratio, the horizontal lines represent 95% CI on the observed odds ratio, and the vertical lines indicate the model estimates. CI, confidence interval; VTE, venous thromboembolism.

When compared with other meta-analyses of anticoagulants for this indication, data for this analysis were incorporated from many more randomized, controlled trials, and included many more studies with enoxaparin (Figures 1 and 2). Trial-to-trial variability in absolute treatment effect was greater than that for relative treatment effect, and the analysis adequately accounted for this heterogeneity and provided a good description of the observed data (Figures 1 to 4). As

described previously,<sup>17</sup> although the absolute event rate differs between THR and TKR, no statistically significant difference in the relative treatment effects by type of surgery could be discerned. Similarly, no impact of frequency of administration (once or twice daily) or treatment duration (when studies with the same duration of treatment for all arms were included) was found. Because the time of first dose relative to surgery was confounded with dose for many treatments,



**Figure 4** Observed and estimated odds ratio vs. control for major bleeding (panel **a**) and clinically relevant bleeding (panel **b**) for all trials that evaluated apixaban, edoxaban, rivaroxaban, and dabigatran at their approved doses. The symbols represent the observed odds ratio, the horizontal lines represent 95% CI on the observed odds ratio, and the vertical lines indicate the model estimates. CI, confidence interval.

i.e., the same dose was always administered at the same time postsurgery, an assessment of the impact of time of first dose relative to surgery independent of dose was not possible.

The results indicate that there is a difference in efficacy and safety between the European and North American dose regimens of enoxaparin, with the 30 mg Q12H regimen estimated to have an odds ratio of 0.68 for major VTE and an odds ratio of 1.2 for major bleeding relative to the 40 mg q.d. regimen (**Table 1**). Consequently, estimates of the

effect for apixaban, edoxaban, rivaroxaban, and dabigatran vs. enoxaparin are dependent on the enoxaparin dose, with greater efficacy and more bleeding relative to the 40 mg q.d. dose than to the 30 mg Q12H dose (**Table 2, Figures 3 and 4**). The direct thrombin inhibitor, dabigatran, at a dose of 220 mg q.d., appears to offer no clear advantage in efficacy or safety over either dose regimen of enoxaparin in THR or TKR surgery, whereas the direct FXa inhibitors, apixaban (2.5 mg b.i.d.), edoxaban (30 mg q.d.), and rivaroxaban

**Table 2** Dose–response model-estimated odds ratio (95% CI) of efficacy and bleeding end points for apixaban, edoxaban, rivaroxaban, and dabigatran at their approved doses vs. 40 mg q.d. and 30 mg Q12H (60 mg/day) enoxaparin

End point	Enoxaparin dose (mg/day)	Odds ratio (95% CI) vs. enoxaparin			
		Apixaban 5 mg/day	Edoxaban 30 mg/day	Rivaroxaban 10 mg/day	Dabigatran 220 mg/day
Total VTE	40	0.53 (0.46–0.62)	0.43 (0.35–0.56)	0.42 (0.37–0.50)	0.89 (0.79–0.99)
	60	0.72 (0.63–0.85)	0.59 (0.48–0.75)	0.58 (0.51–0.68)	1.21 (1.08–1.35)
Major VTE	40	0.51 (0.39–0.68)	0.36 (0.25–0.55)	0.35 (0.27–0.48)	0.66 (0.55–0.80)
	60	0.75 (0.58–1.00)	0.54 (0.37–0.82)	0.52 (0.41–0.69)	0.97 (0.81–1.18)
Major bleeding	40	0.91 (0.78–1.17)	1.07 (0.80–2.04)	1.09 (0.94–1.24)	1.38 (1.13–1.77)
	60	0.76 (0.62–0.96)	0.89 (0.65–1.70)	0.90 (0.73–1.07)	1.15 (0.91–1.48)
Clinically relevant bleeding	40	0.93 (0.84–1.12)	1.05 (0.85–1.66)	1.06 (0.95–1.17)	1.26 (1.09–1.50)
	60	0.82 (0.71–0.97)	0.92 (0.73–1.45)	0.93 (0.79–1.05)	1.10 (0.94–1.32)

CI, confidence interval; Q12H, every 12 h; q.d., once daily; VTE, venous thromboembolism.

(10 mg q.d.) offer a benefit of better efficacy and/or lower bleeding, depending on the dose regimen of the enoxaparin comparator.

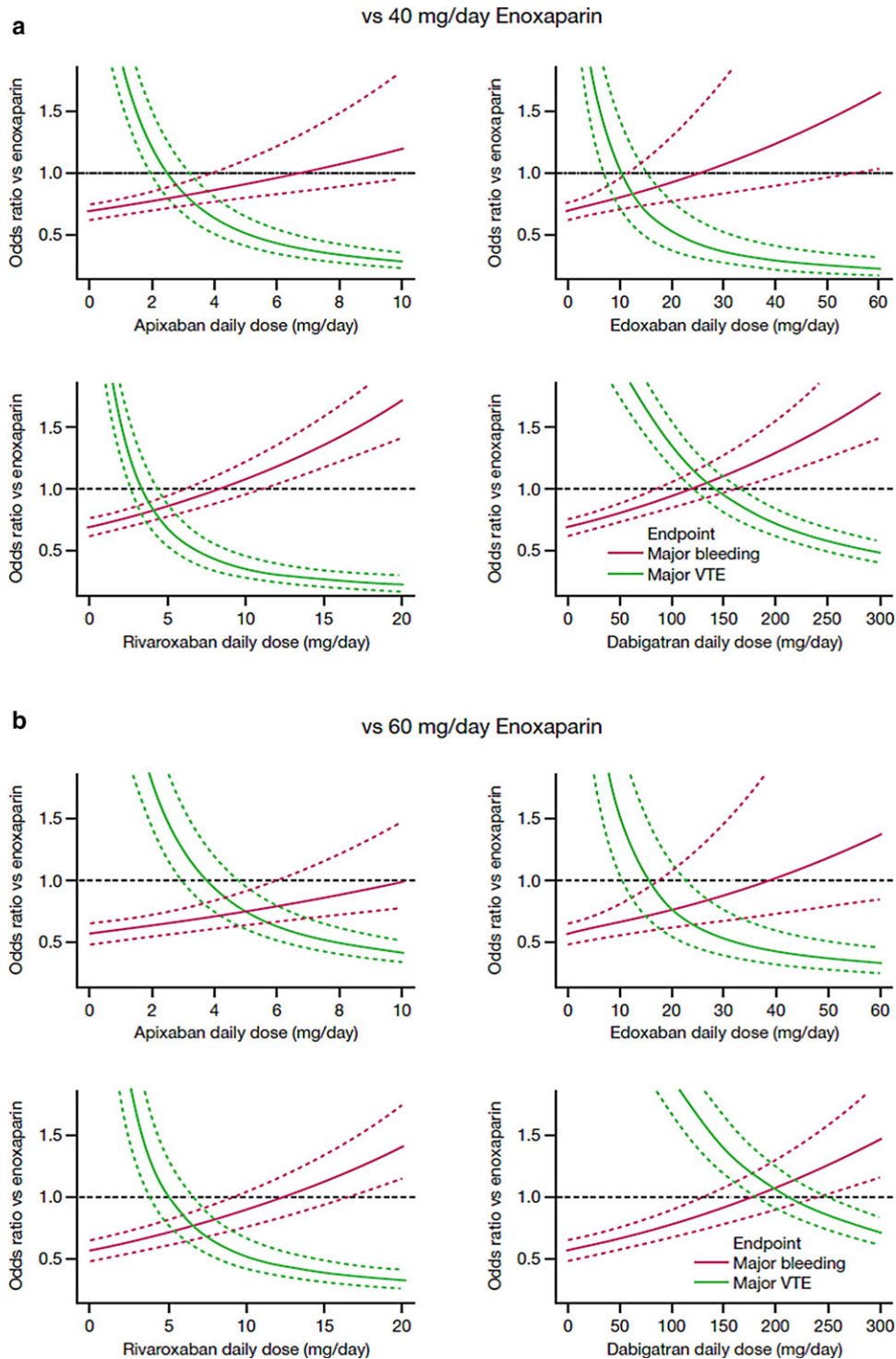
In general, the results of these analyses are consistent with those of previously published meta-analyses in which the dose regimen of enoxaparin was formally considered.<sup>19,20</sup> Kwok *et al.* carried out a fixed-effect meta-analysis of total VTE and major and clinically relevant bleeding (equivalent to our end point of clinically relevant bleeding) from 14 trials of apixaban, dabigatran, and rivaroxaban in THR or TKR surgery with enoxaparin as a comparator, and performed an adjusted indirect comparison to evaluate the relative effects of the two regimens of enoxaparin.<sup>19</sup> The pooled estimate of relative risk (95% CI) for enoxaparin 30 mg Q12H vs. enoxaparin 40 mg q.d. using all three adjusted indirect comparisons was 0.71 (0.61–0.83) for total VTE and 1.27 (0.97–1.65) for clinically relevant bleeding. In a similar analysis conducted by Laporte *et al.*,<sup>20</sup> indirect comparisons of the two enoxaparin regimens for various efficacy and safety outcomes were obtained by a meta-analysis of 40 trials containing 44 randomized comparisons of one of the enoxaparin regimens with an active comparator (apixaban, dabigatran, rivaroxaban, ximelagatran, fondaparinux, semuloparin, unfractionated heparin) or placebo/no treatment. The overall estimate of relative risk (95% CI) for enoxaparin 30 mg Q12H vs. enoxaparin 40 mg q.d. was 0.74 (0.66–0.84) for total VTE and 1.23 (0.96–1.57) for clinically relevant bleeding.

The results for the comparison of enoxaparin 30 mg Q12H to enoxaparin 40 mg q.d. from the dose–response model-based approach were consistent with these results, with odds ratio estimates of 0.73 (0.71–0.76) and 1.14 (1.10–1.21) for total VTE and clinically relevant bleeding, respectively. Furthermore, the estimates of odd ratios for VTE and bleeding outcomes for apixaban, dabigatran, and rivaroxaban compared with each dose regimen of enoxaparin in our

analyses were generally consistent with the relative risk estimates reported in the previous analyses.<sup>19,20</sup> Neither of the previous analyses included comparisons for edoxaban. Furthermore, Kwok *et al.*<sup>19</sup> did not distinguish between 150 and 220 mg q.d. dabigatran in their analysis.

Consistent with our previous analysis that indicated a larger therapeutic index for direct FXa inhibitors as a class, compared with direct thrombin inhibitors and LMWH,<sup>21</sup> the estimated therapeutic index for apixaban and rivaroxaban was significantly greater than that for enoxaparin (relative therapeutic index of 2.73 and 2.46, respectively). The point estimate of relative therapeutic index for edoxaban compared with enoxaparin (2.48) was similar to that for rivaroxaban, but did not achieve statistical significance, possibly due to the lower number of subjects included in clinical trials. The relative therapeutic index for dabigatran compared with enoxaparin (0.83) was not significantly different from 1.0. This is illustrated by the predicted dose–response relationships for relative treatment effects vs. both doses of enoxaparin. This suggests that there is no dose of dabigatran that could achieve both better efficacy and better safety than enoxaparin. For apixaban, edoxaban, and rivaroxaban, however, it may be possible to achieve better efficacy, better safety, or both better efficacy and safety, depending on the dose. Therefore, although the therapeutic index is similar for these three agents, the clinical profile depends on the dose that is chosen. A rivaroxaban dose of 10 mg per day and an edoxaban dose of 30 mg per day are slightly higher on the dose–response curves than a 5 mg daily dose of apixaban, and would therefore be expected to demonstrate relatively more efficacy and relatively more bleeding than apixaban. Furthermore, the approved doses of rivaroxaban and edoxaban are outside the dose range over which a benefit for both efficacy and bleeding compared with both doses of enoxaparin is predicted.





**Figure 5** Estimated dose–response relationships of the odds ratio vs. 40 mg q.d. (panel a) and 30 mg Q12H (panel b) enoxaparin for major VTE and major bleeding for apixaban, edoxaban, rivaroxaban, and dabigatran. The solid lines are the model estimates and the dashed lines indicate the 90% CI. CI, confidence interval; Q12H, every 12 h; q.d., once daily; VTE, venous thromboembolism.

During the development of the oral anticoagulants for prevention of VTE in THR and TKR surgery, multiple phase II dose-finding trials and phase III trials have typically been conducted for the different types of surgery and comparator dose regimens.<sup>25–38</sup> The results of the current analyses

suggest that the outcome of a single study in one type of surgery with one comparator dose regimen, used in conjunction with the model-based meta-analysis, would be sufficient to determine the optimal dose for both types of surgery and compared with both regimens of comparator. This strategy

was implemented in the development of PD 0348292.<sup>39</sup> Furthermore, it may be reasonable to question whether it is necessary to conduct phase III studies for both THR and TKR surgery, when this and other meta-analyses provide evidence that there is no impact of type of surgery on relative treatment effect.

In summary, a dose–response model-based meta-analysis of the efficacy and safety of anticoagulants for the prevention of VTE in THR and TKR surgery has provided evidence that there is a difference in the efficacy and safety of the North American and European dose regimens of enoxaparin, and thus the dose of enoxaparin that is used as a comparator is an important determinant in the assessment of the relative effects of new oral anticoagulants. Furthermore, the results suggest that the FXa inhibitors, apixaban, edoxaban, and rivaroxaban, but not the thrombin inhibitor, dabigatran, have a greater therapeutic index than enoxaparin, and thus it has been possible to achieve generally better efficacy than both doses of enoxaparin, with no increase in bleeding, at the doses evaluated in phase III trials. Finally, the analysis suggests that a single dose-finding study in one type of orthopedic surgery with one enoxaparin regimen would be sufficient for phase III dose selection.

The results of the dose–response model-based meta-analyses for oral anticoagulants illustrate the potential value of such an approach in clinical drug development. As a key component of knowledge management,<sup>23,24</sup> these models can be used in conjunction with emerging data from investigational agents to help inform dose selection and study design, which will ensure efficient clinical development and adequate differentiation from current therapy.

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