Journal of Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics (2011) **36**, 111–124 doi:10.1111/j.1365-2710.2010.01162.x

ORIGINAL ARTICLE

Dabigatran and rivaroxaban for prevention of venous thromboembolism – systematic review and adjusted indirect comparison

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SUMMARY

What is known and objective: **Dabigatran and rivaroxaban are new oral anticoagulants for thromboprophylaxis after elective orthopaedic surgery. We aimed to systematically compare their relative benefits and harms through meta-analysis, and adjusted indirect comparison.**

Methods: **We searched PubMed, EMBASE, trial registries and regulatory documents through May 2009 for randomized controlled trials (RCTs) of dabigatran (150 and 220 mg daily) and rivaroxaban (10 mg daily) compared with enoxaparin (40–60 mg daily) in elective orthopaedic surgery. We used random effects meta-analysis to calculate pooled relative risks (RRs) and 95% confidence intervals (95% CI) for the outcomes of total venous thromboembolism, VTE (deep venous thrombosis, non-fatal pulmonary embolism and all-cause mortality), and haemorrhagic adverse events (major and clinically relevant non-major bleeds). Adjusted indirect comparison was used for the pooled RRs of dabigatran and rivaroxaban with enoxaparin as the common control.**

Results: **Rivaroxaban was superior to enoxaparin for the prevention of venous thromoboembolism (RR 0·56, 95% CI 0·43–0·73, $P < 0·0001$), with a trend for increased haemorrhage (RR 1·26, 95% CI 0·94–1·69, $P = 0·13$). Dabigatran was not superior to enoxaparin for prevention of VTE (RR 1·12, 95% 0·97–1·29, $P = 0·12$), and did not reduce haemorrhage risk (RR 1·10, 95% 0·90–1·35, $P = 0·32$). Adjusted indirect comparison showed that rivaroxaban was superior to dabigatran in preventing VTE, RR 0·50 (95% CI 0·37–0·68), but with a slight trend towards increased haemorrhage RR 1·14 (95% CI 0·80–1·64).**

What is new and conclusion: **Rivaroxaban may be more effective than dabigatran for prevention of VTE after elective orthopaedic surgery but might also slightly increase the risk of haemorrhage.**

Keywords: **anticoagulation, dabigatran, oral direct thrombin inhibitors, oral factor Xa inhibitors, rivaroxaban, venous thromboembolism.**

WHAT IS KNOWN AND OBJECTIVE

Dabigatran and rivaroxaban are oral anticoagulants that are potentially more convenient than subcutaneous low molecular weight heparin in prophylaxis of venous thromboembolism (VTE) after surgery (1). The availability of oral agents removes the need to train patients in injection techniques, provides a pain-free alternative, and could be an economically viable choice in post-operative patients who require nursing support to administer injections.

The National Institute for Clinical Excellence (NICE) in the United Kingdom has approved the use of dabigatran and rivaroxaban in orthopaedic surgery, without making a definitive statement on the preferred agent (2, 3). In contrast, the Canadian Expert Drug Advisory Committee recommended that rivaroxaban, but not dabigatran, had to be listed for use in publicly funded drug plans for VTE prophylaxis after hip or knee replacement surgery (4, 5). In view of the differing recommendations, we aimed to perform a systematic comparison of the relative benefits and harms of rivaroxaban and dabigatran so that patients and healthcare professionals can make an evidence-based decision on their preferred agent.

Received 28 September 2009, Accepted 04 January 2010
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Contributors: Y. K. Loke and C. S. Kwok conceptualised the review, developed the protocol, abstracted and analysed data and wrote the manuscript. Y. K. Loke will act as the guarantor for the paper.

METHODS

Search strategy

Both authors searched MEDLINE (1950 onwards) and EMBASE (1980 onwards) in May 2009 with Ovid SP using the broad terms '(rivaroxaban.mp or dabigatran.mp) and trial.mp' without any language restrictions. In order to reduce the risk of publication bias, we searched the US Food and Drug Administration website and pharmaceutical company clinical trial registers for additional unpublished data. We also checked the bibliographies of included trials for any relevant studies.

Eligibility criteria

The specific inclusion criteria for randomized controlled trials (RCTs) were (i) double-blind parallel group randomized trial; (ii) participants undergoing elective orthopaedic surgery; (iii) intervention of dabigatran (licensed daily doses of 150 and 220 mg) or rivaroxaban (licensed daily dose 10 mg) compared with enoxaparin (40–60 mg daily) over the same treatment duration and (iv) clear reporting of VTE events and haemorrhage.

Data abstraction

Two reviewers (Y. K. Loke and C. S. Kwok) independently and in duplicate assessed the eligibility and extracted numerical outcomes data from the included studies. The reviewers obtained full consensus on inclusion of the studies and data extraction after resolving any discrepancies although discussion.

For the primary outcome, data were extracted on the composite measure of total VTE events, which consisted of deep venous thrombosis, non-fatal pulmonary embolism and all-cause mortality.

We assessed the overall risk of haemorrhage by pooling events from the two main categories reported in the trials – (a) major bleeds and (b) clinically relevant non-major bleeds.

Study characteristics and quality assessment

One reviewer (C. S. Kwok) extracted data on study characteristics, which was then checked by a second reviewer (Y. K. Loke). We recorded the dose and duration of interventions and comparators, as well as the baseline characteristics of participants in the RCTs.

We assessed the reporting of randomization, allocation concealment and the adequacy of follow-up in RCTs. In accordance with the Cochrane handbook of systematic reviews, we assessed the strength of adverse effects data by recording how the investigators defined and recorded haemorrhagic adverse events (6).

Quantitative data synthesis and sensitivity analysis

RevMan 5·021 (Nordic Cochrane Centre, København, Denmark) was used to conduct random effects meta-analysis for the pooled relative risks (RR), with 95% confidence intervals for dichotomous outcomes. The main analysis was on an intention-to-treat basis, and all reported P-values are two-sided, with significance set at $P < 0{\cdot}05$. Statistical heterogeneity was assessed using I^2 statistic, with. I^2 values of 30–60% representing a moderate level of heterogeneity (7). We also carried out predefined sensitivity analysis using the fixed effects model in the meta-analysis, and with the use of per-protocol and safety populations rather than the intention-to-treat dataset. As the manufacturer recommends two different doses of dabigatran (150 or 220 mg depending on patient population), we chose, first of all, to do a meta-analysis on both doses together, and then to assess each dose separately.

Adjusted indirect comparison (Bucher's method) (8) was performed using ITC software (Canadian Health Authority) (9). In this study, pooled RRs from the separate dabigatran and rivaroxaban meta-analyses were indirectly compared using enoxaparin as the common control. We assessed the validity of the adjusted indirect comparison by checking the degree of similarity between the rivaroxaban and dabigatran trials (10).

Calculation of the number needed to treat for benefit and number needed for harm

The number needed to treat (NNT) and number needed for harm (NNH) were calculated by applying the pooled RR from the meta-analysis to the average control event rate using Visual Rx, version 3.0 (Dr Christopher Cates, London, UK) (11).

RESULTS

The Trial selection flow sheet and details of the excluded trials are shown in Fig. 1. The large RECORD2 trial was the major exclusion because of the unequal duration of anticoagulation (enoxaparin for 14 days when compared with 35 days of rivaroxaban) which potentially biases the results towards demonstrating superior efficacy with rivaroxaban (12).

Nine RCTs involving 19 218 participants were included in the analysis. Descriptions of each trial are shown in Table 1 (13–21). Participants were those undergoing elective hip, and knee replacement surgery. Duration of anticoagulation in the trials ranged from 6 to 35 days in duration. Most of the trials used enoxaparin 40 mg once a day, but there were three trials (one dabigatran, two rivaroxaban) (17–19) where the comparator was the North American regimen of enoxaparin 30 mg twice daily.

Quality assessment

All the trials had blinding of participants and investigators using a double-dummy design. Most of the trials had adequate randomization and allocation concealment, but there were two trials where this was unclear because of the lack of explicit description in the trial report (the author did not respond to our enquiry) (13, 14). However, both these trials were multi-centre phase II studies sponsored by the pharmaceutical company and it is possible that the same randomization techniques may have been used as in the other included trials sponsored by the same company (Table 1).

All the trials used independent, blinded committees to adjudicate main outcome measures such as VTE (based on films and images from the radiological tests) and haemorrhagic events. Methods of ascertaining VTE outcomes were fairly similar amongst the trials, with deep venous thrombosis usually defined by ascending venography. Symptomatic pulmonary embolism was diagnosed with either ventilation perfusion scanning or spiral computerized tomography/pulmonary angiography. Trial reports provided breakdown of VTE according to site (distal or proximal for deep venous thrombosis) and clinical presentation (symptomatic or not, fatal or not). The trials used a variety of composite measures to evaluate different combinations of VTE events. A complete listing of the main subcategories of outcome events is provided as an Appendix S1.

Comparability of the dabigatran and rivaroxaban trials

Participants were very similar across both sets of trials with mean age of 65 years, equivalent body weights and proportion of females. Both drugs were tested in international multi-centre trials.

Use of enoxaparin as the common control involved two different dosage regimes. Both enoxaprin doses were similarly represented across the dabigatran and rivarxoban trials, with enoxaparin 30 mg bd contributing about a third of the data, and enoxaparin 40 mg od making up the remaining two-thirds for each set of trials. The time

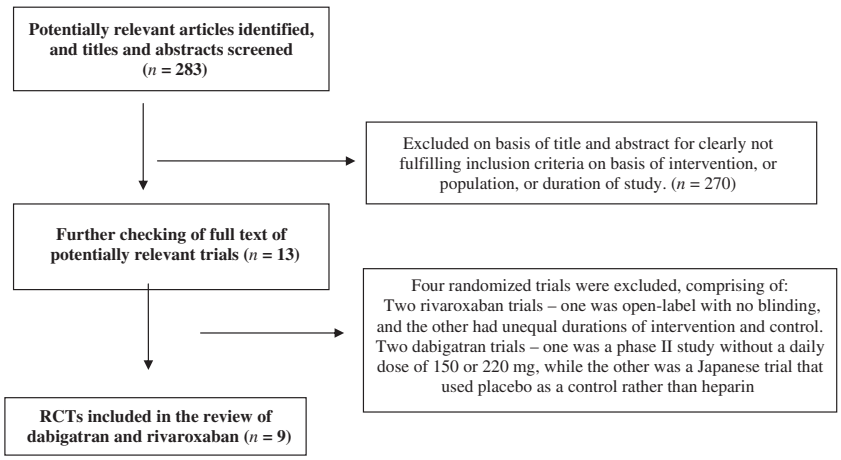

Fig. 1. Flowchart describing study selection for randomized controlled trials of dabigatran or rivaroxaban in elective orthopaedic surgeryRCT: randomised controlled trial.

Table 1. Characteristics of included randomized controlled trials

Study ID	Design	Participants	Intervention drug and comparator	Treatment duration	Ascertainment of primary outcome	Ascertainment of haemorrhage	% Completers
Eriksson *et al.* (13)	Double blind RCT; unclear allocation concealment (double-dummy blinding). Elective total hip arthroplasty	Mean age 65·3 years, mean weight 79 kg, 64% female	Rivaroxaban 5 mg BD 6–8 h after surgery vs. enoxaparin 40 mg OD evening before surgery	5–9 days	Screened for DVT using bilateral venograms (Rabinov & Paulin technique). Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	276 randomized to relevant doses, 77·9% evaluable for primary outcome, 97·8% evaluable for safety population
Eriksson *et al.* (14)	Double blind RCT; unclear allocation concealment (double-dummy blinding). Elective total hip arthroplasty	Mean age 64·9 years, mean weight 76 kg, 64% female	Rivaroxaban 10 mg OD 6–8 h after surgery vs. enoxaparin 40 mg OD evening before surgery	5–9 days	Screened for DVT using bilateral venograms (Rabinov & Paulin technique, with >9 films each leg). Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	307 randomized randomized to relevant doses, 71·7% evaluable for primary outcome, 97·4% evaluable for safety population
RECORD1 (15)	Double blind RCT; adequate allocation concealment. Elective total hip arthroplasty	Mean age 63·2 years, mean weight 78 kg, 55% female	Rivaroxaban 10 mg OD 6–8 h after surgery enoxaparin 40 mg OD 12 h before surgery	35 days	Screened for DVT using bilateral venograms (Rabinov & Paulin technique). Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	4541 randomized 69·4% evaluable for primary outcome, 97·6% evaluable for safety population

Table 1. Continued

Study ID	Design	Participants	Intervention drug and comparator	Treatment duration	Ascertainment of primary outcome	Ascertainment of haemorrhage	% Completers
RECORD3 (16)	Double blind RCT; adequate allocation concealment (double-dummy blinding). Elective total knee arthroplasty;	Mean age 67·6 years, mean weight 80 kg, 70% female	Rivaroxaban 10 mg OD 6–8 h after surgery vs. enoxaparin 40 mg OD 12 h before surgery	10–14 days	Screened for DVT using bilateral venograms (Rabinov & Paulin technique). US used for symptomatic DVT. Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	2531 randomized 67·2% evaluable for primary outcome, 97·1% evaluable for safety population
RECORD4 (17)	Double blind RCT; adequate allocation concealment (double-dummy blinding). Elective total knee arthroplasty	Mean age 64·6 years, mean weight 85 kg, 64% female	Rivaroxaban 10 mg OD 6–8 h after surgery enoxaparin 30 mg BD 12–24 h after surgery	10–14 days	Screened for DVT using bilateral venograms (Rabinov & Paulin technique). US used for symptomatic DVT, with venographic confirmation. Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	3148 randomized 61·1% evaluable for primary outcome, 96·3% evaluable for safety population
Turpie *et al.* (18)	Double blind RCT; adequate allocation concealment (double-dummy blinding). Elective total knee arthroplasty	Mean age 67·6 years, mean weight 89 kg, 64% female	Rivaroxaban 5 mg BD, mean of 7·2 h after surgery enoxaparin 30 mg BD morning after surgery	5–9 days	Screened for DVT using bilateral venograms (modified Rabinov & Paulin technique to ensure visualization of deep veins). Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	207 randomized to relevant doses, 61·4% evaluable for primary outcome, 99·5% evaluable for safety population

Table 1. Continued

Study ID	Design	Participants	Intervention drug and comparator	Treatment duration	Ascertainment of primary outcome	Ascertainment of haemorrhage	% Completers
RE-MOBILIZE (19)	Double blind RCT; adequate allocation concealment (double-dummy blinding). Elective total knee arthroplasty	Mean age 66 years, mean weight 88 kg, 57% female	Dabigatran 150 mg, 220 mg OD mean of 10 h after surgery and enoxaparin 30 mg BD 20 h after surgery	12–15 days	Screened for DVT using bilateral venograms (modified Rabinov & Paulin technique). US or venography used for symptomatic DVT. Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	2615 randomized 72·5% evaluable for primary outcome, 99·3% evaluable for safety population
RE-MODEL (20)	Double blind RCT; adequate allocation concealment (double-dummy blinding). Elective total knee arthroplasty	Mean age 67·7 years, mean weight 83 kg 64% female	Dabigatran 150 mg, (mean of 3·4 h after surgery) 220 mg OD, enoxaparin 40 mg OD evening before surgery	6–10 days	Screened for DVT using bilateral venograms (modified Rabinov & Paulin technique). US or venography used for symptomatic DVT. Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	2101 randomized 73·3% evaluable for primary outcome, 98·8% evaluable for safety population
RE-NOVATE (21)	Double blind RCT; adequate allocation concealment (double-dummy blinding). Elective total hip arthroplasty	Mean age 64·0 years, mean weight 79 kg 56% female	Dabigatran 150 mg, 220 mg OD, (mean of 3·4 h after surgery) enoxaparin 40 mg OD evening before surgery	28–35 days	Screened for DVT using bilateral venograms (modified Rabinov & Paulin technique). US or venography used for symptomatic DVT. Symptomatic PE confirmed by *V/Q* or CT scan or pulmonary angiogram. Adjudicated by blinded independent committee	Independent committee classified all events according to prespecified criteria for severity of bleeding	3493 randomized 75·9% evaluable for primary outcome, 99·1% evaluable for safety population

VQ, ventilation/perfusion; US, ultrasound; CXR, chest X-ray; CT, computerized tomography.

of enoxparin administration and duration (4–5 weeks for hip trials, and <2 weeks for knee trials) were broadly similar.

Measurement of outcomes in the dabigatran and rivaroxaban trials were similar, with primary and secondary outcomes adjudicated by blinded independent monitoring committees. However, examination of the Forest plots (Figs 2 and 3) showed that there were variations in the absolute event rates for VTE and haemorrhage across trials, thus suggesting that there were some differences in the intensity of monitoring and detecting adverse

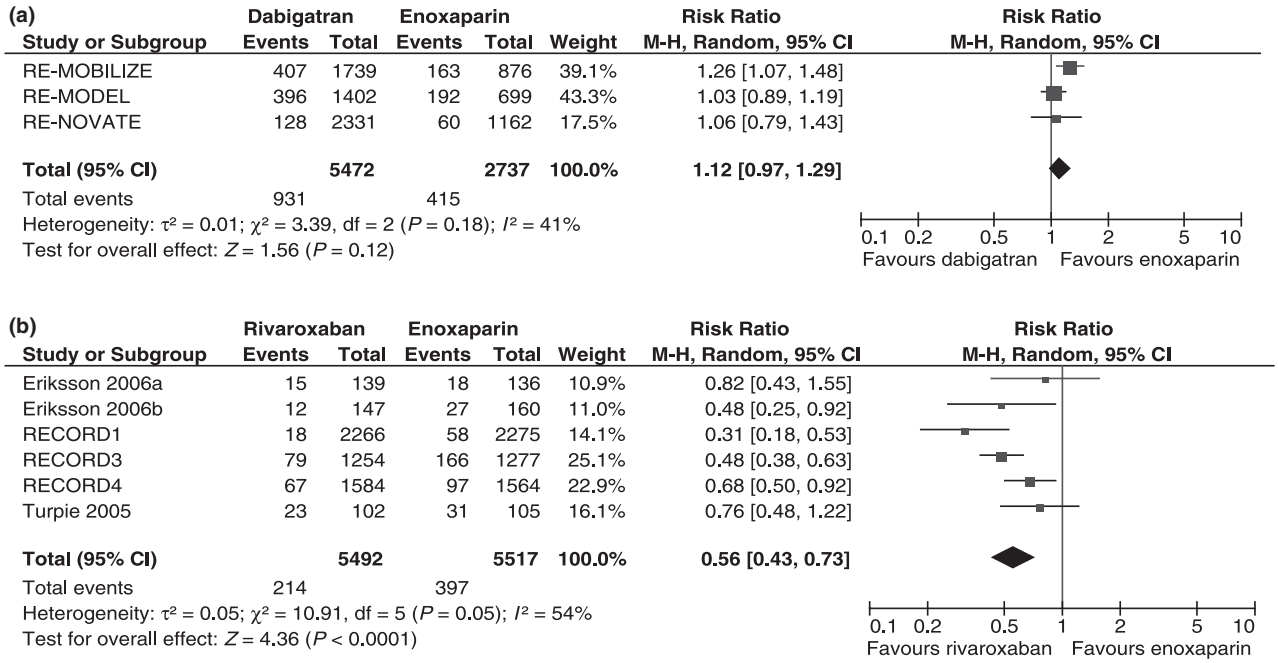

Fig. 2. Total venous thromboembolism events with (a) dabigatran or (b) rivaroxaban, vs. enoxaparin.

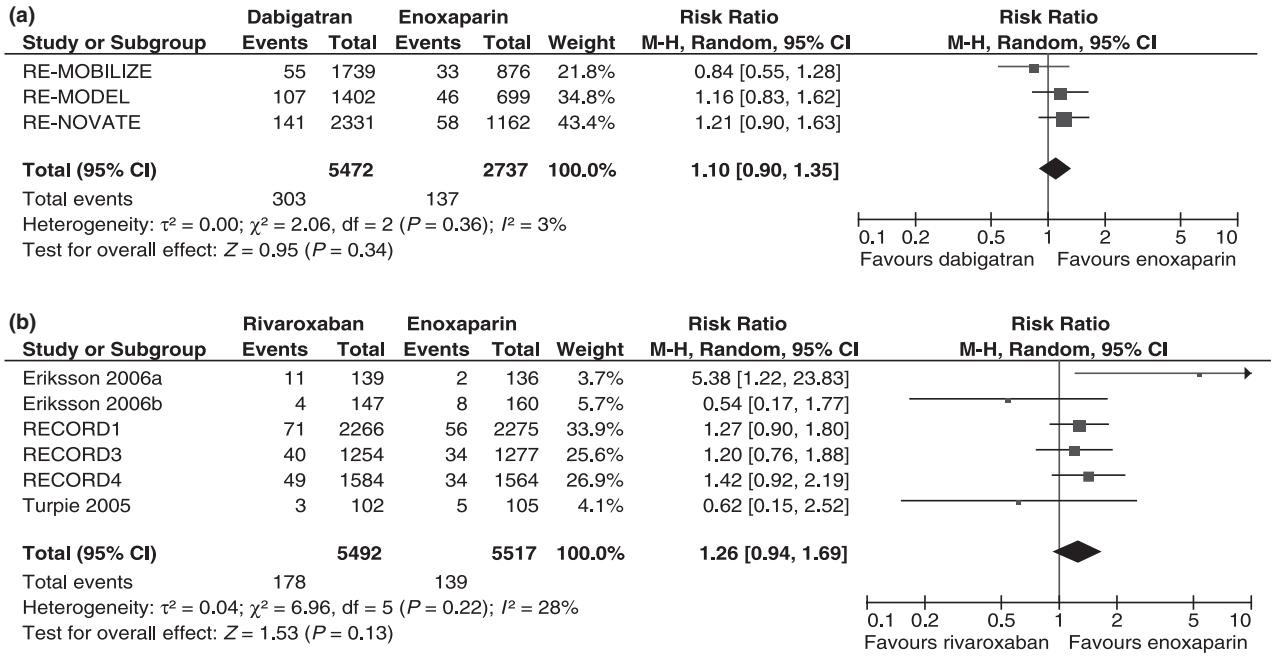

Fig. 3. Major and clinically relevant bleeds with (a) dabigatran or (b) rivaroxaban, vs. enoxaparin.

outcomes (perhaps from diagnostic criteria for VTE in lower limbs, or thresholds for recording clinically relevant haemorrhage). As all the trials had properly blinded independent outcome assessors, any potential misclassification ought to affect both intervention arms equally, and should not then lead to any radical alteration of the estimates of relative treatment effect in the AIC.

Primary outcome: total venous thromboembolism

All the included trials were designed to assess the same (prespecified) composite primary outcome consisting of deep venous thrombosis, non-fatal pulmonary embolism and all-cause mortality.

For dabigatran, the pooled data from three trials involving 8209 patients, showed that dabigatran did not significantly reduce the risk of VTE compared with enoxaparin (RR 1·12; 95% CI 0·97–1·29, $P = 0·12$), with moderate statistical heterogeneity ($I^2 = 41\%$) (Fig. 2a) (19–21).

For rivaroxaban, the pooled data from six trials involving 11 009 patients, showed that rivaroxaban significantly reduced the risk of VTE compared with enoxaparin (RR 0·56; 95% CI 0·43–0·73, $P < 0·0001$), with moderate statistical heterogeneity ($I^2 = 54\%$) (Fig. 2b) (13–18).

Secondary outcome – overall risk of haemorrhage

All the trials used similar pre-specified definitions to capture haemorrhagic adverse events, which were divided into two main categories: (a) major bleeds (b) clinically relevant, non-major bleeds. Trial investigators considered major haemorrhage to be those that led to death, or bleeding into a critical organ, or bleeding necessitating reoperation, or blood transfusion of ≥2 units, or bleeding with a ≥ 2 g/dL fall in haemoglobin. Clinically relevant, non-major bleeding encompassed less severe events such as wound and skin haematomas, epistaxis; macroscopic haematuria, and rectal or gum bleeding. We pooled events from both categories in assessing the overall risk of haemorrhage.

For dabigatran, the pooled data from three trials involving 8209 patients, showed that the risk of haemorrhage (RR 1·10; 95% CI 0·90–1·35, $P = 0·34$) with dabigatran was similar to enoxaparin, with no statistical heterogeneity ($I^2 = 3\%$) (Fig. 3a) (19–21).

For rivaroxaban, the pooled data from six trials involving 11 009 patients, showed a trend towards an increased risk of haemorrhage (RR 1·26; 95% CI 0·94–1·69, $P = 0·13$) rivaroxaban compared with enoxaparin, with mild statistical heterogeneity ($I^2 = 28\%$) (Fig. 3b) (13–18).

Adjusted indirect comparison

The adjusted indirect comparison showed that rivaroxaban was superior to dabigatran in preventing total VTE events, with a RR of 0·50 (95% CI 0·37–0·68) (Table 2).

However, rivaroxaban may possibly be more likely to cause haemorrhage than dabigatran (RR 1·14; 95% CI 0·80–1·64), although the wide confidence intervals preclude any definite conclusions.

The superiority of rivaroxaban for preventing VTE events remained consistent across different doses of dabigatran (150 or 220 mg), site of the surgery (hip or knee), and the use of the North American dose of enoxaparin 30 mg bd as the common control in knee surgery (Table 2).

Restricting the analysis to major outcomes (symptomatic deep venous thrombosis, pulmonary embolism and death, and major haemorrhage) yielded similar directions of effect to that of total VTE events, with rivaroxaban appearing more effective but also more likely to cause major haemorrhage, with wide confidence intervals because of the low incidence of these outcomes (Table 2).

Estimated NNT for Benefit and NNT for Harm: rivaroxaban 10 mg daily versus dabigatran 220 mg daily

The clinical impact of switching to rivaroxaban from dabigatran varies with the background VTE risk and haemorrhagic risk of the patients in the trials. Table 3 shows the impact of rivaroxaban use depending on baseline risk. The benefit:harm ratio derived from the change in event rates from the use of rivaroxaban instead of dabigatran, varies from 3 to 15 VTE events saved by rivaroxaban for every additional haemorrhage caused.

However, a thorough evaluation of the benefit:harm balance needs to also take into account the finding that the most of the VTE events noted in the trials were asymptomatic deep venous

Table 2. Adjusted indirect comparison of relative risks for efficacy and safety outcomes with dabigatran vs. rivaroxaban

Adjusted indirect comparison	Risk of total VTE (RR, 95% CI) with rivaroxaban compared with dabigatran	Overall risk of haemorrhage (RR, 95% CI) with rivaroxaban compared with dabigatran
Overall		
Rivaroxaban 10 mg vs. dabigatran all doses	0·50 (0·37–0·68)	1·14 (0·80–1·64)
Dabigatran by total daily dose		
Rivaroxaban 10 mg vs. dabigatran 150 mg	0·46 (0·34–0·62)	1·13 (0·78–1·63)
Rivaroxaban 10 mg vs. dabigatran 220 mg	0·54 (0·40–0·74)	1·15 (0·79–1·66)
By site of surgery		
Knee replacement: rivaroxaban 10 mg daily vs. dabigatran all doses	0·54 (0·38–0·76)	1·24 (0·80–1·94)
Hip replacement: rivaroxaban 10 mg daily vs. dabigatran all doses	0·46 (0·25–0·87)	1·14 (0·43–3·06)
North American dose of enoxaparin 30 mg bd as common control in knee surgery		
RECORD4 vs. REMOBILIZE	0·54 (0·38–0·76)	1·69 (0·92–3·01)
Analysis focused on major outcomes	Symptomatic DVT, PE or Death	Major haemorrhage
Rivaroxaban 10 mg vs. dabigatran all doses	0·53 (0·11–2·62)	1·56 (0·65–3·74)

RR, relative risk; 95% CI, 95% confidence intervals; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolus.

thrombosis, whereas many of the haemorrhagic events were clinically overt and of possibly greater consequence. Table 4 shows the projected impact of switching to rivaroxaban based on pooled event rate for major outcomes (symptomatic deep venous thrombosis, pulmonary embolism and death and major haemorrhage) with dabigatran 220 mg trials. The perceived advantages of rivaroxaban are less apparent in this model because of the lower symptomatic VTE event rates, thus contributing to higher NNTs, whereas the absolute increase in haemorrhagic events remains a consistent concern. However, the trials were not powered to adequately address these outcomes, so we cannot draw any robust conclusions in this study, given the very wide confidence intervals.

Sensitivity analysis

Choice of dose. If the meta-analysis was conducted on different doses of dabigatran, we found that dabigatran 150 mg daily was significantly less efficacious than enoxaparin (RR 1·21, 95% CI 1·05–1·39, $P = 0·009$), whereas dabigatran 220 mg daily seemed similar to enoxaparin in preventing total VTE events (RR 1·03, 95% CI 0·88–1·20, $P = 0·74$) (Table 5).

For rivaroxaban, exclusion of the two trials that used 5 mg bd doses (rather than 10 mg od) did not lead to any major change in the pooled risk for VTE (RR 0·50, 95% CI 0·37–0·67) or haemorrhage (RR 1·25, 95% CI 1·00–1·57) against enoxaparin.

Choice of statistical model – fixed effects as opposed to random effects. There were two outcomes where the fixed effects meta-analysis yielded markedly different *P*-values from the random effects model. The fixed effects meta-analysis of VTE showed that dabigatran (150 and 220 mg combined) was statistically significantly less efficacious in preventing VTE (RR 1·12, 95% CI 1·01–1·24, $P = 0·03$) than enoxaparin.

This risk of haemorrhage with rivaroxaban was significantly greater (RR 1·29, 95% CI 1·03–1·60, $P = 0·02$) than enoxaparin with the fixed effects model.

Table 3. Projected impact of switching from dabigatran 220 mg to rivaroxaban 10 mg depending on baseline risk of patients

Patients baseline risk level	Risk of total VTE with dabigatran 220 mg	Risk of haemorrhage with dabigatran 220 mg	Change in VTE events if rivaroxaban was used (per 1000 patients)	Change in haemorrahge events if rivaroxaban was used (per 1000 patients)	Number needed to treat to prevent VTE	Number needed to treat for haemorrhage
Low VTE and haemorrhage risk, similar to RENOVATE patients (hip surgery) (21)	6·0%	6·2%	28 events prevented (95% CI 16–36)	9 extra events (95% CI 13 prevented–41 extra)	37 (95% CI 28–65) over 5 weeks	108 (95% CI stretches across both benefit and harm)
High VTE and haemorrhage risk similar to REMODEL patients (knee surgery) (20)	36·4%	7·4%	167 events prevented (95% CI 95–218)	11 extra events (95% CI 16 prevented–49 extra)	6 (95% CI 5–11) over 10 days	91 (95% CI stretches across both benefit and harm)

95% CI, 95% confidence intervals; VTE, venous thromboembolism.

Table 4. Projected impact of switching from dabigatran 220 mg to rivaroxaban 10 mg depending on outcome measure; baseline risks are from the average event rate in dabigatran treated patients

Type of outcome	Risk of VTE	Risk of haemorrhage	Change in VTE events if rivaroxaban was used (per 1000 patients)	Change in haemorrhages if rivaroxaban was used (per 1000 patients)	Number needed to treat to prevent VTE	Number needed to treat for haemorrhage
Major VTE, or major haemorrhage	1·1%	1·4%	5 fewer events (95% CI 10 fewer–17 extra)	8 extra events (95% CI 5 fewer–38 extra)	199 (95% CI stretches across benefit and harm)	128 (95% CI stretches across benefit and harm)
Total VTE, or major and clinically relevant haemorrhage	15·6%	5·5%	72 fewer events prevented (95% CI 41–94)	8 extra events (95% CI 12 fewer–36 extra)	14 (95% CI 11–25)	122 (95% CI stretches across benefit and harm)

95% CI, 95% confidence intervals; VTE, venous thromboembolism.

Choice of population for analysis. The findings of the meta-analysis remained consistent irrespective of whether we used intention-to-treat analysis or the evaluable-for-primary-outcome and safety populations as the denominator.

DISCUSSION

In the absence of any forthcoming head-to-head trials, this meta-analysis and adjusted indirect comparison provides valuable information to

Table 5. Sensitivity analysis: comparison of pooled relative risks with different models

Comparison	Model of analysis	Total VTE (RR, 95% CI, *P*-value)	Overall risk of haemorrhage (RR, 95% CI, *P*-value)
Dabigatran analysis according to dose–response			
Dabigatran vs. enoxaparin	Dabigatran 150 mg daily	1·21 (95% CI 1·05–1·39, $P = 0·009$)	1·12 (0·89–1·40, $P = 0·34$)
	Dabigatran 220 mg daily	1·03 (95% CI 0·88–1·20, $P = 0·74$)	1·10 (0·88–1·38, $P = 0·42$)
Random effects vs. fixed effects analysis			
Dabigatran 150 mg and 220 mg vs. enoxaparin	Random effects	1·12 (95% CI 0·97–1·29, $P = 0·12$)	1·10 (0·90–1·35, $P = 0·32$)
	Fixed effects	1·12 (95% CI 1·01–1·24, $P = 0·03$)	1·10 (0·91–1·34, $P = 0·34$))
Rivaroxaban 10 mg vs. enoxaparin	Random effects	0·56 (95% CI 0·43–0·73, $P < 0·0001$)	1·26 (0·94–1·69, $P = 0·13$)
	Fixed effects	0·54 (95% CI 0·46–0·64, $P < 0·0001$)	1·29 (1·03–1·60, $P = 0·02$)
Intention to treat analysis compared with per protocol and safety populations			
Dabigatran 150 mg and 220 mg vs. enoxaparin	Intention to treat	1·12 (95% CI 0·97–1·29, $P = 0·12$)	1·10 (0·90–1·35, $P = 0·32$)
	Per protocol for primary outcome; safety for bleeds	1·13 (95% CI 0·97–1·32, $P = 0·12$)	1·10 (0·90–1·35, $P = 0·35$)
Rivaroxaban vs. enoxaparin	Intention to treat	0·56 (95% CI 0·43–0·73, $P < 0·0001$)	1·26 (0·94–1·69, $P = 0·13$)
	Per protocol for primary outcome; safety for bleeds	0·58 (95% CI 0·43–0·77, $P < 0·0001$)	1·26 (0·94–1·69, $P = 0·12$)

RR, relative risk; 95% CI, 95% confidence intervals; VTE, venous thromboembolism.

phyisicians, pharmacists and formulary committees who are trying to choose between two newly launched oral anticoagulants in hip or knee surgery. Rivaroxaban offers superior efficacy compared with enoxaparin, and dabigatran, although this is probably associated with some accompanying increase in haemorrhage overall. Our analysis was robust to the choice of dabigatran dose (150 or 220 mg), site of surgery and enoxaparin regimen and appears to support the decision of the Canadian Health Authority to recommend rivaroxaban rather than dabigatran (4, 5).

The apparent disparity in efficacy between dabigatran etexilate and rivaroxaban may arise from their differing actions on the clotting cascade. Dabigatran directly inhibits thrombin whereas rivaroxaban binds to factor Xa which is the clotting factor that catalyzes the conversion of prothrombin to thrombin, with a single molecule of factor Xa able to generate more than a thousand thrombin molecules (22, 23). Some have argued that Factor Xa may be a better target for anticoagulant drugs as it has fewer functions outside of coagulation, and activates clotting over a wider concentration range (24).

Another explanation may be that dabigatran doses are at the lower end of its dose–response curve, while licensed doses of rivaroxaban might be at the upper end of the dose–response curve, thus conferring greater efficacy and a trend towards increased haemorrhage with rivaroxaban. There is also a significant difference in bioavailability between the two drugs. Dabigatran has low oral bioavailability of 6·5% while rivaroxaban has

much higher bioavailability of 80% after oral administration (25, 26). Our meta-analysis showed that dabigatran 220 mg daily was non-inferior to enoxaparin, whereas dabigatran 150 mg daily was significantly inferior to enoxaparin. The value of dabigatran 150 mg daily must be questioned in this study, because it did not seem to offer enhanced safety (the overall risk of haemorrhage did not seem any lower than enoxaparin or dabigatran 220 mg), and its efficacy is significantly poorer than enoxaparin.

The meta-analysis has several limitations. We have relied on data from pharmaceutical company sponsored studies as there are as yet no independently conducted trials. There was moderate heterogeneity in the pooled RRs for VTE prevention with rivaroxaban, although the impact of this is debatable, given that the direction of effect was similar amongst all the trials, with the main difference being in magnitude of benefit. While we used a composite outcome of total VTE, the vast majority (>90%) of events were asymptomatic deep venous thrombosis picked up through mandatory screening, with relatively few clinically manifest VTE events or deaths reported. We also choose to construct our own composite measure for overall risk of haemorrhage rather than rely on the trial category of 'major' bleeds because the 'major' bleeds reported did not necessarily cover surgical site bleeding. Moreover, all the clinical trials excluded patients who were at high risk of haemorrhage, and the real-world adverse outcomes associated with oral anticoagulants may be potentially higher.

There is still considerable debate surrounding the validity of adjusted indirect comparisons, although one large survey has shown AIC to yield results that are often very similar to those obtained from direct or head-to-head trials (27). Assessment of trial similarity is crucial in AIC, and we feel that the rivaroxaban and dabigatran trials shared sufficient similarities for the AIC to have some validity (10). In order to be more certain that we were comparing like-with-like, we attempted to reduce the differences between dabigatran and rivaroxaban trials in the AIC by focusing on specific subgroups according to surgical site, and dosage regimen of the common control (Table 2). The findings of the AIC remained consistent in these narrower subgroups where the rivaroxaban and dabigatran trials shared greater similarity and appeared even more comparable. However, we are aware of some variation in the *absolute* event rates for VTE and haemorrhagic events across the trials which may arise from differing methods of ascertaining outcomes. Nevertheless, all the trials were double-blinded and had independent adjudication committees, and should still give reasonably unbiased estimates of the *relative* treatment effect of dabigatran or rivaroxaban versus enoxaparin.

Despite these limitations, our findings are relevant to current clinical practice, especially as it seems unlikely that either pharmaceutical company would choose to fund a direct dabigatran vs. rivaroxaban trial. Other published meta-analyses have so far looked only at each agent in isolation, and not carried out a statistical comparison of their relative effects (28, 29). Further comparative research would probably require government or research council funding for a head-to-head trial in a wider setting, perhaps also capturing trauma patients with fractured femurs who were not represented in current studies. An intensive prospective observational study would also be helpful in establishing the real-world rates of haemorrhage with these new agents.

In summary, our estimates of the relative and absolute event rates, and the NNT/NNH benefit:harm ratio allows clinicians, patients and policy makers to make better-informed decisions on choice of oral anticoagulant. Patients who are at particular risk of severe haemorrhage may well prefer to have a safer agent (such as dabigatran), even though it is less efficacious. This is especially true if the patient also has a very low risk of VTE, where the absolute benefits of rivaroxaban may not be so manifest. However, we would argue that patients with low VTE risk, but high haemorrhage risk had to avoid anticoagulants, and perhaps concentrate on mechanical methods of thromboprophylaxis instead. Given the absence of any major cost differential between rivaroxaban and dabigatran, it could be argued (as the Canadian Expert Drug Advisory Committee has carried out) that rivaroxaban is a potentially more cost-effective proposition.

WHAT IS NEW AND CONCLUSION

Rivaroxaban may be more effective than dabigatran for prevention of VTE after elective

orthopaedic surgery but might also slightly increase the risk of haemorrhage.

ACKNOWLEDGEMENT

Funding: None. Y. K. Loke and C. S. Kwok have no competing interests to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Table of main outcomes from individual trials.

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