

Rivaroxaban and dabigatran for thromboprophylaxis in patients undergoing total hip or knee replacement

Citation Garrubba M. & Turner T. 2009. Effects of rivaroxaban or dabigatran on venous thromboembolism and heparin-induced thrombocytopenia for patients undergoing total hip or knee replacement: Evidence Review. Centre for Clinical Effectiveness, Southern Health. Melbourne, Australia.

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Abstract

Background The purpose of this review was to identify whether rivaroxaban or dabigatran compared to enoxaparin or other low molecular weight heparins or warfarin reduce rates of venous thromboembolism events (such as pulmonary embolism, deep vein thrombosis) and heparin-induced thrombocytopenia (HIT) in adult patients undergoing either total hip or knee replacement.
This review will be used to inform decision-making by the Southern Health Therapeutics Committee and may be of interest to the Victorian Therapeutics Advisory Group.
During the writing of this Evidence Review the Pharmaceutical Benefits Advisory Committee (PBAC) recommended rivaroxaban for listing for preventing venous thromboembolism after total hip or knee replacement surgery, after concluding that rivaroxaban has uncertain but acceptable cost-effectiveness compared with that of enoxaparin.

Question "In adult patients who have had either total hip or knee replacement does rivaroxaban or dabigatran compared to enoxaparin or other low molecular weight heparins or warfarin reduce rates of venous thromboembolism events (such as pulmonary embolism, deep vein thrombosis) and HIT?"

Methods We included all trials published in English. We searched All EBM, Medline, EMBASE, CINAHL, International Pharmaceutical Abstracts and Biological Abstracts in June 2009. Studies were selected and appraised by two reviewers in consultation with colleagues, using inclusion, exclusion and appraisal criteria established a priori.

Results Three articles, consisting of an evidence-based Clinical Practice Guideline, a Health Technology Assessment (HTA) and a Randomised Controlled Trial (RCT), reporting the results of a total of eight RCTs which included adult patients undergoing surgery for total hip replacement or total knee replacement or total knee replacement alone. The guideline was developed in Australia the HTA was conducted in Canada and the RCT was undertaken internationally (USA, Bulgaria, Canada, Denmark, India, Israel, Lithuania, Mexico, Norway, Pakistan, Poland, Sri Lanka and Sweden). The included studies implemented slight variations of intervention and comparator drugs however all implemented similar doses (eg rivaroxaban 10mg, dabigatran 220mg or 150mg, enoxaparin 30mg or 40mg, and low molecular weight heparin 40mg). All measured outcomes focused on prevention of thromboprophylaxis. Appraisal of these articles indicates that the body of evidence is generally of moderate to low quality, with the HTA and RCT having a high risk of bias. Recommendations and results of all studies should be interpreted with caution due to methodological issues including a lack of information for appraisal criteria, large exclusion numbers and substantial conflicts of interest through the authors association with pharmaceutical companies Bayer Schering Pharmaceuticals and Boehringer Ingelheim Pharmaceuticals which produce rivaroxaban and dabigatran respectively.
Overall the results of these studies do not convincingly demonstrate superior effectiveness of rivaroxaban or dabigatran over enoxaparin or other low molecular weight heparins or warfarin in reducing rates of venous thromboembolism events or HIT.

Conclusion From the three studies, reporting the results of a total of eight RCTs included in this review for patients undergoing total hip or knee replacement, there is uncertain evidence for the effectiveness of rivaroxaban or dabigatran compared with enoxaparin or low molecular weight heparins or warfarin for reducing rates of venous thromboembolism events. The recommendations and results of these studies should be interpreted with caution. Additional post-marketing surveillance is required to determine incidence of adverse events caused by rivaroxaban and dabigatran.

Background

The purpose of this review was to identify whether rivaroxaban or dabigatran compared to enoxaparin or other low molecular weight heparins or warfarin reduce rates of venous thromboembolism events (such as pulmonary embolism, deep vein thrombosis) and heparin induced thrombocytopenia (HIT) in adult patients undergoing either total hip or knee replacement.

Rivaroxaban is available as an oral preparation and may be cheaper than enoxaparin¹ which is in current use but requires subcutaneous administration. If rivaroxaban is as safe and effective as enoxaparin there might be benefits to the patients and the health service.

This review will be used to inform decision-making by the Southern Health Therapeutics Committee and may be of interest to the Victorian Therapeutics Advisory Group.

During the writing of this Evidence Review the Pharmaceutical Benefits Advisory Committee (PBAC) recommended rivaroxaban for listing for preventing venous thromboembolism after total hip or knee replacement surgery, after concluding that rivaroxaban has uncertain but acceptable cost-effectiveness compared with that of enoxaparin².

Question

"In adult patients who have had either total hip or knee replacement does rivaroxaban or dabigatran compared to enoxaparin or other low molecular weight heparins or warfarin reduce rates of venous thromboembolism events (such as pulmonary embolism, deep vein thrombosis) and heparin induced thrombocytopenia (HIT)?"

Methods

Study selection criteria

Patient	Inclusion: Adults (≥ 18 years) who have undergone total hip or knee replacement. Exclusion: Children (< 18 years); patients not undergoing total hip or knee replacement.		
Intervention	Inclusion: Rivaroxaban or dabigatran. Exclusion: Any other anticoagulant.		
Comparison	Inclusion: Enoxaparin or other low molecular weight heparins or warfarin. Exclusion: Any other anticoagulant.		
Outcomes	Inclusion: Rates of venous thromboembolism events (pulmonary embolism, deep vein thrombosis), side effects and HIT. Exclusion: Any non-comparative outcomes.		
Study type	For the specified outcomes, systematic reviews and RCTs addressing the outcomes are sought. If there are outcomes not addressed by RCTs, then evidence from lower quality comparative studies are sought.	Publication Date	1980 onwards
		Language	English

Search strategy

Evidence source	Date of search or issue searched
Medline (Ovid)	June 3 rd 2009. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1950 to Present.
All EBM (Ovid)*	June 3 rd 2009.
CINAHL (Ebscohost)	June 3 rd 2009.
EMBASE (Ovid)	June 3 rd 2009.
International Pharmaceutical Abstracts (CSA)	June 3 rd 2009.
Biological Abstracts (Ovid)	June 3 rd 2009.

*(including The Cochrane Database of Systematic Reviews, DARE, CENTRAL and ACP Journal Club)

Search terms in Medline*

Patient	-
Intervention	Rivaroxaban.mp. OR Xarelto.mp. OR BAY 59-7939.mp. OR Dabigatran.mp. OR Pradaxa.mp. OR BIBR 953.mp.
Comparison	-
Outcomes	-

* Similar terms (appropriately translated) were used in other databases. Details of all searches are available on request from cce@southernhealth.org.au.

Data collection and analysis

Studies were selected and appraised by two reviewers in consultation with colleagues using study selection and appraisal criteria established *a priori*. A relevant evidence-based Clinical Practice Guideline and Health Technology Assessment (HTA), published in 2009, were known to the reviewers and met the inclusion and exclusion criteria for this evidence review. For this reason, only articles returned by the databases published in 2009 were reviewed for relevance.

The initial search returned 479 articles, 47 of which were published in 2009. The 47 articles were reviewed by title and abstract. One of the eight articles retrieved for review in full text met the inclusion criteria.

Results

Three articles met our study selection criteria, an evidence-based Clinical Practice Guideline³, a HTA rapid review⁴ and a RCT⁵. Critical appraisals of the quality of the three papers are presented in Appendix A.

The articles included adult patients undergoing surgery for total hip replacement or total knee replacement^{3, 4} or total knee replacement alone⁵. The guideline was developed in Australia³, the HTA was conducted in Canada⁴ and the RCT was undertaken internationally⁵ (USA, Bulgaria, Canada, Denmark, India, Israel, Lithuania, Mexico, Norway, Pakistan, Poland, Sri Lanka and Sweden).

Appraisal of these articles, reporting the results of a total of eight RCTs, indicates that the body of evidence varies from high to low methodological quality. While the draft guideline is of high quality and would be recommended for use in practice, the HTA and RCT do not meet some of the key methodological criteria, therefore the results of the studies must be interpreted with caution. All of the RCTs were funded by the pharmaceutical companies producing the drugs (Bayer Schering Pharmaceuticals or Boehringer Ingelheim Pharmaceuticals).

National Health and Medical Research Council (NHMRC) 2009³.

The first paper is an evidence-based Clinical Practice Guideline draft published for public consultation by the NHMRC in June 2009. The purpose of the guideline is to provide practical, evidence-based recommendations for the prevention of venous thromboembolism (VTE) in adult surgical and medical patients and pregnant women admitted to Australian metropolitan, regional and rural hospitals. The guideline provides recommendations on thromboprophylaxis for adult patients admitted to hospital in the following categories: patients undergoing surgery including orthopaedic, major general, major gynaecological, urological, cardiothoracic, vascular and neurosurgery; patients with acute medical illnesses, including myocardial infarction, stroke and other medical conditions; trauma patients; patients admitted to intensive care units; cancer patients (active or occult, with or without cancer treatment); and patients admitted during pregnancy and the puerperium.

The methods of this evidence-based Clinical Practice Guideline were well documented, meeting 20 of the 23 AGREE⁶ criteria for development of evidence-based Clinical Practice Guidelines. The guideline scored highly for scope and purpose, rigour of development, clarity and presentation, and stakeholder involvement. Lower scores were received for applicability and editorial independence. Further details are available in appendix 1.

Recommendations for rivaroxaban and dabigatran are “B” grade recommendations. For total hip and knee replacement surgery the draft guideline recommends pharmacological thromboprophylaxis post-operatively for up to 14 days following surgery. It also recommends use of any one of the following drugs: low molecular weight heparin, fondaparinux, rivaroxaban and dabigatran etexilate. The guideline recommends that choice of thromboprophylactic agent after total knee or hip replacement should be based on availability, cost and individual patients’ risk characteristics and preferences. The guideline also notes that both rivaroxaban and dabigatran are newly approved agents with post-marketing surveillance on adverse events not yet available.

The NHMRC describe the grading of their recommendations as follows:

- A grade evidence can be trusted to guide practice
- B grade evidence can be trusted to guide practice in most situations
- C grade evidence provides some support for recommendation(s) but care should be taken in its application
- D grade evidence is weak and recommendations must be applied with caution
- NA is unable to grade the body of evidence
- GPP is a good practice point – consensus-based recommendation

Total Hip Replacement (THR)

Evidence for VTE prophylactic agent – Rivaroxaban

“In two multi-centre international RCTs, rivaroxaban (10mg orally once per day for 35 days) was more effective at reducing the occurrence of deep vein thrombosis (DVT) than low molecular weight heparin (LMWH) (40mg once per day, either for 35 days or 14 days). There were no significant differences in the rates of pulmonary embolism (PE) or adverse events, including death, between the rivaroxaban and LMWH arms.”

Evidence for VTE prophylactic agent – Dabigatran etexilate

“In one multi-centre international RCT, there were no significant differences in rates of DVT or PE with dabigatran etexilate (220mg or 150mg) compared with LMWH (40mg daily). There were no significant differences in the rates of adverse events between the two groups.”

Recommendations for THR

1. Use thromboprophylaxis for all patients admitted to hospital for total hip replacement. (GPP)
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to 35 days following total hip replacement surgery. Use one of the following:
 - low molecular weight heparin (A)
 - fondaparinux (use fondaparinux with caution as it may cause bleeding in those weighing less than 50kg, in the frail, the elderly and those with renal impairment). (B)
 - rivaroxaban (rivaroxaban is a newly approved agent and post-marketing surveillance on adverse events is not yet available). (B)
 - dabigatran etexilate (dabigatran etexilate is a newly approved agent and post-marketing surveillance on adverse events is not yet available). (B)
3. Pre-operative administration of thromboprophylaxis is not recommended for patients undergoing total hip replacement surgery. (C)

Total Knee Replacement (TKR)

Evidence for VTE prophylactic agent – Rivaroxaban

“In two RCTs rivaroxaban (10mg orally once per day for two weeks) was more effective at reducing DVT (asymptomatic, symptomatic and distal DVT) than LMWH (40mg subcutaneously once per day for two weeks). There was no difference in non-fatal PE, death or bleeding between rivaroxaban and LMWH.”

Evidence for VTE prophylactic agent – Dabigatran etexilate

“In two RCTs there was no significant difference in rates of DVT or PE with dabigatran etexilate (220mg or 150mg) compared with LMWH (40mg daily). There was no significant difference in any adverse events between dabigatran etexilate and LMWH.”

Recommendations for TKR

1. Use thromboprophylaxis for all patients admitted to hospital for total knee replacement. (GPP)
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to 14 days following total knee replacement surgery. Use one of the following:
 - low molecular weight heparin (A)
 - fondaparinux (use fondaparinux with caution as it may cause bleeding in those weighing less than 50kg, in the frail, the elderly and those with renal impairment). (B)
 - rivaroxaban (rivaroxaban is a newly approved agent and post-marketing surveillance on adverse events is not yet available). (B)
 - dabigatran etexilate (dabigatran etexilate is a newly approved agent and post-marketing surveillance on adverse events is not yet available). (B)

Ndegwa, S., Moulton, K. And Argaez, C. 2009⁴.

This HTA reviews the evidence for the clinical effectiveness and safety of dabigatran or rivaroxaban compared to low molecular weight heparins, unfractionated heparin, warfarin or fondaparinux for thromboprophylaxis after elective TKR,

elective THR, or hip fracture surgery. Conducted in Canada in May 2009, the HTA includes one systematic review (comprising three phase III RCTs: RECORD 1, RECORD 2, RECORD 3) and four RCTs (RE-NOVATE, RE-MODEL and RE-MOBILIZE, BISTRO II) that evaluated dabigatran compared to enoxaparin for thromboprophylaxis after THR and TKR, and six RCTs which evaluated rivaroxaban compared with enoxaparin for thromboprophylaxis after THR or TKR.

This HTA has a logical search strategy, a good question with appropriate inclusion and exclusion criteria as well as summaries of appraisals of the quality of the included studies. The conflicts of interest of the authors of the primary studies and external reviewers of the HTA with the pharmaceutical companies Bayer Schering and Boehringer Ingelheim as well as the lack of information provided for the criteria used to appraise the included studies increases the potential for bias.

The authors of the HTA⁴ outlined a large number of limitations from the included trials. Limitations included the following:

- Lack of details regarding allocation concealment and efficacy of blinding.
- RE-NOVATE, RE-MODEL and RE-MOBILIZE trials all used large margins for testing non-inferiority.
- RE-NOVATE, RE-MODEL and RE-MOBILIZE trials used a modified intent-to-treat population rather than a per-protocol population for efficacy analyses, potentially biasing the results toward non-inferiority.
- Differences in dose and timing of initiation for enoxaparin, timing of initiation for dabigatran, type of surgery, duration of prophylaxis and time of randomisation between RE-NOVATE, RE-MODEL and RE-MOBILIZE trials may have introduced heterogeneity in the meta-analysis included in the HTA making pooled results difficult to interpret.
- Comparative risk-benefit assessment was difficult due to definitions of major bleeding events differing significantly between the dabigatran and rivaroxaban clinical trials. The exclusion of surgical site bleeding events in the RECORD trials may have resulted in an underestimation of the risk of major bleeding attributable to rivaroxaban, particularly when more than 80% of all major post-operative bleeding events were confined to the surgical site in phase II trials.
- Greater than 25% of patients in the reviewed trials (except RE-NOVATE) were excluded from the primary efficacy analysis because of an inadequate assessment of thromboembolism. The RECORD, RE-MODEL and RE-MOBILIZE trials included non-evaluable rates of 25% in the sample size calculation to ensure adequate recruitment. The investigators of RECORD 1 and RECORD 3 recruited extra patients to maintain statistical power. Although extra recruitment was not performed in RECORD 2, there was sufficient power to detect statistically significant differences between treatment groups. Extra recruitment did not occur in the RE-MODEL or RE-MOBILIZE trials, potentially limiting the accuracy of results. To confirm that missing data did not affect the power of the study or bias any estimation of the treatment effect, sensitivity analyses were performed in all three RECORD trials as well as in the RE-MODEL and RE-MOBILIZE trials.
- Results of the clinical trials reviewed are not generalisable to the following populations in clinical practice as they were excluded from the studies: patients with severe renal insufficiency, severe liver disease and at high risk of bleeding. Also of note are the low numbers of patients with a previous history of VTE, patients over the age of 75 years and patients at extremities of weight.
- Clinically important outcomes such as post-DVT complications, length of hospital stay, health related quality of life and surgical outcomes (infection, wound healing, drainage, range of motion, chronic pain) were not assessed.
- The low occurrence of symptomatic VTE, death, and major bleeding events should be interpreted with caution because the trials were not powered to investigate differences for these low-frequency events.
- With follow-up periods of up to three months after surgery, no definitive statement can be made about the safety of using rivaroxaban or dabigatran until long term data from ongoing trials and post-marketing surveillance are available.

The HTA reports the following results for dabigatran compared with enoxaparin:

“In the systematic, review-based meta-analysis, pooled results from RE-NOVATE, RE-MODEL, and RE-MOBILIZE (8,210 participants) revealed no statistically significant differences between dabigatran and enoxaparin in any of the end points that were used in the evaluation of safety or efficacy of thromboprophylaxis after THR or TKR.”

“In RE-NOVATE (3,494 participants; THR) and RE-MODEL (2,101 participants; TKR), dabigatran at doses of 220 mg (absolute risk difference: RE-NOVATE; -0.7% (95% CI -2.9 to 1.6; P<0.0001), RE-MODEL; -1.3% (95% CI -7.3 to 4.6; P<0.0003)) or 150 mg once daily (absolute risk difference: RE-NOVATE; 1.9% (95% CI -0.6 to 4.4; P<0.0001), RE-MODEL; 2.8% (95% CI -3.1 to 8.7; P<0.017)) was judged to be statistically non-inferior to enoxaparin 40 mg once daily for the primary outcome (a composite of total VTE and all-cause mortality). Both doses of dabigatran (absolute risk difference: 220mg – 5.8% (95% CI 0.8 to 10.8; P=0.0234), 150mg – 8.4% (95% CI 3.4 to 13.3; P=0.009) were judged to be statistically inferior to enoxaparin 30 mg twice daily in the REMOBILIZE trial (2,615 participants; TKR). The safety results from all three trials showed that the rates of bleeding, liver enzyme elevations, and acute coronary events with either dose of dabigatran were comparable to those of enoxaparin.”

It should be noted that the p-values in the above paragraph have been misinterpreted in the HTA. The p-values do not relate to the absolute risk difference but rather to the pre-specified non-inferiority margins, and for the purpose of this review

they can be ignored. In all three trials dabigatran was either inferior or non-inferior to enoxaparin. Dabigatran was not demonstrated to be superior in any of these trials.

The HTA reports the following results for rivaroxaban compared with enoxaparin:

“Four phase II RCTs and three phase III RCTs (RECORD 1 (4,541 participants; THR), RECORD 2 (2,509 participants; THR), and RECORD 3 (2,531 participants; TKR)) compared rivaroxaban with enoxaparin for thromboprophylaxis after TKR or THR. All three phase 3 studies showed the superior clinical-effectiveness of rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily for the primary end point (any DVT, non-fatal PE, and all-cause mortality) (absolute risk difference: RECORD 1; -2.6% (95% CI -3.7 to -1.5; P<0.001), RECORD 2; 7.3% (95% CI 5.2 to 9.4; P<0.0001), -9.2% (95% CI -12.4 to -5.9; P<0.001)). The rates of major bleeding, liver enzyme elevations, and acute coronary events were comparable between treatment groups in all three trials. Preliminary unpublished results from a phase 3 trial, RECORD 4 (3,148 participants; TKR), indicate that rivaroxaban 10 mg once daily produces a statistically significant reduction (6.9% versus 10.1% respectively; P=0.012) in the incidence of the primary end point (a composite of any DVT, non-fatal PE, and all-cause mortality) when compared with enoxaparin 30 mg twice daily, with low rates of major bleeding in both treatment groups.” (The HTA has misreported that “four phase 2 RCTs...compared rivaroxaban with enoxaparin”, this should state “three” phase two studies).

Turpie, A.G.G., Lassen, M. R. Davidson, B.L. et al. 2009⁵.

This paper was a multicentre RCT including adults (≥18 years) scheduled for total knee arthroplasty who received either rivaroxaban or enoxaparin. A total of 3148 participants were recruited and randomly assigned to either intervention or comparison groups. 123 centres across thirteen countries (USA, Bulgaria, Canada, Denmark, India, Israel, Lithuania, Mexico, Norway, Pakistan, Poland, Sri Lanka and Sweden) participated. The intervention group received 10mg of rivaroxaban orally per day and placebo injections for 11 – 15 days until a bilateral venography was undertaken. The comparison group were administered with 30mg subcutaneous enoxaparin every 12 hours and placebo tablets for 11 – 15 days until a bilateral venography was undertaken.

The study looked at the following efficacy outcomes: composite of any DVT, non fatal PE, or death from any cause up to day 17 after surgery; major VTE (ie, proximal DVT, non fatal PE, or death related to VTE); and incidence of asymptomatic DVT (any, any proximal and distal only), symptomatic VTE in the treatment and follow-up periods (after day 17), and death during follow-up period.

As well as efficacy outcomes the study also reports on safety outcomes: incidence of major bleeding (defined as clinically overt bleeding that was fatal, occurred in a clinical organ, necessitated operation, was outside of the surgical site and associated with a fall in haemoglobin of 2g/dL or more, or required an infusion of two or more units of blood) between intake of the first dose of study drug and two days after the last dose (on-treatment); clinically relevant non-major bleeding (defined as multiple-source bleeding, unexpected haematoma (>25cm²), excessive wound haematoma, nose bleeding (>5mins), gingival bleeding (>5mins), macroscopic haematuria, rectal bleeding, coughing or vomiting blood, vaginal bleeding, blood in semen, intra-articular bleeding trauma, or surgical site bleeding); and any on-treatment bleeding, haemorrhagic wound complications, adverse events and death.

The results of this study were presented by three separate study populations: the per-protocol population, the modified intention-to-treat population and the safety population.

Overall we found the risk of bias for this study to be high and results should be interpreted with caution. The RCT has a clearly focused question and specific inclusion and exclusion criteria as well as appropriate methods of randomisation and concealment of allocation. The substantial conflict of interest by the author's association with and funding from the pharmaceutical company Bayer Schering as well as the complex and large numbers of exclusions (up to 45% of randomised participants were excluded for some analyses) and multilayered analysis with several different per protocol and modified intention-to-treat populations increases the potential for bias.

In the RCT 3.7% of the treatment group and 3.6% of the control group were excluded because they did not take the allocated study medication. A further 45% of the total population randomised were excluded from the primary efficacy analyses because they did not undergo planned surgery, had incomplete assessment of thromboembolism, incorrect time interval between end of surgery and first postoperative dose of study drug, incorrect time interval between last dose of study and assessment of VTE, insufficient compliance, compliance >120%, intake of prohibited anticoagulant, no adequate assessment of efficacy or early asymptomatic DVT.

Results obtained from per-protocol population:

The per-protocol population included 1742 of the 3148 participants who were randomly assigned at the beginning of the study. The primary efficacy outcome (composite of any DVT, non-fatal PE or death from any cause up to day 17 after surgery) occurred in 58 (6.7%) of 864 patients receiving rivaroxaban and 82 (9.3%) of 878 receiving enoxaparin. The difference between groups achieved statistical significance (weighted absolute risk reduction (ARR) 2.71%, 95% CI 0.17 to

5-25). Major VTE (proximal DVT, nonfatal PE, or death related to VTE) occurred in 11 (1.1%) of 1011 patients receiving rivaroxaban and in 15 (1.5%) of 1020 patients receiving enoxaparin. This difference was not statistically significant.

Results obtained from the modified intention-to-treat population:

The modified intention-to-treat population included 1924 of the 3148 participants who were randomly assigned at the beginning of the study. The primary efficacy outcome occurred in 67 (6.9%) of 965 patients receiving rivaroxaban and 97 (10.1%) of 959 patients receiving enoxaparin. The difference between groups achieved statistical significance (weighted ARR 3.19%, 95% CI 0.71 to 5.67; $p=0.0118$). Major VTE occurred in 13 (1.2%) of 1122 patients receiving rivaroxaban and 22 (2.0) of 1112 patients receiving enoxaparin. The difference was not statistically significant. The relative risk reduction was also not statistically significant.

Results obtained from the safety population:

The safety population included 3034 of the 3148 participants who were randomly assigned at the beginning of the study. Eleven (0.7%) of 1526 receiving rivaroxaban and 18 (1.2%) of 1508 receiving enoxaparin had symptomatic VTE events. The difference between groups was not statistically significant. The relative risk reduction was also not statistically significant. Ten (0.7%) of 1526 patients receiving rivaroxaban and four (0.3%) of 1508 patients receiving enoxaparin had major bleeding. The difference between these groups was not statistically significant. Forty-six (3.0%) of 1526 patients taking rivaroxaban and 34 (2.3%) of 1508 patients taking enoxaparin had any major or clinically relevant non-major bleeding. The difference between groups was not statistically significant. Cardiovascular events during therapy and in follow-up occurred in seven (0.5%) of 1526 patients in the rivaroxaban group and 11 (0.7%) of 1508 patients in the enoxaparin group (table 4). No p-value was provided for this comparison.

These results indicate that in the per-protocol population rivaroxaban is not inferior to enoxaparin for DVT, non-fatal PE or death from any cause up to day 17 after surgery; however it is unclear if rivaroxaban is inferior to enoxaparin for effectively reducing major VTE events. In the modified intention-to-treat population rivaroxaban was shown to be more effective than enoxaparin at reducing DVT, non-fatal PE or death from any cause up to day 17 after surgery, however it is unclear if rivaroxaban is more effective at reducing major VTE events than enoxaparin. Despite finding some statistically significant results the study did not reach the required sample size and therefore was not powered to detect a difference for the primary outcome.

Discussion

The results of these studies do not indicate superior effectiveness of rivaroxaban or dabigatran over enoxaparin or other LMWH or warfarin in reducing rates of VTE events or HIT.

The body of evidence included in this review is varied from high to low methodological quality. We cannot be certain that the risk of bias in the included studies has not affected the results.

Population:

The guideline presents recommendations for rivaroxaban and dabigatran for total knee and hip replacement patients' separately³. The RCT only looks at rivaroxaban and dabigatran for TKR patients. The significant proportion of participants (45%) excluded from the analysis of the RCT⁵ greatly reduces our ability to generalise the results of the study to a wider population. The HTA presents data from a number of studies where a combined population of total knee and hip replacement patients were included for rivaroxaban and dabigatran⁴. Combining two groups of patients may confound the outcomes in the included studies of the HTA and potentially affect the rate of adverse events.

Intervention and control:

The HTA⁴ and RCT⁵ interventions included either 10mg of rivaroxaban or 220mg or 150mg of dabigatran. These were compared with a 40mg dose of enoxaparin in all but one RCT. The RE-MOBILIZE study included in the HTA compared dabigatran to a 30mg dose of enoxaparin. This disparity may have impacted on the estimates of bleeding risk in the patient population in this study.

Outcomes:

Conflicts of interest are a concern for all studies included in this evidence review. The NHMRC draft guideline noted 11 of the 16 VTE Prevention Guideline Adaptation Committee members declared several conflicts of interest including some with Bayer Schering Pharmaceuticals³. The HTA did not report conflicts of interests from the authors but did highlight that two of the three external reviewers had conflicts of interest with pharmaceutical companies including Bayer Schering Pharmaceutical⁴. Four of the 13 authors of the RCT declared that they were employees of Bayer Schering Pharmaceuticals⁵. All other authors have served as consultants to Bayer at some time and all of the RCTs were funded

either by Bayer Schering Pharmaceuticals or Boehringer Ingelheim Pharmaceuticals.

We did not identify any studies that reported rates of heparin induced thrombocytopenia.

In August 2009, the PBAC recommended a listing for preventing VTE after total hip and knee replacement surgery, after concluding that the rivaroxaban has uncertain but acceptable cost-effectiveness compared with that of enoxaparin, the drug most often used for this purpose. The decision was based on the RECORD 1, RECORD 2 and RECORD 3 clinical trials, along with a cost-effectiveness model incorporating data from these trials. The committee observed that oral rivaroxaban is more effective, but possibly less safe than subcutaneous enoxaparin for this indication².

Comparison of different study designs and searching for English language articles only are limitations of this review.

Conclusion

From the three studies, reporting the results of eight RCTs, included in this review for patients undergoing total hip or knee replacement, there is inconclusive evidence for the effectiveness of rivaroxaban or dabigatran compared with enoxaparin or LMWH or warfarin for reducing rates of VTE events and heparin induced thrombocytopenia. The recommendations and results of these studies should be interpreted with caution. Additional post-marketing surveillance is required to determine incidence of adverse events caused by rivaroxaban and dabigatran³.

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6. The AGREE Collaboration. 2001. *Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument*. www.agreecollaboration.org.

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Appendix A – Critical Appraisal

Guideline: National Health and Medical Research Council (NHMRC). 2009. Clinical Practice Guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals. DRAFT. Commonwealth of Australia.

Description of Guideline

Patient/population	Adult surgical and medical patients and pregnant women admitted to Australian metropolitan, regional and rural hospitals.
Setting	Australian metropolitan, regional and rural hospitals.
Topics covered	Surgical patients (total hip replacement; hip fracture surgery; total knee replacement; knee arthroscopy; lower leg fractures and injuries with immobilisation; general surgery; urological surgery; gynaecological surgery; abdominal surgery; cardiac, thoracic and vascular surgery; neurosurgery; trauma surgery or spinal surgery); anaesthesia; medical patients (stroke, myocardial infarction, general medicine); cancer patients; and pregnancy and childbirth.
Clinicians	This guideline is intended for doctors, nurses, pharmacists and allied health professionals. It also provides useful information for consumers and those responsible for the quality and safety of health care.
Inclusion Criteria	<ul style="list-style-type: none"> - Patients undergoing surgery including orthopaedic, major general, major gynaecological, urological, cardiothoracic, vascular and neurosurgery. - Patients with acute medical illnesses, including myocardial infarction, stroke and other medical conditions. - Trauma patients. - Patients admitted to intensive care units. - Cancer patients (active or occult, with or without cancer treatment). - Patients admitted during pregnancy and the puerperium.
Exclusion Criteria	<ul style="list-style-type: none"> - Patients under the age of 18 years. - Patients attending hospital as outpatients. - Patients who present to emergency departments but are not admitted. - Elderly or immobile patients cared for at home or in external residential accommodation (unless admitted to hospital). - Patients in long-term hospital rehabilitation. - Patients who have not been hospitalised. - Travel-related venous thromboembolism (VTE).
Comment	For the purposes of this evidence review the NHMRC Guideline was appraised based on the relevant sections; THR (6.1.1) and TKR (6.1.3).

AGREE Criteria for Appraising the Quality of Development of Guidelines

<i>Rate each criterion as strongly disagree (1), disagree (2), agree (3) or strongly agree (4)</i>	MG	TT
Scope and purpose	12/12	12/12
1. The overall objective(s) of the guideline is (are) specifically described.	4	4
2. The clinical question(s) covered by the guideline is (are) specifically described.	4	4
3. The patients to whom the guideline is meant to apply are specifically described.	4	4
Stakeholder involvement	12/16	12/16
4. The guideline development group includes individuals from all the relevant professional groups.	3	3
5. The patients' views and preferences have been sought.	4	4
6. The target users of the guideline are clearly defined.	4	4
7. The guideline has been piloted	1	1
Rigour of development	25/28	25/28
8. Systematic methods were used to search for evidence.	4	4
9. The criteria for selecting the evidence are clearly described.	3	3
10. The methods used for formulating the recommendations are clearly described.	4	4

11. The health benefits, side effects and risks have been considered in formulating the recommendations.	3	3
12. There is an explicit link between the recommendations and the supporting evidence.	4	4
13. The guideline has been externally reviewed by experts prior to its publication.	3	3
14. A procedure for updating the guideline is provided.	4	4
Clarity and presentation	15/16	15/16
15. The recommendations are specific and unambiguous.	4	4
16. The different options for management of the condition are clearly presented.	4	4
17. Key recommendations are easily identifiable.	4	4
18. The guideline is supported with tools for application.	3	3
Applicability	7/12	7/12
19. The potential organisational barriers in applying the recommendations have been discussed	3	3
20. The potential cost implications of applying the recommendations have been considered	3	3
21. The guideline presents key review criteria for monitoring and/or audit purposes.	1	1
Editorial independence	5/8	5/8
22. The guideline is editorially independent from the funding body.	1	1
23. Conflicts of interest of guideline development members have been recorded.	4	4
Would you recommend these guidelines for use in practice?	Yes	

Results

Total Hip Replacement (THR)

Evidence for VTE prophylactic agent – Rivaroxaban

“In two multi-centre international RCTs, rivaroxaban (10mg orally once per day for 35 days) was more effective at reducing the occurrence of deep vein thrombosis (DVT) than low molecular weight heparin (LMWH) (40mg once per day, either for 35 days or 14 days). There were no significant differences in the rates of pulmonary embolism (PE) or adverse events, including death, between the rivaroxaban and LMWH arms.”

Evidence for VTE prophylactic agent – Dabigatran etexilate

“In one multi-centre international RCT, there were no significant differences in rates of DVT or PE with dabigatran etexilate (220mg or 150mg) compared with LMWH (40mg daily). There were no significant differences in the rates of adverse events between the two groups.”

Recommendations for THR

1. Use thromboprophylaxis for all patients admitted to hospital for total hip replacement. (GPP)
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to 35 days following total hip replacement surgery. Use one of the following:
 - low molecular weight heparin (A)
 - fondaparinux (use fondaparinux with caution as it may cause bleeding in those weighing less than 50kg, in the frail, the elderly and those with renal impairment). (B)
 - rivaroxaban (rivaroxaban is a newly approved agent and post-marketing surveillance on adverse events is not yet available). (B)
 - dabigatran etexilate (dabigatran etexilate is a newly approved agent and post-marketing surveillance on adverse events is not yet available). (B)
3. Preoperative administration of thromboprophylaxis is not recommended for patients undergoing total hip replacement surgery. (C)

Total Knee Replacement (TKR)

Evidence for VTE prophylactic agent – Rivaroxaban

“In two RCTs rivaroxaban (10mg orally once per day for two weeks) was more effective at reducing DVT (asymptomatic, symptomatic and distal DVT) than LMWH (40mg subcutaneously once per day for two weeks). There was no difference in non-fatal PE, death or bleeding between rivaroxaban and LMWH.”

Evidence for VTE prophylactic agent – Dabigatran etexilate

“In two RCTs there was no significant difference in rates of DVT or PE with dabigatran etexilate (220mg or 150mg) compared with LMWH (40mg daily). There was no significant difference in any adverse events between dabigatran etexilate and LMWH.”

Recommendations for TKR

1. Use thromboprophylaxis for all patients admitted to hospital for total knee replacement. (GPP)
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to 14 days following total knee replacement surgery. Use one of the following:
 - low molecular weight heparin (A)
 - fondaparinux (use fondaparinux with caution as it may cause bleeding in those weighing less than 50kg, in the frail, the elderly and those with renal impairment). (B)
 - rivaroxaban (rivaroxaban is a newly approved agent and post-marketing surveillance on adverse events is not yet available). (B)
 - dabigatran etexilate (dabigatran etexilate is a newly approved agent and post-marketing surveillance on adverse events is not yet available). (B)

The choice of thromboprophylactic agent to be used after total knee and hip replacement should be based on availability, cost and individual patients' risk characteristics and preferences.

Our comments/summary

This guideline is a draft with the final version due for release in August 2009. Authors of the draft guideline were contacted for clarification of systematic methods used to search for evidence. The final version of the guideline will be supported with the following tools for application; a long version of the guideline, a short version and a patient information guide. Implementation resources will also be considered. The risk of bias of this guideline is low. Recommendations for rivaroxaban and dabigatran are "B" grade recommendations. The NHMRC describe "B" grade evidence to be a body of evidence that can be trusted to guide practice in most situations.

It is important to note that 11 of the 16 VTE Prevention Guideline Adaptation Committee members declared several conflicts of interest including some with Bayer Schering Pharmaceuticals. The Prevention Adaptation Committee also included NHMRC staff. This does not appear to present a conflict of interest as these members are present to provide methodological advice.

Study: Ndegwa, S., Moulton, K. and Argaez, C. 2009. *Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical Effectiveness and Safety.* Health Technology Assessment Rapid Review. Canadian Agency for Drugs and Technologies in Health.

Description of study: Health Technology Assessment

Patient/population	Patients who have undergone elective total hip replacement (THR), elective total knee replacement (TKR), or hip fracture surgery.
N	1 Systematic Review, 11 Randomised Controlled Trials. The total number of patients included in these trials is not reported. Please note all these studies may not have assessed our outcomes of interest.
Intervention/indicator	Thromboprophylaxis using dabigatran or rivaroxaban
Comparison/control	Thromboprophylaxis using low molecular weight heparin (LMWH), unfractionated heparin, warfarin or fondaparinux
Outcomes	All-cause mortality, number of patients withdrawing from trials due to an adverse event, number of patients experiencing at least one adverse event including symptomatic or asymptomatic deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), myocardial infarction, stroke, major bleeding, minor bleeding, or any other adverse event during the treatment phase or the study period.
Inclusion Criteria	Patients undergoing elective THR, elective TKR, or hip fracture surgery, thromboprophylaxis using dabigatran or rivaroxaban compared to thromboprophylaxis using LMWH, unfractionated heparin, warfarin, or fondaparinux.
Exclusion Criteria	All studies that presented non-meta-analytic pooled analyses were excluded.
Date of evidence search	3 rd June 2009

Study Validity

Were there any conflicts of interest in the writing or funding of this review?	Unclear	Conflicts of interest of the authors are not reported. Two of the three external reviewers have conflicts of interest. “Dr. Russell Hull participated on the Magellan Steering Committee for Bayer. He has been a consultant for and has received research grants from Sanofi-Aventis. Dr. Hull has received research grants from LEO Pharma and Pfizer. Dr. John Eikelboom has been a speaker for and has received research support from Bayer. He has been a consultant and has received research support from Bristol-Myers Squibb, Boehringer Ingelheim, and Sanofi-Aventis.”
Were reviewers blind to authors, institutions and affiliations?	Not reported	
Does the review have a clearly- focused question?	Yes	What is the clinical-effectiveness and safety of dabigatran or rivaroxaban compared to LMWH, unfractionated heparin, warfarin, or fondaparinux for thromboprophylaxis after elective THR, elective TKR, or hip fracture surgery?
Does the review have specified inclusion/exclusion criteria?	Yes	See page 5 of HTA.
Were 2 or more independent reviewers used for: 1. application of inclusion criteria to assess eligibility of studies?	Yes	Two reviewers independently applied criteria to select articles for inclusion in the report.

2. extraction of data from study reports?	No	The review of evidence was conducted by one internal HTA reviewer.
3. appraisal of study quality?	No	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	Inclusion and exclusion criteria specified are appropriate.
Does the review document a comprehensive search strategy?	Yes	The authors of the HTA were contacted for a copy of the search strategy. The search strategy included only intervention terms. The authors searched PubMed/Medline, EMBASE, CINAHL and Web of Science from 1999 to 2009. CENTRAL was not searched. Websites of regulatory, health technology assessment and other related agencies were searched for additional reports as were specialised databases. Google was also searched for information on the internet. Hand searching of bibliographies of relevant records was also undertaken.
Was the validity of included trials appraised using appropriate criteria?	Not reported	It is not clear whether a structured appraisal was undertaken and criteria for the appraisal are not reported.
Is there a summary of the results of individual studies?	Yes	See page 13 of HTA for example.
Were the strengths and limitations of included studies and potential impact on the results discussed?	Yes	Methodological limitations of included studies are discussed with regard to their potential impact on the results of the individual studies. See page 28 of HTA.
If meta-analyses were conducted, was it reasonable to do so?	Not applicable	A meta-analysis was not undertaken.
If meta-analyses were conducted, was it done appropriately?	Not applicable	
Other		The following limitations of included trials were noted in the HTA: <ul style="list-style-type: none"> - Lack of details regarding allocation concealment and efficacy of blinding. - RE-NOVATE, RE-MODEL and RE-MOBILIZE trials all used large margins for testing non-inferiority - RE-NOVATE, RE-MODEL and RE-MOBILIZE trials used a modified intent-to-treat population rather than a per-protocol population for efficacy analyses, potentially biasing the results toward non-inferiority. - Differences in dose and timing of initiation for enoxaparin, timing of initiation for dabigatran, type of surgery, duration of prophylaxis and time of randomisation between RE-NOVATE, RE-MODEL and RE-MOBILIZE trials may have introduced heterogeneity in the meta-analysis included in the HTA making pooled results difficult to interpret. - Comparative risk-benefit assessment was difficult due to definitions of major bleeding events differing significantly between the dabigatran and rivaroxaban clinical trials. The exclusion of surgical site bleeding events in the RECORD trials may have resulted in an underestimation of the risk of major bleeding attributable to rivaroxaban, particularly when more than 80% of all major post-operative bleeding events were confined to the surgical site in phase II trials.

	<ul style="list-style-type: none"> - “Greater than 25% of patients in the reviewed trials (except RE-NOVATE) were excluded from the primary efficacy analysis because of an inadequate assessment of thromboembolism. The RECORD, RE-MODEL and RE-MOBILIZE trials included non-evaluable rates of 25% in the sample size calculation to ensure adequate recruitment. The investigators of RECORD 1 and RECORD 3 recruited extra patients to maintain statistical power. Although extra recruitment was not performed in RECORD 2, there was sufficient power to detect statistically significant differences between treatment groups. Extra recruitment did not occur in the RE-MODEL or RE-MOBILIZE trials, potentially limiting the accuracy of results.” To confirm that missing data did not affect the power of the study or bias any estimation of the treatment effect, sensitivity analyses were performed in all three RECORD trials as well as in the RE-MODEL and RE-MOBILIZE trials. - Results of the clinical trials reviewed are not generalisable to the following populations in clinical practice as they were excluded from the studies: patients with severe renal insufficiency, severe liver disease and at high risk of bleeding. Also of note are the low numbers of patients with a previous history of VTE, patients over the age of 75 years and patients at extremities of weight. - “Clinically important outcomes such as post-DVT complications, length of hospital stay, health related quality of life and surgical outcomes (infection, wound healing, drainage, range of motion, chronic pain) were not assessed.” - “The low occurrence of symptomatic VTE, death, and major bleeding events should be interpreted with caution because the trials were not powered to investigate differences for these low-frequency events.” - “With follow-up periods of up to three months after surgery, no definitive statement can be made about the safety of using rivaroxaban or dabigatran until long term data from ongoing trials and post-marketing surveillance are available.” 	
What is the overall risk of bias?	Moderate	This systematic review includes a logical search strategy, good question with inclusion and exclusion criteria as well as summaries of appraisals. However, the potential conflict of interest by the author’s association with the pharmaceutical company Bayer (which produces the pharmaceutical) as well as the lack of information provided for the criteria used to appraise the included studies increases the potential for bias.

Results

One systematic review (incorporating the three phase III RCTs RENOVATE, RE-MODEL, and RE-MOBILIZE), one phase II RCT (BISTRO II) compared dabigatran with enoxaparin for thromboprophylaxis after THR or TKR, and three phase III RCTs (RECORD 1, RECORD 2 and RECORD 3) compared rivaroxaban with enoxaparin for thromboprophylaxis after THR or TKR.

The HTA reports the following results:

“In the systematic, review-based meta-analysis, pooled results from RE-NOVATE, RE-MODEL, and RE-MOBILIZE (8,210 participants) revealed no statistically significant differences between dabigatran and enoxaparin in any of the end points that were used in the evaluation of safety or efficacy of thromboprophylaxis after THR or TKR. In RE-NOVATE (3,494 participants; THR) and RE-MODEL (2,101 participants; TKR), dabigatran at doses of 220 mg (absolute risk difference: RE-NOVATE; -0.7% (95% CI -2.9 to 1.6; P<0.0001), RE-MODEL; -1.3% (95% CI -7.3 to 4.6; P<0.0003)) or 150 mg once daily (absolute risk difference: RE-NOVATE; 1.9% (95% CI -0.6 to 4.4; P<0.0001), RE-MODEL; 2.8% (95% CI -3.1 to 8.7; P<0.017)) was judged to be statistically non-inferior to enoxaparin 40 mg once daily for the primary outcome (a composite of total VTE and all-cause mortality). Both doses of dabigatran (absolute risk difference: 220mg – 5.8% (95% CI 0.8 to 10.8; P=0.0234), 150mg – 8.4% (95% CI 3.4 to 13.3; P=0.009) were judged to be statistically inferior to enoxaparin 30 mg twice daily in the REMOBILIZE trial (2,615 participants; TKR). The safety results from all three trials showed that the rates of bleeding, liver enzyme elevations, and acute coronary events with either dose of dabigatran were comparable with those of enoxaparin.” It should be noted that the above p-values have been misinterpreted in the HTA. The p-values in this case do not relate to the absolute risk difference only to the pre-specified non-inferiority margins.

“Four phase II RCTs and three phase III RCTs (RECORD 1 (4,541 participants; THR), RECORD 2 (2,509 participants; THR), and RECORD 3 (2,531 participants; TKR)) compared rivaroxaban with enoxaparin for thromboprophylaxis after TKR or THR. All three phase III studies showed the superior clinical-effectiveness of rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily for the primary end point (any DVT, non-fatal PE, and all-cause mortality) (absolute risk difference: RECORD 1; -2.6% (95% CI -3.7 to -1.5; P<0.001), RECORD 2; 7.3% (95% CI 5.2 to 9.4; P<0.0001), -9.2% (95% CI -12.4 to -5.9; P<0.001)). The rates of major bleeding, liver enzyme

elevations, and acute coronary events were comparable between treatment groups in all three trials. Preliminary unpublished results from a phase 3 trial, RECORD 4 (3,148 participants; TKR), indicate that rivaroxaban 10 mg once daily produces a statistically significant reduction (6.9% versus 10.1% respectively; P=0.012) in the incidence of the primary end point (a composite of any DVT, non-fatal PE, and all-cause mortality) when compared with enoxaparin 30 mg twice daily, with low rates of major bleeding in both treatment groups.” (The HTA has miss reported that “four phase 2 RCTs...compared rivaroxaban with enoxaparin”, this should state “three” phase two studies).

Author’s Conclusions

“The evidence that dabigatran is at least as effective as enoxaparin for thromboprophylaxis after THR or TKR is conflicting. Of three published phase 3 trials comparing dabigatran with enoxaparin, two showed non-inferiority for the prevention of VTE after THR or TKR, and the trial comparing dabigatran with the Health Canada-approved dosing regimen for enoxaparin did not. All three phase 3 trials evaluating rivaroxaban showed superior clinical effectiveness over enoxaparin for the prevention of VTE after THR or TKR. Based on phase 3 trial findings, the Canadian Expert Drug Advisory Committee (CEDAC) recommended that rivaroxaban, but not dabigatran, be listed in publicly funded drug plans for the prophylaxis of VTE after TKR or THR. There are no head-to-head trials comparing rivaroxaban with dabigatran, or comparing either drug to other anticoagulants. As a result, indirect comparisons should be interpreted with caution because of differences in the methods for assessing outcomes among trials. There is no evidence to support the use of dabigatran or rivaroxaban in patients undergoing HFS. In March 2009, an advisory committee recommended that the United States Food and Drug Administration (FDA) approve rivaroxaban for thromboprophylaxis after TKR or THR while considering data that suggested increased bleeding, hepatotoxicity, and number of cardiovascular events. In conclusion, although some efficacy and safety data for dabigatran and rivaroxaban are available, data from additional trials and post-marketing surveillance will be needed to characterize the role of these anticoagulants for thromboprophylaxis in diverse patient populations after major orthopedic surgery.”

Our comments/summary

This HTA has a moderate risk of bias, predominantly arising from limited information provided on the methods used to appraise the quality of the included studies. The authors identify that the included studies are also open to considerable bias, arising from methodological weaknesses such as a lack of details for allocation concealment and efficacy of blinding, use of large margins for testing non-inferiority, undertaking extra recruitment of participants and not assessing clinically important outcomes including post DVT complications, length of hospital stay, health-related quality of life and surgical outcomes (infection, wound healing, drainage, range of motion, chronic pain). Consultation with relevant clinicians highlighted that it may not be appropriate to combine and interpret the outcomes of total hip and total knee replacement with different doses of rivaroxaban and dabigatran as the effectiveness and bleeding risk is likely to be related to dosage. The authors of the HTA also note that the included studies have several important limitations that make them open to bias. The results of this HTA should therefore be interpreted cautiously.

Study: Turpie, A.G.G., Lassen, M. R., Davidson, B.L., Bauer, K.A., Gent, M., Kwong, L.M., Cushner, F.D., Lotke, P.A., Berkowitz, S.D., Bandel, T.J., Benson, A., Misselwitz, F and Fisher, W.D., for the RECORD 4 Investigators. 2009. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD 4): a randomised trial. *Lancet*; 373:1673-80

Description of study: randomised controlled trial

Patient/population	Males and females aged 18 years or older and scheduled for total knee arthroplasty
N	Total sample size for randomisation = 3148 Total population included in modified intention-to-treat (ITT) population for major venous thromboembolism (VTE): 1122 (rivaroxaban), 1112 (enoxaparin) = 2234 Total population included in modified ITT for primary efficacy (superiority test): 965 (rivaroxaban), 959 (enoxaparin) = 1924 Total population included in per protocol population for primary efficacy (non-inferiority test): 864 (rivaroxaban), 878 (enoxaparin) = 1742
Setting	123 centres from 13 countries (USA, Bulgaria, Canada, Denmark, India, Israel, Lithuania, Mexico, Norway, Pakistan, Poland, Sri Lanka and Sweden)
Intervention/indicator	Oral rivaroxaban 10mg daily and placebo injections for 11 – 15 days until bilateral venography was undertaken.
Comparison/control	Subcutaneous enoxaparin 30mg every 12 hours and placebo tablets for 11 – 15 days until bilateral venography was undertaken
Outcomes	<p><u>Primary efficacy outcome:</u></p> <ul style="list-style-type: none"> - composite of any deep-vein thrombosis (DVT), non fatal pulmonary embolism (PE), or death from any cause up to day 17 after surgery <p><u>Secondary efficacy outcome:</u></p> <ul style="list-style-type: none"> - major VTE (ie, proximal DVT, non fatal PE, or death related to VTE) <p><u>Other efficacy outcomes:</u></p> <ul style="list-style-type: none"> - Incidence of asymptomatic DVT (any, any proximal and distal only), symptomatic VTE in the treatment and follow-up (after day 17) periods, and death during follow-up period. <p><u>Primary safety outcome:</u></p> <ul style="list-style-type: none"> - Incidence of major bleeding (defined as clinically overt bleeding that was fatal, occurred in a clinical organ, necessitated operation, was outside of the surgical site and associated with a fall in haemoglobin of 2g/dL or more, or required an infusion of two or more units of blood) between intake of the first does of study drug and two days after the last dose (on-treatment). <p><u>Secondary safety outcome:</u></p> <ul style="list-style-type: none"> - Clinically relevant non-major bleeding (defined as multiple-source bleeding, unexpected haematoma (>25cm²), excessive wound haematoma, nose bleeding (>5mins), gingival bleeding (>5mins), macroscopic haematuria, rectal bleeding, coughing or vomiting blood, vaginal bleeding, blood in semen, intra-articular bleeding trauma, or surgical site bleeding). <p><u>Other safety outcomes:</u></p> <ul style="list-style-type: none"> - Any on-treatment bleeding, haemorrhagic wound complications, adverse events and death.
Inclusion Criteria	Aged 18 years or older and scheduled for total knee arthroplasty
Exclusion Criteria	<ul style="list-style-type: none"> - Patients who had active bleeding or a high risk of bleeding, or any disorder contradicting the use of enoxaparin or that might necessitate enoxaparin dose adjustment. - Disorders preventing bilateral venography, clinically significant liver disease, severe renal impairment (creatinine clearance <30 mL per min), concomitant use of drugs that strongly inhibit cytochrome P450, such as protease inhibitors or ketoconazole, pregnancy or breastfeeding, planned intermittent pneumatic compression, or the requirement for ongoing anticoagulant treatment.

Study Validity		
Were there any conflicts of interest in the writing or funding of this study?	Yes	SDB, TJB, AB and FM are employees of Bayer Schering Pharma AG. All other authors received honoraria as members of the steering committee and have served as consultants to Bayer Schering Pharma AG. The trial was supported and funded by Bayer Schering Pharma AG and Johnson & Johnson Pharmaceutical Research & Development. The study sponsors were involved in the design of the trial and collected and analysed the data.
Does the study have a clearly focused question?	Yes	To assess the efficacy and safety of oral rivaroxaban 10mg once daily compared with 30mg enoxaparin given subcutaneously every 12 hours for the prevention of VTE after elective total knee arthroplasty.
Is a RCT the appropriate method to answer this question?	Yes	
Does the study have specified inclusion/exclusion criteria?	Yes	See page 1673 of RCT.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Did the study have an adequate method of randomisation?	Yes	Method of randomisation involved randomly assigning participants to study drug through a central telephone system, stratified by centre with permuted blocks of four patients, on a double-blind and double-dummy basis.
Was allocation to intervention group concealed?	Yes	Allocation to intervention group was concealed by randomly assigning participants to drugs through a central telephone system.
Were patients blind to intervention group?	Yes	The study is described as “double blind trial”. It is not specifically stated that patients and investigators are blind however the use of a placebo injection and placebo tablets suggests that patients were blind to the treatment. It is not clear if both the dispensing nurse and investigators were blind.
Were investigators and care providers blind to intervention group?	Yes	As above.
Were outcome assessors blind to intervention group?	Yes	The authors note that central independent adjudication committees who were masked to allocation assessed all outcomes.
Aside from the experimental intervention, were the groups treated the same?	Yes	Aside from the experimental intervention both groups were treated the same. The intervention group received oral rivaroxaban once daily and placebo subcutaneous injections every 12 hours. The comparison group received subcutaneous injections of enoxaparin every 12 hours and a placebo tablet once daily.
Was there sufficient duration of follow-up?	Yes	Follow-up was for 30-35 days after the last dose of either rivaroxaban or enoxaparin. Clinically this is an appropriate length of time needed to observe adverse events.

<p>All outcomes were measured in a standard, valid and reliable way?</p>	<p>Partial</p>	<p><u>Efficacy Outcomes:</u> All efficacy outcomes were measured by: venography, ultrasound, pulmonary angiography by ventilation-perfusion lung scintigraphy, chest radiography, and contrast enhanced spiral CT. Clinical advice suggests that these various assessment methods vary in their effectiveness and are often dependant on the clinical experience of the operator.</p> <p><u>Safety Outcomes:</u> Tools used to assess safety outcomes were not detailed.</p>
<p>Were outcomes assessed objectively and independently?</p>	<p>Not reported</p>	<p>The authors do not discuss whether the outcomes were assessed objectively and independently. However, considering that the adjudication committee members were masked, objectivity and subjectivity of outcome assessment is important.</p>
<p>Was the study sufficiently powered to detect any differences between the groups?</p>	<p>Partial</p>	<p><u>Actual recruitment</u> Total sample size for randomisation = 3148 Total population included in modified ITT population for major VTE: 1122 (rivaroxaban), 1112(enoxaparin) = 2234 Total population included in modified ITT for primary efficacy (superiority test): 965 (rivaroxaban), 959 (enoxaparin) = 1924 Total population included in per protocol population for primary efficacy (non-inferiority test): 864 (rivaroxaban), 878 (enoxaparin) = 1742</p> <p><u>Superiority analysis (modified ITT):</u> Sample size was calculated on the basis of an assumed event rate of 27% for the primary efficacy outcome in the enoxaparin group. With a power of 90% and a two-sided type-1 error rate of 5%, 860 patients were needed in each treatment group to show a 25% relative risk reduction in the rivaroxaban group compared to the enoxaparin group. Given the assumption of an inadequate assessment of VTE in 25% of participants, the target sample size was 2300 patients.</p> <p><u>Non-inferiority analysis (per-protocol):</u> Non-inferiority test preceding the superiority test had a statistical power of 91% if an absolute risk reduction of 3% was assumed in the rivaroxaban group compared to the enoxaparin group. If the absolute risk reduction was assumed to be only 2% a statistical power of 80% would be maintained.</p> <p><u>Decision made to amend sample sizes</u> “During the study, sample size was increased from the planned 2300 participants; primarily because preliminary blinded study data indicated a lower overall blinded event rate for the primary efficacy endpoint and a higher number of venograms inadequate for assessment than originally assumed. Furthermore, unblinded data from RECORD3 indicated a higher relative risk reduction than originally assumed in that study (49% vs 25%).⁴ The following assumptions were modified: the event rate for the comparator group was changed from 27% to 13.25%; the relative risk reduction was changed from 25% to 35%; the effective sample size was changed from 860 to 994 subjects per treatment group; the rate of venograms inadequate for assessment was changed from 25% to 35%. On the basis of the above, the total sample size of randomised patients needed was calculated as 3058. For the non-inferiority test, the same non-inferiority limit of -4% was used.” This study did not reach the required sample size and therefore it is not powered to see a difference for the primary outcome. It should be noted however that the study did find a statistically significant result for the primary efficacy outcome in the per-protocol population and a statistically significant result for the modified intention-to-treat population for primary efficacy (superiority test).</p>

If statistical analysis was undertaken, was this appropriate?	Partial	<p>Three analyses were undertaken which excluded substantial proportions of the randomised population. “Efficacy of rivaroxaban was assessed as non-inferiority to that of enoxaparin in the per-protocol population; if non-inferiority was shown, we assessed whether rivaroxaban had superior efficacy to enoxaparin in the modified intention-to-treat population.”</p> <p><u>Primary efficacy analysis:</u> Difference in the incidence of primary efficacy outcome between rivaroxaban and enoxaparin – stratification using Mantel-Haenszel weighting (Odds Ratio and can be extended to Relative Risk – the study states it was used for incidence=risk)? Difference in the incidence of major bleeding between enoxaparin and rivaroxaban was analysed with Mantel-Haenszel weighting. Sex and race analysed with use of Cochran-Mantel-Haenszel test adjusted for geographical region. Age, weight and BMI analysed with two-way ANOVA with treatment and geographical region as fixed effects. All other variables were analysed descriptively and statistical tests were done with two-sided type 1 error rate of 5%. Statistical methods were not provided in the study protocol therefore it is unclear if statistical analysis was planned a priori or analysed according to the study protocol. The authors do not discuss whether the data was checked for normality and thus use of parametric versus non-parametric testing is unknown. Point estimates and measures of variability were presented for the primary outcome. Potential confounders (sex, age, race, weight and BMI) were identified and taken into account in the analysis. The authors did not report if any adjustments were made for multiple testing. All patients with missing data were excluded from the study.</p>
Were the groups similar at baseline with regards to key prognostic variables?	Yes	<p>Key prognostic variables including age, gender, BMI, ethnicity, history of disease, and surgical characteristics were all similar at baseline. See table 2, page 1676.</p>
What percentage of the individuals recruited into each arm of the study dropped out or were excluded?	3.7% treatment 3.6% comparison	<p>At baseline, 3148 patients were randomly assigned to intervention or control. Fifty-eight of the 1584 who were allocated to the intervention group were excluded from the safety population because they did not take the study medication and 56 out of the 1564 who were allocated to the comparison group were excluded from the safety population because they did not take the study medication.</p> <p>More than 45% of patients randomised were excluded from the primary efficacy analyses</p>
Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	<p>Patients were analysed per protocol and by modified intention-to-treat. Patients who did not take the drugs, took an increased dosage of the drug or took the wrong drug were excluded.</p> <p><u>In the intervention group:</u> 1122 included in modified ITT population for major VTE, 965 included in modified ITT for primary efficacy (superiority test), 864 included in per-protocol population for primary efficacy (non-inferiority test)</p> <p><u>In the comparison group:</u> 1112 included in modified ITT population for major VTE, 959 included in modified ITT for primary efficacy (superiority test), 878 included in per protocol population for primary efficacy (non-inferiority test).</p>
Is the paper free of selective outcome reporting?	No	<p>Not all planned outcomes were measured and reported. Several pre-specified outcomes were not reported: incidence of DVT (total, proximal, distal); the composite endpoint comprising major VTE and treatment-emergent major bleeding; incidence of the composite endpoint that results from the primary endpoint by substituting VTE related death for all death; incidence of the composite endpoint that results from major VTE by substituting all cause mortality for VTE-related death; treatment-emergent major bleedings. There also appears to be additional safety outcomes reported. These include: post-operative wound infection; requirement of blood transfusions; mean volume of blood transfusion; patients with post-operative drain; mean volume in drain; drug related adverse events; cardiovascular adverse events (cardiovascular death, ischaemic stroke, myocardial infarction); cardiovascular events during total study period. These additional safety outcomes</p>

		are reported in the paper however do not appear in the study protocol nor are they included in the description of primary, secondary or other safety outcomes. The study also reports outcome data up to day 17 of treatment whereas the study protocol outlines the timeline for outcome measures to be 12+/-4days.
Were the outcomes measured appropriate?	Yes	The outcomes measured seem appropriate to the question being asked.
Other		
What is the overall risk of bias?	High	This RCT has a clearly focused question and specific inclusion and exclusion criteria as well as appropriate methods of randomisation and concealment of allocation. However, the substantial conflict of interest by the author's association with the pharmaceutical company Bayer (which produces the pharmaceutical) as well as the complex and large numbers of exclusions and multilayered analysis increases the potential for bias.

Results

- Mean time from the end of surgery to the first intake of study drug was 7 h 35 min (SD 3 h 28 min) for rivaroxaban compared with 17 h 7 min (4 h 47 min) for enoxaparin.
- Mean duration of taking the study drug was 11.7 days (SD 2.5) with rivaroxaban and 11.0 days (2.4) with enoxaparin.

Per-protocol population:

- The primary efficacy outcome (composite of any DVT, non-fatal PE or death from any cause up to day 17 after surgery) occurred in 58 (6.7%) of 864 patients receiving rivaroxaban and 82 (9.3%) of 878 receiving enoxaparin (weighted absolute risk reduction 2.71%, 95% CI 0.17 to 5.25)
- Major venous thromboembolism (proximal DVT, nonfatal PE, or death related to VTE) occurred in 11 (1.1%) of 1011 patients receiving rivaroxaban and in 15 (1.5%) of 1020 patients receiving enoxaparin (weighted absolute risk reduction 0.37%, 95% CI -0.60 to 1.34)

Modified intention-to-treat population:

- The primary efficacy outcome occurred in 67 (6.9%) of 965 patients receiving rivaroxaban and 97 (10.1%) of 959 patients receiving enoxaparin (weighted absolute risk reduction 3.19%, 95% CI 0.71 to 5.67; p=0.0118)
- Major venous thromboembolism occurred in 13 (1.2%) of 1122 patients receiving rivaroxaban and 22 (2.0) of 1112 patients receiving enoxaparin. The difference was not statistically significant (weighted absolute risk reduction 0.80%, 95% CI -0.22, 1.82; p=0.1237; table 3). The relative risk reduction was 41.44% (95% CI -15.67 to 70.35; p=0.1646).

Safety population:

- 11 (0.7%) of 1526 taking rivaroxaban and 18 (1.2%) of 1508 taking enoxaparin had symptomatic VTE events (weighted absolute risk reduction 0.47%, 95% CI -0.23 to 1.16; p=0.1868; table 3). The relative risk reduction was 39.61% (95% CI -27.43 to 71.38; p=0.2495).
- Ten (0.7%) of 1526 patients receiving rivaroxaban and four (0.3%) of 1508 patients receiving enoxaparin had major bleeding (weighted absolute risk increase 0.39%, 95% CI -0.09 to 0.88; p=0.1096; table 4).
- 46 (3.0%) of 1526 patients taking rivaroxaban and 34 (2.3%) of 1508 patients had any major and clinically relevant non-major bleeding (p=0.1790)
- Cardiovascular events during therapy and in follow-up occurred in seven (0.5%) of 1526 patients in the rivaroxaban group and 11 (0.7%) of 1508 patients in the enoxaparin group (table 4).

Additional safety outcomes measured:

	Rivaroxaban 10 mg once daily (n=1526)	Enoxaparin 30 mg every 12 h (n=1508)	p value
Bleeding outcomes			
Number with major bleeding between start of treatment and 2 days after last dose (%; 95% CI)*	10 (0.7%, 0.3-1.2)	4 (0.3%, 0.1-0.7)	0.1096
Fatal bleeding	1 (0.1%)	0	..
Bleeding into a critical organ	1 (0.1%)	2 (0.1%)†	..
Bleeding leading to reoperation	5 (0.3%)	2 (0.1%)	..
Clinically overt bleeding, outside of surgical site leading to a decreased haemoglobin level	4 (0.3%)‡	0	..
Clinically overt bleeding, outside of surgical site, leading to a transfusion of ≥2 units of blood	4 (0.3%)‡	0	..
Number with clinically relevant non-major bleeding between start of treatment and 2 days after last dose (%; 95% CI)	39 (2.6%, 1.8-3.5)	30 (2.0, 1.4-2.8)	..
Number with non-major bleeding between start of treatment and 2 days after last dose (%; 95% CI)	155 (10.2%, 8.7-11.8)	138 (9.2, 7.7-10.7)	..
Haemorrhagic wound complications§	21 (1.4%)	22 (1.5%)	..
Other non-major bleeding (%; 95% CI)	124 (8.1%, 6.8-9.6)	112 (7.4%, 6.2-8.9)	..
Number with major bleeding plus clinically relevant non-major bleeding between start of treatment and 2 days after last dose (%; 95% CI)*	46 (3.0%, 2.2-4.0)	34 (2.3%, 1.6-3.1)	0.1790
Number with any bleeding between start of treatment and 2 days after last dose (%; 95% CI)	160 (10.5%, 9.0-12.1)	142 (9.4%, 8.0-11.0)	0.3287
Other safety outcomes			
Postoperative wound infection¶	4 (0.3%)	3 (0.2%)	..
Requirement of blood transfusions	628 (41.2%)	597 (39.6%)	..
Mean (SD) volume of blood transfusion (mL)	574 (289)	558 (275)	..
Patients with postoperative drain	1030 (67.5%)	995 (66.0%)	..
Mean (SD) volume in drain (mL)	604 (404)	625 (403)	..
Any adverse event between start of treatment and 2 days after last dose	1222 (80.1%)	1216 (80.6%)	..
Drug-related adverse event	310 (20.3%)	295 (19.6%)	..
Serious adverse event between start of treatment and 2 days after last dose	80 (5.2%)	106 (7.0%)	..
Serious adverse event during the total study period	114 (7.5%)	134 (8.9%)	..
Cardiovascular adverse event ≤1 day after last day of study medication	2 (0.1%)	8 (0.5%)	..
Cardiovascular death	0	3 (0.2%)	..
Ischaemic stroke	1 (0.1%)	2 (0.1%)	..
Myocardial infarction	1 (0.1%)	3 (0.2%)	..
Cardiovascular adverse event > 1 day after the last dose of study medication	5 (0.3%)	3 (0.2%)	..
Cardiovascular death	2 (0.1%)	0	..
Ischaemic stroke	2 (0.1%)	0	..
Myocardial infarction	0	2 (0.1%)	..
Unexplained death	1 (0.1%)	1 (0.1%)	..
Cardiovascular events during total study period	7 (0.5%)	11 (0.7%)	..
*Some patients had events that fall into more than one category. †Includes one patient who had intraspinal bleeding or haemorrhagic spinal puncture. ‡The same four patients. §Haemorrhagic wound complications were defined as a composite of excessive wound haematoma and reported bleeding at the surgical site. ¶Postoperative wound infection was classified according to the Medical Dictionary for Regulatory Activities (http://www.meddr.msso.com/MSSOWeb/index.htm).			

Table 4: Safety outcomes

Author's conclusions

In abstract:

“The primary efficacy outcome occurred in 67 (6.9%) of 965 patients given rivaroxaban and in 97 (10.1%) of 959 given enoxaparin (absolute risk reduction 3.19%, 95% CI 0.71 to 5.67; $p=0.0118$). Ten (0.7%) of 1526 patients given rivaroxaban and four (0.3%) of 1508 given enoxaparin had major bleeding ($p=0.1096$). Oral rivaroxaban 10 mg once daily for 10–14 days was significantly superior to subcutaneous enoxaparin 30 mg given every 12 h for the prevention of venous thromboembolism after total knee arthroplasty.”

In text:

“Rivaroxaban, given as a once-daily 10 mg fixed dose 6–8 h postoperatively, is the first new oral anticoagulant to significantly reduce the incidence of venous thromboembolism after total knee arthroplasty, compared with enoxaparin 30 mg twice daily, starting 12–24 h postoperatively, without a significant difference in the risk of major or clinically relevant bleeding.”

Our comments/summary

This RCT has a high risk of bias, arising from the complex and large numbers of exclusions and multilayered analysis as well as the substantial conflict of interest by the author's association with and funding by the pharmaceutical company Bayer (which produces the pharmaceutical). Safety outcomes do not appear to be powered to detect a difference. The results of this RCT should therefore be interpreted cautiously. Given the exclusion of 45% of patients who met the inclusion criteria the generalisability of this study is low.
