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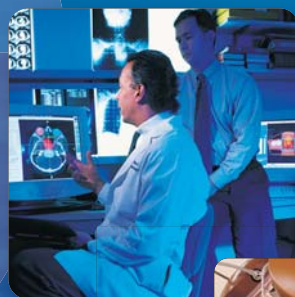
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May 2009
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Dabigatran or Rivaroxaban Versus Other
Anticoagulants for Thromboprophylaxis After
Major Orthopedic Surgery: Systematic Review
of Comparative Clinical-Effectiveness and Safety



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Canadian Agency for Drugs and Technologies in Health

**Dabigatran or Rivaroxaban Versus Other Anticoagulants
for Thromboprophylaxis After Major Orthopedic Surgery:
Systematic Review of Comparative
Clinical-Effectiveness and Safety**

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May 2009

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Canadian Agency for
Drugs and Technologies
in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

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The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness, particularly in the case of new and emerging health technologies for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete, and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

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Industry: The following manufacturers were provided with an opportunity to comment on an earlier version of this report: Bayer HealthCare and Boehringer Ingelheim (Canada) Ltd./Ltée. All comments that were received were considered when preparing the final report.

Conflict 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.

ACRONYMS AND ABBREVIATIONS

ACCP	American College of Chest Physicians
CEDAC	Canadian Expert Drug Advisory Committee
CI	confidence interval
DVT	deep vein thrombosis
FDA	Food and Drug Administration (United States)
HFS	hip fracture surgery
HTIS	Health Technology Inquiry Service
LMWH	low-molecular-weight heparin
mITT	modified intent-to-treat
PE	pulmonary embolism
RCT	randomized controlled trial
THR	total hip replacement
TKR	total knee replacement
qd	once daily
UFH	unfractionated heparin
VTE	venous thromboembolism

TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS	ii
EXECUTIVE SUMMARY	iv
1 CONTEXT AND POLICY ISSUES	1
2 RESEARCH QUESTION.....	2
3 METHODS	2
3.1 Literature Search	2
3.2 Article selection	5
4 SUMMARY OF FINDINGS.....	5
4.1 Health Technology Assessments.....	5
4.2 Systematic Reviews and Meta-Analyses	5
4.2.1 Dabigatran	5
4.3 Randomized Controlled Trials.....	6
4.3.1 Dabigatran	6
4.3.2 Rivaroxaban.....	18
4.4 Limitations	28
4.4.1 Limitations of Systematic Review.....	28
4.4.2 Methodological limitations of included trials	28
4.4.3 Knowledge gaps	29
5 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING.....	29
6 REFERENCES.....	31
APPENDIX 1: Completed (Published and Unpublished) and Ongoing Clinical Trials.....	35
APPENDIX 2: Definitions Used in Clinical Trials for Bleeding.....	36

EXECUTIVE SUMMARY

Context and Policy Issues

Venous thromboembolism (VTE) can lead to increased morbidity and mortality through the clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE). Patients undergoing major orthopedic surgery — including elective total hip replacement (THR), elective total knee replacement (TKR), and hip fracture surgery (HFS) — have an elevated risk of VTE. As a result, it has become standard practice that patients undergoing major orthopedic surgery receive thromboprophylaxis with an anticoagulant. Dabigatran etexilate (Pradax™) and rivaroxaban (Xarelto®) are anticoagulants that were approved by Health Canada in 2008 for the prevention of VTE in patients who have undergone elective THR or TKR. When compared with other anticoagulants, dabigatran and rivaroxaban offer potential advantages that include fixed once-daily dosing, oral administration, rapid onset of action, low potential for interactions with other drugs, and no requirement for anticoagulation monitoring. However, there are several concerns regarding potential harm from using dabigatran and rivaroxaban, including an increased risk for hepatotoxicity, clinically significant bleeding, and acute coronary events. In light of an increasing trend in major orthopedic surgeries being conducted in Canada, this report reviews the evidence for the clinical-effectiveness and safety of dabigatran and rivaroxaban compared with anticoagulants currently being used in clinical practice for the prevention of VTE after major orthopedic surgery.

Research Question

What is the clinical-effectiveness and safety of dabigatran or rivaroxaban compared to low-molecular-weight heparins (LMWH), unfractionated heparin, warfarin, or fondaparinux for thromboprophylaxis after elective total hip replacement, elective total knee replacement, or hip fracture surgery?

Methods

Published English-language reports of any study, regardless of design, were identified by searching electronic databases between 1999 and April 17, 2009. The websites of regulatory, health technology assessment, and other related agencies were searched for additional reports. Searches were supplemented by hand searching the bibliographies of relevant reports. Two reviewers independently selected articles for inclusion using pre-defined criteria.

Summary of Findings

One systematic review, one phase 2 RCT (BISTRO II), and three phase 3 RCTs (RE-NOVATE, RE-MODEL, and RE-MOBILIZE) compared dabigatran with enoxaparin for thromboprophylaxis after THR or TKR. 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 or 150 mg once daily 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 were judged to be statistically inferior to enoxaparin 30 mg twice daily in the RE-MOBILIZE 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.

Four phase 2 RCTs and three phase 3 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). 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 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.

Limitations

Patients with severe renal insufficiency, severe liver disease, or at high risk of bleeding were excluded from the reviewed trials. The low numbers of patients with a previous history of VTE, over the age of 75 years, or at extremities of weight limited the generalizability of the results to populations in clinical practice. Clinically important outcomes such as post-DVT complications, length of hospital stay, health-related quality of life, and surgical outcomes were not assessed. The definitions of major bleeding events differed significantly between the dabigatran and rivaroxaban clinical trials, making comparative risk-benefit assessments difficult. More than 25% of patients (except in RE-NOVATE) were excluded from the primary efficacy analysis due to inadequate assessment of thromboembolism by contrast venography. Asymptomatic DVTs (particularly distal) accounted for most of the primary outcome composite events, but the clinical importance of asymptomatic DVTs as a surrogate measure of symptomatic events has not been fully elucidated. The low occurrence of symptomatic VTE, death, and major bleeding events should be interpreted with caution because the trials were not powered to investigate the differences in these low-frequency events. No definitive statements can be made about the safety of rivaroxaban or dabigatran until long-term data from ongoing trials and post-marketing surveillance are available. There have been no head-to-head comparisons of dabigatran or rivaroxaban with each other or with other

LMWH, warfarin, unfractionated heparin, or fondaparinux. No trials have yet assessed the safety and efficacy of dabigatran or rivaroxaban for HFS.

Conclusions and Implications for Decision or Policy Making

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.

Title: Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety

Date: May 2009

1 CONTEXT AND POLICY ISSUES

Venous thromboembolism (VTE) is a condition that can lead to increased morbidity and mortality through the clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE).¹ The most common form of VTE occurs when a thrombus (blood clot) forms in the calf vein (distal DVT) or thigh vein (proximal DVT).¹ Asymptomatic DVT is more common than symptomatic DVT, and most of these thrombi resolve spontaneously without long-term sequelae. In some cases, the thrombus may propagate and lead to symptoms of venous occlusion (including calf pain and swelling), or dislodge and travel to the lungs, resulting in a pulmonary embolism (PE).¹ PE is the most common cause of preventable death in hospitals.² More than 90% of acute cases of PE are due to proximal DVTs.^{3,4} Contrast venography is the reference test for the confirmatory diagnosis of DVT because it provides the ability to investigate the distal and proximal venous system for thrombosis.⁵

Patients undergoing major orthopedic surgery — including elective total hip replacement (THR), elective total knee replacement (TKR), and hip fracture surgery (HFS) — have an elevated risk of VTE.⁶ The increased risk is believed to stem from stasis of venous blood flow due to reduced mobility and direct injury to the veins during surgery.⁶ Without primary thromboprophylaxis, DVT has been reported to occur in 42% to 57% of patients undergoing THR and 41% to 85% of patients undergoing TKR.⁷ Of the patients developing DVT, fatal PE has been reported to occur in 0.1% to 2.0% of patients undergoing THR and 0.1% to 1.7% of patients undergoing TKR. The rates of DVT after HFS have been

reported to occur in 46% to 60% of patients, with 0.3% to 7.5% developing fatal PE.⁷ As a result, it has become standard practice that patients undergoing major orthopedic surgery receive thromboprophylaxis with anticoagulation therapy.⁶

Evidence-based consensus guidelines that were published in 2008 by the American College of Chest Physicians (ACCP) recommend that patients undergoing THR or TKR receive routine thromboprophylaxis using a low-molecular-weight heparin (LMWH), warfarin, or fondaparinux for 10 to 35 days after surgery.⁶ LMWHs that are approved by Health Canada for thromboprophylaxis after orthopedic surgery include enoxaparin, dalteparin, tinzaparin, and nadroparin.⁸ The ACCP guidelines recommend using fondaparinux, a LMWH, warfarin, or unfractionated heparin (UFH) for at least 10 days (and up to 35 days with the exception of UFH) after HFS.⁶ LMWHs are the most commonly used agents for the prevention of VTE after orthopedic surgery.⁹ In the United States, enoxaparin is the most frequently used LMWH for thromboprophylaxis after major orthopedic surgery.^{9,10} In Canada, there is evidence that dalteparin is preferred over enoxaparin for thromboprophylaxis in acutely ill medical patients.¹¹ This finding could extend to patients undergoing major orthopedic surgery.

Although these anticoagulants have proved to be effective in reducing the risk of thromboembolic disease, they are associated with significant drawbacks that limit their use and acceptability for long-term anticoagulation in an outpatient setting (Table 1).¹²⁻¹⁴ For example, UFH, LMWH, and fondaparinux are administered subcutaneously, which make them less convenient for long-term use.^{8,15,16} Furthermore, the use of UFH and LMWH (to a lesser extent) has been associated with a risk of heparin-induced thrombocytopenia, a rare but potentially serious adverse reaction resulting in a decrease in the number of platelets.^{8,15} Warfarin has a slower onset and offset of action, a narrower therapeutic window, and less predictable patient response, which is influenced by factors such as genetic variations, and food and drug interactions.¹⁷ Therefore, patients receiving

warfarin require anticoagulation monitoring and dose adjustment.¹⁷

Dabigatran etexilate (Pradax™, Boehringer Ingelheim) and rivaroxaban (Xarelto®, Bayer) are anticoagulants that were approved by Health Canada in 2008 for the prevention of VTE in patients who have undergone elective THR or TKR.¹⁸⁻²⁰ Dabigatran etexilate is a pro-drug that acts as a direct thrombin inhibitor after conversion to the active drug.²¹ Rivaroxaban is a selective factor Xa inhibitor.²² The inhibition of thrombin or factor Xa in the blood coagulation cascade prevents the development of blood clots.²³ Dabigatran and rivaroxaban offer several advantages compared to other anticoagulants. Their more predictable pharmacokinetic profiles allow for fixed once daily oral administration. They have a more rapid onset of action, a lower potential for interactions with other drugs, and no requirement for anticoagulation monitoring (Table 1).^{13,24} There are concerns, however, about the potential harm of using dabigatran and rivaroxaban. Ximelagatran, an anticoagulant in the same class as dabigatran, was never approved in North America because it induced hepatotoxicity.²⁵⁻²⁷ Other potential safety concerns relating to the use of rivaroxaban or dabigatran include an increased risk of clinically significant bleeding and an increase in acute coronary events due to rebound activation of the coagulation cascade once the drug is discontinued.^{28,29}

Between 2005 and 2006, there were 68,746 hospitalizations for THR (28,045) and TKR (40,701) in Canada, representing a 10-year increase of 101% and an annual increase of 17%.³⁰ In light of this increasing trend, risk-benefit assessments of new anticoagulants are needed to help determine their role in thromboprophylaxis after orthopedic surgery. This report reviews the evidence for the clinical effectiveness and safety of dabigatran and rivaroxaban compared with anticoagulants

currently being used in clinical practice for the prevention of VTE after major orthopedic surgery.

2 RESEARCH QUESTION

What is the comparative clinical-effectiveness and safety of dabigatran or rivaroxaban versus low-molecular-weight heparins, unfractionated heparin, warfarin, or fondaparinux for thromboprophylaxis after elective total hip replacement, elective total knee replacement, or hip fracture surgery?

3 METHODS

3.1 Literature Search

Published English-language reports, of any study design, were identified through electronic searches of EMBASE, MEDLINE, and CINAHL from 1999 through January 2009. Citation alerts were established in the EMBASE, MEDLINE, and CINAHL databases. Information was retrieved continuously until April 17, 2009. Searches were performed using PubMed and The Cochrane Library (Issue 4, 2008) databases. The websites of regulatory, health technology assessment, and other related agencies were searched for additional reports, as were specialized databases (for example, University of York Centre for Reviews and Dissemination). The Google™ search engine was used to search for information on the Internet. Electronic and web searches were supplemented by hand searching of bibliographies of relevant records to include information from clinical trials and guidelines that was not originally retrieved in the literature search.

Table 1: Comparison of Anticoagulants^{13-17,21,22,31,32}

Parameter	Dabigatran (Pradax™)	Rivaroxaban (Xarelto®)	Fondaparinux (Arixtra®)	LMWH		UFH (Hepalean®)	Warfarin (Coumadin®)
				Enoxaparin (Lovenox®)	Dalteparin (Fragmin®)		
Target	Factor IIa (thrombin) Direct	Factor Xa Direct	Factor Xa Indirect	Factor Xa and Factor IIa (thrombin) Indirect		Antithrombin III	Vitamin K epoxide reductase
Route	Oral	Oral	SC	SC		SC	Oral
Peak Plasma Levels (Healthy Volunteers)*	0.5 to 2 hours <i>Post-surgery:</i> 7 to 9 hours	2 to 4 hours	2 to 3 hours	3 to 5 hours	4 hours	1 to 3 hours	4 hours Therapeutic effect in 5 to 7 days
Half-Life Elimination* (h)	11 <i>Post-surgery:</i> 14 to 17	5 to 9 <i>Post-surgery:</i> 7 to 11	17 to 21	4 to 7	3 to 4	1 to 2	20 to 60
Dosing for Thromboprophylaxis After Orthopedic Surgery	<i>Initial:</i> 110 mg 1 to 4 hours after surgery <i>Maintenance:</i> 220 mg once daily <i>Duration:</i> 10 days for knee replacement or 28 to 35 days for hip replacement	<i>Initial:</i> 10 mg 6 to 10 hours after surgery <i>Maintenance:</i> 10 mg once daily <i>Duration:</i> 14 days for knee replacement or 35 days for hip replacement	2.5 mg once daily 6 to 24 hours after surgery <i>Duration:</i> Up to 11 days following hip or knee replacement or up to 32 days following hip fracture surgery	30 mg twice daily within 12 to 24 hours after surgery <i>Duration:</i> 7 to 14 days	5,000 IU daily starting the evening before surgery <i>Duration:</i> 5 to 7 days minimum	5,000 units every 8 to 12 hours starting 1 to 2 hours after surgery <i>Duration:</i> 5 to 7 days	Individualized once daily dosing based on target INR 2.5 (range 2 to 3) started preoperatively or the evening of surgery <i>Duration:</i> 10 to 35 days

Table 1: Comparison of Anticoagulants^{13-17,21,22,31,32}

Parameter	Dabigatran (Pradax™)	Rivaroxaban (Xarelto®)	Fondaparinux (Arixtra®)	LMWH		UFH (Hepalean®)	Warfarin (Coumadin®)
				Enoxaparin (Lovenox®)	Dalteparin (Fragmin®)		
Routine Coagulation Monitoring Required	No	No	No	No		No	Yes
Use With Renal Insufficiency	<i>Moderate:</i> Dosage adjustment (150 mg daily) <i>Severe:</i> Contraindicated	<i>Moderate:</i> Use caution <i>Severe:</i> Not recommended	<i>Moderate:</i> Use caution <i>Severe:</i> Contraindicated	<i>Moderate:</i> Use caution <i>Severe:</i> Dosage Adjustment		<i>Moderate:</i> Yes <i>Severe:</i> Use with caution	<i>Moderate:</i> Use with caution <i>Severe:</i> Use with caution
Use With Hepatic Insufficiency	Not recommended	Contraindicated	Use with caution	Use with caution		Use with caution	Use with caution
Potential for HIT	No	No	No	Low		High	No
Drug Interactions [†]	Quinidine, amiodarone, antacids, potent P-gp inhibitors (e.g., verapamil, clarithromycin)	Potent inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, voriconazole, ritonavir, rifampicin), strong CYP3A4 inducers (e.g. phenytoin, carbamazepine)	No clinically significant drug interactions known	No clinically significant drug interactions known		No clinically significant drug interactions known	Multiple drugs
Reversal of Anticoagulant Effect	rFVIIa, APCC (in rats) ³³	rFVIIa, APCC (in rats and primates) ^{34,35}	rFVIIa (partial) ³⁶	Protamine sulfate (partial)		Protamine sulfate	Vitamin K ₁ , FFP, PCC

APCC=activated prothrombin complex concentrate; CYP3A4=cytochrome P450 enzyme 3A4; FFP=fresh frozen plasma; HIT=heparin-induced thrombocytopenia; IV=intravenous; INR=International Normalized Ratio; IU=International Units; LMWH=low-molecular-weight heparins; PCC=prothrombin complex concentrate; P-gp=P-glycoprotein; rFVIIa=recombinant activated factor VII; SC=subcutaneous; UFH=unfractionated heparin

* Time to reach peak plasma concentrations and half life elimination may be delayed post-surgery.

†All should be used with caution with other anticoagulants, non-steroidal anti-inflammatory drugs, thrombolytics, or platelet inhibitors because of an increased risk of bleeding.

3.2 Article selection

Two reviewers (SN, KM) independently applied criteria to select articles for inclusion in the report. Both reviewers screened titles and abstracts, and the results were compared. Full-text articles were obtained for all citations that were selected by either individual. Agreement was then reached on which full-text articles would be included in the report.

The criteria for inclusion were:

- Study design: Health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials (RCTs)
- Population: Patients undergoing elective total hip replacement, elective total knee replacement, or hip fracture surgery
- Intervention: Thromboprophylaxis using dabigatran or rivaroxaban
- Comparator: Thromboprophylaxis using 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 DVT, non-fatal pulmonary embolism, myocardial infarction, stroke, major bleeding, minor bleeding, or any other adverse event during the treatment phase or the study period.

Data from published and unpublished trials were considered for inclusion. All studies that presented non—meta-analytic pooled analyses were excluded, except the United States Food and Drug Administration (FDA) briefing document³⁷ discussed in the conclusion. The statistical synthesis of quantitative data in the form of meta-analysis or indirect comparisons was beyond the scope of this report.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first, followed by RCTs.

4 SUMMARY OF FINDINGS

One systematic review³⁸ and four RCTs³⁹⁻⁴² evaluated dabigatran compared to enoxaparin for thromboprophylaxis after THR or TKR. Six RCTs⁴³⁻⁴⁸ evaluated rivaroxaban compared with enoxaparin for thromboprophylaxis after THR or TKR. The preliminary findings from an unpublished RCT⁴⁹ comparing rivaroxaban with enoxaparin for thromboprophylaxis after TKR were identified.

4.1 Health Technology Assessments

No reports of health technology assessments were identified.

4.2 Systematic Reviews and Meta-Analyses

4.2.1 Dabigatran

Wolowacz *et al.* conducted a meta-analysis of published data from three phase 3 RCTs (RE-NOVATE,⁴⁰ RE-MODEL,⁴¹ and RE-MOBILIZE⁴²) comparing dabigatran (220 mg once daily) with enoxaparin for the prevention of VTE after THR or TKR.³⁸ The dose of enoxaparin in the RE-MODEL and RE-NOVATE trials was 40 mg once daily, started pre-operatively. The dose of enoxaparin in the RE-MOBILIZE trial followed the Health Canada-approved regimen of 30 mg twice daily, started post-operatively. A relative risk of < 1 favored dabigatran and a relative risk of > 1 favored enoxaparin. No statistically significant differences were detected between dabigatran and enoxaparin in any end point in the pooled analysis of the RE-NOVATE and RE-MODEL trials (all $P > 0.15$). There was no statistical heterogeneity between RE-MODEL and RE-NOVATE in any outcome ($P > 0.65$ in all analyses). The authors note, however, that because of inherent differences in trial design (including surgery type and duration of thromboprophylaxis) they could not conclude

that the trials were necessarily homogenous. The pooled results from the three trials (a combined total of 8,210 patients undergoing TKR or THR) revealed no statistically significant differences between dabigatran and enoxaparin in any of the end points in the fixed effects or random effects analysis. The relative risk using the random effects model was 1.05 for total VTE and all-cause mortality (95% confidence interval [CI] 0.87 to 1.26; $P = 0.64$), 0.94 for major VTE and VTE-related mortality (95% CI 0.61 to 1.44; $P = 0.76$), 0.94 for major bleeding (95% CI 0.51 to 1.75; $P = 0.85$), 1.15 for clinically relevant bleeding (95% CI 0.88 to 1.50; $P = 0.31$), and 1.00 for clinically relevant or minor bleeding (95% CI 0.85 to 1.16; $P = 0.96$). Tests for heterogeneity did not reach statistical significance at the 95% level in any of the analyses. A P -value below 0.10 ($P = 0.09$), however, was reported for the primary end point (total VTE and all-cause mortality). The meta-analysis of the RE-MODEL and RE-NOVATE trials supports the conclusion in each trial that dabigatran is non-inferior to enoxaparin 40 mg once daily with a similar safety profile. Although the meta-analysis of the RE-NOVATE, RE-MODEL, and RE-MOBILIZE trials found no statistically significant differences between treatments, heterogeneity between the trials due to different enoxaparin regimens could not be ruled out.

4.3 Randomized Controlled Trials

4.3.1 Dabigatran

One phase 2 RCT³⁹ and three phase 3 RCTs⁴⁰⁻⁴² evaluated dabigatran compared with enoxaparin for thromboprophylaxis after TKR or THR (Tables 2 to 5).

BISTRO II, a phase 2, randomized, double-blind, double-dummy, multicenter study was designed to determine the dose-response relationship for the safety and efficacy of dabigatran in patients undergoing THR or TKR.³⁹ Of the 1973 randomized patients, 1,576 patients were randomized to receive dabigatran (50 mg twice daily, 150 mg twice daily, 225 mg twice daily, or 300 mg once daily) and 397 patients were randomized to receive enoxaparin (40 mg once daily). The baseline demographic and surgical characteristics were similar in all five treatment groups. The primary outcome could be evaluated in 1,012 patients who underwent THR and in 452 patients who underwent TKR. The reasons for excluding the remaining 509 randomized patients were: not receiving the study drug, not undergoing surgery, not having data for VTE events, or undergoing venography that could not be evaluated. Treatment was continued for six to 10 days, and patients were followed for four to six weeks after surgery. The primary efficacy outcome was the occurrence of VTE (a composite of symptomatic or venographically detected DVT and/or PE) during the treatment period. The primary safety outcome was major bleeding during the treatment period. A composite end point of major or clinically significant bleeding was used to assess bleeding events, based on the dose that was administered.

Table 2: Results from BISTRO II³⁹

Study	Efficacy Outcomes n(%)	Safety Outcomes n(%)
<p><i>Design:</i> Randomized, multicenter (Europe, South Africa), parallel-group, double-blind, double-dummy (n = 1973)</p> <p><i>Inclusion criteria:</i> Men and women aged 18 years of age or older undergoing THR (n = 1012) or TKR (n = 452) surgery</p> <p><i>Interventions:</i> <i>Dabigatran</i> (n = 1576) 50 mg, 150 mg, 225 mg PO twice daily, or 300 mg PO once daily starting 1 to 4 hours after surgery plus placebo injection versus <i>Enoxaparin</i> (n = 397) 40 mg SC daily starting 12 hours prior to surgery plus placebo capsules</p> <p><i>Duration:</i> 6 to 10 days</p> <p><i>Follow-up:</i> 4 to 6 weeks after surgery</p>	<p><i>Total VTE*:</i> Dabigatran 50 mg: 86 (28.5%) Dabigatran 150 mg: 49 (17.4%) (OR 0.65; P = 0.04 versus enoxaparin) Dabigatran 225 mg: 39 (13.1%) (OR 0.47; P = 0.0007 versus enoxaparin) Dabigatran 300 mg: 47 (16.6%) (OR 0.61; P = 0.02 versus enoxaparin) Enoxaparin: 72 (24.0%)</p> <p><i>Symptomatic VTE during treatment:</i> Dabigatran 50 mg: 2 (0.7%) Dabigatran 150 mg: 2 (0.7%) Dabigatran 225 mg: 0 Dabigatran 300 mg: 0 Enoxaparin: 1 (0.3%)</p> <p><i>Symptomatic VTE during follow-up:</i> Dabigatran 50 mg: 2 (0.7%) Dabigatran 150 mg: 1 (0.4%) Dabigatran 225 mg: 0 Dabigatran 300 mg: 2 (0.7%) Enoxaparin: 0</p> <p><i>Non-fatal PE during treatment:</i> Dabigatran 50 mg: 0 Dabigatran 150 mg: 2 (0.7%) Dabigatran 225 mg: 0 Dabigatran 300 mg: 0 Enoxaparin: 0</p>	<p><i>Major bleeding events:</i> Dabigatran 50 mg: 1 (0.3%) (P = 0.047 versus enoxaparin) Dabigatran 150 mg: 16 (4.1%) (P = 0.10 versus enoxaparin) Dabigatran 225 mg: 15 (3.8%) (P = 0.15 versus enoxaparin) Dabigatran 300 mg: 18 (4.7%) (P = 0.051 versus enoxaparin) Enoxaparin: 8 (2.0%)</p> <p><i>Clinically significant bleeding:</i> Dabigatran 50 mg: 9 (2.3%) Dabigatran 150 mg: 16 (14.1%) Dabigatran 225 mg: 20 (5.1%) Dabigatran 300 mg: 19 (4.9%) Enoxaparin: 10 (2.6%) (P values for comparisons not reported)</p> <p><i>Minor bleeding events:</i> Dabigatran 50 mg: 18 (4.6%) Dabigatran 150 mg: 31 (7.9%) Dabigatran 225 mg: 38 (9.7%) Dabigatran 300 mg: 37 (9.6%) Enoxaparin: 25 (6.4%) (P values for comparisons not reported)</p>

Table 2: Results from BISTRO II³⁹

Study	Efficacy Outcomes n(%)	Safety Outcomes n(%)
	<p><i>Non-fatal PE during follow-up:</i> Dabigatran 50 mg: 1 (0.3%) Dabigatran 150 mg: 0 Dabigatran 225 mg: 0 Dabigatran 300 mg: 0 Enoxaparin: 0</p> <p><i>All-cause mortality during treatment:</i> None</p> <p><i>All-cause mortality during follow-up:</i> Dabigatran 50 mg: 1 (0.3%) Dabigatran 150 mg: 0 Dabigatran 225 mg: 1 (0.3%) Dabigatran 300 mg: 0 Enoxaparin: 0</p>	<p><i>Number of patients experiencing serious adverse events:</i> 98 patients (dosing group not reported)</p> <p><i>Drug-related serious adverse events:</i> Dabigatran 50 mg: 0 Dabigatran 150 mg: 4 Dabigatran 225 mg: 6 Dabigatran 300 mg: 12 Enoxaparin: 2</p> <p><i>Acute coronary events:</i> Not reported</p> <p><i>Patients experiencing at least one adverse event:</i> Not reported</p> <p><i>Withdrawal due to adverse events:</i> 99 patients (dosing group not reported)</p>

OR=odds ratio; PE=pulmonary embolism; PO=oral; SC=subcutaneous; THR=total hip replacement; TKR=total knee replacement; VTE=venous thromboembolism
* Composite of symptomatic or venographically detected DVT and/or PE detected during treatment.

A statistically significant dose-dependent decrease in VTE frequency was observed with increasing doses of dabigatran ($P < 0.0001$). The three highest doses of dabigatran (150 mg twice daily, 225 mg twice daily, or 300 mg once daily) were associated with a statistically significant reduction in the incidence of VTE compared with enoxaparin ($P = 0.04$, $P = 0.0007$, and $P = 0.02$ respectively). Major bleeding was statistically significantly lower in the 50 mg twice daily dose dabigatran group ($P = 0.047$) compared with enoxaparin. There was a non-significant trend for increased bleeding in those receiving the three highest doses of dabigatran (150 mg twice daily, 225 mg twice daily, or 300 mg once daily ($P = 0.10$, $P = 0.15$, and $P = 0.051$ respectively). No deaths occurred during the treatment period. No dose-response relationship was observed for elevations in liver enzymes, which were all mild. During follow-up, two patients died. They both had active malignancy and were part of the 50 mg twice daily and 225 mg twice daily groups. Fatal PE could not be excluded as a cause of death in one of these patients. Overall, these findings indicated that a total daily dose of dabigatran between 100 mg and 300 mg provided an optimal balance between efficacy and risk of bleeding for phase 3 trials.

As part of the RE-VOLUTION phase 3 clinical trial program, the RE-NOVATE,⁴⁰ RE-MODEL,⁴¹ and RE-MOBILIZE⁴² trials were conducted to assess the safety and efficacy of dabigatran compared with enoxaparin in patients undergoing THR or TKR. The primary efficacy outcome for all three trials was a composite of total VTE (defined as a composite of venographic or symptomatic DVT and/or symptomatic PE) and all-cause mortality during treatment. Secondary efficacy outcomes included a composite of major VTE (defined as a composite of proximal DVT, PE, and VTE-related mortality). Symptomatic VTE, which was evaluated as a composite outcome, included symptomatic DVT, PE, or death due to PE. The primary safety outcome was bleeding events during study treatment, including major bleeding events, clinically relevant non-major bleeding events, and minor bleeding events. The definitions of bleeding events appear in Appendix 2. All three trials were designed to assess non-inferiority between dabigatran and enoxaparin for the primary efficacy outcome. Unlike typical superiority trials, non-

inferiority trials are designed to detect if a treatment is no worse than a reference treatment by more than a specified margin.⁵⁰ Non-inferiority was established if the upper limit of the 95% confidence interval for the difference between dabigatran and enoxaparin was less than 7.7% in the RE-NOVATE trial or 9.2% in the RE-MODEL and RE-MOBILIZE trials. These non-inferiority margins were determined a priori. If non-inferiority was shown in the RE-MODEL and RE-MOBILIZE trials, then the superiority of dabigatran, compared with enoxaparin, was tested. The baseline demographic and surgical characteristics were similar among groups in all three trials.

The results from the RE-NOVATE and RE-MODEL trials showed that dabigatran at a dose of 220 mg or 150 mg was statistically non-inferior to enoxaparin 40 mg once daily for reducing the risk of total VTE and all-cause mortality. Superiority testing in the RE-MODEL trial revealed that neither dose of dabigatran was superior to enoxaparin (results not reported). The RE-MOBILIZE trial compared dabigatran with the Health Canada-approved regimen of enoxaparin (30 mg twice daily started post-operatively) after TKR. Both doses of dabigatran were inferior to enoxaparin for reducing the rate of total VTE and all-cause mortality. Several factors may explain the differences in the results obtained from the RE-MOBILIZE and RE-MODEL trials. First, a higher dose of enoxaparin was used in RE-MOBILIZE (30 mg twice daily compared with 40 mg once daily in RE-MODEL). Second, enoxaparin and dabigatran were administered a mean of five days longer in RE-MOBILIZE (13 days versus eight days). Finally, the randomization in RE-MOBILIZE was performed after surgery and included only patients who showed adequate hemostasis. In the RE-MODEL trial, randomization was performed the day before surgery. These differences make meaningful comparisons between these trials difficult. All three trials showed no statistically significant difference in the rates of major VTE with either dose of dabigatran versus enoxaparin. The rates of symptomatic VTE and all-cause mortality during treatment and on follow-up (when reported) were low and comparable across all treatment groups for all three studies.

Table 3: Design of Published Phase 3 RCTs Evaluating Dabigatran for Thromboprophylaxis

Trial	Methods	Interventions	Patient Populations
<p>Eriksson <i>et al.</i>, 2007⁴⁰</p> <p>RE-NOVATE</p>	<p><i>Design:</i> Randomized, double-blind, double-dummy, multicenter (Europe, Australia, South Africa), parallel group, active control, non-inferiority (margin of 7.7%)</p> <p><i>Inclusion criteria:</i> Men and women over the age of 18 years undergoing elective THR surgery</p> <p><i>Follow-up:</i> 3 months after surgery</p>	<p><i>Dabigatran</i> 220 mg PO once daily or, 150 mg PO once daily (started 1 to 4 hours after surgery with a ½ dose of 75 mg or 110 mg respectively) plus placebo injection</p> <p>versus</p> <p><i>Enoxaparin</i> 40 mg SC once daily (started the evening before surgery) plus placebo capsules</p> <p><i>Duration:</i> 28 to 35 days</p>	<p><i>Randomized:</i> 3,494 (1,157 dabigatran 220 mg, 1,174 dabigatran 150 mg, 1,162 enoxaparin)</p> <p><i>Safety population*:</i> 3,463 (1,146 dabigatran 220 mg, 1,163 dabigatran 150 mg, 1,154 enoxaparin)</p> <p><i>mITT†:</i> 2651 (880 dabigatran 220 mg, 874 dabigatran 150 mg, 897 enoxaparin)</p> <p><i>mITT (Major VTE‡):</i> 2,714 (909 dabigatran 220 mg, 888 dabigatran 150 mg, 917 enoxaparin)</p> <p><i>Symptomatic VTE¶:</i> 3,435 (1,137 dabigatran 220 mg, 1,156 dabigatran 150 mg, 1,142 enoxaparin)</p>
<p>Eriksson <i>et al.</i>, 2007⁴¹</p> <p>RE-MODEL</p>	<p><i>Design:</i> Randomized, double-blind, double-dummy, multicenter (Europe, Australia, South Africa), parallel group, active control, non-inferiority (margin of 9.2%)</p>	<p><i>Dabigatran</i> 220 mg PO once daily or, 150 mg PO once daily (started 1 to 4 hours after surgery with a ½ dose of 75 mg or 110 mg, respectively) plus placebo injection</p> <p>versus</p>	<p><i>Randomized:</i> 2,101 (694 dabigatran 220 mg, 708 dabigatran 150 mg, 699 enoxaparin)</p> <p><i>Safety population:</i> 2,076 (679 dabigatran 220 mg, 703 dabigatran 150 mg, 694 enoxaparin)</p>

Table 3: Design of Published Phase 3 RCTs Evaluating Dabigatran for Thromboprophylaxis

Trial	Methods	Interventions	Patient Populations
	<p><i>Inclusion criteria:</i> Men and women over the age of 18 years undergoing elective TKR surgery</p> <p><i>Follow-up:</i> 3 months after surgery</p>	<p><i>Enoxaparin</i> 40 mg SC once daily (started the evening before surgery) plus placebo capsules</p> <p><i>Duration:</i> 6 to 10 days</p>	<p><i>mITT:</i> 1,541 (503 dabigatran 220 mg, 526 dabigatran 150 mg, 512 enoxaparin)</p> <p><i>mITT (major VTE):</i> 1,544 (506 dabigatran 220 mg, 527 dabigatran 150 mg, 511 enoxaparin)</p> <p><i>Symptomatic VTE:</i> 2,056 (675 dabigatran 220 mg, 696 dabigatran 150 mg, 685 enoxaparin)</p>
<p>Ginsberg <i>et al.</i>, 2009⁴²</p> <p>RE-MOBILIZE</p>	<p><i>Design:</i> Randomized, double-blind, double-dummy, multicenter (58 centers in North America, one center in UK), parallel group, active control, non-inferiority (margin of 9.2%)</p> <p><i>Inclusion criteria:</i> Men and women over the age of 18 years undergoing elective TKR surgery</p> <p><i>Follow-up:</i> 3 months after surgery</p>	<p><i>Dabigatran</i> 220 mg PO once daily or, 150 mg PO once daily (started 6 to 12 hours after surgery with a ½ dose of 75 mg or 110 mg, respectively) plus placebo injection versus</p> <p><i>Enoxaparin</i> 30 mg SC twice daily (started 12 to 24 hours after surgery) plus placebo capsules</p> <p><i>Duration:</i> 12 to 15 days</p>	<p><i>Randomized:</i> 2,615 (862 dabigatran 220 mg, 877 dabigatran 150 mg, 876 enoxaparin)</p> <p><i>Safety population:</i> 2,596 (857 dabigatran 220 mg, 871 dabigatran 150 mg, 868 enoxaparin)</p> <p><i>mITT:</i> 1,896 (604 dabigatran 220 mg, 649 dabigatran 150 mg, 643 enoxaparin)</p> <p><i>mITT (major VTE):</i> 1,942 (618 dabigatran 220 mg, 656 dabigatran 150 mg, 668 enoxaparin)</p>

Table 3: Design of Published Phase 3 RCTs Evaluating Dabigatran for Thromboprophylaxis

Trial	Methods	Interventions	Patient Populations
			Symptomatic VTE: 2,596 (857 dabigatran 220 mg, 871dabigatran 150 mg, 868 enoxaparin)

DVT=deep vein thrombosis; mITT= modified intent-to-treat; PE=pulmonary embolism; PO=oral; RCTs=randomized controlled trials; SC=subcutaneous; THR=total hip replacement; TKR=total knee replacement; VTE=venous thromboembolism

*Safety population: All randomized patients who received at least one dose of study treatment.

†mITT (total VTE and all-cause mortality)=Patients must have undergone the appropriate surgery, taken the study drug, and had an evaluable venogram for distal and proximal DVT, or verified symptomatic DVT, PE, or death of any cause.

‡mITT (major VTE)=Patients must have undergone the appropriate surgery, taken the study drug, and had an evaluable venogram for proximal DVT or confirmed symptomatic DVT, PE, or VTE-related death.

§Symptomatic VTE= Included the safety population of patients who underwent surgery (independent of obtaining evaluable venograms).

Table 4: Efficacy Outcomes of Published RCTs Evaluating Dabigatran for Thromboprophylaxis

Outcome	RE-NOVATE⁴⁰ n (%)	RE-MODEL⁴¹ n (%)	RE-MOBILIZE⁴² n (%)
Total VTE and all-cause mortality (primary efficacy outcome)	Dabigatran 220 mg: 53 (6.0%) Dabigatran 150 mg: 75 (8.6%) Enoxaparin: 60 (6.7%) <i>Absolute risk difference:</i> Dabigatran 220 mg: -0.7% (95% CI -2.9 to 1.6; P < 0.0001) Dabigatran 150 mg: 1.9% (95% CI -0.6 to 4.4; P < 0.0001)	Dabigatran 220 mg: 183 (36.4%) Dabigatran 150 mg: 213 (40.5%) Enoxaparin: 193 (37.7%) <i>Absolute risk difference:</i> Dabigatran 220 mg: -1.3% (95% CI -7.3 to 4.6; P = 0.0003) Dabigatran 150 mg: 2.8% (95% CI -3.1 to 8.7; P = 0.017)	Dabigatran 220 mg: 188 (31.1%) Dabigatran 150 mg: 219 (33.7%) Enoxaparin: 163 (25.3%) <i>Absolute risk difference:</i> Dabigatran 220 mg: 5.8% (95% CI 0.8 to 10.8; P = 0.0234) Dabigatran 150 mg: 8.4% (95% CI 3.4 to 13.3; P = 0.009)
Major VTE* (secondary efficacy outcome)	Dabigatran 220 mg: 28 (3.1%) Dabigatran 150 mg: 38 (4.3%) Enoxaparin: 36 (3.9%) <i>Absolute risk difference:</i> Dabigatran 220 mg: -0.8% (95% CI -2.5 to 0.8; P = 0.33) Dabigatran 150 mg: 0.4% (95% CI -1.5 to 2.2; P = 0.71)	Dabigatran 220 mg: 13 (2.6%) Dabigatran 150 mg: 20 (3.8%) Enoxaparin (n=511): 18 (3.5%) <i>Absolute risk difference:</i> Dabigatran 220 mg: -1.0% (95% CI -3.1 to 1.2; P = 0.38) Dabigatran 150 mg: 0.3% (95% CI -2.0 to 2.6; P = 0.82)	Dabigatran 220 mg: 21 (3.4%) Dabigatran 150 mg: 20 (3.0%) Enoxaparin: 15 (2.2%) <i>Absolute risk difference:</i> Dabigatran 220 mg: 1.2% (95% CI -0.7 to 3.0; P = 0.21) Dabigatran 150 mg: 0.8% (95% CI -0.9 to 2.5; P = 0.36)
Proximal asymptomatic DVT during treatment	Dabigatran 220 mg: 18 (2.0%) Dabigatran 150 mg: 28 (3.2%) Enoxaparin: 32 (3.5%)	Dabigatran 220 mg: 13 (2.6%) Dabigatran 150 mg: 18 (3.4%) Enoxaparin: 16 (3.1%)	Dabigatran 220 mg: 14 [†] (2.3%) Dabigatran 150 mg: 20 [†] (3.1%) Enoxaparin: 10 [†] (1.6%)

Table 4: Efficacy Outcomes of Published RCTs Evaluating Dabigatran for Thromboprophylaxis

Outcome	RE-NOVATE⁴⁰ n (%)	RE-MODEL⁴¹ n (%)	RE-MOBILIZE⁴² n (%)
Distal asymptomatic DVT during treatment	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: -1.5% Dabigatran 150 mg: -0.3 %</p> <p>Dabigatran 220 mg: 22 (2.5%) Dabigatran 150 mg: 35 (4.0%) Enoxaparin: 24 (2.7%)</p>	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: -0.5% Dabigatran 150 mg: 0.3%</p> <p>Dabigatran 220 mg: 168 (33.4%) Dabigatran 150 mg: 190 (36.3%) Enoxaparin: 168 (32.9%)</p>	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.7% Dabigatran 150 mg: 1.5%</p> <p>Dabigatran 220 mg: 167[‡] (27.6%) Dabigatran 150 mg: 198[‡] (30.5%) Enoxaparin: 148[‡] (23%)</p>
DVT during follow-up	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: -0.2% Dabigatran 150 mg: 1.3%</p> <p>Not reported</p>	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.5% Dabigatran 150 mg: 3.4%</p> <p>Not reported</p>	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: 4.6% Dabigatran 150 mg: 7.5%</p> <p>Not reported</p>
Symptomatic VTE			
Symptomatic PE during treatment	<p>Dabigatran 220 mg: 5 (0.4%) Dabigatran 150 mg: 1 (0.1%) Enoxaparin: 3 (0.3%)</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.1%</p>	<p>Dabigatran 220 mg: 0 Dabigatran 150 mg: 1 (0.1%) Enoxaparin: 1§ (0.1%)</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: -0.1%</p>	<p>Dabigatran 220 mg: 6 (0.7%) Dabigatran 150 mg: 0 Enoxaparin: 5 (0.6%)</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.1%</p>
Symptomatic DVT during treatment	<p>Dabigatran 150 mg: -0.2% Dabigatran 220 mg: 6 (0.5%) Dabigatran 150 mg: 9 (0.8%) Enoxaparin: 1 (0.1%)</p>	<p>Dabigatran 150 mg: 0% Dabigatran 220 mg: 1 (0.1%) Dabigatran 150 mg: 3 (0.4%) Enoxaparin: 8 (1.2%)</p>	<p>Dabigatran 150 mg: -0.6% Dabigatran 220 mg: 7 (0.8%) Dabigatran 150 mg: 6 (0.7%) Enoxaparin: 5 (0.6%)</p>

Table 4: Efficacy Outcomes of Published RCTs Evaluating Dabigatran for Thromboprophylaxis

Outcome	RE-NOVATE⁴⁰ n (%)	RE-MODEL⁴¹ n (%)	RE-MOBILIZE⁴² n (%)
Total symptomatic VTE during follow-up	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.4% Dabigatran 150 mg: 0.7%</p> <p>Dabigatran 220 mg: 1 (0.1%) Dabigatran 150 mg: 1 (0.1%) Enoxaparin: 1 (0.1%)</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0% Dabigatran 150 mg: 0%</p>	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: -1.1% Dabigatran 150 mg: -0.8%</p> <p>Dabigatran 220 mg: 3 (0.4%) Dabigatran 150 mg: 2 (0.3%) Enoxaparin: 0</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.4% Dabigatran 150 mg: 0.3%</p>	<p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.2% Dabigatran 150 mg: 0.1%</p> <p>Dabigatran 220 mg: 4[†] (0.5%) Dabigatran 150 mg: 4[†] (0.5%) Enoxaparin: 4[†](0.5%)</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0% Dabigatran 150 mg: 0%</p>
All-cause mortality			
During treatment	<p>Dabigatran 220 mg: 3^{**} (0.3%) Dabigatran 150 mg: 3^{**}(0.3%) Enoxaparin: 0</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.3% Dabigatran 150 mg: 0.3%</p>	<p>Dabigatran 220 mg: 1 (0.1%) Dabigatran 150 mg: 1^{††}(0.1%) Enoxaparin: 1^{§§} (0.1%)</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0% Dabigatran 150 mg: 0%</p>	<p>Dabigatran 220 mg: 1^{††} (0.1%) Dabigatran 150 mg: 1^{††}(0.1%) Enoxaparin: 0</p> <p><i>Absolute risk difference:</i> Dabigatran 220 mg: 0.1% Dabigatran 150 mg: 0.1%</p>
During follow-up	Not reported	Not reported	<p>Dabigatran 220 mg: 1 (0.1%) Dabigatran 150 mg: 2 (0.3%) Enoxaparin: 2 (0.2%)</p>

Table 4: Efficacy Outcomes of Published RCTs Evaluating Dabigatran for Thromboprophylaxis

Outcome	RE-NOVATE ⁴⁰ n (%)	RE-MODEL ⁴¹ n (%)	RE-MOBILIZE ⁴² n (%)
			<i>Absolute risk difference:</i> Dabigatran 220 mg: -0.1% Dabigatran 150 mg: 0.1%

CI=confidence interval; DVT=deep vein thrombosis; PE=pulmonary embolism; RCTs=randomized controlled trials; VTE=venous thromboembolism

*Major VTE was a composite of proximal DVT, non-fatal PE, and VTE-related death.

† Total number of patients with proximal DVT (symptomatic and asymptomatic) during treatment.

‡ Total number of patients with distal DVT (symptomatic and asymptomatic) during treatment.

§ Fatal PE same patient.

¶ 2 symptomatic DVT, 2 PE in dabigatran 220 mg group, 4 symptomatic DVT in dabigatran 150 mg group, and 2 symptomatic DVT, 2 PE in enoxaparin group.

** VTE could not be ruled out as a cause of death for one patient in the dabigatran 220 mg group and two patients in the dabigatran 150 mg group.

††VTE could not be excluded as cause of death.

‡‡ Fatal PE could not be ruled out for the patient who died in the dabigatran 220 mg group. Cause of death for the patient who died in the 150 mg group was not associated with PE.

Overall, the safety results were comparable in all three trials for rates of bleeding, liver enzyme elevations, and acute coronary events with either dose of dabigatran or enoxaparin. Fatal bleeding events occurred in one patient receiving

dabigatran 150 mg and one patient receiving 220 mg in the RE-NOVATE trial. No fatal bleeding events were reported in the RE-MODEL or the RE-MOBILIZE trials.

Table 5: Safety Outcomes of Published RCTs Evaluating Dabigatran for Thromboprophylaxis

Outcome	RE-NOVATE ⁴⁰ n (%)	RE-MODEL ⁴¹ n (%)	RE-MOBILIZE ⁴² n (%)
Major bleeding			
During treatment	Dabigatran 220 mg: 23 (2.0%) (95% CI 1.3 to 3.0) Dabigatran 150 mg: 15 (1.3%) (95% CI 0.7 to 2.1) Enoxaparin: 18 (1.6%) (95% CI 0.9 to 2.5) (P values not reported)	Dabigatran 220 mg: 10 (1.5%) (95% CI 0.7 to 2.7) (P = 0.82 versus enoxaparin) Dabigatran 150 mg: 9 (1.3%) (95% CI 0.6 to 2.4) (P = 1.0 versus enoxaparin) Enoxaparin: 9 (1.3%) (95% CI 0.6 to 2.4)	Dabigatran 220 mg: 5 (0.6%) Dabigatran 150 mg: 5 (0.6%) Enoxaparin: 12 (1.4%) (P values not reported)
During follow-up	Not reported	Not reported	Dabigatran 220 mg: 1 (0.1%) Dabigatran 150 mg: 2 (0.2%) Enoxaparin: 0

Table 5: Safety Outcomes of Published RCTs Evaluating Dabigatran for Thromboprophylaxis			
Outcome	RE-NOVATE⁴⁰ n (%)	RE-MODEL⁴¹ n (%)	RE-MOBILIZE⁴² n (%)
Clinically relevant non-major bleeding			
During treatment	Dabigatran 220 mg: 48 (4.2%) Dabigatran 150 mg: 55 (4.7%) Enoxaparin: 40 (3.5%)	Dabigatran 220 mg: 40 (5.9%) Dabigatran 150 mg: 48 (6.8%) Enoxaparin: 37 (5.3%)	Dabigatran 220 mg: 23 (2.7%) Dabigatran 150 mg: 22 (2.5%) Enoxaparin: 21 (2.4%)
During follow-up	Not reported	Not reported	Dabigatran 220 mg: 6 (0.7%) Dabigatran 150 mg: 5 (0.5%) Enoxaparin: 3 (0.3%)
Minor bleeding during treatment	Dabigatran 220 mg: 70 (6.1%) Dabigatran 150 mg: 72 (6.2%) Enoxaparin: 74 (6.4%)	Dabigatran 220 mg: 60 (8.8%) Dabigatran 150 mg: 59 (8.4%) Enoxaparin: 69 (9.9%)	Not reported
Total with adverse events	Dabigatran 220 mg: 879 (77%) Dabigatran 150 mg: 895 (77%) Enoxaparin: 892(77%)	Not reported	Not reported
Serious adverse events during treatment	Dabigatran 220 mg: 89 (8%) Dabigatran 150 mg: 91 (8%) Enoxaparin: 82(7%)	Not reported	Dabigatran 220 mg: 59 (6.9%) Dabigatran 150 mg: 57 (6.5%) Enoxaparin: 45 (5.2%)
Acute coronary events*			
During treatment	Dabigatran 220 mg: 5 (0.44%) Dabigatran 150 mg: 8 (0.69%) Enoxaparin: 9 (0.78%)	Dabigatran 220 mg: 3 (0.4%) Dabigatran 150 mg: 7 (1.0%) Enoxaparin: 4 (0.6%)	Dabigatran 220 mg: 9 (1.1%) Dabigatran 150 mg: 10 (1.1%) Enoxaparin: 9 (1.0%)
During follow-up	Dabigatran 220 mg: 0 Dabigatran 150 mg: 0 Enoxaparin: 3 (0.26%)	Dabigatran 220 mg: 0 Dabigatran 150 mg: 1 (0.1%) Enoxaparin: 2 (0.3%)	Not reported

Table 5: Safety Outcomes of Published RCTs Evaluating Dabigatran for Thromboprophylaxis

Outcome	RE-NOVATE ⁴⁰ n (%)	RE-MODEL ⁴¹ n (%)	RE-MOBILIZE ⁴² n (%)
Study withdrawal due to adverse effect	Dabigatran 220 mg: 74 (6%) Dabigatran 150 mg: 88 (8%) Enoxaparin: 66 (6%)	Dabigatran 220 mg: 25 (3.7%) Dabigatran 150 mg: 26 (3.7%) Enoxaparin: 32 (4.6%)	Not reported

CI=confidence intervals; RCTs=randomized controlled trials

* Acute coronary events defined as confirmed unstable angina, myocardial infarction, and cardiac death in RE-NOVATE and RE-MODEL.

4.3.2 Rivaroxaban

Three phase 2 RCTs⁴³⁻⁴⁵ and three phase 3 RCTs⁴⁶⁻⁴⁸ evaluated rivaroxaban compared to enoxaparin for thromboprophylaxis after TKR or THR (Tables 6 to 9).

Three double-blind, double-dummy, dose-ranging studies compared rivaroxaban with enoxaparin in patients undergoing THR^{44,45} or TKR.⁴³ For consistency so that results could be compared across studies, each study used the same assessment parameters, end points, and blinded central adjudication committee. Either male patients who were 18 years of age or older, or postmenopausal patients scheduled for elective TKR or THR, were eligible for inclusion. Treatment was continued until mandatory bilateral venography was performed five to nine days after surgery. Patients were followed for 30 to 60 days after receiving the last dose of the study drug. The primary efficacy end point was a composite of the incidence of proximal and/or distal DVT, non-fatal PE, and all-cause mortality during the treatment period. Secondary end points included the incidence of major VTE (composite of proximal DVT, symptomatic or objectively confirmed PE, and VTE-related death) and symptomatic VTE during the treatment period. The primary safety end point was major, post-operative bleeding. In each phase 2 trial, all groups were balanced for baseline demographic and surgical characteristics. The results are presented in Table 6.

Turpie *et al.* compared rivaroxaban (2.5 mg, 5 mg, 10 mg, 20 mg, or 30 mg) twice daily

started six to eight hours after surgery, with enoxaparin 30 mg twice daily started 12 to 24 hours after surgery in 621 patients undergoing TKR.⁴³ This is the only published trial that compared rivaroxaban with the Health Canada-approved dose of enoxaparin. Based on the total daily dose, no statistically significant trend was observed for the primary efficacy end point ($P = 0.29$). Rivaroxaban was associated with a dose-dependent increase in major bleeding ($P = 0.0007$), but there was no difference when rivaroxaban was compared with enoxaparin. During treatment, six patients developed symptomatic VTE (two with PE in the rivaroxaban 5 mg twice daily group, one with DVT in each of the rivaroxaban 2.5 mg and 20 mg twice daily groups, and two with DVT in the enoxaparin group). During follow-up, four patients developed symptomatic VTE (three with PE and one with DVT; the groups were not reported). No deaths occurred during treatment. During follow-up, two patients receiving rivaroxaban 2.5 mg twice daily died from PE and cardiorespiratory failure, and one patient receiving rivaroxaban 10 mg twice daily died from PE. These patients did not receive thromboprophylaxis after the five- to nine-day treatment period. The short treatment duration could have been a factor in these deaths. A total of 23 patients experienced treatment-related serious adverse events. The incidence ranged between 0% and 4% at lower doses (2.5 mg to 10 mg twice daily) and was more frequent in the 20 mg and 30 mg twice daily groups (7% and 8% respectively). The incidence that was reported for treatment-related serious adverse effects in the enoxaparin group was 3%.

Eriksson *et al.* compared rivaroxaban (2.5 mg, 5 mg, 10 mg, 20 mg, or 30 mg) twice daily started six to eight hours after surgery with enoxaparin 40 mg daily started the evening before surgery in 726 patients undergoing THR.⁴⁴ The dose-response relationship between rivaroxaban and the primary efficacy end point was not statistically significant ($P = 0.932$). There was a dose-dependent increase in major bleeding with rivaroxaban ($P = 0.045$), but there was no difference when rivaroxaban was compared to enoxaparin. There were no reports of symptomatic VTE during the treatment period. During follow-up, five cases of symptomatic VTE (three with DVT and two with PE) were reported. No information was provided about the treatment group. No patients died during active treatment. Two deaths in the rivaroxaban group were reported during follow-up (one in the 5 mg twice daily group and the other in the 10 mg twice daily group). The cause of these deaths was not attributed to the study drug. Fewer patients in the 2.5 mg, 5 mg, and 10 mg twice daily groups experienced serious treatment-related adverse events (7.6%, 8.8%, and 10.5%, respectively), compared with enoxaparin (11.4%). The percentage of patients experiencing serious treatment-related adverse events was higher in the 20 mg and 30 mg twice daily groups (14.9% and 16.2%, respectively) compared to the enoxaparin group.

Eriksson *et al.* performed a follow-up phase 2 study comparing rivaroxaban (5 mg, 10 mg, 20 mg, 30 mg, or 40 mg) once daily started six to eight hours after surgery with enoxaparin 40 mg daily started the evening before surgery in 873 patients undergoing THR.⁴⁵ The efficacy of rivaroxaban across the dosing range was similar to that of enoxaparin. The dose-response relationship between rivaroxaban and the primary end point was not statistically significant ($P = 0.0852$). There was a statistically significant trend in the dose-response relationship between rivaroxaban and major VTE ($P = 0.0072$). There was also a statistically significant dose-dependent increase in the risk of major bleeding ($P = 0.039$). There were no significant differences between any

dose of rivaroxaban and enoxaparin for major bleeding, although the study was not powered to detect differences between the two drugs. One PE was reported in a patient who received 40 mg rivaroxaban and in one patient receiving 10 mg rivaroxaban. One case of symptomatic DVT was reported during the treatment period in the enoxaparin group. Three cases of symptomatic VTE were reported during follow-up (two with DVT in each of the rivaroxaban 20 mg and 40 mg groups and one with PE in the rivaroxaban 40 mg group). No patient died during treatment or follow-up. Based on the comparable efficacy between doses and an increase in major bleeding from 0.7% in the 10 mg group to 4.3% in the 20 mg group, the authors recommended a 10 mg total daily dose for future phase 3 trials.

None of the phase 2 studies showed any dose-dependency between rivaroxaban and liver enzyme elevations. The numbers of patients experiencing at least one adverse event or who withdrew from the study due to an adverse event were not reported in these trials. The number of patients experiencing an acute coronary event was not reported. Two trials^{43,44} stated that rivaroxaban did not have any negative effects on electrocardiogram parameters.

RECORD (REGulation of Coagulation in major Orthopedic surgery to prevent the Risk of DVT and PE) is the clinical phase 3 program evaluating the safety and efficacy of rivaroxaban for thromboprophylaxis after orthopedic surgery. RECORD 1, 2, and 3 were multinational, double-blind, double-dummy comparisons of the efficacy and safety of rivaroxaban (10 mg twice daily) to enoxaparin (40 mg once daily) when used for thromboprophylaxis after THR or TKR. The primary efficacy outcome was a composite of any DVT (symptomatic or detected by bilateral venography if the patient was asymptomatic), non-fatal PE, or all-cause mortality. The main secondary efficacy outcome was major VTE (a composite of proximal DVT, non-fatal PE, or VTE-related mortality). The primary safety outcome was major bleeding.

Table 6: Safety and Efficacy Outcomes in Phase 2 Double-Blind RCTs Evaluating Rivaroxaban for Thromboprophylaxis

Outcome	Rivaroxaban (Total Daily Dose)						P-value for Dosing Trend	Enoxaparin
	5 mg	10 mg	20 mg	30 mg	40 mg	60 mg		
Total VTE*: n (%)								
TKR b.i.d. study ⁴³	20 (31.7)	23 (40.4)	14 (23.3)	NR	20 (35.1)	15 (25.4)	0.29	31 (44.3)
THR b.i.d. study ⁴⁴	16 (15.4)	15 (13.8)	12 (11.9)	NR	18 (18.2)	2 [‡] (6.9)	0.932	18 (17.0)
THR q.d. study ⁴⁵	14 (14.9)	12 (10.6)	9 (8.5)	14 (13.5)	6 (6.4)	NR	0.085	27 (25.2)
Major VTE[†]: n (%)								
TKR b.i.d. study ⁴³	2 (3.2)	3 (5.3)	4 (6.7)	NR	2 (3.5)	0	NR	3 (4.3)
THR b.i.d. study ⁴⁴	3 (2.9)	1 (0.9)	1 (1.0)	NR	3 (3.0)	1 [‡] (3.4)	NR	5 (4.7)
THR q.d. study ⁴⁵	8 (8.5)	3 (2.7)	1 (0.9)	2 (1.9)	1 (1.1)	NR	0.0072	3 (2.8)
Major bleeding: n (%)								
TKR b.i.d. study ⁴³	1 (1.0)	0	2 (1.9)	NR	3 (3.1)	8 (7.5)	0.0007	2 (1.9)
THR b.i.d. study ⁴⁴	1 (0.8)	3 (2.2)	3 (2.3)	NR	6 (4.5)	2 [‡] (5.4)	0.045	2 (1.5)
THR q.d. study ⁴⁵	3 (2.3)	1 (0.7)	6 (4.3)	7 (4.9)	7 (5.1)	NR	0.039	3 (1.9)
Clinically relevant non-major bleeding: n (%)								
TKR b.i.d. study ⁴³	2 (2.0)	3 (2.9)	1 (1.0)	NR	5 (5.1)	7 (6.6)	NR	3 (2.9)
THR b.i.d. study ⁴⁴	2 (1.5)	8 (5.9)	3 (2.3)	NR	6 (4.5)	1 (2.7)	NR	0
THR q.d. study ⁴⁵	2 (1.6)	3 (2.1)	1 (0.7)	3 (2.1)	4 (2.9)	NR	NR	5 (3.2)
Minor bleeding: n (%)								
TKR b.i.d. study ⁴³	6 (6.0)	6 (5.9)	6 (5.8)	NR	10 (10.2)	12 (11.3)	NR	3 (2.9)
THR b.i.d. study ⁴⁴	4 (3.0)	6 (4.4)	11 (8.3)	NR	14 (10.4)	1 (2.7)	NR	6 (4.5)
THR q.d. study ⁴⁵	5 (3.9)	5 (3.5)	6 (4.3)	8 (5.6)	14 (10.2)	NR	NR	6 (3.8)

b.i.d.=twice daily; DVT=deep vein thrombosis; NR=not reported; PE=pulmonary embolism; q.d.=once daily; TKR=total knee replacement; THR=total hip replacement; VTE=venous thromboembolism

* Composite of DVT, non-fatal PE, and all-cause mortality

† Composite of proximal DVT, non-fatal PE, and VTE-related death

‡ Dose arm suspended due to regulatory request

The definition of major bleeding differed between phase 3 clinical trials of dabigatran and rivaroxaban (Appendix 2). In the RE-MODEL, RE-NOVATE, and RE-MOBILIZE trials, surgical site bleeding was included in major bleeding events. In all three RECORD trials, surgical site bleeding was excluded from major bleeding events (unless it required re-operation or was fatal). Instead, surgical site bleeding was categorized as a non-major bleeding event, as part of the hemorrhagic wound complications composite end point. RECORD 1 and RECORD 3 were designed to accept non-inferiority for the primary outcome if the upper limit of the 95% confidence interval for the absolute treatment difference was below 3.5% or 4%, respectively. These margins were determined a priori. If non-inferiority was established in the per-protocol population, a pre-specified superiority analysis was performed in a modified intent-to-treat (mITT) population. RECORD 2 was designed to assess the superiority of rivaroxaban compared with enoxaparin for the prevention of VTE after THR. Baseline demographic and surgical characteristics were similar between the two groups for all trials except for a significantly larger number of females in RECORD 3 (rivaroxaban 70% and enoxaparin 66%).

An analysis of the per-protocol population showed non-inferiority for the primary outcome in RECORD 1 (absolute risk reduction 2.5%; 95% CI 1.5% to 3.6%) and RECORD 3 (absolute risk reduction 8.7%; 95% CI 5.4% to 12.0%). Because non-inferiority was shown, a pre-specified superiority analysis was

undertaken to determine if the efficacy of rivaroxaban was superior to that of enoxaparin in the mITT population. All three studies showed the superior efficacy of rivaroxaban regarding the primary end point when compared with enoxaparin. This difference was mainly due to the reduced rate of symptomatic and asymptomatic DVT in the rivaroxaban group. The incidence of major VTE was also statistically significantly reduced with rivaroxaban compared with enoxaparin in all three trials. The incidence of symptomatic VTE was statistically significantly lower in the rivaroxaban treatment arm compared to enoxaparin in RECORD 2 and 3, but not in RECORD 1. The rate of symptomatic VTE during follow-up did not differ significantly between the two treatment groups in all three trials. There were no statistically significant differences between rivaroxaban and enoxaparin for all-cause mortality and non-fatal PE, but none of these studies were powered to detect such a difference. Overall, the results from RECORD 1 and 3 indicated that rivaroxaban was statistically significantly more effective than enoxaparin for thromboprophylaxis after THR or TKR, respectively. RECORD 2 showed that extended thromboprophylaxis with rivaroxaban was statistically significantly more effective than short-term thromboprophylaxis with enoxaparin after THR. Considering that the two treatments in RECORD 2 were of unequal length, this study did not necessarily show head-to-head superiority of rivaroxaban over enoxaparin as indicated in RECORD 1 and RECORD 3.

Table 7: Design of Published Phase 3 RCTs Evaluating Rivaroxaban for Thromboprophylaxis

Trial	Methods	Interventions	Patient Populations
Eriksson <i>et al.</i> , 2008 ⁴⁶ RECORD 1	<i>Design:</i> Randomized, double-blind, double-dummy, non-inferiority (margin of 3.5%), multicenter (US, Australia, Canada, Europe, South Africa, South America), parallel group, active control <i>Inclusion criteria:</i> Men and women over the age of 18 undergoing elective THR surgery <i>Follow-up:</i> 30 to 35 days after last dose of study drug	<i>Rivaroxaban</i> 10 mg PO once daily started 6 to 8 hours after surgery plus placebo injection versus <i>Enoxaparin</i> 40 mg SC once daily started the evening before surgery plus placebo tablet <i>Duration:</i> 31 to 39 days	<i>Randomized:</i> 4,541 (2,266 rivaroxaban, 2,275 enoxaparin) <i>Safety population</i> [*] : 4,433 (2,209 rivaroxaban, 2,224 enoxaparin) <i>mITT</i> [†] : 3,153 (1,595 rivaroxaban, 1,558 enoxaparin) <i>mITT (Major VTE)</i> [‡] : 3 364 (1,686 rivaroxaban, 1,678 enoxaparin) <i>Per-protocol</i> [§] : 3028 (1,537 rivaroxaban, 1,492 enoxaparin) <i>Symptomatic VTE</i> [¶] : 4,399 (2,193 rivaroxaban, 2,206 enoxaparin)
Kakkar <i>et al.</i> , 2008 ⁴⁷ RECORD 2	<i>Design:</i> Randomized, double-blind, double-dummy, superiority, multicenter (US, Australia, Canada, Europe, South Africa, South America), parallel group, active control <i>Inclusion criteria:</i> Men and women over the age of 18 undergoing elective THR surgery <i>Follow-up:</i> 30 to 35 days after last dose of study drug	<i>Rivaroxaban</i> 10 mg PO once daily started 6 to 8 hours after surgery plus placebo injection versus <i>Enoxaparin</i> 40 mg SC once daily started the evening before surgery plus placebo tablet <i>Duration:</i> Rivaroxaban: 31 to 39 days Enoxaparin: 10 to 14 days	<i>Randomized:</i> 2,509 (1 252 rivaroxaban, 1,257 enoxaparin) <i>Safety population:</i> 2,457 (1,228 rivaroxaban, 1,229 enoxaparin) <i>mITT:</i> 1,733 (864 rivaroxaban, 869 enoxaparin) <i>mITT (Major VTE):</i> 1,923 (961 rivaroxaban, 962 enoxaparin) <i>Per-protocol:</i> 1,615 (812 rivaroxaban, 803 enoxaparin) <i>Symptomatic VTE:</i> 2,419 (1,212 rivaroxaban, 1,207 enoxaparin)
Lassen <i>et al.</i> , 2008 ⁴⁸ RECORD 3	<i>Design:</i> Randomized, double-blind, double-dummy, non-inferiority (margin of 4%), multicenter (Canada, Europe, South Africa,	<i>Rivaroxaban</i> 10 mg PO once daily started 6 to 8 hours after surgery plus placebo injection	<i>Randomized:</i> 2,531 (1,254 rivaroxaban, 1,277 enoxaparin) <i>Safety population:</i> 2,459 (1,220 rivaroxaban,

Table 7: Design of Published Phase 3 RCTs Evaluating Rivaroxaban for Thromboprophylaxis

Trial	Methods	Interventions	Patient Populations
	South America), parallel group, active control <i>Inclusion criteria:</i> Men and women over the age of 18 undergoing elective TKR surgery <i>Follow-up:</i> 30 to 35 days after last dose of study drug	versus <i>Enoxaparin</i> 40 mg SC once daily started the evening before surgery plus placebo tablet <i>Duration:</i> 10 to 14 days	1,239 enoxaparin) <i>mITT</i> : 1,702 (824 rivaroxaban, 878 enoxaparin) <i>mITT (Major VTE)</i> : 1,833 (908 rivaroxaban, 925 enoxaparin) <i>Per-protocol</i> : 1631 (793 rivaroxaban, 838 enoxaparin) <i>Symptomatic VTE</i> : 2,418 (1,201 rivaroxaban, 1,217 enoxaparin)

mITT=modified intent-to-treat; PO=oral; RCTs=randomized controlled trials; SC=subcutaneous; THR=total hip replacement; TKR=total knee replacement; VTE= venous thromboembolism

†Safety population comprised of those participants who received at least one dose of study drug.

†mITT (Any DVT, non-fatal PE, or all-cause mortality) refers to patients who were considered valid for mITT analysis if they had undergone the appropriate surgery, had taken the study drug, and had an adequate assessment for thromboembolism.

‡mITT (Major VTE) refers to patients who were valid for MITT analysis for major VTE if they had undergone the appropriate surgery, had taken the study drug, and had an adequate assessment for thromboembolism in proximal veins.

§Per-protocol population included patients who were valid for mITT analysis and had an adequate assessment of thromboembolism with no major protocol deviations.

¶Symptomatic VTE included the safety population of patients who underwent surgery (independent of obtaining evaluable venograms).

Table 8: Results for Superiority Efficacy Analysis in Published Phase 3 RCTs Evaluating Rivaroxaban for Thromboprophylaxis

Outcome	RECORD 1 ⁴⁶ n (%)	RECORD 2 ⁴⁷ n (%)	RECORD 3 ⁴⁸ n (%)
Any DVT, non-fatal PE, or all-cause mortality (primary efficacy outcome)	Rivaroxaban: 18 (1.1%) Enoxaparin: 58 (3.7%) <i>Absolute risk difference:</i> -2.6% (95% CI -3.7 to -1.5; P < 0.001)	Rivaroxaban: 17 (2.0%) Enoxaparin: 81 (9.3%) <i>Absolute risk difference:</i> 7.3% (95% CI 5.2 to 9.4; P < 0.0001)	Rivaroxaban: 79 (9.6%) Enoxaparin: 166 (18.9%) <i>Absolute risk difference:</i> -9.2% (95% CI -12.4 to -5.9; P < 0.001)
Major VTE* (secondary efficacy outcome)	Rivaroxaban: 4 (0.2%) Enoxaparin: 33 (2.0%) <i>Absolute risk difference:</i> -1.7% (95% CI -2.5 to -1.0; P < 0.001)	Rivaroxaban: 6 (0.6%) Enoxaparin: 49 (5.1%) <i>Absolute risk difference:</i> 4.5% (95% CI 3.0 to 6.0; P < 0.0001)	Rivaroxaban: 9 (1.0%) Enoxaparin: 24 (2.6%) <i>Absolute risk difference:</i> -1.6% (95% CI -2.8 to -0.4; P < 0.01)

Table 8: Results for Superiority Efficacy Analysis in Published Phase 3 RCTs Evaluating Rivaroxaban for Thromboprophylaxis

Outcome	RECORD 1 ⁴⁶ n (%)	RECORD 2 ⁴⁷ n (%)	RECORD 3 ⁴⁸ n (%)
Non-fatal PE			
During treatment	Rivaroxaban: 4 (0.3%) Enoxaparin: 1 (0.1%) <i>Absolute risk difference:</i> 0.2% (95% CI -0.1 to 0.6; P = 0.37)	Rivaroxaban: 1 (0.1%) Enoxaparin: 4 (0.5%) <i>Absolute risk difference:</i> 0.3% (95% CI -0.2 to 1.1; P = 0.37)	Rivaroxaban: 0 Enoxaparin: 4 (0.5%) <i>Absolute risk difference:</i> -0.5% (95% CI -1.2 to 0.0; P = 0.06)
During follow-up	Not reported	Not reported	Not reported
Proximal DVT			
During treatment	Rivaroxaban: 1 (0.1%) Enoxaparin: 31 (2.0%) <i>Absolute risk difference:</i> -1.9 (95% CI -2.7 to -1.2; P < 0.001)	Rivaroxaban: 5 (0.6%) Enoxaparin: 44 (5.1%) <i>Absolute risk difference:</i> 4.5 (95% CI 2.9 to 6.0; P < 0.0001)	Rivaroxaban: 9 (1.1%) Enoxaparin: 20 (2.3%) <i>Absolute risk difference:</i> -1.1 (95% CI -2.3 to 0.1; P = 0.07)
Distal DVT during treatment	Rivaroxaban: 11 (0.7%) Enoxaparin: 22 (1.4%) <i>Absolute risk difference:</i> -0.7 (95% CI -1.5 to 0.0; P = 0.04)	Rivaroxaban: 9 (1.0%) Enoxaparin: 27(3.1%) <i>Absolute risk difference:</i> 2.0 (95% CI 0.7 to 3.3; P = 0.0025)	Rivaroxaban: 70 (8.5%) Enoxaparin: 140 (15.9%) <i>Absolute risk difference:</i> -7.3 (95% CI -10.4 to -4.3; P < 0.001)
DVT during follow-up	Not reported	Not reported	Not reported
Symptomatic VTE[†]			
During treatment	Rivaroxaban: 6 (0.3%) Enoxaparin: 11 (0.5%) <i>Absolute risk difference:</i> -0.2 (95% CI -0.6 to 0.1; P = 0.22)	Rivaroxaban: 3 (0.2%) Enoxaparin: 15 (1.2%) <i>Absolute risk difference:</i> 1.0 (95% CI 0.3 to 1.8; P = 0.0040)	Rivaroxaban: 8 (0.7%) Enoxaparin: 24 (2.0%) <i>Absolute risk difference:</i> -1.3 (95% CI -2.2 to -0.4; P = 0.005)

Table 8: Results for Superiority Efficacy Analysis in Published Phase 3 RCTs Evaluating Rivaroxaban for Thromboprophylaxis

Outcome	RECORD 1 ⁴⁶ n (%)	RECORD 2 ⁴⁷ n (%)	RECORD 3 ⁴⁸ n (%)
During follow-up	Rivaroxaban: 1 (<0.1%) Enoxaparin: 4 (0.2%) <i>Absolute risk difference:</i> -0.1 (95% CI -0.4 to 0.1; P = 0.37)	Rivaroxaban: 1 [‡] (0.1%) Enoxaparin: 2 [‡] (0.2%) <i>Absolute risk difference:</i> 0.1 (95% CI -0.2 to 0.4; P = 0.62)	Rivaroxaban: 5 (0.4%) Enoxaparin: 3 (0.2%) <i>Absolute risk difference:</i> 0.2 (95% CI -0.3 to 0.6; P = 0.44)
All-cause mortality			
During treatment	Rivaroxaban: 4 [¶] (0.3%) Enoxaparin: 4 ^{††} (0.3%) <i>Absolute risk difference:</i> 0.0 (95% CI -0.4 to 0.4; P = 1.00)	Rivaroxaban: 2 ^{**} (0.2%) Enoxaparin: 6 ^{**} (0.7%) <i>Absolute risk difference:</i> 0.5 (95% CI -0.2 to 1.1; P = 0.29)	Rivaroxaban: 0 Enoxaparin: 2 (0.2%) <i>Absolute risk difference:</i> -0.2 (95% CI -0.8 to 0.2; P = 0.23)
During follow-up	Rivaroxaban: 1 [¶] (0.1%) Enoxaparin: 0 <i>Absolute risk difference:</i> 0.1 (95% CI -0.2 to 0.4; P = 1.00)	Rivaroxaban: 0 Enoxaparin: 2 ^{‡‡} (0.2%) <i>Absolute risk difference:</i> 0.2 (95% CI -0.1 to 0.6; P = 0.50)	Rivaroxaban: 0 Enoxaparin: 4 (0.3%) <i>Absolute risk difference:</i> -0.3 (95% CI -0.8 to 0.0; P = 0.05)

VTE=Venous thromboembolism, PE=Pulmonary embolism, DVT=Deep vein thrombosis, CI=Confidence Interval

*Major VTE was a composite of proximal DVT, non-fatal PE, and VTE-related death.

† Symptomatic VTE included any symptomatic DVT (proximal or distal) and non-fatal or fatal symptomatic PE among patients in the safety population who had undergone surgery.

¶ Two deaths during treatment in the rivaroxaban group were possibly related to VTE; the other two deaths were unrelated to VTE. One death in the rivaroxaban group during follow-up was unrelated to VTE.

†† One death during treatment in the enoxaparin group was possibly related to VTE; the other three deaths were unrelated to VTE.

‡ During follow-up, symptomatic VTE occurring in one patient in the rivaroxaban group was non-fatal PE and two in the enoxaparin group were one fatal PE and one non-fatal PE.

** Both deaths in the rivaroxaban group were judged to be of cardiovascular cause. In the enoxaparin group, one death was related to VTE, four were unrelated to VTE, and one was unexplained.

‡‡ In the follow-up period, one death in the enoxaparin group was adjudicated as related to PE, and the other was unexplained.

The rates of major bleeding were comparable between treatment groups in all three trials. The exclusion of surgical site bleeding from the estimation of major bleeding events decreased the likelihood of detecting a difference between rivaroxaban and enoxaparin. One case of fatal bleeding was reported in RECORD 1 in a patient who was randomized to receive rivaroxaban, but never received the first dose. No differences were reported between rivaroxaban and enoxaparin in the liver function test results. Higher numbers of cardiovascular events (including cardiovascular death, ischemic stroke, and myocardial infarction) were reported during the follow-up period in patients receiving rivaroxaban versus enoxaparin in the RECORD 1 (8/2209 versus 1/2224) and RECORD 2 (5/1228 versus 0/1229) trials. Statistical significance was not reported for potential differences in cardiovascular events between groups in any of the RECORD trials.

Preliminary unpublished results from RECORD 4 were presented at the 2008 annual meeting of the European Federation of National Associations of Orthopedics and Traumatology.^{49,51} This is the first phase 3 trial that has compared rivaroxaban with the Health

Canada-approved regimen for enoxaparin. A total of 3,148 individuals who were undergoing TKR were randomized to receive 10 mg of rivaroxaban six to eight hours after surgery or 30 mg of enoxaparin twice daily started 12 to 24 hours after surgery. Both treatments were administered for 10 to 14 days, and patients were followed for 40 days. The available results indicate that similar to previous RECORD studies, the use of rivaroxaban statistically significantly reduces the incidence of the primary end point (a composite of any DVT, non-fatal PE, and all-cause mortality) when compared with enoxaparin (6.9% versus 10.1% respectively; $P = 0.012$). The rate of major VTE (a composite of proximal DVT, non-fatal PE, and VTE-related death) was not significantly different among those receiving rivaroxaban or enoxaparin (1.2% versus 2.0% respectively; $P = 0.124$). The incidence of symptomatic VTE did not differ significantly among those receiving rivaroxaban or enoxaparin (0.7% versus 1.2% respectively; $P = 0.187$). The rates of major bleeding were low in both treatment groups, but numerically greater in rivaroxaban-treated patients (0.7%) compared to patients receiving enoxaparin (0.3%). This was not statistically significant ($P = 0.110$).

Table 9: Safety Outcomes of Published Phase 3 RCTs Evaluating Rivaroxaban for Thromboprophylaxis

Outcome	RECORD 1⁴⁶ n (%)	RECORD 2⁴⁷ n (%)	RECORD 3⁴⁸ n (%)
Major bleeding during treatment (Primary safety outcome)	Rivaroxaban: 6 (0.3%) (95% CI 0.1 to 0.6) Enoxaparin: 2 (0.1%) (95% CI < 0.1 to 0.3) (P = 0.18)	Rivaroxaban: 1 (< 0.1%) (95% CI < 0.1 to 0.5) Enoxaparin: 1 (< 0.1%) (95% CI < 0.1 to 0.5) (P value not reported)	Rivaroxaban: 7 (0.6%) (95% CI 0.2 to 1.2) Enoxaparin: 6 (0.5%) (95% CI 0.2 to 1.1) (P = 0.77)
Non-major bleeding during treatment	Rivaroxaban: 128 (5.8%) Enoxaparin: 129 (5.8%)	Rivaroxaban: 80 (6.5%) Enoxaparin: 67 (5.5%)	Rivaroxaban: 53 (4.3%) Enoxaparin: 54 (4.4%)
Any on-treatment adverse event	Rivaroxaban: 1,413 (64.0%) Enoxaparin: 1,439 (64.7%)	Rivaroxaban: 768 (62.5%) Enoxaparin: 807 (65.7%)	Rivaroxaban: 776 (63.6%) Enoxaparin: 844 (68.1%)
Drug-related adverse event during treatment	Rivaroxaban: 270 (12.2%) Enoxaparin: 265 (11.9%)	Rivaroxaban: 245 (20.0%) Enoxaparin: 249 (20.3%)	Rivaroxaban: 146 (12.0%) Enoxaparin: 161 (13.0%)
Serious adverse events during treatment	Rivaroxaban: 146 (6.6%) Enoxaparin: 181 (8.1%)	Rivaroxaban: 90 (7.3%) Enoxaparin: 131 (10.7%)	Rivaroxaban: 90 (7.4%) Enoxaparin: 110 (8.9%)
Cardiovascular events during treatment	<i>Cardiovascular Death:</i> Rivaroxaban: 1 (< 0.1%) Enoxaparin: 0 <i>Ischemic Stroke:</i> Rivaroxaban: 1 (< 0.1%) Enoxaparin: 3 (0.1%) <i>Myocardial Infarction:</i> Rivaroxaban: 3 (0.1%) Enoxaparin: 6 (0.3%)	<i>Cardiovascular Death:</i> Rivaroxaban: 0 Enoxaparin: 0 <i>Ischemic Stroke:</i> Rivaroxaban: 1 (<0.1%) Enoxaparin: 1 (<0.1%) <i>Myocardial Infarction:</i> Rivaroxaban: 2 (0.2%) Enoxaparin: 3 (0.2%)	<i>Cardiovascular Death:</i> Rivaroxaban: 0 Enoxaparin: 1 (0.1%) <i>Ischemic Stroke:</i> Rivaroxaban: 3 (0.2%) Enoxaparin: 0 <i>Myocardial Infarction:</i> Rivaroxaban: 1 (0.1%) Enoxaparin: 2 (0.2%)
Cardiovascular events during follow-up	<i>Cardiovascular Death:</i> Rivaroxaban: 2* (< 0.1%) Enoxaparin: 1 (< 0.1%) <i>Ischemic Stroke:</i> Rivaroxaban: 2† (< 0.1%)	<i>Cardiovascular Death:</i> Rivaroxaban: 2 (0.2%) Enoxaparin: 0 <i>Ischemic Stroke:</i> Rivaroxaban: 1 (< 0.1%)	Rivaroxaban: 0 Enoxaparin: 6 (0.5%) (details not reported)

Table 9: Safety Outcomes of Published Phase 3 RCTs Evaluating Rivaroxaban for Thromboprophylaxis

Outcome	RECORD 1 ⁴⁶ n (%)	RECORD 2 ⁴⁷ n (%)	RECORD 3 ⁴⁸ n (%)
	Enoxaparin: 0 <i>Myocardial Infarction:</i> Rivaroxaban: 4 [†] (0.2%) Enoxaparin: 0	Enoxaparin: 0 <i>Myocardial Infarction:</i> Rivaroxaban: 2 [‡] (0.2%) Enoxaparin: 0	
Study withdrawal due to adverse effect:	Rivaroxaban: 85 (3.8%) Enoxaparin 100 (4.5%)	Rivaroxaban: 46 (3.8%) Enoxaparin 64 (5.2%)	Rivaroxaban: 39 (3.2%) Enoxaparin: 56 (4.5%)

* One patient also had an on-treatment cardiovascular event.

† One patient had an ischemic stroke and a myocardial infarction during follow-up.

‡ One event occurred in a patient who had received one placebo injection only.

4.4 Limitations

4.4.1 Limitations of Systematic Review

- The literature search was limited to published reports in English. Only abstracts that were obtained from limited web searches and hand searching the bibliographies of relevant records were considered for inclusion.
- The scope of this report was limited to the comparative clinical-effectiveness and safety of dabigatran or rivaroxaban compared with other anticoagulants. Other factors important for the uptake of these anticoagulants, including the cost-effectiveness relative to alternative therapies, were not considered.

4.4.2 Methodological limitations of included trials

- Although all trials were double-blinded, the details regarding allocation concealment and the efficacy of blinding were not provided.
- Large margins were used for testing non-inferiority in the RE-NOVATE, RE-MODEL, and RE-MOBILIZE trials. Furthermore, a modified intent-to-treat population rather than a per-protocol population was used for

efficacy analyses in all three trials. This could have biased the results toward non-inferiority.⁵⁰

- The dose and timing of initiation for enoxaparin, the timing of initiation for dabigatran, the type of surgery, the duration of prophylaxis, and the time of randomization differed in the RE-NOVATE, RE-MODEL, and RE-MOBILIZE trials. These differences may have introduced heterogeneity in the meta-analysis conducted by Wolowacz *et al.*,³⁸ making interpretation of the pooled results difficult. A meta-analysis of trials comparing dabigatran with different enoxaparin regimens may be less appropriate than a meta-analysis of the trials assessing different types of surgery.
- The definitions of major bleeding events differed significantly between the dabigatran and rivaroxaban clinical trials, making comparative risk-benefit assessments difficult. The exclusion of surgical site bleeding (unless it required re-operation or was fatal) from the estimation of major 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 2 trials.⁴³⁻⁴⁵

- 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. Sensitivity analyses were performed, however, in all three RECORD trials, as well as in the RE-MODEL and RE-MOBILIZE trials, to confirm that missing data did not affect the power of the study or bias any estimation of the treatment effect.
- Asymptomatic DVTs (particularly distal) that were identified through screening venograms accounted for most of the primary outcome composite events. The clinical importance of asymptomatic distal DVTs as a surrogate measure of symptomatic events has not been fully elucidated.⁵² The use of venographically detected asymptomatic DVTs, however, is still regarded as an acceptable surrogate measure by regulatory agencies such as the European Medicines Agency (EMA)⁵, Health Canada, and the FDA³⁷.
- Patients with severe renal insufficiency, severe liver disease, or at high risk of bleeding were excluded from the reviewed trials. Furthermore, the low numbers of patients with a previous history of VTE, over the age of 75 years, or at extremities of weight limited the generalizability of these results to populations in clinical practice.
- Clinically important outcomes, such as post DVT complications (e.g., post thrombotic syndrome), length of hospital stay, health-related quality of life, and surgical outcomes (including infection, wound healing,

drainage, range of motion, and 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 statements can be made about the safety of using rivaroxaban or dabigatran until long-term data from ongoing trials and post-marketing surveillance are available.

4.4.3 Knowledge gaps

- Because head-to-head trials comparing dabigatran with rivaroxaban are yet to be conducted, direct evidence of relative efficacy and safety is lacking.
- There have been no head-to-head comparisons of dabigatran or rivaroxaban with other LMWH, warfarin, UFH, or fondaparinux. Comparisons to fondaparinux are of particular interest, due to evidence for the superior clinical-effectiveness of fondaparinux compared with enoxaparin for the prevention of VTE after major orthopedic surgery.⁵³
- No trials have assessed the safety and efficacy of dabigatran or rivaroxaban for HFS.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence that dabigatran is at least as effective as enoxaparin for thromboprophylaxis after THR or TKR is conflicting. Of the three published phase 3 trials, two showed the non-inferiority of dabigatran in the prevention of VTE after THR or TKR, but the trial comparing dabigatran with the Health Canada-approved regimen for enoxaparin showed dabigatran to be inferior. As a result, the Canadian Expert Drug Advisory Committee (CEDAC) recommended

that dabigatran not be listed in publicly funded drug plans.⁵⁴ Additional trials comparing dabigatran with the Health Canada-approved dose of enoxaparin are needed. The results from three phase 3 trials indicate the superior clinical-effectiveness of rivaroxaban compared with enoxaparin for the prevention of VTE after THR or TKR. Based on these results, CEDAC recommended that rivaroxaban be listed in publicly funded drug plans for the prophylaxis of VTE after TKR or THR for up to two weeks as an alternative to LWMH.⁵⁵ CEDAC also recommended that reimbursement for the extended prophylaxis of VTE with other agents after two weeks of rivaroxaban use should not be provided because the cost-effectiveness of VTE prophylaxis beyond two weeks has not been established.⁵⁵ CEDAC's recommendation for reimbursement does not follow the ACCP recommendations⁶ for outpatient extended prophylaxis of up to 35 days after THR or TKR. This could be of concern for practising clinicians. CEDAC's decision was largely based on trials using the European dosing recommendations for enoxaparin; the final results from a fourth phase 3 trial⁵⁶ are needed to reduce uncertainty about the effectiveness of using the Health Canada approved dosing regimen.

There is no compelling evidence that thromboprophylaxis with dabigatran or rivaroxaban leads to a significantly higher incidence of adverse effects, including hepatotoxicity or cardiovascular events when compared with enoxaparin. Similar rates of major bleeding and all-cause mortality were reported for dabigatran and for rivaroxaban when compared with enoxaparin. None of the trials, however, were sufficiently powered to detect a difference between drugs. The exclusion of surgical site bleeding from the estimation of major bleeding events in phase 3 rivaroxaban trials may have led to an underestimation of major bleeding attributable to rivaroxaban. Furthermore, in a briefing document prepared for the United States FDA advisory committee, a trend toward an increased incidence of major bleeding among patients who received rivaroxaban compared with patients who received enoxaparin (0.39% versus 0.21%

respectively; P-value for time to first event = 0.08; P-value for time to multiple event = 0.05) was reported in an integrated analysis of all four phase 3 trials for rivaroxaban.³⁷ Similar results were reported for the proportion of subjects with major bleeding combined with surgical site bleeding (1.80% versus 1.37%; P-value for time to first event = 0.06), or major or non-major clinically relevant bleeding (3.19% versus 2.55%; P-value for time to first event = 0.039) among patients receiving rivaroxaban and enoxaparin, respectively. The briefing document indicates that hepatotoxicity and cardiovascular events (particularly ischemic stroke occurring early after treatment discontinuation) are of concern with the use of rivaroxaban, pending results from long-term clinical trials. Considering these data, the FDA advisory committee recommended in March 2009 that the FDA approve rivaroxaban for VTE thromboprophylaxis after elective THR or TKR.^{37,57} The results from ongoing trials assessing dabigatran (RE-NOVATE II)⁵⁸ and rivaroxaban⁵⁹ will further reduce uncertainty about the safety and efficacy when used for thromboprophylaxis after orthopedic surgery.

Available trials have only compared dabigatran or rivaroxaban with enoxaparin. Without head-to-head trials comparing rivaroxaban with dabigatran or either drug to other anticoagulants, indirect comparisons⁶⁰ should be interpreted with caution due to differences in the methods that were used for assessing outcomes among trials and particularly because of differences in the definitions of major bleeding events, dosing regimens, and duration of treatment. Clinically important outcomes such as post-DVT complications, length of hospital stay, health-related quality of life, and surgical outcomes have not yet been assessed in clinical trials. The effect of dabigatran or rivaroxaban on these outcomes should be considered when making decisions about the choice of therapy. Patients with severe renal insufficiency, severe liver disease, or at high risk of bleeding were excluded from the reviewed trials. Furthermore, the low numbers of patients in clinical trials with a previous history of VTE, over the age of 75 years, or at extremities of weight limited the generalizability of the results to populations in

clinical practice. There is no evidence to support the use of dabigatran or rivaroxaban in patients undergoing HFS.

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 among diverse patient populations after major orthopedic surgery.

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APPENDIX 1: COMPLETED (PUBLISHED AND UNPUBLISHED) AND ONGOING CLINICAL TRIALS

Rivaroxaban. In: *ClinicalTrials.gov* [website]. Bethesda (MD): National Institutes of Health; 2009. <http://clinicaltrials.gov/ct2/results?term=rivaroxaban> (accessed 2009 Mar 13)

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APPENDIX 2: DEFINITIONS USED IN CLINICAL TRIALS FOR BLEEDING

Study	Definition of Major Bleeding	Additional Criteria
Dabigatran		
BISTRO II ³⁹ RE-NOVATE ⁴⁰ RE-MODEL ⁴¹ RE-MOBILIZE ⁴²	Fatal retroperitoneal, intracranial, intraocular, or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation; clinically overt bleeding associated with a decrease in hemoglobin of 2 g/dL or more, or requiring a transfusion of ≥ 2 units of packed red blood cells	<i>Clinically relevant non-major bleeding:</i> Spontaneous hematoma ≥ 25 cm ² ; wound hematoma ≥ 100 cm ² ; epistaxis lasting more than 5 minutes; macroscopic hematuria (spontaneous or lasting greater than 24 hours if associated with an intervention); spontaneous rectal bleeding; gingival bleeding lasting more than 5 minutes; any other bleeding event judged by investigator to be clinically significant <i>Minor bleeding:</i> (for BISTRO II, RE-NOVATE, RE-MODEL) Any bleeding not fulfilling criteria of major or clinically relevant bleeding
Rivaroxaban		
Phase 2 trials ⁴³⁻⁴⁵	Fatal; bleeding into a critical organ (e.g., retroperitoneal, intracranial, intraspinal, or intraocular); bleeding requiring reoperation or treatment cessation; clinically overt bleeding associated with a decrease in hemoglobin of 2 g/dL or more, or leading to a transfusion of at least 2 units of blood; starting after the first dose of study medication, and up to 2 days after the last administration of study drug	<i>Clinically relevant, non-major bleeding:</i> Spontaneous hematoma > 25 cm ² ; wound hematoma > 100 cm ² ; multiple site or extrasurgical site bleeding; epistaxis lasting more than 5 minutes; macroscopic hematuria (spontaneous or lasting longer than 24 hours if associated with an intervention); spontaneous rectal bleeding; gingival bleeding lasting longer than 5 minutes, hemoptysis; hematemeses; prolonged bleeding longer than 5 minutes after venipuncture <i>Minor bleeding:</i> Any bleeding event not fulfilling the criteria for major, postoperative bleeding or clinically relevant, non-major bleeding
RECORD 1,2,3 ⁴⁶⁻⁴⁸	Fatal; bleeding into a critical organ (e.g., retroperitoneal, intracranial, intraspinal, or intraocular); bleeding requiring reoperation; clinically overt extra-surgical site bleeding associated with a decrease in hemoglobin of 2 g/dL or more, or requiring a transfusion of at least 2 units of whole blood or packed cells; starting after the first dose of study medication, and up to 2 days after the last administration of study drug	<i>Non-major bleeding:</i> Any bleeding not adjudicated as major bleeding, including clinically relevant non-major bleeding events (definition same as phase 2 trials) and hemorrhagic wound complications (a composite of excessive wound hematoma and surgical site bleeding)