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Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement (Review)

Salazar CA, Malaga G, Malasquez G

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[Intervention Review]

Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

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ABSTRACT

Background

Patients who have undergone total hip or knee replacement (THR, TKR) have a high risk of developing venous thromboembolism (VTE) following surgery, despite appropriate anticoagulation with warfarin or low molecular weight heparin (LMWH). New anticoagulants are under investigation.

Objectives

To examine the efficacy and safety of prophylactic anticoagulation with direct thrombin inhibitors (DTIs) versus LMWH or vitamin K antagonists in the prevention of VTE in patients undergoing THR or TKR.

Search methods

The Cochrane Peripheral Vascular Disease Group searched their Specialized Register (last searched 12 March 2010) and CENTRAL (last searched 2010, Issue 1).

Selection criteria

Randomised controlled trials.

Data collection and analysis

Three reviewers independently assessed methodological quality and extracted data in pre-designed tables. The reported follow-up events were included

Main results

We included 14 studies involving 21,642 patients evaluated for efficacy and 27,360 for safety. No difference was observed in major VTE in DTIs compared with LMWH in both types of operations (odds ratio (OR) 0.91; 95% confidence interval (CI) 0.69 to 1.19), with high heterogeneity (I^2 71%). No difference was observed with warfarin (OR 0.85; 95% CI 0.63 to 1.15) in TKR, with no heterogeneity (I^2 0%).

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More total bleeding events were observed in the DTI group (in ximelagatran and dabigatran but not in desirudin) in patients subjected to THR (OR 1.40; 95% CI 1.06, 1.85; I^2 41%) compared with LMWH. No difference was observed with warfarin in TKR (OR 1.76; 95% CI 0.91 to 3.38; I^2 0%).

All-cause mortality was higher in the DTI group when the reported follow-up events were included (OR 2.06; 95% CI 1.10 to 3.87).

Studies that initiated anticoagulation before surgery showed less VTE events; those that began anticoagulation after surgery showed more VTE events in comparison with LMWH. Therefore, the effect of the DTIs compared with LMWH appears to be influenced by the time of initiation of coagulation more than the effect of the drug itself.

The results obtained from sensitivity analysis, did not differ from the analysed results; this strengthens the value of the results.

Authors' conclusions

Direct thrombin inhibitors are as effective in the prevention of major venous thromboembolism in THR or TKR as LMWH and vitamin K antagonists. However, they show higher mortality and cause more bleeding than LMWH. No severe hepatic complications were reported in the analysed studies. Use of ximelagatran is not recommended for VTE prevention in patients who have undergone orthopedic surgery. More studies are necessary regarding dabigatran.

PLAIN LANGUAGE SUMMARY

New types of anticoagulants to prevent deep vein thrombosis and pulmonary embolism following total hip or knee replacement surgery

Venous thromboembolism is the presence of a blood clot that blocks a blood vessel within the venous system; it includes deep vein thrombosis (DVT) and pulmonary embolism (PE) which can be fatal. Venous thromboembolism occurs in 44% to 90% of those patients who undergo total hip or knee replacement and who do not receive anticoagulants (blood thinning drugs).

The standard treatment is prophylaxis with an anticoagulant such as low molecular weight heparin (known as an indirect thrombin inhibitor), or warfarin or coumarin (vitamin K antagonists). New types of anticoagulants termed direct thrombin inhibitors have advantages over heparin as they can be given by mouth, do not require laboratory control and no relevant interaction with food or alcohol is known.

This review found that direct thrombin inhibitors are as effective in the prevention of major venous thromboembolism in total hip or knee replacement compared with low molecular weight heparin and vitamin K antagonists. However, the newer anticoagulants showed higher mortality and caused more bleeding than low molecular weight heparin. No severe liver complications complications were reported in the analysed studies.

The review also showed that the timing of the start of giving anticoagulants influences the results.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Direct Thrombin Inhibitors versus Low Molecular Weight Heparins for prevention of venous thromboembolism following total hip or knee replacement.						
Patient or population: patients with prevention of venous thromboembolism following total hip or knee replacement Settings: elective surgery Intervention: Direct Thrombin Inhibitors Comparison: Low molecular Weight Heparins						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low molecular Weight Heparins	Direct Thrombin Inhibitors				
Major VTE events bilateral ascending venography ¹ Follow-up: 4-6 weeks ²	Medium risk population		OR 0.91 (0.69 to 1.19)	17428 (11 studies)	⊕⊕○○ low ^{3,4,5}	
	66 per 1000	60 per 1000 (46 to 78)				
All-cause Mortality events Follow-up: 4-6 weeks ²	Medium risk population		OR 2.06 (1.1 to 3.87)	22065 (11 studies)	⊕⊕⊕○ moderate ^{3,5,6}	
	1 per 1000	2 per 1000 (1 to 4)				
Total Bleeding events Follow-up: 4-6 weeks ²	Medium risk population		OR 1.17 (0.98 to 1.41)	22109 (11 studies)	⊕⊕○○ low ^{3,5,7}	
	107 per 1000	123 per 1000 (105 to 145)				
ALT >3 times the upper normal limit Follow-up: 4-6 weeks ²	Medium risk population		OR 0.41 (0.23 to 0.72)	12580 (7 studies)	⊕⊕○○ low ^{3,4,5}	

	57 per 1000	24 per 1000 (14 to 42)	
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Two of 11 studies performed only unilateral venography

² optimal follow-up time for DVT more than 8 weeks

³ No adequate ITT analysis were performed in the original studies, however the review included all the reported follow-up events.

⁴ High unexplained heterogeneity (75%² I² >50%)

⁵ Funnel plot assymetric

⁶ RR>2

⁷ High unexplained heterogeneity (I² > 50%)

BACKGROUND

Venous thromboembolism (VTE) has been observed three months post operatively in 2.4% of patients who have undergone hip arthroplasty (replacement), and in 1.7% of the patients who have undergone knee arthroplasty despite their having received prophylaxis (White 1998). Symptomatic venous thromboembolism occurs after the patients leave hospital, and the risk increases for at least two months after surgery (Douketis 2002; Leclerc 1998; Pellegrini 1996; White 1998). Thromboembolism is a common cause of re-admission to hospital subsequent to total hip replacement surgery (Seagroatt 1991). New anticoagulants are under investigation.

Description of the condition

Venous thromboembolism is the presence of a blood clot that blocks a blood vessel within the venous system; it includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thromboembolism occurs in 44% to 90% of those patients who undergo total hip or knee replacement and who do not receive anticoagulants. Proximal venous thrombosis occurs in another 20% of those patients who do not receive prophylactic anticoagulants (Geerts 2001), and PE develops in up to 7% (Stringer 1989), of which 0.7% may be fatal (Ansari 1997). The standard treatment is prophylaxis with the indirect thrombin inhibitor, low molecular weight heparin (LMWH) (Geerts 2001), or vitamin K antagonists (VKAs) such as warfarin or coumarin (Gross 1999; Hill 2007; Mesko 2001).

Description of the intervention

More recently, direct thrombin inhibitors (DTIs) with properties that give them potential mechanistic advantages over indirect thrombin inhibitors such as heparin, have been used (Weitz 2002a; Weitz 2002b; Weitz 2004). Direct thrombin inhibitors do not require laboratory control (Desai 2004; Pengo 2004). Most direct thrombin inhibitors (hirudin, argatroban, bivalirudin, etc) need to be given by injection (parenterally). However, ximelagatran, a melagatran prodrug, is the first oral direct thrombin inhibitor (Weitz 2004) and its metabolism is not affected by the age, sex, body weight, or ethnic origin of the recipient, and no relevant interaction with food or alcohol is known (Desai 2004). They could be used in the treatment of patients with heparin induced thrombocytopenia (HIT) (DTI TGC 2002; Eikelboom 2002; Lewis 2003). Its use is associated with an increase of alanine aminotransferase (ALT) (an enzyme found primarily in the liver and which is released into the blood stream as the result of liver damage) up to three times its nominal value (Lazerow 2005; Olsson 2002; Olsson 2003; Petersen 2003; Schulman 2003) although even severe and fatal hepatopathy (liver disease) has been reported (Albers 2005; Desai 2004; O' Brien 2005; Spell-Lesane

2004). Dabigatran, a newer DTI has the same advantages of ximelagatran, and apparently is not associated with hepatopathy.

How the intervention might work

The use of ximelagatran was approved in European countries for short-term treatment and prevention of thromboembolism subsequent to total knee and hip replacement surgery, but later on it was removed due to hepatocellular damage (EMA 2006a; EMA 2006b). Dabigatran has been approved for VTE treatment in many countries.

The purpose of this review is to summarize the evidence from randomised clinical trials that evaluate the efficacy (demonstrated by less VTE events) and safety (less bleeding and adverse events) of all the direct thrombin inhibitors compared with vitamin K antagonists or low molecular weight heparins in the prevention of venous thromboembolism (deep vein thrombosis or pulmonary embolism) in patients who have undergone total hip or knee replacement. Moreover, we endeavoured to review the risk estimate of serious adverse events associated with the analysed therapies.

Why it is important to do this review

The effectiveness of classic anticoagulants, such as heparin and warfarin, has been proven in numerous studies. However, 47% of the patients treated with warfarin and 31% of the patients treated with low molecular weight heparins develop thrombosis after knee replacement (Geerts 2001). Warfarin is administered orally, has a narrow therapeutic window and also requires periodic laboratory controls (Geerts 2001). It is associated with an increased risk of haemorrhage of 3% to 4% annually. Coagulation monitoring and dose adjustment are routine during treatment with vitamin K antagonists (Ansell 2001; Hirsh 2001; Schulman 2003). Low molecular weight heparins do not require laboratory control, but all of them are given parenterally.

OBJECTIVES

1. To examine the existing clinical evidence on the efficacy of prophylactic anticoagulation with direct thrombin inhibitors versus vitamin K antagonists in the prevention of venous thromboembolism in patients who have undergone total hip or knee replacement.
2. To examine the existing clinical evidence on the efficacy of prophylactic anticoagulation with direct thrombin inhibitors versus low molecular weight heparins, in the prevention of venous

thromboembolism in patients who have undergone total hip or knee replacement.

3. To evaluate the existing clinical evidence on the risks including any adverse event (serious or not) of bleeding, skin necrosis, heparin-induced thrombocytopenia (HIT) or hepatopathy associated with the analysed therapies, in the prevention of venous thromboembolism in patients who have undergone total hip or knee replacement.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) designed to compare prophylactic anticoagulation with direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins in the prevention of venous thromboembolism.

Types of participants

Patients who have undergone total hip or knee replacement.

Types of interventions

The intervention of interest was the administration of prophylactic anticoagulation with direct thrombin inhibitors, compared with vitamin K antagonists or low molecular weight heparins.

Types of outcome measures

For efficacy

- VTE events (DVT, PE): dichotomous
- Mortality events due to VTE: dichotomous

For safety

- Bleeding events: dichotomous
- Hepatopathy events: dichotomous
- Mortality events due to bleeding or others: dichotomous
- Bleeding volume: continuous

Primary outcomes

Mortality associated with venous thromboembolism (PE or DVT). The incidence of proximal venous thromboembolism (includes DVT from the popliteal vein, symptomatic DVT and PE). Pulmonary embolism was defined by positive pulmonary angiography, high probability ventilation /perfusion scan, positive helical tomography, evidence from post mortem, or any validated method). The diagnosis of DVT was accepted if made by positive venography, or ultrasonography, or any validated method. Incidence was defined as the appearance of thrombosis in an area where it did not exist prior to the study. Mortality associated with treatment. The appearance of serious hepatopathy (liver disease), defined as fulminant hepatitis, symptoms of liver failure, or life-threatening hepatopathy. The appearance of other serious adverse effects associated with the treatment including: significant haemorrhagic events (defined by a decrease in haemoglobin concentration of more than 2 g/dl, retroperitoneal or intracranial bleeding, or the requirement of transfusion of two or more globular packets); heparin-induced thrombocytopenia (HIT) (reduced numbers of platelets), or any life-threatening event. Heparin-induced thrombocytopenia was defined by the formation of HIT-specific antibodies accompanied by an otherwise unexplained decrease in platelet count (usually > 50% fall, even if at its lowest point, the platelet count remained $>150 \times 10^9/L$), or by skin lesions at heparin injection sites, or acute systemic reactions for example, chills or cardiorespiratory distress after intravenous heparin bolus administration

Primary outcomes

1. Mortality associated with venous thromboembolism (PE or DVT).
2. The incidence of proximal venous thromboembolism (includes DVT from the popliteal vein, symptomatic DVT and PE). Pulmonary embolism was defined by positive pulmonary angiography, high probability ventilation /perfusion scan, positive helical tomography, evidence from post mortem, or any validated method). The diagnosis of DVT was accepted if made by positive venography, or ultrasonography, or any validated method. Incidence was defined as the appearance of thrombosis in an area where it did not exist prior to the study.
3. Mortality associated with treatment.
4. The appearance of serious hepatopathy (liver disease), defined as fulminant hepatitis, symptoms of liver failure, or life-threatening hepatopathy.
5. The appearance of other serious adverse effects associated with the treatment including: significant haemorrhagic events (defined by a decrease in haemoglobin concentration of more than 2 g/dl, retroperitoneal or intracranial bleeding, or the requirement of transfusion of two or more globular packets); heparin-induced thrombocytopenia (HIT) (reduced numbers of platelets), or any life-threatening event. Heparin-induced

thrombocytopenia was defined by the formation of HIT-specific antibodies accompanied by an otherwise unexplained decrease in platelet count (usually > 50% fall, even if at its lowest point, the platelet count remained >150 x 10⁹/L), or by skin lesions at heparin injection sites, or acute systemic reactions for example, chills or cardiorespiratory distress after intravenous heparin bolus administration

Secondary outcomes

1. The incidence of distal venous thromboembolism (asymptomatic distal DVT below popliteal vein). Incidence was defined as the appearance of thrombosis in an area where it did not exist prior to the study.
2. The presence of hepatopathy after the treatment (whether or not there was a temporary elevation of hepatic enzymes).
3. Morbidity associated with treatment (the appearance of non fatal or significant haemorrhagic events, uncomplicated skin necrosis, or any non life-threatening event).

Search methods for identification of studies

Electronic searches

The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Specialised Register (last searched 12 March 2010) and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (last searched 2010, Issue 1); see [Appendix 1](#) for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the Trials Search Co-ordinator and is constructed from back searches and continued weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the [Specialised Register](#) section of the Cochrane PVD Group module in *The Cochrane Library*.

We also searched in LILACS (Latin American and Caribbean Health Sciences Literature - is a cooperative database built by the institutions which integrate the Latin American and Caribbean of Health Sciences Information System) (last searched 12 March 2010) for publications that described randomised controlled trials of anticoagulation with direct thrombin inhibitors (ximelagatran, dabigatran, melagatran, argatroban, hirudin, lepirudin, bivalirudin, efegatran and inogatran) versus vitamin K antagonists (warfarin or coumarin), or low molecular weight heparins (nadroparin calcium (Fraxiparin), enoxaparin sodium (Lovenox, Clexane), dalteparin (Fragmin) and tinzaparin (Innohep)), in the prevention of venous thromboembolism (DVT or PE, or both) in patients who have undergone total hip or knee replacement (see [Appendix 2](#) for details of search strategy).

Searching other resources

Reference lists of identified studies were reviewed to locate relevant randomised controlled clinical trials. In addition, a search was carried out to find unpublished randomised clinical trials through personal communication with colleagues, experts, authors of published studies, and representatives of pharmaceutical companies. We performed a manual search of relevant national and international journals.

We also searched the databases mentioned above, and toxicity data of prophylactic anticoagulation for the secondary review of adverse events with minor, significant, and fatal bleeding; hepatopathy; heparin-induced thrombocytopenia; or necrosis due to anticoagulant treatment for DVT or PE.

Data collection and analysis

All three review authors independently evaluated the titles and abstracts of the reports of trials identified by the electronic searches. Printed copies of the full text were obtained of those trials that met the selection criteria.

Selection of studies

Critical Evaluation of the Studies

All three review authors independently evaluated the methodological quality of each trial and any differences of opinion were resolved by consensus. We recorded details of randomisation (sequence and masking), blinding, incomplete outcome data, and the number of patients lost to follow up.

We employed two approaches to evaluate the methodological quality of studies: the Cochrane risk of bias approach and the one used by Handoll et al ([Handoll 2002](#)) which was modified for the purposes of this review. The latter approach evaluates twelve aspects of internal and external validity specifically for anticoagulation in orthopaedic surgery for VTE prevention (See [Appendix 3](#)).

We also determined the external validity of each trial by considering the characteristics of the participants (inclusion and exclusion criteria; clinical and laboratory diagnosis criteria; number of participants; age; sex; duration of follow up; duration of the study, and setting where the trial was carried out); interventions (type of prophylactic anticoagulant; duration of the prophylactic anticoagulation treatment); anticoagulation laboratory control; and results.

Data extraction and management

All three authors independently extracted data using pre-designed data extraction sheets and verified the data. Data from any studies that had been published twice were extracted from the more complete article.

Assessment of risk of bias in included studies

All three authors independently evaluated the quality of the studies according to the Cochrane risk of bias approach. The review authors were not biased with regard to journal, institution, or study results. We intended to have titles and abstracts of articles in languages other than English or Spanish translated into either language and then evaluated with subsequent translation of the entire text of the article if the title and the abstract met the inclusion criteria. This proved to be unnecessary.

Measures of treatment effect

We summarized the dichotomous results for each study using the odds ratio (OR), and for the continuous results we used mean differences (MD).

Unit of analysis issues

We used the Mantel-Haenszel fixed effects meta-analysis for dichotomous outcomes (Mantel 1959), and the generic inverse variance for continuous outcomes and the DerSimonian and Laird random effects meta-analysis even for dichotomous and continuous outcomes (DerSimonian 1986). We performed sensitivity analyses.

Dealing with missing data

We will re-evaluate those studies without complete information if the additional information from the authors becomes available. Reasons for exclusion of the studies were documented. We resolved differences of opinion by consensus.

Regarding the missing data in the included studies, we re-included in the analysis the PE or DVT reported events which were omitted from the analysis and only figured as reasons for discontinuation.

Assessment of heterogeneity

We used the I^2 test instead of the chi-square test to ascertain homogeneity among the studies since it is a more useful method to analyse heterogeneity when there are only a few studies (as is the case in this review) and allows comparison among subgroups. The I^2 is expressed in percentages and describes the proportion of variability that is due to heterogeneity rather than sampling error. Based on Higgins 2003, we have tentatively assigned low heterogeneity with I^2 values less than 25%, and we defined moderate heterogeneity with $I^2 \geq 25\%$, but $< 50\%$ and high heterogeneity with $I^2 \geq 50\%$, but $< 75\%$.

Assessment of reporting biases

Regarding the analysis of studies according to methodological quality, we considered the following:

- generation of the randomisation sequence and allocation concealment (Yes, Unclear, No);
- blinding (partially open, double blind, triple blind);
- randomisation analysis (intention-to-treat analysis, or per-protocol analysis);
- duration of the follow up (optimum: follow up for more than eight weeks; adequate: at least 10 days; inadequate or not defined: less than 10 days).

We also created a table showing a methodological comparison of included studies which describes the rate of randomised patients that were analysed (Table 1). Finally we elaborated the risk of bias table, methodological quality summary and graphic according to the risk of bias criteria.

Data synthesis

Where heterogeneity of included studies was low we analysed the results using fixed-effect meta-analysis. Where the heterogeneity was considered to be moderate or high, the results were analysed using a random-effects meta-analysis, because even though this model does not correct the heterogeneity, it considers its existence. But, for very high heterogeneity ($I^2 \geq 75\%$), we did not use joint combined analysis of these data and the results are presented separately.

Subgroup analysis and investigation of heterogeneity

Two subgroups analyses were relevant in the type of studies available: according to the duration of the prophylactic anticoagulation (standard versus extended) and according to the time of initiation of prophylactic anticoagulation (before surgery versus after surgery).

Where there was significant heterogeneity among the studies, we explored the reasons for such heterogeneity and the best conclusions were obtained from the observations. Moreover, the heterogeneity among studies was evaluated subjectively by means of clinical judgment based on the differences in patient population, interventions and measurement of the results. Bearing in mind that not all the trials were designed to measure adverse events, the secondary results were interpreted with caution.

Sensitivity analysis

There are different ways to analyse a systematic review. Therefore, if results vary, the analysis of the review should consider other type of evaluations. We measured the robustness of the results through the analysis of the following study categories:

- events reported in the follow up;
- according to the type of surgery (THR, TKR, or both);
- effect of the time of initiation of anticoagulation;

- re-analysis of the data using another statistical approach (using randomised effect meta-analysis instead of fixed and vice versa);
- evaluation of the more extensive results: total thromboembolism for effectiveness and total bleeding for safety;
- according to their methodological quality.

Due to the results obtained, we considered it necessary to perform other sensitivity analyses (a posteriori) including or excluding variables, or studies.

RESULTS

Description of studies

Results of the search

The search was carried out to find all types of DTIs used in patients subjected to total hip or knee replacement surgery. All trials included in the review were identified via electronic database searches. No relevant study was found by local handsearching. We did not find any information on unpublished trials. No translation was necessary since all the studies were in English.

We identified 56 citations to 30 potential trials that appeared to comply with the specified search criteria.

Currently, there is one study pending evaluation; the [RE-NOVATE II 2009](#) trial which compares dabigatran versus LMWH for extended anticoagulation in total hip arthroplasty surgery. More details in the [Characteristics of ongoing studies](#) table.

Included studies

Details of the individual studies are given in the [Characteristics of included studies](#) table.

We included 14 randomised controlled trials in the review. In total we found 35 references to these studies including abstracts or subsequent analyses of the interested studies. In all the 14 included studies, only patients subjected to elective THR or TKR were included but no patients with hip repair or hip fracture.

Nine of the 14 studies investigated ximelagatran ([Colwell 2003](#); [EXPRESS 2003](#); [EXULT A 2003](#); [EXULT B 2005](#); [Francis 2002](#); [Heit 2001](#); [METHRO I 2002](#); [METHRO II 2002](#); [METHRO III 2003](#)), whether given orally or in combination with subcutaneous melagatran. Five studies were found that used other DTIs: four used oral dabigatran ([BISTRO II 2005](#); [RE-MOBILIZE 2009](#); [RE-MODEL 2007](#); [RE-NOVATE 2007](#)), and one used subcutaneous desirudin ([Eriksson 1997](#)).

Three of the six studies that compared ximelagatran with LMWH began prophylaxis for venous thromboembolism after surgery (

[Colwell 2003](#); [Heit 2001](#); [METHRO III 2003](#)) which corresponds to 52.1% of the randomised patients in this group.

All the randomised patients in the studies that compared ximelagatran with warfarin ([EXULT A 2003](#); [EXULT B 2005](#); [Francis 2002](#)) also began prophylaxis after surgery.

Four studies compared dabigatran with LMWH; three studies commenced treatment 1 to 4 hours after surgery ([BISTRO II 2005](#); [RE-MODEL 2007](#); [RE-NOVATE 2007](#)); the [RE-MOBILIZE 2009](#) study commenced treatment 6 to 12 hours after surgery. The [Eriksson 1997](#) study that compared desirudin with LMWH began prophylaxis before surgery.

It is important to notice that four studies ([BISTRO II 2005](#); [METHRO III 2003](#); [RE-MODEL 2007](#); [RE-NOVATE 2007](#)) began anticoagulation with DTIs after surgery, but LMWH anticoagulation began before surgery (as European centres do). The [RE-MOBILIZE 2009](#) study began DTI and LMWH after surgery which is the North American Anticoagulation Regime.

Eleven RCTs ([BISTRO II 2005](#); [Colwell 2003](#); [Eriksson 1997](#); [EXPRESS 2003](#); [Heit 2001](#); [METHRO I 2002](#); [METHRO II 2002](#); [METHRO III 2003](#); [RE-MOBILIZE 2009](#); [RE-MODEL 2007](#); [RE-NOVATE 2007](#)) analysed the efficacy of the treatment in 17,305 patients: 10661 patients in the DTIs group compared with 6644 patients in the control group who received LMWH. Three RCTs ([EXULT A 2003](#); [EXULT B 2005](#); [Francis 2002](#)) analysed the efficacy in 4337 patients: 2501 patients in the DTIs group and compared them with 1836 patients in the warfarin group. All 11 studies were used to evaluate the safety analysis.

The safety analysis in studies comparing DTIs with LMWH included 22,101 patients of whom 13,749 received DTIs compared with 8352 who received LMWH. Regarding the safety analysis with warfarin, 3022 patients who received DTIs were compared with 2237 patients who received warfarin, making a total of 5259 patients.

Of the 27,746 randomised patients who underwent surgery, 10,928 were subjected to total hip replacement (THR). All those who underwent surgery for total hip replacement received DTIs or LMWH. The remainder underwent total knee replacement (TKR) with approximately 31% of them receiving DTIs compared with warfarin, and the rest receiving DTIs compared with LMWH. All studies that compared DTIs with warfarin were carried out in patients who were subjected to total knee replacement.

Of the total randomised patients, 15,493 (56%) come from European hospitals and 7722 (44%) from North American centres. All patients for whom ximelagatran and warfarin are compared came from North American centres. There was no information regarding the origin of the randomised patients in the [METHRO II 2002](#) study.

Sixty per cent of the randomised patients were female and all the studies also included a significant number of elderly patients since the mean age is 66.4 years (range 64 to 69) with the extremes of the randomised population between 18 to 93 years.

Ximelagatran versus LMWH Studies

Six RCTS were included (Colwell 2003; EXPRESS 2003; Heit 2001; METHRO I 2002; METHRO II 2002; METHRO III 2003) that analysed 10,200 patients, mainly female (57.2% of those randomised in this group), and elderly (mean ages ranging between 64 to 69 years). Three of these studies (Heit 2001; METHRO I 2002; METHRO II 2002) compared different doses of oral ximelagatran (6 mg, 8 mg, 12 mg, 18 mg and 24 mg) with prior application of diverse doses of subcutaneous melagatran. In order to synthesize the evidence, we grouped minor different doses of ximelagatran / melagatran in the group called **ximelagatran < 24 mg** which was analysed separately from **ximelagatran 24 mg**. Only Heit 2001 and Colwell 2003 analysed ximelagatran without prior application of melagatran.

The patients in the control groups of these studies received different types and doses of LMWH and the studies also differed regarding the time that the first dose of medicine was initiated; (EXPRESS 2003 and METHRO III 2003 gave enoxaparin 40 mg before surgery; METHRO I 2002 and METHRO II 2002 gave dalteparin 5000 IU before surgery; Colwell 2003; and Heit 2001 gave enoxaparin 30 mg twice daily after surgery).

All the studies analysed patients subjected to both types of surgery (THR and TKR) except Heit 2001 which only evaluated patients subjected to TKR, and Colwell 2003 which only evaluated patients subjected to THR.

A bilateral venography was carried out on all patients in the METHRO I 2002; METHRO II 2002; and METHRO III 2003 studies and on those of the EXPRESS 2003 study. In the Colwell 2003; and Heit 2001 studies only a unilateral venography was carried out at the end of the treatment period.

Dabigatran versus LMWH studies

There were four studies (10183 randomised patients) that evaluated dabigatran in orthopaedic surgeries. BISTRO II 2005 used oral dabigatran in different doses 50 mg twice daily, 150 mg twice daily, 300 mg once daily, and 225 mg twice daily. The RE-MOBILIZE 2009, RE-MODEL 2007 and RE-NOVATE 2007 studies used 150 mg and 220 mg once daily. In order to synthesize the evidence, we analysed all combined doses and also performed a sensitivity analysis on each individual dose group. The control groups of these studies used LMWH. All of them compared DTI with subcutaneous enoxaparin 40 mg before surgery, but in some BISTRO II 2005; RE-MODEL 2007 and

RE-NOVATE 2007 centres, the LMWH was administered after surgery.

RE-MOBILIZE 2009; RE-MODEL 2007; and RE-NOVATE 2007 only evaluated patients subjected to TKR and in BISTRO II 2005 patients were subjected to both types of surgery. A bilateral venography was carried out on all patients of these four studies. The RE-NOVATE 2007 study is the only one of the 14 studies included that evaluated extended prophylactic anticoagulation (up to 35 days) in orthopaedic surgery. The duration range of treatment with DTI in the remaining studies included in this review was seven to 14 days.

Other Direct thrombin inhibitors versus LMWH studies

There was only one study (2079 randomised patients) that compared a DTI other than ximelagatran: Eriksson 1997 used desirudin (an hirudin analog) 15 mg twice daily subcutaneously before surgery. Eriksson 1997 only evaluated patients subjected to THR.

Direct thrombin inhibitor (Ximelagatran) versus vitamin K antagonist (warfarin) studies

Three studies compared DTIs versus warfarin (EXULT A 2003; EXULT B 2005; Francis 2002), analysing 5284 randomised patients, mainly female (62.1% of those randomised in this group), and elderly (the mean ages ranged between 66.9 to 68.5 years). The only direct thrombin inhibitor compared with warfarin was ximelagatran; Francis 2002 only used the 24 mg ximelagatran dose and EXULT A 2003 study compared two doses of ximelagatran: 24 mg and 36 mg. The EXULT B 2005 study only evaluated a 36 mg ximelagatran dose. The three studies administered the first dose of the drugs after surgery.

The objective of the treatment in the control groups of the three studies was to obtain an Internationalized Normalized Ratio (INR) of 1.8 to 3.0, which was variedly achieved in the third day of treatment in each study; 33% in Francis 2002, 65% in EXULT A 2003 and 67% in EXULT B 2005. At the end of the study period, the INR was found in the preset ranges in 50% of the patients treated with warfarin in the Francis 2002 study, in 76% of the EXULT A 2003 patients and in 73% of the EXULT B 2005 patients. The three studies only evaluated patients subjected to TKR.

A bilateral venography was carried out on less than 10% of the Francis 2002 study patients. In some EXULT A 2003 patients, only a unilateral venography was carried out and in the EXULT B 2005 study all patients were evaluated with a bilateral venography.

Other Direct thrombin inhibitors versus vitamin K antagonist studies

We could not find a study that made this comparison.

Excluded studies

Details of these individual studies are given in the [Characteristics of excluded studies](#) table.

We excluded 16 studies (21 citations) for various reasons. Four studies because they proved not to be randomised controlled trials ([Eriksson 2003](#); [Mouret 2002](#); [Troceniz 2007](#); [Wahlander 2002](#)); five because they did not evaluate direct thrombin inhibitors ([ODIXa-HIP 2006](#); [ODIXa-Knee 2005](#); [ONYX 2007](#); [RECORD 2007](#); [Turpie 2005](#); two studies because they did not have a comparison group (phase 2 studies) ([Eriksson 2002](#); [Eriksson 2003b](#)); and three studies because the comparison group was not relevant to this review (unfractionated heparin) ([Cofrancesco 1996](#); [Ekman 1995](#); [Eriksson 1996](#)). Moreover, the THRIVE study was not included because they did not evaluate the intervention of interest but evaluated the recurrence of venous thromboembolism ([Harenberg 2006](#)). The [EXTEND 2009](#) study, which fulfilled all the inclusion criteria regarding PICO elements (Participants, Interventions, Comparisons, Outcomes), was excluded due to methodological deficiencies; the evaluation of DVT was with compression ultrasound not the gold standards (venography). This study was stopped prematurely on 13 February 2006 for safety reasons. At that time, only 55% of the randomised patients had completed the 35-day treatment.

Risk of bias in included studies

Methodological quality of included studies

Methodological quality assessment was based on six independent measures of:

1. generation of randomisation sequence (Score A, B, or C);
2. adequate allocation concealment (Cochrane score A, B or C);
3. blinding (partially open, double blind, triple blind);
4. incomplete outcome data with emphasis on randomisation analysis (intention-to-treat analysis, or per protocol analysis);
5. duration of the follow up (A or optimum: follow up for more than eight weeks; B or adequate: at least 10 days; C or inadequate or not defined: less than 10 days) and;
6. internal and external validity, that includes 12 questions (eight of internal validity and four of external validity).

Internal and external validity: 12 questions

There are numerous scales to evaluate the methodological quality of RCTs ([Handoll 2002](#); [Guyatt 1993](#); [Guyatt 1994](#); [Jadad 1996](#)). Moher et al ([Moher 2005](#)), found up to 25 scales and nine checklists to qualify RCTs. The use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews. We analysed the methodological quality of the included studies without using scales.

The parameters to quantify the methodological quality of the studies in this review is based on the 12 questions proposed by the Cochrane PVD Group and the questions used in the systematic review by [Handoll 2002](#), which has been modified for the purposes of this review (as detailed in the [Appendix 3](#)) and on the Cochrane's risk of bias proposal.

The risk of bias for each of the 12 questions are tabulated pursuant to the comparison carried out. More details can be found in the additional tables section ([Table 2](#); [Table 1](#)) and ([Figure 1](#); [Figure 2](#)).

There were two open-label studies for enoxaparin ([Heit 2001](#); [METHRO I 2002](#)) but these were blinded for ximelagatran. The rest of the studies refer to double or triple blind and mention certain effective measures to achieve it; none of these detail who were blinded (outcome assessors, patients, treatment providers or analyst).

All the studies consider in their criteria the exclusion of women with childbearing potential (except [METHRO III 2003](#)), only including postmenopausal women, surgically sterile or with reliable contraception. But none detail what percentage of the randomised population corresponds to women using hormonal contraception or hormone replacement, which are known risk factors for thromboembolic events.

With regard to care programmes, none of the 14 studies compared all the characteristics or interventions that in the review authors' judgment are clinically relevant (as detailed in the [Appendix 3](#)).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies. Note: data from EXTEND 2009a (an excluded study) is shown.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study. Note: data from EXTEND 2009a study is shown to allow comparisons.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
BISTRO II 2005	+	+	+	-	?	?
Colwell 2003	+	+	+	-	?	?
Eriksson 1997	?	?	+	-	?	?
EXPRESS 2003	+	+	+	-	?	+
EXULT B 2005	+	+	+	-	?	+
EXULT A 2003	+	+	+	-	?	?
Francis 2002	+	+	+	-	?	?
Heit 2001	+	+	?	-	?	?
METHRO I 2002	?	?	?	-	?	?
METHRO II 2002	+	+	+	-	?	?
METHRO III 2003	+	+	+	-	?	?
RE-MOBILIZE 2009	+	+	+	-	?	?
RE-MODEL 2007	+	+	+	-	?	+
RE-NOVATE 2007	+	+	+	-	?	+

Only five studies had a follow-up period of more than eight weeks (Francis 2002; Heit 2001; RE-MOBILIZE 2009; RE-MODEL 2007; RE-NOVATE 2007).

Allocation

Only two of the 11 studies (Eriksson 1997; METHRO I 2002) did not mention whether the generation of randomisation sequence or allocation concealment were adequate or not, the rest carried it out by computerized means.

Blinding

Two studies (Heit 2001; METHRO I 2002) did not blind the patients or those in charge of providing treatment, only the results evaluator (partially open). The Eriksson 1997 study did not indicate adequate blinding of the evaluator (double blind). The rest of the studies describe triple blind.

Incomplete outcome data

The results for this review initially presents the evaluation of the individual study results and details the modifications or adaptations carried out by the review authors to be able to achieve the combined analysis of the studies.

Randomisation analysis (intention-to-treat analysis)

In none of the studies were the losses or withdrawals more than 10%. The study with the highest percentage was Heit 2001 (9.2%). The patients whose venographies were not adequate (20.2% of the total randomised patients, range, 15.8% to 26.7%) are not included in these losses.

The total number of randomised patients in the 14 studies was 27,746 patients; 27,360 patients were included in the safety analysis (98.5 % of the total randomised patients, range 95.6% to 99.8%) and 21,642 patients in the efficacy analysis (78.0% of the total randomised patients, range 72.5% to 84.6%). The percentage of not treated or withdrawn patients (and not included in the safety analysis) with regard to the total randomised patients was 1.49% (range, 0.2% to 9.2%) and the percentage of patients not included in the efficacy analysis with regard to the total number of patients included in the total safety population is 20.24% (5617 randomised patients not analysed) with 97.9% of this due to venograms not carried or not conclusive. None of the studies details the follow up on these patients. These percentages do not significantly differ from the treatment or control group. More details in the additional tables section: Methodological Comparison of Included Studies Table (Table 1).

Only four out of the 14 studies (Heit 2001; METHRO I 2002; METHRO III 2003; RE-MOBILIZE 2009) mention ITT population and RE-NOVATE 2007 stated that they performed a modified ITT analysis, but none of the 14 studies analysed all the patients initially randomised.

The review authors decided to include in the analysis all the non included VTE events reported in each study and all the events reported in the follow-up period. Next, we present all the inclusions or assumptions made in each study to develop the review analysis. It is important to mention that all these assumptions were made before the pooled analysis was carried out.

BISTRO II 2005

This study evaluated several different oral dabigatran doses. We divided them in two dose groups: The **dabigatran 50 to 150 mg** twice daily and **300 mg** once daily group and the **dabigatran 225 mg** twice daily group. The SD was calculated based on the standard error (SE) for the continuous data presented with SE in the original study using the formula: SD = SE multiplied by the square root of the group sample size.

Colwell 2003

One patient was excluded in the enoxaparin group in proximal DVT/PE because she had confirmed distal DVT rather than proximal. We included this patient in these analyses. There were 11 VTE events not included in the efficacy analysis of the original study (seven ximelagatran / four enoxaparin). We included all of them. Four of the ximelagatran group and two of the enoxaparin group were symptomatic events without venography, so based on the ITT analysis, we included all of them in the efficacy population. This was the only study that reported gamma-glutamyl transpeptidase (GGT) and aspartate aminotransferase (AST) elevated values. We only included the alanine aminotransferase (ALT) values in the analysis because we suspect that it may overvalue the results. We calculated the standard deviation (SD) based on the 95% Confidence Interval (CI) in the continuous variables using the formula: SD results by calculating the square root of group sample size multiplied by the difference of the upper and lower 95% CI and all of this divided by 3.92 (This is valid when group sample size is larger than 100).

Eriksson 1997

We did not analyse the continuous data because they are expressed in median and range (as in the METHRO I 2002 study).

EXPRESS 2003

We included eight follow-up VTE events reported in the ximelagatran group and six in the enoxaparin group not included in the original study analysis, but there is no indication regarding the type of surgery they belong to, so we included these events in the THR group and used the total number of that surgery group (not the total of both groups).

EXULT A 2003

Seventeen patients included in the population for the safety analysis (eight in ximelagatran 36 mg, five in ximelagatran 24 mg and four in warfarin) presented confirmed VTE but discontinued treatment. We included them in the proximal DVT and in the efficacy analysis population. Four patients in the higher-dose ximelagatran group, two in the lower-dose ximelagatran group, and two in the Warfarin group, did not have a venogram that was adequate for evaluation, but had confirmed symptomatic venous thromboembolism, they had died, or both. We also included them in the analysis.

[EXULT B 2005](#)

Six patients in the ximelagatran group and eight patients in the warfarin group with confirmed symptomatic VTE were excluded from analysis because they discontinued treatment; we included them in the efficacy analysis. Initially, we included the two patients with symptomatic DVT in the follow-up period without venography in the 36 mg ximelagatran group, but then we received the extra required data from Dr. CW Colwell (trialist from [EXULT B 2005](#)) who stated: "An additional two patients developed symptomatic venous thromboembolism during the follow-up period but did not have mandatory venography" (One in the ximelagatran group and one in the warfarin group). "One patient received five days of treatment with ximelagatran and then withdrew consent and had a proximal deep vein thrombosis objectively confirmed on postoperative day 26. The other patient received 2 days of warfarin, discontinued because of an adverse event, and had a confirmed pulmonary embolism on postoperative day 14". It was then decided to include these patients in the groups to which they were randomised for the sensitivity analysis including the follow-up events.

[Francis 2002](#)

Five patients included in the population for the safety analysis in warfarin presented with confirmed VTE (two DVT and three PE) but discontinued treatment prematurely. We included them in the efficacy analysis population assuming that all the DVT were proximal. We decided to use the information from central adjudication.

[Heit 2001](#)

The original data are expressed as percentages of cumulative incidence without decimals. We estimated the true values up or down to its next entire number. In order to synthesize the evidence, we grouped the 8 mg, 12 mg and 18 mg of ximelagatran in the group denominated **ximelagatran < 24 mg**. We defined major deep vein thrombosis (DVT) as the combination of proximal deep vein thrombosis (pDVT) + pulmonary embolism (PE) + DVT > 10 cm.

[METHRO I 2002](#)

There was one study participant with DVT who discontinued treatment and was not included in the efficacy analysis. We could not include this patient because we had no information regarding the group it belonged to (this information is being requested from the trialist). In the ximelagatran < 24 mg group, two patients with

DVT developed PE in the follow-up period, but there are no data to which surgery group they belonged. We decided to include these data in the THR group. We decided to include the excessive bleeding data in the THR group.

[METHRO II 2002](#)

Two PE were reported in the follow-up period but the trial authors did not state to which surgery group they belonged. We included these data in the THR group. There was a fatal PE reported in the follow-up period. We included these data in the TKR group that received ximelagatran < 24 mg. The ALT values were included in the ximelagatran 24 mg group.

[METHRO III 2003](#)

All reported follow-up events (seven in the ximelagatran and 16 in the enoxaparin groups) were included in the THR group. In the graphs of events with both surgeries, a combined value was used when it was available, except in a table where the summation of the partials was higher than the total events in the control group (major bleeding: THR+TKR in ximelagatran 24 mg twice daily versus LMWH), for which it was decided to use the sum of the partials instead of the combined total.

[RE-MOBILIZE 2009](#)

A non-inferiority trial comparing two doses of oral dabigatran. Thirteen patients in the 220 mg dabigatran group, eight patients in the 150 mg dabigatran group and nine patients in the enoxaparin group were excluded from analysis due to discontinued treatment. We included all of them in the efficacy analysis.

[RE-MODEL 2007](#)

Is a non-inferiority trial. The trialists do not report transfusions events and blood losses. The detailed results of the transaminases were reported in another document. The two oral dabigatran doses were 150 mg once daily and 220 mg once daily, so we analysed these results with the combination of both doses and individually.

[RE-NOVATE 2007](#)

A non-inferiority trial, of the same design as the [RE-MODEL 2007](#) study. It is the only trial that evaluated extended anticoagulation. The trialists do not report transfusions events and blood losses. For total VTE, we included the asymptomatic and symptomatic DVT and PE; we included only the deaths due to VTE.

Selective reporting

None of the included studies have reported if the protocol was available. Some show the registered code at www.clinicaltrials.gov. However the data stated in this web page does not comply with a protocol format and some important information is not presented.

Other potential sources of bias

Only four studies: [EXPRESS 2003](#); [EXULT B 2005](#); [RE-MODEL 2007](#) and [RE-NOVATE 2007](#) are probably free of other bias

sources; in the remaining included studies, it is unclear if other biases could exist, mainly detection bias due to unilateral venography instead of bilateral venography, and insufficient sample (lower than expected). More details in [Characteristics of included studies](#) tables.

Effects of interventions

See: [Summary of findings for the main comparison Direct thrombin inhibitors versus low molecular weight heparins](#); [Summary of findings 2 Direct thrombin inhibitors versus vitamin K antagonists](#)

The analysis of the results are presented in two main groups: efficacy analysis and safety analysis.

Efficacy analysis

This includes all thromboembolic events reported in the individual studies. We have subdivided these based on the comparison carried out.

1. Direct thrombin inhibitor (any dose) versus LMWH.
2. Direct thrombin inhibitor (any dose) versus vitamin K antagonist (warfarin).

Each of these two groups is subdivided into major thromboembolic events (**major VTE**) confirmed by the total patients who presented proximal DVT + PE + unexplained death, the **symptomatic VTE** events, and thromboembolic events in total (**Total VTE**) confirmed by the patients who presented a major thromboembolic event plus those that presented distal DVT. The results of the total VTE are reported as a efficacy sensitivity analysis, only when there is a difference with the results of major VTE. The results are shown in summary graphs (Forest plot) of each of these efficacy subgroups.

Safety analysis

This includes all adverse events not due to thromboembolism reported in the original studies, differentiating, where possible, adverse events due to bleeding (according to severity), and those not due to bleeding. The rise in transaminases was analysed separately. These events have been subdivided for their analysis into the same subgroups as those of the efficacy analysis.

1. Direct thrombin inhibitor (any dose) versus LMWH.
2. Direct thrombin inhibitor (any dose) versus vitamin K antagonist (warfarin).

Each of these two groups is subdivided into five analysis variables: **major/ significant bleeding** events, **total bleeding** events, **all-cause mortality** (due to VTE events, due to bleeding events and due to treatment: not due to bleeding nor VTE events), **ALT > three times the upper normal limit**, and **volume of blood loss**. The results of total bleeding are reported only when there is a difference with the results of major bleeding. The results are

presented in summary graphs (Forest plot) of each of these safety subgroups.

Sensitivity analysis

A sensitivity analysis of the efficacy and safety results was carried out according to the type of surgery to which they were randomised (THR, TKR, and the total THR+TKR). The individual results of each type of surgery are reported only when there is a difference with the combined results (THR+TKR). Also, a sensitivity analysis was carried out, including the reported events in the follow up of these groups.

1. Direct thrombin inhibitor (any dose) versus LMWH + reported events in the follow up.
 2. Direct thrombin inhibitor (any dose) versus vitamin K antagonist (warfarin) + reported events in the follow up.
- According to that found in the description of the studies, classification of the subgroups (according to DTI type and dose) is required for the efficacy and safety of sensitivity analysis.

For those that compare DTI versus LMWH:

- ximelagatran 24 mg twice daily versus LMWH;
- ximelagatran < 24 mg twice daily versus LMWH;
- dabigatran 225 mg twice daily versus LMWH;
- dabigatran 300 mg once daily or 150mg twice daily versus LMWH;
- dabigatran 50 to 100 mg twice daily versus LMWH;
- dabigatran 150 mg once daily versus LMWH;
- dabigatran 220 mg once daily versus LMWH;
- desirudin (subcutaneous) 15 mg twice daily versus LMWH.

For those that compare DTI versus vitamin K antagonist (warfarin):

- ximelagatran 24 mg twice daily versus warfarin;
- ximelagatran 36 mg twice daily versus warfarin.

In the description of the results, the individual results of each DTI are mentioned, which we subdivided based on the dose only if they differed from the combined result.

Regarding the primary outcome measures initially proposed in the preparation of the protocol for this review, it was decided to group mortality associated with VTE with the incidence of proximal VTE in the major VTE group (the results of mortality due to VTE were also analysed separately) so that the analysis would be more practical due to the reduced number of individual events.

The original studies do not report any serious hepatopathy defined as fulminant hepatitis, symptoms of liver failure, or life-threatening hepatopathy. Moreover, no heparin-induced thrombocytopenia (HIT), skin lesions at heparin injection sites, or acute systemic reactions were reported. They reported some other events that are not relevant for this review such as: surgical wound events, transfusion events, transfusion volume and wound drainage volume.

With regard to the secondary outcome measures, the distal VTE incident was evaluated jointly with the proximal VTE incident and mortality associated with VTE in the total VTE group.

The original studies do not report the presence of hepatopathy after the treatment.

The results described below are presented by means of the fixed-effect meta-analysis when the heterogeneity was low.

Major venous thromboembolism

All 11 studies that compared DTIs versus LMWH and the three studies that compared DTIs versus warfarin reported major VTE, but some reported the events individually (proximal DVT, pulmonary embolism, and unexplained death or death due to confirmed VTE) and others were already grouped. The [Heit 2001](#) study classified all VTE events in pulmonary embolism, proximal, distal DVT and DVT > 10 cm independently. It was decided in this case to include DVT > 10 cm as part of the major VTE, but in all cases the distal DVT was classified as part of the total VTE.

All Direct Thrombin Inhibitors versus LMWH

When evaluating the combination of both surgery groups in the 17428 analysed patients including the follow-up events, no difference was observed between both groups (557 events/ 10736 patients in the DTI group versus 392 events/ 6692 patients in the LMWH group) (OR 0.91; 95% CI 0.69 to 1.19; I^2 71%) ([Analysis 1.1](#)). The heterogeneity was high due to two studies ([Colwell 2003](#); [EXPRESS 2003](#)).

In the sensitivity analysis, not taking into consideration the results of the [Colwell 2003](#) study, or [EXPRESS 2003](#) study or both studies, still no difference was observed between DTIs and LMWH but with moderate heterogeneity (I^2 29%).

In the individual evaluation of each surgery, there was no difference between DTI and LMWH. There was also no difference in THR or TKR when excluding the follow-up events. In the sensitivity analysis including only the higher doses (ximelagatran 24 mg, dabigatran 220 mg, 300 mg and 450 mg) and the one desirudin dose studied, there was also no difference between DTI and LMWH.

Ximelagatran versus vitamin K antagonist (warfarin)

All three studies that compared DTIs versus warfarin ([EXULT A 2003](#); [EXULT B 2005](#); [Francis 2002](#)) (4327 analysed patients) used ximelagatran but [Francis 2002](#) only evaluated the 24 mg dose; [EXULT A 2003](#) used 24 mg and 36 mg doses, while [EXULT B 2005](#) only analysed the 36 mg dose. All patients were only subjected to TKR surgery.

Regarding major VTE, no statistical difference was observed between both treatment groups. When including the follow-up events, no significant difference was observed between both groups (95 events/ 2498 patients in the DTI group versus 83 events /

1829 patients in the warfarin group) (OR 0.85; 95% CI 0.63 to 1.15) without heterogeneity (I^2 0%) ([Analysis 5.1](#)). There was also no significant difference observed between both groups when the follow-up events were excluded. When carrying out the sensitivity analysis, evaluating independently the two ximelagatran doses (24 mg and 36 mg), no variation was observed in the results.

Total venous thromboembolism

All Direct Thrombin Inhibitors versus LMWH

As in major VTE, no difference was observed even when the follow-up events were included ([Analysis 1.2](#)).

Ximelagatran versus vitamin K antagonist (warfarin)

There were fewer total VTE events in the DTI group (555 events/ 2514 patients in the DTI group versus 543 events / 1840 patients in the warfarin group) (OR 0.68; 95% CI 0.59 to 0.78; I^2 0%). When evaluating the sensitivity analysis including the follow-up events, this difference is maintained ([Analysis 5.2](#)).

Symptomatic venous thromboembolism

All Direct Thrombin Inhibitors versus LMWH

No difference was observed between both treatment groups even when the follow-up events were included (234 events/ 12,056 patients in the DTI group versus 143 events / 7563 patients in the LMWH group) (OR 1.04; 95% CI 0.84 to 1.29; I^2 0%) ([Analysis 1.3](#)).

The [RE-MODEL 2007](#) (OR 0.63; 95% CI 0.29 to 1.40) and [RE-NOVATE 2007](#) (OR 2.51; 95% CI 0.96 to 6.57) studies showed different tendencies despite having a very similar design. When carrying out the sensitivity analysis excluding the [RE-NOVATE 2007](#) study (because it was the only trial which studied extended prophylactic anticoagulation), no variation was observed in the results.

Ximelagatran versus vitamin K antagonist (warfarin)

There was no difference between both treatment groups even when the follow-up events were included (47 events/ 3022 patients in the DTI group versus 48 events / 2237 patients in the warfarin group) (OR 0.80; 95% CI 0.53 to 1.21; I^2 0%) ([Analysis 5.3](#)).

Major/ significant bleeding events

Major or significant bleeding events were reported in all eleven studies that compared DTIs versus LMWH and in all the three studies that compared DTIs versus warfarin. The definition was varied among the studies; all the studies defined severe bleeding if it involved a critical site (intracranial, intraocular, intraspinal or retroperitoneal bleeding). Some studies also included pericardial bleeding and overt bleeding. Some studies included fatal bleeding events in this definition ([Colwell 2003](#); [EXPRESS 2003](#); [EXULT A 2003](#); [EXULT B 2005](#)), score bleeding index ≥ 2 ([Colwell 2003](#); [EXULT A 2003](#); [EXULT B 2005](#); [Francis 2002](#); [Heit 2001](#)), severity definition based on transfusion needs and volume > 3500

ml (Eriksson 1997). Some studies included bleeding from the operation wound (EXPRESS 2003). All studies also defined severity as judged by a researcher (independent expert in METHRO II 2002), and as judged by central adjudication even if they did not fulfil these criteria (METHRO III 2003).

This variable largely depends on the subjectivity of the researcher or central adjudication in defining the severity of the bleeding. So these conclusions must be taken with caution.

All Direct Thrombin Inhibitors versus LMWH

In the combined analysis of both surgeries in 22,109 patients, there were more bleeding events in the DTI group in comparison with LMWH. However, the difference was not statistically significant (334 events/ 13,753 patients in the DTI group versus 138 events /8356 patients in the LMWH group) (OR 1.17; 95% CI 0.87 to 1.58; I^2 46%) (Analysis 2.1). It must be considered that this heterogeneity is partly due to the fact that the results of different drugs at different doses are combined and in two different types of operations. When the sensitivity analysis was carried out, excluding the follow-up events reported in the original studies but not included in their analyses, the type of surgery (THR or TKR) and the dose (excluding the lower doses), no significant variation was observed in any of the DTIs compared with LMWH. In the comparison of each independent doses, only dabigatran 225 mg twice daily showed more major bleeding events in the DTI group (OR 1.90; 95% CI 1.05 to 3.44) in the combination of both surgeries and specially in THR (26 events/ 270 patients in the DTI group versus 13 events /270 patients in the LMWH group (OR 2.11; 95% CI 1.06 to 4.19).

Ximelagatran versus vitamin K antagonist (warfarin)

In the 5259 analysed patients, more bleeding events were observed in the ximelagatran group however the difference was not statistically significant (30 events/ 3022 patients in the ximelagatran group versus 13 events /2237 patients in the warfarin group) (OR 1.76; 95% CI 0.91 to 3.38; I^2 0%). These results also do not vary when including the reported follow-up events (Analysis 6.1) or when excluding the lower doses.

Total bleeding events

Total bleeding events were reported in ten of the 11 studies that compared DTIs versus LMWH (not reported in Eriksson 1997; the results of major bleeding were used), and in all three studies that compared DTIs versus warfarin. The definition varies between the studies because some only considered perioperative bleeding, others postoperative bleeding, some considered both, and other studies did not mention this characteristic.

This variable is less influenced by the researcher's judgment than major bleeding. But even so, the conclusions must be taken with caution.

All Direct Thrombin Inhibitors versus LMWH

As in major bleeding, no difference was observed between both treatment groups, even when the follow-up events were included

(Analysis 2.2). However, more bleeding events were observed in the DTI group (in ximelagatran and dabigatran or desirudin) in the patients subjected to THR (2370 events/ 5949 patients in the DTI group versus 1374 events /4378 patients in the LMWH group) (OR 1.40; 95% CI 1.06 to 1.85; I^2 41%). No difference was observed regarding TKR. Also, there was no difference when excluding the lower doses.

Ximelagatran versus vitamin K antagonist (warfarin)

The partial and total results were very similar than those presented in major bleeding events (Analysis 6.2).

All-cause mortality

All studies reported mortality events. Mortality associated with VTE events (included in the major VTE variable), mortality associated with bleeding events (included in the major bleeding variable), and mortality associated with treatment (not due to VTE nor bleeding events) were evaluated separately. No difference was observed in any of these three groups individually, even when the follow-up events were included. Due to the low number of events, the combined analyses of these three mortality groups are presented in the variable called "all-cause mortality".

All Direct Thrombin Inhibitors versus LMWH

More all-cause mortality events were observed in the DTI group in comparison with LMWH (15 events / 13730 patients in DTI versus four events / 8335 patients in LMWH) but the difference was not statically significant (OR 1.72; 95% CI 0.68 to 4.35) with no heterogeneity (I^2 0%). When including the events reported in the follow up, more events were also observed in the DTI group (41 events / 13730 patients in DTI versus 11 events / 8335 patients in LMWH) with statistically significance (OR 2.06; 95% CI 1.10 to 3.87) without heterogeneity (I^2 0%) (Analysis 2.4).

When the sensitivity analysis was carried out, excluding the studies that evaluated ximelagatran, still more mortality events in the DTI group in comparison with LMWH were observed, but the difference was not statically significant (19 events / 6949 patients in DTI versus five events / 3087 patients in LMWH: OR 1.56; 95% CI 0.63 to 3.90) without heterogeneity (I^2 0%).

No sensitivity analyses regarding type of surgery or doses were performed because in most studies no complete information about mortality was available in both the treatment period and mainly in the follow-up period.

Ximelagatran versus vitamin K antagonist (warfarin)

Three studies reported mortality events (6 events / 3013 patients in ximelagatran versus four events / 2230 patients in warfarin). No difference was found regarding all-cause mortality events (OR 1.19; 95% CI 0.36 to 4.01; I^2 0%), even when the reported follow-up events were included (10 events / 3013 patients in ximelagatran versus five events / 2230 patients in warfarin: OR 1.62; 95% CI 0.57 to 4.58; I^2 0%) (Analysis 6.3). No difference was observed in the individual sensitivity analysis of each mortality group.

Alanine aminotransferase (ALT) > 3 times the upper normal limit

The EXPRESS 2003; Heit 2001; METHRO III 2003, and Eriksson 1997 studies did not analyse this variable. Regarding the increase of transaminases, all the studies stated that it was transitory and did not derive into a significant hepatopathy, except in the RE-NOVATE 2007 study (one patient who received dabigatran had unexplained raised concentrations of ALT and a two-fold increase in bilirubin concentration; and one patient in the group receiving 150 mg of dabigatran in which the baseline ALT concentration was 1.7 times the upper limit of normal had not returned to normal or baseline value after two years of follow up). Only the studies that evaluated DTIs versus warfarin and the RE-MODEL 2007 and RE-NOVATE 2007 studies described the rise of transaminases at the end of the treatment period and at the end of the follow up. The remaining studies that evaluated DTIs versus LMWH which included this important variable, only reported the rise of transaminases at the end of the treatment period, but did not detail the events at the end of the follow-up period.

All Direct Thrombin Inhibitors versus LMWH

In the seven studies (BISTRO II 2005; Colwell 2003; METHRO I 2002; METHRO II 2002; RE-MOBILIZE 2009; RE-MODEL 2007; RE-NOVATE 2007), the heterogeneity was too high to analyse the combined events (I^2 82%), fewer events were observed in the DTI group in comparison with the LMWH group but with high heterogeneity (I^2 63%) in the ximelagatran studies. However, in the studies that evaluated dabigatran no difference was observed in comparison with LMWH but with very high heterogeneity (I^2 84%). The heterogeneity was caused by the BISTRO II study (Analysis 2.3). When only the 220 mg and 150 mg dabigatran doses were analysed still no difference was observed in comparison with LMWH (138 events / 5298 patients in dabigatran versus 99 events / 2660 patients in LMWH (OR 0.72; 95% CI 0.49 to 1.05; I^2 40%).

When evaluating the rise of transaminases including the reported follow-up events only the data of the RE-MODEL 2007 study were available. The difference was not significant between both groups (15 events / 1329 patients in dabigatran versus four events / 670 patients in LMWH (OR 1.90; 95% CI 0.63 to 5.75).

Ximelagatran versus vitamin K antagonist (warfarin)

Francis 2002 did not report elevation of transaminases in the treatment period nor during follow up. Two studies (EXULT A 2003; EXULT B 2005) described the transitory rise of transaminases at the end of the treatment and follow-up periods. When comparing the ximelagatran 24 mg twice daily and 36 mg twice daily doses versus warfarin at the end of treatment period, fewer events were observed in the ximelagatran group (18 events / 2493 patients in ximelagatran versus 21 events / 1768 patients in warfarin (OR 0.52; 95% CI 0.27 to 0.97; I^2 0%) (Analysis 6.4). However, when evaluating the events at the end of the follow-up period, more events were observed in the ximelagatran group, but the difference was not statistically significant (11 events / 2484 patients in xime-

lagatran versus one event / 1783 patients in warfarin (OR 5.61; 95% CI 1.00 to 31.64; I^2 0%) (Analysis 6.5).

The authors of the original studies indicated that all patients who presented a transitory rise of transaminases still present at the end of the follow-up period, eventually reverted without any significant clinical manifestation. We would like to highlight the response for extra data required from Dr. C W Colwell (trialist from EXULT B 2005) who indicated that "Alanine aminotransferase values normalized in all ximelagatran-treated patients within four weeks of onset. No clinical signs or symptoms were attributed to the Alanine Aminotransferase elevations."

Volume of blood loss

Volume of blood loss was reported in five out of eleven studies that compared DTIs versus LMWH (BISTRO II 2005; Heit 2001; METHRO II 2002; METHRO III 2003), and in all three studies that compared DTIs versus warfarin. In METHRO I 2002 the data are presented in box graph with no exact values given and showing the median instead of the mean. EXPRESS 2003 used the geometrical mean to present its results and Eriksson 1997 the median. The data on the mean have been requested from the trialist. The definition is variable among the studies; some studies only included postoperative bleeding, others all perioperative bleeding + postoperative bleeding, and some studies included bleeding from the wound (EXPRESS 2003). Due to the above, the conclusions must be taken with caution.

All Direct Thrombin Inhibitors versus LMWH

No difference was observed between both treatment groups in the 8782 analysed patients (WMD 5.12; 95% CI -33.81 to 44.04) but with high heterogeneity (I^2 67%). The results did not change with the sensitivity analysis by type of surgery (blood loss was not evaluated in dabigatran because the BISTRO II 2005 study did not mention the individual results by type of surgery and the RE-MOBILIZE 2009; RE-MODEL 2007 and RE-NOVATE 2007 studies did not show this variable). It must be taken into consideration that this high heterogeneity is due in part to the fact that different drugs are combined, at different doses, and in two types of different operations with different concepts of the variable. The independent evaluation of each drug did not greatly alter the result, even when the lower doses were excluded.

Ximelagatran versus vitamin K antagonist (warfarin)

In the 5259 analysed patients, no difference was observed between both treatment groups (WMD -7.12; 95% CI -17.08 to 2.84) without heterogeneity (I^2 0%).

Results of sensitivity analysis

Regarding the results of the study analysis, including the events reported in the follow up, according to the type of surgery (THR, TKR, or both), drug (Ximelagatran, Dabigatran, Desidurin), dose (higher doses, lower doses), excluding the Colwell 2003 study or

re-analysing the data using randomised effect meta-analysis instead of fixed and vice versa, these were presented, if relevant, during the analysis and the description of results.

Evaluation of more extensive results

Total thromboembolism for efficacy and total bleeding for safety, did not reveal more differences than the analysis of major events.

Time effect of the beginning of anticoagulation

Four studies (Eriksson 1997; EXPRESS 2003; METHRO I 2002; METHRO II 2002) (efficacy analyses: 5845, safety analyses: 6827) reported having initiated DTI and LMWH anticoagulation just before surgery (according to the “knife-to-skin” concept), but only three studies (Colwell 2003; Heit 2001; RE-MOBILIZE 2009) (efficacy analyses: 3953, safety analyses: 5006) began DTI and LMWH anticoagulation approximately 12 hours after surgery was initiated.

The other four studies (BISTRO II 2005; METHRO III 2003; RE-MODEL 2007; RE-NOVATE 2007) began DTI anticoagulation after surgery, but LMWH anticoagulation began before surgery. These studies were not included in the sensitivity analysis. Regarding efficacy, the studies that began anticoagulation before surgery evidenced fewer major and total VTE in the DTI group in both surgery groups; for major VTE: (OR 0.54; 95% CI 0.35 to 0.83; I^2 57%) (Analysis 4.1); and for total VTE: (OR 0.72; 95% CI 0.63 to 0.82; I^2 0%). There was no significant difference regarding symptomatic VTE events (Analysis 4.2).

The combination of results of the studies that began anticoagulation after surgery evidenced more major and total VTE events in the DTI group in both surgery groups for major VTE. There was a statistically significant difference in major VTE: (OR 1.68; 95% CI 1.12 to 2.52) I^2 34%) (Analysis 4.1) however, without any difference regarding total VTE: (OR 1.29; 95% CI 0.69 to 2.39; I^2 72%). There was no significant difference regarding symptomatic VTE events Analysis 4.2.

Regarding the safety analysis, the studies that began anticoagulation before surgery evidenced more major and total bleeding events in the DTI group than in the LMWH group but the difference was not statistically significant for major bleeding (OR 1.64; 95% CI 0.85 to 3.15; I^2 62%) and for total bleeding (OR 1.45; 95% CI 0.93 to 2.28; I^2 50%) (Analysis 4.3) in both combined surgeries and in the individual analysis of each surgery. There was no significant difference regarding mortality (Analysis 4.4).

The combination of bleeding event results of the studies that began anticoagulation after surgery did not evidence a significant difference between both treatments in any of the two surgery groups (in THR + TKR). In major bleeding: (OR 0.96; 95% CI 0.48 to 1.93; I^2 0%) and in total bleeding: (OR 1.29; 95% CI 0.92 to 1.81; I^2 0%) (Analysis 4.3). There was also no difference regarding mortality (Analysis 4.4).

In summary, it is proposed that the time of initiation of anticoagulation can influence the efficacy of treatment more than the drug itself. To explore this effect, a sensitivity analysis was carried out, taking into consideration the time effect by comparing DTI and LMWH. In the DTI group, the studies that initiated anticoagulation before surgery evidenced less VTE events, and those that began anticoagulation after surgery evidenced more VTE events in comparison with LMWH (Analysis 4.1). There was no significant difference regarding bleeding (Analysis 4.3) and mortality events (Analysis 4.4).

Extended prophylactic anticoagulation versus standard prophylactic anticoagulation

The duration range of treatment with DTIs in the original studies included in this review was seven to 12 days except in the RE-NOVATE 2007 study which analysed extended prophylactic anticoagulation (duration range 28 to 35 days). The RE-NOVATE 2007 study evaluated dabigatran versus LMWH in TKR patients. (EXTEND 2009 was designed to evaluate extended anticoagulation with ximelagatran versus LMWH was excluded because it was prematurely stopped due to the withdrawing of ximelagatran from the market). Regarding standard prophylactic anticoagulation, the included studies were those which evaluated any DTI versus LMWH in TKR patients. The follow-up events were included in both groups. Regarding efficacy, no difference was found in major VTE (extended anticoagulation: 68 events/1797 patients in DTI group versus 37 events/917 patients in the LMWH group: OR 0.94; 95% CI 0.62 to 1.41) in comparison with (235 events/4124 patients in the DTI group versus 123 events/2171 patients in the LMWH group: OR 0.86; 95% CI 0.57 to 1.28; I^2 56%) (Analysis 3.1). Also no difference was found in total VTE. Regarding symptomatic VTE events in extended anticoagulation, there were more events in the dabigatran group in comparison with LMWH (25 events/2293 patients in the DTI group versus 5 events/1142 patients in the LMWH group), but the difference was not statistically significant (OR 2.51; 95% CI 0.96 to 6.57). In standard anticoagulation no difference was found (76 events/3351 patients in the DTI group versus 37 events/1542 patients in the LMWH group: OR 0.99; 95% CI 0.67 to 1.48; I^2 0%) (Analysis 3.2).

Regarding safety, no difference was found in major or total bleeding (Analysis 3.3).

Regarding all-cause mortality, transaminase levels and blood loss were not evaluated since there were not specific individualized data.

Methodological Quality

Regarding the analysis of studies according to methodological quality, the following characteristics were analysed based on efficacy (major VTE) and safety (major bleeding) for the combination

of both surgeries (THR+TKR). In Figure 3 and Figure 4 the following study characteristics were analysed: generation of the randomisation sequence and allocation concealment, blinding, randomisation analysis, intention to treat (ITT), and duration of follow-up.

Figure 3. Sensitivity Analysis of Efficacy: DTI vs. LMWH in Major VTE in THR+TKR

Figure 4. Sensitivity Analysis of Safety: DTI vs. LMWH in Major Bleeding in THR+TKR

The results obtained from the sensitivity analysis did not differ from the analysed results regarding efficacy and safety; this strengthens the value of the results. It was observed that the studies with methodological deficiencies tended to show differences in results that did not exist in the original analysis. However, the original results were unaffected, probably due to the small weight of these low methodological studies (Figure 3; Figure 4).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Direct Thrombin Inhibitors compared to Vitamin K Antagonists for patients with prevention of venous thromboembolism following total hip or knee replacement							
Patient or population: patients with prevention of venous thromboembolism following total hip or knee replacement Settings: elective surgery Intervention: Direct Thrombin Inhibitors Comparison: Vitamin K Antagonists							
Outcomes	Illustrative comparative risks* (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk		Corresponding risk				
	Vitamin K Antagonists	Direct Thrombin Inhibitors					
Major VTE events in TKR combined doses bilateral ascending venography Follow-up: 4-6 weeks ¹	Medium risk population			OR 0.85 (0.63 to 1.15)	4327 (3 studies)	⊕⊕○○ low ^{2,3}	
	48 per 1000	41 per 1000 (31 to 55)					
All-cause Mortality events in TKR combined doses Follow-up: 4-6 weeks ¹	Medium risk population			OR 1.62 (0.57 to 4.58)	5243 (3 studies)	⊕⊕○○ low ^{2,3}	
	3 per 1000	5 per 1000 (2 to 14)					
Total Bleeding events in TKR combined doses Follow-up: 4-6 weeks ¹	Medium risk population			OR 1.26 (0.97 to 1.62)	5259 (3 studies)	⊕⊕○○ low ^{2,3}	
	46 per 1000	57 per 1000 (45 to 72)					

ALT >3 times the upper normal limit at the end of Follow-up in TKR combined doses Follow-up: 4-6 weeks ¹	Medium risk population		OR 5.61 (1 to 31.64)	4267 (2 studies)	⊕⊕○○ low ^{2,3}
	1 per 1000	6 per 1000 (1 to 31)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ optimal follow-up time for DVT more than 8 weeks

² No adequate ITT analysis were performed in the original studies, however the review included all the reported follow-up events.

³ Funnel plot assymetric

DISCUSSION

Current indications supported by evidence for VTE prophylaxis in orthopaedically surgical patients are:

- 1) general measures: early mobilization, leg exercises, and adequate hydration.
- 2) mechanical prophylaxis: graduated elastic compression stockings (GECS) with or without intermittent pneumatic compression (IPC) and mechanical foot pumps and foot impulse technology;
- 3) pharmacological therapy with LMWH, warfarin and fondaparinux (Hill 2007; SIGN 2002).

The limited efficacy of classic anticoagulants, such as LMWH and warfarin, has been proven in numerous studies. However, 47% of the patients treated with warfarin and 31% of the patients treated with LMWH developed thrombosis after total knee replacement according to (Fitzgerald 2001; Francis 1996; Geerts 2001; Hamulyak 1995; Heit 1997; Hull 1993; Leclerc 1996). These data coincide with the events reported in the studies included in this review. The incidence of VTE events in patients treated with LMWH after TKR was 40% and 30% in patients treated with warfarin.

Summary of main results

Regarding the efficacy results, when using the previously defined analysis strategy, larger heterogeneity was observed in the studies that compared ximelagatran 24 mg twice daily versus LMWH. The heterogeneity in this case was marked by Colwell 2003; the results from this study differ significantly from the rest of the studies and contributed 30% of the patients and 22% of the events of this subgroup. The arguments that might explain the heterogeneity caused by Colwell 2003 could be its methodological quality (B), that no ITT analysis was carried out, that it evaluated VTE events only by unilateral venography, or that anticoagulation was initiated post surgery. When Colwell 2003 was not included, fewer major VTE events were observed but still with high heterogeneity. From the review authors criteria, the heterogeneity is too high to be able to conclude that this study is the only important cause of the heterogeneity, so it is recommended that the combined results be taken with caution. In the studies that evaluated oral dabigatran no difference were observed in comparison with LMWH regarding major, total and symptomatic VTE events, even if the lower doses were not taken into consideration. When evaluating the only study that compared subcutaneous desirudin versus LMWH, fewer major and total VTE events were observed in the desirudin group. There were no studies available that analysed this drug in TKR surgery. Due to the high heterogeneity observed when combining all the DTIs versus LMWH, we preferred presenting individual results. Inclusion of the follow-up events did not alter these individual results (Analysis 1.1).

The variability in reported VTE rates in different studies may be due to duration of the anticoagulation, variation in demographic characteristics of the study population, differences in venographic technique, or variations between observers in the interpretation of the venograms. Therefore, between-study comparisons should be made with caution.

Excessive bleeding is a potential risk associated with prophylaxis with any anticoagulant in patients undergoing orthopaedic surgery. When evaluating safety in terms of bleeding in DTIs, in the studies that compared DTIs with LMWH regarding major bleeding (Analysis 2.1) and total bleeding (Analysis 2.2), a tendency towards fewer events was observed in the LMWH group, especially in THR patients where it was statistically significant for both ximelagatran and dabigatran. An explanation of why TKR presents less bleeding than in THR is that an arterial tourniquet was applied as a routine technique in most of the TKR studies. Regarding blood loss volume, there was no difference between both treatment groups in both types of surgery. When evaluating the studies that compared different doses of ximelagatran with warfarin, a tendency towards more bleeding in ximelagatran was observed regarding major (Analysis 6.1) or total bleeding events (Analysis 6.2). However, the difference was not statistically significant, no difference was found regarding blood loss volume between both drugs. Due to the high variability in the definition of this variable and since it largely depends on the subjectivity of the researcher or the central adjudication in defining the severity of the bleeding, the conclusions must be taken with caution. No differences were found regarding mortality due to bleeding between DTIs versus LMWH or warfarin, including the follow-up events.

The use of ximelagatran was associated with an increase of alanine aminotransferase up to three times its normal value (Lazerow 2005; Olsson 2002; Olsson 2003; Petersen 2003; Schulman 2003). When evaluating safety in terms of the rise of transaminases in DTIs in this review, in the studies that compared it with LMWH and warfarin, fewer events were observed in the DTI group at the end of the treatment period (Analysis 6.4), but in the studies that compared DTI with warfarin that evaluated this transitory rise up to the end of the follow-up period, fewer events were observed in the warfarin group that was compared with ximelagatran 36 mg twice daily group, and without any difference in the number of events in the ximelagatran 24 mg twice daily group (Analysis 6.5). The authors of the original studies indicate that all the patients presented transitory elevation of transaminases and they were still high at the end of the follow-up period, eventually reverting without presenting any significant clinical manifestation.

Regarding symptomatic VTE events no difference was observed between both treatment groups even when the follow-up events were included (Analysis 1.3). Symptomatic events, death to any cause and major events (VTE or bleeding) are clinically more

important VTE outcomes than all venographic detected DVT. The problem is that symptomatic and death events are infrequent, so these outcomes need a sample size of thousands of patients (Geerts 2004). According to an erratum from RE-MODEL 2007 (Eriksson 2007), approximately 25,000 patients are required. In this review the efficacy population analysed for the comparison of DTI versus LMWH (larger than with DTI versus warfarin) was 17,305 patients and 22,101 patients for safety. Due to this, clinically relevant outcomes such as symptomatic events or death to any cause, could not had the necessary sample size to be properly evaluated. Thus this non difference result must be taken with caution until adequate sample size are available.

When evaluating safety in terms of all-cause mortality (the individual analysis was not possible due to the low number of events) including the follow up events, there were more deaths due to all causes in the DTI group in comparison with LMWH (41 events / 13,730 patients in DTI versus 11 events / 8335 patients in LMWH) with statistical significance (OR 2.06; 95% CI 1.10 to 3.87) without heterogeneity (I^2 0%) (Analysis 2.4). When the ximelagatran events were excluded, and only dabigatran and desirudin were evaluated, still more deaths events in the DTI group in comparison with LMWH were observed (23 events / 7977 patients in DTI versus seven events / 4110 patients in LMWH), but the difference was statically not significant (OR 1.66; 95% CI 0.73 to 3.69) without heterogeneity (I^2 0%) probably due to insufficient power.

Regarding ximelagatran, severe hepatocellular damage was reported (Albers 2005; Desai 2004; Halperin 2005; O' Brien 2005; Olsson 2003) as well as fatal hepatic damage, whose progression could not be prevented even though the drug was stopped when the hepatic damage was detected (Spell-Lesane 2004). After reviewing the SPORTIF trials and other data, the FDA Advisory Committee concluded that the risks of ximelagatran outweigh the benefits (Spell-Lesane 2004). As a result, it was removed from the market due to hepatocellular damage in February 2006 (EMA 2006a; EMA 2006b). No fatal events from hepatopathy were reported in the analysed studies in this review, but this information has been specifically requested from the trialist. The only response up to now is from Dr. CW Colwell (trialist from EXULT B 2005) who states that "There was no unexplained death in this study with related ALT, AST or liver failure". It is debated whether the question of rare, serious liver toxicity can be fully addressed in 19,000 patients, in particular when the follow-up period is short. Therefore conclusions about this must be taken with caution.

Overall completeness and applicability of evidence

The results obtained from sensitivity analysis, did not differ from the analysed results regarding efficacy and safety, this strength-

ens the value of the results. It was observed that the studies with methodological deficiencies trended to show differences in results that did not exist in the original analysis, however the original results were unaffected probably due to the small weight of these low methodological studies (Figure 3; Figure 4).

Efficacy and safety results did not vary significantly when the follow-up events were included (except in mortality events). The data generated during the follow-up period should be interpreted with caution, since concomitant medications were not all recorded and screening for thromboembolic events was not performed systematically during this period. In EXPRESS 2003, 71% of patients continued on LMWH during the follow-up period, irrespective of previous treatment group allocation.

Quality of the evidence

In this systematic review the DTI comparison was carried out with the current standard therapy (LMWH or warfarin). The DTIs we found that are used for the prevention of VTE in patients who have undergone THR or TKR are ximelagatran, dabigatran (both by oral administration) and desirudin (subcutaneous). Only 15 RCTs were found. One study (EXTEND 2009) was excluded due methodological deficiencies. Most had an acceptable methodology quality pursuant to the risk of bias analysis. But it must be highlighted that no study carried out a strict ITT analysis (Table 1). Due to this, we included all reported patients that presented an event of interest and who had not been included in the original study analysis. Moreover, a sensitivity analysis was carried out on all reported patients who presented an event of interest during the follow up. This does not replace an ITT analysis but it is the most rescuable approach that can be carried out with the data provided in the original studies. The trialists have been asked to provide the necessary extra data.

In the 14 included studies, despite of the fact that this is a small number, a large number of patients were evaluated (the efficacy in 21,642 patients and safety in 27,360 patients). These numbers differ from those presented in the Description of studies section because in it were included some patients not analysed in the original studies). Forty three percent were subjected to THR surgery, the remainder to TKR surgery. There was no information available regarding DTIs versus warfarin in patients subjected to THR surgery and the only DTI compared with warfarin was ximelagatran. It must be pointed out that the only drugs that had several studies for its comparison whether to LMWH or warfarin were ximelagatran and dabigatran. There was only one study that evaluated desirudin (and only in patients who have undergone THR surgery), so their conclusions must be taken with caution when generalizing results.

Potential biases in the review process

The optimal duration of thromboprophylaxis after major orthopedic surgery is controversial (O'Donnell 2003; Hull 2001a; EXPERT 2007). The duration range of treatment with DTI in the original studies included in this review was seven to 12 days except in the RE-NOVATE 2007 study (evaluated extended prophylactic anticoagulation) where the duration range was 28 to 35 days. A sensitivity analysis was carried out to compare the effect of this study to those with similar characteristics with the exception of the duration of anticoagulation (DTI versus LMWH in TKR), the follow-up events were included. No difference was found regarding major and total VTE for efficacy and major and total bleeding for safety. Regarding symptomatic VTE, more events were seen in the DTI group in extended anticoagulation, but the difference was not statistically significant (OR 2.51; 95% CI 0.96 to 6.57) (Analysis 3.2). In standard anticoagulation, no difference was found. All-cause mortality, transaminase level and blood loss were not evaluated since there was not specific individualized data. Due to this, the inclusion of the RE-NOVATE 2007 study did not significantly affect the results of the combination of studies with standard anticoagulation.

Preventive therapy with LMWH has traditionally been started 12 hours before surgery in Europe, or 12 to 24 hours after surgery in North America. According to recent evidence, thromboprophylaxis

should probably be initiated close to surgery. The likely importance of the timing of the first administration of antithrombotic agents can be inferred from the findings of the systematic review and meta-analysis by Hull et al (Hull 2001). It is suggested that this timing effect can influence the efficacy of the treatment more than the drug itself. To explore this effect, a sensitivity analysis was carried out in this review considering the effect of the beginning of anticoagulation when comparing DTI versus LMWH. What was observed was that the studies that initiated anticoagulation before surgery evidenced less VTE events, and those that began anticoagulation after surgery evidenced more VTE events in comparison with LMWH (Analysis 4.1). There was no significant difference regarding bleeding and mortality events, which agrees with that found by Hull 2001. Therefore, the effect of the DTIs described in the results regarding efficacy, compared to LMWH, seem to be influenced by the time of initiation of coagulation more than the effect of the drug itself.

Although the number of analysed patients was high, few studies were found and the obtainment of studies by manual search was null. Most of the funnel plots in this review are asymmetrical (Figure 5; Figure 6; Figure 7; Figure 8) which suggests certain publication bias. Although there was no restriction regarding languages, only studies in English were found. Bias in this review is not discarded despite the developed methodology.

Figure 5. Funnel plot of comparison: Efficacy DTI (any dose) vs. LMWH + follow up events, outcome: Major VTE events in THR + TKR combined doses.

Figure 6. Funnel plot of comparison: Safety DTI (any dose) vs. LMWH + follow up events, outcome: Total Bleeding events in THR + TKR combined doses.

Figure 7. Funnel plot of comparison: Efficacy DTI (any dose) vs. VKA (Warfarin) + follow-up events, outcome: Major VTE events in TKR combined doses.

Figure 8. Funnel plot of comparison: Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events, outcome: Major/ Significant Bleeding events in TKR combined doses.

Agreements and disagreements with other studies or reviews

In the included studies of this review the International Normalized Ratio (INR) objective range (2.0 to 3.0) was achieved between 33% and 67% of the patients on the third day of treatment and at the end of the treatment period in the 50% to 76% range of the patients treated with warfarin, which is a somewhat higher proportion than usual.

The percentage of patients with venographically-confirmed DVT following THR or TKR in the LMWH group of this review was similar to rates reported previously in studies with LMWH (Clagett 1998; Eriksson 1991; Hull 1993). The only trial found which evaluated extended prophylactic anticoagulation in patients subjected to TKR was the RE-NOVATE 2007 study, and it had an incidence of VTE events in LMWH of 7%, much lower than the rest of the studies.

In the only placebo-controlled prophylaxis trial after TKR, the incidence of major bleeding was 2% in the placebo group (Leclerc 1992). Published studies using warfarin in TKR have shown major bleeding in 0.9% (Leclerc 1996) and 1.8% (Hull 1993). In

this review, the major bleeding rate was much lower to the ones reported (0.36%). The explanation for this according to some of the trialist of the original studies may be related to improvements in general surgical care and to the strict, predefined guidelines used for central adjudication.

More recently, the NICE Appraisal Committee (NICE 2008 guideline) considered evidence submitted by the manufacturer of dabigatran etexilate for the prevention of venous thromboembolism (VTE) after hip or knee replacement surgery in adults and a review of this submission by the Evidence Review Group (ERG). The manufacturer conducted a systematic review which included three randomised, active-controlled parallel-group, non-inferiority trials of dabigatran etexilate (each including two dosing regimes) versus enoxaparin. These trials were: RE-MOBILIZE 2009, RE-MODEL 2007, and RE-NOVATE 2007. Outcomes analysed included: mortality; incidence of deep vein thrombosis; incidence of pulmonary embolism; adverse effects of treatment including bleeding events; post-DVT complications including post-thrombotic syndrome; length of hospital stay; and health-related quality of life. This document was extensively revised and commented by Holmes 2008. According to his report, "the processes undertaken by the manufacturer for screening studies, data extrac-

tion and applying quality assessment criteria to included studies are not made explicitly clear in the Manufacturer's Submission". The main differences with our review are that the manufacturer's submission (MS) did not include in the analysis the follow-up events, all-cause mortality was not an individual outcome; it was analysed combined with total VTE events. The outcome measure in the MS report was Absolute risk differences and Relative risks; in our review the Odds ratio was employed as the outcome measure. We also included the rescuable data of the [BISTRO II 2005](#). [NICE 2008](#) states that "Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery." However In the economic evaluation they performed analysing the three pivotal studies, dabigatran was more costly and less effective than LMWH.

AUTHORS' CONCLUSIONS

Implications for practice

Direct thrombin inhibitors (DTIs) (ximelagatran, dabigatran and desirudin) seem at least equally effective than conventional drugs (LMWH or warfarin) for prevention of venous thromboembolism in patients subjected to total hip replacement (THR) or total knee replacement (TKR).

However, the DTIs (specially ximelagatran) evidence higher mortality tendency with regard to LMWH in the prophylactic anticoagulation of venous thromboembolism in patients subjected to orthopedic surgery. More total bleeding events were observed in the DTI group in comparison with LMWH in the prophylactic anticoagulation of venous thromboembolism in patients subjected to THR.

The DTI effects regarding efficacy (major VTE), in comparison with LMWH seem to be influenced by the time of initiation of coagulation more than the effect of the drug itself.

No severe hepatic complications or fatal events from hepatopathy were reported in the analysed studies.

Safety and efficacy results must be taken with caution because of the variability found in the studies due to the variation in demographic characteristics of the study population, differences in venographic technique, variations between observers in the interpretation of venograms, different drugs, doses, types of surgery, and initiation and duration of the treatment.

Moreover, the presentation of the combined results, both in the efficacy and safety analyses, must be taken with caution due to the different methodological characteristics of the studies (no ITT analysis, some studies not blinded, difference in the presentation of results, etc.).

Due to all of these findings, the use of ximelagatran is not recommended for VTE prevention in patients who have undergone orthopaedic surgery. There is insufficient evidence to support the use of dabigatran and desirudin in VTE prevention in orthopaedic surgery.

Implications for research

More studies of DTIs are required, specially on dabigatran compared with LMWH and vitamin K antagonist (warfarin). The effect of the coagulation time of initiation needs to be properly analysed for dabigatran. It is debated whether the question of rare, serious liver toxicity can be fully addressed in 19,000 patients, specially when the follow-up period is short. This serious complications needs to be adequately evaluated. Also mortality and symptomatic VTE events needs a detailed evaluation in dabigatran. Due to this, there is currently insufficient data to support their use in preference to LMWH.

It was not possible to analyse part of the information presented in the original studies due to the various ways of showing the results and, also, in the review authors' opinion, certain relevant information was not available for analysis of this review. The trialists' answers with the requested information is being awaited, which will be included in the updating of this review.

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Our thanks in advance to all those interested in the presented topic and hope that they will send us their criticisms and comments as well as information on any publication regarding this subject that could be included in the updating of this systematic review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

BISTRO II 2005

Methods	<p>Method of allocation/randomisation: Computer-generated scheme.</p> <p>Blinded: Triple.</p> <p>Design: RCT parallel group.</p> <p>Power calculation: 90%.</p> <p>Number of patients randomised: 1973.</p> <p>Number of patients analysed: Security analysis 1949; efficacy analysis 1464.</p> <p>Number of withdrawals and reasons: Reactive malignant disease; current cytostatic treatment or recent treatment with an investigational drug. Women of childbearing potential, those with leg amputations and known alcohol or drug abuse were also excluded.</p> <p>Dabigatran Group: 21 only received one dose of subcutaneous or oral drug; 11 no data concerning VTE events; 335 venography not performed or inadequate (194 venography not performed; 136 venography could not be evaluated; 5 Inconclusive venography data).</p> <p>Enoxaparin Group: 7 only received one dose of sc. or oral drug; 1 no data concerning VTE events; 82 venography not performed or inadequate (36 venography not performed; 44 venography could not be evaluated; 2 Inconclusive venography data).</p> <p>After the treatment period, 9 (0.6%) of 1557 patients in the dabigatran etexilate group and 3 (0.8%) of 392 patients in the enoxaparin group were lost to follow up at 4 to 6 weeks.</p> <p>Intention-to-treat analysis: 1464.</p> <p>Bilateral venography was done.</p> <p>Source of funding: Pharmaceutical: Boehringer Ingellheim.</p>
Participants	<p>Country: 60 Europe; 2 South Africa.</p> <p>Number of centres: 62.</p> <p>Location: Hospitals.</p> <p>Source of patients: Consecutive patients scheduled for primary elective THR or TKR.</p> <p>Age: 65 (20 to 93) years.</p> <p>Sex: Female: 1191 (61%).</p> <p>Inclusion criteria: Patients aged 18 years or older, weighing at least 40 kg, scheduled for primary elective THR or TKR and who signed an informed consent were eligible for the study.</p> <p>Exclusion criteria: Any bleeding diathesis; coagulation disorders; history of or acute intracranial disease; major surgery or trauma within the last 3 months; cardiovascular disease including uncontrolled hypertension or history of MI within the last 6 months; history of stroke; DVT, GI or pulmonary bleeding within the last year; known liver disease AST or ALT > 3 times the upper limit of normal; renal disease (serum creatinine > 1.5 upper limit of normal); use of long-term anticoagulants, antiplatelet drugs (except low-dose aspirin up to 160 mg daily), or fibrinolytic within 7 days prior to surgery (also contraindicated during the treatment period); allergy to radiopaque active malignant disease; current cytostatic treatment or recent treatment with an investigational drug. Women of childbearing potential, those with leg amputations and known alcohol or drug abuse were also excluded.</p>

Interventions	<p>Treatment(s): Patients were assigned to either oral dabigatran etexilate with doses of 50 mg and 150 mg bid, 300 mg od, and 225 mg bid, or 40 mg of enoxaparin sc.od. First dose 1 to 4 hours after operation.</p> <p>Control /Placebo: 40 mg of enoxaparin sc., od. First dose evening before operation. Both study groups received active or matching placebo medications.</p> <p>Duration: 7 days.</p> <p>Follow up: 4 to 6 weeks.</p>
Outcomes	<p>Primary outcomes: The primary efficacy outcome was the incidence of VTE, being symptomatic, or venographically detected DVT, or PE, or both detected during the treatment period.</p> <p>Secondary outcomes: The primary safety outcome was major bleeding during the treatment period, as clinically overt bleeding associated with $\pm$ 20g/L) fall in Hb; clinically overt leading to transfusion of $\pm$ 2 units packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to re-operation</p>
Notes	<p>Extra data required:</p> <p>Hormonal contraception not reported.</p> <p>No information from 7 patients in dabigatran group</p> <p>Follow up VTE events: in which surgery group?</p> <p>Unexplained death relation with ALT, AST or liver failure?</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer-generated scheme
Allocation concealment?	Low risk	Central randomisation in groups of 10
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	<p>Quote: "All statistical analyses were performed on an intention-to-treat basis. The safety population comprised all randomised patients who received at least one sc. injection, or one oral dose of study drug. Those patients who also underwent surgery and had centrally adjudicated data on VTE (venography or symptomatic con-firmed event) by day 10 were considered for the efficacy analysis."</p> <p>Data from: dabigatran 50 mg bid, 150 mg bid, 300 mg qd, 225 mg bid, all combined doses, enoxaparin</p> <p>Primary efficacy outcome: VTE during</p>

		<p>treatment: 86/302, 49/282, 47/283, 39/297, 72/300</p> <p>Treatment patients analysed: 302, 282, 283, 297, 300 1164, 300</p> <p>Randomised patients: 389, 390, 385, 393 (total: 1557 + 19 not treated: not analysed), 392 (+ 5 not treated: not analysed)</p> <p>Attrition and exclusions were reported but not in detail.</p>
Free of selective reporting?	Unclear risk	No description if the protocol was registered.
Free of other bias?	Unclear risk	Quote: "...To demonstrate these differences with 90% power at a 5% level of significance, randomisation of 2000 patients (400 per treatment group) was required, assuming that 25% of patients would not have evaluable venograms."

Colwell 2003

Methods	<p>Method of allocation/randomisation: Computer-generated randomisation schedule.</p> <p>Blinded: Triple.</p> <p>Design: Randomised double-dummy controlled non inferiority study.</p> <p>Power calculation: > 90%.</p> <p>Number of patients randomised: 1838.</p> <p>Number of patients analysed: Safety analysis 1816; efficacy analysis 1557.</p> <p>Number of withdrawals and reasons: 22 not treated; 107 discontinued treatment (42 adverse events; 29 consent withdrawn; 2 not eligible; 3 PE; 2 DVT; other 29).</p> <p>Intention-to-treat analysis: No.</p> <p>Source of funding: Not stated.</p> <p>Notes: Unilateral venography.</p>
Participants	<p>Country: USA 89, Canada 24, Israel 5, Mexico 4, 3 Argentina, 1 South Africa.</p> <p>Number of centres: 126.</p> <p>Location: Hospitals.</p> <p>Source of patients: schedule for elective THR.</p> <p>Age: Ximelagatran (64.5 ± 12.8); enoxaparin (64 ± 13.1) years</p> <p>Sex: Female 808 (52%).</p> <p>Inclusion criteria: >18 years, prescreening 1 to 30 days before operation and on the day of their operation; weight 40 to 125 kg, written informed consent. Women surgically sterile, > 2 years postmenopausal, or reliable contraception.</p> <p>Exclusion criteria: Scheduled hemiarthroplasty; surface replacement, or revisionary surgery; planned external pneumatic compression prophylaxis; immobilization for > 3 days within 30 days preoperatively; prior major surgery; ischaemic stroke; MI; or administration of any investigational drug within 30 days prior to surgery; history of intracranial, retroperitoneal or intraocular bleeding or other disorder associated with increased risk of bleeding; GI bleeding within 90 days; and/or endoscopically verified ulcer</p>

	within 30 days before surgery; uncontrolled hypertension; malignancy currently under cytostatic treatment or being the reason for hip replacement; known significant liver disorder or ALT or AST > 3 times the upper limit of the normal range; thrombocytopenia; history of drug or alcohol abuse in the past 6 months; known allergy to contrast media or iodine; contraindication to enoxaparin use; significant renal impairment; and traumatic spinal/epidural puncture just prior to surgery	
Interventions	Treatment(s): Ximelagatran 24 mg orally bid morning after operation (12h post operation). Control /Placebo: Enoxaparin 30 mg sc. od. Duration: 7 to 12 days. Follow up: 6 ± 2weeks after operation.	
Outcomes	Primary outcomes: Composite endpoint of DVT (symptomatic or detected by routine venography) and /or PE during treatment. Secondary outcomes: incidence of proximal DVT and/or PE.	
Notes	Extra data required: Hormonal contraception data. AST, ALT data required. Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer-generated scheme
Allocation concealment?	Low risk	Central randomisation
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran, enoxaparin Primary outcome: VTE during treatment: 62/782, 36/775 Analyzed patients:782, 775 Randomised patients: 918, 920 Attrition and exclusions were reported but not in detail Re-inclusion in analysis by the review authors: PE or DVT as reasons for discontinuation: 3 + 4, 2 + 2
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Unclear risk	Unilateral venography

Methods	Method of allocation/randomisation: Not Stated. Notes: Bilateral venography. Blinded: Double. Design: RCT multicentre. Power calculation: 80% Number of patients randomised: 2079. Number of patients analysed: efficacy 1587 safety 2051. Number of withdrawals and reasons: 492 venography not performed or inadequate. Intention-to-treat analysis: No. Source of funding: Pharmaceutical Novartis.	
Participants	Country: 10 European. Number of centres: 31. Location: Hospitals. Source of patients: Scheduled to undergo elective primary total hip replacement. Age: Desidurin 66(18 to 87); Enoxaparin 66 (27 to 90) years. Sex: Female 1212 (58%). Inclusion criteria: > 18 years, > 50 kg, elective primary THR. Exclusion criteria: Childbearing potential; previous inclusion in the trial; bilateral hip operation; hip surgery or fracture of the leg within the previous three months; other major surgery within the past month; haemostatic or bleeding disorders; a history of hemorrhagic stroke, intracranial or intraocular bleeding, or cerebral Ischaemic attacks within the past 6 months; GI or pulmonary bleeding within the past 3 months; uncontrolled hypertension; renal impairment, nephrectomy, or kidney transplantation; and known allergy to hirudin, heparin, or contrast medium	
Interventions	Treatment(s): Desirudin 15 mg bid sc. First dose 30min after operation. Control /Placebo: Enoxaparin 40 mg od sc.evening before operation. Duration: 8 to 12 days. Follow-up period: 6 weeks.	
Outcomes	Primary outcomes: Confirmed major thromboembolic events (proximal DVT, fatal and non-fatal PE, unexplained death). Secondary outcomes: Bleeding complications (blood loss; number and volume of transfusions; serious bleeding episodes; wound dehiscence; deep wound infections; wound hematoma; injection-site hematoma)	
Notes	Extra data required: Hormonal contraception. Means instead of medians. AST, ALT data. Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not stated

Eriksson 1997 (Continued)

Allocation concealment?	Unclear risk	Not stated
Blinding? All outcomes	Low risk	Double. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: desirudin, enoxaparin Primary outcome: major VTE during treatment: 39/802, 60/785 Analyzed patients: 802, 785 Randomised patients: 1043, 1036 Attrition and exclusions were reported but not in detail
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Unclear risk	Quote: "The planned size of the sample for this study was 1000 patients in each treatment group." Number of patients analysed: efficacy 1587 (desirudin 802/ enoxaparin 785)

EXPRESS 2003

Methods	<p>Method of allocation/randomisation: Computer-generated central randomisation.</p> <p>Blinded: Triple.</p> <p>Design: multicenter randomised parallel group. Double dummy.</p> <p>Power calculation: 90%</p> <p>Number of patients randomised: 2835</p> <p>Number of patients analysed: 2316 (first stage) / 2326 (second stage).</p> <p>Number of withdrawals and reasons: 14 did not receive drugs, 57 no operation; 2 patients in enoxaparin group excluded because of traumatic spinal puncture. The rest due to non evaluable venograms.</p> <p>Intention-to-treat analysis: 2765.</p> <p>Source of funding: Pharmaceutical Astra Zeneca.</p> <p>Notes: First stage: Non inferior analysis; second stage: more effective analysis. Bilateral venography.</p>
Participants	<p>Country: European.</p> <p>Number of centres: 77.</p> <p>Location: Hospitals.</p> <p>Source of patients: Consecutive primary elective unilateral THR or TKR.</p> <p>Age: Ximelagatran 67(24 to 88); enoxaparin 67(20 to 89) years.</p> <p>Sex: Female 1713 (62%).</p> <p>Inclusion criteria: Weight: Not stated</p> <p>Exclusion criteria: Stroke < 1m, recent trauma or major operation; history of intracranial bleeding or intraocular bleeding < 1 y; history of GI bleeding < 3m; endoscopically verified ulcer diseases; ongoing malignancy; uncontrolled hypertension; bleeding disorder.</p>

	ders; severe renal impairment; known active liver disease or liver insufficiency. Women of childbearing age without effective contraception	
Interventions	Treatment(s): Melagatran sc. 2 mg before operation (after induction) and 3 mg evening after operation until tolerated VO, then 24 mg Ximelagatran bid. Control /Placebo: Enoxaparin 40 mg sc. od (12h before operation). Duration: 8 to11 days. Follow up: 4 to 6 weeks after operation.	
Outcomes	Primary outcomes: Major VTE treatment period (proximal DVT, PE and/or death where PE could not be ruled out). Total VTE during treatment period (DVT distal or proximal, PE and/or death any cause). Secondary outcomes: Bleeding, other adverse events and laboratory parameters. Blood loss and transfusions	
Notes	Extra data required: To assess comparative demographic groups: % women with hormonal contraception. Proximal DVT, PE. In follow-up period there were 12 confirmed symptomatic VTE (six in each treatment group) but in which surgery group? In follow-up period there were 2 unexplained deaths in ximelagatran group but in which surgery group? Arithmetic means. Laboratory parameters (ALT,AST). Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer-generated scheme
Allocation concealment?	Low risk	Central randomisation
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran, enoxaparin Primary outcome: major VTE during treatment: 26/1138, 74/1178 Analyzed patients:1138, 1178 Randomised patients: 1410, 1425 Attrition and exclusions were reported but not in detail
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Low risk	

Methods	<p>Method of allocation/randomisation: Computer-generated list.</p> <p>Blinded: Triple.</p> <p>Design: RCT, double dummy.</p> <p>Power calculation: 90%.</p> <p>Number of patients randomised: 2303.</p> <p>Number of patients analysed: 2299 safety population / 1949 efficacy population.</p> <p>Number of withdrawals and reasons: Did not receive treatment: 1 ximelagatran, 3 warfarin. No information about 5 patients in ximelagatran group and 4 patients in warfarin group.</p> <p>29 patients did not receive ximelagatran by adverse events; 11 consent withdrawn; 1 patient was not eligible; 6 by confirmed symptomatic VTE; and 6 by other reasons.</p> <p>In the warfarin group discontinued treatment 52 patients: 34 by adverse events, 6 consent withdrawn, 8 confirmed symptomatic VTE and 4 by other reasons.</p> <p>Intention-to-treat analysis: 1949.</p> <p>Source of funding: Pharmaceutical Astra Zeneca</p> <p>Bilateral venography</p>
Participants	<p>Country: United States, Canada, Israel, Mexico and Brasil.</p> <p>Number of centres: 115.</p> <p>Location: Hospital.</p> <p>Source of patients: Patients undergoing primary total knee arthroplasty.</p> <p>Age: 66.9 ± 9.4 ximelagatran / 67.1 ± 9.4 warfarin.</p> <p>Sex: Female: 705 (61.3%) ximelagatran/ 733 (63.9%) warfarin.</p> <p>Inclusion criteria: >18 years, patients undergoing primary total knee arthroplasty, either women without childbearing potential or men, who were at least 18 years old, weighing between 40 kg and 136 kg, and who had provided written informed consent were enrolled.</p> <p>Exclusion criteria: The criteria for exclusion were major surgery; stroke; MI; or administration of any investigational drug within thirty days before surgery; immobilization for three or more days before surgery; traumatic epidural and/or spinal puncture at surgery; planned pneumatic leg compression; a history of intracranial, retroperitoneal, or intraocular bleeding; a history of GI bleeding or other disorder associated with an increased risk of bleeding within ninety days before surgery; an endoscopically verified peptic ulcer disease within thirty days of surgery; uncontrolled hypertension; a malignant tumour receiving cytostatic treatment or being the reason for the knee arthroplasty; an ALT or ASP level greater than two times the upper limit of normal; renal impairment (defined as estimated creatinine clearance of < 30 mL/min); thrombocytopenia; a history of drug or alcohol abuse in the past six months; an allergy to venographic contrast media or iodine; and a contraindication to warfarin</p>
Interventions	<p>Treatment(s): Ximelagatran 36 mg orally bid was initiated as early as possible in the morning after surgery.</p> <p>Control /Placebo: Warfarin was initiated in the evening of the day of surgery and titrated to INR = 2.5(1.8-2.5).</p> <p>Duration: 7 to 12 days.</p> <p>Follow up: 4 to 6 weeks after operation.</p>
Outcomes	<p>Primary outcomes: The composite primary efficacy end point was the incidence of total VTE (DVT and PE) and mortality from all causes during treatment, as determined by an Independent Central Adjudication Committee.</p>

	Secondary outcomes: The composite secondary efficacy end point was the incidence of proximal DVT, PE, and mortality from all causes during treatment. DVT was evaluated with bilateral ascending venography performed seven to twelve days after the initiation of study treatment. Major or minor bleeding occurring up to 48 hours after the last dose of the study drug had been administered.	
	Any adverse event that was reported as a bleeding event was reviewed by the Independent Central Adjudication Committee	
Notes	Extra data required: Women with hormonal contraception? 2 patients in follow up period had symptomatic DVT but no venography: in which group? Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer-generated scheme
Allocation concealment?	Low risk	Central randomisation
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran 36 mg, warfarin Prymary outcome:VTE and mortality during treatment: 221/982, 308/967 Analyzed patients:982, 967 Randomised patients: 1152, 1151 Attrition and exclusions were reported but not in detail Re-inclusion in analysis by the review authors: PE or DVT as reasons for discontinuation: 6, 8
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Low risk	

Methods	<p>Method of allocation/randomisation: Randomisation was performed with the use of a computer-generated system, with stratification at each centre according to whether patients underwent unilateral or bilateral surgery.</p> <p>Blinded: Triple.</p> <p>Design: Prospective, randomised trial.</p> <p>Power calculation: 80%.</p> <p>Number of patients randomised: 2301.</p> <p>Number of patients analysed: Safety analysis: 2285; efficacy analysis: 85.1</p> <p>Number of withdrawals and reasons: 16 underwent randomisation but did not receive treatment; in the case of the remaining 434 patients, the presence or absence of an end point could not be determined because venography either was not performed or was indeterminate or because there was no confirmed symptomatic venous thromboembolic event or death.</p> <p>Intention-to-treat analysis: Not stated.</p> <p>Source of funding: Pharmaceutical Astra Zeneca.</p> <p>Notes: Bilateral ascending venography (some just with unilateral venography)</p>
Participants	<p>Country: United States, Canada, Israel, Mexico, and Brazil.</p> <p>Number of centres: 116.</p> <p>Location: Hospitals.</p> <p>Source of patients: Patients undergoing primary TKR.</p> <p>Age: Not stated (average age 67.8 ± 9.7). Ximelagatran 36 mg (68.5 ± 9.5); Ximelagatran 24 mg (67.7 ± 9.7) / Warfarin (67.8 ± 9.6) years.</p> <p>Sex: Female 1416 (62%).</p> <p>Inclusion criteria: Eligible patients were women without childbearing potential and men who weighed between 40 and 136 kg. Only patients undergoing primary YKR were included.</p> <p>Exclusion criteria: Pneumatic leg compression; immobilization for 3 or more days; major surgery, stroke, MI, or receipt of any investigational drug within 30 days before surgery; intracranial, retroperitoneal, or intraocular bleeding or any other disorder associated with an increased risk of bleeding within 90 days before surgery; GI bleeding within 90 days before surgery, ulcer disease verified by endoscopic examination within 30 days before surgery, or both; uncontrolled hypertension; cancer that required cytostatic treatment or was itself the reason for TKR; an ALT or AST level greater than two times the upper limit of the normal range; thrombocytopenia; drug or alcohol abuse within the previous 6 months; allergy to contrast medium or iodine; a contraindication to warfarin therapy; impaired renal function (defined by an estimated creatinine clearance of less than 30 ml per minute) 18; and traumatic epidural or lumbar puncture. If the use of an epidural or spinal catheter continued into the treatment period, the catheter was to be removed during trough levels of melagatran (the active metabolite of ximelagatran). Treatment with thrombolytic, anticoagulant, or antiplatelet agents, including heparins, warfarin, direct thrombin inhibitors, dipyridamole, sulphinyprazone, ticlopidine, clopidogrel, acetylsalicylic acid at a dose greater than 500 mg per day, and dextran, was not allowed within seven days before surgery or during the period of administration of the study drug</p>
Interventions	<p>Treatment(s): Ximelagatran at a dose of 24 mg or 36 mg orally 12 hours after operation.</p> <p>Control /Placebo: Warfarin INR 2.5 range (2 to 3) first dose evening after operation.</p> <p>Duration: 7 to 12 days.</p> <p>Follow-up period: 4 to 6 weeks after operation.</p>

Outcomes	Primary outcomes: The composite primary end point for efficacy comprised total (distal and proximal) DVT, PE, and death from all causes during treatment . Secondary outcomes: The composite secondary end point for efficacy comprised proximal DVT, PE, and death from all causes during treatment. Major bleeding and major or minor bleeding occurring up to 48 hours after the last dose of the study drug had been administered	
Notes	Extra data required: women with hormonal contraception. Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer-generated scheme
Allocation concealment?	Low risk	Central randomisation
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran 36 mg, ximelagatran 24 mg, warfarin Prymary outcome:VTE and mortality during treatment: 128/629, 153/614, 168/608 Analyzed patients:629, 614, 608 RandomisedMI patients: 775, 762, 774 Attrition and exclusions were reported but not in detail Re-inclusion in analysis by the review authors: PE or DVT as reasons for discontinuation: 8+4, 5+2, 4+2
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Unclear risk	Quote: "...We planned to enrol approximately 2250 patients in order to detect a 25 percent risk reduction with the lower dose, given the assumption that 25 percent of venograms would be inadequate for evaluation."

Methods	<p>Method of allocation/randomisation: Computer generated.</p> <p>Blinded: Triple.</p> <p>Design: RCT. Randomisation was stratified by unilateral or bilateral surgery.</p> <p>Power calculation: 95%.</p> <p>Number of patients randomised: 680.</p> <p>Number of withdrawals and reasons: death from MI (1 patient in the ximelagatran group), withdrawn consent (1 patient in each group), use of prohibited medication (1 patient in the ximelagatran group), and unfulfilled eligibility criteria (1 patient in the warfarin group).</p> <p>Number of patients analysed: Safety 675 patients (330 ximelagatran/ 345 warfarin); efficacy: 537 patients (276 ximelagatran/ 261 warfarin). Within this sample, 21 patients from the ximelagatran group and 30 from the warfarin group discontinued treatment prematurely because of adverse events (14 and 17 patients, respectively), withdrawn consent (2 and 4 patients, respectively), and "other reasons" (5 and 9 patients, respectively). "Other reasons" in the warfarin group included confirmed pulmonary embolism (3 patients) and confirmed DVT (2 patients).</p> <p>Intention-to-treat analysis: 537.</p> <p>Source of funding: Pharmaceutical Astra Zeneca</p> <p>Notes: Venography was done mainly unilateral rather than bilateral (<10%). We decided to use the information from central adjudication.</p>
Participants	<p>Country: United States and Canada.</p> <p>Number of centres: 74.</p> <p>Location: Hospital.</p> <p>Source of patients: Patients for elective total knee arthroplasty.</p> <p>Age: 67.8 ± 10.1 ximelagatran/ 67.7 ± 10.4 warfarin.</p> <p>Sex: 433 Women %: 63.2 ximelagatran / 64.2 warfarin.</p> <p>Inclusion criteria: Patients were eligible if they were scheduled for elective total knee arthroplasty, were at least 18 years of age, weighed 40 to 125 kg, and provided consent. Women had to be surgically sterile, postmenopausal for at least 2 years, or using reliable contraception.</p> <p>Exclusion criteria: Criteria for exclusion were scheduled hemiarthroplasty, surface repair, or revisionary surgery; planned external pneumatic compression prophylaxis; immobilization for 3 or more days before surgery; major surgery, Ischaemic stroke, MI, or administration of any investigational drug within 30 days before surgery; a history of intracranial, retroperitoneal, or intraocular bleeding or any other disorder associated with increased risk for bleeding; gastrointestinal bleeding within 90 days before surgery or endoscopically verified ulcer disease within 30 days before surgery; uncontrolled hypertension; cytotoxic treatment for active malignancy; clinically significant liver disease; thrombocytopenia; drug or alcohol abuse in the past 6 months; allergy to contrast media or iodine; contraindication to warfarin; severe renal impairment (defined as estimated creatinine clearance 0.5 mL/s (30 mL/min)); or traumatic epidural or spinal puncture before surgery</p>
Interventions	<p>Treatment(s): Ximelagatran 24 mg/placebo. First dose 12h after operation.</p> <p>Control /Placebo: Warfarin 5 mg (titrated). First dose evening after operation.</p> <p>Duration: 7 to 12 days.</p> <p>Follow up: 4 to 8 weeks.</p>

Outcomes	Primary outcomes: The primary efficacy variable was the incidence of DVT (proximal or distal) or pulmonary embolism. Secondary outcomes: All bleeding events were recorded, including bleeding at the site of surgery, volumes of blood loss and transfusion, and wound appearance. Notes: Clinical chemistry and hematology variables were assessed at screening, on the last day of study drug administration, and at the 6-week follow-up examination	
Notes	Extra data required: Data about liver function. Women with hormonal contraception? Respect mean transfusion volume we need the data in ml instead of units. unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer generated scheme
Allocation concealment?	Low risk	Central randomisation
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran 24mg, warfarin Primary outcome:VTE during treatment: 221/276, 308/261 Analyzed patients:276, 261 Randomised patients: 348, 332 Attrition and exclusions were reported but not in detail Re-inclusion in analysis by the review authors: PE or DVT as reasons for discontinuation: not stated, 3+2
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Unclear risk	Venography was done mainly unilateral rather than bilateral (<10%)

Methods	<p>Method of allocation/randomisation: Computed-generated randomisation list. Stratified in blocks of five patients. Phase II study.</p> <p>Blinded: No.</p> <p>Design: Multicentre randomized parallel open label for eoxaparin.</p> <p>Power calculation: 80%.</p> <p>Number of patients randomised: 600.</p> <p>Number of patients analysed: 415.</p> <p>Number of withdrawals and reasons: 55 (adverse event, lost to follow up, stopped by sponsor or investigator, ineligible, withdrawn consent. Venography not done or inadequate: 157.</p> <p>Intention-to-treat analysis: 546.</p> <p>Source of funding: Pharmaceutical Astra Zeneca.</p> <p>Notes: Unilateral venography. 8 mg ximelagatran suspended and mixed in the remaining groups</p>
Participants	<p>Country: USA.</p> <p>Number of centres: 68.</p> <p>Location: hospitals.</p> <p>Source of patients: scheduled for elective primary unilateral total knee replacement.</p> <p>Age: 66.9 (SD11) ximelagatran / 68(SD10) enoxaparin .</p> <p>Sex: Female 373 (62%).</p> <p>Inclusion criteria: 18 or more years, not of childbearing potential, weight 40 to 125 kg.</p> <p>Exclusion criteria: Previous DVT or PE; anticipated use of epidural or spinal catheter > 12h after surgery or within 2h of administration of the first dose of study medication; traumatic epidural puncture; planned external pneumatic compression prophylaxis (except stockings); immobilization within 12 weeks before surgery; long term anticoagulant or antiplatelet therapy; allergy to contrast media or iodine; clinical bleeding disorder; renal impairment or transplant; previous intracranial or retinal bleeding; drug or alcohol abuse; ischaemic stroke within the previous 3 months; GI bleeding or ulcer within the previous year; major surgery (3 months); malignant neoplasm being actively treated; uncontrolled hypertension; liver disease (ALT or AST levels > 2-fold higher than normal) ; anaemia; thrombocytopenia; previous included in this study; or other investigational agent (30 days)</p>
Interventions	<p>Treatment(s): 4 arms: oral ximelagatran 8 mg, 12 mg, 18 mg, 24 mg bid first dose within 12 to 24 hours after surgery.</p> <p>Control /Placebo: Enoxaparin 30 mg sc. bid. First dose within 12 to 24 hours after surgery.</p> <p>Duration: 6 to 12 days.</p> <p>Follow-up period: 4 to 10 weeks.</p>
Outcomes	<p>Primary outcomes: Assess the dose range of ximelagatran. Primary Efficacy measure: cumulative incidence of verified VTE (DVT: unilateral venography; PE: v/q perfusions test, spiral CT, or angiogram).</p> <p>Secondary outcomes: Compare the efficacy and safety ximelagatran versus enoxaparin. Bleeding: (major, minor)</p>

Notes	Extra data required: Number of women with hormonal contraception. Transfusion Volume SD. ALT, AST information. Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer generated scheme
Allocation concealment?	Low risk	Central randomisation in blocks of five
Blinding? All outcomes	Unclear risk	Partially open
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran 8 mg,12 mg,18 mg, 24 mg, enoxaparin Efficacy outcome: VTE during treatment: 27/63, 20/101, 29/87, 16/95, 23/97 Analyzed patients:63, 101, 87, 95, 97 Randomised patients: 85, 134, 126, 130, 125 Attrition and exclusions were reported but not in detail
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Unclear risk	(1) Unilateral venography (2) Quote:”we estimated that 80 evaluable patients per dose group would provided 80% power (alpha: 0.05) to detect a dose response.“

Methods	<p>Method of allocation/randomisation: Not clear. Stratified according to centre and to procedure.</p> <p>Blinded: No.</p> <p>Design: RandomisedMI, parallel-group, controlled study, blinded to ximelagatran groups but open label with respect to the dalteparin group.</p> <p>Power calculation: Not stated.</p> <p>Number of patients randomised: 137.</p> <p>Number of patients analysed: 135 efficacy analysis, 136 safety analysis.</p> <p>Number of withdrawals and reasons: 2; Two patients did not undergo surgery, and one of these, randomised to sc. melagatran and oral ximelagatran, did not receive treatment.</p> <p>Intention-to-treat analysis: Said yes but not really</p> <p>Source of funding: Not stated .</p> <p>Notes: Bilateral venography on the final day of treatment. 19 serious adverse events in follow up period not described. Not ITT in efficacy analysis. Not included the DVT or PE occurred in the follow up period</p>
Participants	<p>Country: Sweden.</p> <p>Number of centres: 8.</p> <p>Location: Hospitals.</p> <p>Source of patients: Scheduled for primary elective THR or TKR.</p> <p>Age: 69 (47 to 84) years.</p> <p>Sex: Female 80 (59%).</p> <p>Inclusion criteria: Patients between 18 and 85 years old, weighing 50 to 110 kg and scheduled for primary elective THR or TKR. All patients provided signed informed consent and all of the Ethics Committees involved in the study approved the protocol.</p> <p>Exclusion criteria: History of DVT or PE or a suspected post-thrombotic state; immobilization up to 12 weeks before surgery; anticoagulant or antiplatelet drugs within 7 days prior to surgery; a history of Ischaemic stroke, intracranial or intraocular bleeding or a disorder associated with increased risk of bleeding; a history of GI bleeding and/or endoscopically verified ulcer disease within the past year; ongoing malignancy or cytostatic treatment within the past 6 months; uncontrolled hypertension; renal impairment or a nephrectomy; liver disease; anaemia; thrombocytopenia; drug addiction or a known allergy to contrast media or iodine; child-bearing potential</p>
Interventions	<p>Treatment(s):</p> <ol style="list-style-type: none"> 1) 1 mg melagatran bid followed by 6 mg ximelagatran bid; 2) 2 mg melagatran bid followed by 12 mg ximelagatran bid; or 3) 4 mg melagatran bid followed by 24 mg ximelagatran bid. <p>Patients received sc. melagatran bid for 2 days followed by oral ximelagatran bid for 6 to 9 days.</p> <p>4) dalteparin 5000 IU sc. od.</p> <p>The first injection of melagatran (Day 1) was given after induction of anaesthesia, immediately before surgery, and the second at 20:00 h the same day. Injections of melagatran on Day 2 and oral dosing of ximelagatran from Day 3 were at 08:00 h and 20:00 h. The fourth treatment group received dalteparin 5000 IU sc. once daily at 20:00 h, starting in the evening before the day of surgery (Day 0). The total treatment period was 8 to 11</p>

	days for all groups. Control /Placebo: Dalteparin 5000 IU sc. once daily. Duration: 8 to 11 days. Follow up: 4 to 6 weeks after operation.	
Outcomes	Primary outcomes: To assess the pharmacokinetics, safety and efficacy of sequential therapy, initiated preoperatively, with three dose levels of sc. melagatran followed by oral ximelagatran in the prophylaxis of VTE in patients undergoing THR or total knee replacement (TKR). Secondary outcomes: The relationship between the plasma concentrations of melagatran and the coagulation parameter activated partial thromboplastin time (aPTT)	
Notes	Extra data required: Mean instead of median and SD. Women with hormonal contraception? Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not stated
Allocation concealment?	Unclear risk	Not stated
Blinding? All outcomes	Unclear risk	Partially open
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran 6 mg,12 mg, 24 mg, enoxaparin Efficacy outcome: VTE during treatment: 6/29, 6/24, 4/25, 5/27 Analyzed patients:29, 24, 25, 27 Randomised patients: 34, 34, 34, 33. (= 135 + 2: treatment group not stated) Attrition and exclusions were reported but not in detail Re-inclusion in analysis by the review authors: PE or DVT as reasons for discontinuation: 1; treatment group not stated
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Unclear risk	Sample size was calculated to estimate the ximelagatran' s pharmacodynamic and pharmacokinetic parameters not efficacy or safety outcomes (32 patients per group) (phase II study)

Methods	<p>Method of allocation/randomisation: Computer-generated randomisation lists provided by the sponsor.</p> <p>Blinded: Triple.</p> <p>Design: Randomised, controlled, double-dummy, dose-response trial.</p> <p>Power calculation: 90%.</p> <p>Number of patients randomised: 1916.</p> <p>Number of patients analysed: 1872 safety analysis, 1477 efficacy analysis.</p> <p>Number of withdrawals and reasons: 16 patients did not receive the study drug, and 24 patients did not undergo surgery; 329 venograms not evaluable.</p> <p>Intention-to-treat analysis: not really.</p> <p>Source of funding: Pharmaceutical Astra Zeneca.</p> <p>Notes: Bilateral venography. Women with hormonal contraception? Melagatran 1 to 3 days after operation.</p>
Participants	<p>Country: 13 countries.</p> <p>Number of centres: 59.</p> <p>Location: Hospitals.</p> <p>Source of patients: Primary elective THR or TKR.</p> <p>Age: 66.4 (29 to 85) years.</p> <p>Sex: Female 736/1140 (61%).</p> <p>Inclusion criteria: Patients for primary elective THR or TKR were aged between 18 years and 85 years, and weighed between 50 kg and 110 kg. Those eligible were recruited consecutively into the study after providing written informed consent.</p> <p>Exclusion criteria: A history of DVT or PE; a suspected post-thrombotic state; immobility for up to 12 weeks before surgery; disorders associated with an increased risk of bleeding; a history of intracranial bleeding, Ischaemic stroke, intraocular bleeding, or previous history of GI bleeding or endoscopically verified ulcer disease within the previous 12 months; a major surgical procedure during the 12 weeks before the study-related operation; malignant disease; cytostatic treatment within the previous 6 months; uncontrolled hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg); renal impairment (serum creatinine > 150 μmol/L); nephrectomy or kidney transplantation; liver disease; anaemia (haemoglobin < 100 g/L); thrombocytopenia (platelet count < 100-10⁹/L); drug addiction; and known allergy to contrast media, LMWH, or iodine. Women of child-bearing potential were excluded</p>
Interventions	<p>Treatment(s): One of four bid doses of sc. melagatran followed by bid oral ximelagatran: 1-00 mg sc. melagatran followed by 8 mg oral ximelagatran; 1-50 mg sc. melagatran followed by 12 mg oral ximelagatran; 2-25 mg sc. melagatran followed by 18 mg oral ximelagatran; or 3 mg sc. melagatran followed by 24 mg oral ximelagatran. First dose after spinal puncture immediately before operation.</p> <p>Control /Placebo: Subcutaneous dalteparin 5000 IU (once daily). First dose evening before operation.</p> <p>Duration: 7 to 10 days.</p> <p>Follow-up period: 4 to 6 weeks after operation.</p>
Outcomes	<p>Primary outcomes: To assess the relationship of response in VTE frequency to dose with sequential administration of sc. melagatran and oral ximelagatran in a large number of patients undergoing major joint - replacement surgery.</p>

	Secondary outcomes: To assess the efficacy and safety compared with the recommended dalteparin regimen in Europe	
Notes	Extra data required: Women with hormonal contraception? On follow-up period there were 17 symptomatic DVT: in which groups? On follow-up period there were 2 PE in ximelagatran < 24 mg: in which surgery group? On follow-up period there were 4 deaths (one due to PE) in ximelagatran’ s groups: in which ones? Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer generated scheme
Allocation concealment?	Low risk	Central randomisation in blocks of five
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran 8 mg,12 mg, 18 mg, 24 mg, enoxaparin efficacy outcome:VTE during treatment: 111/294, 70/290, 71/300, 43/285, 87/308 Analyzed patients:294, 290, 300, 285, 308 Randomised patients: 364, 377, 375, 379, 381 Attrition and exclusions were reported but not in detail
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Unclear risk	Quote:”...we calculated that 1900 patients (380 per treatment group) would be required for randomisation to treatment obtain 90% statistical power...”

Methods	<p>Method of allocation/randomisation: Patients were consecutively randomised in permuted blocks of four, supplied to each centre, using a computer-generated randomisation list.</p> <p>Blinded: Triple.</p> <p>Design: Multicentre, randomised, triple dummy, parallel-group study.</p> <p>Power calculation: 90%.</p> <p>Number of patients randomised: 2874.</p> <p>Number of patients analysed: 2788 safety analysis / 2268 efficacy analysis.</p> <p>Number of withdrawals and reasons: 716</p> <ul style="list-style-type: none"> -21 did not receive any study drug; -53 did not undergo surgery; -122 ? other type of surgery; -520 venography non evaluable; <p>Intention-to-treat analysis: Said yes but not really.</p> <p>Source of funding: Astra Zeneca.</p> <p>Notes:</p> <ul style="list-style-type: none"> -Bilateral venography -No laboratory data
Participants	<p>Country: 13 European countries and 1 Republic of South Africa.</p> <p>Number of centres: 80.</p> <p>Location: Hospitals.</p> <p>Source of patients: Scheduled for primary elective THR or TKR surgery.</p> <p>Age: Ximelagatran 66.4 (25 to 93) / enoxaparin 65.8 (26 to 93) years.</p> <p>Sex: Female 1064/1724 (62%).</p> <p>Inclusion criteria: Patients aged 18 years or older, weighing at least 40 kg and scheduled for primary elective THR or TKR surgery.</p> <p>Exclusion criteria: Ischaemic stroke; recent trauma or major surgical procedure; history of intracranial or intraocular bleeding; history of GI bleeding within 3 months before surgery; endoscopically verified ulcer disease within 14 days before surgery; ongoing malignancy; uncontrolled arterial hypertension; any disorder associated with increased risk of bleeding; severe renal impairment; and known active liver disease or liver insufficiency</p>
Interventions	<p>Treatment(s): - 3 mg of melagatran (AstraZeneca, Mölndal, Sweden) sc. 4 to 12 h after surgery; followed by 24 mg of ximelagatran (AstraZeneca, Mölndal, Sweden) administered orally twice daily (hereafter referred to as the ximelagatran group); ximelagatran was to be initiated the day after surgery. However, if the patient was unable to tolerate oral treatment, this oral ximelagatran could be replaced by further subcutaneous injections of 3 mg of melagatran bid on the first two postoperative days.</p> <p>Control /Placebo: 40 mg of enoxaparin (Aventis Pharma, Bridgewater, NJ, USA) sc. od. Enoxaparin was to be started 12h before surgery.</p> <p>Duration: 8 to 11 days.</p> <p>Follow-up period: 4 to 6 weeks.</p>
Outcomes	<p>Primary outcomes: Total VTE (DVT + PE + Unexplained death) during the treatment period.</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> -Major VTE (proximal DVT, PE + Unexplained death) -Bleeding events -Blood lost

	<div>-Wound characteristics</div> <div>-Transfusions</div>	
Notes	Extra data required: In follow-up period there were 23 symptomatic VTE (7 in xime- lagatran and 9 in enoxaparin) in which surgery group? Women with hormonal contraception. In other dx procedures: were AST, ALT data included? Unexplained death relation with ALT, AST or liver failure?	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer-generated scheme
Allocation concealment?	Low risk	Central randomisation in permuted blocks of four
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: ximelagatran 24 mg, enoxa- parin Prymary outcome: VTE during treatment: 355/1146, 306/1122. Treatment patients analysed:1146, 1122 (2268) RandomisedMI patients: 2874 Attrition and exclusions were reported but not in detail
Free of selective reporting?	Unclear risk	No description if the protocol was regis- tered
Free of other bias?	Unclear risk	Quote: "the planned sample size for this study was 1300 patients in each treatment group"

Methods	<p>Method of allocation/randomisation: Computer generated with Interactive Voice Response System. Randomisation was performed in blocks of six based on an independently generated scheme.</p> <p>Blinded: Triple.</p> <p>Design: RCT non inferiority.</p> <p>Power calculation: 90% (required 2610 patients randomised, assuming 25% of patients would not have evaluable venograms).</p> <p>Number of patients randomised: 2615.</p> <p>Number of patients analysed: 1896(efficacy); 2596 (safety).</p> <p>Number of withdrawals and reasons: (dabigatran 220 mg; dabigatran 150 mg; enoxaparin): Not treated (5-6-8), no operation (4,7,9), venography inadequate or not performed (258 = 29.9%, 228 = 26.4%, 233 = 26.6%), discontinued treatment (71,63,80) : adverse events, bleeding events, symptomatic DVT or PE, deaths, consent withdrawn, or non compliance with protocol. Not complete follow-up period (51, 48, 49).</p> <p>Intention-to-treat analysis: No.</p> <p>Source of funding: Pharmaceutical; Boehringer Ingelheim.</p> <p>Notes: Number of patients completing the study period: dabigatran 220 mg: 806 (93.5%); dabigatran 150 mg: 823 (93.8%); enoxaparin: 819 (93.5%)</p>
Participants	<p>Country: United States, 30 in Canada, 8 in Mexico, and 1 in the United Kingdom.</p> <p>Number of centres: 58.</p> <p>Location: Hospitals.</p> <p>Source of patients: Scheduled for primary elective unilateral TKR.</p> <p>Age: 66 ± 9.6 years.</p> <p>Sex: Women 1497 (58%).</p> <p>Inclusion criteria: >18 years, weight at least 40 kg, provided signed informed consent.</p> <p>Exclusion criteria: Any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery; trauma; uncontrolled hypertension or MI within the past 3 months; GI or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; AST or ALT levels more than two times the upper limit of the normal range within the past month; severe renal insufficiency (creatinine clearance <30 mL/min); concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindicated during study treatment); active malignant disease; and being female and of childbearing potential; platelet count less than 100 × 10⁹/L</p>
Interventions	<p>Treatment(s): 3 groups: dabigatran 220 mg od or 150 mg od orally (in USA centres: 6 to 12 hours after surgery and continued study drugs until venography at approximately day 13, in European centres: oral study drug was begun 1 to 4 hours after surgery, and study drug discontinuation and venography occurred at days 6 to 10).</p> <p>Control /Placebo: 30 mg Enoxaparin sc. bid. (12 to 24 hours after surgery).</p> <p>Duration: 12 to 15 days or 3 days after the last dose), follow up with lab 3 months after surgery</p>
Outcomes	<p>Primary outcomes: Efficacy: composite total VTE events (venographic DVT or symptomatic PE) and all-cause mortality during treatment.</p> <p>Safety: bleeding during treatment.</p> <p>Secondary outcomes: major VTE (proximal DVT, PE), and VTE related mortality, proximal DVT and all-cause mortality during follow up.</p> <p>Safety: liver enzymes.</p>

Notes	Concomitant use of <160mg aspirin or selective cox-2 inhibitors allowed. Elastic compression stockings were permitted. Bilateral venography. First dose of dabigatran etexilate was one-half of subsequent doses	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer-generated scheme
Allocation concealment?	Low risk	Central randomisation. Voice system
Blinding? All outcomes	Low risk	Triple. Double-dummy. Randomisation in groups of 6
Incomplete outcome data addressed? All outcomes	High risk	Data from: dabigatran 220 mg, dabigatran 150 mg, enoxaparin Total VTE+ death during treatment: 188/604,219/649, 163/343. Treatment patients analysed:604, 649, 343 Randomised patients: 862, 877, 876 Attrition and exclusions were reported but not in detail Re-inclusion in analysis by the review authors: symptomatic VTE or PE as reasons for discontinuation: 13, 8, 9
Free of selective reporting?	Unclear risk	<i>No description if the protocol was registered</i>
Free of other bias?	Unclear risk	Quote: "It was determined that a study with 1950 evaluable patients (650 per group) would have 90% power, with a type I error of 0.025, to reject the hypothesis that the primary outcome with dabigatran would be 9.2% higher than enoxaparin if the VTE rate were as high as 48%."

Methods	<p>Method of allocation/randomisation: computer generated. Randomisation was performed in blocks of six.</p> <p>Blinded: Triple</p> <p>Design: RCT non inferiority.</p> <p>Power calculation: 90% (required 2100 patients randomised).</p> <p>Number of patients randomised: 2101.</p> <p>Number of patients analysed: 1541 (efficacy); 2076 (safety).</p> <p>Number of withdrawals and reasons: (dabigatran 220 mg; dabigatran 150 mg, enoxaparin): Not treated (15-5-5), no operation (4,7,9), venography inadequate or not performed (172, 170, 173), not complete study (67,71,69): consent withdrawn, adverse events or non compliance with protocol.</p> <p>Intention-to-treat analysis: No.</p> <p>Source of funding: Boehringer Ingelheim.</p> <p>Notes: Number of patients complete the study period: dabigatran 220 mg: 608 (87.6%), dabigatran 150 mg: 625 (88.3%); enoxaparin: 616 (88.1%)</p>
Participants	<p>Country: Europe, Australia, and South Africa.</p> <p>Number of centres: 105.</p> <p>Location: Hospitals.</p> <p>Source of patients: scheduled for primary elective unilateral TKR.</p> <p>Age: 67 ± 9 years.</p> <p>Sex: Female 1370 (64% to 69%).</p> <p>Inclusion criteria: >18 years, weight at least 40 kg, provided signed informed consent.</p> <p>Exclusion criteria: Any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or MI within the past 3 months; GI or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; AST or ALT levels more than two times the upper limit of the normal range within the past month; severe renal insufficiency (creatinine clearance < 30 mL/min); concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindicated during study treatment); active malignant disease; and being female and of childbearing potential</p>
Interventions	<p>Treatment(s): 3 groups: dabigatran 220 mg od or 150 mg od orally (evening before operation: not in all centres).</p> <p>Control /Placebo: 40 mg Enoxaparin sc. (evening before operation: not in all centres).</p> <p>Duration: 6 to 10 days.</p> <p>Follow up: with lab 2 to 3 months after surgery.</p>
Outcomes	<p>Primary outcomes: Efficacy: composite total VTE events (venographic DVT or symptomatic PE) and all-cause mortality during treatment.</p> <p>Safety: Bleeding during treatment.</p> <p>Secondary outcomes: major VTE (proximal DVT, PE), and VTE related mortality, proximal DVT and all-cause mortality during follow up.</p> <p>Safety: liver enzymes.</p>
Notes	<p>Extra data required: Women with hormonal contraception? Transfusion volume data? Concomitant use of < 160 mg aspirin or selective cox-2 inhibitors allowed.</p> <p>Elastic compression stockings were permitted.</p> <p>Bilateral venography.</p>

RE-MODEL 2007 (Continued)

First dose of dabigatran etexilate was one-half of subsequent doses		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer- generated scheme
Allocation concealment?	Low risk	Central randomisation performed in blocks of six
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: dabigatran 220 mg, dabigatran 150 mg, enoxaparin Primary efficacy outcome: Total VTE + death during treatment: 183/503, 213/526, 193/512 Treatment patients: 503, 526, 512 Randomised patients: 694, 708, 699 Attrition and exclusions were reported but not in detail
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Low risk	

RE-NOVATE 2007

Methods	<p>Method of allocation/randomisation: Computer generated. Randomisation was performed in blocks of six.</p> <p>Blinded: Triple.</p> <p>Design: RCT non inferiority.</p> <p>Power calculation: 95% (required 3330 patients randomised).</p> <p>Number of patients randomised: 3494.</p> <p>Number of patients analysed: 2651 (efficacy); 3463 (safety).</p> <p>Number of withdrawals and reasons: (dabigatran 220 mg; dabigatran 150mg, enoxaparin): Not treated (11-11-8), no operation (9,7,12), venography inadequate or not performed (257, 282, 245), not complete study (108,102,112): consent withdrawn, adverse events or non compliance with protocol.</p> <p>Intention-to-treat analysis: No.</p> <p>Source of funding: Boehringer Ingelheim.</p> <p>Notes: Number of patients completing the study period: dabigatran 220 mg: 1029 (88.9%), dabigatran 150 mg: 1054 (89.7%); enoxaparin: 1030 (88.6%)</p>
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Participants	Country: Europe, Australia, and South Africa. Number of centres: 115. Location: Hospitals. Source of patients: scheduled for primary elective unilateral THR. Age: 64 ± 11 years. Sex: Female 1954 (56%). Inclusion criteria: > 18 years, weight at least 40 kg, provided signed informed consent. Exclusion criteria: Any bleeding diathesis; history of acute intracranial disease or haemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or MI within the past 3 months; GI or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; AST or ALT levels more than two times the upper limit of the normal range within the past month; severe renal insufficiency (creatinine clearance <30 mL/ min); concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindicated during study treatment); active malignant disease; allergy to radiopaque contrast media or heparin; and childbearing potential	
Interventions	Treatment(s): 3 groups: dabigatran 220 mg or 150 mg od orally (evening before operation: not in all centres). Control /Placebo: 40 mg enoxaparin sc. (evening before operation: not in all centres). Duration: 28 to 35 days, follow up with lab 2 to 3 months after surgery	
Outcomes	Primary outcomes: Efficacy: composite total VTE events (venographic DVT or symptomatic PE) and all-cause mortality during treatment. Safety: Bleeding during treatment. Secondary outcomes: Major VTE (DVTp, PE), and VTE related mortality, proximal DVT. Safety: Liver enzymes.	
Notes	Extra data required: Women with hormonal contraception? Transfusion volume data? Concomitant use of <160 mg aspirin or selective cox-2 inhibitors allowed. Elastic compression stockings were permitted. Bilateral venography. First dose of dabigatran etexilate was one-half of subsequent doses	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Central computer generated scheme
Allocation concealment?	Low risk	Central randomisation performed in blocks of six.
Blinding? All outcomes	Low risk	Triple. Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from: dabigatran 220 mg, dabigatran 150 mg, enoxaparin

		Primary efficacy outcome: Total VTE + death during treatment: 53/880, 75/874, 60/897 Treatment patients: 880, 874, 897 Randomised patients: 1157, 1174, 1162 Attrition and exclusions were reported but not in detail
Free of selective reporting?	Unclear risk	No description if the protocol was registered
Free of other bias?	Low risk	

ALT: alanine aminotransferase
 APTT: activated partial thromboplastin time
 AST: aspartate aminotransferase
 bid: twice daily
 CT: computed tomography
 DVT: deep vein thrombosis
 GI: gastrointestinal
 Hb: haemoglobin
 INR: international normalised ratio
 ITT: Intention to treat
 MI: myocardial infarction
 od: once daily
 PE: pulmonary embolism
 qd: four times / day
 RCT: randomised controlled trial
 sc.: subcutaneous
 SD: standard deviation

THR: total hip replacement
 TKR: total knee replacement
 VTE: venous thromboembolism

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cofrancesco 1996	Compares with unfractionated heparin
Ekman 1995	Compares with unfractionated heparin
Eriksson 1996	Compares with unfractionated heparin

(Continued)

Eriksson 2002	Don't compare with low molecular weight heparin or vitamin K antagonist
Eriksson 2003	Not randomised controlled study. Narrative review of METHRO II and III
Eriksson 2003b	Don't compare with low molecular weight heparin or vitamin K antagonist
EXTEND 2009	This study was stopped prematurely on 13 February 2006 for safety reasons. At that time, only 55% of the randomised patients had completed the 35-day treatment
Harenberg 2006	Evaluate recurrence of venous thromboembolism (THRIVE studies)
Mouret 2002	Not randomised controlled study. Narrative review of METHRO II and III
ODIXa-HIP 2006	Evaluate a factor Xa direct inhibitor. Not a direct thrombin inhibitor (factor IIa)
ODIXa-Knee 2005	Evaluate a factor Xa direct inhibitor. Not a direct thrombin inhibitor (factor IIa)
ONYX 2007	Evaluate a factor Xa direct inhibitor. Not a direct thrombin inhibitor (factor IIa)
RECORD 2007	Evaluate a factor Xa direct inhibitor. Not a direct thrombin inhibitor (factor IIa)
Troceniz 2007	Not a randomised controlled study.
Turpie 2005	Not evaluate a Direct Thrombin Inhibitor
Wahlander 2002	Not a randomised controlled study. Pharmacokinetic analysis of dabigatran

Characteristics of ongoing studies [ordered by study ID]

RE-NOVATE II 2009

Trial name or title	Dabigatran Etexilate Compared With Enoxaparin in Prevention of VTE Following Total Hip Arthroplasty
Methods	A Phase III Randomised, Parallel Group, Double-blind, Active Controlled Study
Participants	<p>18 Years and older. Inclusion Criteria:</p> <ul style="list-style-type: none"> • Patients scheduled to undergo primary, unilateral, elective total hip arthroplasty. • Male or female 18 years of age or older. • Patients giving written informed consent for study participation. <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Patients weighing less than 40 kg. • History of bleeding diathesis. • Patients who in the investigators judgement are perceived as having an excessive risk of bleeding, for example, constitutional or acquired coagulation disorders or because of anticipated need of quinidine, verapamil or other restricted medication during the treatment period (see Section 4.2.2). • Major surgery or trauma (e.g., hip fracture) within 3 months of enrolment.

	<ul style="list-style-type: none"> Recent unstable cardiovascular disease (in the investigators opinion) such as uncontrolled hypertension, that is ongoing at the time of enrolment or history of myocardial infarction within 3 months of enrolment. Any history of haemorrhagic stroke or any of the following intracranial pathologies: bleeding, neoplasm, AV malformation or aneurysm. Ongoing treatment for VTE. Clinically relevant bleeding (gastrointestinal, pulmonary, intraocular or urogenital bleeding) within 6 months of enrolment. Gastric or duodenal ulcer within one year of enrolment. Liver disease expected to have any potential impact on survival (ie, hepatitis B or C, cirrhosis). This does not include Gilberts syndrome or hepatitis A with complete recovery. Active liver disease or liver disease decreasing survival (e.g., acute hepatitis, chronic active hepatitis, cirrhosis) or ALT >3 x ULN. Known severe renal insufficiency (CrCl <30 ml/min). Note: CrCl should be calculated only if serum creatinine is elevated or renal insufficiency is suspected. See Appendix 10.1 for calculation. Elevated creatinine that, in the investigators opinion, contraindicates venography. Treatment with anticoagulants, clopidogrel, ticlopidine, abciximab, aspirin >162.5 mg/day or NSAID with t 1/2 >12 hours within 7 days prior to hip replacement surgery or anticipated need while the patient is receiving study medication and prior to 24 hours after the last administration of any blinded study medication (COX-2 selective inhibitors are allowed). Anticipated required use of intermittent pneumatic compression and electric stimulation of lower limb. Pre-menopausal women (last menstruation within 1 year prior to signing informed consent) who: Are pregnant. Are nursing. Are of child-bearing potential and are not practicing acceptable methods of birth control, or do not plan to continue practicing an acceptable method throughout the study. Acceptable methods of birth control include intrauterine device; oral, implantable or injectable contraceptives and surgical sterility. Known allergy to radio opaque contrast media. History of thrombocytopenia, including heparin-induced thrombocytopenia, or a platelet count <100,000 cells/microlitre at randomisation. Allergy to heparins or dabigatran etexilate. Active malignant disease or current cytostatic treatment. Patients should be disease free for at least 5 years. Participation in a clinical trial within 30 days of randomisation. Leg amputee. Known alcohol or drug abuse which would interfere with completion of the study. Contraindications to enoxaparin. Previous participation in this study.
Interventions	Orally Administered 220 mg Dabigatran Etexilate Capsules (110 mg Administered on the Day of Surgery Followed by 220 mg Once Daily) Compared to Subcutaneous 40 mg Enoxaparin Once Daily for 28-35 Days, in Prevention of Venous Thromboembolism in Patients With Primary Elective Total Hip Arthroplasty Surgery
Outcomes	<p>Primary Outcome Measures: The primary efficacy endpoint of this study is the composite of total venous thromboembolic events and all cause mortality during the treatment period. [Time Frame: 28-35 days after surgery]</p> <p>Secondary Outcome Measures: Secondary endpoints include major VTE and VTE related mortality. Safety endpoints include Major bleeding events, clinically relevant bleeding events, any bleeding events. [Time Frame: 28-35 days after surgery]</p>

RE-NOVATE II 2009 (Continued)

Starting date	March 2008. Estimated Enrollment:1920 patients
Contact information	Boehringer Ingelheim Pharmaceuticals
Notes	Estimated Primary Completion Date:September 2009.(Final data collection date for primary outcome measure)

DATA AND ANALYSES

Comparison 1. Efficacy DTI (any dose) vs. LMWH + follow up events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major VTE events in THR + TKR combined doses	11	17428	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.69, 1.19]
1.1 Ximelagatran	6	8177	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.57, 1.57]
1.2 Dabigatran	4	7664	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.29]
1.3 Desidurin 15mg bid SC	1	1587	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.45, 0.97]
2 Total VTE events in THR + TKR combined doses	11	17325	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.83, 1.19]
2.1 Ximelagatran	6	8186	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.78, 1.33]
2.2 Dabigatran	4	7552	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.85, 1.38]
2.3 Desidurin 15mg bid SC	1	1587	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.53, 0.85]
3 Symptomatic VTE	11	19619	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
3.1 Ximelagatran	6	9135	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.66, 1.21]
3.2 Dabigatran	4	8897	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.82, 1.71]
3.3 Desidurin 15mg bid SC	1	1587	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.71, 2.21]

Comparison 2. Safety DTI (any dose) vs. LMWH + follow up events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major/Significant Bleeding events in THR + TKR combined doses	11	22109	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.87, 1.58]
1.1 Ximelagatran	6	9974	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.76, 2.28]
1.2 Dabigatran	4	10084	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.70, 1.58]
1.3 Desidurin 15mg bid SC	1	2051	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.56, 1.94]
2 Total Bleeding events in THR + TKR combined doses	11	22109	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.98, 1.41]
2.1 Ximelagatran	6	9974	Odds Ratio (M-H, Random, 95% CI)	1.41 [1.11, 1.78]
2.2 Dabigatran	4	10084	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.83, 1.24]
2.3 Desidurin 15mg bid SC	1	2051	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.56, 1.94]
3 ALT >3 times the upper normal limit combined doses	7	12580	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.23, 0.72]
3.1 Ximelagatran	3	3599	Odds Ratio (M-H, Random, 95% CI)	0.29 [0.13, 0.67]
3.2 Dabigatran	4	8981	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.24, 1.05]
3.3 Desidurin 15mg bid SC	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 All-cause Mortality events combined doses in THR+TKR	11	22065	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [1.10, 3.87]
4.1 Ximelagatran	6	9978	Odds Ratio (M-H, Fixed, 95% CI)	2.84 [1.02, 7.90]
4.2 Dabigatran	4	10036	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.63, 3.90]

4.3 Desidurin 15mg bid SC	1	2051	Odds Ratio (M-H, Fixed, 95% CI)	1.99 [0.36, 10.91]
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Comparison 3. Sensitivity Analysis 1: Extended prophylactic anticoagulation vs. Standard prophylactic anticoagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major VTE events in TKR combined doses + follow-up events	9	9009	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.22]
1.1 Extended Anticoagulation	1	2714	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.62, 1.41]
1.2 Standard Anticoagulation	8	6295	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.57, 1.28]
2 Symptomatic VTE in TKR combined doses + follow-up events	5	8328	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.82, 1.69]
2.1 Extended Anticoagulation	1	3435	Odds Ratio (M-H, Fixed, 95% CI)	2.51 [0.96, 6.57]
2.2 Standard Anticoagulation	4	4893	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.67, 1.48]
3 Total Bleeding events in TKR combined doses + follow-up events	9	11782	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.17]
3.1 Extended Anticoagulation	1	3463	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.75, 1.27]
3.2 Standard Anticoagulation	8	8319	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]

Comparison 4. Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major VTE events in THR + TKR combined doses	7	9438	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.53, 1.54]
1.1 Before Surgery	4	5485	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.35, 0.83]
1.2 After Surgery	3	3953	Odds Ratio (M-H, Random, 95% CI)	1.68 [1.12, 2.52]
2 Symptomatic VTE	7	9876	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.38]
2.1 Before Surgery	4	5934	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.70, 1.43]
2.2 After Surgery	3	3942	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.77, 1.68]
3 Total Bleeding events in THR + TKR combined doses	7	11833	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.99, 1.66]
3.1 Before Surgery	4	6827	Odds Ratio (M-H, Random, 95% CI)	1.45 [0.93, 2.28]
3.2 After Surgery	3	5006	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.86, 1.44]
4 All-cause Mortality events combined doses in THR+TKR	7	11837	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.82, 4.32]
4.1 Before Surgery	4	6825	Odds Ratio (M-H, Fixed, 95% CI)	2.32 [0.75, 7.16]
4.2 After Surgery	3	5012	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.41, 4.93]

Comparison 5. Efficacy DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major VTE events in TKR combined doses	3	4327	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.15]
1.1 Ximelagatran	3	4327	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.15]
2 Total VTE events in TKR combined doses	3	4354	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.60, 0.79]
2.1 Ximelagatran	3	4354	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.60, 0.79]
3 Symptomatic VTE events in TKR combined doses	3	5259	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.53, 1.21]
3.1 Ximelagatran	3	5259	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.53, 1.21]

Comparison 6. Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major/ Significant Bleeding events in TKR combined doses	3	5259	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [0.95, 3.33]
1.1 Ximelagatran	3	5259	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [0.95, 3.33]
2 Total Bleeding events in TKR combined doses	3	5259	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.97, 1.62]
2.1 Ximelagatran	3	5259	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.97, 1.62]
3 All-cause Mortality events in TKR combined doses	3	5243	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.57, 4.58]
3.1 Ximelagatran	3	5243	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.57, 4.58]
4 ALT >3 times the upper normal limit at the end of Treatment in TKR combined doses	2	4261	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.27, 0.97]
4.1 Ximelagatran	2	4261	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.27, 0.97]
5 ALT >3 times the upper normal limit at the end of Follow-up in TKR combined doses	2	4267	Odds Ratio (M-H, Fixed, 95% CI)	5.61 [1.00, 31.64]
5.1 Ximelagatran	2	4267	Odds Ratio (M-H, Fixed, 95% CI)	5.61 [1.00, 31.64]

Analysis 1.1. Comparison 1 Efficacy DTI (any dose) vs. LMWH + follow up events, Outcome 1 Major VTE events in THR + TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 1 Efficacy DTI (any dose) vs. LMWH + follow up events

Outcome: 1 Major VTE events in THR + TKR combined doses

Analysis 1.2. Comparison 1 Efficacy DTI (any dose) vs. LMWH + follow up events, Outcome 2 Total VTE events in THR + TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 1 Efficacy DTI (any dose) vs. LMWH + follow up events

Outcome: 2 Total VTE events in THR + TKR combined doses

(. . . Continued)

Study or subgroup	DTI n/N	LMWH n/N	Odds Ratio M- H,Random,95% CI	Weight	Odds Ratio M- H,Random,95% CI
Test for overall effect: $Z = 3.34$ ($P = 0.00083$)					
Total (95% CI)	10671	6654		100.0 %	0.99 [0.83, 1.19]
Total events: 2408 (DTI), 1499 (LMWH)					
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 47.85$, $df = 10$ ($P < 0.00001$); $I^2 = 79\%$					
Test for overall effect: $Z = 0.06$ ($P = 0.95$)					
Test for subgroup differences: $\chi^2 = 0.0$, $df = 2$ ($P = 0.0$), $I^2 = 0.0\%$					

0.2 0.5 2 5
Favours DTI Favours LMWH

Analysis 1.3. Comparison 1 Efficacy DTI (any dose) vs. LMWH + follow up events, Outcome 3 Symptomatic VTE.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 1 Efficacy DTI (any dose) vs. LMWH + follow up events

Outcome: 3 Symptomatic VTE

Study or subgroup	DTI n/N	LMWH n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Ximelagatran					
Colwell 2003	18/782	16/775		9.7 %	1.12 [0.57, 2.21]
EXPRESS 2003	16/1378	18/1387		10.9 %	0.89 [0.45, 1.76]
Heit 2001	5/346	0/97		0.5 %	3.14 [0.17, 57.29]
METHRO I 2002	3/78	0/27		0.4 %	2.55 [0.13, 50.96]
METHRO II 2002	38/1169	13/308		12.3 %	0.76 [0.40, 1.45]
METHRO III 2003	25/1399	32/1389		19.5 %	0.77 [0.45, 1.31]
Subtotal (95% CI)	5152	3983		53.3 %	0.89 [0.66, 1.21]

Total events: 105 (DTI), 79 (LMWH)

Heterogeneity: $\chi^2 = 2.14$, $df = 5$ ($P = 0.83$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.73$ ($P = 0.47$)

2 Dabigatran

0.5 0.7 1.5 2
Favours DTI Favours LMWH

(Continued . . .)

Analysis 2.1. Comparison 2 Safety DTI (any dose) vs. LMWH + follow up events, Outcome 1 Major/Significant Bleeding events in THR + TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 2 Safety DTI (any dose) vs. LMWH + follow up events

Outcome: 1 Major/Significant Bleeding events in THR + TKR combined doses

Analysis 2.2. Comparison 2 Safety DTI (any dose) vs. LMWH + follow up events, Outcome 2 Total Bleeding events in THR + TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 2 Safety DTI (any dose) vs. LMWH + follow up events

Outcome: 2 Total Bleeding events in THR + TKR combined doses

(Continued . . .)

Analysis 2.3. Comparison 2 Safety DTI (any dose) vs. LMWH + follow up events, Outcome 3 ALT >3 times the upper normal limit combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 2 Safety DTI (any dose) vs. LMWH + follow up events

Outcome: 3 ALT >3 times the upper normal limit combined doses

(Continued . . .)

Analysis 2.4. Comparison 2 Safety DTI (any dose) vs. LMWH + follow up events, Outcome 4 All-cause Mortality events combined doses in THR+TKR.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 2 Safety DTI (any dose) vs. LMWH + follow up events

Outcome: 4 All-cause Mortality events combined doses in THR+TKR

Analysis 3.1. Comparison 3 Sensitivity Analysis 1: Extended prophylactic anticoagulation vs. Standard prophylactic anticoagulation, Outcome 1 Major VTE events in TKR combined doses + follow-up events.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 3 Sensitivity Analysis 1: Extended prophylactic anticoagulation vs. Standard prophylactic anticoagulation

Outcome: 1 Major VTE events in TKR combined doses + follow-up events

Analysis 3.2. Comparison 3 Sensitivity Analysis 1: Extended prophylactic anticoagulation vs. Standard prophylactic anticoagulation, Outcome 2 Symptomatic VTE in TKR combined doses + follow-up events.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 3 Sensitivity Analysis 1: Extended prophylactic anticoagulation vs. Standard prophylactic anticoagulation

Outcome: 2 Symptomatic VTE in TKR combined doses + follow-up events

Analysis 3.3. Comparison 3 Sensitivity Analysis 1: Extended prophylactic anticoagulation vs. Standard prophylactic anticoagulation, Outcome 3 Total Bleeding events in TKR combined doses + follow-up events.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 3 Sensitivity Analysis 1: Extended prophylactic anticoagulation vs. Standard prophylactic anticoagulation

Outcome: 3 Total Bleeding events in TKR combined doses + follow-up events

Analysis 4.1. Comparison 4 Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH, Outcome 1 Major VTE events in THR + TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 4 Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH

Outcome: 1 Major VTE events in THR + TKR combined doses

Analysis 4.2. Comparison 4 Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH, Outcome 2 Symptomatic VTE.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 4 Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH

Outcome: 2 Symptomatic VTE

Analysis 4.3. Comparison 4 Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH, Outcome 3 Total Bleeding events in THR + TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 4 Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH

Outcome: 3 Total Bleeding events in THR + TKR combined doses

Analysis 4.4. Comparison 4 Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH, Outcome 4 All-cause Mortality events combined doses in THR+TKR.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 4 Sensitivity Analysis 2: Time of Initiation of Therapy in DTI vs. LMWH

Outcome: 4 All-cause Mortality events combined doses in THR+TKR

Analysis 5.1. Comparison 5 Efficacy DTI (any dose) vs. VKA (Warfarin) + follow-up events, Outcome 1 Major VTE events in TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 5 Efficacy DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome: 1 Major VTE events in TKR combined doses

Analysis 5.2. Comparison 5 Efficacy DTI (any dose) vs. VKA (Warfarin) + follow-up events, Outcome 2 Total VTE events in TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 5 Efficacy DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome: 2 Total VTE events in TKR combined doses

Analysis 5.3. Comparison 5 Efficacy DTI (any dose) vs. VKA (Warfarin) + follow-up events, Outcome 3 Symptomatic VTE events in TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 5 Efficacy DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome: 3 Symptomatic VTE events in TKR combined doses

Analysis 6.1. Comparison 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events, Outcome 1 Major/ Significant Bleeding events in TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome: 1 Major/ Significant Bleeding events in TKR combined doses

Analysis 6.2. Comparison 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events, Outcome 2 Total Bleeding events in TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome: 2 Total Bleeding events in TKR combined doses

Analysis 6.3. Comparison 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events, Outcome 3 All-cause Mortality events in TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome: 3 All-cause Mortality events in TKR combined doses

Analysis 6.4. Comparison 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events, Outcome 4 ALT >3 times the upper normal limit at the end of Treatment in TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome: 4 ALT >3 times the upper normal limit at the end of Treatment in TKR combined doses

Analysis 6.5. Comparison 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events, Outcome 5 ALT >3 times the upper normal limit at the end of Follow-up in TKR combined doses.

Review: Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement

Comparison: 6 Safety DTI (any dose) vs. VKA (Warfarin) + follow-up events

Outcome: 5 ALT >3 times the upper normal limit at the end of Follow-up in TKR combined doses

ADDITIONAL TABLES

Table 1. Methodological Comparison of Included Studies (ITT analysis)

Study	Randomized	Not treated or withdraw	Analyzed safety	Venography performed or inadequate	not Analyzed efficacy
	(DTI/Control)	(DTI/Control) [%]	(DTI/Control) [%] !	(DTI/Control) [%]	(DTI/Control) [%] !!
Colwell 2003	1838 (918/920)	22 (12/10) [1.2]	1816 (906/910)	249 (124/125)	1557 (782/775) [84.7]
EXPRESS 2003	2835(1410/1425)	71 (33/38) [2.5]	2765 (1378/1387) + [97.5]	448 (239/209)	2316 (1138/1178) [81.7]
Heit 2001	600 (475/125)	55 (43/12) [9.2]	594 (469/125) [99]	157 (129/28)	443 (346/97)- [73.8]

Table 1. Methodological Comparison of Included Studies (ITT analysis) (Continued)

METHRO I 2002	137 (104/33)	2 (not stated) [1.5]	131 (102/29)* [95.6]	30 (not stated)	105 (78/27)* [76.6]
METHRO II 2002	1916 (1515/385)	40 (not stated) [2.1]	1872 (1491/381) [97.7]	403 (329/74)	1477 (1169/308) [77.1]
METHRO III 2003	2874 (not stated)	74 (not stated) [2.6]	2788 (1399/1389)- [97]	520 (not stated)	2268 (1146/1122) [78.9]
BISTRO II 2005	1973 (1576/397)	24 (19/5) [1.2]	1949 (1557/392) [98.8]	417 (335/82)	1464 (1164/300) [74.2]
REMOBILIZE 2009	2615 (1739/836)	19 (11/8) [0.9]	2596 (1728/868) [99.1]	700 (475/225)	1896 (1253/643) [72.5]
REMODEL 2007	2101 (1402/699)	25 (20/5) [1.2]	2076 (1382/694) [98.8]	515 (342/173)	1541 (1029/512) [73.3]
RENOVATE 2007	3494 (2331/1162)	30 (22/8) [0.9]	3463 (2309/1154) [99.1]	784 (539/245)	2651 (1754/897) [75.9]
Eriksson 1997	2079 (1043/1036)	28 (15/13) [1.3]	2051 (1028/1023) [98.7]	451 (210/221)	1587 (802/785) [76.3]
EXULT A 2003	2301 (1537/764)	16 (11/5) [0.7]	2285 (1526/759) [99.3]	442 (289/153)	1851 (1243/608) [80.4]
EXULT B 2005	2303 (1152/1151)	4 (1/3) [0.2]	2299 (1151/1148) [99.8]	363 (175/188)	1949 (982/967) [84.6]
Francis 2002	680 (348/332)	5 (3/2) [0.7]	675 (345/330) [99.3]	138 (69/69)	537 (276/261) [78.9]
TOTAL	27746	415 [1.49]	27360 [98.51]	5617 [20.24]	21642 [78.0]

*136 ITT safety population; 135 ITT efficacy population.

+ ITT 2788 (1377/1387) population.

- ITT 443 population

Table 1. Methodological Comparison of Included Studies (ITT analysis) (Continued)

! Percentage of patients included in the safety analysis out of the total randomised patients
 !! Percentage of patients included in the efficacy analysis out of the total randomised patients
 Note: EXTEND 2009 study was not included in this analysis (it was stopped prematurely for safety reasons)

Table 2. Quality Table: DTIs vs. LMWH and VKA

	Internal Validity								External Validity			
Study / Question	1	2	3	4	5	6	7	8	9	10	11	12
Ximelagatran vs. LMWH												
Colwell 2003	+	-	+	?	+	+	?	+	+	+	-	?
EX-PRESS 2003	+	-	+	?	+	+	?	+	+	+	+	?
Heit 2001	+	-	?	?	-	-	?	+	+	+	-	?
METHR I 2002	?	-	?	?	?	?	?	+	+	+	+	?
METHR II 2002	+	-	+	?	+	+	?	+	+	+	+	?
METHR III 2003	+	-	+	?	+	+	?	+	+	+	+	?
Other DTI vs. LMWH												
BISTRO II 2005	+	?	+	?	+	+	?	+	+	+	+	?
Eriksson 1997	?	-	+	?	+	?	?	+	+	+	+	?

Table 2. Quality Table: DTIs vs. LMWH and VKA (Continued)

RE-MOBI-LIZE 2009	+	?	+	?	+	+	?	+	+		+	+	+
RE-MODEL 2007	+	?	+	?	+	+	?	+	+		+	+	+
REN-O-VATE 2007	+	?	+	?	+	+	?	+	+		+	+	+
Ximelagatran vs. VKA (Warfarin)													
EX-ULT A 2003	+	?	+	?	+	+	?	+	+		+	?	?
EX-ULT B 2005	+	?	+	?	+	+	?	+	+		+	+	?
Francis 2002	+	?	+	?	+	+	-	+	+		+	-	+
Note: + = YES ? = UNCLEAR - = NO													

APPENDICES

Appendix I. CENTRAL search strategy

#1	Direct near thromb* near inhib*	233
#2	DTI	62
#3	(#1 OR #2)	285
#4	MeSH descriptor Hirudins, this term only	175
#5	MeSH descriptor Hirudin Therapy, this term only	79
#6	hirudin* or argatroban or bivalirud* or melagatran* or xime- lagatran* or dabigatran* or lepirudin or desirudin or rivarox- aban or YM150 or BAY 597939 or BAY 59-7939	608
#7	(#4 OR #5 OR #6)	608
#8	(#3 OR #7)	690
#9	vitamin near K near (antag* or inhib*)	143
#10	VKA* or warfarin or dicoum* or phenprocoum* or couma* or acenocoum*	2274
#11	(#9 OR #10)	2342
#12	MeSH descriptor Heparin, Low-Molecular-Weight explode all trees	1486
#13	low near molecular near weight	2555
#14	low molecular weight heparin OR LMWH OR low-molec- ular-weight-heparin OR nadroparin* OR fraxiparin* OR enoxaparin OR Clexane OR klexane OR lovenox OR dal- teparin OR Fragmin OR ardeparin OR normiflo OR tin- zaparin OR logiparin OR Innohep OR certoparin OR san- doparin OR reviparin OR clivarin* OR danaproid OR dana- paroid	2995
#15	(#12 OR #13 OR #14)	3346
#16	(#8 OR #11 OR #15)	5804
#17	MeSH descriptor Arthroplasty explode all trees	2083
#18	arthroplast*	3279

(Continued)

#19	(hip or knee) near rep*	3663
#20	(#17 OR #18 OR #19)	4803
#21	(#16 AND #20)	537

Appendix 2. LILACS search strategy

We searched on the Web page: <http://regional.bvsalud.org>, using the DeCS/MeSH descriptors: (1) [MH] "Arthroplasty, Replacement, Hip" OR "Arthroplasty, Replacement, Knee" OR "Venous Thromboembolism" [Words]

(2) [MH] "Clinical Trials as topic"

(1) AND (2)

There were no relevant RCTs found among the 253 RCTs from LILACS database.

Appendix 3. Scoring System of Selected Studies

Section I Internal Validity

1). Was the assigned treatment adequately concealed prior to allocation?

YES = method did not allow disclosure of assignment.

UNCLEAR = small but possible chance of disclosure of assignment or unclear.

NO = quasi-randomised or open list/tables.

2). Were the outcomes of patients who withdrew described and included in the analysis (intention to treat)?

YES = withdrawals well described and accounted for in the analysis.

UNCLEAR = withdrawals described and analysis not possible.

NO = no mention, inadequate mention, or obvious differences and no adjustment.

3). Were the outcome assessors blinded to treatment status?

YES = effective action taken to blind assessors.

UNCLEAR = small or moderate chance of unblinding of assessors.

NO = not mentioned or not possible.

4). Were the treatment and control group comparable at entry?

The principal confounders were considered to be age (>5 years difference), previous DVT (> 5% difference), known malignancy (> 5% difference) and type of fracture (intra/extracapsular) (> 5% difference). Women with hormonal contraception (> 5% difference)

YES = good comparability of groups, or confounding adjusted for in analysis.

UNCLEAR = confounding small; mentioned but not adjusted for.

NO = large potential for confounding, or not discussed.

5). Were the patients blind to assignment status after allocation?

YES = effective action taken to blind patients.

UNCLEAR = small or moderate chance of unblinding of patients.

NO = not possible, or not mentioned (unless double-blind), or possible but not done.

6). Were the treatment providers blind to assignment status?

YES = effective action taken to blind treatment providers.

UNCLEAR = small or moderate chance of unblinding of treatment providers.

NO = not possible, or not mentioned (unless double-blind), or possible but not done.

7). Were care programmes, other than the trial options, identical?

Examples of clinically important differences in other interventions which could act as active measures for DVT prevention, or possible risk factors, were considered to be: time of operation (12 hour difference), duration of operation (30 minutes

difference), type of implant/fixation (> 5% difference), anaesthetic used within broad categories (> 5% difference), difference in rehabilitation (> 5% difference).

YES = care programmes clearly identical.

UNCLEAR = clear but trivial differences.

NO = not mentioned or clear and important differences in care programmes.

8). Were the withdrawals < 10% of the study population?

YES = < 10%.

UNCLEAR = Not defined.

NO = > 10%.

Section II External Validity

9). Were the inclusion and exclusion criteria for entry clearly defined?

YES = clearly defined.

UNCLEAR = inadequately defined.

NO = not defined.

10). Were the outcome measures used clearly defined (by outcome measure)?

YES = clearly defined.

UNCLEAR = inadequately defined.

NO = not defined.

11). Were the accuracy, precision, and observer variation of the outcome measures adequate (and clinically useful) (by outcome measure)?

YES = optimal. For DVT if: a) all participants underwent bilateral ascending venography, b) all participants underwent bilateral duplex ultrasound scanning with radioactive fibrinogen scan followed by venography in limbs found positive or equivocal, or c) all participants underwent bilateral strain gauge plethysmography followed by venography in limbs found positive.

UNCLEAR = adequate. For DVT if a) participants underwent bilateral duplex ultrasound scanning, radioactive fibrinogen scan, or plethysmography alone, or b) participants underwent evaluation using the techniques listed in the previous category, of operated limb only.

NO = not defined, not adequate. None of the above.

12). Was the timing (e.g. duration of surveillance) clinically appropriate (by outcome measure)?

YES = optimal. For DVT: if minimum eight week follow-up.

UNCLEAR = adequate. For DVT: if 10 days, under eight weeks.

NO = not defined, For DVT: not adequate, if under 10 days.

(Reference: [Handoll 2002](#))

FEEDBACK

Anticoagulant feedback, 14 February 2011

Summary

Feedback received on this review, and other reviews and protocols on anticoagulants, is available on the Cochrane Editorial Unit website at <http://www.editorial-unit.cochrane.org/anticoagulants-feedback>.

WHAT'S NEW

Date	Event	Description
14 February 2011	Amended	Link to anticoagulant feedback added

HISTORY

Date	Event	Description
11 May 2010	Amended	Slight amendments to text.
31 March 2010	Amended	Slight amendment to formatting of text

CONTRIBUTIONS OF AUTHORS

The three authors participated in all the review process.

DECLARATIONS OF INTEREST

None of the authors has any working contact with pharmaceutical companies or companies that could influence the review results.

The authors' interest and commitment was to apply without any intentional bias the techniques and methodology developed by The Cochrane Collaboration for the preparation of systematic reviews to obtain precise and objective results.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Regarding the primary outcome measures initially proposed in the preparation of the protocol for this review, it was decided to group mortality associated with VTE with the incidence of proximal VTE in the major VTE group (the results of mortality due to VTE were also analysed separately) so that the analysis would be more practical due to the reduced number of individual events.

With regard to the secondary outcome measures, the distal VTE incident was evaluated jointly with the proximal VTE incident and mortality associated with VTE in the total VTE group.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [*therapeutic use]; Antifibrinolytic Agents [therapeutic use]; Arthroplasty, Replacement, Hip [*adverse effects]; Arthroplasty, Replacement, Knee [*adverse effects]; Azetidines; Benzimidazoles [therapeutic use]; Benzylamines; Contraindications; Dabigatran; Heparin, Low-Molecular-Weight [*therapeutic use]; Pyridines [therapeutic use]; Randomized Controlled Trials as Topic; Thrombin [*antagonists & inhibitors]; Venous Thromboembolism [etiology; *prevention & control]; Vitamin K [*antagonists & inhibitors]; Warfarin [therapeutic use]

MeSH check words

Humans