Contents

0.1 Synthesis of the meta-analysis results

In all 18 randomised controlled trials (RCTs) were included. These included 11 studies of **direct factor Xa inhibitors** involving 25,702 patients and 7 studies of **oral direct thrombin inhibitor**
(1 unpublished) involving 12,959 patients. Results obtained by the meta-analysis are reported in the following tables, with the endpoints categorized according their results. Three classes are considered: endpoints for wich a benefit effect was detected, endpoints revealing a harmful effect and the other for wich no statistically significant difference was obtained (no evidence).

0.1.1 Direct factor Xa inhibitors

Reports of 8 trials (including 25,702 patients) were identified .
Among these comparisons, 4 trials are about apixaban,one about edoxaban,5 about rivaroxaban and one about rivaroxaban (long duration).
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Apixaban

Results obtained with apixaban for all the endpoints with data in at least one trial are summarized table **??**.

Table 1: *Results summary - Apixaban*

Benefit	Harmful	No evidence
	Apixaban versus enoxaparin	
↓ major VTE (fatal and non fatal DVT,PE) RR=0.40* [0.19;0.83] k=1 ↓ deep vein thrombosis RR=0.32¶ [0.20;0.51] k=1 ↓ total VTE and all-cause mortality RR=0.36¶ [0.23;0.56] k=1 ↓ asymptomatic DVT RR=0.33¶ [0.20;0.54] k=1 ↓ proximal DVT RR=0.35* [0.15;0.82] k=1		→ symptomatic deep-vein thrombosis RR=0.20^{NS} [0.02;1.71] k=1 → non-fatal pulmonary embolism RR=0.40^{NS} [0.08;2.05] k=1 → symptomatic venous thromboembolism (DVT, PE) RR=0.40^{NS} [0.13;1.27] k=1 → major or clinically relevant non-major bleeding RR=0.96^{NS} [0.76;1.21] k=1 → all cause death RR=2.99^{NS} [0.31;28.73] k=1 → major bleeding RR=1.22^{NS} [0.65;2.26] k=1
	Apixaban versus enoxaparin (europe regimen)	
↓ major VTE (fatal and non fatal DVT,PE) RR=0.50* [0.26;0.97] k=1 ↓ deep vein thrombosis RR=0.60¶ [0.50;0.72] k=1 ↓ total VTE and all-cause mortality RR=0.62¶ [0.51;0.74] k=1 ↓ proximal DVT RR=0.35† [0.16;0.74] k=1		→ symptomatic deep-vein thrombosis RR=0.43^{NS} [0.11;1.66] k=1 → symptomatic venous thromboembolism (DVT, PE) RR=1.00^{NS} [0.35;2.85] k=1 → major or clinically relevant non-major bleeding RR=0.74^{NS} [0.52;1.05] k=1 → all cause death RR=4.00^{NS} [0.18;88.69] k=1 → major bleeding RR=0.65^{NS} [0.28;1.49] k=1
	Apixaban versus enoxaparin (US regimen)	

continued...

Benefit	Harmful	No evidence
↓ major or clinically relevant non-major bleeding RR=0.67* [0.47;0.97] k=1		→ symptomatic deep-vein thrombosis RR=0.98^{NS} [0.06;15.50] k=1 → major VTE (fatal and non fatal DVT,PE) RR=0.58^{NS} [0.28;1.20] k=1 → deep vein thrombosis RR=0.95^{NS} [0.72;1.26] k=1 → any bleedings RR=0.73^{NS} [0.26;2.04] k=1 → total VTE and all-cause mortality RR=0.90^{NS} [0.48;1.68] k=2 → asymptomatic DVT RR=0.63^{NS} [0.29;1.40] k=1 → proximal DVT RR=0.70^{NS} [0.31;1.59] k=2 → symptomatic venous thromboembolism (DVT, PE) RR=1.46^{NS} [0.72;2.94] k=1 → all cause death RR=1.13^{NS} [0.27;4.79] k=2 → major bleeding RR=0.51^{NS} [0.25;1.03] k=2

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Edoxaban

Results obtained with edoxaban for all the endpoints with data in at least one trial are summarized table **??**.

Table 2: *Results summary - Edoxaban*

Benefit	Harmful	No evidence
Edoxaban versus enoxaparin (short duration)		
↓ major VTE (fatal and non fatal DVT,PE) RR=0.34* [0.14;0.86] k=1 ↓ asymptomatic DVT RR=0.38* [0.16;0.89] k=1 ↓ distal DVT RR=0.36* [0.15;0.92] k=1		→ symptomatic deep-vein thrombosis RR=0.97^{NS} [0.02;48.83] k=1 → proximal DVT RR=0.49^{NS} [0.04;5.33] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Rivaroxaban

Results obtained with rivaroxaban for all the endpoints with data in at least one trial are summarized table **??**.

Table 3: *Results summary - Rivaroxaban*

Benefit	Harmful	No evidence
Rivaroxaban versus enoxaparin		

continued...

Benefit	Harmful	No evidence
↓ major VTE (fatal and non fatal DVT,PE) RR=0.12¶ [0.04;0.34] k=1 ↓ deep vein thrombosis RR=0.23¶ [0.12;0.43] k=1 ↓ total VTE and all-cause mortality RR=0.30¶ [0.18;0.51] k=1 ↓ proximal DVT RR=0.03¶ [0.00;0.23] k=1		→ non-fatal pulmonary embolism RR=3.91^{NS} [0.44;34.92] k=1 → distal DVT RR=0.49^{NS} [0.24;1.00] k=1 → symptomatic venous thromboembolism (DVT, PE) RR=0.55^{NS} [0.20;1.48] k=1 → all cause death RR=0.98^{NS} [0.24;3.90] k=1 → major bleeding RR=3.02^{NS} [0.61;14.95] k=1
Rivaroxaban versus enoxaparin (europe regimen)		
↓ major VTE (fatal and non fatal DVT,PE) RR=0.38* [0.18;0.82] k=1 ↓ deep vein thrombosis RR=0.53¶ [0.41;0.68] k=1 ↓ total VTE and all-cause mortality RR=0.51¶ [0.39;0.65] k=1 ↓ distal DVT RR=0.53¶ [0.41;0.70] k=1 ↓ symptomatic venous thromboembolism (DVT, PE) RR=0.34† [0.15;0.75] k=1		→ non-fatal pulmonary embolism RR=0.27^{NS} [0.01;5.90] k=1 → proximal DVT RR=0.48^{NS} [0.22;1.05] k=1 → all cause death RR=0.08^{NS} [0.00;1.51] k=1 → major bleeding RR=1.19^{NS} [0.40;3.53] k=1
Rivaroxaban versus enoxaparin (short duration)		
↓ deep vein thrombosis RR=0.42† [0.22;0.79] k=1 ↓ total VTE and all-cause mortality RR=0.42† [0.22;0.79] k=1 ↓ distal DVT RR=0.36† [0.17;0.73] k=1		→ non-fatal pulmonary embolism RR=0.95^{NS} [0.02;47.30] k=1 → proximal DVT RR=0.95^{NS} [0.20;4.59] k=1
Rivaroxaban versus enoxaparin (US regimen)		
↓ total VTE and all-cause mortality RR=0.69* [0.51;0.92] k=1 ↓ proximal DVT RR=0.23* [0.07;0.80] k=1		→ symptomatic deep-vein thrombosis RR=0.60^{NS} [0.22;1.63] k=1 → major VTE (fatal and non fatal DVT,PE) RR=0.59^{NS} [0.30;1.16] k=1 → asymptomatic DVT RR=0.72^{NS} [0.51;1.01] k=1 → non-fatal pulmonary embolism RR=0.49^{NS} [0.15;1.64] k=1 → distal DVT RR=0.82^{NS} [0.57;1.17] k=1 → symptomatic venous thromboembolism (DVT, PE) RR=0.60^{NS} [0.29;1.27] k=1 → major or clinically relevant non-major bleeding RR=1.34^{NS} [0.86;2.07] k=1 → all cause death RR=0.66^{NS} [0.11;3.94] k=1 → major bleeding RR=1.27^{NS} [0.17;9.63] k=2

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Rivaroxaban (long duration)

Results obtained with rivaroxaban (long duration) for all the endpoints with data in at least one trial are summarized table **??**.

Table 4: *Results summary - Rivaroxaban (long duration)*

Benefit	Harmful	No evidence
Rivaroxaban (long duration) versus enoxaparin (short duration)		
↓ major VTE (fatal and non fatal DVT,PE) RR=0.12¶ [0.05;0.28] k=1 ↓ deep vein thrombosis RR=0.20¶ [0.11;0.35] k=1 ↓ total VTE and all-cause mortality RR=0.21¶ [0.13;0.35] k=1 ↓ distal DVT RR=0.34† [0.16;0.71] k=1 ↓ proximal DVT RR=0.11¶ [0.05;0.29] k=1 ↓ symptomatic venous thromboembolism (DVT, PE) RR=0.20* [0.06;0.69] k=1		→ non-fatal pulmonary embolism RR=0.25NS [0.03;2.25] k=1 → major or clinically relevant non-major bleeding RR=1.20NS [0.93;1.54] k=1 → all cause death RR=0.34NS [0.07;1.66] k=1 → major bleeding RR=1.00NS [0.06;15.98] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

0.1.2 Oral direct thrombin inhibitor

Reports of 4 trials (including 12,959 patients) were identified (including 1 unpublished). Among these comparisons, 3 trials are about dabigatran 150mg and 4 about dabigatran 220mg. During the selection 1 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Dabigatran 150mg

Results obtained with dabigatran 150mg for all the endpoints with data in at least one trial are summarized table **??**.

Table 5: *Results summary - Dabigatran 150mg*

Benefit	Harmful	No evidence
Dabigatran 150mg versus enoxaparin		
	↑ symptomatic deep-vein thrombosis RR=8.89* [1.13;70.07] k=1	→ major VTE (fatal and non fatal DVT,PE) RR=1.09NS [0.70;1.70] k=1 → total VTE and all-cause mortality RR=1.28NS [0.93;1.78] k=1 → asymptomatic DVT RR=1.15NS [0.82;1.63] k=1 → non-fatal pulmonary embolism RR=0.33NS [0.03;3.16] k=1 → distal DVT RR=1.50NS [0.90;2.50] k=1 → proximal DVT RR=0.90NS [0.55;1.49] k=1 → all cause death RR=0.98NS [0.02;49.28] k=1 → major bleeding RR=0.83NS [0.42;1.63] k=1
Dabigatran 150mg versus enoxaparin (europe regimen)		

continued...

Benefit	Harmful	No evidence
		→ symptomatic deep-vein thrombosis RR=0.37^{NS} [0.10;1.37] k=1 → major VTE (fatal and non fatal DVT,PE) RR=1.08^{NS} [0.58;2.01] k=1 → total VTE and all-cause mortality RR=1.07^{NS} [0.92;1.25] k=1 → asymptomatic DVT RR=1.10^{NS} [0.94;1.29] k=1 → non-fatal pulmonary embolism RR=1.95^{NS} [0.07;57.91] k=1 → distal DVT RR=1.07^{NS} [0.91;1.27] k=1 → proximal DVT RR=1.03^{NS} [0.54;1.98] k=1 → major or clinically relevant non-major bleeding RR=1.22^{NS} [0.84;1.78] k=1 → all cause death RR=0.98^{NS} [0.06;15.70] k=1 → major bleeding RR=0.99^{NS} [0.39;2.47] k=1
Dabigatran 150mg versus enoxaparin (US regimen)		
	↑ total VTE and all-cause mortality RR=1.33¶ [1.12;1.58] k=1 ↑ distal DVT RR=1.33† [1.10;1.59] k=1	→ major VTE (fatal and non fatal DVT,PE) RR=1.36^{NS} [0.70;2.63] k=1 → non-fatal pulmonary embolism RR=0.10^{NS} [0.01;1.81] k=1 → major or clinically relevant non-major bleeding RR=0.82^{NS} [0.49;1.34] k=1 → all cause death RR=2.00^{NS} [0.07;59.47] k=1 → major bleeding RR=0.42^{NS} [0.15;1.17] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Dabigatran 220mg

Results obtained with dabigatran 220mg for all the endpoints with data in at least one trial are summarized table **??**.

Table 6: *Results summary - Dabigatran 220mg*

Benefit	Harmful	No evidence
Dabigatran 220mg versus enoxaparin		

continued...

Benefit	Harmful	No evidence
		→ symptomatic deep-vein thrombosis RR=6.03^{NS} [0.73;49.98] k=1 → major VTE (fatal and non fatal DVT,PE) RR=0.78^{NS} [0.48;1.27] k=1 → total VTE and all-cause mortality RR=0.90^{NS} [0.63;1.29] k=1 → asymptomatic DVT RR=0.73^{NS} [0.49;1.08] k=1 → non-fatal pulmonary embolism RR=1.70^{NS} [0.41;7.09] k=1 → distal DVT RR=0.94^{NS} [0.53;1.66] k=1 → proximal DVT RR=0.57^{NS} [0.32;1.00] k=1 → all cause death RR=6.03^{NS} [0.30;120.18] k=1 → major bleeding RR=1.29^{NS} [0.70;2.37] k=1
Dabigatran 220mg versus enoxaparin (europe regimen)		
		→ symptomatic deep-vein thrombosis RR=0.13^{NS} [0.02;1.01] k=1 → major VTE (fatal and non fatal DVT,PE) RR=0.73^{NS} [0.36;1.47] k=1 → total VTE and all-cause mortality RR=0.97^{NS} [0.82;1.13] k=1 → asymptomatic DVT RR=1.00^{NS} [0.85;1.18] k=1 → distal DVT RR=1.02^{NS} [0.85;1.21] k=1 → proximal DVT RR=0.82^{NS} [0.40;1.69] k=1 → major or clinically relevant non-major bleeding RR=1.11^{NS} [0.76;1.63] k=1 → all cause death RR=1.01^{NS} [0.06;16.19] k=1 → major bleeding RR=1.14^{NS} [0.46;2.78] k=1
Dabigatran 220mg versus enoxaparin (US regimen)		
	↑ total VTE and all-cause mortality RR=1.23* [1.03;1.47] k=1	→ major VTE (fatal and non fatal DVT,PE) RR=1.51^{NS} [0.79;2.91] k=1 → distal DVT RR=1.20^{NS} [0.99;1.45] k=1 → proximal DVT RR=1.49^{NS} [0.67;3.33] k=1 → major or clinically relevant non-major bleeding RR=0.86^{NS} [0.52;1.41] k=1 → major bleeding RR=0.42^{NS} [0.15;1.19] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

1 Introduction

1.1 Aim of the report

This report review all the randomized clinical trials of new oral anticoagulants for the treatment of DVT prophylaxis in orthopaedic surgery. The following classes of treatment are considered:

1. direct factor Xa inhibitors
2. oral direct thrombin inhibitor

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of new oral anticoagulants for the treatment of DVT prophylaxis in orthopaedic surgery.

1.2.1 Sources searched

The following electronic databases were searched for relevant published literature for the period up to 2012 - 9 - 20:

- MEDLINE,
- EMBASE,
- Cochrane Database of Systematic Reviews (CDSR),
- Cochrane Central Register of Controlled Trials (CCTR),
- Health Technology Assessment (HTA) database,
- ISI Web of Science âĂŞ Proceedings (Index to Scientific and Technical Proceedings),
- ISI Web of Science âĂŞ Science Citation Index Expanded,

Each database was searched as far back as possible, with no language restrictions.
Search strategies of relevant clinical keywords were developed through reference to published strategies, and by iterative searching, whereby keywords identified in references retrieved by initial scoping searches were used to extend the search strategy and so increase the sensitivity of retrieval.
In addition, the reference lists of relevant articles were handsearched.
Attempts to identify further studies were made by consulting health technology assessment and guideline producing agencies, and research and trials registers via the Internet.
Titles and, when available, abstracts of all studies identified in the searches were assessed by a single researcher for relevance to the review. In cases of doubt, the full article was obtained.

1.2.2 Search restrictions

No language, study/publication or date restrictions were applied to the main searches.

1.3 Inclusion criteria

Participants only those studies were included in which the participants had been diagnosed as having established DVT prophylaxis.

Interventions studies in which new oral anticoagulants was used.
Studies using other interventions in addition to new oral anticoagulants therapy were included only if the treatment received by the intervention and control groups was identical in all respects other than the use of new oral anticoagulants.

Methodology randomised controlled trials (RCTs). Trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind.

1.4 Exclusion criteria

Studies considered methodologically unsound. The list of excluded studies with reason of their exclusion are given in a separate section for each treatment categories considered.

1.5 Meta-analysis strategy

Studies that met the reviewâĂŹs entry criteria were eligible for inclusion in the meta-analyses provided that they reported outcomes in terms of the number of subjects suffering clinical outcomes, as only this would allow calculation of the relative risk of subjects in the intervention group developing each outcome, compared with subjects in the control group.
Studies that only presented results in the form of relative risks, relative hazards or odds ratios, without the underlying numbers were also include in the meta-analyses.
Binary outcomes were analysed using the fixed-effect model. For continuous outcomes, weighted mean differences (WMDs) were analysed, using a fixed-effect model.
Heterogeneity was tested by the chi-2 test and the I2 statistic was obtained to describe the proportion of the variability.
Where quantitative heterogeneity was indicated, analysis using a random-effects model was conducted for comparison with results of fixed effect-based analysis. Results of the meta-analysis should be considered as being based on fixed-effect model unless stated otherwise.
Meta-analyses were conducted for data on proximal DVT, total VTE and all-cause mortality, Major bleeding, major VTE (fatal and non fatal DVT,PE), All cause death, Deep vein thrombosis, Symptomatic venous thromboembolism (DVT, PE), distal DVT, non-fatal pulmonary embolism, Symptomatic deep-vein thrombosis, asymptomatic DVT, major or clinically relevant non-major bleeding, any bleedings, .

1.6 Structure of the report

Each of the eligible studies is summarised in part **??**. A summary of the studies together with an evaluation of their quality is given in part **??** to **??**, listed by therapeutic class. The therapeutic classes included direct factor Xa inhibitors, oral direct thrombin inhibitor,
In these sections, studies in which an active intervention was compared with placebo or no treatment are discussed first, by intervention, followed by a discussion of those studies in which two or more active interventions were compared.

Part I

Direct factor Xa inhibitors

2 Overview of direct factor Xa inhibitors

2.1 Included trials

A total of 11 randomized comparisons which enrolled 25702 patients were identified. In all, 4 randomized comparisons concerned apixaban , one edoxaban , 5 rivaroxaban and one rivaroxaban (long duration).
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for apixaban, in section **??** (page **??**) for edoxaban, in section **??** (page **??**) for rivaroxaban and in section **??** (page **??**) for rivaroxaban (long duration).

The average study size was 2336 patients (range 207 to 5407). The first study was published in 2005, and the last study was published in 2010.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

2.2 Summary of meta-analysis results

The meta-analysis of the available trials about direct factor Xa inhibitors provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

2.2.1 Apixaban

Apixaban was superior to **enoxaparin** in terms of major VTE (fatal and non fatal DVT,PE) (RR=0.40, 95% CI 0.19 to 0.83, p=0.0138, 1 trial), deep vein thrombosis (RR=0.32, 95% CI 0.20 to 0.51, p=0.0000, 1 trial), total VTE and all-cause mortality (RR=0.36, 95% CI 0.23 to 0.56, p=0.0000, 1 trial), asymptomatic DVT (RR=0.33, 95% CI 0.20 to 0.54, p=0.0000, 1 trial)and proximal DVT (RR=0.35, 95% CI 0.15 to 0.82, p=0.0163, 1 trial). However, no significant difference was found on symptomatic deep-vein thrombosis (RR=0.20, 95% CI 0.02 to 1.71, p=0.1408, 1 trial), non-fatal pulmonary embolism (RR=0.40, 95% CI 0.08 to 2.05, p=0.2714, 1 trial), symptomatic venous thromboembolism (DVT, PE) (RR=0.40, 95% CI 0.13 to 1.27, p=0.1197, 1 trial), all cause death (RR=2.99, 95% CI 0.31 to 28.73, p=0.3427, 1 trial)and major bleeding (RR=1.22, 95% CI 0.65 to 2.26, p=0.5371, 1 trial).

Apixaban was superior to **enoxaparin (europe regimen)** in terms of major VTE (fatal and non fatal DVT,PE) (RR=0.50, 95% CI 0.26 to 0.97, p=0.0408, 1 trial), deep vein thrombosis (RR=0.60, 95% CI 0.50 to 0.72, p=0.0000, 1 trial), total VTE and all-cause mortality (RR=0.62, 95% CI 0.51 to 0.74, p=0.0000, 1 trial)and proximal DVT (RR=0.35, 95% CI 0.16 to 0.74, p=0.0061, 1 trial). However, no significant difference was found on symptomatic deep-vein thrombosis (RR=0.43, 95% CI 0.11 to 1.66, p=0.2192, 1 trial), symptomatic venous thromboembolism (DVT, PE) (RR=1.00, 95% CI 0.35 to 2.85, p=0.9990, 1 trial), all cause death (RR=4.00, 95% CI 0.18 to 88.69, p=0.3803, 1 trial)and major bleeding (RR=0.65, 95% CI 0.28 to 1.49, p=0.3044, 1 trial).

No significant difference was found between **apixaban** and **enoxaparin (US regimen)** in terms of symptomatic deep-vein thrombosis (RR=0.98, 95% CI 0.06 to 15.50, p=0.9897, 1 trial), major VTE (fatal and non fatal DVT,PE) (RR=0.58, 95% CI 0.28 to 1.20, p=0.1434, 1 trial), deep vein thrombosis (RR=0.95, 95% CI 0.72 to 1.26, p=0.7216, 1 trial), total VTE and all-cause mortality

(RR=0.90, 95% CI 0.48 to 1.68, p=0.7325, 2 trials), asymptomatic DVT (RR=0.63, 95% CI 0.29 to 1.40, p=0.2565, 1 trial), proximal DVT (RR=0.70, 95% CI 0.31 to 1.59, p=0.3947, 2 trials), symptomatic venous thromboembolism (DVT, PE) (RR=1.46, 95% CI 0.72 to 2.94, p=0.2918, 1 trial), all cause death (RR=1.13, 95% CI 0.27 to 4.79, p=0.8690, 2 trials)and major bleeding (RR=0.51, 95% CI 0.25 to 1.03, p=0.0613, 2 trials). There is a statistically significant difference in favour of apixaban for major or clinically relevant non-major bleeding (RR=0.67, 95% CI 0.47 to 0.97, p=0.0348, 1 trial).

2.2.2 Edoxaban

Edoxaban was superior to **enoxaparin (short duration)** in terms of major VTE (fatal and non fatal DVT,PE) (RR=0.34, 95% CI 0.14 to 0.86, p=0.0219, 1 trial), asymptomatic DVT (RR=0.38, 95% CI 0.16 to 0.89, p=0.0259, 1 trial)and distal DVT (RR=0.36, 95% CI 0.15 to 0.92, p=0.0320, 1 trial). However, no significant difference was found on symptomatic deep-vein thrombosis (RR=0.97, 95% CI 0.02 to 48.83, p=0.9889, 1 trial)and proximal DVT (RR=0.49, 95% CI 0.04 to 5.33, p=0.5550, 1 trial).

2.2.3 Rivaroxaban

Rivaroxaban was superior to **enoxaparin** in terms of major VTE (fatal and non fatal DVT,PE) (RR=0.12, 95% CI 0.04 to 0.34, p=0.0000, 1 trial), deep vein thrombosis (RR=0.23, 95% CI 0.12 to 0.43, p=0.0000, 1 trial), total VTE and all-cause mortality (RR=0.30, 95% CI 0.18 to 0.51, p=0.0000, 1 trial)and proximal DVT (RR=0.03, 95% CI 0.00 to 0.23, p=0.0000, 1 trial). However, no significant difference was found on non-fatal pulmonary embolism (RR=3.91, 95% CI 0.44 to 34.92, p=0.2226, 1 trial), distal DVT (RR=0.49, 95% CI 0.24 to 1.00, p=0.0512, 1 trial), symptomatic venous thromboembolism (DVT, PE) (RR=0.55, 95% CI 0.20 to 1.48, p=0.2361, 1 trial), all cause death (RR=0.98, 95% CI 0.24 to 3.90, p=0.9735, 1 trial)and major bleeding (RR=3.02, 95% CI 0.61 to 14.95, p=0.1755, 1 trial).

Rivaroxaban was superior to **enoxaparin (europe regimen)** in terms of major VTE (fatal and non fatal DVT,PE) (RR=0.38, 95% CI 0.18 to 0.82, p=0.0132, 1 trial), deep vein thrombosis (RR=0.53, 95% CI 0.41 to 0.68, p=0.0000, 1 trial), total VTE and all-cause mortality (RR=0.51, 95% CI 0.39 to 0.65, p=0.0000, 1 trial), distal DVT (RR=0.53, 95% CI 0.41 to 0.70, p=0.0000, 1 trial)and symptomatic venous thromboembolism (DVT, PE) (RR=0.34, 95% CI 0.15 to 0.75, p=0.0075, 1 trial). However, no significant difference was found on non-fatal pulmonary embolism (RR=0.27, 95% CI 0.01 to 5.90, p=0.4026, 1 trial), proximal DVT (RR=0.48, 95% CI 0.22 to 1.05, p=0.0651, 1 trial), all cause death (RR=0.08, 95% CI 0.00 to 1.51, p=0.0930, 1 trial)and major bleeding (RR=1.19, 95% CI 0.40 to 3.53, p=0.7562, 1 trial).

Rivaroxaban was superior to **enoxaparin (short duration)** in terms of deep vein thrombosis (RR=0.42, 95% CI 0.22 to 0.79, p=0.0068, 1 trial), total VTE and all-cause mortality (RR=0.42, 95% CI 0.22 to 0.79, p=0.0068, 1 trial)and distal DVT (RR=0.36, 95% CI 0.17 to 0.73, p=0.0048, 1 trial). However, no significant difference was found on non-fatal pulmonary embolism (RR=0.95, 95% CI 0.02 to 47.30, p=0.9782, 1 trial)and proximal DVT (RR=0.95, 95% CI 0.20 to 4.59, p=0.9460, 1 trial).

Rivaroxaban was superior to **enoxaparin (US regimen)** in terms of total VTE and all-cause mortality (RR=0.69, 95% CI 0.51 to 0.92, p=0.0134, 1 trial)and proximal DVT (RR=0.23, 95% CI 0.07 to 0.80, p=0.0212, 1 trial). However, no significant difference was found on symptomatic deep-vein thrombosis (RR=0.60, 95% CI 0.22 to 1.63, p=0.3148, 1 trial), major VTE (fatal and non fatal DVT,PE) (RR=0.59, 95% CI 0.30 to 1.16, p=0.1234, 1 trial), asymptomatic DVT (RR=0.72, 95% CI 0.51 to 1.01, p=0.0540, 1 trial), non-fatal pulmonary embolism (RR=0.49, 95% CI 0.15 to 1.64, p=0.2488, 1 trial), distal DVT (RR=0.82, 95% CI 0.57 to 1.17, p=0.2756,

1 trial), symptomatic venous thromboembolism (DVT, PE) (RR=0.60, 95% CI 0.29 to 1.27, p=0.1856, 1 trial), all cause death (RR=0.66, 95% CI 0.11 to 3.94, p=0.6473, 1 trial)and major bleeding (RR=1.27, 95% CI 0.17 to 9.63, p=0.8179, 2 trials).

2.2.4 Rivaroxaban (long duration)

Rivaroxaban (long duration) was superior to **enoxaparin (short duration)** in terms of major VTE (fatal and non fatal DVT,PE) (RR=0.12, 95% CI 0.05 to 0.28, p=0.0000, 1 trial), deep vein thrombosis (RR=0.20, 95% CI 0.11 to 0.35, p=0.0000, 1 trial), total VTE and all-cause mortality (RR=0.21, 95% CI 0.13 to 0.35, p=0.0000, 1 trial), distal DVT (RR=0.34, 95% CI 0.16 to 0.71, p=0.0042, 1 trial), proximal DVT (RR=0.11, 95% CI 0.05 to 0.29, p=0.0000, 1 trial)and symptomatic venous thromboembolism (DVT, PE) (RR=0.20, 95% CI 0.06 to 0.69, p=0.0106, 1 trial). However, no significant difference was found on non-fatal pulmonary embolism (RR=0.25, 95% CI 0.03 to 2.25, p=0.2165, 1 trial), all cause death (RR=0.34, 95% CI 0.07 to 1.66, p=0.1800, 1 trial)and major bleeding (RR=1.00, 95% CI 0.06 to 15.98, p=0.9995, 1 trial).

Table 2.1: *Main study characteristics - direct factor Xa inhibitors*

Trial	Patients	Treatments	Trial design and method
Apixaban			
Apixaban versus enoxaparin			
ADVANCE 3, 2010 [?] n = 2708 vs. 2699	patients undergoing elective total hip replacement surgery	apixaban 2.5mg twice daily for 35 days **versus** enoxaparin 40mg once daily for 35 days	double blind parallel groups Primary endpoint: asymptomatic and symptomatic DVT, PE,all-cause death 160 centres, 21 countries mean follow-up: 35 days test intervalle: 2-4 (3)
Apixaban versus enoxaparin (europe regimen)			
ADVANCE 2, 2010 [?] n = 1528 vs. 1529	patients undergoing elective unilateral or bilateral total knee replacement	apixaban 2.5mg twice daily during 12 days **versus** enoxaparin 40mg once daily 12 days	double blind parallel groups Primary endpoint: asymptomatic and symptomatic proximal DVT, PE, VTE-related death 125 centres, 27 countries mean follow-up: 12 days test intervalle: 2-4 (3)
Apixaban versus enoxaparin (US regimen)			
APROPOS 2.5mg, 2007 [?] n = 153 vs. 152	patients undergoing elective total knee replacement surgery	apixaban 2.5mg BID for 12 days **versus** enoxaparin 30mg twice daily for 12 days	double blind parallel groups Primary endpoint: VTE events and all-cause death 148 centres, mean follow-up: 12 days test intervalle: 2-4 (3)
ADVANCE-1, 2008 [?] n = 1599 vs. 1596	patients undergoing knee-replacement surgery	apixaban 2.5 mg orally twice daily for 10 to 14 days **versus** enoxaparin 30mg subcutaneously every 12 hours for 10-14 days	double blind parallel groups Primary endpoint: a- and symptomatic DVT, non fatal PE, death 129 centres, 14 countries mean follow-up: 12 days test intervalle: 2-4 (3)
Edoxaban			
Edoxaban versus enoxaparin (short duration)			

continued...

Trial	Patients	Treatments	Trial design and method
STARS J-V, 0 n = 255 vs. 248	total hip arthroplasty	edoxaban 30 mg once daily for 11 to 14 days **versus** subcutaneous enoxaparin 2,000 IU, equivalent to 20 mg, twice daily (BID) for 11 to 14 days	double-blind parallel groups Primary endpoint: all DVT,PE japan test intervalle: 2-4 (3)
Rivaroxaban			
Rivaroxaban versus enoxaparin			
RECORD 1, 2008 [?] n = 2266 vs. 2275	patients undergoing total hip arthroplasty	rivaroxaban 10mg once daily for 35 days **versus** enoxaparin 40mg subcutaneous once daily for 31-39 days	double blind parallel groups Primary endpoint: DVT, PE, death multicentre, 27 countries worldwide mean follow-up: 46 days test intervalle: 2-4 (3)
Rivaroxaban versus enoxaparin (europe regimen)			
RECORD 3, 2008 [?] n = 1254 vs. 1277	patients undergoing total knee arthroplasty	rivaroxaban 10 mg once daily for 10- 14 days **versus** enoxaparin 40 mg subcutaneous once daily for 10-14 days	double blind parallel groups Primary endpoint: DVT, PE all cause mortality 147 centers, 19 countries worldwide mean follow-up: 15 days test intervalle: 2-4 (3)
Rivaroxaban versus enoxaparin (short duration)			
ODIXa-HIP 10mg, 2006 [?, ?] n = 142 vs. 157	patients undergoing elective total hip replacement	rivaroxaban 10mg daily for 59 days **versus** once-daily subcutaneous enoxaparin dose of 40 mg for 59 days	double blind parallel groups Primary endpoint: any DVT, PE, all cause death 48 centres, Europe, Israel mean follow-up: 7 days test intervalle: 2-4 (3)
Rivaroxaban versus enoxaparin (US regimen)			
ODIXa-KNEE, 2005 [?] n = 102 vs. 105	patients undergoing elective total knee replacement	BAY 59-7939 5mg b.i.d. for 59 days **versus** enoxaparin 30 mg b.i.d. for 59 days	double blind parallel groups 43 centres, North America mean follow-up: 7 days test intervalle: 2-4 (3)

continued...

Trial	Patients	Treatments	Trial design and method
RECORD 4, 2009 [?] n = 1584 vs. 1564	patients who had undergone total-knee-replacement surgery	rivaroxaban 10mg once daily for 10 to 14 days **versus** enoxaparin 30 mg twice daily by subcutaneous injection for 10-14 days	double blind parallel groups Primary endpoint: total VTE events 131 centres, 12 countries mean follow-up: 40 days test intervalle: 2-4 (3)
Rivaroxaban (long duration)			
Rivaroxaban (long duration) versus enoxaparin (short duration)			
RECORD 2, 2008 [?] n = 1252 vs. 1257	patients undergoing elective total hip replacement	extended thromboprophylaxis with rivaroxaban 10mg once daily for 31-39 days **versus** enoxaparin 40mg subcutaneous once daily for 10-14 days	double blind parallel groups Primary endpoint: DVT, PE , all cause death 123 centres, 21 countries worldwide mean follow-up: 36 days test intervalle: 2-4 (3)

Table 2.2: *Summary of all results for apixaban*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
apixaban versus enoxaparin						
symptomatic deep-vein thrombosis	RR=0.20	0.02;1.71	0.1408	1.0000 (0.00)	1	5407
major VTE (fatal and non fatal DVT,PE)	RR=0.40	0.19;0.83	0.0138	1.0000 (0.00)	1	4394
deep vein thrombosis	RR=0.32	0.20;0.51	0.0000	1.0000 (1.00)	1	3855
total VTE and all-cause mortality	RR=0.36	0.23;0.56	0.0000	1.0000 (0.00)	1	3866
asymptomatic DVT	RR=0.33	0.20;0.54	0.0000	1.0000 (0.00)	1	5407
non-fatal pulmonary embolism	RR=0.40	0.08;2.05	0.2714	1.0000 (0.00)	1	5407
proximal DVT	RR=0.35	0.15;0.82	0.0163	1.0000 (1.00)	1	4386
symptomatic venous thromboembolism (DVT, PE)	RR=0.40	0.13;1.27	0.1197	1.0000 (0.00)	1	5407
major or clinically relevant non-major bleeding	RR=0.96	0.76;1.21	0.7190	1.0000 (0.00)	1	5332
all cause death	RR=2.99	0.31;28.73	0.3427	1.0000 (0.00)	1	5407
major bleeding	RR=1.22	0.65;2.26	0.5371	1.0000 (0.00)	1	5332
apixaban versus enoxaparin (europe regimen)						
symptomatic deep-vein thrombosis	RR=0.43	0.11;1.66	0.2192	1.0000 (1.00)	1	3057
major VTE (fatal and non fatal DVT,PE)	RR=0.50	0.26;0.97	0.0408	1.0000 (0.00)	1	2394
deep vein thrombosis	RR=0.60	0.50;0.72	0.0000	1.0000 (0.00)	1	1968
total VTE and all-cause mortality	RR=0.62	0.51;0.74	0.0000	1.0000 (0.00)	1	1973
proximal DVT	RR=0.35	0.16;0.74	0.0061	1.0000 (0.00)	1	2391
symptomatic venous thromboembolism (DVT, PE)	RR=1.00	0.35;2.85	0.9990	1.0000 (0.00)	1	3057
major or clinically relevant non-major bleeding	RR=0.74	0.52;1.05	0.0888	1.0000 (0.00)	1	3009
all cause death	RR=4.00	0.18;88.69	0.3803	1.0000 (0.00)	1	3057
major bleeding	RR=0.65	0.28;1.49	0.3044	1.0000 (0.00)	1	3009
apixaban versus enoxaparin (US regimen)						
symptomatic deep-vein thrombosis	RR=0.98	0.06;15.50	0.9897	1.0000 (0.00)	1	220
major VTE (fatal and non fatal DVT,PE)	RR=0.58	0.28;1.20	0.1434	1.0000 (0.00)	1	220
deep vein thrombosis	RR=0.95	0.72;1.26	0.7216	1.0000 (0.00)	1	2264
any bleedings	RR=0.73	0.26;2.04	0.5434	1.0000 (0.00)	1	303
total VTE and all-cause mortality	RR=0.90	0.48;1.68	0.7325	0.2560 (0.22)	2	2507
asymptomatic DVT	RR=0.63	0.29;1.40	0.2565	1.0000 (0.00)	1	220
proximal DVT	RR=0.70	0.31;1.59	0.3947	0.4758 (0.00)	2	2681
symptomatic venous thromboembolism (DVT, PE)	RR=1.46	0.72;2.94	0.2918	1.0000 (0.00)	1	3195
major or clinically relevant non-major bleeding	RR=0.67	0.47;0.97	0.0348	1.0000 (1.00)	1	3184
all cause death	RR=1.13	0.27;4.79	0.8690	0.7230 (0.00)	2	3415
major bleeding	RR=0.51	0.25;1.03	0.0613	0.7432 (0.00)	2	3487

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.3: *Summary of all results for edoxaban*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
edoxaban versus enoxaparin (short duration)						
symptomatic deep-vein thrombosis	RR=0.97	0.02;48.83	0.9889	1.0000 (0.00)	1	503
major VTE (fatal and non fatal DVT,PE)	RR=0.34	0.14;0.86	0.0219	1.0000 (0.00)	1	503
asymptomatic DVT	RR=0.38	0.16;0.89	0.0259	1.0000 (0.00)	1	503
distal DVT	RR=0.36	0.15;0.92	0.0320	1.0000 (0.00)	1	503
proximal DVT	RR=0.49	0.04;5.33	0.5550	1.0000 (0.00)	1	503

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.4: *Summary of all results for rivaroxaban*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
rivaroxaban versus enoxaparin						
major VTE (fatal and non fatal DVT,PE)	RR=0.12	0.04;0.34	0.0000	1.0000 (0.00)	1	3364
deep vein thrombosis	RR=0.23	0.12;0.43	0.0000	1.0000 (0.00)	1	4433
total VTE and all-cause mortality	RR=0.30	0.18;0.51	0.0000	1.0000 (0.00)	1	3153
non-fatal pulmonary embolism	RR=3.91	0.44;34.92	0.2226	1.0000 (0.00)	1	3153
distal DVT	RR=0.49	0.24;1.00	0.0512	1.0000 (0.00)	1	3153
proximal DVT	RR=0.03	0.00;0.23	0.0000	1.0000 (0.00)	1	3153
symptomatic venous thromboembolism (DVT, PE)	RR=0.55	0.20;1.48	0.2361	1.0000 (0.00)	1	4399
all cause death	RR=0.98	0.24;3.90	0.9735	1.0000 (0.00)	1	3153
major bleeding	RR=3.02	0.61;14.95	0.1755	1.0000 (0.00)	1	4433
rivaroxaban versus enoxaparin (europe regimen)						
major VTE (fatal and non fatal DVT,PE)	RR=0.38	0.18;0.82	0.0132	1.0000 (0.00)	1	1833
deep vein thrombosis	RR=0.53	0.41;0.68	0.0000	1.0000 (0.00)	1	1702
total VTE and all-cause mortality	RR=0.51	0.39;0.65	0.0000	1.0000 (0.00)	1	1702
non-fatal pulmonary embolism	RR=0.27	0.01;5.90	0.4026	1.0000 (0.00)	1	1702
distal DVT	RR=0.53	0.41;0.70	0.0000	1.0000 (0.00)	1	1702
proximal DVT	RR=0.48	0.22;1.05	0.0651	1.0000 (0.00)	1	1702
symptomatic venous thromboembolism (DVT, PE)	RR=0.34	0.15;0.75	0.0075	1.0000 (0.00)	1	2418
all cause death	RR=0.08	0.00;1.51	0.0930	1.0000 (1.00)	1	2418
major bleeding	RR=1.19	0.40;3.53	0.7562	1.0000 (0.00)	1	2531
rivaroxaban versus enoxaparin (short duration)						
deep vein thrombosis	RR=0.42	0.22;0.79	0.0068	1.0000 (1.00)	1	220
total VTE and all-cause mortality	RR=0.42	0.22;0.79	0.0068	1.0000 (1.00)	1	220
non-fatal pulmonary embolism	RR=0.95	0.02;47.30	0.9782	1.0000 (0.00)	1	220
distal DVT	RR=0.36	0.17;0.73	0.0048	1.0000 (0.00)	1	220
proximal DVT	RR=0.95	0.20;4.59	0.9460	1.0000 (0.00)	1	220
rivaroxaban versus enoxaparin (US regimen)						

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
symptomatic deep-vein thrombosis	RR=0.60	0.22;1.63	0.3148	1.0000 (0.00)	1	1924
major VTE (fatal and non fatal DVT,PE)	RR=0.59	0.30;1.16	0.1234	1.0000 (0.00)	1	2234
total VTE and all-cause mortality	RR=0.69	0.51;0.92	0.0134	1.0000 (0.00)	1	1924
asymptomatic DVT	RR=0.72	0.51;1.01	0.0540	1.0000 (0.00)	1	1924
non-fatal pulmonary embolism	RR=0.49	0.15;1.64	0.2488	1.0000 (1.00)	1	3034
distal DVT	RR=0.82	0.57;1.17	0.2756	1.0000 (0.00)	1	1924
proximal DVT	RR=0.23	0.07;0.80	0.0212	1.0000 (0.00)	1	1924
symptomatic venous thromboembolism (DVT, PE)	RR=0.60	0.29;1.27	0.1856	1.0000 (0.00)	1	3034
major or clinically relevant non-major bleeding	RR=1.34	0.86;2.07	0.1933	1.0000 (0.00)	1	3034
all cause death	RR=0.66	0.11;3.94	0.6473	1.0000 (0.00)	1	3034
major bleeding	RR=1.27	0.17;9.63	0.8179	0.1769 (0.45)	2	3240

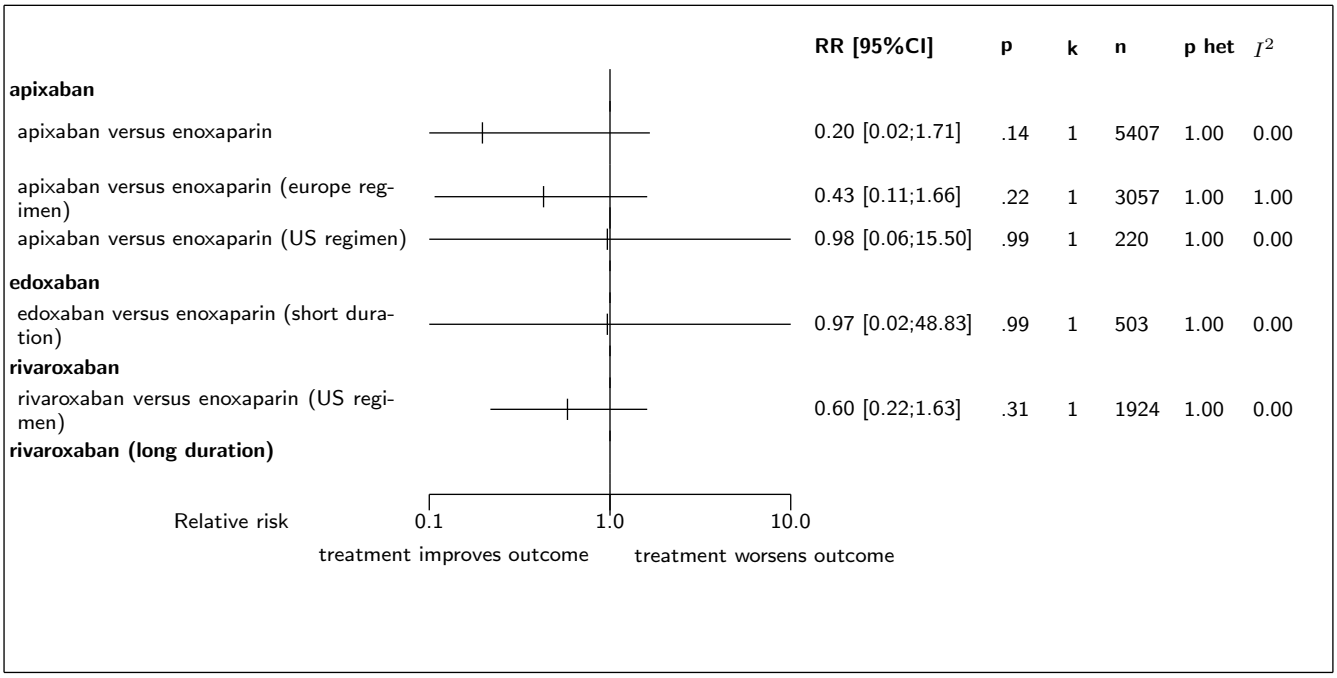
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.5: *Summary of all results for rivaroxaban (long duration)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
rivaroxaban (long duration) versus enoxaparin (short duration)						
major VTE (fatal and non fatal DVT,PE)	RR=0.12	0.05;0.28	0.0000	1.0000 (0.00)	1	1923
deep vein thrombosis	RR=0.20	0.11;0.35	0.0000	1.0000 (0.00)	1	1733
total VTE and all-cause mortality	RR=0.21	0.13;0.35	0.0000	1.0000 (0.00)	1	1733
non-fatal pulmonary embolism	RR=0.25	0.03;2.25	0.2165	1.0000 (1.00)	1	1733
distal DVT	RR=0.34	0.16;0.71	0.0042	1.0000 (0.00)	1	1733
proximal DVT	RR=0.11	0.05;0.29	0.0000	1.0000 (0.00)	1	1733
symptomatic venous thromboembolism (DVT, PE)	RR=0.20	0.06;0.69	0.0106	1.0000 (1.00)	1	2419
major or clinically relevant non-major bleeding	RR=1.20	0.93;1.54	0.1582	1.0000 (1.00)	1	2457
all cause death	RR=0.34	0.07;1.66	0.1800	1.0000 (1.00)	1	1733
major bleeding	RR=1.00	0.06;15.98	0.9995	1.0000 (0.00)	1	2457

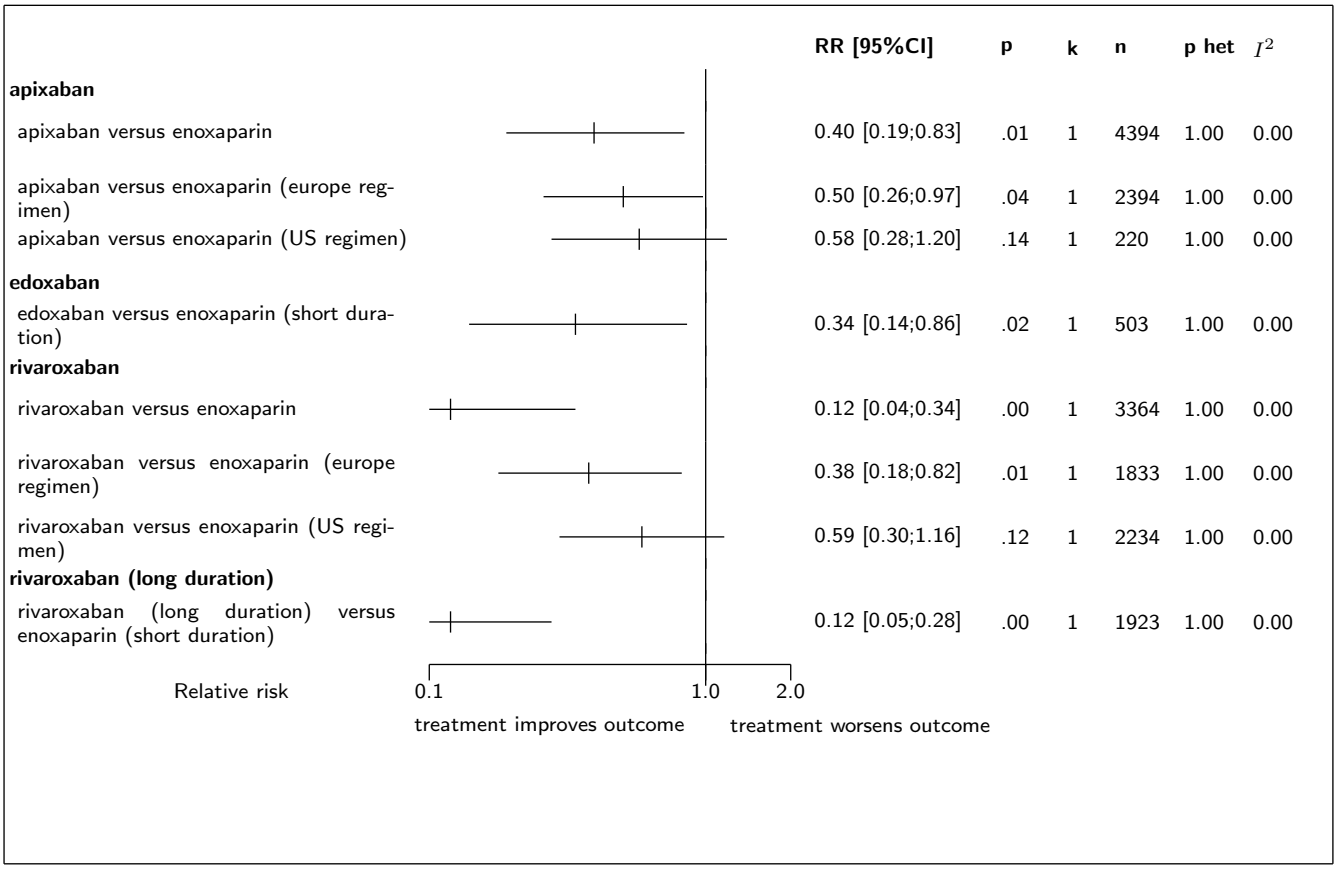
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 2.1: *Forest's plot for symptomatic deep-vein thrombosis*



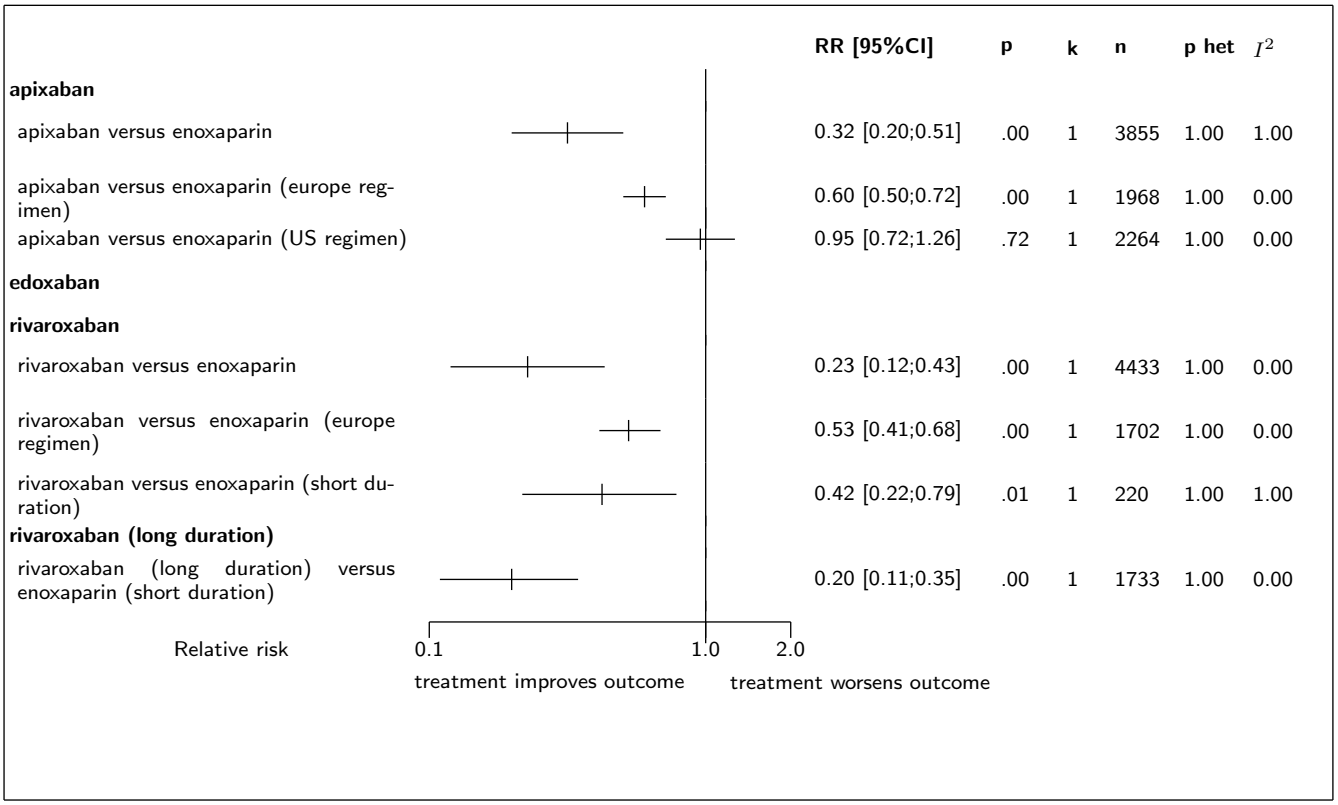
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*



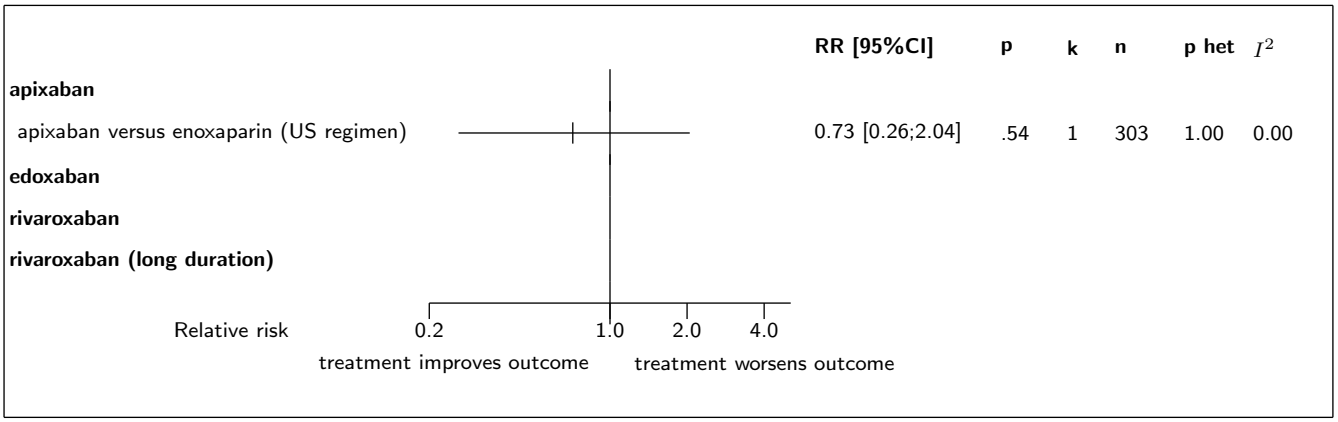
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.3: *Forest's plot for deep vein thrombosis*



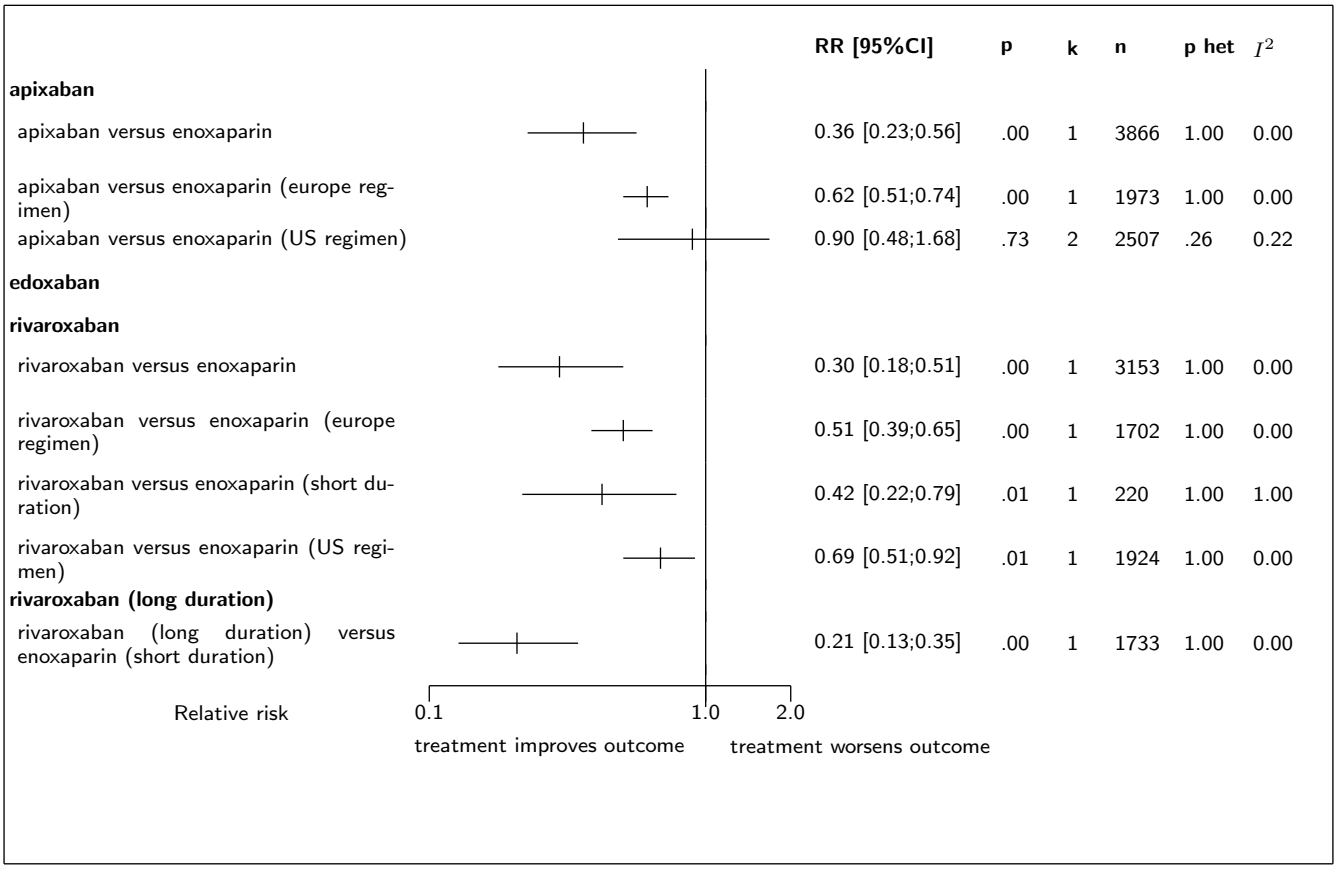
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.4: *Forest's plot for any bleedings*



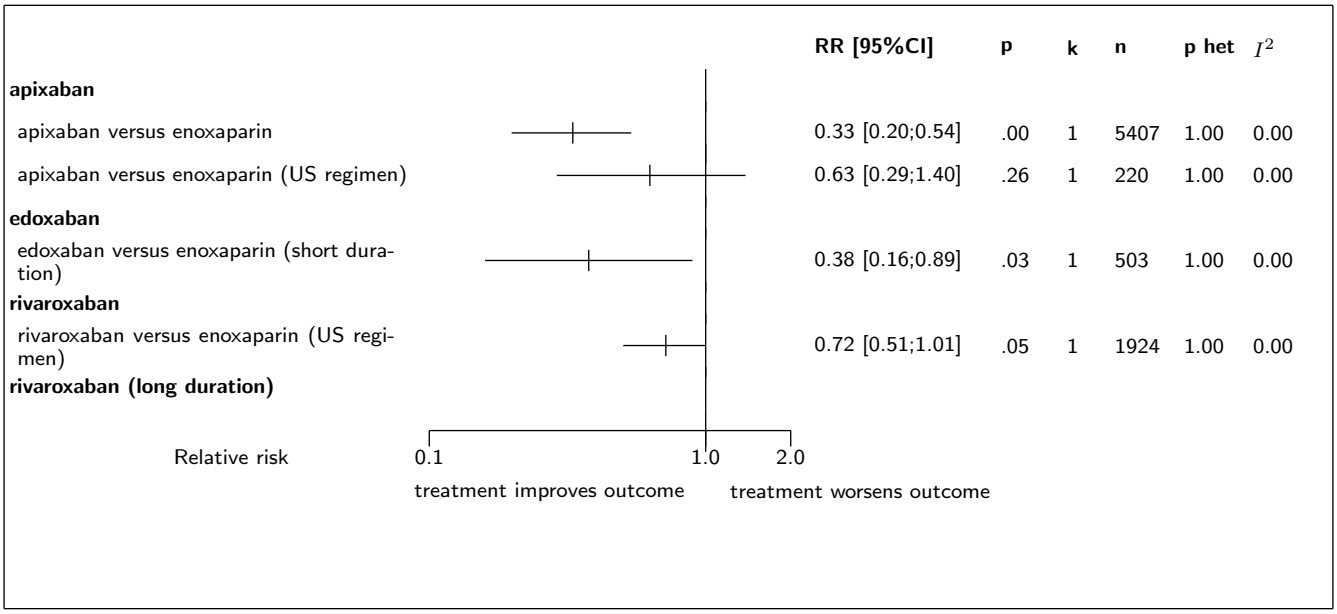
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.5: *Forest's plot for total VTE and all-cause mortality*



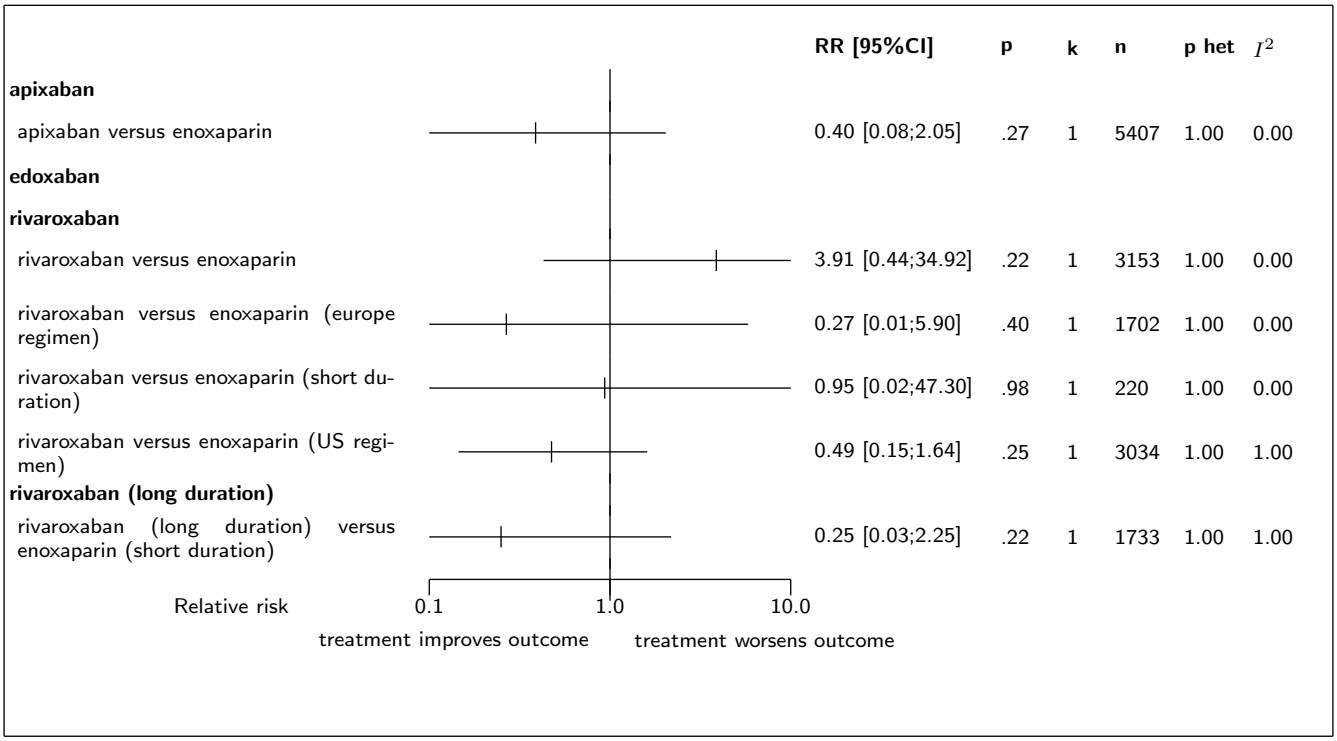
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.6: *Forest's plot for asymptomatic DVT*



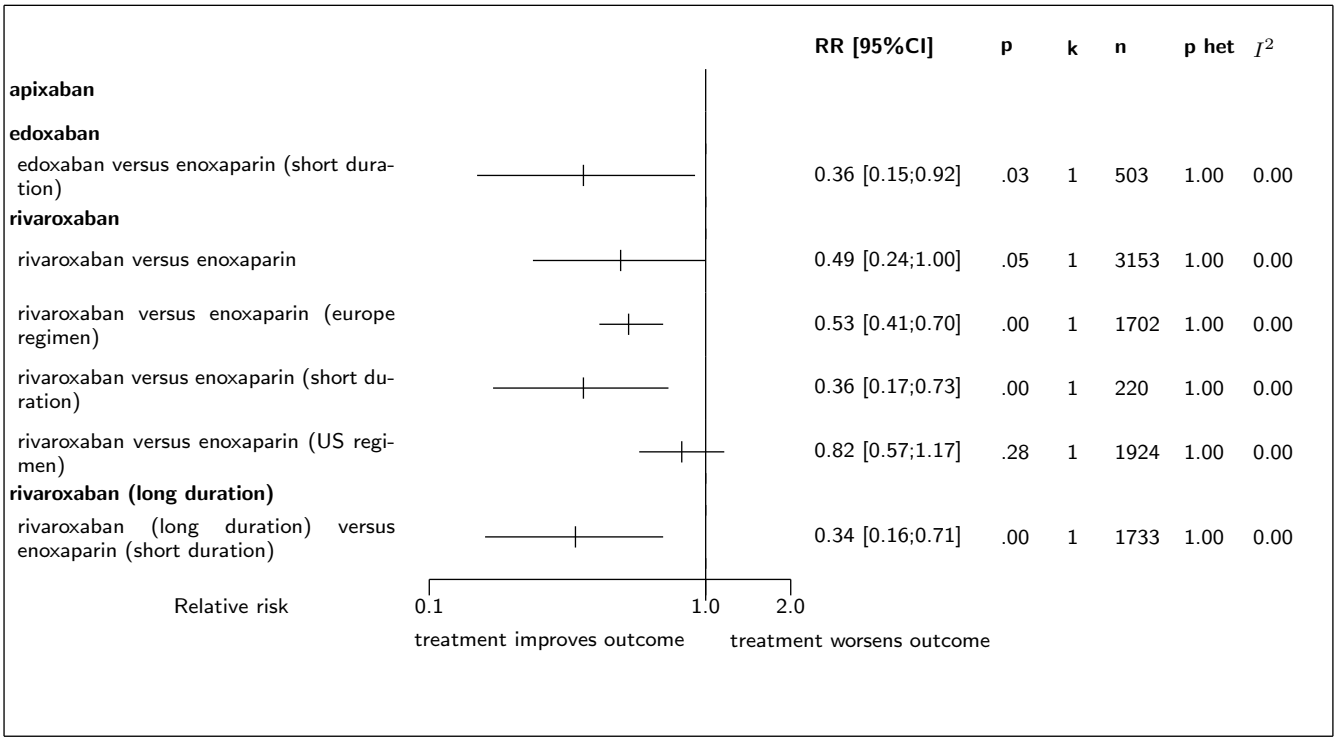
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.7: *Forest's plot for non-fatal pulmonary embolism*



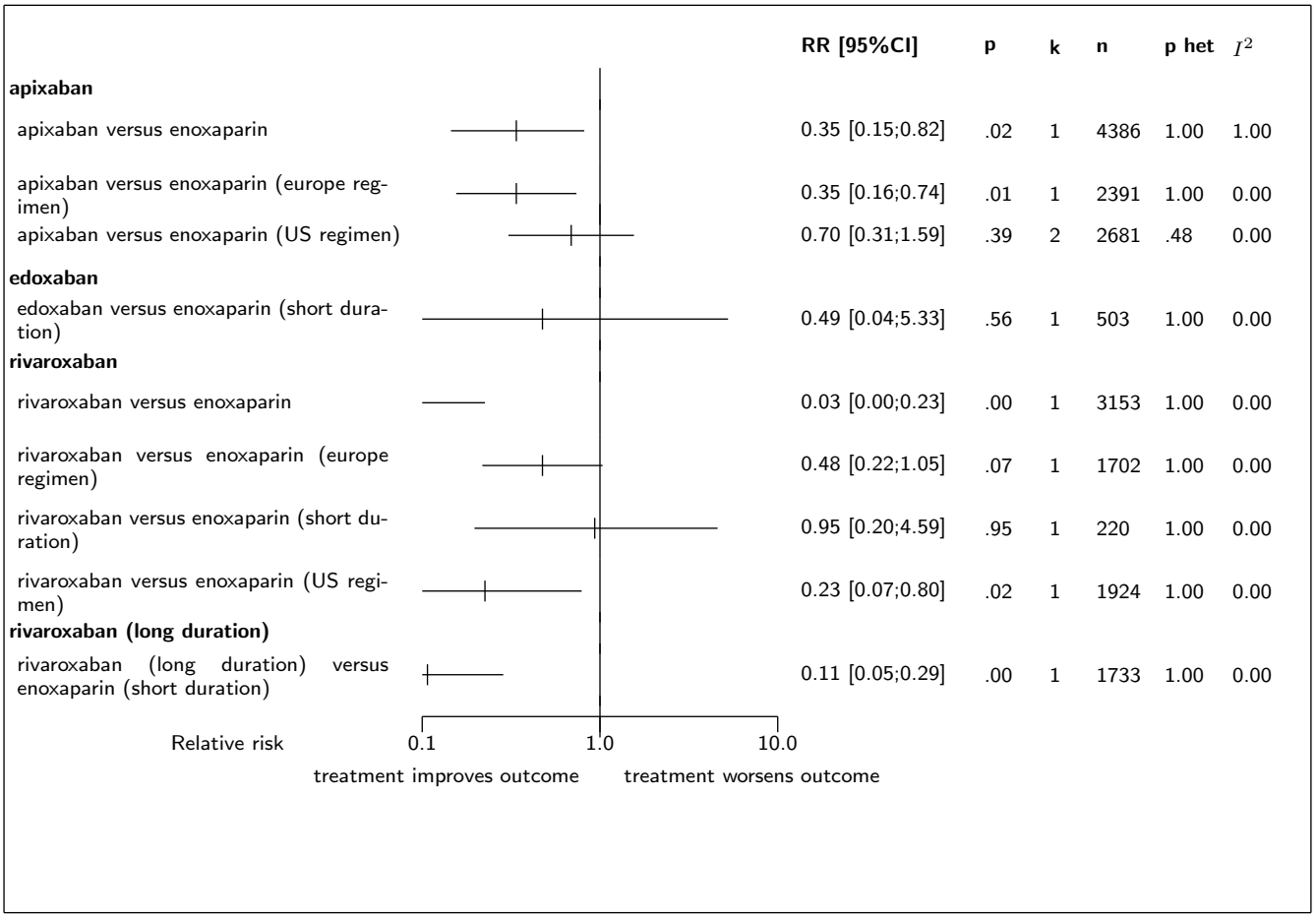
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.8: *Forest's plot for distal DVT*



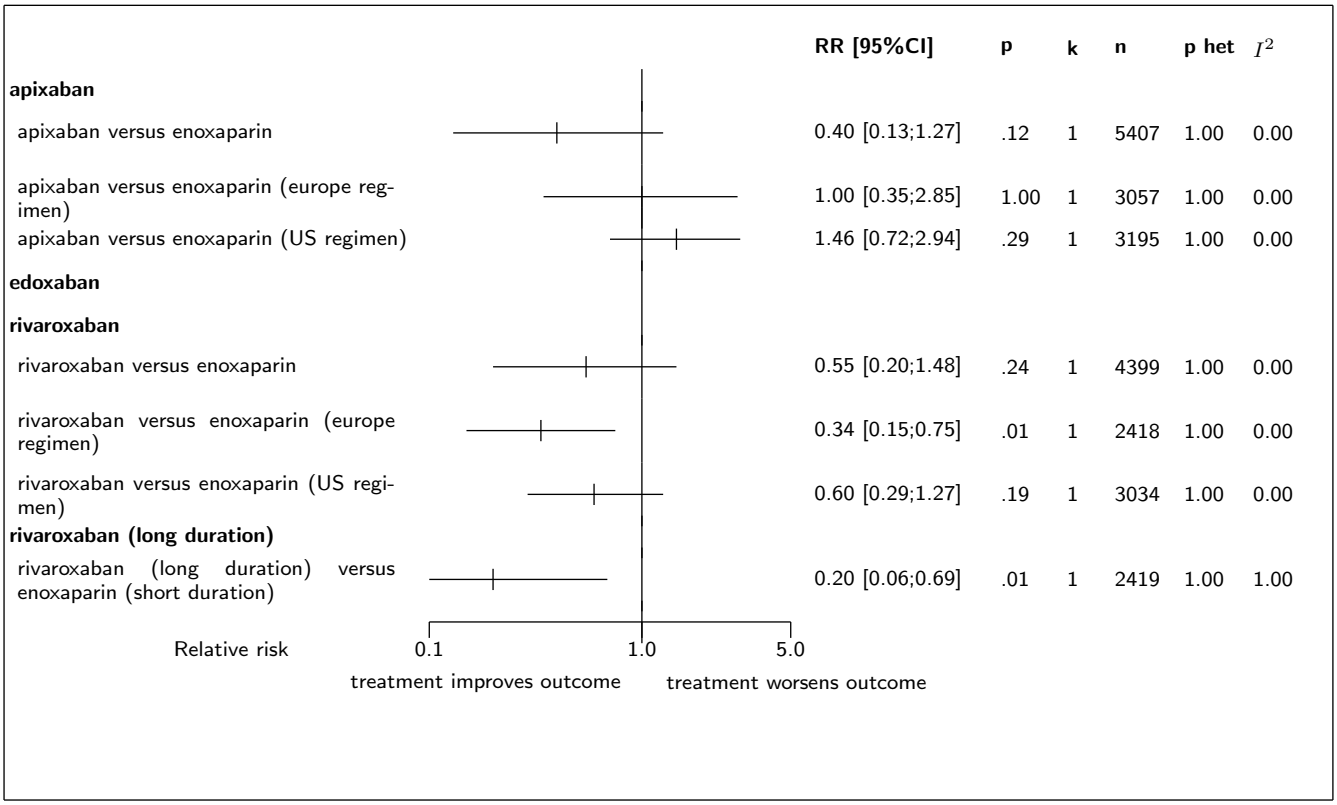
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.9: *Forest's plot for proximal DVT*



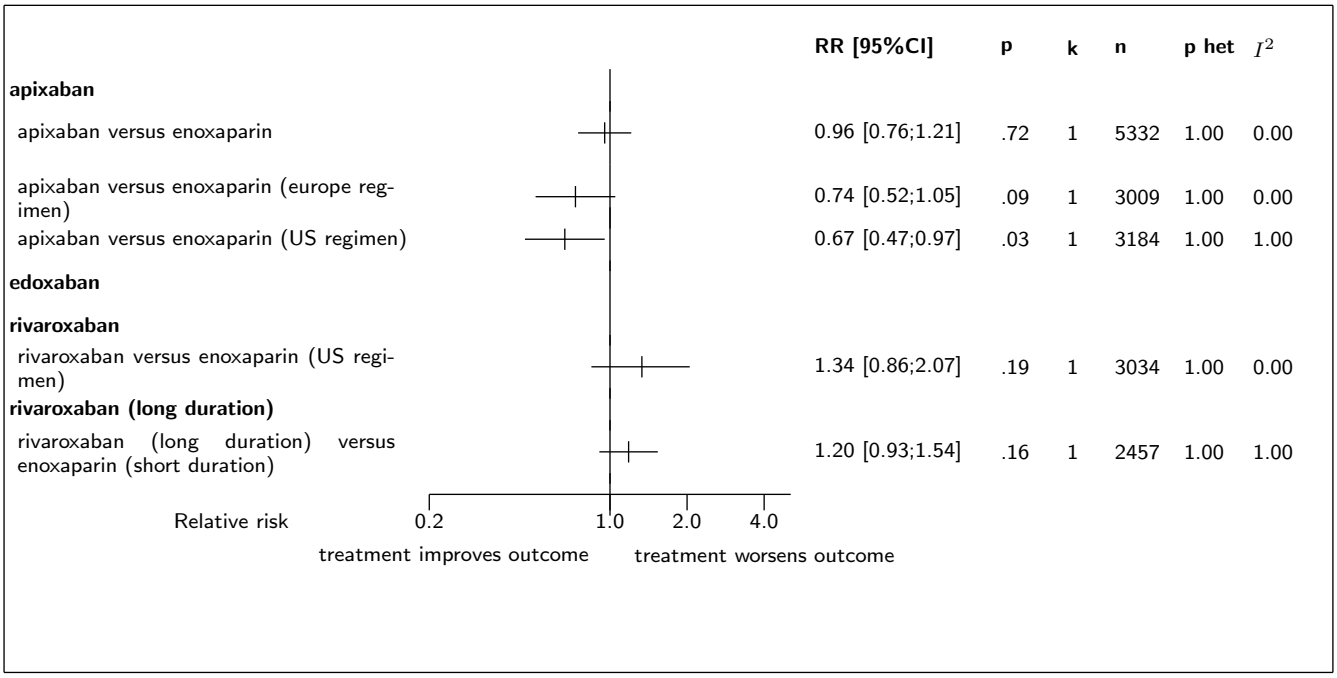
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.10: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*



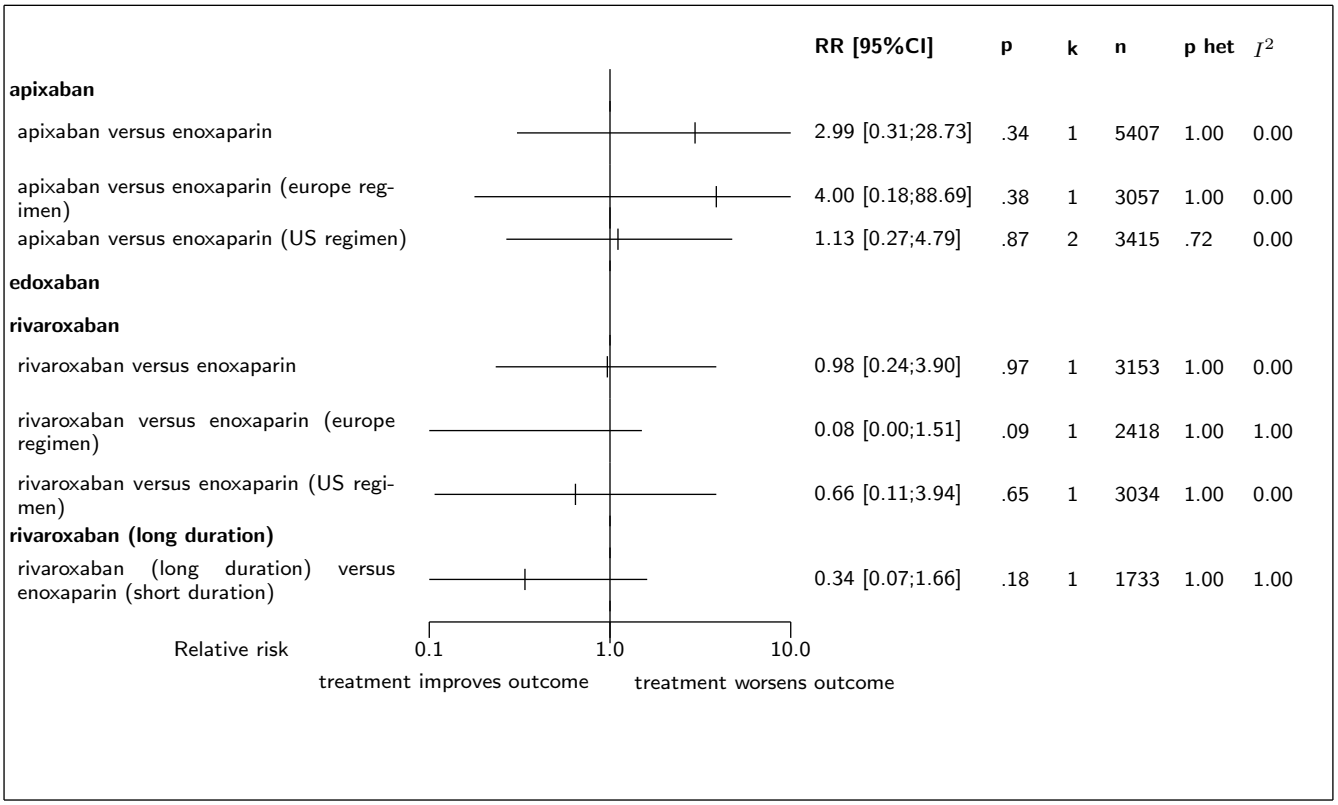
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.11: *Forest's plot for major or clinically relevant non-major bleeding*



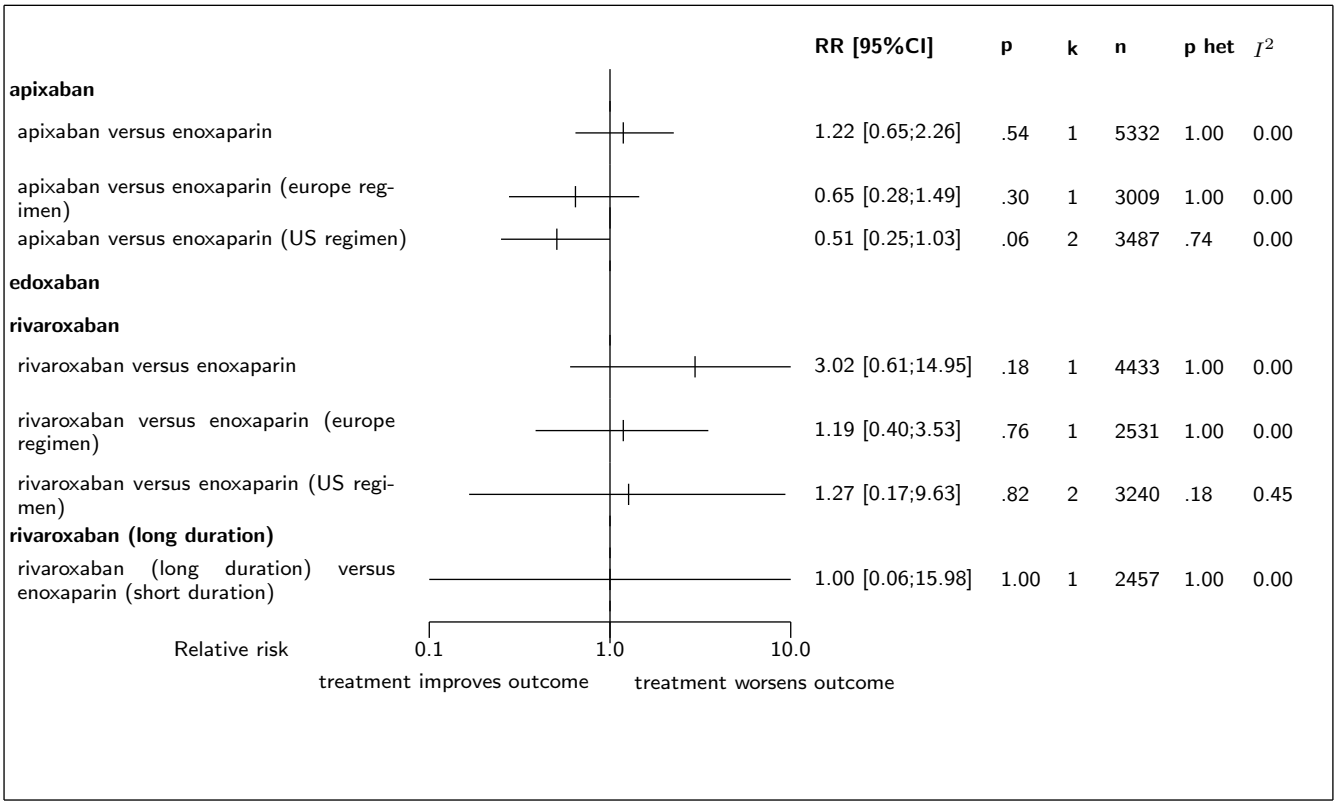
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.12: *Forest's plot for all cause death*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.13: *Forest's plot for major bleeding*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

3 Detailed results for apixaban

3.1 Available trials

A total of 4 RCTs which randomized 11964 patients were identified: it compared apixaban with enoxaparin , it compared apixaban with enoxaparin (europe regimen) and 2 trials compared apixaban with enoxaparin (US regimen).
The average study size was 2991 patients (range 305 to 5407). The first study was published in 2007, and the last study was published in 2010.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 4 trials; 4 trials reported data on total VTE and all-cause mortality; 4 trials reported data on major bleeding; 4 trials reported data on proximal DVT; 3 trials reported data on deep vein thrombosis; 3 trials reported data on major VTE (fatal and non fatal DVT,PE); 3 trials reported data on symptomatic deep-vein thrombosis; 3 trials reported data on symptomatic venous thromboembolism (DVT, PE); 2 trials reported data on asymptomatic DVT; 1 trials reported data on non-fatal pulmonary embolism; 3 trials reported data on major or clinically relevant non-major bleeding; and 1 trials reported data on any bleedings.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of apixaban.

Table 3.1: *Treatment description - direct factor Xa inhibitors - apixaban*

Trial	Studied treatment	Control treatment
Apixaban versus enoxaparin		
ADVANCE 3 (2010) [**?**]	apixaban 2.5mg twice daily for 35 days given 12 to 24 hours following surgery	enoxaparin 40mg once daily for 35 days started the evening before surgery
Apixaban versus enoxaparin (europe regimen)		
ADVANCE 2 (2010) [**?**] [a]	apixaban 2.5mg twice daily during 12 days started 1224 h after wound closure	enoxaparin 40mg once daily 12 days started 12 h before surgery
Apixaban versus enoxaparin (US regimen)		
APROPOS 2.5mg (2007) [**?**] [a]	apixaban 2.5mg BID for 12 days	enoxaparin 30mg twice daily for 12 days began 1224 h after skin woundclosure,
ADVANCE-1 (2008) [**?**]	apixaban 2.5 mg orally twice daily for 10 to 14 days started 12 to 24 hours after surgery and continued for 10 to 14 days	enoxaparin 30mg subcutaneously every 12 hours for 10-14 days started 12 to 24 hours after surgery and continued for 10 to 14 days

a) "European" enoxaprin regimen a) 8 arms: apixaban 2.5mg BID, 5mg BID, 10mg BID, 5mgQD, 20mg QD for 12 days, enoxaparin 30mg twice daily, warfarin INR 1.8-3.0

Table 3.2: *Descriptions of participants - direct factor Xa inhibitors - apixaban*

Trial	Patients
Apixaban versus enoxaparin	

continued...

Trial	Patients	
ADVANCE 3 (2010) [?]	Patients undergoing elective total hip replacement surgery	
	Inclusion criteria: scheduled to undergo-elective total hip replacement or revision ofa previously inserted hip prosthesis	**Exclusion criteria:** active bleeding; contraindication to anticoagulant prophylaxis; need for ongoing anticoagulant or antiplatelet treatment
Apixaban versus enoxaparin (europe regimen)		
ADVANCE 2 (2010) [?]	Patients undergoing elective unilateral or bilateral total knee replacement	
	Inclusion criteria: scheduled to have unilateral elective total knee replacement or same-day bilateral knee replacement, including revision	**Exclusion criteria:** active bleeding or a contraindication to anticoagulant prophylaxis, or needed continuing anticoagulant or antiplatelet treatment; uncontrolled hypertension; active hepatobiliary disease; impaired renal function; thrombocytopenia, anaemia, heparin allergy; allergy to radiographic contrast dye; other disorders preventing bilateral venography
Apixaban versus enoxaparin (US regimen)		
APROPOS 2.5mg (2007) [?]	Patients undergoing elective total knee replacement surgery	
ADVANCE-1 (2008) [?]	Patients undergoing knee-replacement surgery	
	Inclusion criteria: scheduled to undergo total knee replacement surgery for one or both knees, including revision of a previously inserted artificial joint	**Exclusion criteria:** active bleeding or a contraindication to anticoagulant prophylaxis; ongoing anticoagulant or antiplatelet treatment;uncontrolled hypertension, active hepatobiliary disease; clinically significant impairment of renal function, thrombocytopenia; anemia; allergy to heparin, and allergy to radiographic contrast dye or another contraindication to bilateral venography

Table 3.3: *Design and methodological quality of trials - direct factor Xa inhibitors - apixaban*

Trial	Design	Duration	Centre	Primary endpoint
Apixaban versus enoxaparin				
ADVANCE 3, 2010 [?] n=5407	Parallel groups double blind confirmatory trial at low risk of bias	35 days (+60) inclusion period: mar 2007 - may 2009	21 countries 160 centres	asymptomatic and symptomatic DVT, PE,all-cause death
Apixaban versus enoxaparin (europe regimen)				
ADVANCE 2, 2010 [?] n=3057	Parallel groups double blind confirmatory trial at low risk of bias	12 days inclusion period: jun 2007 - nov 2008	27 countries 125 centres	asymptomatic and symptomatic proximal DVT, PE, VTE-related death
Apixaban versus enoxaparin (US regimen)				
APROPOS 2.5mg, 2007 [?] [(a)] n=305	Parallel groups double blind exploratory trial	12 days inclusion period: oct 2004 - dec 2005	148 centres	VTE events and all-cause death

continued...

Trial	Design	Duration	Centre	Primary endpoint
ADVANCE-1, 2008 [?] n=3195	Parallel groups double blind confirmatory trial at low risk of bias	10-14 days	14 countries 129 centres	a- and symptomatic DVT, non fatal PE, death

a) phase 2 dose ranging study

Table 3.4: *Trial characteristics - direct factor Xa inhibitors - apixaban*

Trial	**mean follow-up**	**test intervalle**
Apixaban versus enoxaparin		
ADVANCE 3, 2010 [?]	35 days	2-4 (3)
Apixaban versus enoxaparin (europe regimen)		
ADVANCE 2, 2010 [?]	12 days	2-4 (3)
Apixaban versus enoxaparin (US regimen)		
APROPOS 2.5mg, 2007 [?]	12 days	2-4 (3)
ADVANCE-1, 2008 [?]	12 days	2-4 (3)

3.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Apixaban versus enoxaparin

The single study eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between apixaban and enoxaparin, with a RR of 0.20 (95%CI 0.02 to 1.71, p=0.1408) in favour of apixaban. In other words, symptomatic deep-vein thrombosis was slightly lower in the apixaban group , but this was not statistically significant.
The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. The analysis detected a statistically significant difference in favor of apixaban in major VTE (fatal and non fatal DVT,PE), with a RR of 0.40 (95% CI 0.19 to 0.83, p=0.0138).
The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of apixaban in deep vein thrombosis, with a RR of 0.32 (95% CI 0.20 to 0.51, p=0.0000).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of apixaban in total VTE and all-cause mortality, with a RR of 0.36 (95% CI 0.23 to 0.56, p=0.0000).
The single study eligible for this comparison provided data on **asymptomatic DVT**. The analysis detected a statistically significant difference in favor of apixaban in asymptomatic DVT, with a RR of 0.33 (95% CI 0.20 to 0.54, p=0.0000).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.40 (95% CI 0.08 to 2.05, p=0.2714).
The single study eligible for this comparison provided data on **proximal DVT**. The analysis detected a statistically significant difference in favor of apixaban in proximal DVT, with a RR of 0.35 (95% CI 0.15 to 0.82, p=0.0163).
The single study eligible for this comparison provided data on **symptomatic venous thromboembolism (DVT, PE)**. No statistically significant difference between the groups was found in symptomatic venous thromboembolism (DVT, PE), with a RR of 0.40 (95% CI 0.13 to 1.27, p=0.1197).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 2.99 (95% CI 0.31 to 28.73, p=0.3427).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 1.22 (95% CI 0.65 to 2.26, p=0.5371).

Apixaban versus enoxaparin (europe regimen)

The single study eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between apixaban and enoxaparin (europe regimen), with a RR of 0.43 (95%CI 0.11 to 1.66, p=0.2192) in favour of apixaban. In other words, symptomatic deep-vein thrombosis was slightly lower in the apixaban group , but this was not statistically significant.
The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. The analysis detected a statistically significant difference in favor of apixaban in major VTE (fatal and non fatal DVT,PE), with a RR of 0.50 (95% CI 0.26 to 0.97, p=0.0408).
The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of apixaban in deep vein thrombosis, with a RR of 0.60 (95% CI 0.50 to 0.72, p=0.0000).

The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of apixaban in total VTE and all-cause mortality, with a RR of 0.62 (95% CI 0.51 to 0.74, p=0.0000).
The single study eligible for this comparison provided data on **proximal DVT**. The analysis detected a statistically significant difference in favor of apixaban in proximal DVT, with a RR of 0.35 (95% CI 0.16 to 0.74, p=0.0061).
The single study eligible for this comparison provided data on **symptomatic venous thromboembolism (DVT, PE)**. No statistically significant difference between the groups was found in symptomatic venous thromboembolism (DVT, PE), with a RR of 1.00 (95% CI 0.35 to 2.85, p=0.9990).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 4.00 (95% CI 0.18 to 88.69, p=0.3803).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 0.65 (95% CI 0.28 to 1.49, p=0.3044).

Apixaban versus enoxaparin (US regimen)

Only one of the 2 studies eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between apixaban and enoxaparin (US regimen), with a RR of 0.98 (95%CI 0.06 to 15.50, p=0.9897) in favour of apixaban. In other words, symptomatic deep-vein thrombosis was slightly lower in the apixaban group , but this was not statistically significant.
Only one of the 2 studies eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. No statistically significant difference between the groups was found in major VTE (fatal and non fatal DVT,PE), with a RR of 0.58 (95% CI 0.28 to 1.20, p=0.1434).
Only one of the 2 studies eligible for this comparison provided data on **deep vein thrombosis**. No statistically significant difference between the groups was found in deep vein thrombosis, with a RR of 0.95 (95% CI 0.72 to 1.26, p=0.7216).
All the 2 studies had extractable data about the number of participants with **total VTE and all-cause mortality**. When pooled together, there was no statistically significant difference between the groups in total VTE and all-cause mortality, with a RR of 0.90 (95% CI 0.48 to 1.68, p=0.7325). No heterogeneity was detected (p = 0.2560, $I^2 = 0.22\%$).
Only one of the 2 studies eligible for this comparison provided data on **asymptomatic DVT**. No statistically significant difference between the groups was found in asymptomatic DVT, with a RR of 0.63 (95% CI 0.29 to 1.40, p=0.2565).
All the 2 studies had extractable data about the number of participants with **proximal DVT**. When pooled together, there was no statistically significant difference between the groups in proximal DVT, with a RR of 0.70 (95% CI 0.31 to 1.59, p=0.3947). No heterogeneity was detected (p = 0.4758, $I^2 = 0.00\%$).
Only one of the 2 studies eligible for this comparison provided data on **symptomatic venous thromboembolism (DVT, PE)**. No statistically significant difference between the groups was found in symptomatic venous thromboembolism (DVT, PE), with a RR of 1.46 (95% CI 0.72 to 2.94, p=0.2918).
All the 2 studies had extractable data about the number of participants with **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 1.13 (95% CI 0.27 to 4.79, p=0.8690). No heterogeneity was detected (p = 0.7230, $I^2 = 0.00\%$).
All the 2 studies had extractable data about the number of participants with **major bleeding**. When pooled together, there was no statistically significant difference between the groups in

major bleeding, with a RR of 0.51 (95% CI 0.25 to 1.03, p=0.0613). No heterogeneity was detected (p = 0.7432, I^2 = 0.00%).

Table 3.5: *Results details - direct factor Xa inhibitors - apixaban*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
apixaban versus enoxaparin						
symptomatic deep-vein thrombosis	RR=0.20	[0.02;1.71]	0.1408	1.0000 (I^2=0.00)	1	5407
major VTE (fatal and non fatal DVT,PE)	RR=0.40	[0.19;0.83]	0.0138	1.0000 (I^2=0.00)	1	4394
deep vein thrombosis	RR=0.32	[0.20;0.51]	0.0000	1.0000 (I^2=1.00)	1	3855
total VTE and all-cause mortality	RR=0.36	[0.23;0.56]	0.0000	1.0000 (I^2=0.00)	1	3866
asymptomatic DVT	RR=0.33	[0.20;0.54]	0.0000	1.0000 (I^2=0.00)	1	5407
non-fatal pulmonary embolism	RR=0.40	[0.08;2.05]	0.2714	1.0000 (I^2=0.00)	1	5407
proximal DVT	RR=0.35	[0.15;0.82]	0.0163	1.0000 (I^2=1.00)	1	4386
symptomatic venous thromboembolism (DVT, PE)	RR=0.40	[0.13;1.27]	0.1197	1.0000 (I^2=0.00)	1	5407
major or clinically relevant non-major bleeding	RR=0.96	[0.76;1.21]	0.7190	1.0000 (I^2=0.00)	1	5332
all cause death	RR=2.99	[0.31;28.73]	0.3427	1.0000 (I^2=0.00)	1	5407
major bleeding	RR=1.22	[0.65;2.26]	0.5371	1.0000 (I^2=0.00)	1	5332
apixaban versus enoxaparin (europe regimen)						
symptomatic deep-vein thrombosis	RR=0.43	[0.11;1.66]	0.2192	1.0000 (I^2=1.00)	1	3057
major VTE (fatal and non fatal DVT,PE)	RR=0.50	[0.26;0.97]	0.0408	1.0000 (I^2=0.00)	1	2394
deep vein thrombosis	RR=0.60	[0.50;0.72]	0.0000	1.0000 (I^2=0.00)	1	1968
total VTE and all-cause mortality	RR=0.62	[0.51;0.74]	0.0000	1.0000 (I^2=0.00)	1	1973
proximal DVT	RR=0.35	[0.16;0.74]	0.0061	1.0000 (I^2=0.00)	1	2391
symptomatic venous thromboembolism (DVT, PE)	RR=1.00	[0.35;2.85]	0.9990	1.0000 (I^2=0.00)	1	3057
major or clinically relevant non-major bleeding	RR=0.74	[0.52;1.05]	0.0888	1.0000 (I^2=0.00)	1	3009
all cause death	RR=4.00	[0.18;88.69]	0.3803	1.0000 (I^2=0.00)	1	3057
major bleeding	RR=0.65	[0.28;1.49]	0.3044	1.0000 (I^2=0.00)	1	3009
apixaban versus enoxaparin (US regimen)						
symptomatic deep-vein thrombosis	RR=0.98	[0.06;15.50]	0.9897	1.0000 (I^2=0.00)	1	220
major VTE (fatal and non fatal DVT,PE)	RR=0.58	[0.28;1.20]	0.1434	1.0000 (I^2=0.00)	1	220
deep vein thrombosis	RR=0.95	[0.72;1.26]	0.7216	1.0000 (I^2=0.00)	1	2264
any bleedings	RR=0.73	[0.26;2.04]	0.5434	1.0000 (I^2=0.00)	1	303
total VTE and all-cause mortality	RR=0.90	[0.48;1.68]	0.7325	0.2560 (I^2=0.22)	2	2507
asymptomatic DVT	RR=0.63	[0.29;1.40]	0.2565	1.0000 (I^2=0.00)	1	220
proximal DVT	RR=0.70	[0.31;1.59]	0.3947	0.4758 (I^2=0.00)	2	2681

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
symptomatic venous thromboembolism (DVT, PE)	RR=1.46	[0.72;2.94]	0.2918	1.0000 (I^2=0.00)	1	3195
major or clinically relevant non-major bleeding	RR=0.67	[0.47;0.97]	0.0348	1.0000 (I^2=1.00)	1	3184
all cause death	RR=1.13	[0.27;4.79]	0.8690	0.7230 (I^2=0.00)	2	3415
major bleeding	RR=0.51	[0.25;1.03]	0.0613	0.7432 (I^2=0.00)	2	3487

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 3.1: *Forest's plot for symptomatic deep-vein thrombosis*

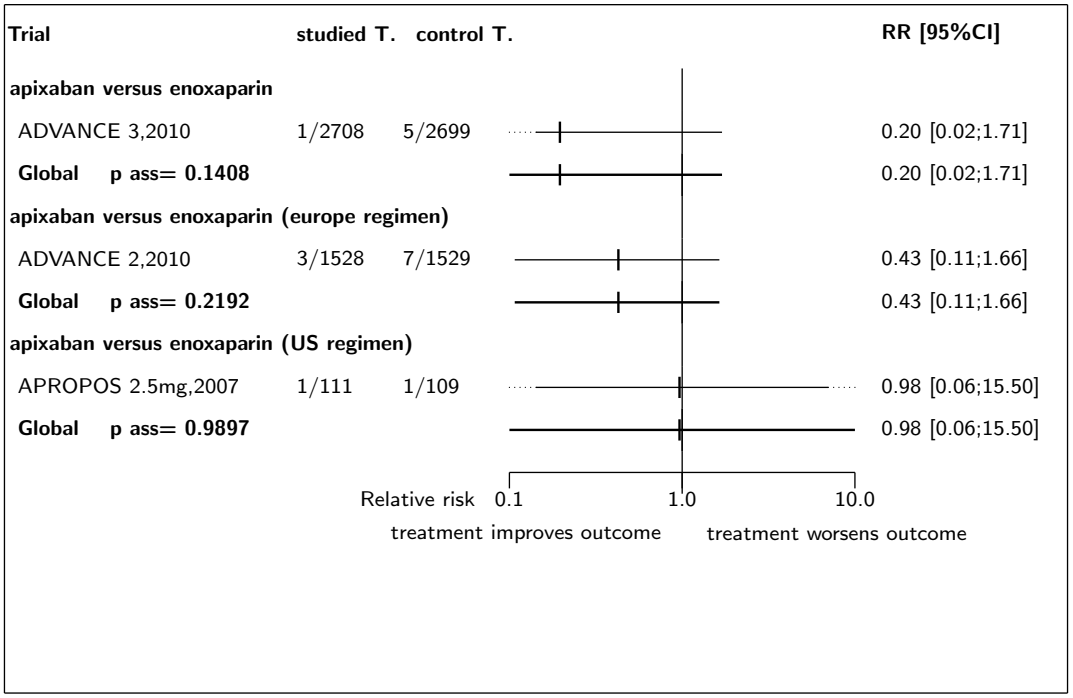


Figure 3.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

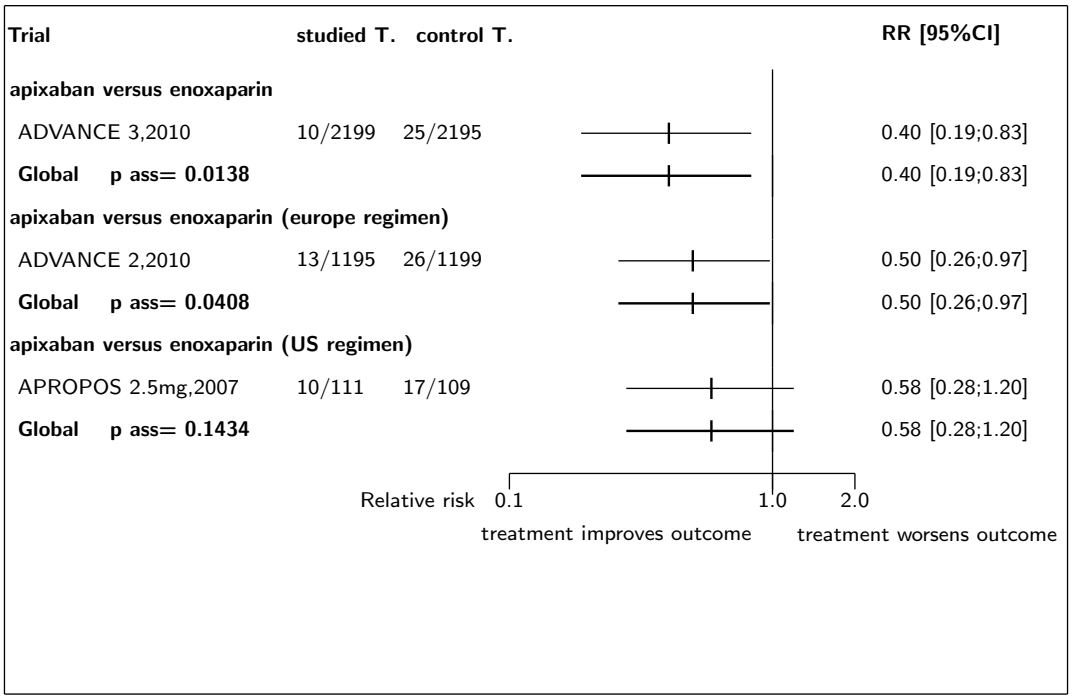


Figure 3.3: *Forest's plot for deep vein thrombosis*

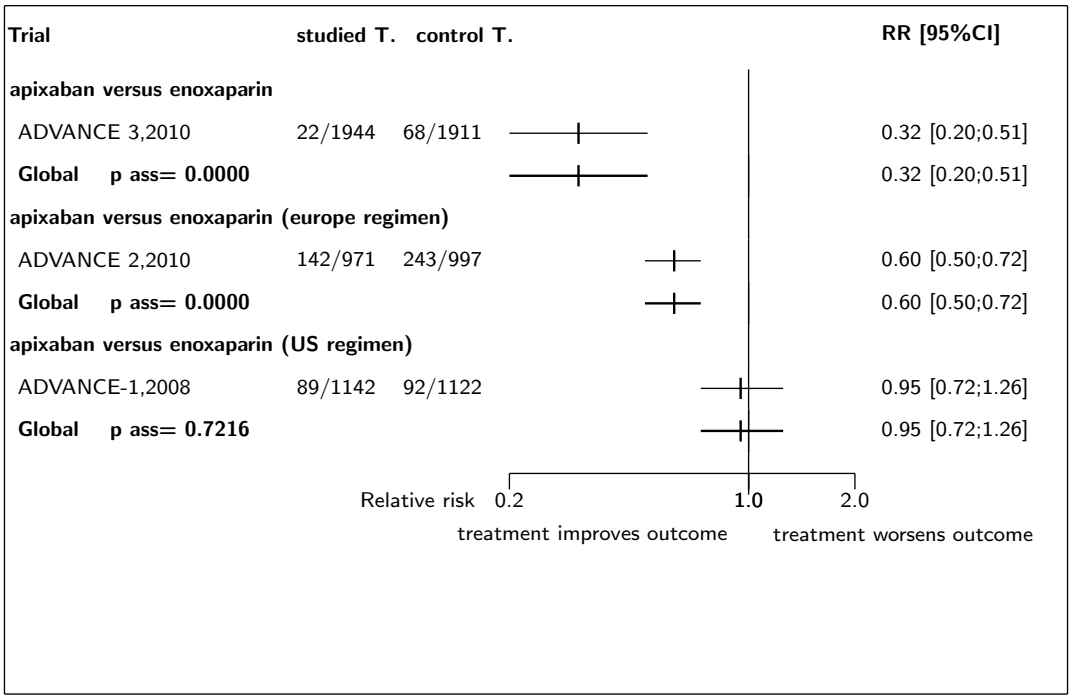


Figure 3.4: *Forest's plot for any bleedings*

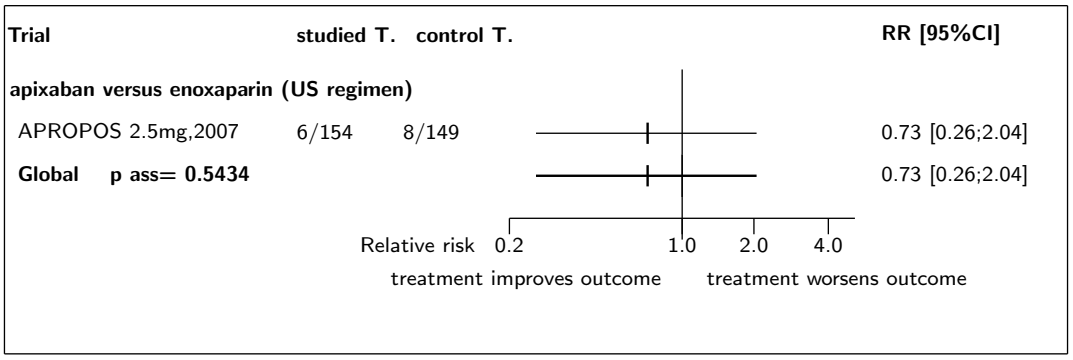


Figure 3.5: *Forest's plot for total VTE and all-cause mortality*

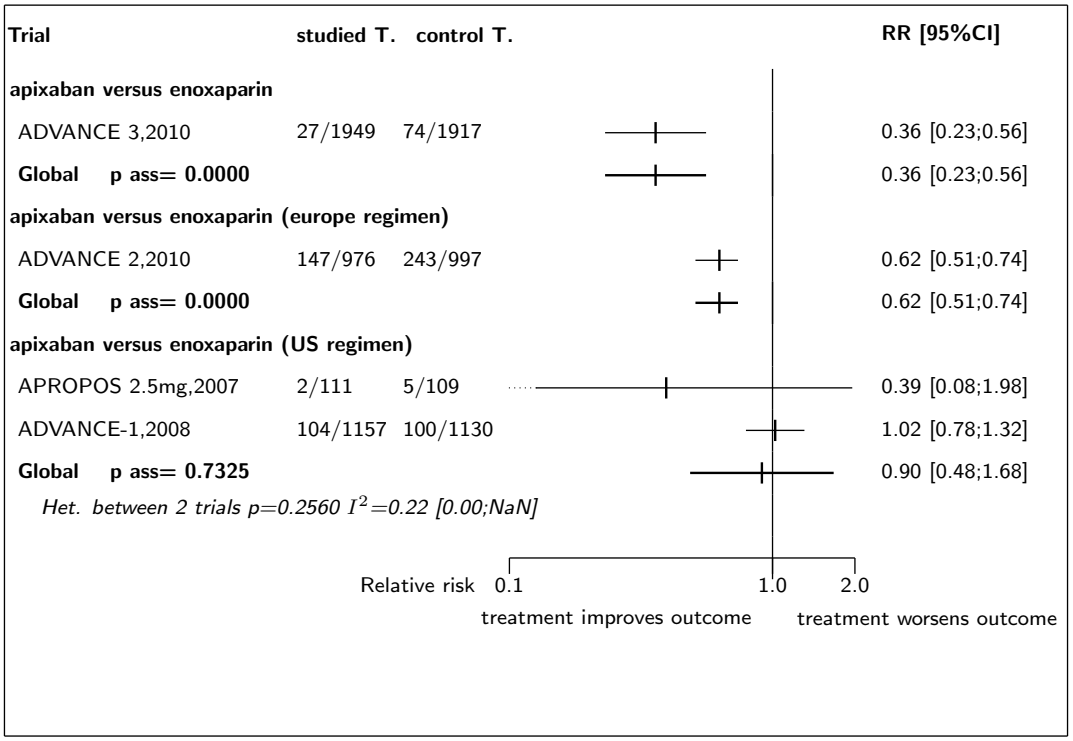


Figure 3.6: *Forest's plot for asymptomatic DVT*

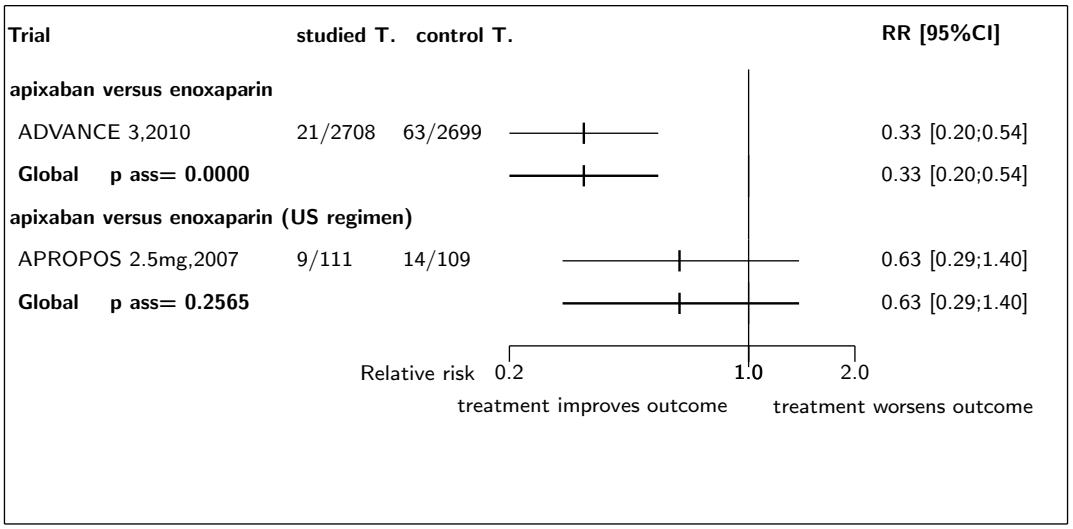


Figure 3.7: *Forest's plot for non-fatal pulmonary embolism*

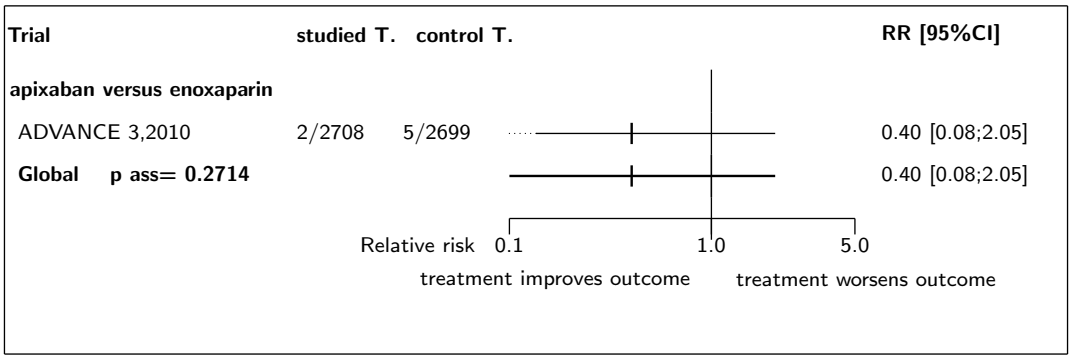


Figure 3.8: *Forest's plot for proximal DVT*

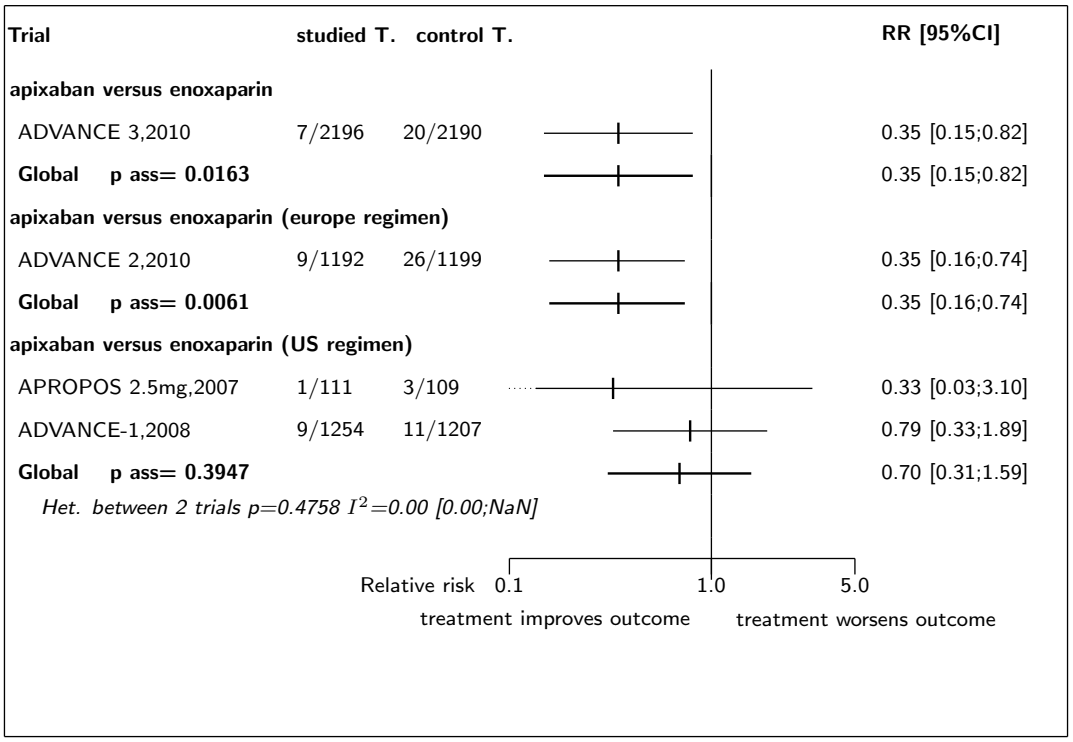


Figure 3.9: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

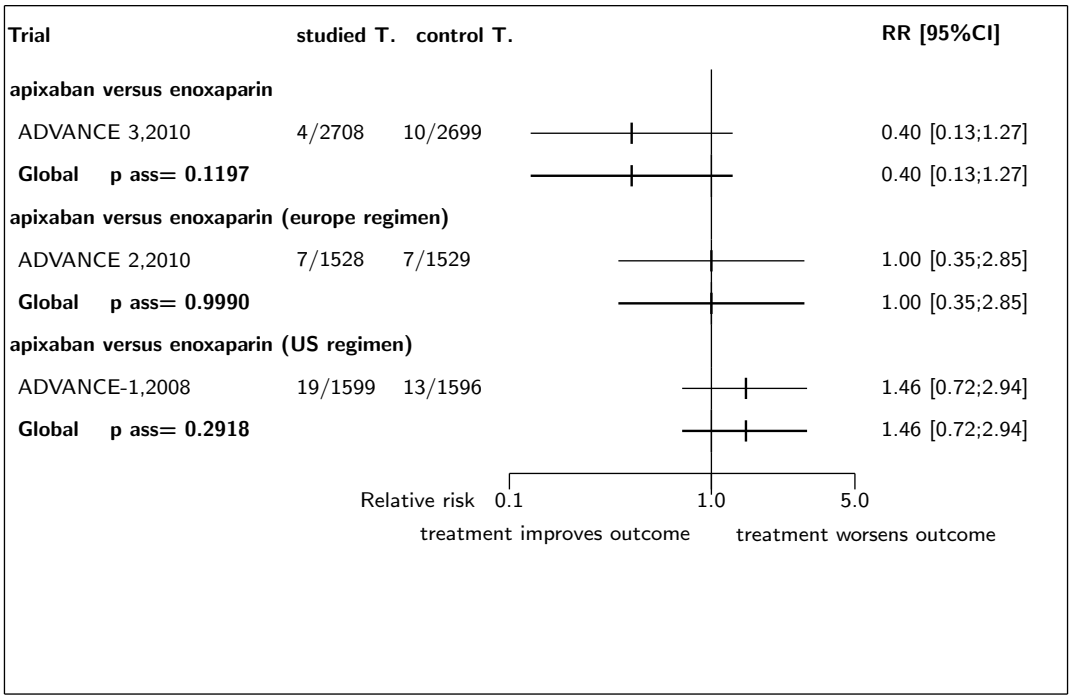


Figure 3.10: *Forest's plot for major or clinically relevant non-major bleeding*

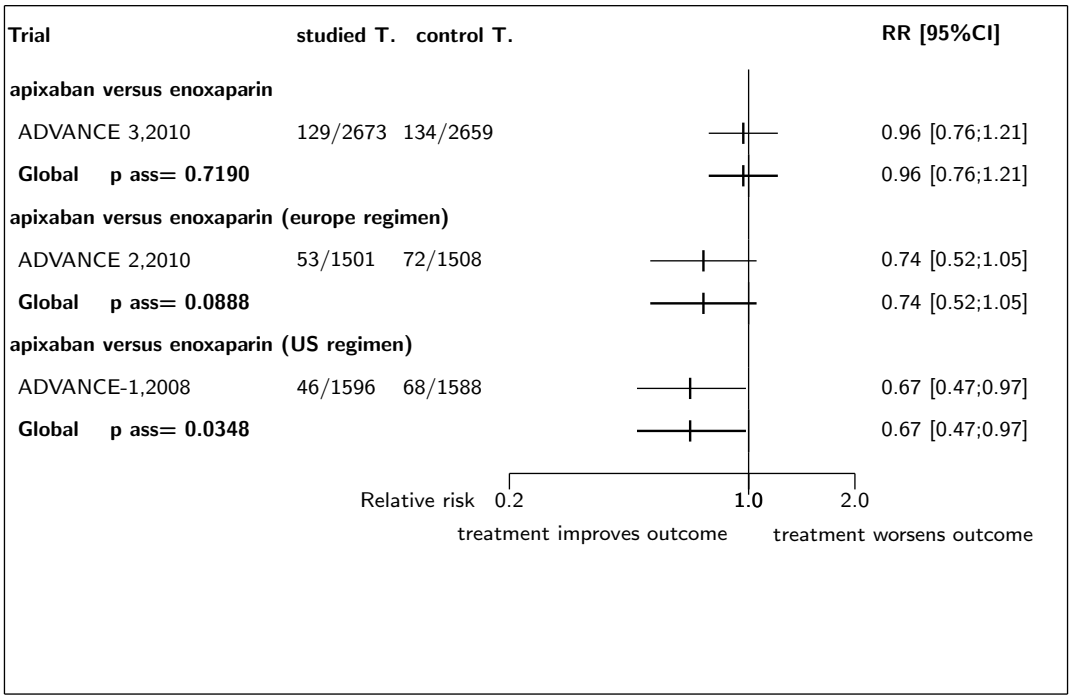


Figure 3.11: *Forest's plot for all cause death*

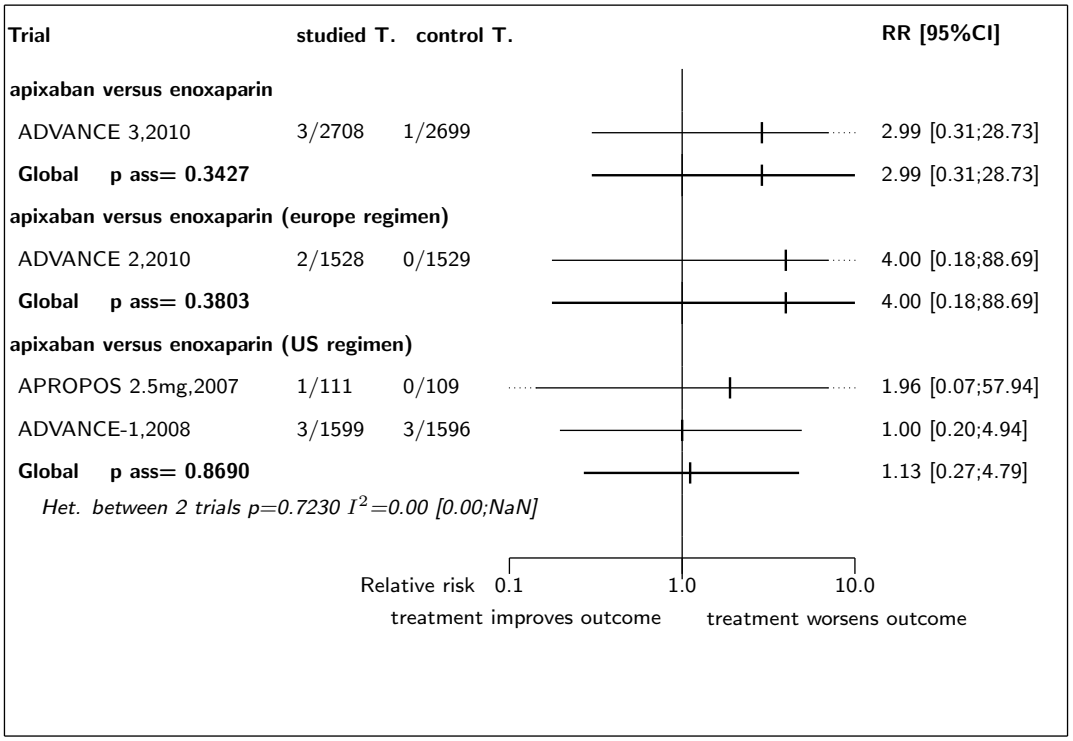
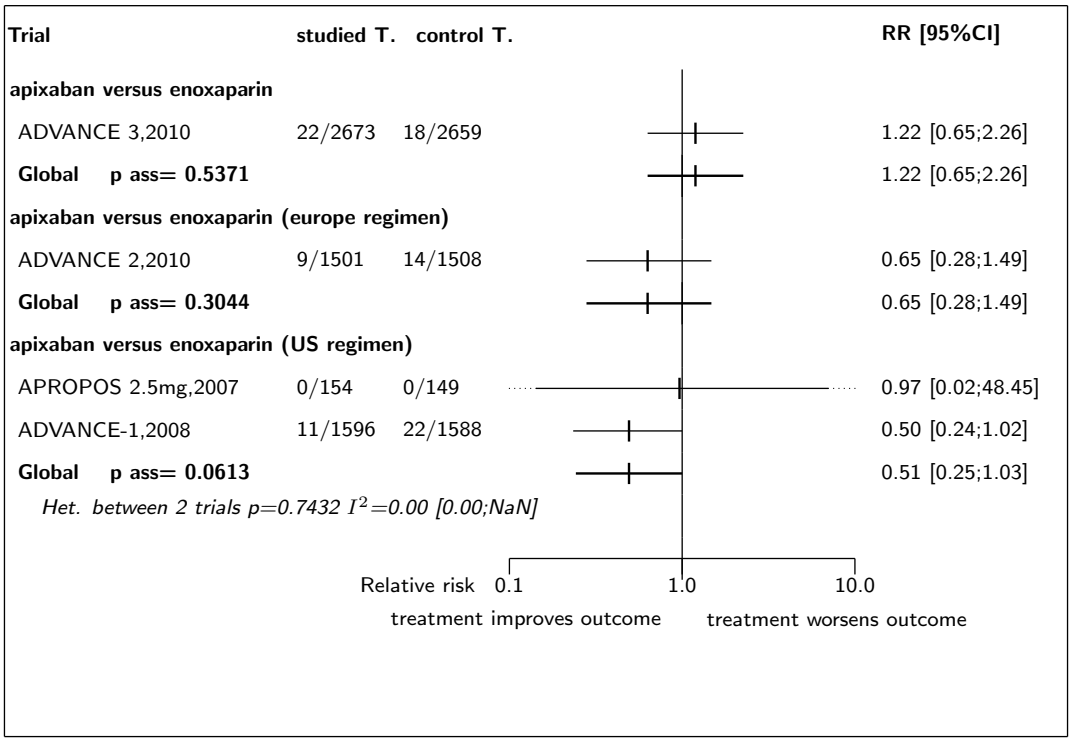


Figure 3.12: *Forest's plot for major bleeding*



References

[1] Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement. N Engl J Med 2010;363:2487-2498. [PMID=21175312]

[2] Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010 Mar 6;375:807-15. [PMID=20206776]

[3] Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost 2007 Dec;5:2368-75. [PMID=17868430]

[4] Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009;361:594-604. [PMID=19657123]

3.3 Individual trial summaries

Table 3.6: *ADVANCE 3, 2010 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=5407 (2708 vs. 2699) **Follow-up duration:** 35 days (+60) **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 21 countries, 160 centres **Inclusion period:** mar 2007 - may 2009	Patients undergoing elective total hip replacement surgery **Inclusion criteria:** scheduled to undergoelective total hip replacement or revision ofa previously inserted hip prosthesis **Exclusion criteria:** active bleeding; contraindication to anticoagulant prophylaxis; need for ongoing anticoagulant or antiplatelet treatment	**Studied treatment:** apixaban 2.5mg twice daily for 35 days given 12 to 24 hours following surgery **Control treatment:** enoxaparin 40mg once daily for 35 days started the evening before surgery	Symptomatic deep-vein thrombosis RR=0.20 [0.02;1.71] Major VTE (fatal and non fatal DVT,PE) RR=0.40 [0.19;0.83] Deep vein thrombosis RR=0.32 [0.20;0.51] Total VTE and all-cause mortality RR=0.36 [0.23;0.56] Asymptomatic DVT RR=0.33 [0.20;0.54] Non-fatal pulmonary embolism RR=0.40 [0.08;2.05] Proximal DVT RR=0.35 [0.15;0.82] Symptomatic venous thromboembolism (DVT, PE) RR=0.40 [0.13;1.27] (Symptomatic VTE and death from venous thromboembolism) Major or clinically relevant non-major bleeding RR=0.96 [0.76;1.21]

Reference
Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement. N Engl J Med 2010;363:2487-2498 [PMID=21175312]

Table 3.7: *ADVANCE 2, 2010 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3057 (1528 vs. 1529) **Follow-up duration:** 12 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 27 countries, 125 centres **Inclusion period:** jun 2007 - nov 2008	Patients undergoing elective unilateral or bilateral total knee replacement **Inclusion criteria:** scheduled to have unilateral elective total knee replacement or same-day bilateral knee replacement, including revision **Exclusion criteria:** active bleeding or a contraindication to anticoagulant prophylaxis, or needed continuing anticoagulant or antiplatelet treatment; uncontrolled hypertension; active hepatobiliary disease; impaired renal function; thrombocytopenia, anaemia, heparin allergy; allergy to radiographic contrast dye; other disorders preventing bilateral venography	**Studied treatment:** apixaban 2.5mg twice daily during 12 days started 1224 h after wound closure **Control treatment:** enoxaparin 40mg once daily 12 days started 12 h before surgery **note:** "European" enoxaprin regimen	Symptomatic deep-vein thrombosis RR=0.43 [0.11;1.66] (During intended treatment) Major VTE (fatal and non fatal DVT,PE) RR=0.50 [0.26;0.97] (During intended treatment) Deep vein thrombosis RR=0.60 [0.50;0.72] (During intended treatment) Total VTE and all-cause mortality RR=0.62 [0.51;0.74] Proximal DVT RR=0.35 [0.16;0.74] (symptomatic or asymptomatic) Symptomatic venous thromboembolism (DVT, PE) RR=1.00 [0.35;2.85] (or venous thromboembolism-related death) Major or clinically relevant non-major bleeding RR=0.74 [0.52;1.05]

Reference

Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thrombo-prophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010 Mar 6;375:807-15 [PMID=20206776]

Table 3.8: *APROPOS 2.5mg, 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=305 (153 vs. 152) **Follow-up duration:** 12 days **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial 148 centres **Inclusion period:** oct 2004 - dec 2005	Patients undergoing elective total knee replacement surgery	**Studied treatment:** apixaban 2.5mg BID for 12 days **Control treatment:** enoxaparin 30mg twice daily for 12 days began 1224 h after skin woundclosure, **note:** 8 arms: apixaban 2.5mg BID, 5mg BID, 10mg BID, 5mgQD, 20mg QD for 12 days, enoxaparin 30mg twice daily, warfarin INR 1.8-3.0	Symptomatic deep-vein thrombosis RR=0.98 [0.06;15.50] Major VTE (fatal and non fatal DVT,PE) RR=0.58 [0.28;1.20] (total VTE) Any bleedings RR=0.73 [0.26;2.04] Total VTE and all-cause mortality RR=0.39 [0.08;1.98] (proximal DVT + PE + death) Asymptomatic DVT RR=0.63 [0.29;1.40] Proximal DVT RR=0.33 [0.03;3.10]

Reference

Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost 2007 Dec;5:2368-75 [PMID=17868430]

Table 3.9: *ADVANCE-1, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3195 (1599 vs. 1596) **Follow-up duration:** 10-14 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 14 countries, 129 centres	Patients undergoing knee-replacement surgery **Inclusion criteria:** scheduled to undergo total knee replacement surgery for one or both knees, including revision of a previously inserted artificial joint **Exclusion criteria:** active bleeding or a contraindication to anticoagulant prophylaxis; ongoing anticoagulant or antiplatelet treatment;uncontrolled hypertension, active hepatobiliary disease; clinically significant impairment of renal function, thrombocytopenia; anemia; allergy to heparin, and allergy to radiographic contrast dye or another contraindication to bilateral venography	**Studied treatment:** apixaban 2.5 mg orally twice daily for 10 to 14 days started 12 to 24 hours after surgery and continued for 10 to 14 days **Control treatment:** enoxaparin 30mg subcutaneously every 12 hours for 10-14 days started 12 to 24 hours after surgery and continued for 10 to 14 days	Deep vein thrombosis RR=0.95 [0.72;1.26] (all DVT) Total VTE and all-cause mortality RR=1.02 [0.78;1.32] (Intended treatment period) Proximal DVT RR=0.79 [0.33;1.89] Symptomatic venous thromboembolism (DVT, PE) RR=1.46 [0.72;2.94] (Symptomatic VTE and VTE related death) Major or clinically relevant non-major bleeding RR=0.67 [0.47;0.97]

Reference

Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009;361:594-604 [PMID=19657123]

4 Detailed results for edoxaban

4.1 Available trials

Only one trial which randomized 503 patients was identified: it compared edoxaban with enoxaparin (short duration).
This trial included 503 patients and was published in .
This trial was double blind in design.
It was reported in English language.
Symptomatic deep-vein thrombosis data was reported in 1 trials; 1 trials reported data on major VTE (fatal and non fatal DVT,PE); 1 trials reported data on distal DVT; 1 trials reported data on asymptomatic DVT; and 1 trials reported data on proximal DVT.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of edoxaban.

Table 4.1: *Treatment description - direct factor Xa inhibitors - edoxaban*

Trial	Studied treatment	Control treatment
Edoxaban versus enoxaparin (short duration)		
STARS J-V (0)	edoxaban 30 mg once daily for 11 to 14 days initiated 6-24 hours after surgery	subcutaneous enoxaparin 2,000 IU, equivalent to 20 mg, twice daily (BID) for 11 to 14 days initiated 24-36 hours after surgery (Japanese standard)

Table 4.2: *Descriptions of participants - direct factor Xa inhibitors - edoxaban*

Trial	Patients
Edoxaban versus enoxaparin (short duration)	
STARS J-V (0)	Total hip arthroplasty

Table 4.3: *Design and methodological quality of trials - direct factor Xa inhibitors - edoxaban*

Trial	Design	Duration	Centre	Primary endpoint
Edoxaban versus enoxaparin (short duration)				
STARS J-V, 0 n=503	Parallel groups double-blind confirmatory trial at low risk of bias		japan	all DVT,PE

Table 4.4: *Trial characteristics - direct factor Xa inhibitors - edoxaban*

Trial	**mean follow-up**	**test intervalle**
Edoxaban versus enoxaparin (short duration)		
STARS J-V, 0		2-4 (3)

4.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Edoxaban versus enoxaparin (short duration)

The single study eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between edoxaban and enoxaparin (short duration), with a RR of 0.97 (95%CI 0.02 to 48.83, p=0.9889) in favour of edoxaban. In other words, symptomatic deep-vein thrombosis was slightly lower in the edoxaban group , but this was not statistically significant.
The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. The analysis detected a statistically significant difference in favor of edoxaban in major VTE (fatal and non fatal DVT,PE), with a RR of 0.34 (95% CI 0.14 to 0.86, p=0.0219).
The single study eligible for this comparison provided data on **asymptomatic DVT**. The analysis detected a statistically significant difference in favor of edoxaban in asymptomatic DVT, with a RR of 0.38 (95% CI 0.16 to 0.89, p=0.0259).
The single study eligible for this comparison provided data on **distal DVT**. The analysis detected a statistically significant difference in favor of edoxaban in distal DVT, with a RR of 0.36 (95% CI 0.15 to 0.92, p=0.0320).
The single study eligible for this comparison provided data on **proximal DVT**. No statistically significant difference between the groups was found in proximal DVT, with a RR of 0.49 (95% CI 0.04 to 5.33, p=0.5550).

Table 4.5: *Results details - direct factor Xa inhibitors - edoxaban*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
edoxaban versus enoxaparin (short duration)						
symptomatic deep-vein thrombosis	RR=0.97	[0.02;48.83]	0.9889	1.0000 (I^2=0.00)	1	503
major VTE (fatal and non fatal DVT,PE)	RR=0.34	[0.14;0.86]	0.0219	1.0000 (I^2=0.00)	1	503
asymptomatic DVT	RR=0.38	[0.16;0.89]	0.0259	1.0000 (I^2=0.00)	1	503
distal DVT	RR=0.36	[0.15;0.92]	0.0320	1.0000 (I^2=0.00)	1	503
proximal DVT	RR=0.49	[0.04;5.33]	0.5550	1.0000 (I^2=0.00)	1	503

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 4.1: *Forest's plot for symptomatic deep-vein thrombosis*

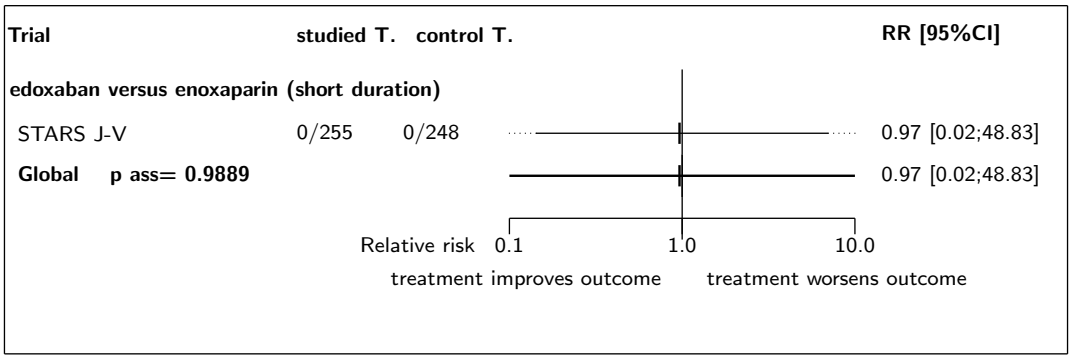


Figure 4.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

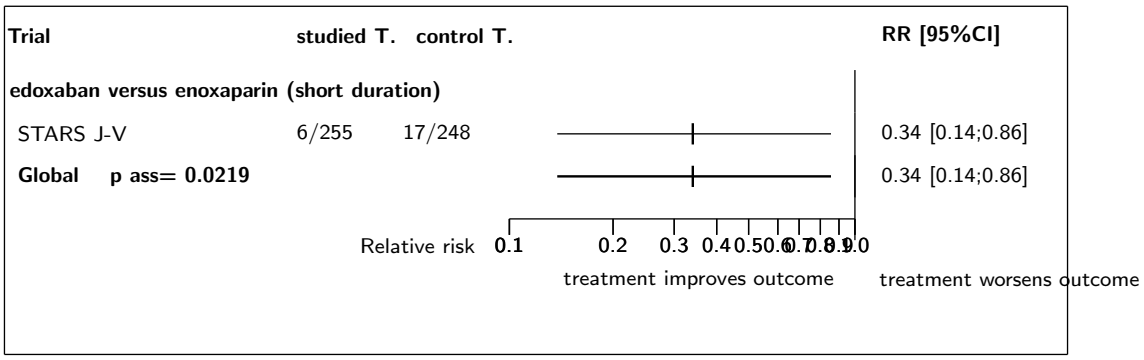


Figure 4.3: *Forest's plot for asymptomatic DVT*

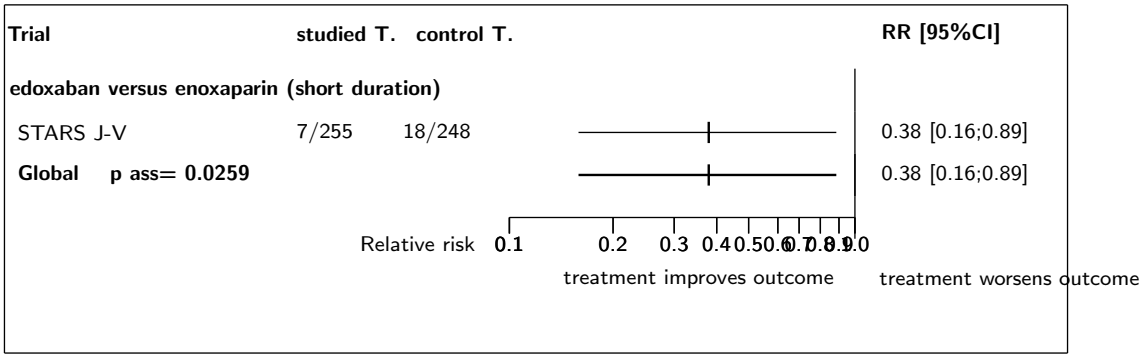


Figure 4.4: *Forest's plot for distal DVT*

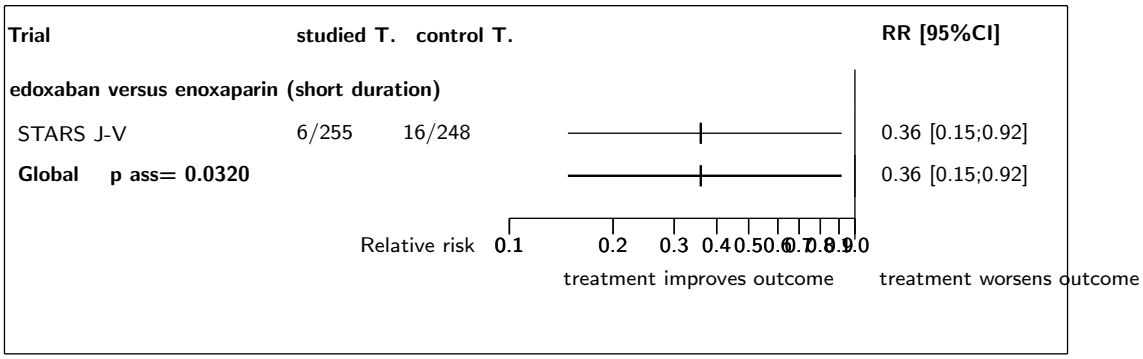
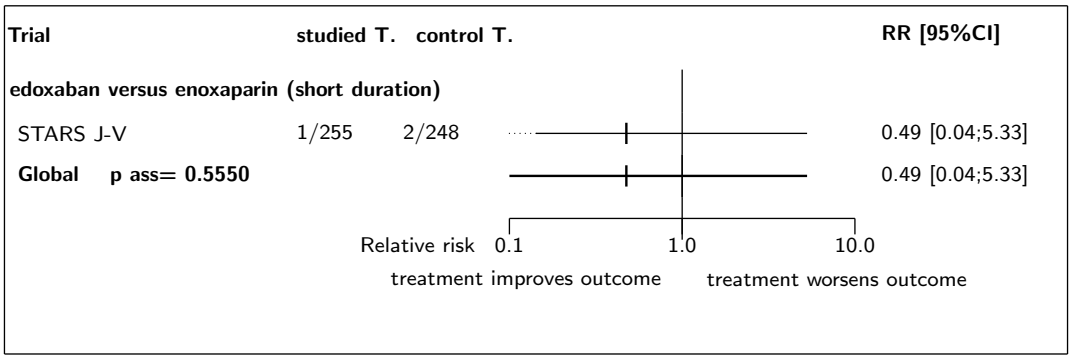


Figure 4.5: *Forest's plot for proximal DVT*



References

4.3 Individual trial summaries

Table 4.6: *STARS J-V, 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=503 (255 vs. 248) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias japan	Total hip arthroplasty	**Studied treatment:** edoxaban 30 mg once daily for 11 to 14 days initiated 6-24 hours after surgery **Control treatment:** subcutaneous enoxaparin 2,000 IU, equivalent to 20 mg, twice daily (BID) for 11 to 14 days initiated 24-36 hours after surgery (Japanese standard)	Major VTE (fatal and non fatal DVT,PE) RR=0.34 [0.14;0.86] (Any VTE) Asymptomatic DVT RR=0.38 [0.16;0.89] (calculated) Distal DVT RR=0.36 [0.15;0.92] (Asymptomatic Distal DVT) Proximal DVT RR=0.49 [0.04;5.33] (Asymptomatic Proximal DVT)
Reference			

5 Detailed results for rivaroxaban

5.1 Available trials

A total of 5 RCTs which randomized 10726 patients were identified: it compared rivaroxaban with enoxaparin , it compared rivaroxaban with enoxaparin (europe regimen) , it compared rivaroxaban with enoxaparin (short duration) and 2 trials compared rivaroxaban with enoxaparin (US regimen).
The average study size was 2145 patients (range 207 to 4541). The first study was published in 2005, and the last study was published in 2009.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Non-fatal pulmonary embolism data was reported in 4 trials; 4 trials reported data on distal DVT; 4 trials reported data on total VTE and all-cause mortality; 4 trials reported data on major bleeding; 4 trials reported data on proximal DVT; 3 trials reported data on all cause death; 3 trials reported data on major VTE (fatal and non fatal DVT,PE); 3 trials reported data on deep vein thrombosis; 3 trials reported data on symptomatic venous thromboembolism (DVT, PE); 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on asymptomatic DVT; and 1 trials reported data on major or clinically relevant non-major bleeding.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of rivaroxaban.

Table 5.1: *Treatment description - direct factor Xa inhibitors - rivaroxaban*

Trial	Studied treatment	Control treatment
Rivaroxaban versus enoxaparin		
RECORD 1 (2008) [**?**]	rivaroxaban 10mg once daily for 35 days started 6 to 8 hours after wound closure	enoxaparin 40mg subcutaneous once daily for 31-39 days initiated 12 hours before surgery and restarted 6 to8 hours after wound closur
Rivaroxaban versus enoxaparin (europe regimen)		
RECORD 3 (2008) [**?**]	rivaroxaban 10 mg once daily for 10- 14 days beginning 6 to 8 hours after surgery	enoxaparin 40 mg subcutaneous once daily for 10-14 days beginning 12hours before surgery
Rivaroxaban versus enoxaparin (short duration)		
ODIXa-HIP 10mg (2006) [**?**, **?**] [a]	rivaroxaban 10mg daily for 59 days initiated 6 to 8 hours after surgery	once-daily subcutaneous enoxaparin dose of 40 mg for 59 days started on the evening before surgery and at least 6 to 8 hours after wound closure in accordance with European practice
Rivaroxaban versus enoxaparin (US regimen)		
ODIXa-KNEE (2005) [**?**] [a]	BAY 59-7939 5mg b.i.d. for 59 days initiated 6-8 h postsurgery	enoxaparin 30 mg b.i.d. for 59 days initiated 12-24 h postsurgery
RECORD 4 (2009) [**?**]	rivaroxaban 10mg once daily for 10 to 14 days starting six to eight hours postsurgery	enoxaparin 30 mg twice daily by subcutaneous injection for 10-14 days started 12 to 24 hours postsurgery

a) dose finding study (doses of 5, 10, 20, 30, or 40 mg) a) dose ranging study with doses 2.5, 5, 10, 20, and 30 mg

Table 5.2: *Descriptions of participants - direct factor Xa inhibitors - rivaroxaban*

Trial	Patients	
Rivaroxaban versus enoxaparin		
RECORD 1 (2008) [?]	Patients undergoing total hip arthroplasty	
	Inclusion criteria: men and women of at least 18 years of age; scheduled to undergo elective total hip arthroplasty	**Exclusion criteria:** staged, bilateral hip arthroplasty; pregnant or breastfeeding; active bleeding or high risk of bleeding;contraindication for prophylaxis with enoxaparin or condition requiring an adjusted dose of enoxaparin; conditions preventing bilateral venography; substantial liver disease; severe renal impairment ; concomitant use of protease inhibitors for the treatment of human immunodeficiency virus infection; planned intermittent pneumatic compression; requirement for anticoagulant therapy that could not be stopped
Rivaroxaban versus enoxaparin (europe regimen)		
RECORD 3 (2008) [?]	Patients undergoing total knee arthroplasty	
	Inclusion criteria: 18 years of age or older; scheduled for total knee arthroplasty	**Exclusion criteria:** active bleeding or a high risk of bleeding that contraindicated the use of low-molecular-weight heparin; any contraindication to the use of enoxaparin; or necessitating adjustment of its dose;conditions preventing bilateral venography, clinically significant liver disease, concomitant use of protease inhibitors of the human immunodeficiency virus or fibrinolytic agents; planned intermittent pneumatic compression; requirement of ongoing anticoagulant therapy; pregnancy or breast-feeding
Rivaroxaban versus enoxaparin (short duration)		
ODIXa-HIP 10mg (2006) [?, ?]	Patients undergoing elective total hip replacement	
Rivaroxaban versus enoxaparin (US regimen)		
ODIXa-KNEE (2005) [?]	Patients undergoing elective total knee replacement	
RECORD 4 (2009) [?]	Patients who had undergone total-knee-replacement surgery	
	Inclusion criteria: aged 18 years or older and were scheduled for total knee arthroplasty	**Exclusion criteria:** active bleeding or a high risk of bleeding; any disorder contraindicating the use of enoxaparin or that might necessitate enoxaparin dose adjustment; disorders preventing bilateral venography; clinically signifi cant liver disease, severe renal impairment (creatinine clearance <30 mL per min); concomitant use of drugs that strongly inhibit cytochrome P450, such as protease inhibitors or ketoconazole; pregnancy; breastfeeding; planned intermittent pneumatic compression; requirement for ongoing anticoagulant therapy

Table 5.3: *Design and methodological quality of trials - direct factor Xa inhibitors - rivaroxaban*

Trial	Design	Duration	Centre	Primary endpoint
Rivaroxaban versus enoxaparin				
RECORD 1, 2008 [?] n=4541	Parallel groups double blind confirmatory trial at low risk of bias	36 days (range 30-42) inclusion period: Feb 2006 - March 2007	27 countries worldwide multicentre	DVT, PE, death
Rivaroxaban versus enoxaparin (europe regimen)				
RECORD 3, 2008 [?] n=2531	Parallel groups double blind confirmatory trial at low risk of bias	13-17 days inclusion period: Feb 2006 - nov 2006	19 countries worldwide 147 centers	DVT, PE all cause mortality
Rivaroxaban versus enoxaparin (short duration)				
ODIXa-HIP 10mg, 2006 [?, ?] n=299	Parallel groups double blind exploratory trial	5-9 days inclusion period: Nov 2007 - Jul 2007	Europe, Israel 48 centres	any DVT, PE, all cause death
Rivaroxaban versus enoxaparin (US regimen)				
ODIXa-KNEE, 2005 [?] n=207	Parallel groups double blind exploratory trial	5-9 days inclusion period: Feb 2004 - Nov 2004	North America 43 centres	
RECORD 4, 2009 [?] n=3148	Parallel groups double blind confirmatory trial at low risk of bias	40 days inclusion period: Jun 2006 - oct 2007	12 countries 131 centres	total VTE events

Table 5.4: *Trial characteristics - direct factor Xa inhibitors - rivaroxaban*

Trial	mean follow-up	test intervalle
Rivaroxaban versus enoxaparin		
RECORD 1, 2008 [?]	46 days	2-4 (3)
Rivaroxaban versus enoxaparin (europe regimen)		
RECORD 3, 2008 [?]	15 days	2-4 (3)
Rivaroxaban versus enoxaparin (short duration)		
ODIXa-HIP 10mg, 2006 [?, ?]	7 days	2-4 (3)
Rivaroxaban versus enoxaparin (US regimen)		
ODIXa-KNEE, 2005 [?]	7 days	2-4 (3)
RECORD 4, 2009 [?]	40 days	2-4 (3)

5.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Rivaroxaban versus enoxaparin

The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. The analysis detected a statistically significant difference in favor of rivaroxaban in major VTE (fatal and non fatal DVT,PE), with a RR of 0.12 (95% CI 0.04 to 0.34, p=0.0000).
The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of rivaroxaban in deep vein thrombosis, with a RR of 0.23 (95% CI 0.12 to 0.43, p=0.0000).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of rivaroxaban in total VTE and all-cause mortality, with a RR of 0.30 (95% CI 0.18 to 0.51, p=0.0000).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 3.91 (95% CI 0.44 to 34.92, p=0.2226).
The single study eligible for this comparison provided data on **distal DVT**. No statistically significant difference between the groups was found in distal DVT, with a RR of 0.49 (95% CI 0.24 to 1.00, p=0.0512).
The single study eligible for this comparison provided data on **proximal DVT**. The analysis detected a statistically significant difference in favor of rivaroxaban in proximal DVT, with a RR of 0.03 (95% CI 0.00 to 0.23, p=0.0000).
The single study eligible for this comparison provided data on **symptomatic venous thromboembolism (DVT, PE)**. No statistically significant difference between the groups was found in symptomatic venous thromboembolism (DVT, PE), with a RR of 0.55 (95% CI 0.20 to 1.48, p=0.2361).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.98 (95% CI 0.24 to 3.90, p=0.9735).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 3.02 (95% CI 0.61 to 14.95, p=0.1755).

Rivaroxaban versus enoxaparin (europe regimen)

The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. The analysis detected a statistically significant difference in favor of rivaroxaban in major VTE (fatal and non fatal DVT,PE), with a RR of 0.38 (95% CI 0.18 to 0.82, p=0.0132).
The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of rivaroxaban in deep vein thrombosis, with a RR of 0.53 (95% CI 0.41 to 0.68, p=0.0000).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of rivaroxaban in total VTE and all-cause mortality, with a RR of 0.51 (95% CI 0.39 to 0.65, p=0.0000).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.27 (95% CI 0.01 to 5.90, p=0.4026).

The single study eligible for this comparison provided data on **distal DVT**. The analysis detected a statistically significant difference in favor of rivaroxaban in distal DVT, with a RR of 0.53 (95% CI 0.41 to 0.70, p=0.0000).
The single study eligible for this comparison provided data on **proximal DVT**. No statistically significant difference between the groups was found in proximal DVT, with a RR of 0.48 (95% CI 0.22 to 1.05, p=0.0651).
The single study eligible for this comparison provided data on **symptomatic venous thromboembolism (DVT, PE)**. The analysis detected a statistically significant difference in favor of rivaroxaban in symptomatic venous thromboembolism (DVT, PE), with a RR of 0.34 (95% CI 0.15 to 0.75, p=0.0075).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.08 (95% CI 0.00 to 1.51, p=0.0930).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 1.19 (95% CI 0.40 to 3.53, p=0.7562).

Rivaroxaban versus enoxaparin (short duration)

The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of rivaroxaban in deep vein thrombosis, with a RR of 0.42 (95% CI 0.22 to 0.79, p=0.0068).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of rivaroxaban in total VTE and all-cause mortality, with a RR of 0.42 (95% CI 0.22 to 0.79, p=0.0068).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.95 (95% CI 0.02 to 47.30, p=0.9782).
The single study eligible for this comparison provided data on **distal DVT**. The analysis detected a statistically significant difference in favor of rivaroxaban in distal DVT, with a RR of 0.36 (95% CI 0.17 to 0.73, p=0.0048).
The single study eligible for this comparison provided data on **proximal DVT**. No statistically significant difference between the groups was found in proximal DVT, with a RR of 0.95 (95% CI 0.20 to 4.59, p=0.9460).

Rivaroxaban versus enoxaparin (US regimen)

Only one of the 2 studies eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between rivaroxaban and enoxaparin (US regimen), with a RR of 0.60 (95%CI 0.22 to 1.63, p=0.3148) in favour of rivaroxaban. In other words, symptomatic deep-vein thrombosis was slightly lower in the rivaroxaban group , but this was not statistically significant.
Only one of the 2 studies eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. No statistically significant difference between the groups was found in major VTE (fatal and non fatal DVT,PE), with a RR of 0.59 (95% CI 0.30 to 1.16, p=0.1234).
Only one of the 2 studies eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of rivaroxaban in total VTE and all-cause mortality, with a RR of 0.69 (95% CI 0.51 to 0.92, p=0.0134).
Only one of the 2 studies eligible for this comparison provided data on **asymptomatic DVT**. No statistically significant difference between the groups was found in asymptomatic DVT, with a RR of 0.72 (95% CI 0.51 to 1.01, p=0.0540).
Only one of the 2 studies eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.49 (95% CI 0.15 to 1.64, p=0.2488).

Only one of the 2 studies eligible for this comparison provided data on **distal DVT**. No statistically significant difference between the groups was found in distal DVT, with a RR of 0.82 (95% CI 0.57 to 1.17, p=0.2756).
Only one of the 2 studies eligible for this comparison provided data on **proximal DVT**. The analysis detected a statistically significant difference in favor of rivaroxaban in proximal DVT, with a RR of 0.23 (95% CI 0.07 to 0.80, p=0.0212).
Only one of the 2 studies eligible for this comparison provided data on **symptomatic venous thromboembolism (DVT, PE)**. No statistically significant difference between the groups was found in symptomatic venous thromboembolism (DVT, PE), with a RR of 0.60 (95% CI 0.29 to 1.27, p=0.1856).
Only one of the 2 studies eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.66 (95% CI 0.11 to 3.94, p=0.6473).
All the 2 studies had extractable data about the number of participants with **major bleeding**. When pooled together, there was no statistically significant difference between the groups in major bleeding, with a RR of 1.27 (95% CI 0.17 to 9.63, p=0.8179). No heterogeneity was detected (p = 0.1769, I^2 = 0.45%).

Table 5.5: *Results details - direct factor Xa inhibitors - rivaroxaban*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
rivaroxaban versus enoxaparin						
major VTE (fatal and non fatal DVT,PE)	RR=0.12	[0.04;0.34]	0.0000	1.0000 (I^2=0.00)	1	3364
deep vein thrombosis	RR=0.23	[0.12;0.43]	0.0000	1.0000 (I^2=0.00)	1	4433
total VTE and all-cause mortality	RR=0.30	[0.18;0.51]	0.0000	1.0000 (I^2=0.00)	1	3153
non-fatal pulmonary embolism	RR=3.91	[0.44;34.92]	0.2226	1.0000 (I^2=0.00)	1	3153
distal DVT	RR=0.49	[0.24;1.00]	0.0512	1.0000 (I^2=0.00)	1	3153
proximal DVT	RR=0.03	[0.00;0.23]	0.0000	1.0000 (I^2=0.00)	1	3153
symptomatic venous thromboembolism (DVT, PE)	RR=0.55	[0.20;1.48]	0.2361	1.0000 (I^2=0.00)	1	4399
all cause death	RR=0.98	[0.24;3.90]	0.9735	1.0000 (I^2=0.00)	1	3153
major bleeding	RR=3.02	[0.61;14.95]	0.1755	1.0000 (I^2=0.00)	1	4433
rivaroxaban versus enoxaparin (europe regimen)						
major VTE (fatal and non fatal DVT,PE)	RR=0.38	[0.18;0.82]	0.0132	1.0000 (I^2=0.00)	1	1833
deep vein thrombosis	RR=0.53	[0.41;0.68]	0.0000	1.0000 (I^2=0.00)	1	1702
total VTE and all-cause mortality	RR=0.51	[0.39;0.65]	0.0000	1.0000 (I^2=0.00)	1	1702
non-fatal pulmonary embolism	RR=0.27	[0.01;5.90]	0.4026	1.0000 (I^2=0.00)	1	1702
distal DVT	RR=0.53	[0.41;0.70]	0.0000	1.0000 (I^2=0.00)	1	1702
proximal DVT	RR=0.48	[0.22;1.05]	0.0651	1.0000 (I^2=0.00)	1	1702
symptomatic venous thromboembolism (DVT, PE)	RR=0.34	[0.15;0.75]	0.0075	1.0000 (I^2=0.00)	1	2418
all cause death	RR=0.08	[0.00;1.51]	0.0930	1.0000 (I^2=1.00)	1	2418
major bleeding	RR=1.19	[0.40;3.53]	0.7562	1.0000 (I^2=0.00)	1	2531
rivaroxaban versus enoxaparin (short duration)						

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
deep vein thrombosis	RR=0.42	[0.22;0.79]	0.0068	1.0000 (I^2=1.00)	1	220
total VTE and all-cause mortality	RR=0.42	[0.22;0.79]	0.0068	1.0000 (I^2=1.00)	1	220
non-fatal pulmonary embolism	RR=0.95	[0.02;47.30]	0.9782	1.0000 (I^2=0.00)	1	220
distal DVT	RR=0.36	[0.17;0.73]	0.0048	1.0000 (I^2=0.00)	1	220
proximal DVT	RR=0.95	[0.20;4.59]	0.9460	1.0000 (I^2=0.00)	1	220
rivaroxaban versus enoxaparin (US regimen)						
symptomatic deep-vein thrombosis	RR=0.60	[0.22;1.63]	0.3148	1.0000 (I^2=0.00)	1	1924
major VTE (fatal and non fatal DVT,PE)	RR=0.59	[0.30;1.16]	0.1234	1.0000 (I^2=0.00)	1	2234
total VTE and all-cause mortality	RR=0.69	[0.51;0.92]	0.0134	1.0000 (I^2=0.00)	1	1924
asymptomatic DVT	RR=0.72	[0.51;1.01]	0.0540	1.0000 (I^2=0.00)	1	1924
non-fatal pulmonary embolism	RR=0.49	[0.15;1.64]	0.2488	1.0000 (I^2=1.00)	1	3034
distal DVT	RR=0.82	[0.57;1.17]	0.2756	1.0000 (I^2=0.00)	1	1924
proximal DVT	RR=0.23	[0.07;0.80]	0.0212	1.0000 (I^2=0.00)	1	1924
symptomatic venous thromboembolism (DVT, PE)	RR=0.60	[0.29;1.27]	0.1856	1.0000 (I^2=0.00)	1	3034
major or clinically relevant non-major bleeding	RR=1.34	[0.86;2.07]	0.1933	1.0000 (I^2=0.00)	1	3034
all cause death	RR=0.66	[0.11;3.94]	0.6473	1.0000 (I^2=0.00)	1	3034
major bleeding	RR=1.27	[0.17;9.63]	0.8179	0.1769 (I^2=0.45)	2	3240

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 5.1: *Forest's plot for symptomatic deep-vein thrombosis*

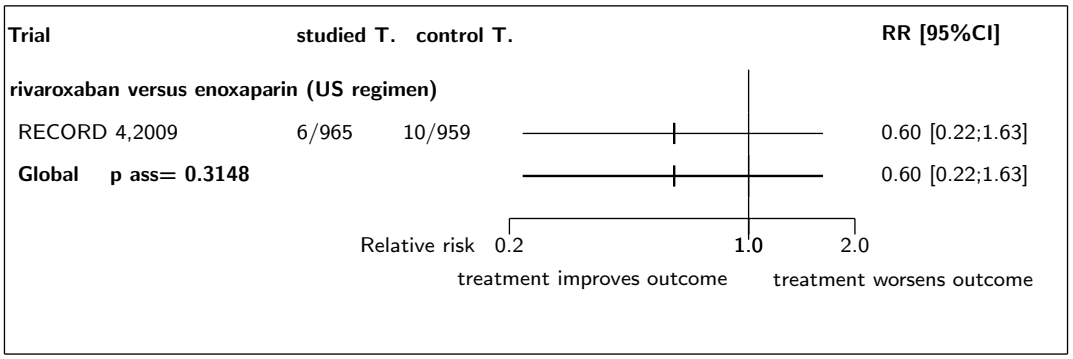


Figure 5.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

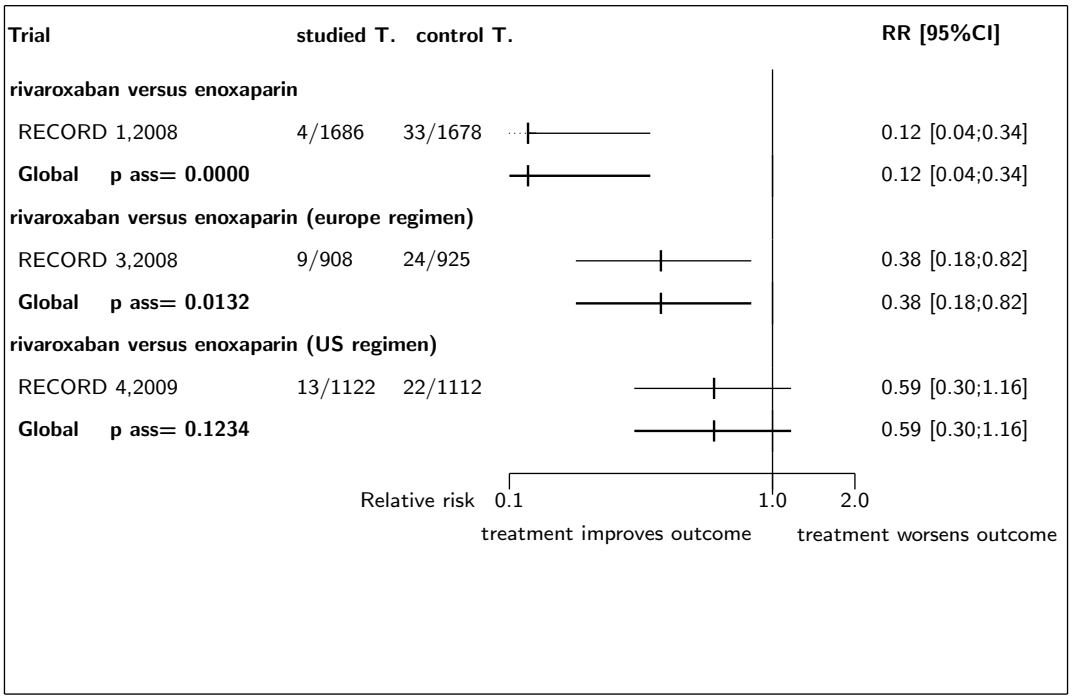


Figure 5.3: *Forest's plot for deep vein thrombosis*

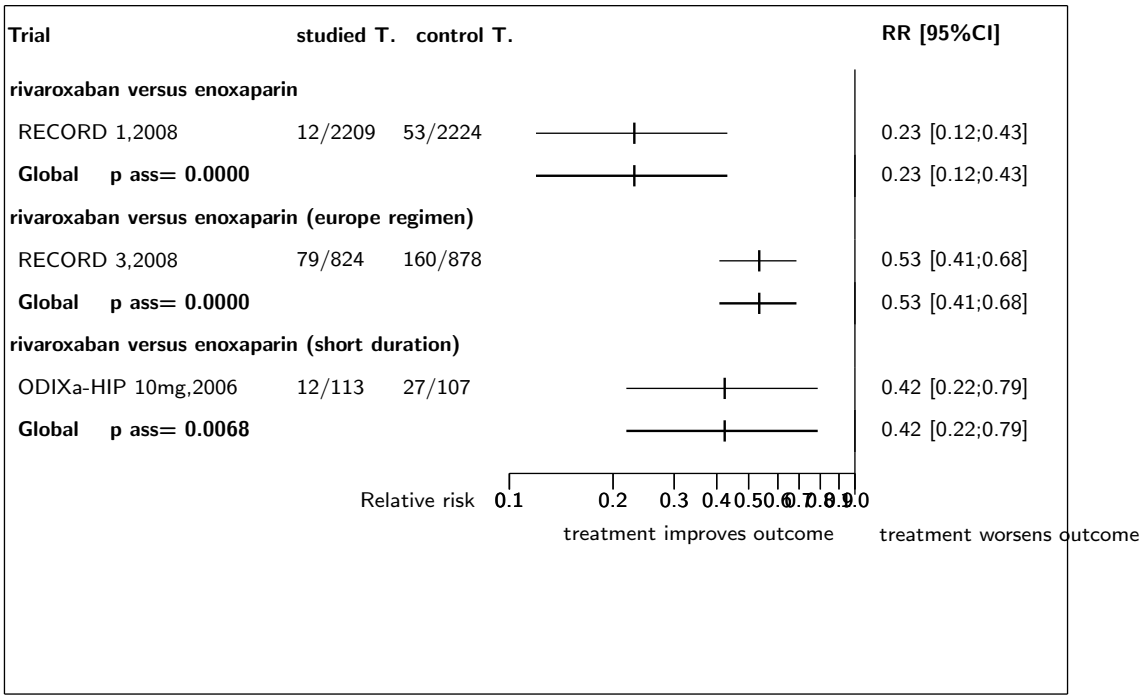


Figure 5.4: *Forest's plot for total VTE and all-cause mortality*

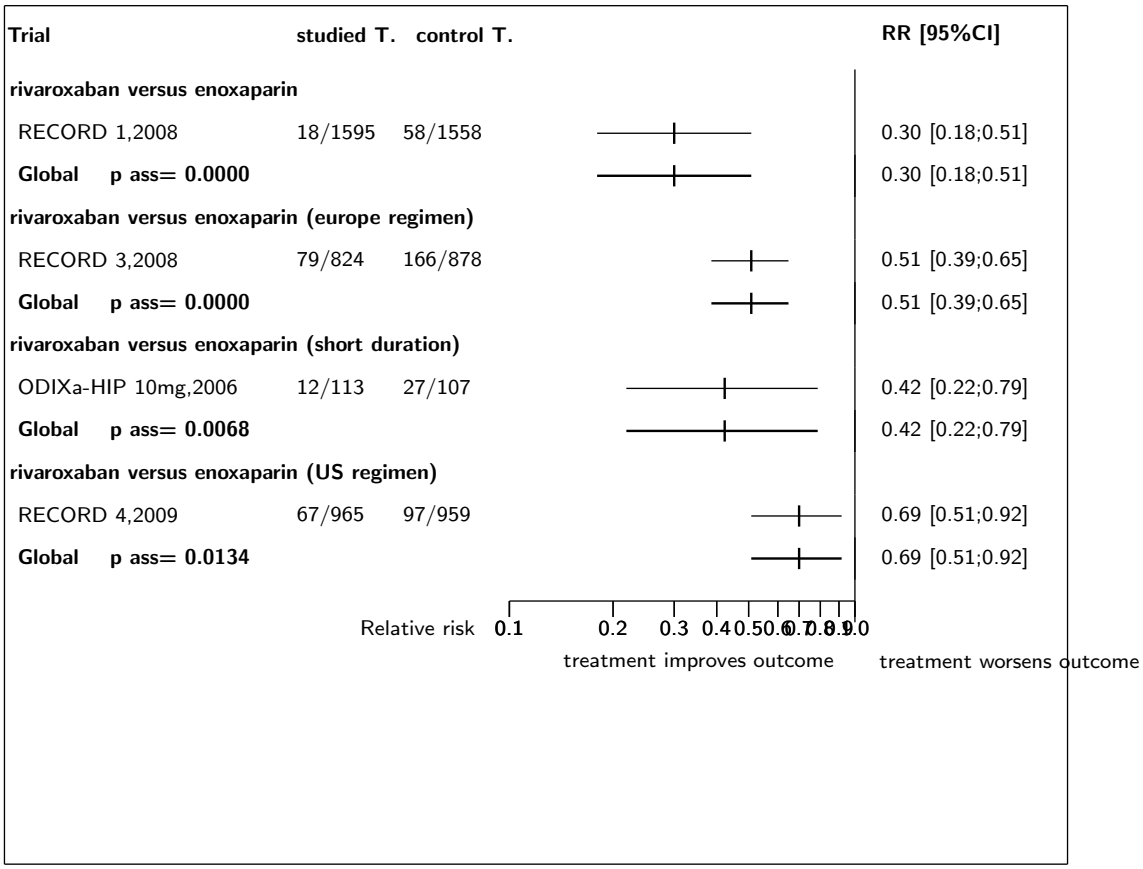


Figure 5.5: *Forest's plot for asymptomatic DVT*

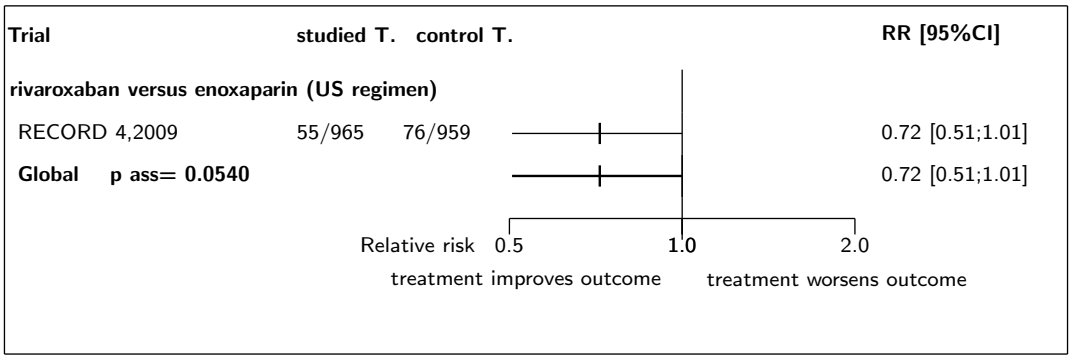


Figure 5.6: *Forest's plot for non-fatal pulmonary embolism*

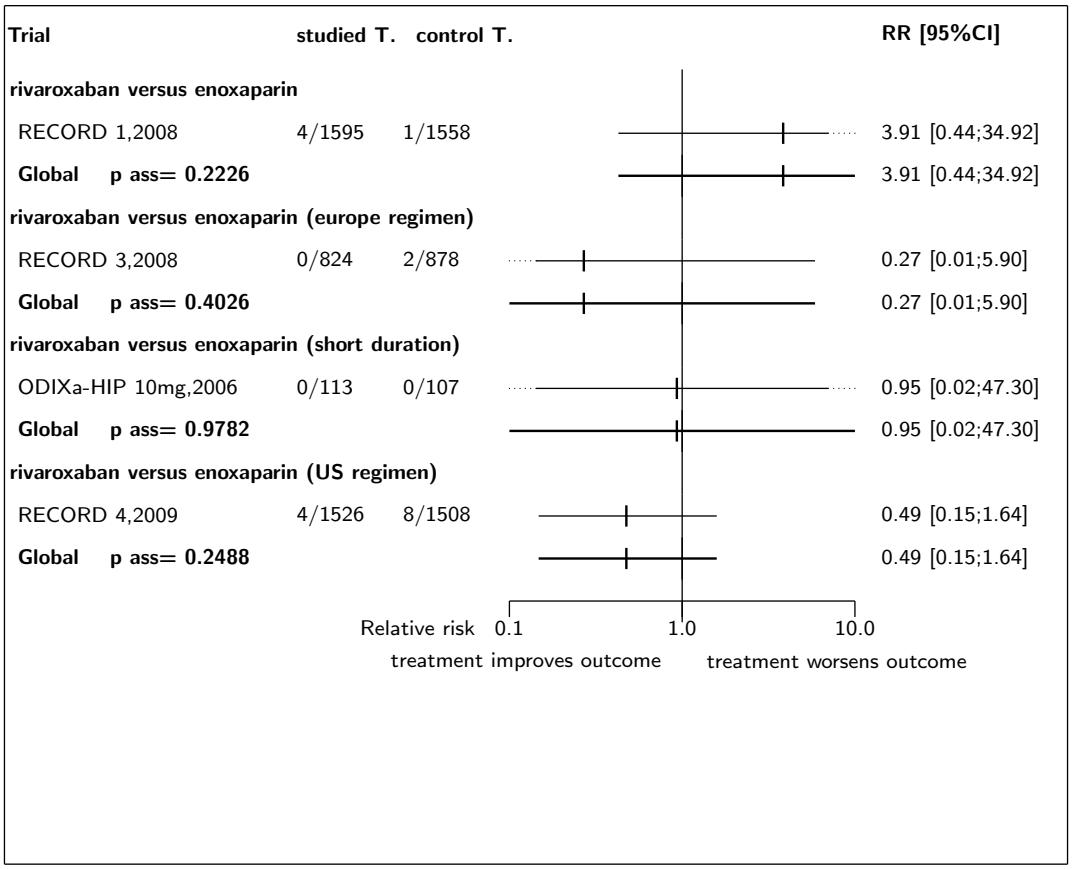


Figure 5.7: *Forest's plot for distal DVT*

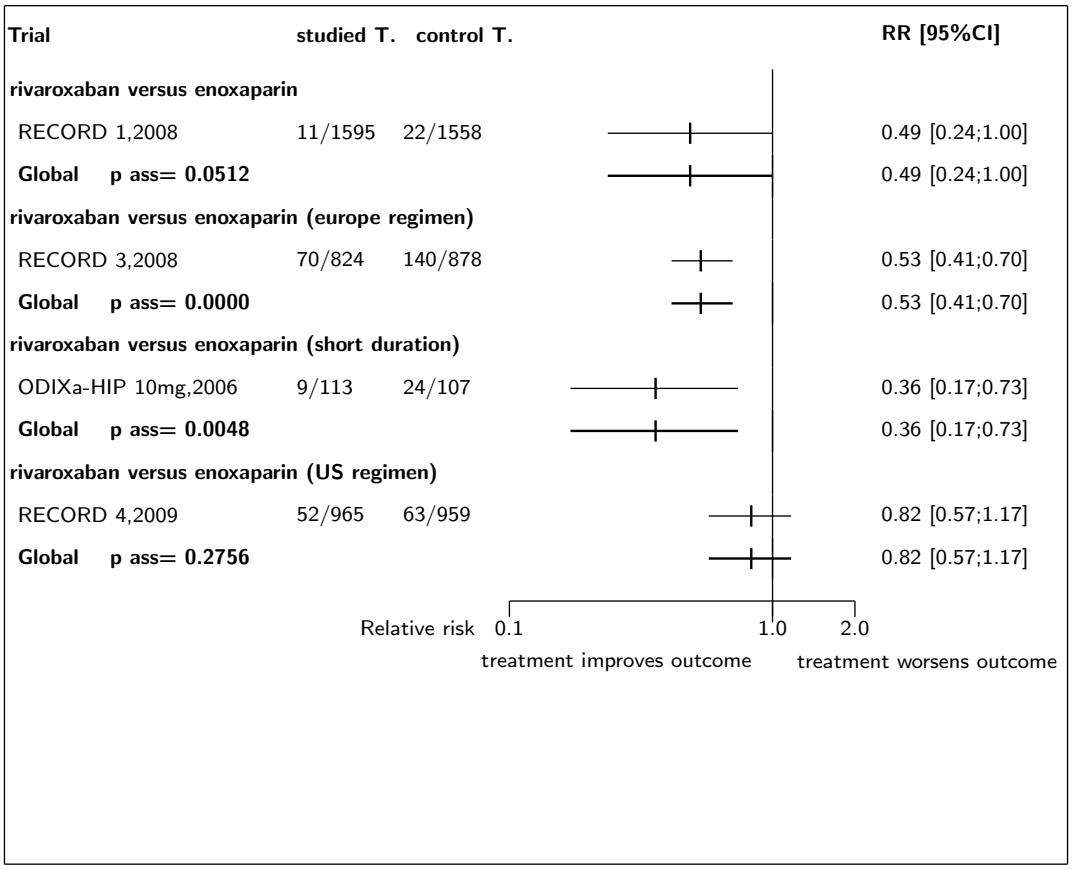


Figure 5.8: *Forest's plot for proximal DVT*

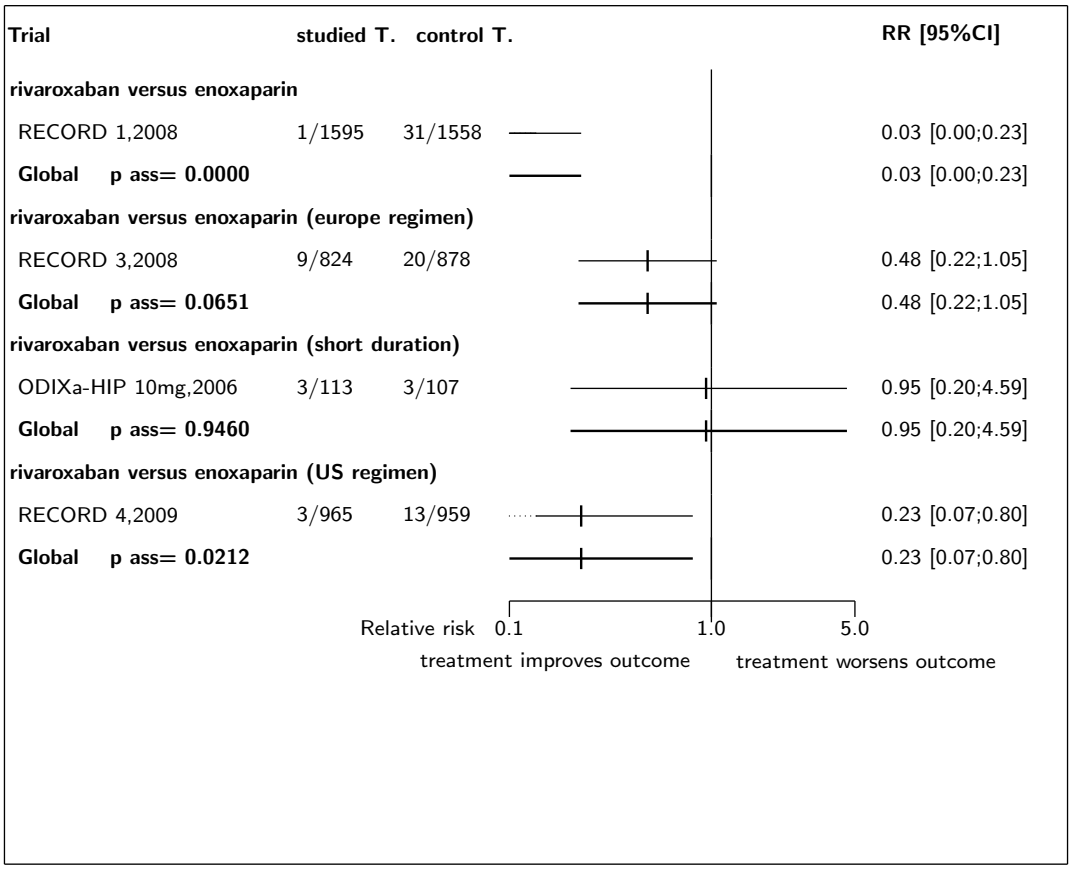


Figure 5.9: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

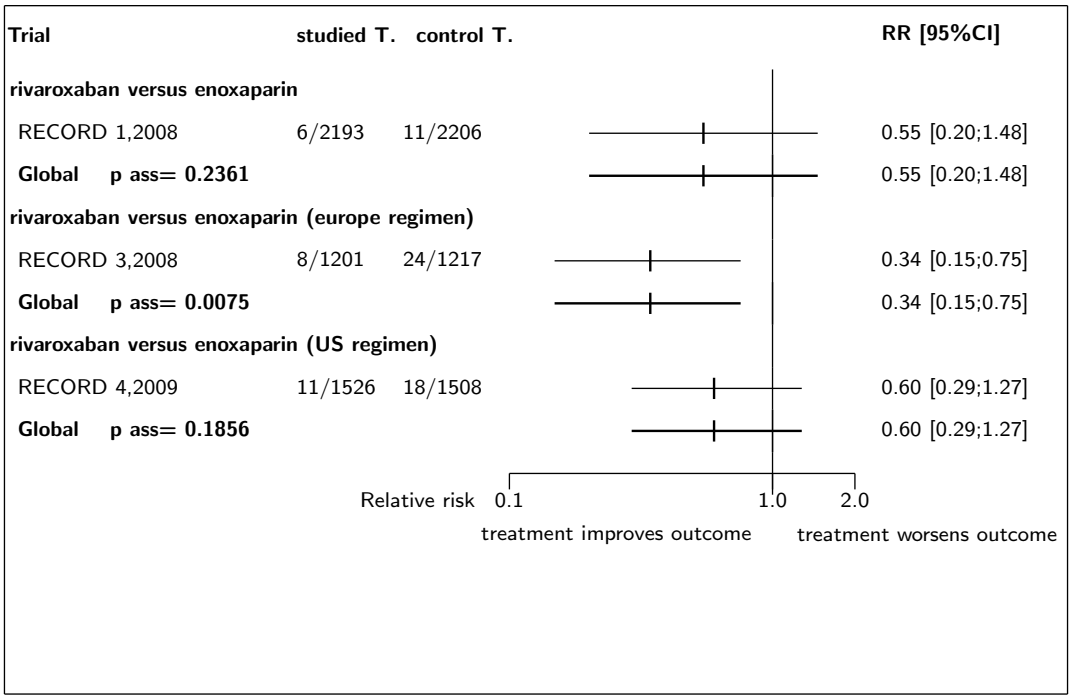


Figure 5.10: *Forest's plot for major or clinically relevant non-major bleeding*

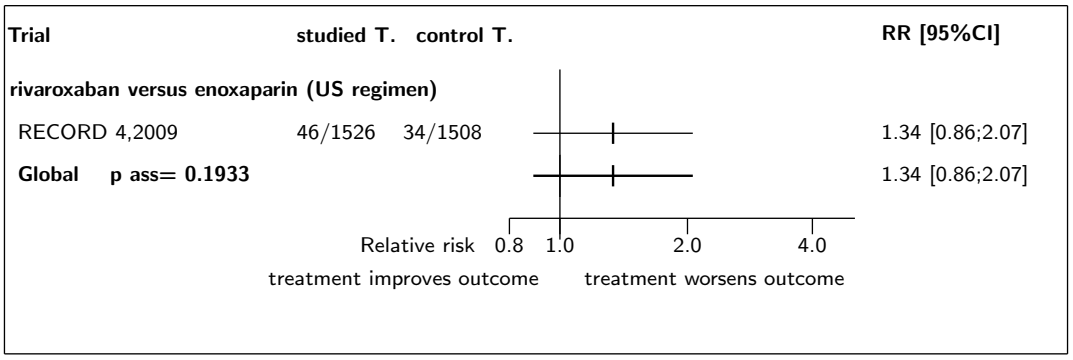


Figure 5.11: *Forest's plot for all cause death*

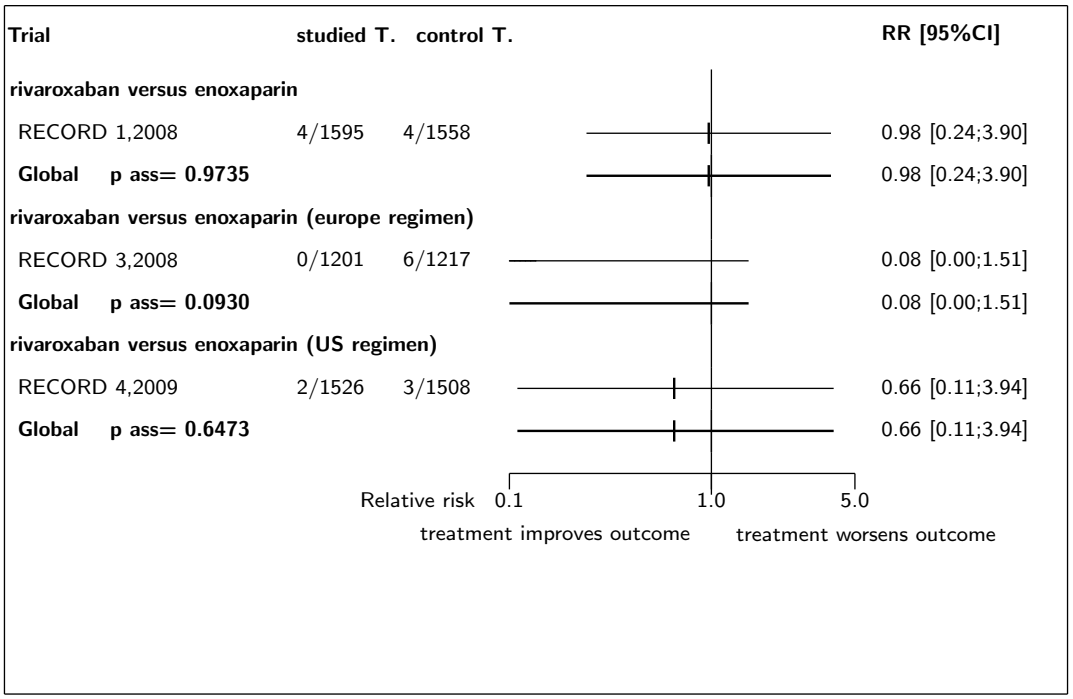
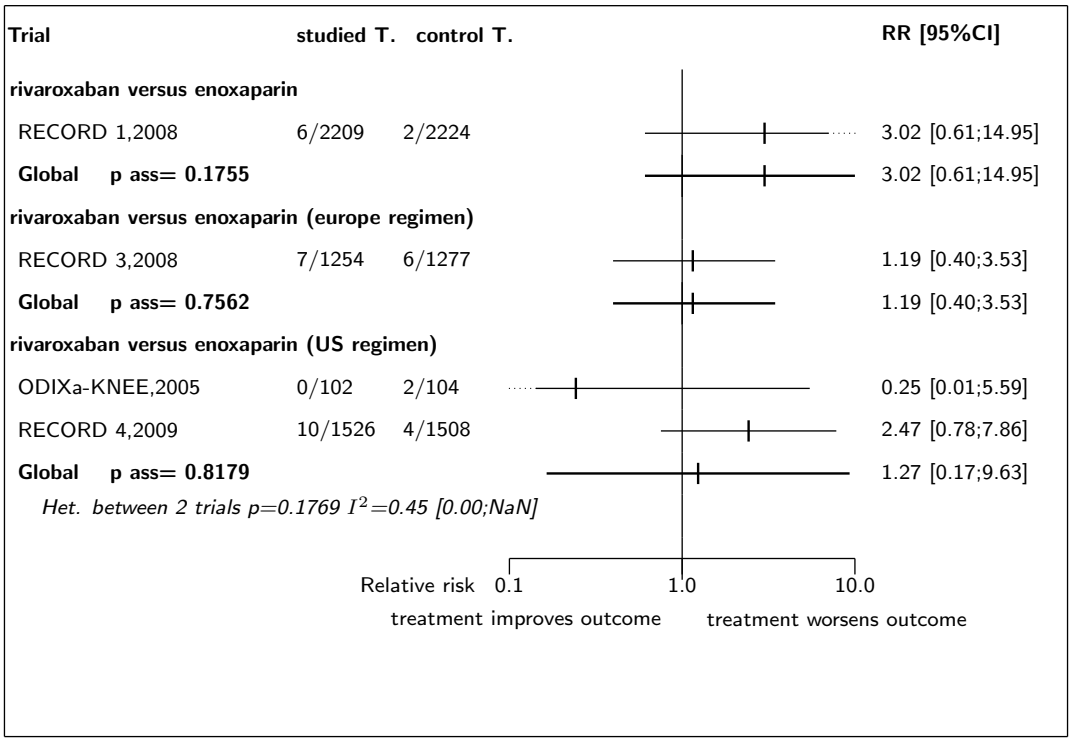


Figure 5.12: *Forest's plot for major bleeding*



References

[1] Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-75. [PMID=18579811]

[2] Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008 Jun 26;358:2776-86. [PMID=18579812]

[3] Eriksson BI, Borris L, Dahl OE, Haas S, Huisman MV, Kakkar AK, Misselwitz F, Klebo P. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost 2006 Jan;4:121-8. [PMID=16409461]

[4] Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Muehlhofer E, Dierig C, Misselwitz F, Klebo P. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006 Nov 28;114:2374-81. [PMID=17116766]

[5] Turpie AG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Klebo P, Misselwitz F, Gent M. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. J Thromb Haemost 2005 Nov;3:2479-86. [PMID=16241946]

[6] Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009 May 16;373:1673-80. [PMID=19411100]

5.3 Individual trial summaries

Table 5.6: *RECORD 1, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4541 (2266 vs. 2275) **Follow-up duration:** 36 days (range 30-42) **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 27 countries worldwide, multicentre **Inclusion period:** Feb 2006 - March 2007	Patients undergoing total hip arthroplasty **Inclusion criteria:** men and women of at least 18 years of age; scheduled to undergo elective total hip arthroplasty **Exclusion criteria:** staged, bilateral hip arthroplasty; pregnant or breastfeeding; active bleeding or high risk of bleeding;contraindication for prophylaxis with enoxaparin or condition requiring an adjusted dose of enoxaparin; conditions preventing bilateral venography; substantial liver disease; severe renal impairment ; concomitant use of protease inhibitors for the treatment of human immunodeficiency virus infection; planned intermittent pneumatic compression; requirement for anticoagulant therapy that could not be stopped	**Studied treatment:** rivaroxaban 10mg once daily for 35 days started 6 to 8 hours after wound closure **Control treatment:** enoxaparin 40mg subcutaneous once daily for 31-39 days initiated 12 hours before surgery and restarted 6 to8 hours after wound closur	Major VTE (fatal and non fatal DVT,PE) RR=0.12 [0.04;0.34] Deep vein thrombosis RR=0.23 [0.12;0.43] Total VTE and all-cause mortality RR=0.30 [0.18;0.51] Non-fatal pulmonary embolism RR=3.91 [0.44;34.92] Distal DVT RR=0.49 [0.24;1.00] Proximal DVT RR=0.03 [0.00;0.23] Symptomatic venous thromboembolism (DVT, PE) RR=0.55 [0.20;1.48] (during treatment)

Reference

Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-75 [PMID=18579811]

Table 5.7: *RECORD 3, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2531 (1254 vs. 1277) **Follow-up duration:** 13-17 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 19 countries worldwide, 147 centers **Inclusion period:** Feb 2006 - nov 2006	Patients undergoing total knee arthroplasty **Inclusion criteria:** 18 years of age or older; scheduled for total knee arthroplasty **Exclusion criteria:** active bleeding or a high risk of bleeding that contraindicated the use of low-molecular-weight heparin; any contraindication to the use of enoxaparin; or necessitating adjustment of its dose;conditions preventing bilateral venography, clinically significant liver disease, concomitant use of protease inhibitors of the human immunodeficiency virus or fibrinolytic agents; planned intermittent pneumatic compression; requirement of ongoing anticoagulant therapy; pregnancy or breast-feeding	**Studied treatment:** rivaroxaban 10 mg once daily for 10- 14 days beginning 6 to 8 hours after surgery **Control treatment:** enoxaparin 40 mg subcutaneous once daily for 10-14 days beginning 12hours before surgery	Major VTE (fatal and non fatal DVT,PE) RR=0.38 [0.18;0.82] Deep vein thrombosis RR=0.53 [0.41;0.68] Total VTE and all-cause mortality RR=0.51 [0.39;0.65] Distal DVT RR=0.53 [0.41;0.70] Proximal DVT RR=0.48 [0.22;1.05] Symptomatic venous thromboembolism (DVT, PE) RR=0.34 [0.15;0.75]

Reference

Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008 Jun 26;358:2776-86 [PMID=18579812]

Table 5.8: *ODIXa-HIP 10mg, 2006 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=299 (142 vs. 157) **Follow-up duration:** 5-9 days **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Europe, Israel, 48 centres **Inclusion period:** Nov 2007 - Jul 2007	Patients undergoing elective total hip replacement	**Studied treatment:** rivaroxaban 10mg daily for 59 days initiated 6 to 8 hours after surgery **Control treatment:** once-daily subcutaneous enoxaparin dose of 40 mg for 59 days started on the evening before surgery and at least 6 to 8 hours after wound closure in accordance with European practice **note:** dose finding study (doses of 5, 10, 20, 30, or 40 mg)	Deep vein thrombosis RR=0.42 [0.22;0.79] Total VTE and all-cause mortality RR=0.42 [0.22;0.79] Distal DVT RR=0.36 [0.17;0.73] Proximal DVT RR=0.95 [0.20;4.59]

References

Eriksson BI, Borris L, Dahl OE, Haas S, Huisman MV, Kakkar AK, Misselwitz F, Klebo P. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost 2006 Jan;4:121-8 [PMID=16409461]

Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Muehlhofer E, Dierig C, Misselwitz F, Klebo P. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006 Nov 28;114:2374-81 [PMID=17116766]

Table 5.9: *ODIXa-KNEE, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=207 (102 vs. 105) **Follow-up duration:** 5-9 days **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial North America, 43 centres **Inclusion period:** Feb 2004 - Nov 2004	Patients undergoing elective total knee replacement	**Studied treatment:** BAY 59-7939 5mg b.i.d. for 59 days initiated 6-8 h postsurgery **Control treatment:** enoxaparin 30 mg b.i.d. for 59 days initiated 12-24 h postsurgery **note:** dose ranging study with doses 2.5, 5, 10, 20, and 30 mg	

Reference

Turpie AG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Klebo P, Misselwitz F, Gent M. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. J Thromb Haemost 2005 Nov;3:2479-86 [PMID=16241946]

Table 5.10: *RECORD 4, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3148 (1584 vs. 1564) **Follow-up duration:** 40 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 12 countries, 131 centres **Inclusion period:** Jun 2006 - oct 2007	Patients who had undergone total-knee-replacement surgery **Inclusion criteria:** aged 18 years or older and were scheduled for total knee arthroplasty **Exclusion criteria:** active bleeding or a high risk of bleeding; any disorder contraindicating the use of enoxaparin or that might necessitate enoxaparin dose adjustment; disorders preventing bilateral venography; clinically signifi cant liver disease, severe renal impairment (creatinine clearance <30 mL per min); concomitant use of drugs that strongly inhibit cytochrome P450, such as protease inhibitors or ketoconazole; pregnancy; breastfeeding; planned intermittent pneumatic compression; requirement for ongoing anticoagulant therapy	**Studied treatment:** rivaroxaban 10mg once daily for 10 to 14 days starting six to eight hours postsurgery **Control treatment:** enoxaparin 30 mg twice daily by subcutaneous injection for 10-14 days started 12 to 24 hours postsurgery	Symptomatic deep-vein thrombosis RR=0.60 [0.22;1.63] Major VTE (fatal and non fatal DVT,PE) RR=0.59 [0.30;1.16] Total VTE and all-cause mortality RR=0.69 [0.51;0.92] Asymptomatic DVT RR=0.72 [0.51;1.01] Non-fatal pulmonary embolism RR=0.49 [0.15;1.64] Distal DVT RR=0.82 [0.57;1.17] Proximal DVT RR=0.23 [0.07;0.80] Symptomatic venous thromboembolism (DVT, PE) RR=0.60 [0.29;1.27] Major or clinically relevant non-major bleeding RR=1.34 [0.86;2.07]

Reference

Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009 May 16;373:1673-80 [PMID=19411100]

6 Detailed results for rivaroxaban (long duration)

6.1 Available trials

Only one trial which randomized 2509 patients was identified: it compared rivaroxaban (long duration) with enoxaparin (short duration).
This trial included 2509 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
Non-fatal pulmonary embolism data was reported in 1 trials; 1 trials reported data on all cause death; 1 trials reported data on deep vein thrombosis; 1 trials reported data on major VTE (fatal and non fatal DVT,PE); 1 trials reported data on distal DVT; 1 trials reported data on total VTE and all-cause mortality; 1 trials reported data on symptomatic venous thromboembolism (DVT, PE); 1 trials reported data on major bleeding; 1 trials reported data on proximal DVT; and 1 trials reported data on major or clinically relevant non-major bleeding.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of rivaroxaban (long duration).

Table 6.1: *Treatment description - direct factor Xa inhibitors - rivaroxaban (long duration)*

Trial	Studied treatment	Control treatment
Rivaroxaban (long duration) versus enoxaparin (short duration)		
RECORD 2 (2008) [**?**]	extended thromboprophylaxis with rivaroxaban 10mg once daily for 31-39 days started6 to 8 hours after wound closure	enoxaparin 40mg subcutaneous once daily for 10-14 days initiated12 h before surgery and restarted 68 h after woundclosure

Table 6.2: *Descriptions of participants - direct factor Xa inhibitors - rivaroxaban (long duration)*

Trial	Patients	
Rivaroxaban (long duration) versus enoxaparin (short duration)		
RECORD 2 (2008) [**?**]	Patients undergoing elective total hip replacement	
	Inclusion criteria: male and female patients aged 18 years or above; patients scheduled for elective total hip replacement	**Exclusion criteria:** planned, staged total bilateral hip replacement Active bleeding or high risk of bleeding contraindicating treatment with low molecular weight heparin; Contraindication listed in the labeling or conditions precluding patient treatment with enoxaparin; conditions prohibiting bilateral venography (e.g. amputation of one leg, allergy to contrast media)

Table 6.3: *Design and methodological quality of trials - direct factor Xa inhibitors - rivaroxaban (long duration)*

Trial	Design	Duration	Centre	Primary endpoint
Rivaroxaban (long duration) versus enoxaparin (short duration)				
RECORD 2, 2008 [?] n=2509	Parallel groups double blind confirmatory trial at low risk of bias	30-42 days inclusion period: Feb 2006 - Apr 2007	21 countries worldwide 123 centres	DVT, PE , all cause death

Table 6.4: *Trial characteristics - direct factor Xa inhibitors - rivaroxaban (long duration)*

Trial	mean follow-up	test intervalle
Rivaroxaban (long duration) versus enoxaparin (short duration)		
RECORD 2, 2008 [?]	36 days	2-4 (3)

6.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Rivaroxaban (long duration) versus enoxaparin (short duration)

The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. The analysis detected a statistically significant difference in favor of rivaroxaban (long duration) in major VTE (fatal and non fatal DVT,PE), with a RR of 0.12 (95% CI 0.05 to 0.28, p=0.0000).
The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of rivaroxaban (long duration) in deep vein thrombosis, with a RR of 0.20 (95% CI 0.11 to 0.35, p=0.0000).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of rivaroxaban (long duration) in total VTE and all-cause mortality, with a RR of 0.21 (95% CI 0.13 to 0.35, p=0.0000).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.25 (95% CI 0.03 to 2.25, p=0.2165).
The single study eligible for this comparison provided data on **distal DVT**. The analysis detected a statistically significant difference in favor of rivaroxaban (long duration) in distal DVT, with a RR of 0.34 (95% CI 0.16 to 0.71, p=0.0042).
The single study eligible for this comparison provided data on **proximal DVT**. The analysis detected a statistically significant difference in favor of rivaroxaban (long duration) in proximal DVT, with a RR of 0.11 (95% CI 0.05 to 0.29, p=0.0000).
The single study eligible for this comparison provided data on **symptomatic venous thromboembolism (DVT, PE)**. The analysis detected a statistically significant difference in favor of rivaroxaban (long duration) in symptomatic venous thromboembolism (DVT, PE), with a RR of 0.20 (95% CI 0.06 to 0.69, p=0.0106).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.34 (95% CI 0.07 to 1.66, p=0.1800).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 1.00 (95% CI 0.06 to 15.98, p=0.9995).

Table 6.5: *Results details - direct factor Xa inhibitors - rivaroxaban (long duration)*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
rivaroxaban (long duration) versus enoxaparin (short duration)						
major VTE (fatal and non fatal DVT,PE)	RR=0.12	[0.05;0.28]	0.0000	1.0000 (I^2=0.00)	1	1923
deep vein thrombosis	RR=0.20	[0.11;0.35]	0.0000	1.0000 (I^2=0.00)	1	1733
total VTE and all-cause mortality	RR=0.21	[0.13;0.35]	0.0000	1.0000 (I^2=0.00)	1	1733
non-fatal pulmonary embolism	RR=0.25	[0.03;2.25]	0.2165	1.0000 (I^2=1.00)	1	1733
distal DVT	RR=0.34	[0.16;0.71]	0.0042	1.0000 (I^2=0.00)	1	1733
proximal DVT	RR=0.11	[0.05;0.29]	0.0000	1.0000 (I^2=0.00)	1	1733

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
symptomatic venous thromboembolism (DVT, PE)	RR=0.20	[0.06;0.69]	0.0106	1.0000 (I^2=1.00)	1	2419
major or clinically relevant non-major bleeding	RR=1.20	[0.93;1.54]	0.1582	1.0000 (I^2=1.00)	1	2457
all cause death	RR=0.34	[0.07;1.66]	0.1800	1.0000 (I^2=1.00)	1	1733
major bleeding	RR=1.00	[0.06;15.98]	0.9995	1.0000 (I^2=0.00)	1	2457

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 6.1: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

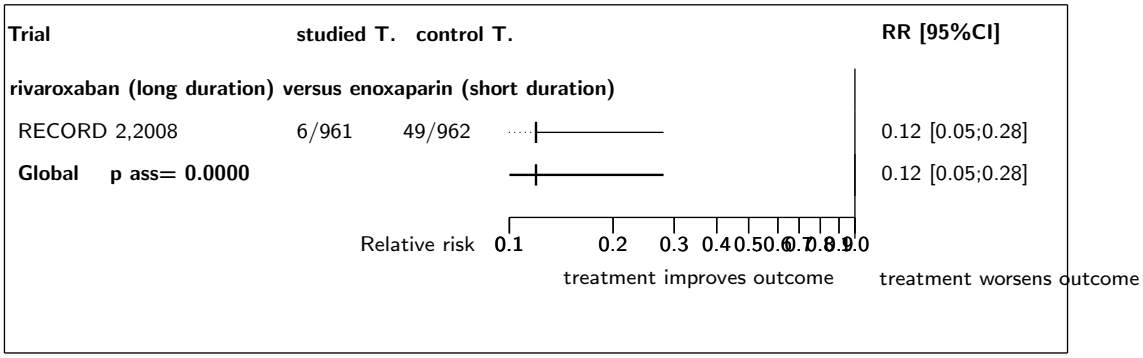


Figure 6.2: *Forest's plot for deep vein thrombosis*

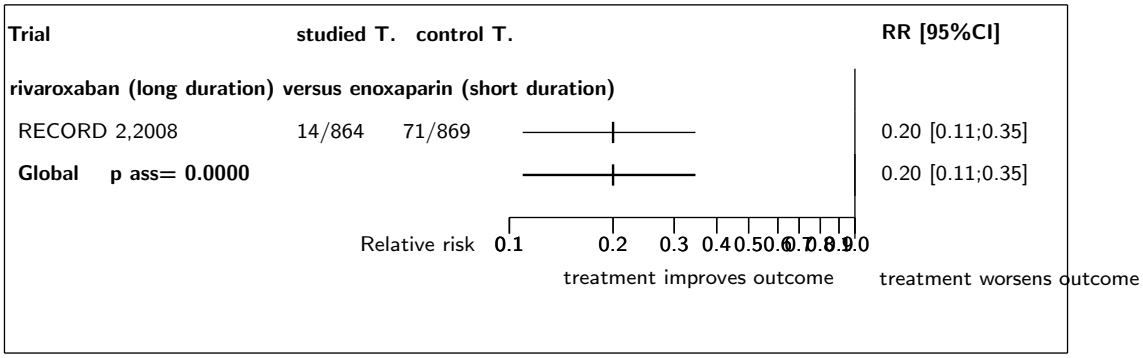


Figure 6.3: *Forest's plot for total VTE and all-cause mortality*

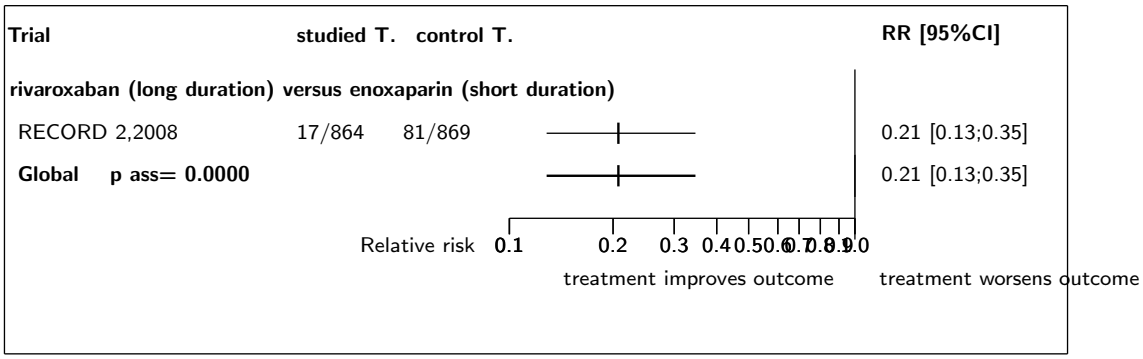


Figure 6.4: *Forest's plot for non-fatal pulmonary embolism*

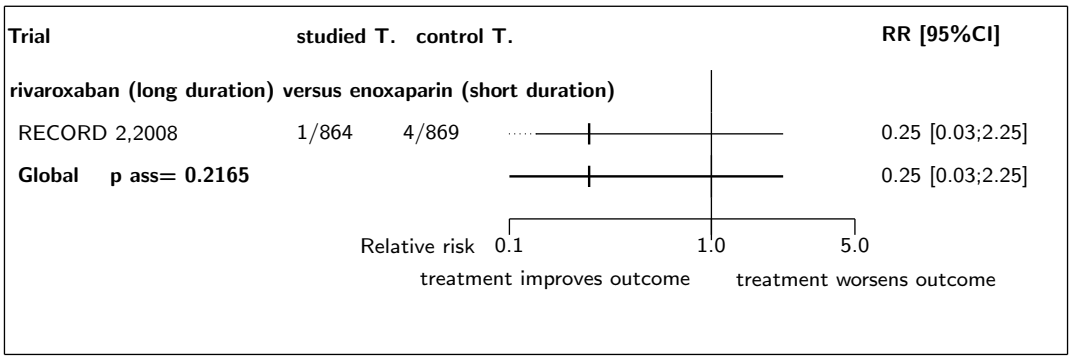


Figure 6.5: *Forest's plot for distal DVT*

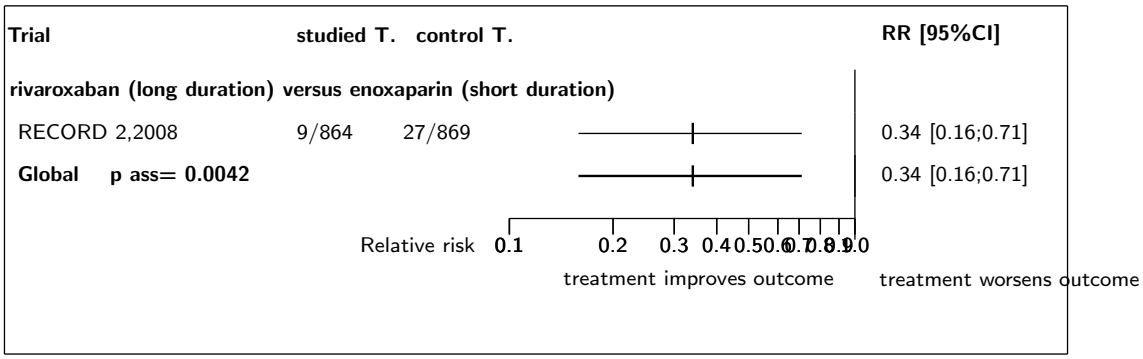


Figure 6.6: *Forest's plot for proximal DVT*

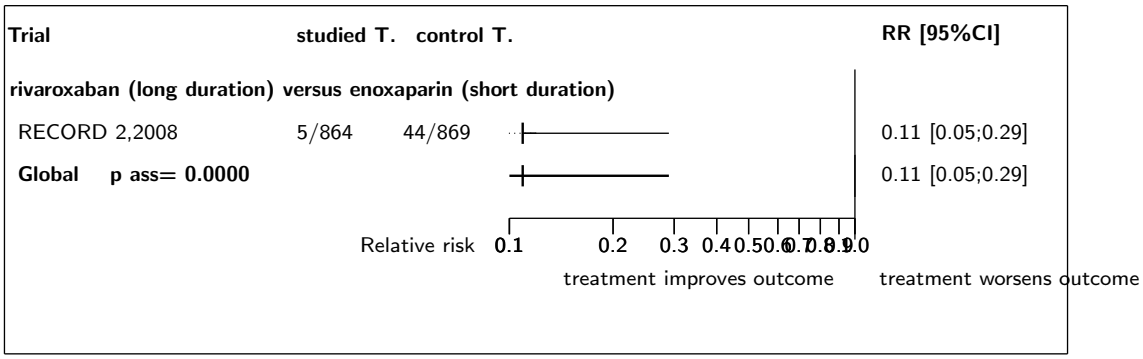


Figure 6.7: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

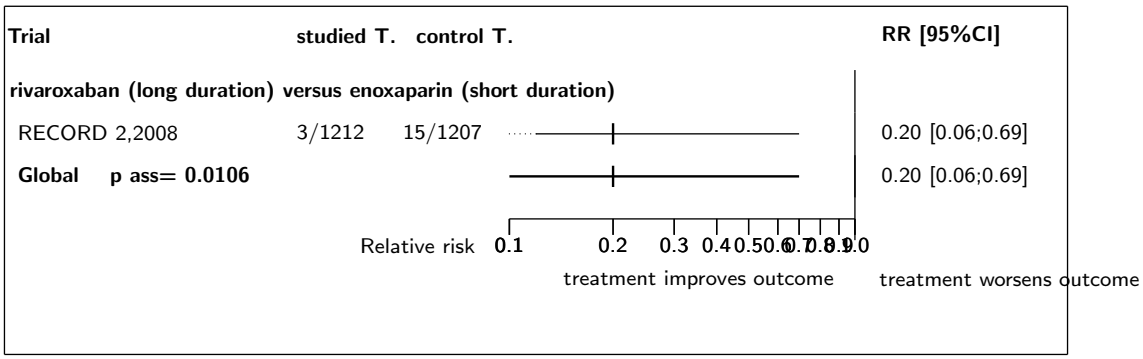


Figure 6.8: *Forest's plot for major or clinically relevant non-major bleeding*

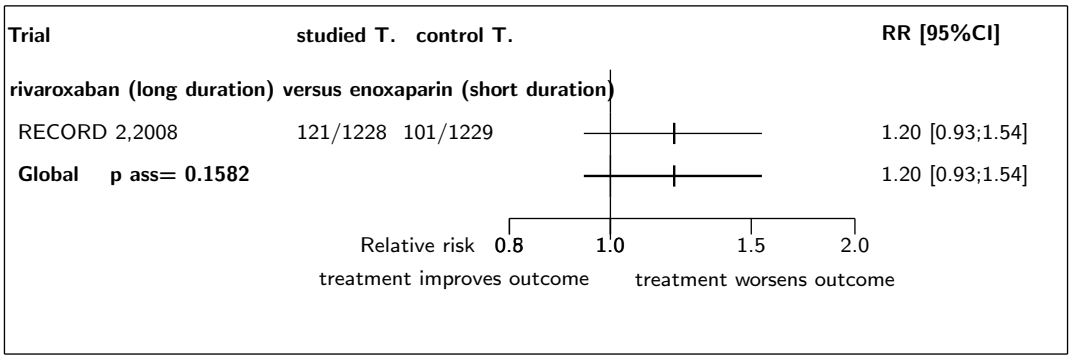


Figure 6.9: *Forest's plot for all cause death*

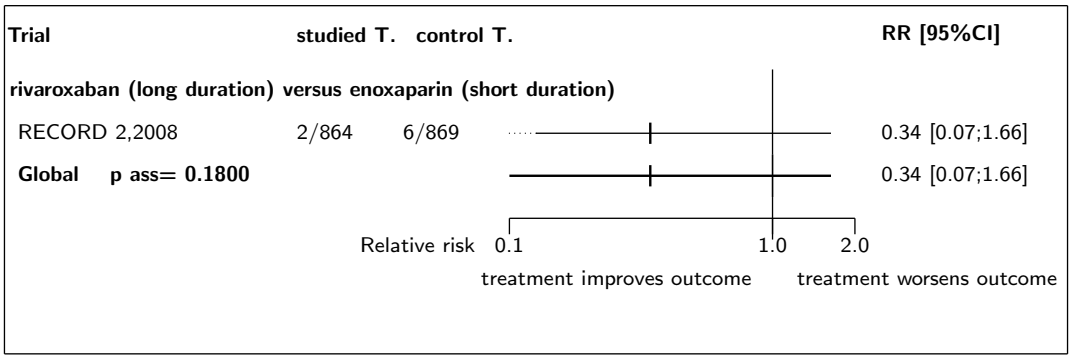
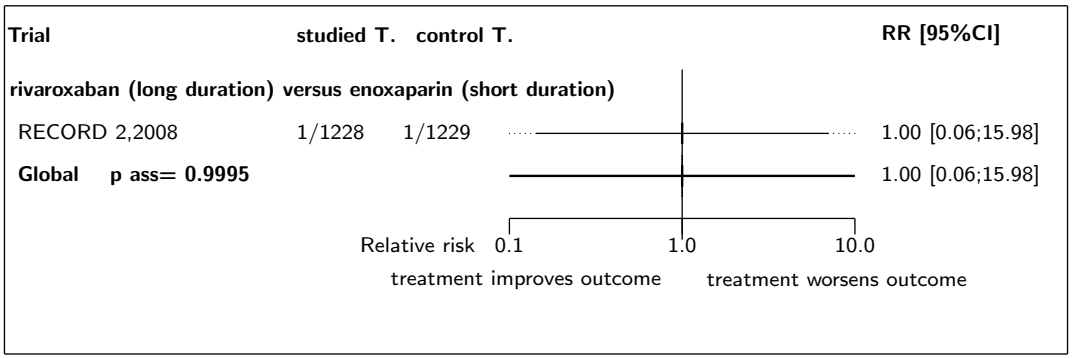


Figure 6.10: *Forest's plot for major bleeding*



References

[1] Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008 Jun 24;:. [PMID=18582928]

6.3 Individual trial summaries

Table 6.6: *RECORD 2, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2509 (1252 vs. 1257) **Follow-up duration:** 30-42 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 21 countries worldwide, 123 centres **Inclusion period:** Feb 2006 - Apr 2007	Patients undergoing elective total hip replacement **Inclusion criteria:** Male and female patients aged 18 years or above; patients scheduled for elective total hip replacement **Exclusion criteria:** Planned, staged total bilateral hip replacement Active bleeding or high risk of bleeding contraindicating treatment with low molecular weight heparin; Contraindication listed in the labeling or conditions precluding patient treatment with enoxaparin; conditions prohibiting bilateral venography (e.g. amputation of one leg, allergy to contrast media)	**Studied treatment:** extended thromboprophylaxis with rivaroxaban 10mg once daily for 31-39 days started6 to 8 hours after wound closure **Control treatment:** enoxaparin 40mg subcutaneous once daily for 10-14 days initiated12 h before surgery and restarted 68 h after woundclosure	Major VTE (fatal and non fatal DVT,PE) RR=0.12 [0.05;0.28] Deep vein thrombosis RR=0.20 [0.11;0.35] Total VTE and all-cause mortality RR=0.21 [0.13;0.35] Non-fatal pulmonary embolism RR=0.25 [0.03;2.25] Distal DVT RR=0.34 [0.16;0.71] Proximal DVT RR=0.11 [0.05;0.29] Symptomatic venous thromboembolism (DVT, PE) RR=0.20 [0.06;0.69] Major or clinically relevant non-major bleeding RR=1.20 [0.93;1.54]

Reference

Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008 Jun 24;: [PMID=18582928]

7 Global meta-analysis: all direct factor Xa inhibitors

7.1 Global meta-analysis: all direct factor Xa inhibitors versus enoxaparin

Table 7.1: *All direct factor Xa inhibitorsversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=0.20	0.02;1.71	0.1408	1.0000 (0.00)	1	5407
major VTE (fatal and non fatal DVT,PE)	RR=0.23	0.07;0.75	0.0144	0.0642 (0.71)	2	7758
deep vein thrombosis	RR=0.28	0.19;0.41	0.0000	0.4057 (0.00)	2	8288
total VTE and all-cause mortality	RR=0.33	0.24;0.47	0.0000	0.6276 (0.00)	2	7019
asymptomatic DVT	RR=0.33	0.20;0.54	0.0000	1.0000 (0.00)	1	5407
non-fatal pulmonary embolism	RR=1.11	0.12;10.23	0.9289	0.1020 (0.63)	2	8560
distal DVT	RR=0.49	0.24;1.00	0.0512	1.0000 (0.00)	1	3153
proximal DVT	RR=0.12 [1]	0.01;1.29	0.0803	0.0297 (0.79) †	2	7539
symptomatic venous thromboembolism (DVT, PE)	RR=0.48	0.23;1.02	0.0558	0.6816 (0.00)	2	9806
all cause death	RR=1.32	0.41;4.31	0.6407	0.4084 (0.00)	2	8560
major bleeding	RR=1.40	0.73;2.69	0.3068	0.2985 (0.07)	2	9765

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.2 Global meta-analysis: all direct factor Xa inhibitors versus enoxaparin (europe regimen)

Table 7.2: *All direct factor Xa inhibitorsversus enoxaparin (europe regimen)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=0.43	0.11;1.66	0.2192	1.0000 (1.00)	1	3057
major VTE (fatal and non fatal DVT,PE)	RR=0.45	0.27;0.73	0.0000	0.5961 (0.00)	2	4227
deep vein thrombosis	RR=0.57	0.49;0.67	0.0000	0.4121 (0.00)	2	3670
total VTE and all-cause mortality	RR=0.57	0.47;0.69	0.0000	0.2131 (0.35)	2	3675
non-fatal pulmonary embolism	RR=0.27	0.01;5.90	0.4026	1.0000 (0.00)	1	1702
distal DVT	RR=0.53	0.41;0.70	0.0000	1.0000 (0.00)	1	1702
proximal DVT	RR=0.41	0.24;0.70	0.0000	0.5634 (0.00)	2	4093

continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.24 95% CI 0.11;0.53

Endpoint	Effect	95% CI	p ass	p het	k	n
symptomatic venous thromboembolism (DVT, PE)	RR=0.55	0.19;1.59	0.2689	0.1052 (0.62)	2	5475
all cause death	RR=0.56	0.01;24.41	0.7614	0.0740 (0.69)	2	5475
major bleeding	RR=0.81	0.42;1.57	0.5314	0.3835 (0.00)	2	5540

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.3 Global meta-analysis: all direct factor Xa inhibitors versus enoxaparin (short duration)

Table 7.3: *All direct factor Xa inhibitorsversus enoxaparin (short duration)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=0.97	0.02;48.83	0.9889	1.0000 (0.00)	1	503
major VTE (fatal and non fatal DVT,PE)	RR=0.20	0.07;0.55	0.0019	0.1046 (0.62)	2	2426
deep vein thrombosis	RR=0.29	0.14;0.60	0.0000	0.0806 (0.67)	2	1953
total VTE and all-cause mortality	RR=0.29	0.15;0.57	0.0000	0.0952 (0.64)	2	1953
asymptomatic DVT	RR=0.38	0.16;0.89	0.0259	1.0000 (0.00)	1	503
non-fatal pulmonary embolism	RR=0.35	0.05;2.33	0.2749	0.5620 (0.00)	2	1953
distal DVT	RR=0.35	0.22;0.55	0.0000	0.9891 (0.00)	3	2456
proximal DVT	RR=0.32	0.07;1.44	0.1379	0.0594 (0.65)	3	2456
symptomatic venous thromboembolism (DVT, PE)	RR=0.20	0.06;0.69	0.0106	1.0000 (1.00)	1	2419
all cause death	RR=0.34	0.07;1.66	0.1800	1.0000 (1.00)	1	1733
major bleeding	RR=1.00	0.06;15.98	0.9995	1.0000 (0.00)	1	2457

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.4 Global meta-analysis: all direct factor Xa inhibitors versus enoxaparin (US regimen)

Table 7.4: *All direct factor Xa inhibitorsversus enoxaparin (US regimen)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=0.63	0.25;1.63	0.3428	0.7393 (0.00)	2	2144
major VTE (fatal and non fatal DVT,PE)	RR=0.58	0.35;0.96	0.0336	0.9785 (0.00)	2	2454
deep vein thrombosis	RR=0.95	0.72;1.26	0.7216	1.0000 (0.00)	1	2264
total VTE and all-cause mortality	RR=0.81	0.56;1.17	0.2595	0.0992 (0.57)	3	4431
asymptomatic DVT	RR=0.71	0.52;0.96	0.0267	0.7670 (0.00)	2	2144
non-fatal pulmonary embolism	RR=0.49	0.15;1.64	0.2488	1.0000 (1.00)	1	3034
distal DVT	RR=0.82	0.57;1.17	0.2756	1.0000 (0.00)	1	1924

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
proximal DVT	RR=0.46	0.20;1.09	0.0770	0.2652 (0.25)	3	4605
symptomatic venous thromboembolism (DVT, PE)	RR=0.95	0.40;2.25	0.9028	0.0917 (0.65)	2	6229
all cause death	RR=0.91	0.30;2.81	0.8733	0.8451 (0.00)	3	6449
major bleeding	RR=0.86	0.28;2.60	0.7895	0.1213 (0.48)	4	6727

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

8 Ongoing studies of direct factor Xa inhibitors

No ongoing trial was identified.

9 Excluded studies for direct factor Xa inhibitors

No trial was excluded.

References

Part II

Oral direct thrombin inhibitor

10 Overview of oral direct thrombin inhibitor

10.1 Included trials

A total of 7 randomized comparisons which enrolled 12959 patients were identified. In all, 3 randomized comparisons concerned dabigatran 150mg and 4 dabigatran 220mg.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for dabigatran 150mg and in section **??** (page **??**) for dabigatran 220mg.

The average study size was 1851 patients (range 1393 to 2336). The first study was published in 2007, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We found one unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

10.2 Summary of meta-analysis results

The meta-analysis of the available trials about oral direct thrombin inhibitor provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

10.2.1 Dabigatran 150mg

Dabigatran 150mg was inferior to **enoxaparin** in terms of symptomatic deep-vein thrombosis (RR=8.89, 95% CI 1.13 to 70.07, p=0.0380, 1 trial). No significant difference was found on major VTE (fatal and non fatal DVT,PE) (RR=1.09, 95% CI 0.70 to 1.70, p=0.7051, 1 trial), total VTE and all-cause mortality (RR=1.28, 95% CI 0.93 to 1.78, p=0.1347, 1 trial), asymptomatic DVT (RR=1.15, 95% CI 0.82 to 1.63, p=0.4174, 1 trial), non-fatal pulmonary embolism (RR=0.33, 95% CI 0.03 to 3.16, p=0.3357, 1 trial), distal DVT (RR=1.50, 95% CI 0.90 to 2.50, p=0.1218, 1 trial), proximal DVT (RR=0.90, 95% CI 0.55 to 1.49, p=0.6906, 1 trial), all cause death (RR=0.98, 95% CI 0.02 to 49.28, p=0.9914, 1 trial)and major bleeding (RR=0.83, 95% CI 0.42 to 1.63, p=0.5840, 1 trial).

No significant difference was found between **dabigatran 150mg** and **enoxaparin (europe regimen)** in terms of symptomatic deep-vein thrombosis (RR=0.37, 95% CI 0.10 to 1.37, p=0.1349, 1 trial), major VTE (fatal and non fatal DVT,PE) (RR=1.08, 95% CI 0.58 to 2.01, p=0.8152, 1 trial), total VTE and all-cause mortality (RR=1.07, 95% CI 0.92 to 1.25, p=0.3560, 1 trial), asymptomatic DVT (RR=1.10, 95% CI 0.94 to 1.29, p=0.2315, 1 trial), non-fatal pulmonary embolism (RR=1.95, 95% CI 0.07 to 57.91, p=0.7003, 1 trial), distal DVT (RR=1.07, 95% CI 0.91 to 1.27, p=0.3980, 1 trial), proximal DVT (RR=1.03, 95% CI 0.54 to 1.98, p=0.9277, 1 trial), all cause death (RR=0.98, 95% CI 0.06 to 15.70, p=0.9910, 1 trial)and major bleeding (RR=0.99, 95% CI 0.39 to 2.47, p=0.9781, 1 trial).

Dabigatran 150mg was inferior to **enoxaparin (US regimen)** in terms of total VTE and all-cause mortality (RR=1.33, 95% CI 1.12 to 1.58, p=0.0000, 1 trial)and distal DVT (RR=1.33, 95% CI 1.10 to 1.59, p=0.0025, 1 trial). No significant difference was found on major VTE (fatal and non fatal DVT,PE) (RR=1.36, 95% CI 0.70 to 2.63, p=0.3643, 1 trial), non-fatal pulmonary embolism (RR=0.10, 95% CI 0.01 to 1.81, p=0.1188, 1 trial), all cause death (RR=2.00, 95% CI 0.07 to 59.47, p=0.6894, 1 trial)and major bleeding (RR=0.42, 95% CI 0.15 to 1.17, p=0.0973, 1 trial).

10.2.2 Dabigatran 220mg

No significant difference was found between **dabigatran 220mg** and **enoxaparin** in terms of symptomatic deep-vein thrombosis (RR=6.03, 95% CI 0.73 to 49.98, p=0.0961, 1 trial), major VTE (fatal and non fatal DVT,PE) (RR=0.78, 95% CI 0.48 to 1.27, p=0.3273, 1 trial), total VTE and all-cause mortality (RR=0.90, 95% CI 0.63 to 1.29, p=0.5652, 1 trial), asymptomatic DVT (RR=0.73, 95% CI 0.49 to 1.08, p=0.1153, 1 trial), non-fatal pulmonary embolism (RR=1.70, 95% CI 0.41 to 7.09, p=0.4671, 1 trial), distal DVT (RR=0.94, 95% CI 0.53 to 1.66, p=0.8251, 1 trial), proximal DVT (RR=0.57, 95% CI 0.32 to 1.00, p=0.0519, 1 trial), all cause death (RR=6.03, 95% CI 0.30 to 120.18, p=0.2395, 1 trial)and major bleeding (RR=1.29, 95% CI 0.70 to 2.37, p=0.4190, 1 trial).

No significant difference was found between **dabigatran 220mg** and **enoxaparin (europe regimen)** in terms of symptomatic deep-vein thrombosis (RR=0.13, 95% CI 0.02 to 1.01, p=0.0513, 1 trial), major VTE (fatal and non fatal DVT,PE) (RR=0.73, 95% CI 0.36 to 1.47, p=0.3787, 1 trial), total VTE and all-cause mortality (RR=0.97, 95% CI 0.82 to 1.13, p=0.6649, 1 trial), asymptomatic DVT (RR=1.00, 95% CI 0.85 to 1.18, p=0.9877, 1 trial), distal DVT (RR=1.02, 95% CI 0.85 to 1.21, p=0.8596, 1 trial), proximal DVT (RR=0.82, 95% CI 0.40 to 1.69, p=0.5985, 1 trial), all cause death (RR=1.01, 95% CI 0.06 to 16.19, p=0.9917, 1 trial)and major bleeding (RR=1.14, 95% CI 0.46 to 2.78, p=0.7804, 1 trial).

Dabigatran 220mg was inferior to **enoxaparin (US regimen)** in terms of total VTE and all-cause mortality (RR=1.23, 95% CI 1.03 to 1.47, p=0.0238, 1 trial). No significant difference was found on major VTE (fatal and non fatal DVT,PE) (RR=1.51, 95% CI 0.79 to 2.91, p=0.2141, 1 trial), distal DVT (RR=1.20, 95% CI 0.99 to 1.45, p=0.0604, 1 trial), proximal DVT (RR=1.49, 95% CI 0.67 to 3.33, p=0.3306, 1 trial)and major bleeding (RR=0.42, 95% CI 0.15 to 1.19, p=0.1036, 1 trial).

Table 10.1: *Main study characteristics - oral direct thrombin inhibitor*

Trial	Patients	Treatments	Trial design and method
Dabigatran 150mg			
Dabigatran 150mg versus enoxaparin			
RE-NOVATE (150mg), 2007 [**?**] n = 1174 vs. 1162	total hip replacement	dabigatran etexilate 150 mg q.d. 28-35 days **versus** enoxaparin 40 mg q.d. for 28-25 days	double blind Primary endpoint: total VTE and all-cause mortality 115 centres, Europe, Australia, South Africa mean follow-up: 33 days test intervalle: 2-4 (3)
Dabigatran 150mg versus enoxaparin (europe regimen)			
RE-MODEL (150mg), 2007 [**?**] n = 708 vs. 699	total knee replacement	dabigatran etexilate 150 mg q.d. for 6-10 days **versus** enoxaparin 40 mg q.d. for 6-10 days	double blind parallel groups Primary endpoint: total VTE and all-cause mortality 105 centres, Europe, Australia, South Africa mean follow-up: 8 days test intervalle: 2-4 (3)
Dabigatran 150mg versus enoxaparin (US regimen)			
RE-MOBILIZE (150mg), 2008 [**?**] n = 877 vs. 876	total knee replacement	dabigatran etexilate 150 mg q.d. for 12-15 days **versus** enoxaparin 30 mg SC BID after surgery for 12-15 days	double blind Primary endpoint: total VTE and all-cause mortality 97 centres, US, Canada, Mexico, UK mean follow-up: 14 days test intervalle: 2-4 (3)
Dabigatran 220mg			
Dabigatran 220mg versus enoxaparin			
RE-NOVATE 2, 0 n = 1010 vs. 1003	patients undergoing total hip-replacement surgery	dabigatran 220mg once daily for 28-35 Days **versus** enoxaparin 40mg subcutaneous once daily for 28-35 Days	double-blind parallel groups Primary endpoint: venous thromboembolism or death 108 centres, mean follow-up: 32 days test intervalle: 2-4 (3)

continued...

Trial	Patients	Treatments	Trial design and method
RE-NOVATE (220mg), 2007 [?] n = 1157 vs. 1162	total hip replacement	dabigatran etexilate 220 mg q.d. for 28-35 days **versus** enoxaparin 40 mg q.d. for 23-35 days	double blind parallel groups Primary endpoint: total VTE and all-cause mortality 115 centres, Europe, Australia, South Africa mean follow-up: 33 days test intervalle: 2-4 (3)
Dabigatran 220mg versus enoxaparin (europe regimen)			
RE-MODEL (220mg), 2007 [?] n = 694 vs. 699	patients undergoing total knee replacement	dabigatran etexilate 220 mg q.d. 6-10 days **versus** enoxaparin 40 mg q.d. for 6-10 days	double blind Primary endpoint: total VTE and all-cause mortality 105 centres, Europe, Australia, South Africa mean follow-up: 8 days test intervalle: 2-4 (3)
Dabigatran 220mg versus enoxaparin (US regimen)			
RE-MOBILIZE (220mg), 2008 [?] n = 862 vs. 876	total knee replacement	dabigatran etexilate 220 mg for 12-15 days **versus** enoxaparin 30mg SC BID after surgery for 12-15 days	double blind parallel groups Primary endpoint: total VTE and all-cause mortality 97 centres, US, Canada, Mexico, UK mean follow-up: 14 days test intervalle: 2-4 (3)

Table 10.2: *Summary of all results for dabigatran 150mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
dabigatran 150mg versus enoxaparin						
symptomatic deep-vein thrombosis	RR=8.89	1.13;70.07	0.0380	1.0000 (0.00)	1	2298
major VTE (fatal and non fatal DVT,PE)	RR=1.09	0.70;1.70	0.7051	1.0000 (0.00)	1	1805
total VTE and all-cause mortality	RR=1.28	0.93;1.78	0.1347	1.0000 (0.00)	1	1771
asymptomatic DVT	RR=1.15	0.82;1.63	0.4174	1.0000 (1.00)	1	1765
non-fatal pulmonary embolism	RR=0.33	0.03;3.16	0.3357	1.0000 (0.00)	1	2298
distal DVT	RR=1.50	0.90;2.50	0.1218	1.0000 (0.00)	1	1765
proximal DVT	RR=0.90	0.55;1.49	0.6906	1.0000 (0.00)	1	1799
all cause death	RR=0.98	0.02;49.28	0.9914	1.0000 (0.00)	1	2309
major bleeding	RR=0.83	0.42;1.63	0.5840	1.0000 (0.00)	1	2317
dabigatran 150mg versus enoxaparin (europe regimen)						
symptomatic deep-vein thrombosis	RR=0.37	0.10;1.37	0.1349	1.0000 (0.00)	1	1038
major VTE (fatal and non fatal DVT,PE)	RR=1.08	0.58;2.01	0.8152	1.0000 (0.00)	1	1038
total VTE and all-cause mortality	RR=1.07	0.92;1.25	0.3560	1.0000 (1.00)	1	1038
asymptomatic DVT	RR=1.10	0.94;1.29	0.2315	1.0000 (0.00)	1	1038
non-fatal pulmonary embolism	RR=1.95	0.07;57.91	0.7003	1.0000 (0.00)	1	1038
distal DVT	RR=1.07	0.91;1.27	0.3980	1.0000 (0.00)	1	1038
proximal DVT	RR=1.03	0.54;1.98	0.9277	1.0000 (0.00)	1	1038
major or clinically relevant non-major bleeding	RR=1.22	0.84;1.78	0.2910	1.0000 (0.00)	1	1397
all cause death	RR=0.98	0.06;15.70	0.9910	1.0000 (0.00)	1	1381
major bleeding	RR=0.99	0.39;2.47	0.9781	1.0000 (0.00)	1	1397
dabigatran 150mg versus enoxaparin (US regimen)						
major VTE (fatal and non fatal DVT,PE)	RR=1.36	0.70;2.63	0.3643	1.0000 (0.00)	1	1324
total VTE and all-cause mortality	RR=1.33	1.12;1.58	0.0000	1.0000 (0.00)	1	1292
non-fatal pulmonary embolism	RR=0.10	0.01;1.81	0.1188	1.0000 (0.00)	1	1292
distal DVT	RR=1.33	1.10;1.59	0.0025	1.0000 (0.00)	1	1292
major or clinically relevant non-major bleeding	RR=0.82	0.49;1.34	0.4235	1.0000 (0.00)	1	1739
all cause death	RR=2.00	0.07;59.47	0.6894	1.0000 (0.00)	1	1753
major bleeding	RR=0.42	0.15;1.17	0.0973	1.0000 (0.00)	1	1739

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 10.3: *Summary of all results for dabigatran 220mg*

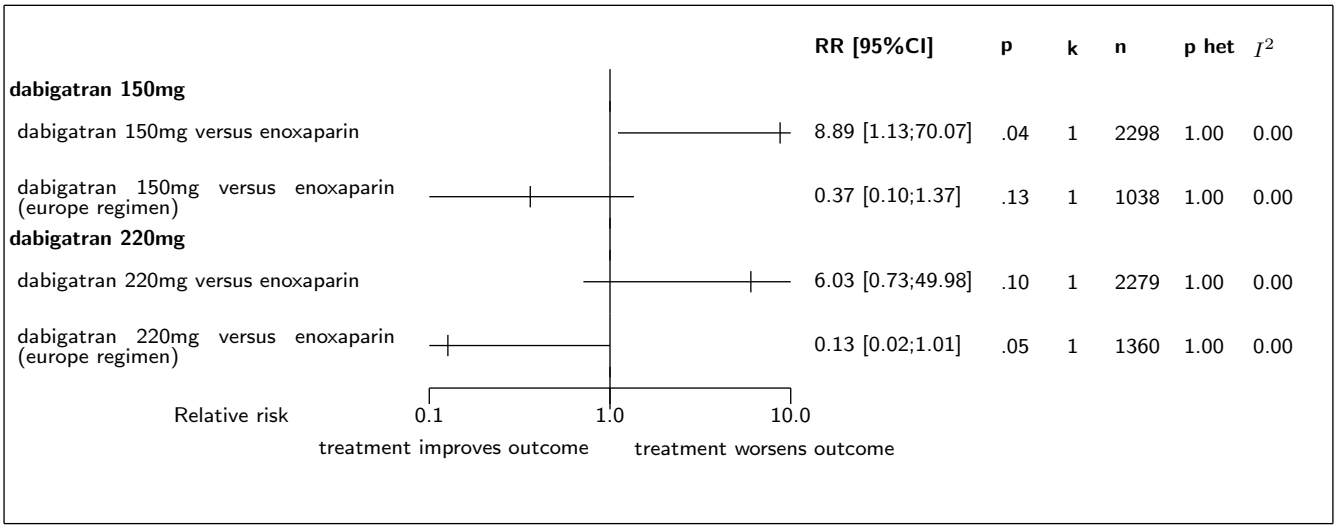
Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
dabigatran 220mg versus enoxaparin						
symptomatic deep-vein thrombosis	RR=6.03	0.73;49.98	0.0961	1.0000 (0.00)	1	2279

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
major VTE (fatal and non fatal DVT,PE)	RR=0.78	0.48;1.27	0.3273	1.0000 (0.00)	1	1826
total VTE and all-cause mortality	RR=0.90	0.63;1.29	0.5652	1.0000 (0.00)	1	1777
asymptomatic DVT	RR=0.73	0.49;1.08	0.1153	1.0000 (0.00)	1	1777
non-fatal pulmonary embolism	RR=1.70	0.41;7.09	0.4671	1.0000 (0.00)	1	1777
distal DVT	RR=0.94	0.53;1.66	0.8251	1.0000 (0.00)	1	1768
proximal DVT	RR=0.57	0.32;1.00	0.0519	1.0000 (0.00)	1	1819
all cause death	RR=6.03	0.30;120.18	0.2395	1.0000 (0.00)	1	2279
major bleeding	RR=1.29	0.70;2.37	0.4190	1.0000 (0.00)	1	2300
dabigatran 220mg versus enoxaparin (europe regimen)						
symptomatic deep-vein thrombosis	RR=0.13	0.02;1.01	0.0513	1.0000 (0.00)	1	1360
major VTE (fatal and non fatal DVT,PE)	RR=0.73	0.36;1.47	0.3787	1.0000 (0.00)	1	1017
total VTE and all-cause mortality	RR=0.97	0.82;1.13	0.6649	1.0000 (0.00)	1	1015
asymptomatic DVT	RR=1.00	0.85;1.18	0.9877	1.0000 (0.00)	1	1015
distal DVT	RR=1.02	0.85;1.21	0.8596	1.0000 (0.00)	1	1014
proximal DVT	RR=0.82	0.40;1.69	0.5985	1.0000 (0.00)	1	1013
major or clinically relevant non-major bleeding	RR=1.11	0.76;1.63	0.5933	1.0000 (0.00)	1	1373
all cause death	RR=1.01	0.06;16.19	0.9917	1.0000 (0.00)	1	1360
major bleeding	RR=1.14	0.46;2.78	0.7804	1.0000 (0.00)	1	1373
dabigatran 220mg versus enoxaparin (US regimen)						
major VTE (fatal and non fatal DVT,PE)	RR=1.51	0.79;2.91	0.2141	1.0000 (0.00)	1	1286
total VTE and all-cause mortality	RR=1.23	1.03;1.47	0.0238	1.0000 (0.00)	1	1247
distal DVT	RR=1.20	0.99;1.45	0.0604	1.0000 (1.00)	1	1247
proximal DVT	RR=1.49	0.67;3.33	0.3306	1.0000 (1.00)	1	1247
major or clinically relevant non-major bleeding	RR=0.86	0.52;1.41	0.5482	1.0000 (0.00)	1	1725
major bleeding	RR=0.42	0.15;1.19	0.1036	1.0000 (0.00)	1	1725

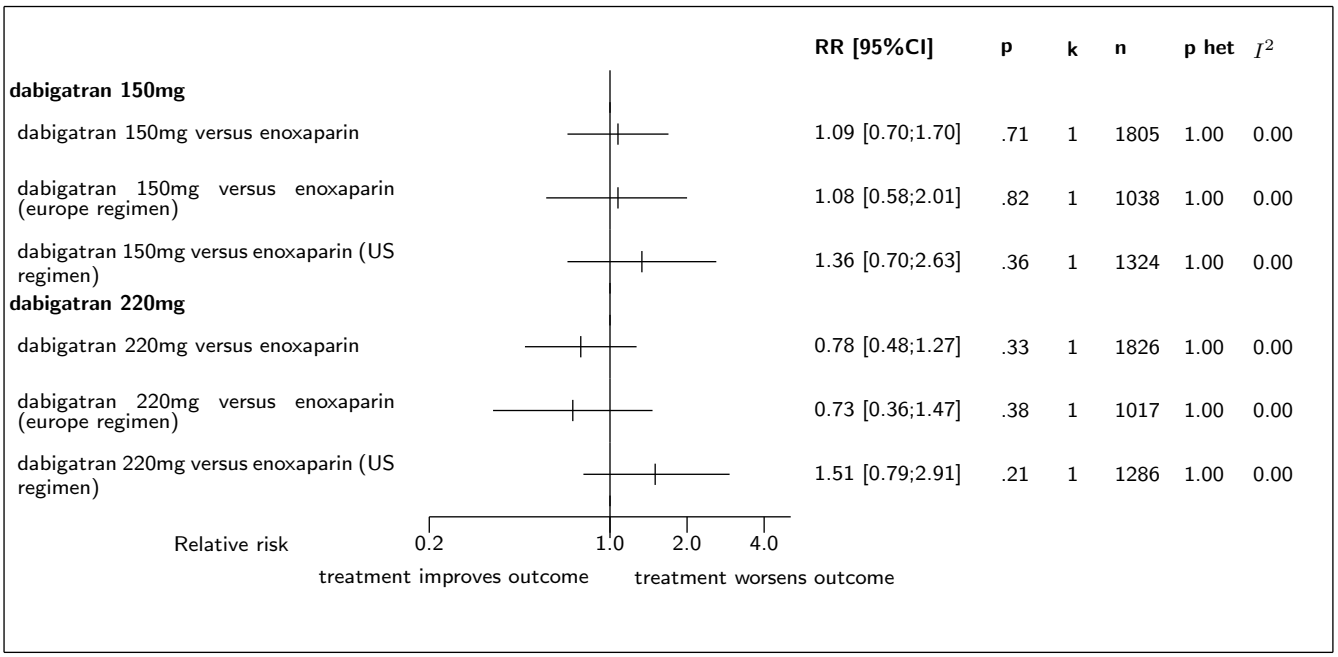
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 10.1: *Forest's plot for symptomatic deep-vein thrombosis*



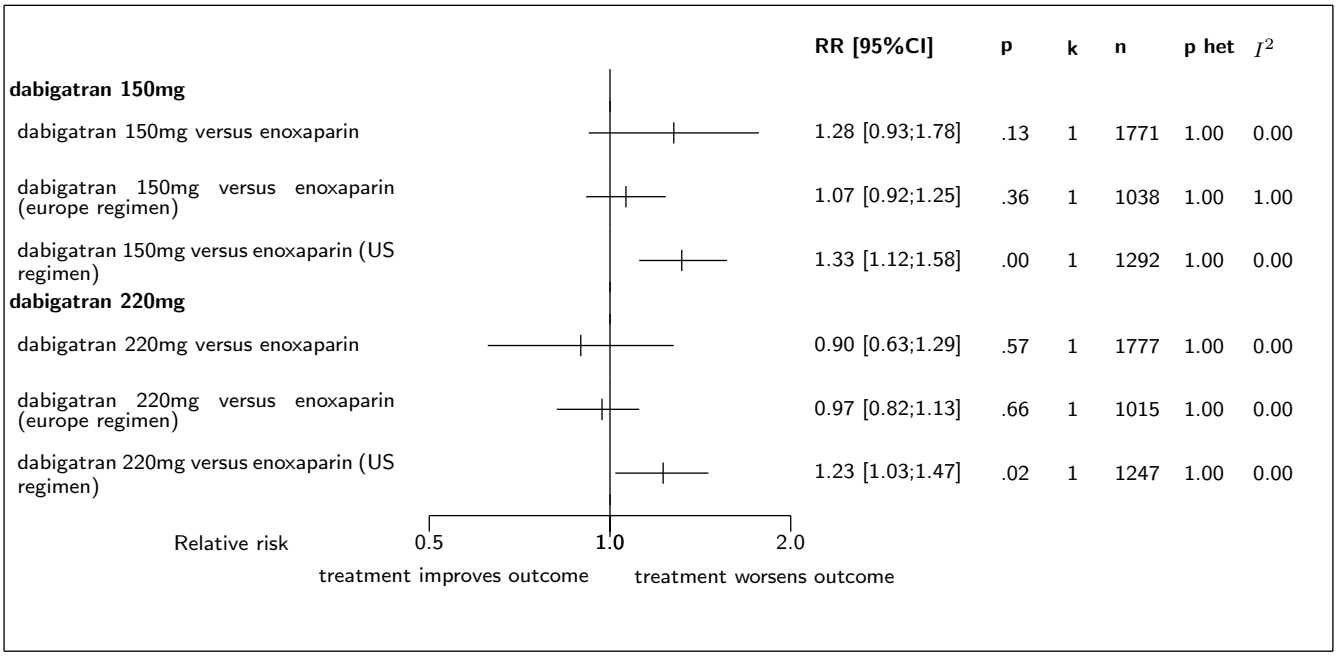
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 10.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*



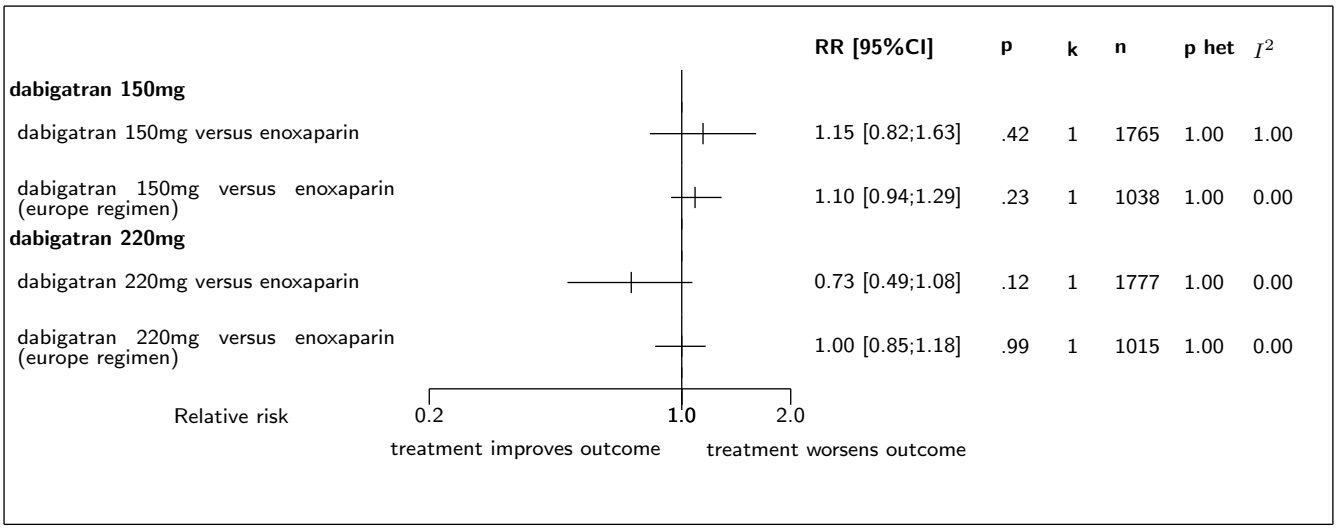
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 10.3: *Forest's plot for total VTE and all-cause mortality*



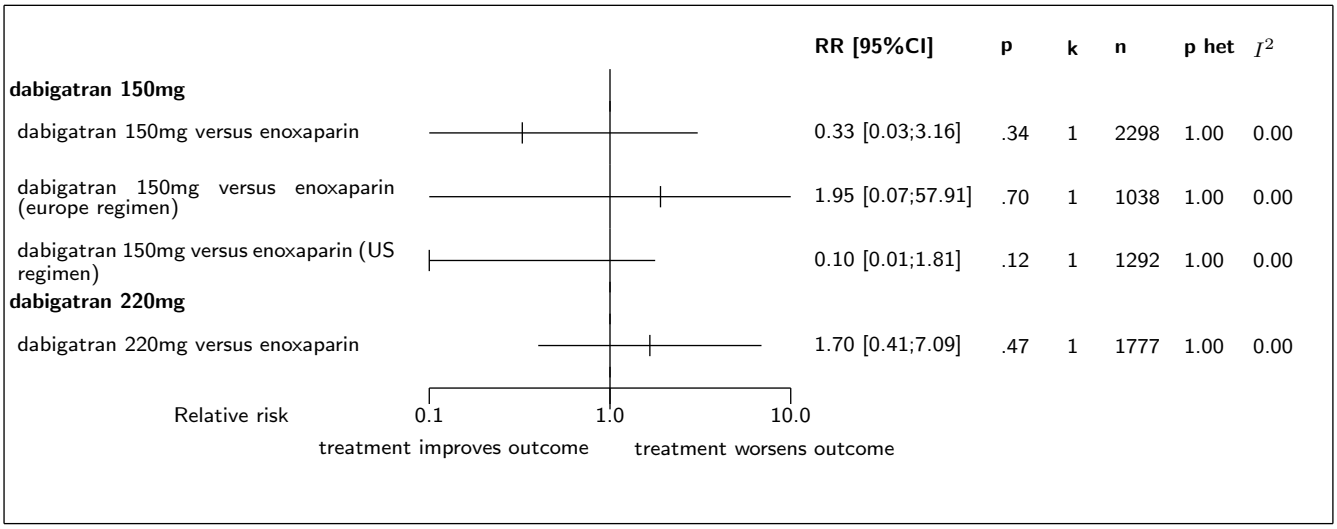
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 10.4: *Forest's plot for asymptomatic DVT*



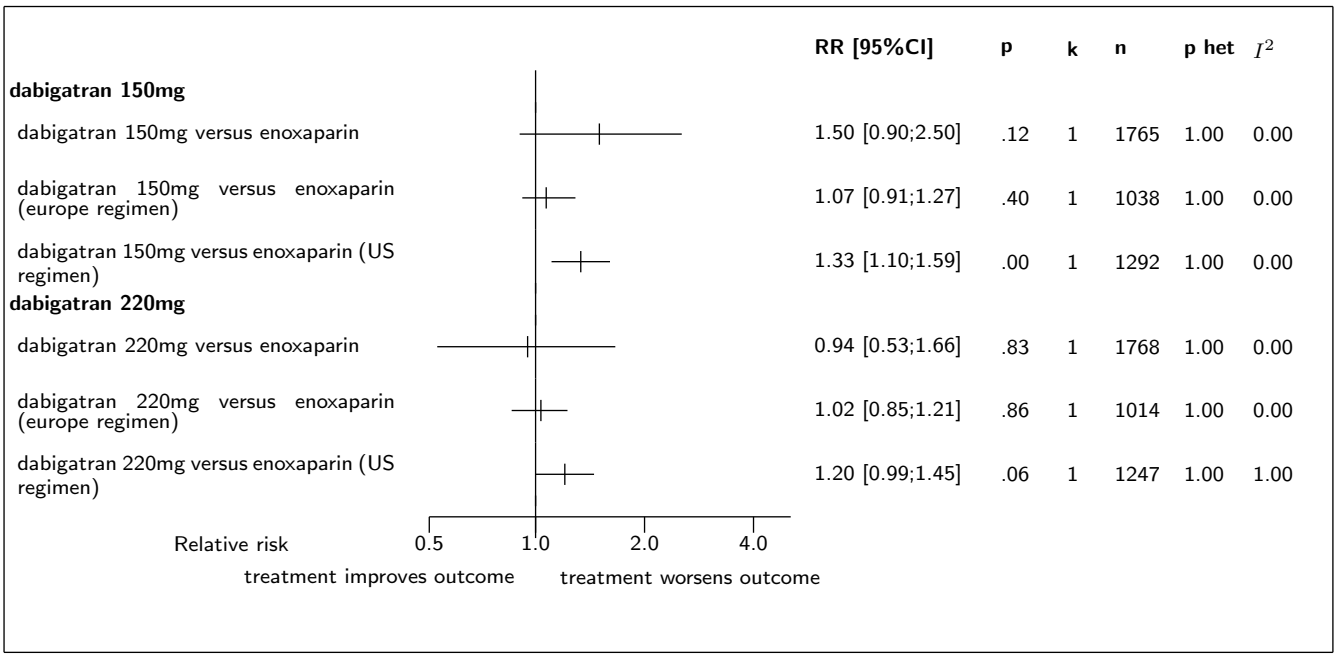
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 10.5: *Forest's plot for non-fatal pulmonary embolism*



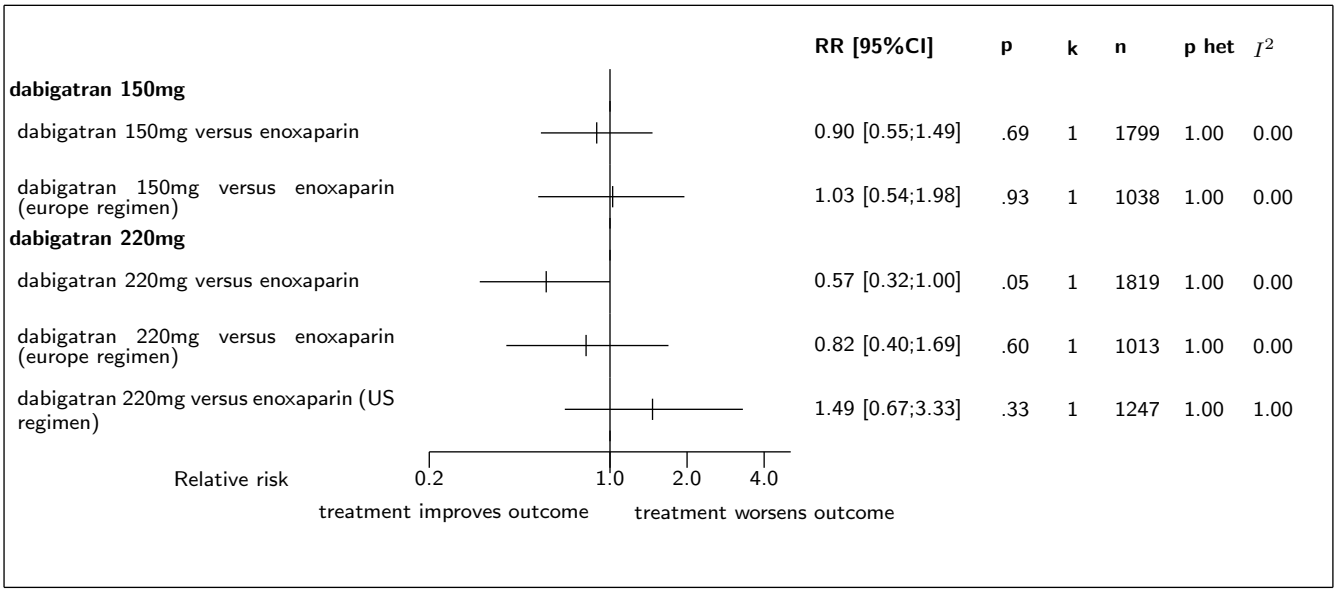
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 10.6: *Forest's plot for distal DVT*



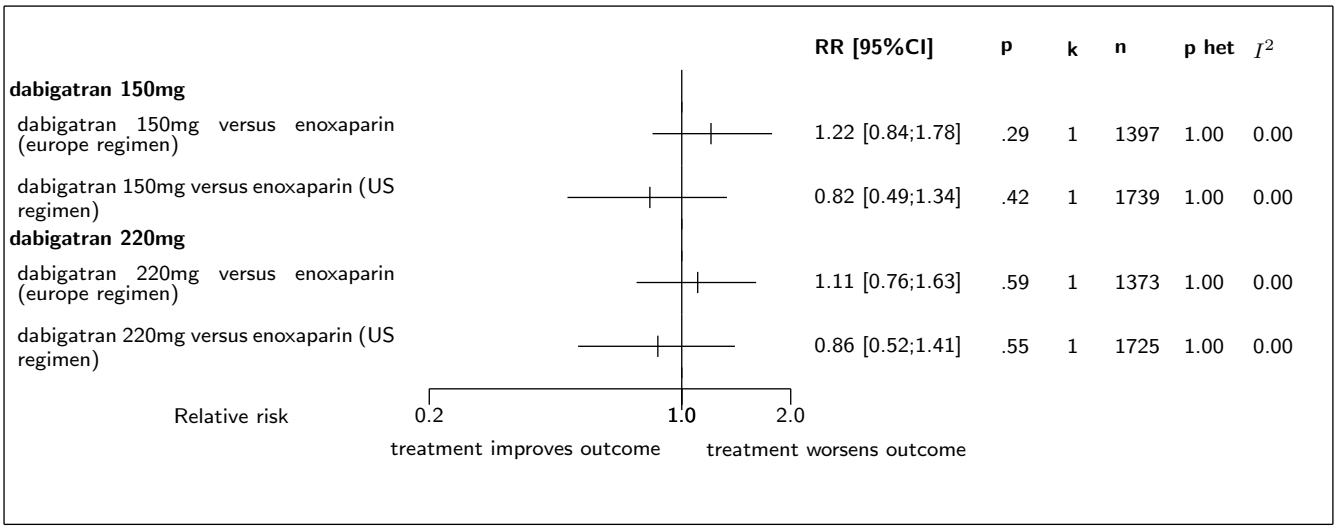
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 10.7: *Forest's plot for proximal DVT*



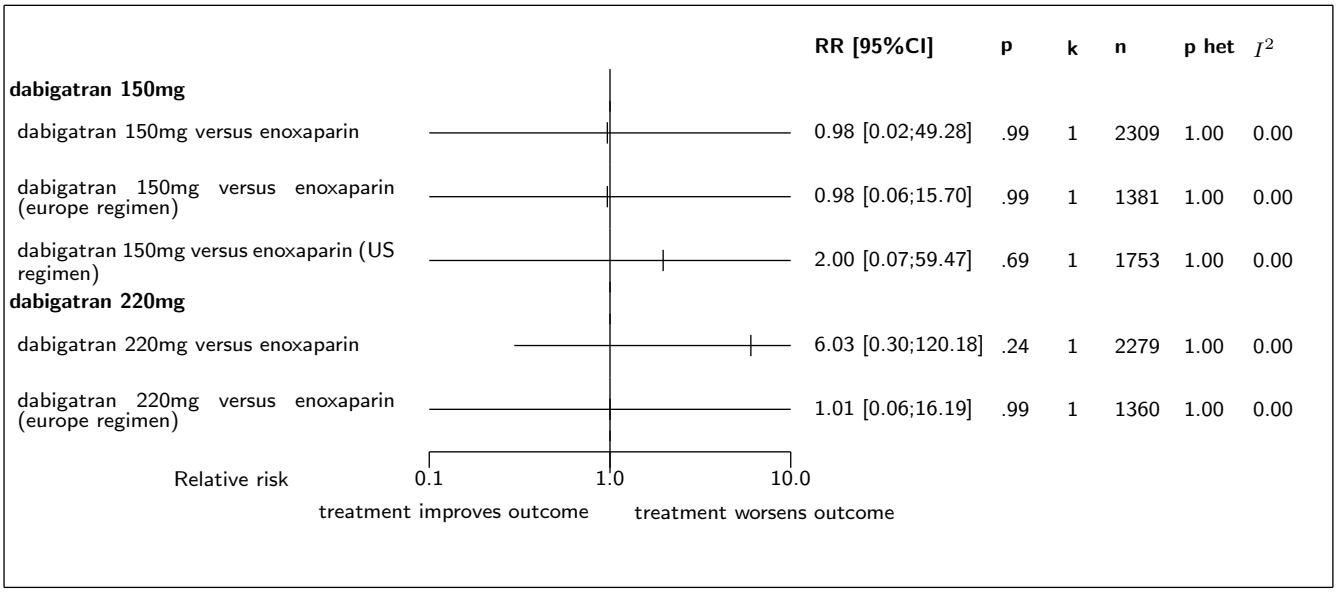
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 10.8: *Forest's plot for major or clinically relevant non-major bleeding*



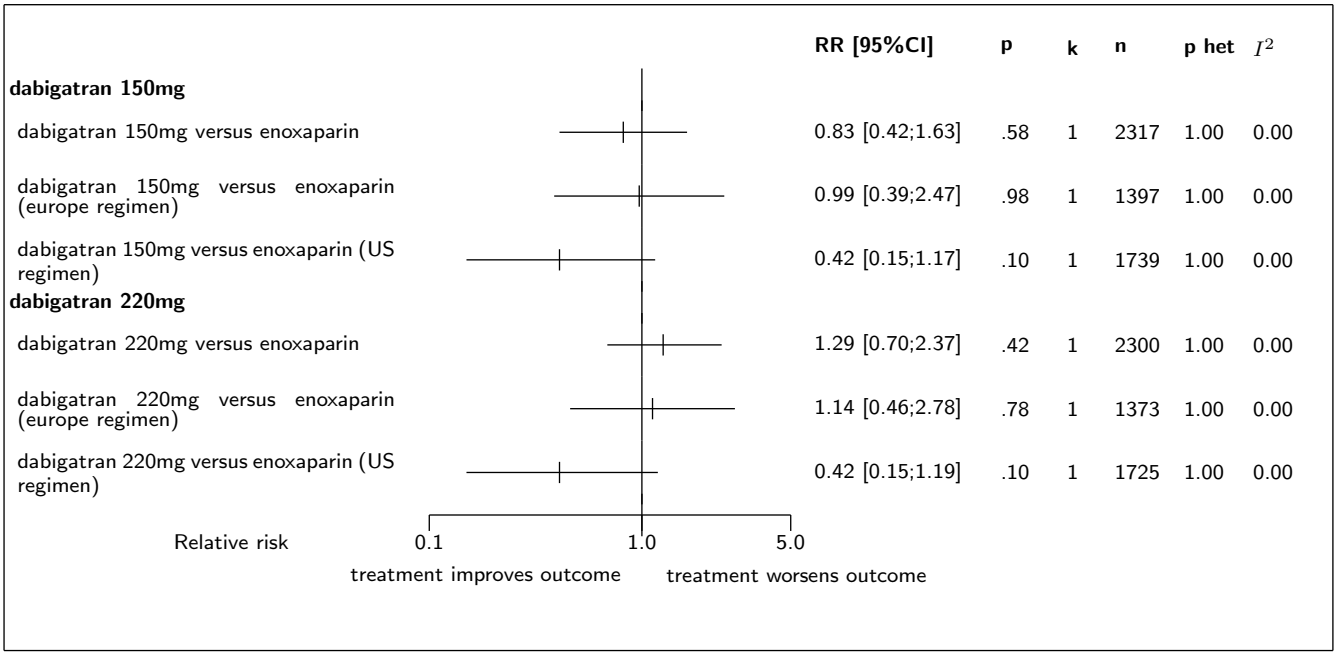
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 10.9: *Forest's plot for all cause death*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 10.10: *Forest's plot for major bleeding*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

11 Detailed results for dabigatran 150mg

11.1 Available trials

A total of 3 RCTs which randomized 5496 patients were identified: it compared dabigatran 150mg with enoxaparin , it compared dabigatran 150mg with enoxaparin (europe regimen) and it compared dabigatran 150mg with enoxaparin (US regimen).
The average study size was 1832 patients (range 1407 to 2336). The first study was published in 2007, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 3 trials; 3 trials reported data on major VTE (fatal and non fatal DVT,PE); 3 trials reported data on distal DVT; 3 trials reported data on total VTE and all-cause mortality; 3 trials reported data on major bleeding; 3 trials reported data on non-fatal pulmonary embolism; 2 trials reported data on asymptomatic DVT; 2 trials reported data on symptomatic deep-vein thrombosis; 2 trials reported data on proximal DVT; and 2 trials reported data on major or clinically relevant non-major bleeding.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of dabigatran 150mg.

Table 11.1: *Treatment description - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Studied treatment	Control treatment
Dabigatran 150mg versus enoxaparin		
RE-NOVATE (150mg) (2007) [**?**] [a]	dabigatran etexilate 150 mg q.d. 28-35 days	Enoxaparin 40 mg q.d. for 28-25 days starting the evening before surgery
Dabigatran 150mg versus enoxaparin (europe regimen)		
RE-MODEL (150mg) (2007) [**?**]	dabigatran etexilate 150 mg q.d. for 6-10 days administered 14 h after completion of surgery	Enoxaparin 40 mg q.d. for 6-10 days started on the evening before surgery
Dabigatran 150mg versus enoxaparin (US regimen)		
RE-MOBILIZE (150mg) (2008) [**?**]	dabigatran etexilate 150 mg q.d. for 12-15 days started 6 to 12 hours after completion of surgery	enoxaparin 30 mg SC BID after surgery for 12-15 days started 12 to 24 hours after surgery, usually on the morning after the day of surgery

a) 3 arms dabigatran 220mg, 150mg and placebo

Table 11.2: *Descriptions of participants - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Patients
Dabigatran 150mg versus enoxaparin	

continued...

Trial	Patients	
RE-NOVATE (150mg) (2007) [?]	Total hip replacement **Inclusion criteria:** aged 18 years or older; weight at least 40 kg; scheduled for primary elective unilateral totalhip replacement	**Exclusion criteria:** any bleeding diathesis; history ofacute intracranial disease or haemorrhagic stroke;major surgery, trauma, uncontrolled hypertension, ormyocardial infarction in the past 3 months;gastrointestinal or urogenital bleeding, or ulcer diseasein the past 6 months; severe liver disease; alanine oraspartate aminotransferase concentrations greater thantwo times the upper limit of the normal range in thepast month; severe renal insuffi ciency (creatinineclearance less than 30 mL/min); use of long-actingnon-steroidal anti-infl ammatory drugs
Dabigatran 150mg versus enoxaparin (europe regimen)		
RE-MODEL (150mg) (2007) [?]	Total knee replacement **Inclusion criteria:** patients <=18 years; >40 kg; scheduled for primary elective unilateral total knee replacement	**Exclusion criteria:** any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the normal range (ULN) 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
Dabigatran 150mg versus enoxaparin (US regimen)		
RE-MOBILIZE (150mg) (2008) [?]	Total knee replacement **Inclusion criteria:** patients 18 years or older and weighing more than 40 kg who had undergone primary elective unilateral total knee arthroplasty	**Exclusion criteria:** known inherited or acquired clinically significant bleeding disorder; major surgery, trauma, uncontrolled hypertension, or myocardial infarction within the last 3 months; history of acute intracranial disease or hemorrhagic stroke; gastrointestinal or urogenital bleeding or ulcer disease within the last 6 months; severe liver disease; aspartate or alanine aminotransferase (AST, ALT) levels higher than 2x the upper limit of the normal range (ULN) within the last month; severe renal insufficiency (creatinine clearance <30 mL/min); need for concomitant longacting nonsteroidal anti-inflammatory drug therapy or treatment with an anticoagulant during study drug treatment; active malignant disease; platelet count less than 100 10^9/L,

Table 11.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 150mg versus enoxaparin				
RE-NOVATE (150mg), 2007 [?] n=2336	double blind confirmatory trial at low risk of bias	28-35 days, median 33d inclusion period: dec 2004 - apr 2006	Europe, Australia, South Africa 115 centres	total VTE and all-cause mortality
Dabigatran 150mg versus enoxaparin (europe regimen)				
RE-MODEL (150mg), 2007 [?] n=1407	Parallel groups double blind confirmatory trial at low risk of bias	6-10 days, mean 8 days inclusion period: nov 2004 - mar 2006	Europe, Australia, South Africa 105 centres	total VTE and all-cause mortality
Dabigatran 150mg versus enoxaparin (US regimen)				
RE-MOBILIZE (150mg), 2008 [?] n=1753	double blind confirmatory trial at low risk of bias	12-15 days, median 14d inclusion period: nov 2004 - jun 2006	US, Canada, Mexico, UK 97 centres	total VTE and all-cause mortality

Table 11.4: *Trial characteristics - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	**mean follow-up**	**test intervalle**
Dabigatran 150mg versus enoxaparin		
RE-NOVATE (150mg), 2007 [?]	33 days	2-4 (3)
Dabigatran 150mg versus enoxaparin (europe regimen)		
RE-MODEL (150mg), 2007 [?]	8 days	2-4 (3)
Dabigatran 150mg versus enoxaparin (US regimen)		
RE-MOBILIZE (150mg), 2008 [?]	14 days	2-4 (3)

11.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Dabigatran 150mg versus enoxaparin

The single study eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. The analysis detected a statistically significant difference in favor of enoxaparin in symptomatic deep-vein thrombosis, with a RR of 8.89 (95% CI 1.13 to 70.07, p=0.0380).
The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. No statistically significant difference between the groups was found in major VTE (fatal and non fatal DVT,PE), with a RR of 1.09 (95% CI 0.70 to 1.70, p=0.7051).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. No statistically significant difference between the groups was found in total VTE and all-cause mortality, with a RR of 1.28 (95% CI 0.93 to 1.78, p=0.1347).
The single study eligible for this comparison provided data on **asymptomatic DVT**. No statistically significant difference between the groups was found in asymptomatic DVT, with a RR of 1.15 (95% CI 0.82 to 1.63, p=0.4174).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.33 (95% CI 0.03 to 3.16, p=0.3357).
The single study eligible for this comparison provided data on **distal DVT**. No statistically significant difference between the groups was found in distal DVT, with a RR of 1.50 (95% CI 0.90 to 2.50, p=0.1218).
The single study eligible for this comparison provided data on **proximal DVT**. No statistically significant difference between the groups was found in proximal DVT, with a RR of 0.90 (95% CI 0.55 to 1.49, p=0.6906).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.98 (95% CI 0.02 to 49.28, p=0.9914).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 0.83 (95% CI 0.42 to 1.63, p=0.5840).

Dabigatran 150mg versus enoxaparin (europe regimen)

The single study eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between dabigatran 150mg and enoxaparin (europe regimen), with a RR of 0.37 (95%CI 0.10 to 1.37, p=0.1349) in favour of dabigatran 150mg. In other words, symptomatic deep-vein thrombosis was slightly lower in the dabigatran 150mg group , but this was not statistically significant.
The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. No statistically significant difference between the groups was found in major VTE (fatal and non fatal DVT,PE), with a RR of 1.08 (95% CI 0.58 to 2.01, p=0.8152).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. No statistically significant difference between the groups was found in total VTE and all-cause mortality, with a RR of 1.07 (95% CI 0.92 to 1.25, p=0.3560).
The single study eligible for this comparison provided data on **asymptomatic DVT**. No statistically significant difference between the groups was found in asymptomatic DVT, with a RR of 1.10 (95% CI 0.94 to 1.29, p=0.2315).

The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 1.95 (95% CI 0.07 to 57.91, p=0.7003).
The single study eligible for this comparison provided data on **distal DVT**. No statistically significant difference between the groups was found in distal DVT, with a RR of 1.07 (95% CI 0.91 to 1.27, p=0.3980).
The single study eligible for this comparison provided data on **proximal DVT**. No statistically significant difference between the groups was found in proximal DVT, with a RR of 1.03 (95% CI 0.54 to 1.98, p=0.9277).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.98 (95% CI 0.06 to 15.70, p=0.9910).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 0.99 (95% CI 0.39 to 2.47, p=0.9781).

Dabigatran 150mg versus enoxaparin (US regimen)

The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. No statistically significant difference between the groups was found in major VTE (fatal and non fatal DVT,PE), with a RR of 1.36 (95% CI 0.70 to 2.63, p=0.3643).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of enoxaparin (US regimen) in total VTE and all-cause mortality, with a RR of 1.33 (95% CI 1.12 to 1.58, p=0.0000).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.10 (95% CI 0.01 to 1.81, p=0.1188).
The single study eligible for this comparison provided data on **distal DVT**. The analysis detected a statistically significant difference in favor of enoxaparin (US regimen) in distal DVT, with a RR of 1.33 (95% CI 1.10 to 1.59, p=0.0025).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 2.00 (95% CI 0.07 to 59.47, p=0.6894).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 0.42 (95% CI 0.15 to 1.17, p=0.0973).

Table 11.5: *Results details - oral direct thrombin inhibitor - dabigatran 150mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dabigatran 150mg versus enoxaparin						
symptomatic deep-vein thrombosis	RR=8.89	[1.13;70.07]	0.0380	1.0000 (I^2=0.00)	1	2298
major VTE (fatal and non fatal DVT,PE)	RR=1.09	[0.70;1.70]	0.7051	1.0000 (I^2=0.00)	1	1805
total VTE and all-cause mortality	RR=1.28	[0.93;1.78]	0.1347	1.0000 (I^2=0.00)	1	1771
asymptomatic DVT	RR=1.15	[0.82;1.63]	0.4174	1.0000 (I^2=1.00)	1	1765
non-fatal pulmonary embolism	RR=0.33	[0.03;3.16]	0.3357	1.0000 (I^2=0.00)	1	2298
distal DVT	RR=1.50	[0.90;2.50]	0.1218	1.0000 (I^2=0.00)	1	1765

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
proximal DVT	RR=0.90	[0.55;1.49]	0.6906	1.0000 (I^2=0.00)	1	1799
all cause death	RR=0.98	[0.02;49.28]	0.9914	1.0000 (I^2=0.00)	1	2309
major bleeding	RR=0.83	[0.42;1.63]	0.5840	1.0000 (I^2=0.00)	1	2317
dabigatran 150mg versus enoxaparin (europe regimen)						
symptomatic deep-vein thrombosis	RR=0.37	[0.10;1.37]	0.1349	1.0000 (I^2=0.00)	1	1038
major VTE (fatal and non fatal DVT,PE)	RR=1.08	[0.58;2.01]	0.8152	1.0000 (I^2=0.00)	1	1038
total VTE and all-cause mortality	RR=1.07	[0.92;1.25]	0.3560	1.0000 (I^2=1.00)	1	1038
asymptomatic DVT	RR=1.10	[0.94;1.29]	0.2315	1.0000 (I^2=0.00)	1	1038
non-fatal pulmonary embolism	RR=1.95	[0.07;57.91]	0.7003	1.0000 (I^2=0.00)	1	1038
distal DVT	RR=1.07	[0.91;1.27]	0.3980	1.0000 (I^2=0.00)	1	1038
proximal DVT	RR=1.03	[0.54;1.98]	0.9277	1.0000 (I^2=0.00)	1	1038
major or clinically relevant non-major bleeding	RR=1.22	[0.84;1.78]	0.2910	1.0000 (I^2=0.00)	1	1397
all cause death	RR=0.98	[0.06;15.70]	0.9910	1.0000 (I^2=0.00)	1	1381
major bleeding	RR=0.99	[0.39;2.47]	0.9781	1.0000 (I^2=0.00)	1	1397
dabigatran 150mg versus enoxaparin (US regimen)						
major VTE (fatal and non fatal DVT,PE)	RR=1.36	[0.70;2.63]	0.3643	1.0000 (I^2=0.00)	1	1324
total VTE and all-cause mortality	RR=1.33	[1.12;1.58]	0.0000	1.0000 (I^2=0.00)	1	1292
non-fatal pulmonary embolism	RR=0.10	[0.01;1.81]	0.1188	1.0000 (I^2=0.00)	1	1292
distal DVT	RR=1.33	[1.10;1.59]	0.0025	1.0000 (I^2=0.00)	1	1292
major or clinically relevant non-major bleeding	RR=0.82	[0.49;1.34]	0.4235	1.0000 (I^2=0.00)	1	1739
all cause death	RR=2.00	[0.07;59.47]	0.6894	1.0000 (I^2=0.00)	1	1753
major bleeding	RR=0.42	[0.15;1.17]	0.0973	1.0000 (I^2=0.00)	1	1739

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 11.1: *Forest's plot for symptomatic deep-vein thrombosis*

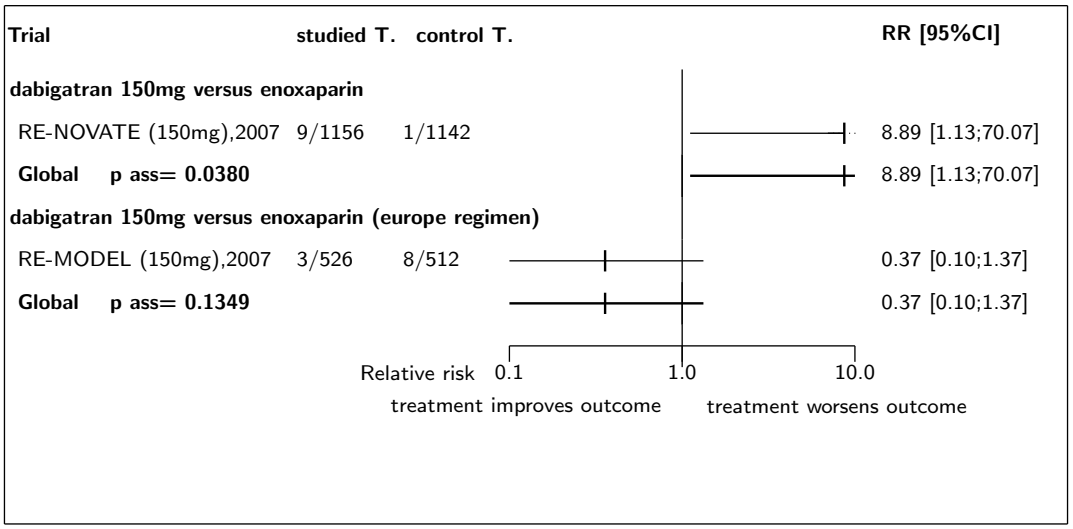


Figure 11.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

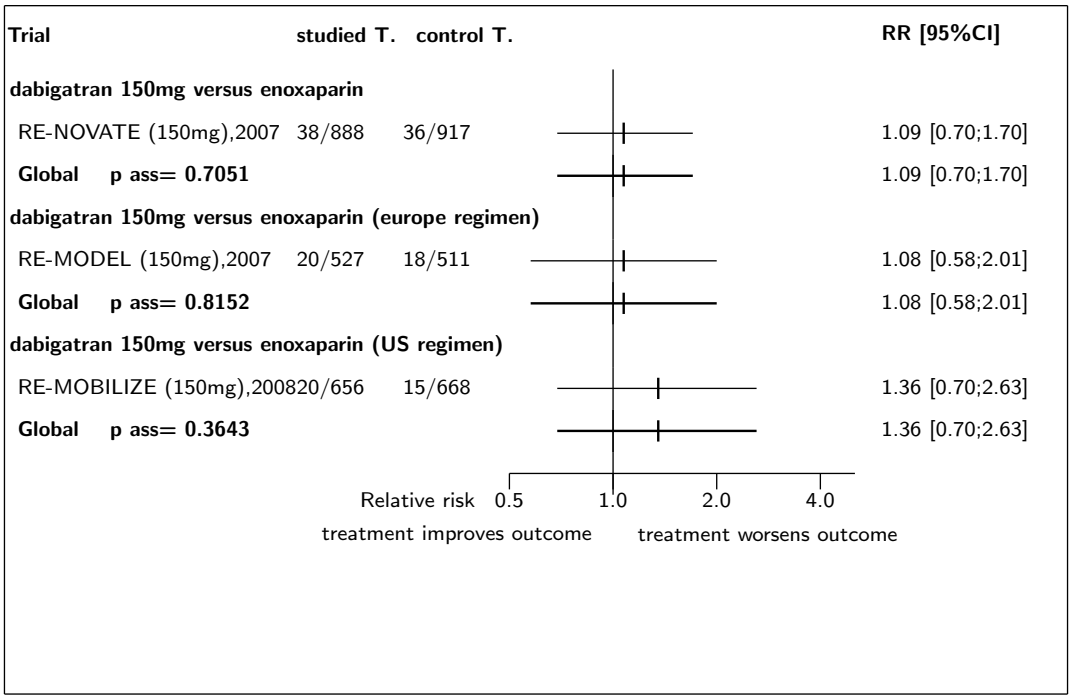


Figure 11.3: *Forest's plot for total VTE and all-cause mortality*

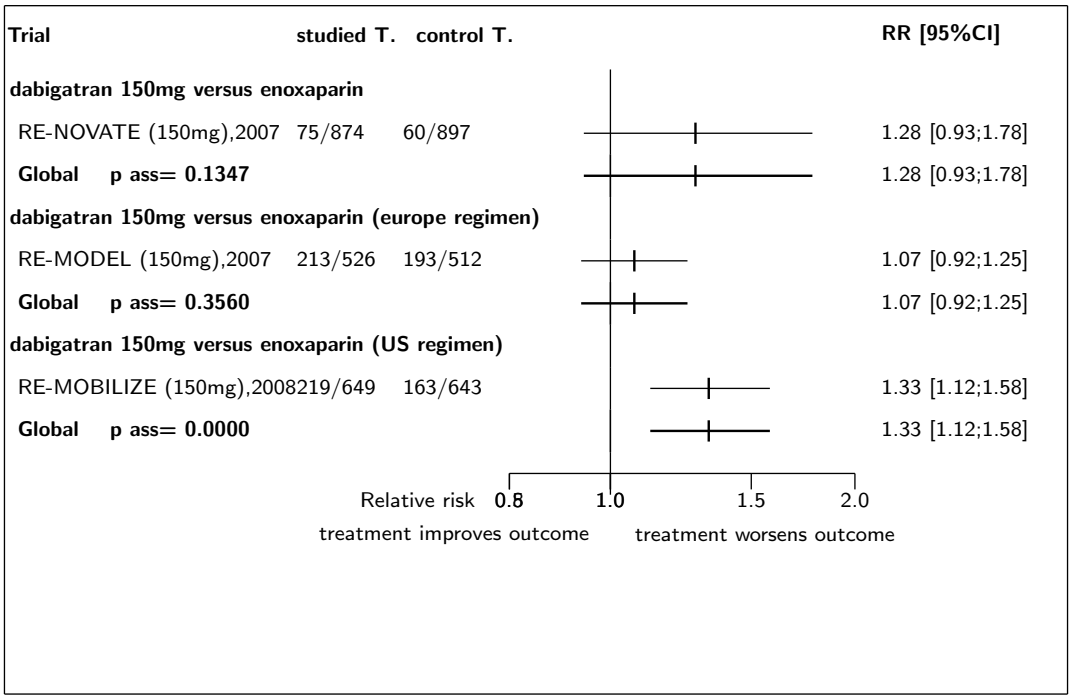


Figure 11.4: *Forest's plot for asymptomatic DVT*

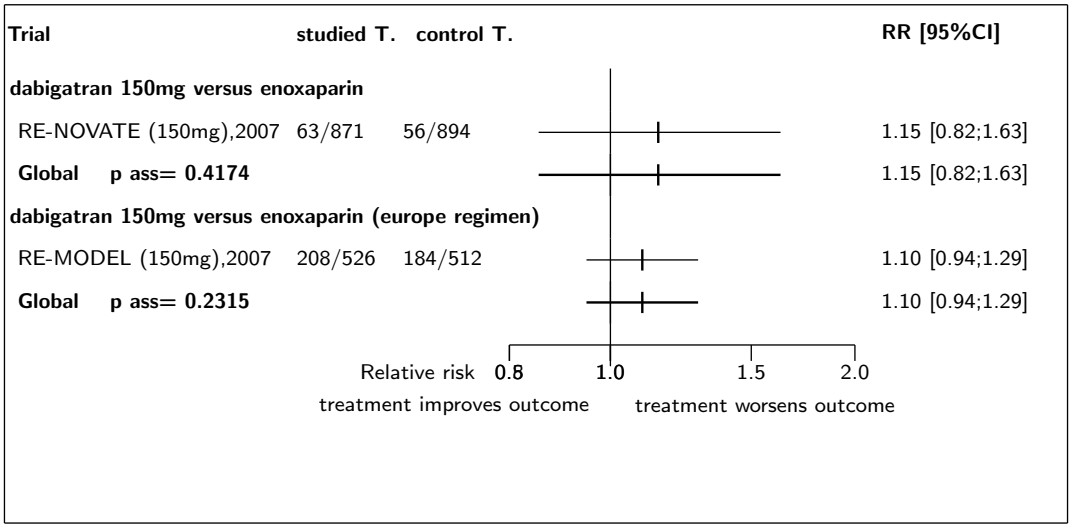


Figure 11.5: *Forest's plot for non-fatal pulmonary embolism*

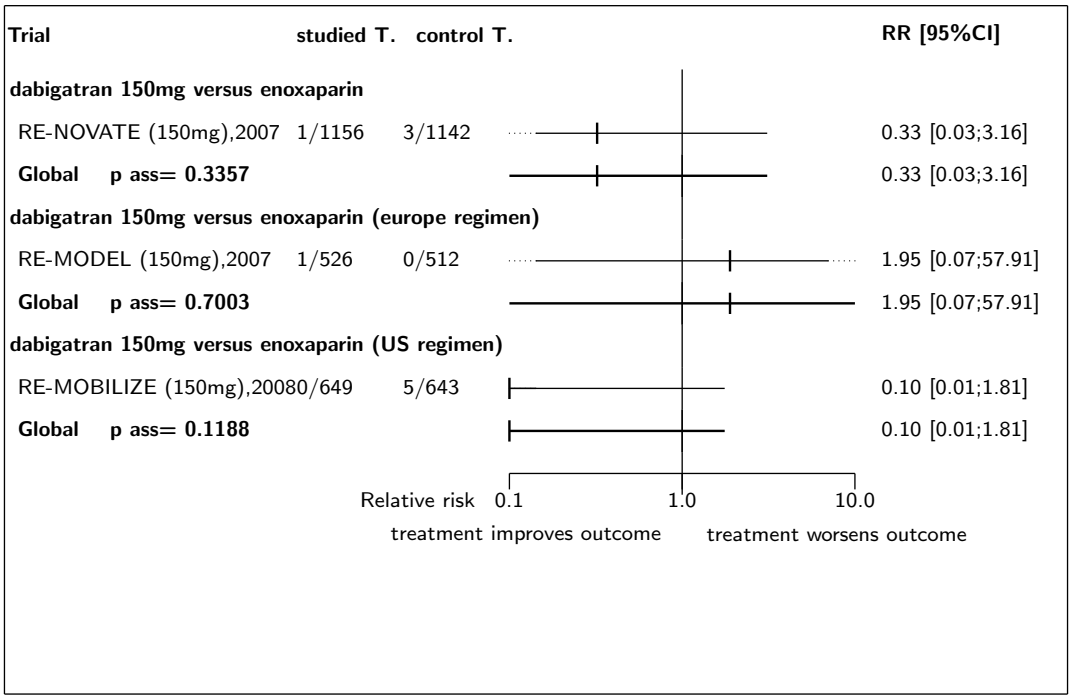


Figure 11.6: *Forest's plot for distal DVT*

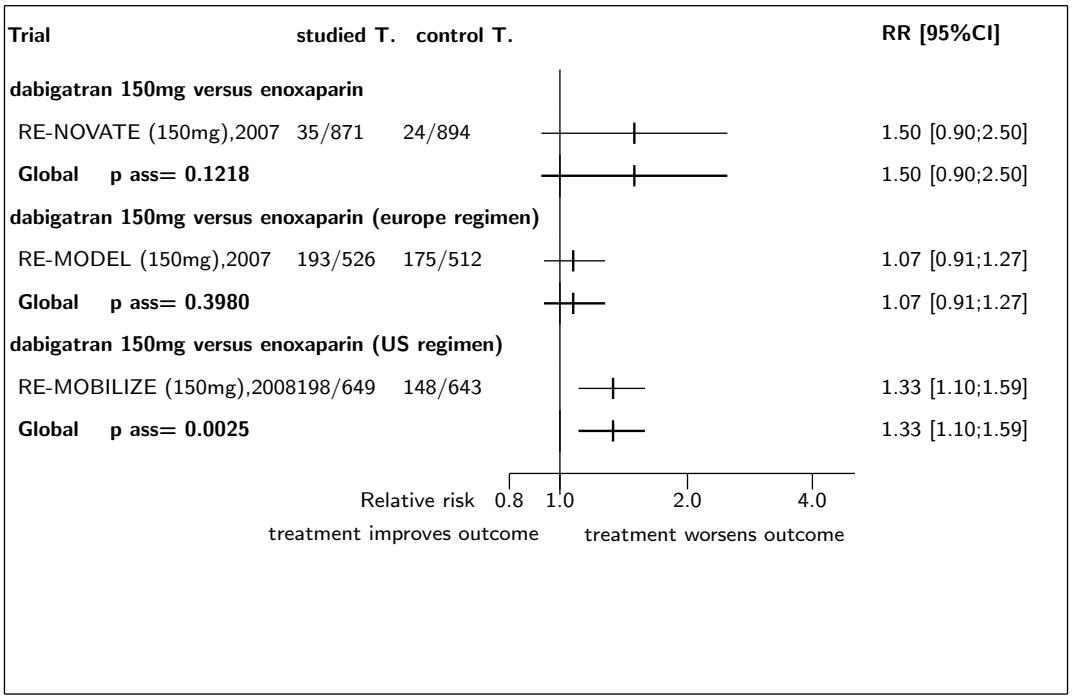


Figure 11.7: *Forest's plot for proximal DVT*

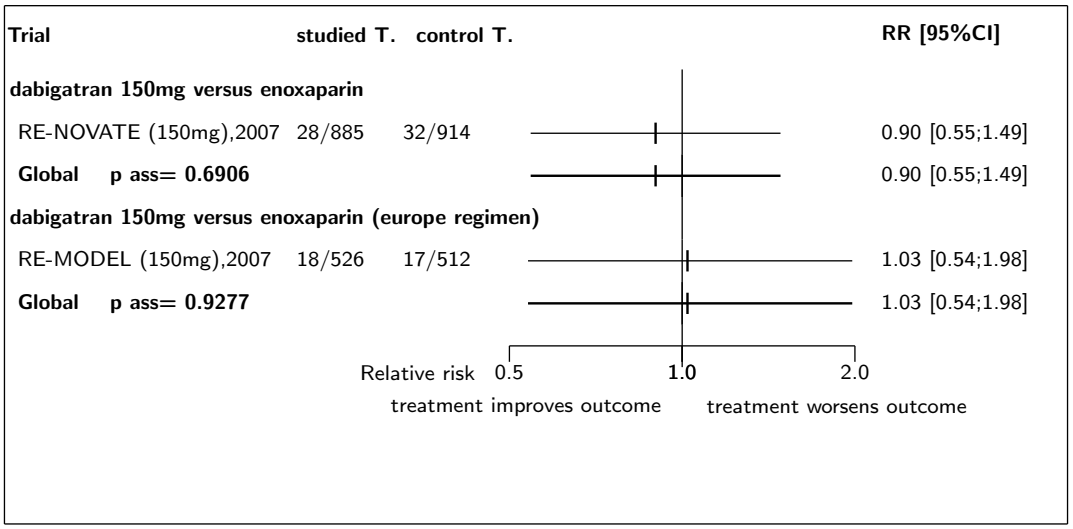


Figure 11.8: *Forest's plot for major or clinically relevant non-major bleeding*

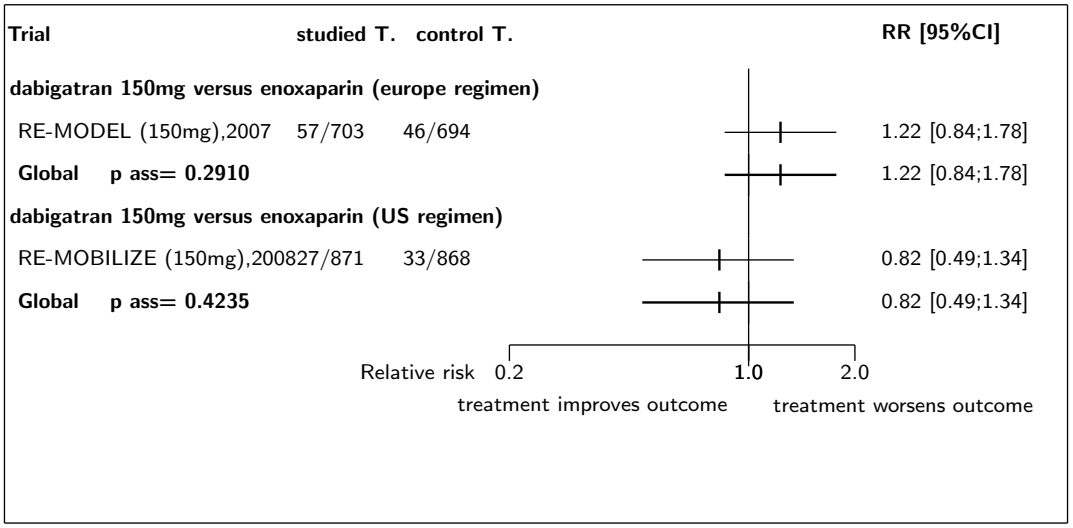


Figure 11.9: *Forest's plot for all cause death*

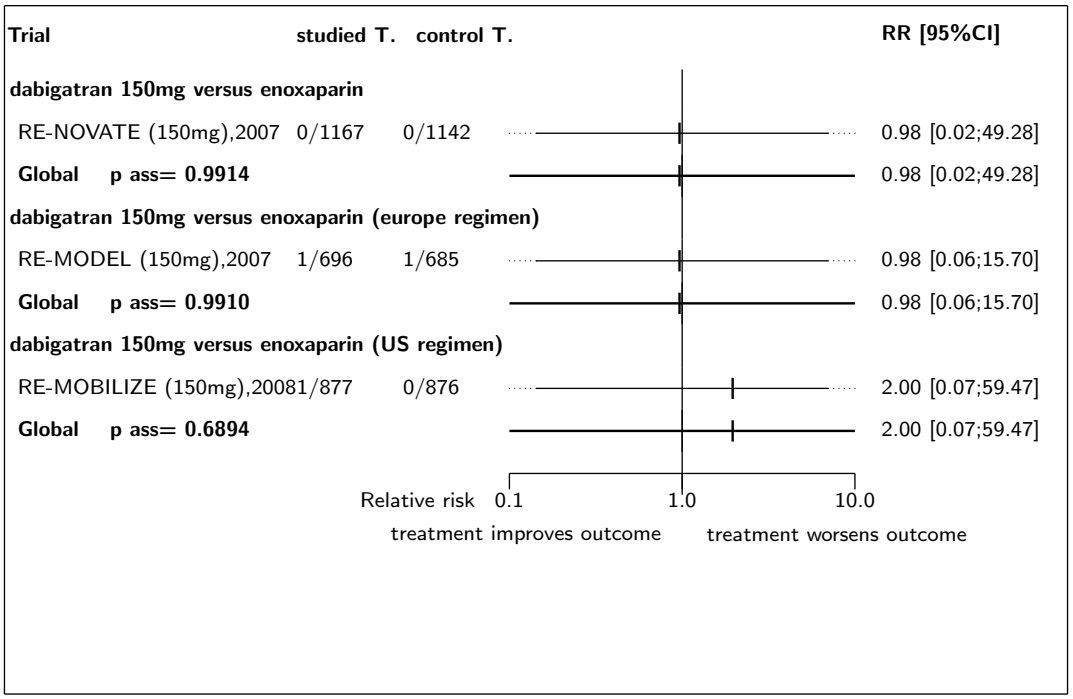
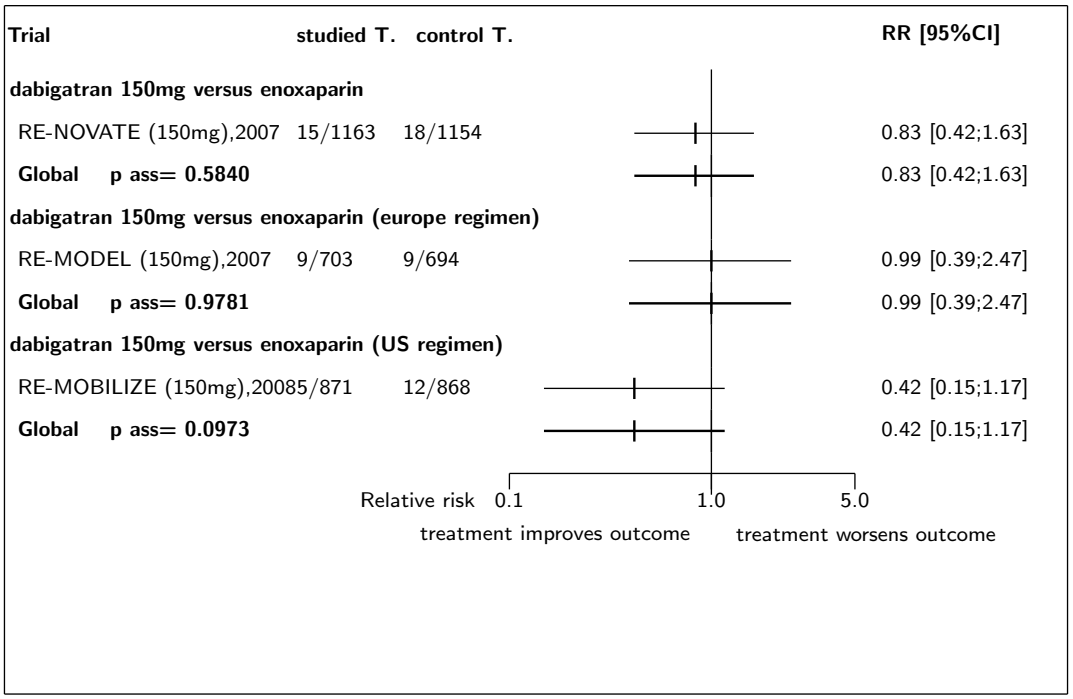


Figure 11.10: *Forest's plot for major bleeding*



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[1] Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Bller HR. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949-56. [PMID=17869635]

[2] Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Klebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Bller HR. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 2007;5:2178-85. [PMID=17764540]

[3] Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, Lieberman JR, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee JM, Caprini JA. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty 2009;24:1-9. [PMID=18534438]

11.3 Individual trial summaries

Table 11.6: *RE-NOVATE (150mg), 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2336 (1174 vs. 1162) **Follow-up duration:** 28-35 days, median 33d **Study design:** Randomized controlled trial Double blind Confirmatory trial at low risk of bias Europe, Australia, South Africa, 115 centres **Inclusion period:** dec 2004 - apr 2006	Total hip replacement **Inclusion criteria:** aged 18 years or older; weight at least 40 kg; scheduled for primary elective unilateral totalhip replacement **Exclusion criteria:** any bleeding diathesis; history ofacute intracranial disease or haemorrhagic stroke;major surgery, trauma, uncontrolled hypertension, ormyocardial infarction in the past 3 months;gastrointestinal or urogenital bleeding, or ulcer diseasein the past 6 months; severe liver disease; alanine oraspartate aminotransferase concentrations greater thantwo times the upper limit of the normal range in thepast month; severe renal insuffi ciency (creatinineclearance less than 30 mL/min); use of long-actingnon-steroidal anti-infl ammatory drugs	**Studied treatment:** dabigatran etexilate 150 mg q.d. 28-35 days **Control treatment:** Enoxaparin 40 mg q.d. for 28-25 days starting the evening before surgery **note:** 3 arms dabigatran 220mg, 150mg and placebo	Symptomatic deep-vein thrombosis RR=8.89 [1.13;70.07] Major VTE (fatal and non fatal DVT,PE) RR=1.09 [0.70;1.70] Total VTE and all-cause mortality RR=1.28 [0.93;1.78] Asymptomatic DVT RR=1.15 [0.82;1.63] Non-fatal pulmonary embolism RR=0.33 [0.03;3.16] Distal DVT RR=1.50 [0.90;2.50] (asymptomatic) Proximal DVT RR=0.90 [0.55;1.49] (asymptomatic)

Reference

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Bller HR. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949-56 [PMID=17869635]

Table 11.7: *RE-MODEL (150mg), 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1407 (708 vs. 699) **Follow-up duration:** 6-10 days, mean 8 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Europe, Australia, South Africa, 105 centres **Inclusion period:** nov 2004 - mar 2006	Total knee replacement **Inclusion criteria:** Patients <=18 years; >40 kg; scheduled for primary elective unilateral total knee replacement **Exclusion criteria:** any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the normal range (ULN) within the past month; severe renal insufficiency (creatinine clearance <30 mL/min); concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindi	**Studied treatment:** dabigatran etexilate 150 mg q.d. for 6-10 days administered 14 h after completion of surgery **Control treatment:** Enoxaparin 40 mg q.d. for 6-10 days started on the evening before surgery	Symptomatic deep-vein thrombosis RR=0.37 [0.10;1.37] Major VTE (fatal and non fatal DVT,PE) RR=1.08 [0.58;2.01] Total VTE and all-cause mortality RR=1.07 [0.92;1.25] Asymptomatic DVT RR=1.10 [0.94;1.29] Distal DVT RR=1.07 [0.91;1.27] Proximal DVT RR=1.03 [0.54;1.98] Major or clinically relevant non-major bleeding RR=1.22 [0.84;1.78]

Reference

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Klebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Bller HR. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 2007;5:2178-85 [PMID=17764540]

Table 11.8: *RE-MOBILIZE (150mg), 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1753 (877 vs. 876) **Follow-up duration:** 12-15 days, median 14d **Study design:** Randomized controlled trial Double blind Confirmatory trial at low risk of bias US, Canada, Mexico, UK, 97 centres **Inclusion period:** nov 2004 - jun 2006	Total knee replacement **Inclusion criteria:** Patients 18 years or older and weighing more than 40 kg who had undergone primary elective unilateral total knee arthroplasty **Exclusion criteria:** known inherited or acquired clinically significant bleeding disorder; major surgery, trauma, uncontrolled hypertension, or myocardial infarction within the last 3 months; history of acute intracranial disease or hemorrhagic stroke; gastrointestinal or urogenital bleeding or ulcer disease within the last 6 months; severe liver disease; aspartate or alanine aminotransferase (AST, ALT) levels higher than 2x the upper limit of the normal range (ULN) within the last month; severe renal insufficiency (creatinine clearance <30 mL/min); need for concomitant longacting nonsteroidal anti-infla	**Studied treatment:** dabigatran etexilate 150 mg q.d. for 12-15 days started 6 to 12 hours after completion of surgery **Control treatment:** enoxaparin 30 mg SC BID after surgery for 12-15 days started 12 to 24 hours after surgery, usually on the morning after the day of surgery	Major VTE (fatal and non fatal DVT,PE) RR=1.36 [0.70;2.63] Total VTE and all-cause mortality RR=1.33 [1.12;1.58] Distal DVT RR=1.33 [1.10;1.59] Major or clinically relevant non-major bleeding RR=0.82 [0.49;1.34]

Reference

Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, Lieberman JR, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee JM, Caprini JA. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty 2009;24:1-9 [PMID=18534438]

12 Detailed results for dabigatran 220mg

12.1 Available trials

A total of 4 RCTs which randomized 7463 patients were identified: 2 trials compared dabigatran 220mg with enoxaparin , it compared dabigatran 220mg with enoxaparin (europe regimen) and it compared dabigatran 220mg with enoxaparin (US regimen).
The average study size was 1865 patients (range 1393 to 2319). The first study was published in 2007, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We found one unpublished trial.
Distal DVT data was reported in 3 trials; 3 trials reported data on major bleeding; 3 trials reported data on proximal DVT; 3 trials reported data on total VTE and all-cause mortality; 3 trials reported data on major VTE (fatal and non fatal DVT,PE); 2 trials reported data on all cause death; 2 trials reported data on asymptomatic DVT; 2 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on non-fatal pulmonary embolism; and 2 trials reported data on major or clinically relevant non-major bleeding.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of dabigatran 220mg.

Table 12.1: *Treatment description - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Studied treatment	Control treatment
Dabigatran 220mg versus enoxaparin		
RE-NOVATE 2 (0)	dabigatran 220mg once daily for 28-35 Days (110 mg administered on the day of surgery)	enoxaparin 40mg subcutaneous once daily for 28-35 Days
RE-NOVATE (220mg) (2007) [**?**] [b]	dabigatran etexilate 220 mg q.d. for 28-35 days starting the evening before surgery	Enoxaparin 40 mg q.d. for 23-35 days
Dabigatran 220mg versus enoxaparin (europe regimen)		
RE-MODEL (220mg) (2007) [**?**]	dabigatran etexilate 220 mg q.d. 6-10 days administered 14 h after completion of surgery	Enoxaparin 40 mg q.d. for 6-10 days started on the evening before surgery
Dabigatran 220mg versus enoxaparin (US regimen)		
RE-MOBILIZE (220mg) (2008) [**?**]	dabigatran etexilate 220 mg for 12-15 days started 6 to 12 hours after completion of surgery	Enoxaparin 30mg SC BID after surgery for 12-15 days started 12 to 24 hours after surgery, usually on the morning after the day of surgery

b) 3 arms dabigatran 220mg, 150mg and placebo

Table 12.2: *Descriptions of participants - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Patients
Dabigatran 220mg versus enoxaparin	

continued...

Trial	Patients	
RE-NOVATE 2 (0)	Patients undergoing total hip-replacement surgery	
	Inclusion criteria: patients scheduled to undergo primary, unilateral, elective total hip arthroplasty; male or female 18 years of age or older.	**Exclusion criteria:** 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;major surgery or trauma (e.g., hip fracture) within 3 months of enrolment;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;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 or are nursing. or are of child-bearing potential and are NOT practicing acceptable methods of birth control;known allergy to radio opaque contrast media;history of thrombocytopenia, including heparin-induced thrombocytopenia, or a platelet count <100,000 cells/microliter 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;leg amputee;known alcohol or drug abuse which would interfere with completion of the study;contraindications to enoxaparin;

continued...

Trial	Patients	
RE-NOVATE (220mg) (2007) [?]	Total hip replacement	
	Inclusion criteria: aged 18 years or older; weight at least 40 kg; scheduled for primary elective unilateral total hip replacement	**Exclusion criteria:** any bleeding diathesis; history of acute intracranial disease or haemorrhagic stroke; major surgery, trauma, uncontrolled hypertension, or myocardial infarction in the past 3 months; gastrointestinal or urogenital bleeding, or ulcer disease in the past 6 months; severe liver disease; alanine or aspartate aminotransferase concentrations greater than two times the upper limit of the normal range in the past month; severe renal insuffi ciency (creatinine clearance less than 30 mL/min); use of long-acting non-steroidal anti-infl ammatory drugs
Dabigatran 220mg versus enoxaparin (europe regimen)		
RE-MODEL (220mg) (2007) [?]	Patients undergoing total knee replacement	
	Inclusion criteria: patients >=18 years; >40 kg; scheduled for primary elective unilateral total knee replacement	**Exclusion criteria:** any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the normal range (ULN) 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
Dabigatran 220mg versus enoxaparin (US regimen)		
RE-MOBILIZE (220mg) (2008) [?]	Total knee replacement	
	Inclusion criteria: patients 18 years or older and weighing more than 40 kg who had undergone primary elective unilateral total knee arthroplasty	**Exclusion criteria:** known inherited or acquired clinically significant bleeding disorder; major surgery, trauma, uncontrolled hypertension, or myocardial infarction within the last 3 months; history of acute intracranial disease or hemorrhagic stroke; gastrointestinal or urogenital bleeding or ulcer disease within the last 6 months; severe liver disease; aspartate or alanine aminotransferase (AST, ALT) levels higher than 2x the upper limit of the normal range (ULN) within the last month; severe renal insufficiency (creatinine clearance <30 mL/min); need for concomitant longacting nonsteroidal anti-inflammatory drug therapy or treatment with an anticoagulant during study drug treatment; active malignant disease; platelet count less than 100 10^9/L,

Table 12.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 220mg versus enoxaparin				
RE-NOVATE 2, 0 n=2013	Parallel groups double-blind confirmatory trial at low risk of bias	28-35 days (mean 32d) inclusion period: mar 2008- sept 2009	108 centres	venous thromboembolism or death
RE-NOVATE (220mg), 2007 [**?**] n=2319	Parallel groups double blind confirmatory trial at low risk of bias	28-35 days, median 33d inclusion period: dec 2004 - apr 2006	Europe, Australia, South Africa 115 centres	total VTE and all-cause mortality
Dabigatran 220mg versus enoxaparin (europe regimen)				
RE-MODEL (220mg), 2007 [**?**] n=1393	double blind confirmatory trial at low risk of bias	6-10 days, mean 8 days inclusion period: nov 2004 - mar 2006	Europe, Australia, South Africa 105 centres	total VTE and all-cause mortality
Dabigatran 220mg versus enoxaparin (US regimen)				
RE-MOBILIZE (220mg), 2008 [**?**] n=1738	Parallel groups double blind confirmatory trial at low risk of bias	12-15 days, median 14d inclusion period: nov 2004 - jun 2006	US, Canada, Mexico, UK 97 centres	total VTE and all-cause mortality

Table 12.4: *Trial characteristics - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	**mean follow-up**	**test intervalle**
Dabigatran 220mg versus enoxaparin		
RE-NOVATE 2, 0	32 days	2-4 (3)
RE-NOVATE (220mg), 2007 [?]	33 days	2-4 (3)
Dabigatran 220mg versus enoxaparin (europe regimen)		
RE-MODEL (220mg), 2007 [?]	8 days	2-4 (3)
Dabigatran 220mg versus enoxaparin (US regimen)		
RE-MOBILIZE (220mg), 2008 [?]	14 days	2-4 (3)

12.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Dabigatran 220mg versus enoxaparin

Only one of the 2 studies eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between dabigatran 220mg and enoxaparin, with a RR of 6.03 (95%CI 0.73 to 49.98, p=0.0961) in favour of enoxaparin. In other words, symptomatic deep-vein thrombosis was slightly lower in the enoxaparin group , but this was not statistically significant.
Only one of the 2 studies eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. No statistically significant difference between the groups was found in major VTE (fatal and non fatal DVT,PE), with a RR of 0.78 (95% CI 0.48 to 1.27, p=0.3273).
Only one of the 2 studies eligible for this comparison provided data on **total VTE and all-cause mortality**. No statistically significant difference between the groups was found in total VTE and all-cause mortality, with a RR of 0.90 (95% CI 0.63 to 1.29, p=0.5652).
Only one of the 2 studies eligible for this comparison provided data on **asymptomatic DVT**. No statistically significant difference between the groups was found in asymptomatic DVT, with a RR of 0.73 (95% CI 0.49 to 1.08, p=0.1153).
Only one of the 2 studies eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 1.70 (95% CI 0.41 to 7.09, p=0.4671).
Only one of the 2 studies eligible for this comparison provided data on **distal DVT**. No statistically significant difference between the groups was found in distal DVT, with a RR of 0.94 (95% CI 0.53 to 1.66, p=0.8251).
Only one of the 2 studies eligible for this comparison provided data on **proximal DVT**. No statistically significant difference between the groups was found in proximal DVT, with a RR of 0.57 (95% CI 0.32 to 1.00, p=0.0519).
Only one of the 2 studies eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 6.03 (95% CI 0.30 to 120.18, p=0.2395).
Only one of the 2 studies eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 1.29 (95% CI 0.70 to 2.37, p=0.4190).

Dabigatran 220mg versus enoxaparin (europe regimen)

The single study eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between dabigatran 220mg and enoxaparin (europe regimen), with a RR of 0.13 (95%CI 0.02 to 1.01, p=0.0513) in favour of dabigatran 220mg. In other words, symptomatic deep-vein thrombosis was slightly lower in the dabigatran 220mg group , but this was not statistically significant.
The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. No statistically significant difference between the groups was found in major VTE (fatal and non fatal DVT,PE), with a RR of 0.73 (95% CI 0.36 to 1.47, p=0.3787).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. No statistically significant difference between the groups was found in total VTE and all-cause mortality, with a RR of 0.97 (95% CI 0.82 to 1.13, p=0.6649).
The single study eligible for this comparison provided data on **asymptomatic DVT**. No statistically significant difference between the groups was found in asymptomatic DVT, with a RR of 1.00 (95% CI 0.85 to 1.18, p=0.9877).

The single study eligible for this comparison provided data on **distal DVT**. No statistically significant difference between the groups was found in distal DVT, with a RR of 1.02 (95% CI 0.85 to 1.21, p=0.8596).
The single study eligible for this comparison provided data on **proximal DVT**. No statistically significant difference between the groups was found in proximal DVT, with a RR of 0.82 (95% CI 0.40 to 1.69, p=0.5985).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.01 (95% CI 0.06 to 16.19, p=0.9917).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 1.14 (95% CI 0.46 to 2.78, p=0.7804).

Dabigatran 220mg versus enoxaparin (US regimen)

The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. No statistically significant difference between the groups was found in major VTE (fatal and non fatal DVT,PE), with a RR of 1.51 (95% CI 0.79 to 2.91, p=0.2141).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of enoxaparin (US regimen) in total VTE and all-cause mortality, with a RR of 1.23 (95% CI 1.03 to 1.47, p=0.0238).
The single study eligible for this comparison provided data on **distal DVT**. No statistically significant difference between the groups was found in distal DVT, with a RR of 1.20 (95% CI 0.99 to 1.45, p=0.0604).
The single study eligible for this comparison provided data on **proximal DVT**. No statistically significant difference between the groups was found in proximal DVT, with a RR of 1.49 (95% CI 0.67 to 3.33, p=0.3306).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 0.42 (95% CI 0.15 to 1.19, p=0.1036).

Table 12.5: *Results details - oral direct thrombin inhibitor - dabigatran 220mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dabigatran 220mg versus enoxaparin						
symptomatic deep-vein thrombosis	RR=6.03	[0.73;49.98]	0.0961	1.0000 (I^2=0.00)	1	2279
major VTE (fatal and non fatal DVT,PE)	RR=0.78	[0.48;1.27]	0.3273	1.0000 (I^2=0.00)	1	1826
total VTE and all-cause mortality	RR=0.90	[0.63;1.29]	0.5652	1.0000 (I^2=0.00)	1	1777
asymptomatic DVT	RR=0.73	[0.49;1.08]	0.1153	1.0000 (I^2=0.00)	1	1777
non-fatal pulmonary embolism	RR=1.70	[0.41;7.09]	0.4671	1.0000 (I^2=0.00)	1	1777
distal DVT	RR=0.94	[0.53;1.66]	0.8251	1.0000 (I^2=0.00)	1	1768
proximal DVT	RR=0.57	[0.32;1.00]	0.0519	1.0000 (I^2=0.00)	1	1819
all cause death	RR=6.03	[0.30;120.18]	0.2395	1.0000 (I^2=0.00)	1	2279
major bleeding	RR=1.29	[0.70;2.37]	0.4190	1.0000 (I^2=0.00)	1	2300
dabigatran 220mg versus enoxaparin (europe regimen)						
symptomatic deep-vein thrombosis	RR=0.13	[0.02;1.01]	0.0513	1.0000 (I^2=0.00)	1	1360

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
major VTE (fatal and non fatal DVT,PE)	RR=0.73	[0.36;1.47]	0.3787	1.0000 (I^2=0.00)	1	1017
total VTE and all-cause mortality	RR=0.97	[0.82;1.13]	0.6649	1.0000 (I^2=0.00)	1	1015
asymptomatic DVT	RR=1.00	[0.85;1.18]	0.9877	1.0000 (I^2=0.00)	1	1015
distal DVT	RR=1.02	[0.85;1.21]	0.8596	1.0000 (I^2=0.00)	1	1014
proximal DVT	RR=0.82	[0.40;1.69]	0.5985	1.0000 (I^2=0.00)	1	1013
major or clinically relevant non-major bleeding	RR=1.11	[0.76;1.63]	0.5933	1.0000 (I^2=0.00)	1	1373
all cause death	RR=1.01	[0.06;16.19]	0.9917	1.0000 (I^2=0.00)	1	1360
major bleeding	RR=1.14	[0.46;2.78]	0.7804	1.0000 (I^2=0.00)	1	1373
dabigatran 220mg versus enoxaparin (US regimen)						
major VTE (fatal and non fatal DVT,PE)	RR=1.51	[0.79;2.91]	0.2141	1.0000 (I^2=0.00)	1	1286
total VTE and all-cause mortality	RR=1.23	[1.03;1.47]	0.0238	1.0000 (I^2=0.00)	1	1247
distal DVT	RR=1.20	[0.99;1.45]	0.0604	1.0000 (I^2=1.00)	1	1247
proximal DVT	RR=1.49	[0.67;3.33]	0.3306	1.0000 (I^2=1.00)	1	1247
major or clinically relevant non-major bleeding	RR=0.86	[0.52;1.41]	0.5482	1.0000 (I^2=0.00)	1	1725
major bleeding	RR=0.42	[0.15;1.19]	0.1036	1.0000 (I^2=0.00)	1	1725

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 12.1: *Forest's plot for symptomatic deep-vein thrombosis*

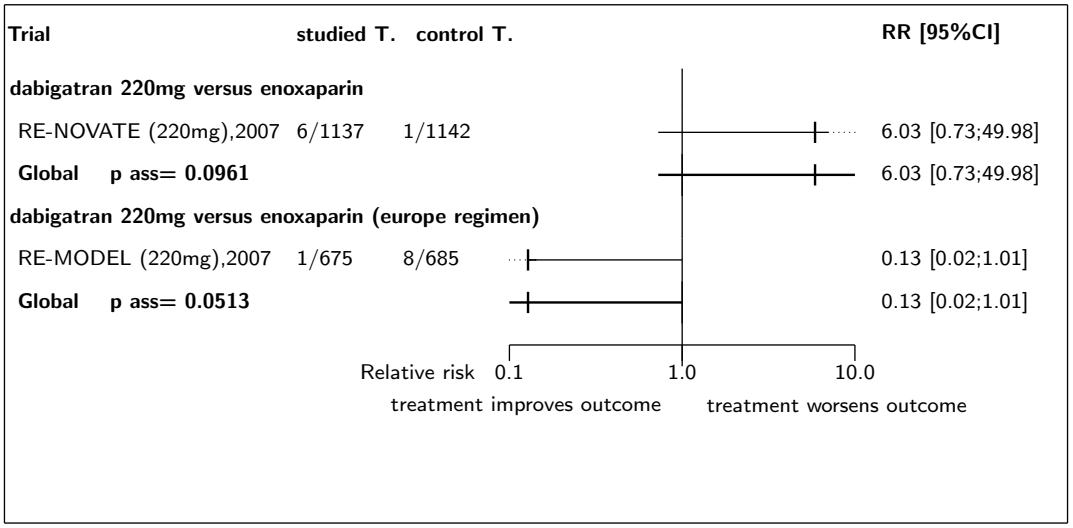


Figure 12.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

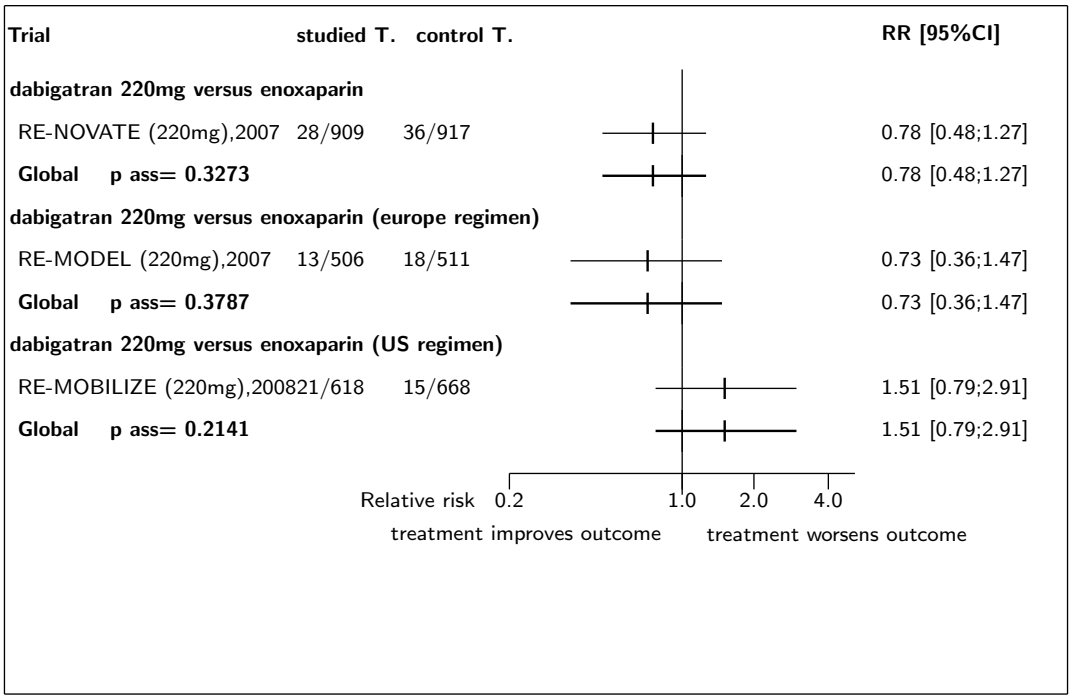


Figure 12.3: *Forest's plot for total VTE and all-cause mortality*

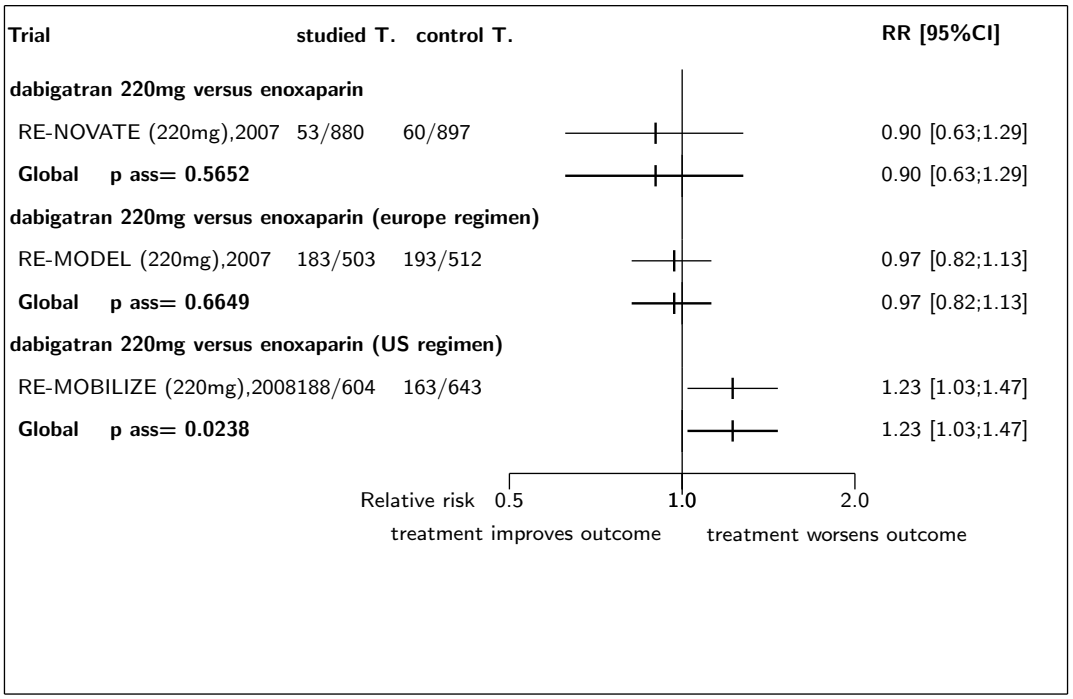


Figure 12.4: *Forest's plot for asymptomatic DVT*

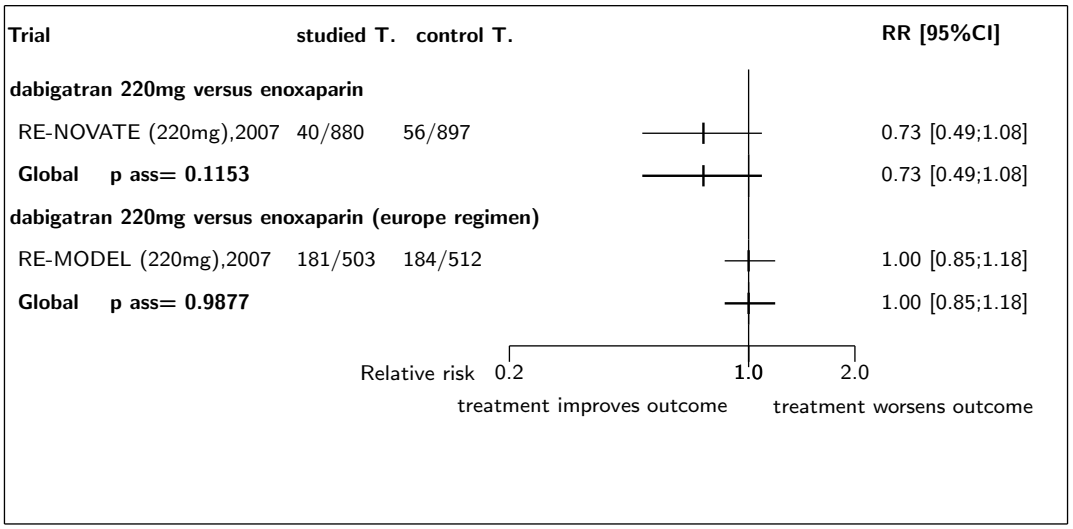


Figure 12.5: *Forest's plot for non-fatal pulmonary embolism*

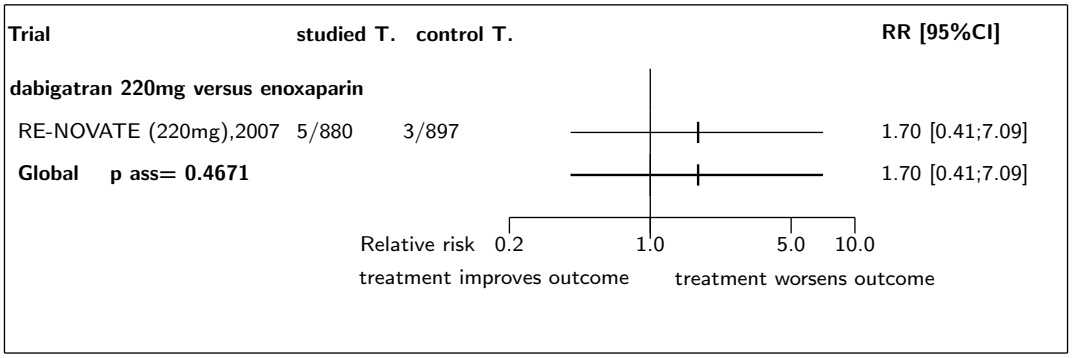


Figure 12.6: *Forest's plot for distal DVT*

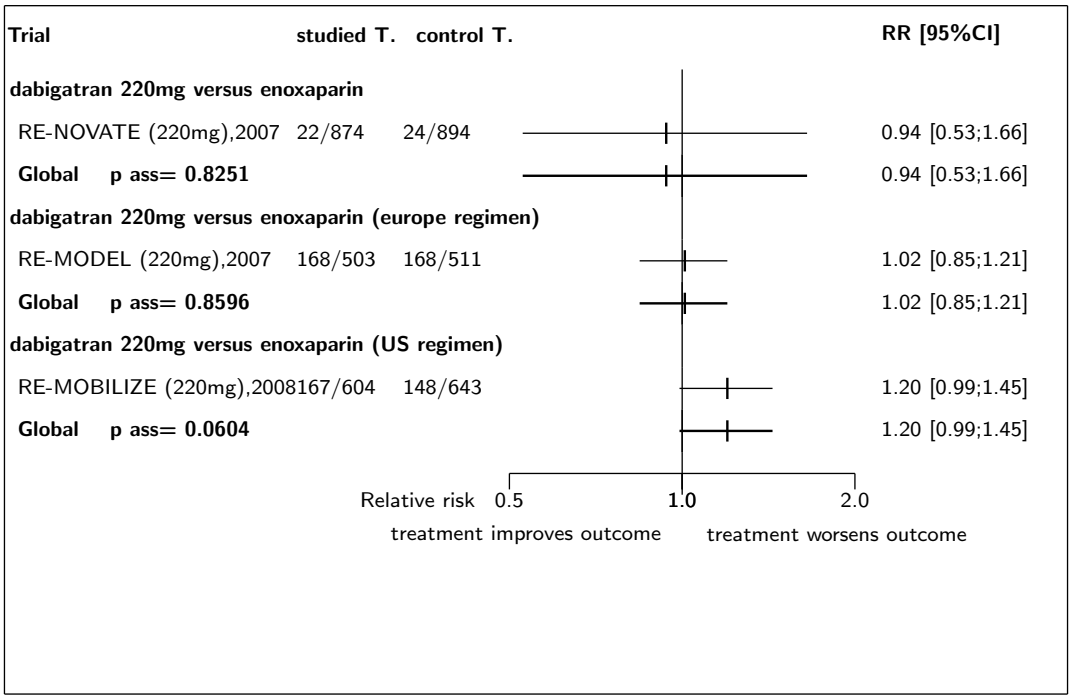


Figure 12.7: *Forest's plot for proximal DVT*

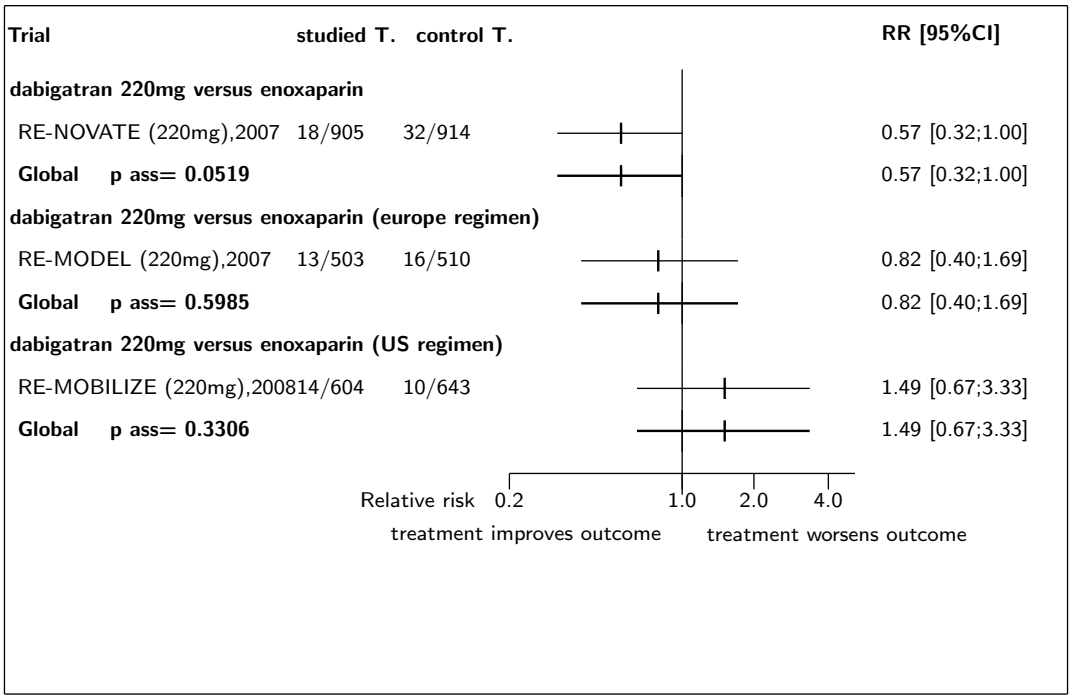


Figure 12.8: *Forest's plot for major or clinically relevant non-major bleeding*

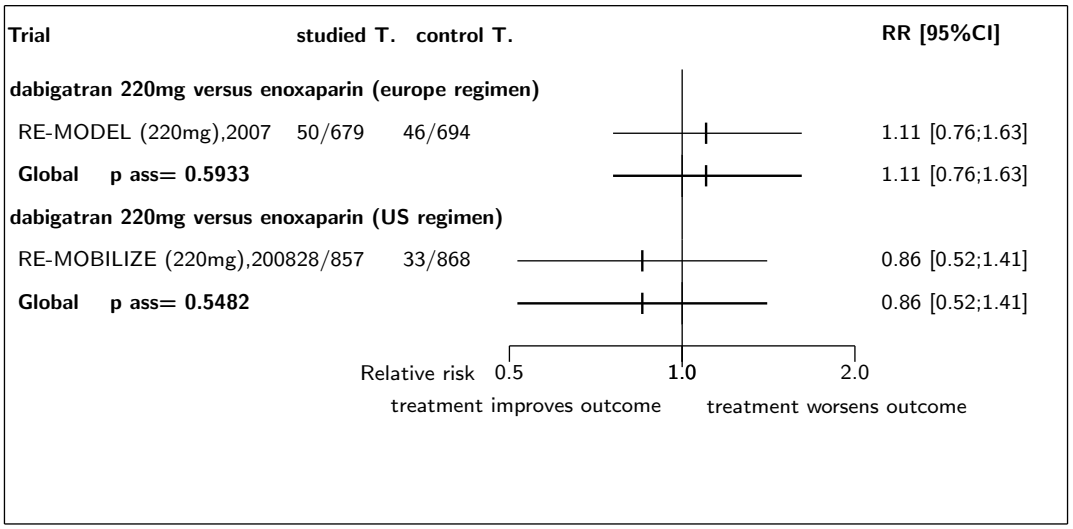


Figure 12.9: *Forest's plot for all cause death*

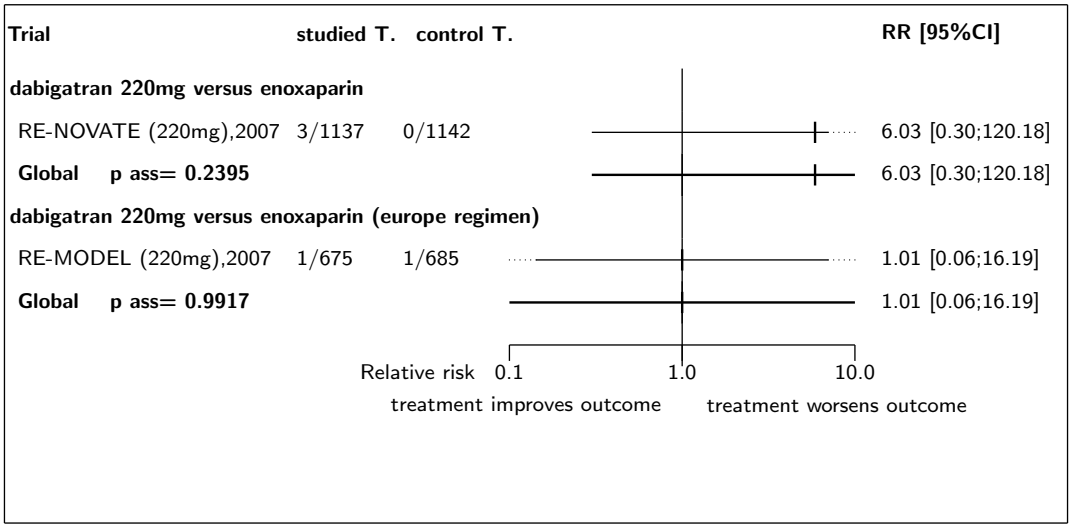
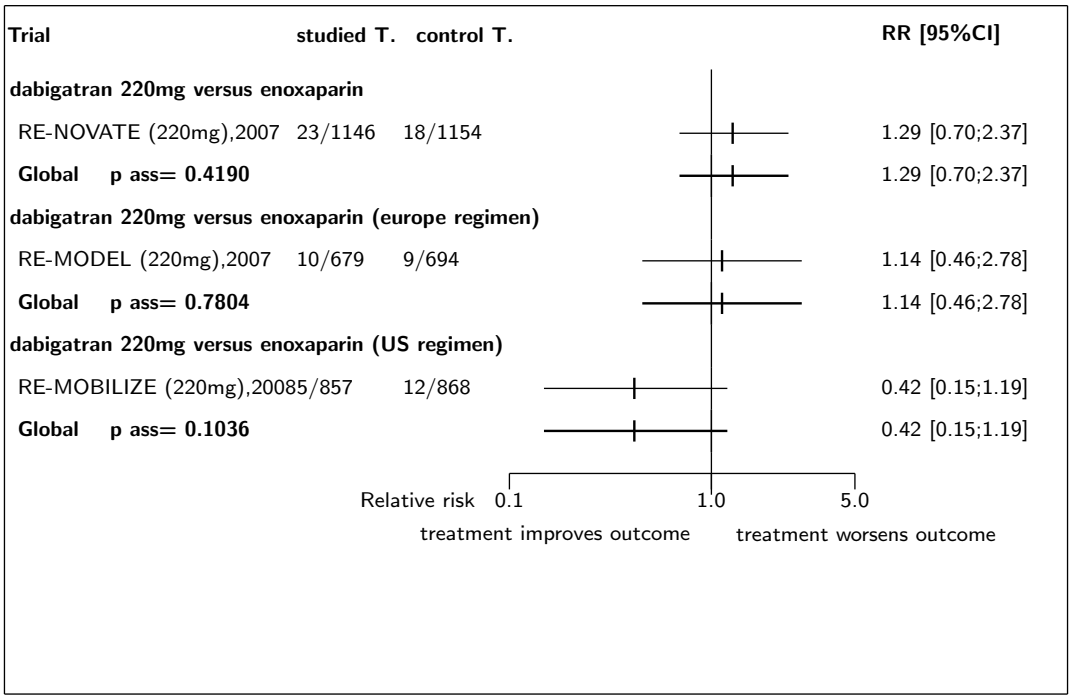


Figure 12.10: *Forest's plot for major bleeding*



References

[1] Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Bller HR. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949-56. [PMID=17869635]

[2] Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Klebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Bller HR. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 2007 Nov;5:2178-85. [PMID=17764540]

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12.3 Individual trial summaries

Table 12.6: *RE-NOVATE 2, 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2013 (1010 vs. 1003) **Follow-up duration:** 28-35 days (mean 32d) **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias 108 centres **Inclusion period:** mar 2008- sept 2009	Patients undergoing total hip-replacement surgery **Inclusion criteria:** patients scheduled to undergo primary, unilateral, elective total hip arthroplasty; male or female 18 years of age or older. **Exclusion criteria:** 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;major surgery or trauma (e.g., hip fracture) within 3 months of enrolment;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 withi	**Studied treatment:** dabigatran 220mg once daily for 28-35 Days (110 mg administered on the day of surgery) **Control treatment:** enoxaparin 40mg subcutaneous once daily for 28-35 Days	
Reference			

Table 12.7: *RE-NOVATE (220mg), 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2319 (1157 vs. 1162) **Follow-up duration:** 28-35 days, median 33d **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Europe, Australia, South Africa, 115 centres **Inclusion period:** dec 2004 - apr 2006	Total hip replacement **Inclusion criteria:** aged 18 years or older; weight at least 40 kg; scheduled for primary elective unilateral total hip replacement **Exclusion criteria:** any bleeding diathesis; history of acute intracranial disease or haemorrhagic stroke; major surgery, trauma, uncontrolled hypertension, or myocardial infarction in the past 3 months; gastrointestinal or urogenital bleeding, or ulcer disease in the past 6 months; severe liver disease; alanine or aspartate aminotransferase concentrations greater than two times the upper limit of the normal range in the past month; severe renal insuffi ciency (creatinine clearance less than 30 mL/min); use of long-acting non-steroidal anti-infl ammatory drugs	**Studied treatment:** dabigatran etexilate 220 mg q.d. for 28-35 days starting the evening before surgery **Control treatment:** Enoxaparin 40 mg q.d. for 23-35 days **note:** 3 arms dabigatran 220mg, 150mg and placebo	Symptomatic deep-vein thrombosis RR=6.03 [0.73;49.98] Major VTE (fatal and non fatal DVT,PE) RR=0.78 [0.48;1.27] Total VTE and all-cause mortality RR=0.90 [0.63;1.29] (during treatment period) Asymptomatic DVT RR=0.73 [0.49;1.08] Non-fatal pulmonary embolism RR=1.70 [0.41;7.09] Distal DVT RR=0.94 [0.53;1.66] (asymptomatic distal) Proximal DVT RR=0.57 [0.32;1.00] (asymptomatic)

Reference

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Bller HR. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949-56 [PMID=17869635]

Table 12.8: *RE-MODEL (220mg), 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1393 (694 vs. 699) **Follow-up duration:** 6-10 days, mean 8 days **Study design:** Randomized controlled trial Double blind Confirmatory trial at low risk of bias Europe, Australia, South Africa, 105 centres **Inclusion period:** nov 2004 - mar 2006	Patients undergoing total knee replacement **Inclusion criteria:** Patients >=18 years; >40 kg; scheduled for primary elective unilateral total knee replacement **Exclusion criteria:** any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the normal range (ULN) within the past month; severe renal insufficiency (creatinine clearance <30 mL/min); concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindi	**Studied treatment:** dabigatran etexilate 220 mg q.d. 6-10 days administered 14 h after completion of surgery **Control treatment:** Enoxaparin 40 mg q.d. for 6-10 days started on the evening before surgery	Symptomatic deep-vein thrombosis RR=0.13 [0.02;1.01] Major VTE (fatal and non fatal DVT,PE) RR=0.73 [0.36;1.47] Total VTE and all-cause mortality RR=0.97 [0.82;1.13] Asymptomatic DVT RR=1.00 [0.85;1.18] Distal DVT RR=1.02 [0.85;1.21] Proximal DVT RR=0.82 [0.40;1.69] Major or clinically relevant non-major bleeding RR=1.11 [0.76;1.63]

Reference

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Klebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Bller HR. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 2007 Nov;5:2178-85 [PMID=17764540]

Table 12.9: *RE-MOBILIZE (220mg), 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1738 (862 vs. 876) **Follow-up duration:** 12-15 days, median 14d **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias US, Canada, Mexico, UK, 97 centres **Inclusion period:** nov 2004 - jun 2006	Total knee replacement **Inclusion criteria:** Patients 18 years or older and weighing more than 40 kg who had undergone primary elective unilateral total knee arthroplasty **Exclusion criteria:** known inherited or acquired clinically significant bleeding disorder; major surgery, trauma, uncontrolled hypertension, or myocardial infarction within the last 3 months; history of acute intracranial disease or hemorrhagic stroke; gastrointestinal or urogenital bleeding or ulcer disease within the last 6 months; severe liver disease; aspartate or alanine aminotransferase (AST, ALT) levels higher than 2x the upper limit of the normal range (ULN) within the last month; severe renal insufficiency (creatinine clearance <30 mL/min); need for concomitant longacting nonsteroidal anti-infla	**Studied treatment:** dabigatran etexilate 220 mg for 12-15 days started 6 to 12 hours after completion of surgery **Control treatment:** Enoxaparin 30mg SC BID after surgery for 12-15 days started 12 to 24 hours after surgery, usually on the morning after the day of surgery	Major VTE (fatal and non fatal DVT,PE) RR=1.51 [0.79;2.91] Total VTE and all-cause mortality RR=1.23 [1.03;1.47] Distal DVT RR=1.20 [0.99;1.45] Proximal DVT RR=1.49 [0.67;3.33] Major or clinically relevant non-major bleeding RR=0.86 [0.52;1.41]

Reference

. The Oral Thrombin Inhibitor Dabigatran Etexilate vs the North American Enoxaparin Regimen for the Prevention of Venous Thromboembolism after Knee Arthroplasty Surgery. J Arthroplasty 2008;: [PMID=18534438]

13 Global meta-analysis: all oral direct thrombin inhibitor

13.1 Global meta-analysis: all oral direct thrombin inhibitor versus enoxaparin

Table 13.1: *All oral direct thrombin inhibitorversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=7.35	1.68;32.23	0.0081	0.7965 (0.00)	2	4577
major VTE (fatal and non fatal DVT,PE)	RR=0.94	0.68;1.30	0.7005	0.3285 (0.00)	2	3631
total VTE and all-cause mortality	RR=1.08	0.77;1.53	0.6513	0.1518 (0.51)	2	3548
asymptomatic DVT	RR=0.93	0.59;1.45	0.7387	0.0858 (0.66)	2	3542
non-fatal pulmonary embolism	RR=0.95	0.21;4.43	0.9527	0.2293 (0.31)	2	4075
distal DVT	RR=1.21	0.76;1.91	0.4212	0.2315 (0.30)	2	3533
proximal DVT	RR=0.73	0.47;1.15	0.1770	0.2297 (0.31)	2	3618
all cause death	RR=3.09	0.29;33.29	0.3532	0.4700 (0.00)	2	4588
major bleeding	RR=1.06	0.67;1.66	0.8141	0.3434 (0.00)	2	4617

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

13.2 Global meta-analysis: all oral direct thrombin inhibitor versus enoxaparin (europe regimen)

Table 13.2: *All oral direct thrombin inhibitorversus enoxaparin (europe regimen)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=0.27	0.09;0.82	0.0210	0.3999 (0.00)	2	2398
major VTE (fatal and non fatal DVT,PE)	RR=0.91	0.57;1.45	0.6815	0.4162 (0.00)	2	2055
total VTE and all-cause mortality	RR=1.02	0.91;1.14	0.7099	0.3425 (0.00)	2	2053
asymptomatic DVT	RR=1.05	0.94;1.18	0.3808	0.4153 (0.00)	2	2053
non-fatal pulmonary embolism	RR=1.95	0.07;57.91	0.7003	1.0000 (0.00)	1	1038
distal DVT	RR=1.05	0.93;1.18	0.4612	0.6525 (0.00)	2	2052
proximal DVT	RR=0.93	0.57;1.51	0.7752	0.6515 (0.00)	2	2051
all cause death	RR=1.00	0.14;7.08	0.9995	0.9878 (0.00)	2	2741
major bleeding	RR=1.06	0.56;2.01	0.8568	0.8304 (0.00)	2	2770

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

13.3 Global meta-analysis: all oral direct thrombin inhibitor versus enoxaparin (US regimen)

Table 13.3: *All oral direct thrombin inhibitorversus enoxaparin (US regimen)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
major VTE (fatal and non fatal DVT,PE)	RR=1.43	0.90;2.28	0.1282	0.8191 (0.00)	2	2610
total VTE and all-cause mortality	RR=1.28	1.13;1.45	0.0000	0.5211 (0.00)	2	2539
non-fatal pulmonary embolism	RR=0.10	0.01;1.81	0.1188	1.0000 (0.00)	1	1292
distal DVT	RR=1.26	1.11;1.44	0.0000	0.4663 (0.00)	2	2539
proximal DVT	RR=1.49	0.67;3.33	0.3306	1.0000 (1.00)	1	1247
all cause death	RR=2.00	0.07;59.47	0.6894	1.0000 (0.00)	1	1753
major bleeding	RR=0.42	0.20;0.87	0.0202	0.9828 (0.00)	2	3464

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

14 Ongoing studies of oral direct thrombin inhibitor

No ongoing trial was identified.

15 Excluded studies for oral direct thrombin inhibitor

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 15.1: *Excluded studies of oral direct thrombin inhibitor*

Study	Exclusion reason
BISTRO II (225mg bid) (2005) [**?**]	

References

[1] Eriksson BI, Dahl OE, Bller HR, Hettiarachchi R, Rosencher N, Bravo ML, Ahnfelt L, Piovella F, Stangier J, Klebo P, Reilly P. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. J Thromb Haemost 2005 Jan;3:103-11. [PMID=15634273]