Antithrombotics for DVT prophylaxis in elective major knee surgery

A systematic review and meta-analysis of randomized clinical trials

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This report should be referenced as follows:
TrialResults-center.org; Results of all major randomized clinical trials about Antithrombotics for DVT prophylaxis in elective major knee surgery .

Contents

0.1 Synthesis of the meta-analysis results

In all 18 randomised controlled trials (RCTs) were included. These included 5 studies of **direct factor Xa inhibitors** involving 9,248 patients, 2 studies of **low molecular weight heparin** involving 375 patients, 8 studies of **oral direct thrombin inhibitor** involving 12,617 patients, 1 studie of **platelet aggregation inhibitors** involving 36 patients and 2 studies of **synthetic oligosaccharide** involving 1,085 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 5 trials (including 9,248 patients) were identified .
Among these comparisons, two trials are about apixaban and 3 about rivaroxaban.
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 1.

Table 1: *Results summary - Apixaban*

Benefit	Harmful	No evidence
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 → myocardial infarction (fatal and non fatal) RR=1.00^{NS} [0.06;15.98] k=1 → coronary event RR=1.00^{NS} [0.06;16.05] 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
		→ 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 → any bleedings RR=0.73^{NS} [0.26;2.04] k=1 → total VTE and all-cause mortality RR=0.39^{NS} [0.08;1.98] k=1 → asymptomatic DVT RR=0.63^{NS} [0.29;1.40] k=1 → proximal DVT RR=0.33^{NS} [0.03;3.10] k=1 → all cause death RR=1.96^{NS} [0.07;57.94] k=1 → major bleeding RR=0.97^{NS} [0.02;48.45] 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 2.

Table 2: *Results summary - Rivaroxaban*

Benefit	Harmful	No evidence
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 → myocardial infarction (fatal and non fatal) RR=0.51^{NS} [0.05;5.61] k=1 → coronary event RR=0.51^{NS} [0.05;5.59] 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 (US regimen)		

continued...

Benefit	Harmful	No evidence
↓ 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 → myocardial infarction (fatal and non fatal) RR=0.20^{NS} [0.02;1.69] k=1 → coronary event RR=0.33^{NS} [0.03;3.16] 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)

0.1.2 Low molecular weight heparin

Reports of 2 trials (including 375 patients) were identified .
Among these comparisons, one trial are about ardeparin and one about enoxaparin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Ardeparin

Results obtained with ardeparin for all the endpoints with data in at least one trial are summarized table 3.

Table 3: *Results summary - Ardeparin*

Benefit	Harmful	No evidence
Ardeparin versus placebo		
↓ deep vein thrombosis RR=0.50¶ [0.35;0.71] k=1		→ bleeding RR=1.02^{NS} [0.21;4.94] 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)

Enoxaparin

Results obtained with enoxaparin for all the endpoints with data in at least one trial are summarized table 4.

Table 4: *Results summary - Enoxaparin*

Benefit	Harmful	No evidence
	Enoxaparin versus placebo	
↓ deep vein thrombosis RR=0.29¶ [0.16;0.52] k=1		→ bleeding RR=0.79^{NS} [0.22;2.80] 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)

0.1.3 Oral direct thrombin inhibitor

Reports of 5 trials (including 12,617 patients) were identified .
Among these comparisons, two trials are about dabigatran 150mg,two about dabigatran 220mg and 4 about ximelagatran.
No trial was excluded on grounds 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 5.

Table 5: *Results summary - Dabigatran 150mg*

Benefit	Harmful	No evidence
	Dabigatran 150mg versus enoxaparin (europe regimen)	
		→ 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)	

continued...

Benefit	Harmful	No evidence
	↑ 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=1.36NS [0.70;2.63] k=1 → non-fatal pulmonary embolism RR=0.10NS [0.01;1.81] k=1 → major or clinically relevant non-major bleeding RR=0.82NS [0.49;1.34] k=1 → all cause death RR=2.00NS [0.07;59.47] k=1 → major bleeding RR=0.42NS [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 6.

Table 6: *Results summary - Dabigatran 220mg*

Benefit	Harmful	No evidence
Dabigatran 220mg versus enoxaparin (europe regimen)		
		→ symptomatic deep-vein thrombosis RR=0.13NS [0.02;1.01] k=1 → major VTE (fatal and non fatal DVT,PE) RR=0.73NS [0.36;1.47] k=1 → total VTE and all-cause mortality RR=0.97NS [0.82;1.13] k=1 → asymptomatic DVT RR=1.00NS [0.85;1.18] k=1 → distal DVT RR=1.02NS [0.85;1.21] k=1 → proximal DVT RR=0.82NS [0.40;1.69] k=1 → coronary event RR=1.26NS [0.40;3.99] k=1 → major or clinically relevant non-major bleeding RR=1.11NS [0.76;1.63] k=1 → all cause death RR=1.01NS [0.06;16.19] k=1 → major bleeding RR=1.14NS [0.46;2.78] k=1
Dabigatran 220mg versus enoxaparin (US regimen)		

continued...

Benefit	Harmful	No evidence
	↑ 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 → coronary event RR=1.05^{NS} [0.48;2.31] 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)

Ximelagatran

Results obtained with ximelagatran for all the endpoints with data in at least one trial are summarized table 7.

Table 7: *Results summary - Ximelagatran*

Benefit	Harmful	No evidence
	Ximelagatran versus Dalteparin	
		→ venous thromboembolism RR=0.83^{NS} [0.25;2.76] k=1 → major bleeding RR=0.97^{NS} [0.02;47.50] k=1
	Ximelagatran versus Enoxaparin	
		→ venous thromboembolism RR=0.88^{NS} [0.63;1.24] H k=3 → major bleeding RR=1.44^{NS} [0.49;4.22] H k=3

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

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

0.1.4 Platelet aggregation inhibitors

Only one trials including 36 patients was found.
Among these comparisons, one trial are about Aspirin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with aspirin for all the endpoints with data in at least one trial are summarized table 8.

Table 8: *Results summary - Aspirin*

Benefit	Harmful	No evidence
	Aspirin versus placebo	
↓ deep vein thrombosis RR=0.44* [0.23;0.85] k=1		→ non-fatal pulmonary embolism RR=0.38^{NS} [0.10;1.41] k=1 → proximal DVT RR=0.33^{NS} [0.06;1.73] k=1 → fatal pulmonary embolism RR=0.50^{NS} [0.01;23.69] k=1 → bleeding RR=1.00^{NS} [0.04;27.75] k=1

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

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

0.1.5 Synthetic oligosaccharide

Reports of 2 trials (including 1,085 patients) were identified .
Among these comparisons, two trials are about fondaparinux.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with fondaparinux for all the endpoints with data in at least one trial are summarized table 9.

Table 9: *Results summary - Fondaparinux*

Benefit	Harmful	No evidence
	Fondaparinux versus enoxaparin	
↓ deep vein thrombosis RR=0.46¶ [0.33;0.63] k=1 ↓ proximal DVT RR=0.45* [0.21;0.99] k=1 ↓ venous thromboembolism RR=0.45¶ [0.33;0.62] k=2		→ symptomatic deep-vein thrombosis RR=0.75^{NS} [0.17;3.33] k=1 → symptomatic pulmonary embolism RR=0.25^{NS} [0.03;2.23] k=1 → non-fatal pulmonary embolism RR=0.25^{NS} [0.03;2.23] k=1 → symptomatic venous thromboembolism (DVT, PE) RR=0.43^{NS} [0.11;1.65] k=1 → fatal pulmonary embolism RR=1.00^{NS} [0.02;50.30] k=1 → all cause death RR=0.67^{NS} [0.11;3.97] k=1 → major bleeding RR=5.19^{NS} [0.52;52.10] k=2

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

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

1 Introduction

1.1 Aim of the report

This report review all the randomized clinical trials of antithrombotics for the treatment of DVT prophylaxis in elective major knee surgery . The following classes of treatment are considered:

1. direct factor Xa inhibitors
2. Low molecular weight heparin
3. oral direct thrombin inhibitor
4. platelet aggregation inhibitors
5. synthetic oligosaccharide

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of antithrombotics for the treatment of DVT prophylaxis in elective major knee surgery .

1.2.1 Sources searched

The following electronic databases were searched for relevant published literature for the period up to 2017 - 7 - 1:

- MEDLINE,
- EMBASE,
- Cochrane Database of Systematic Reviews (CDSR),
- Cochrane Central Register of Controlled Trials (CCTR),
- Health Technology Assessment (HTA) database,
- ISI Web of Science Proceedings (Index to Scientific and Technical Proceedings),
- ISI Web of Science 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 antithrombotics was used.
Studies using other interventions in addition to antithrombotics therapy were included only if the treatment received by the intervention and control groups was identical in all respects other than the use of antithrombotics.

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 reviews 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 Major bleeding, All cause death, proximal DVT, major VTE (fatal and non fatal DVT,PE), total VTE and all-cause mortality, myocardial infarction (fatal and non fatal), Symptomatic venous thromboembolism (DVT, PE), Symptomatic deep-vein thrombosis, Deep vein thrombosis, non-fatal pulmonary embolism, asymptomatic DVT, distal DVT, Coronary event, 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 I to **??**, listed by therapeutic class. The therapeutic classes included direct factor Xa inhibitors, Low molecular weight heparin, oral direct thrombin inhibitor, platelet aggregation inhibitors, synthetic oligosaccharide,
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 5 randomized comparisons which enrolled 9248 patients were identified. In all, 2 randomized comparisons concerned apixaban and 3 rivaroxaban.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 33) for apixaban and in section 4 (page 47) for rivaroxaban.

The average study size was 1849 patients (range 207 to 3148). 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 2.1 (page 21) 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 2.2 to 2.3 (page 23) and in the following graphs.

2.2.1 Apixaban

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), myocardial infarction (fatal and non fatal) (RR=1.00, 95% CI 0.06 to 15.98, p=0.9996, 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), total VTE and all-cause mortality (RR=0.39, 95% CI 0.08 to 1.98, p=0.2578, 1 trial), asymptomatic DVT (RR=0.63, 95% CI 0.29 to 1.40, p=0.2565, 1 trial), proximal DVT (RR=0.33, 95% CI 0.03 to 3.10, p=0.3301, 1 trial)and major bleeding (RR=0.97, 95% CI 0.02 to 48.45, p=0.9868, 1 trial).

2.2.2 Rivaroxaban

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), myocardial infarction (fatal and non fatal) (RR=0.51, 95% CI 0.05 to 5.61, p=0.5814, 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 (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), myocardial infarction (fatal and non fatal) (RR=0.20, 95% CI 0.02 to 1.69, p=0.1384, 1 trial)and major bleeding (RR=1.27, 95% CI 0.17 to 9.63, p=0.8179, 2 trials).

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

Trial	Patients	Treatments	Trial design and method
Apixaban			
Apixaban versus enoxaparin (europe regimen)			
ADVANCE 2, 2010 [1] 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 [2] 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)
Rivaroxaban			
Rivaroxaban versus enoxaparin (europe regimen)			
RECORD 3, 2008 [1] 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 (US regimen)			

continued...

Trial	Patients	Treatments	Trial design and method
ODIXa-KNEE, 2005 [2] 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)
RECORD 4, 2009 [3] 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)

Table 2.2: *Summary of all results for apixaban*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
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
myocardial infarction (fatal and non fatal)	RR=1.00	0.06;15.98	0.9996	1.0000 (0.00)	1	3057
coronary event	RR=1.00	0.06;16.05	0.9974	1.0000 (0.00)	1	3009
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
any bleedings	RR=0.73	0.26;2.04	0.5434	1.0000 (0.00)	1	303
total VTE and all-cause mortality	RR=0.39	0.08;1.98	0.2578	1.0000 (0.00)	1	220
asymptomatic DVT	RR=0.63	0.29;1.40	0.2565	1.0000 (0.00)	1	220
proximal DVT	RR=0.33	0.03;3.10	0.3301	1.0000 (0.00)	1	220
all cause death	RR=1.96	0.07;57.94	0.6959	1.0000 (0.00)	1	220
major bleeding	RR=0.97	0.02;48.45	0.9868	1.0000 (0.00)	1	303

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 rivaroxaban*

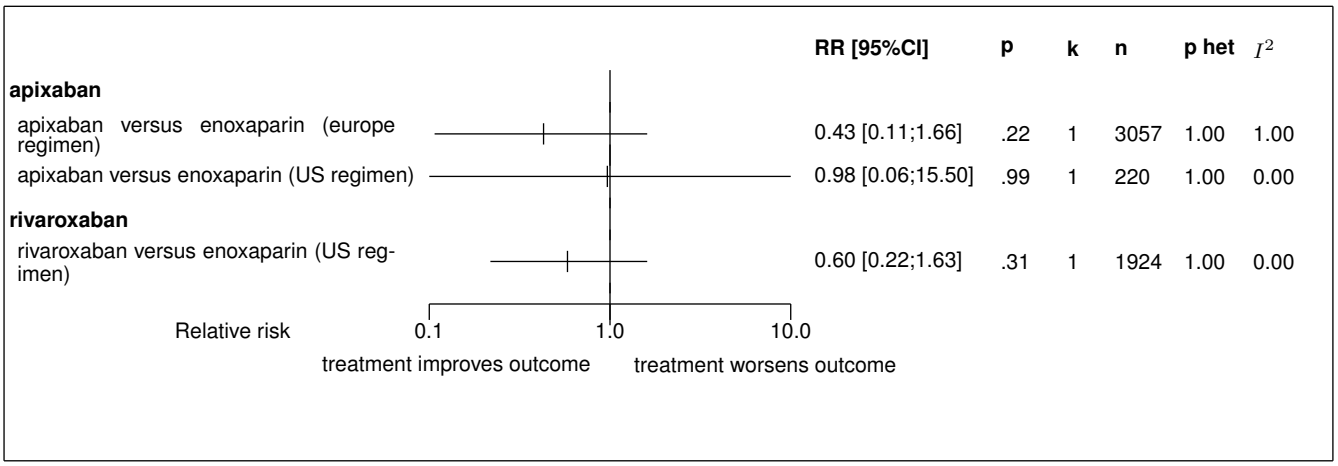
Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
rivaroxaban versus enoxaparin (europe regimen)						
major VTE (fatal and non fatal DVT,PE)	RR=0.38	0.18;0.82	0.0132	1.0000 (0.00)	1	1833
deep vein thrombosis	RR=0.53	0.41;0.68	0.0000	1.0000 (0.00)	1	1702
total VTE and all-cause mortality	RR=0.51	0.39;0.65	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
myocardial infarction (fatal and non fatal)	RR=0.51	0.05;5.61	0.5814	1.0000 (0.00)	1	2531
coronary event	RR=0.51	0.05;5.59	0.5798	1.0000 (0.00)	1	2459
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 (US regimen)						
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
myocardial infarction (fatal and non fatal)	RR=0.20	0.02;1.69	0.1384	1.0000 (0.00)	1	3148
coronary event	RR=0.33	0.03;3.16	0.3360	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

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
major bleeding	RR=1.27	0.17;9.63	0.8179	0.1769 (0.45)	2	3240

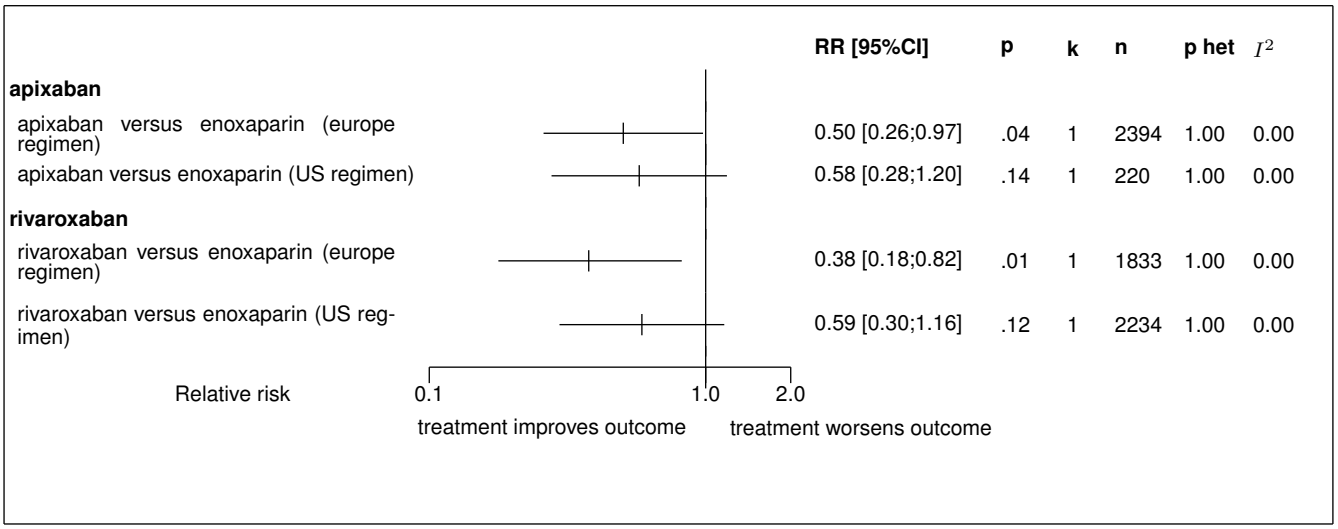
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



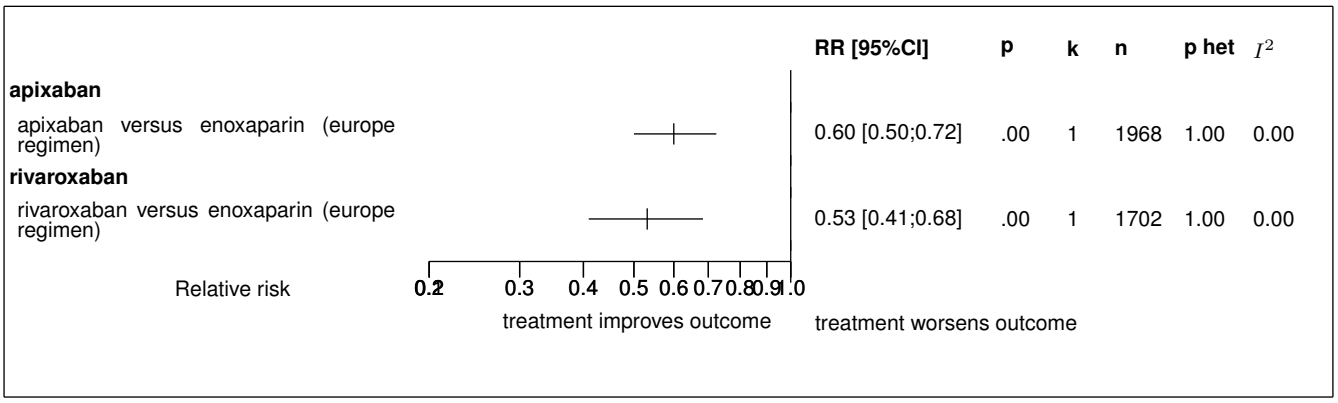
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



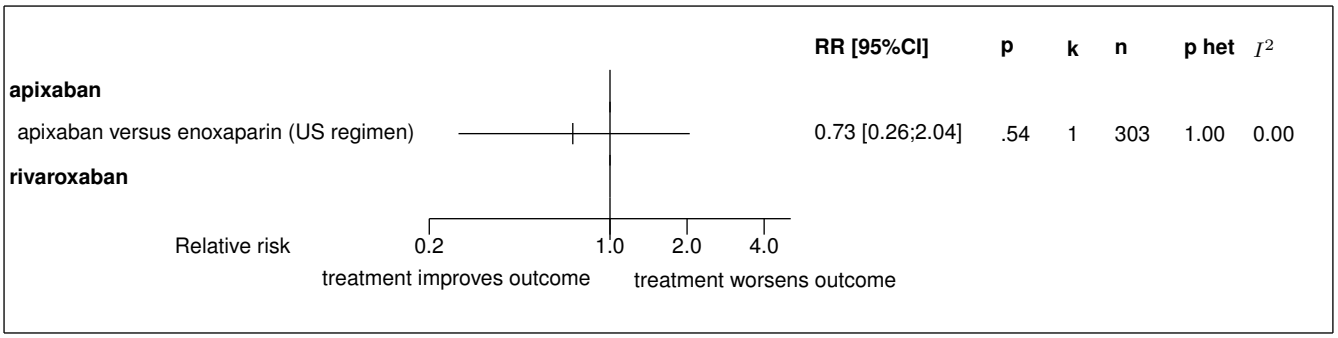
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



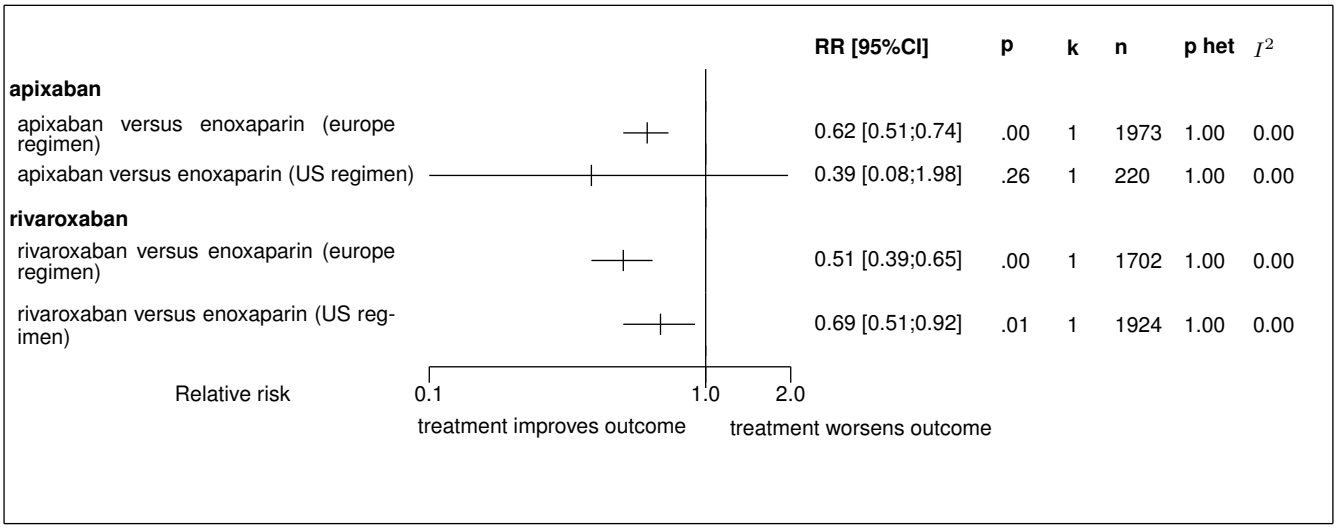
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



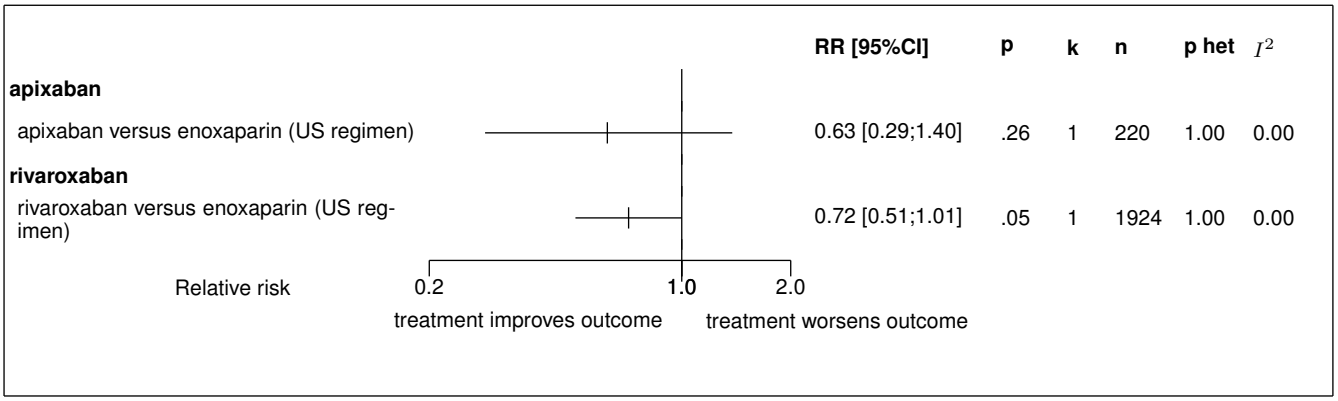
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



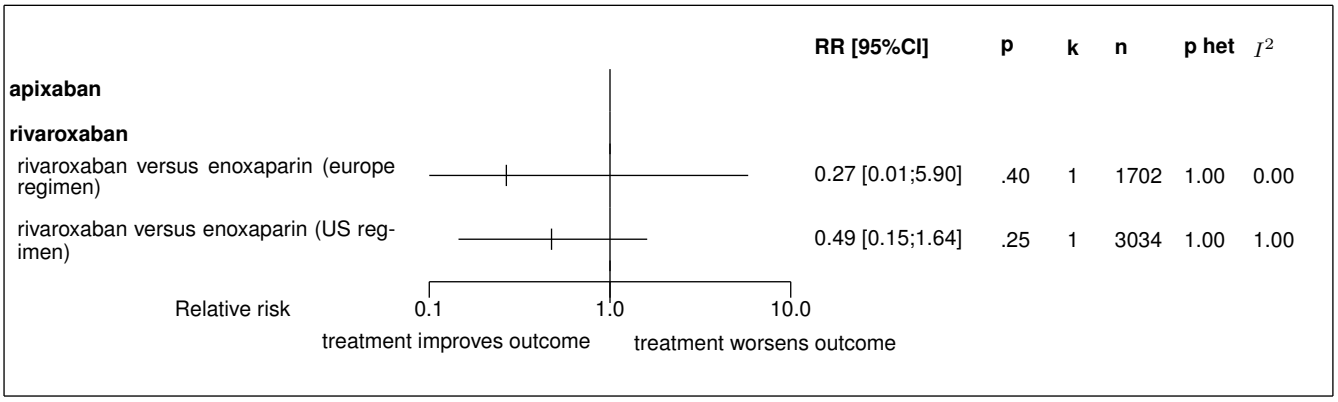
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



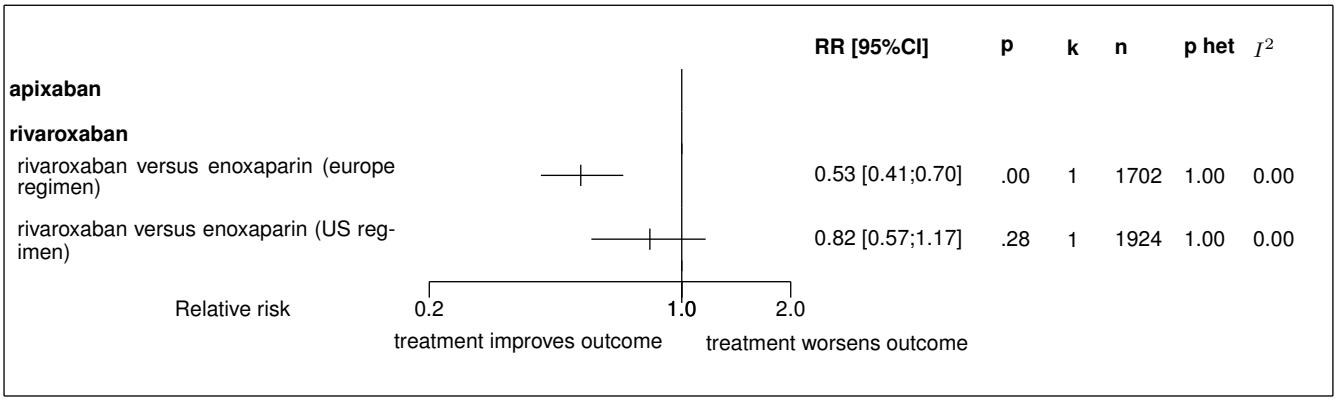
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



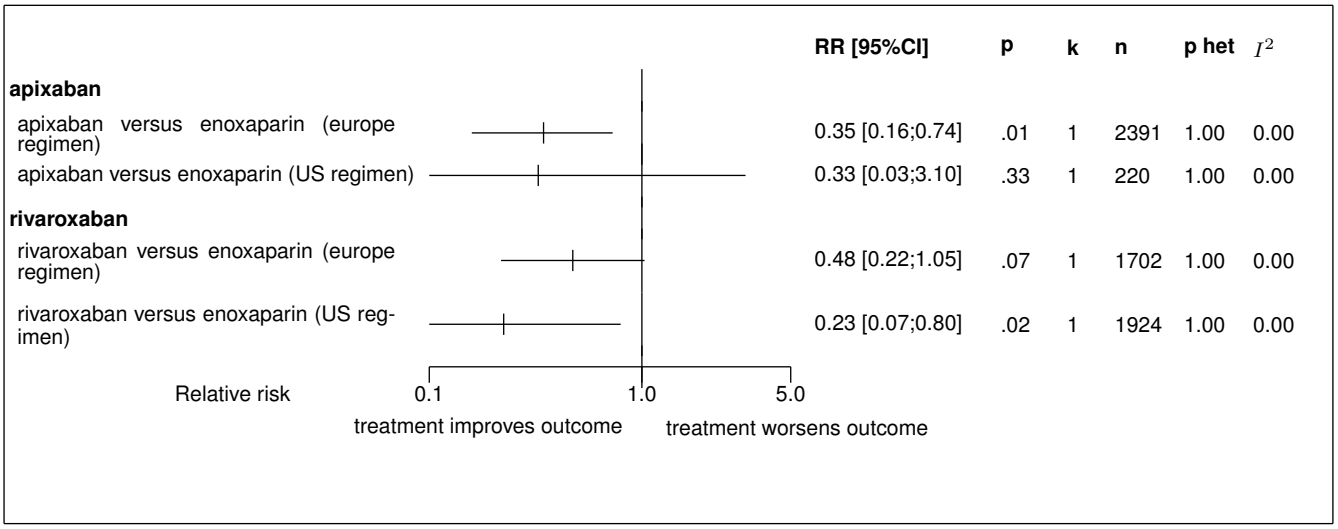
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



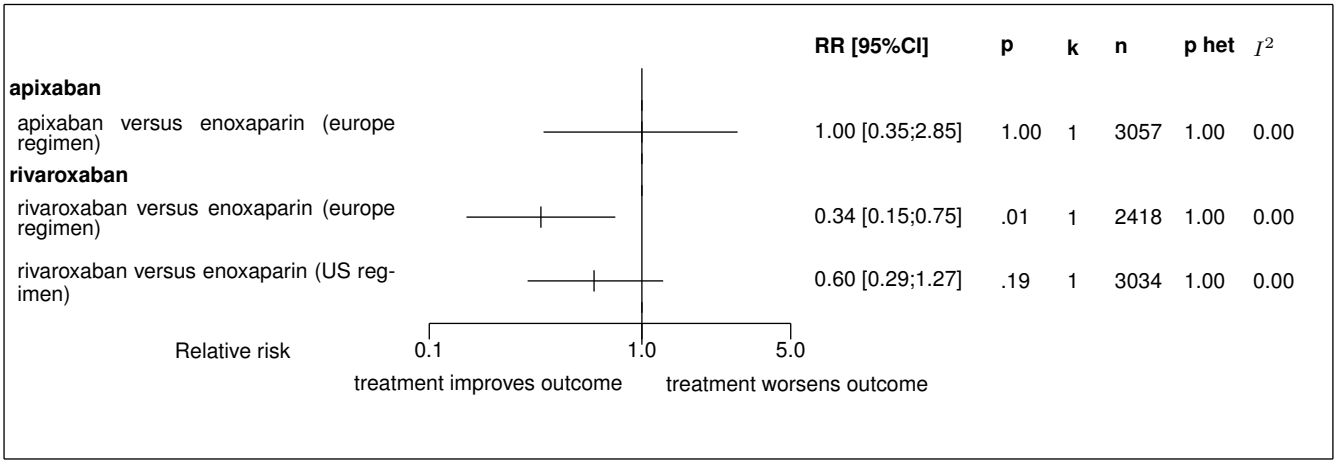
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



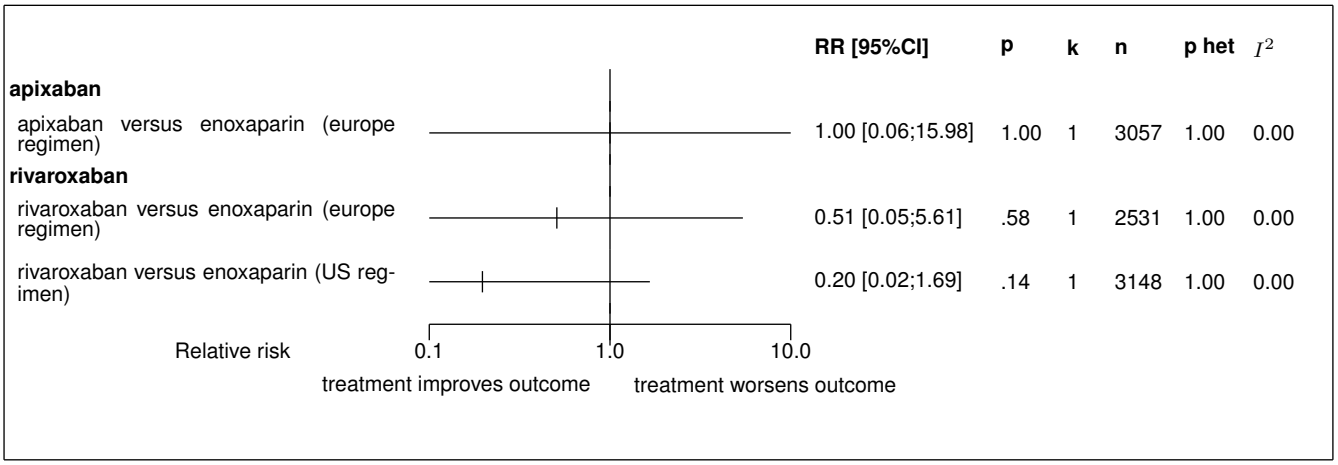
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



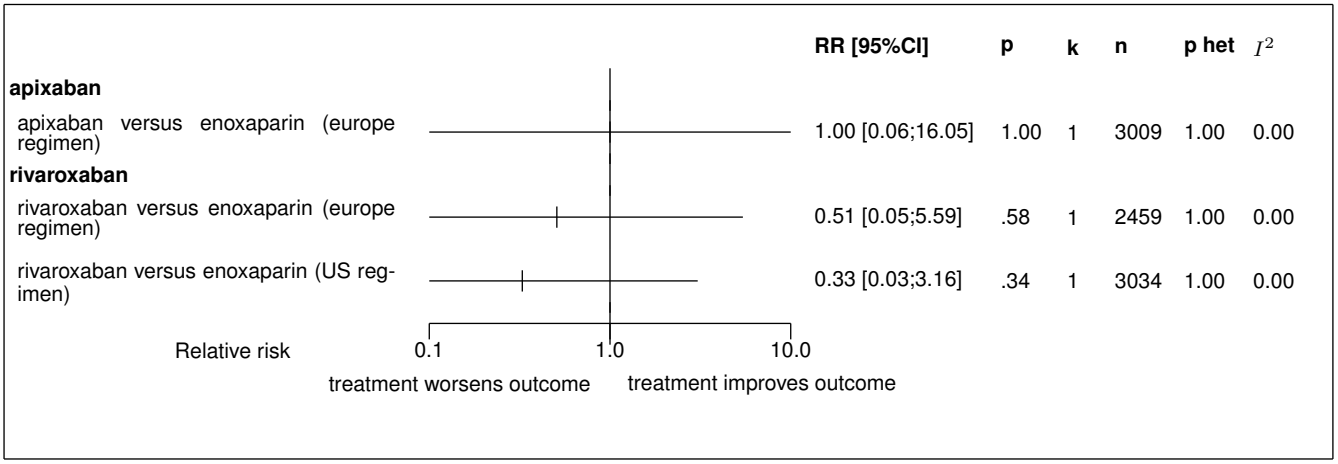
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.11: *Forest's plot for myocardial infarction (fatal and non fatal)*



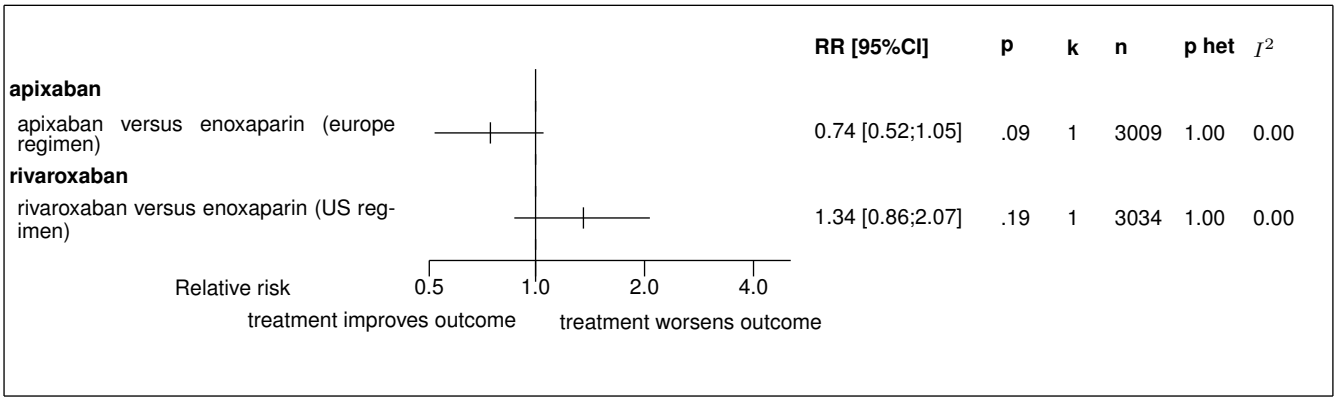
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.12: *Forest's plot for coronary event*



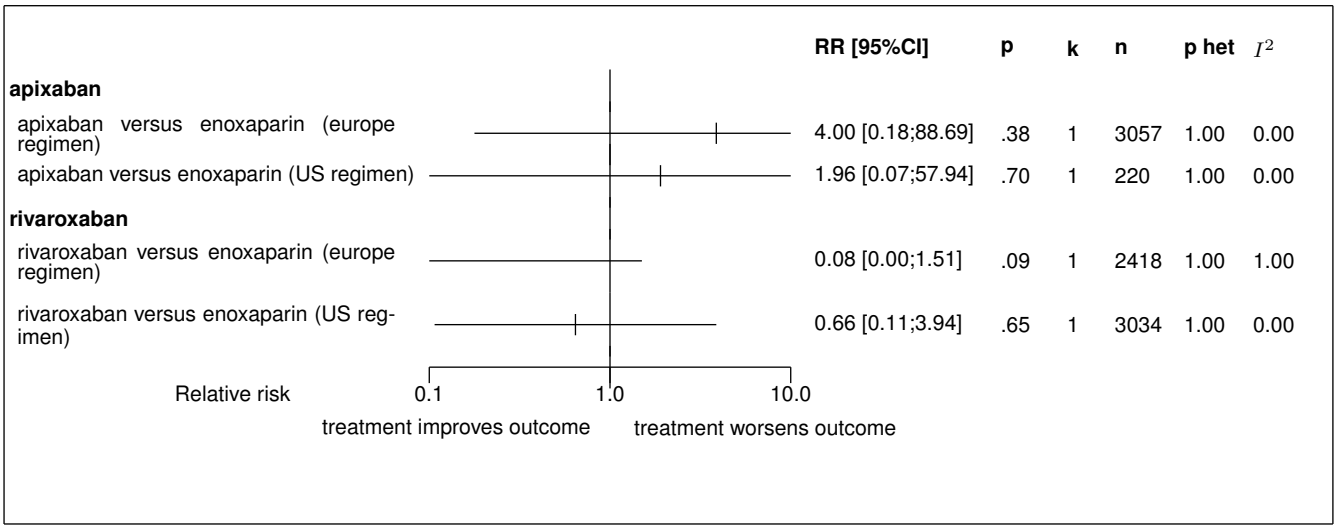
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.13: *Forest's plot for major or clinically relevant non-major bleeding*



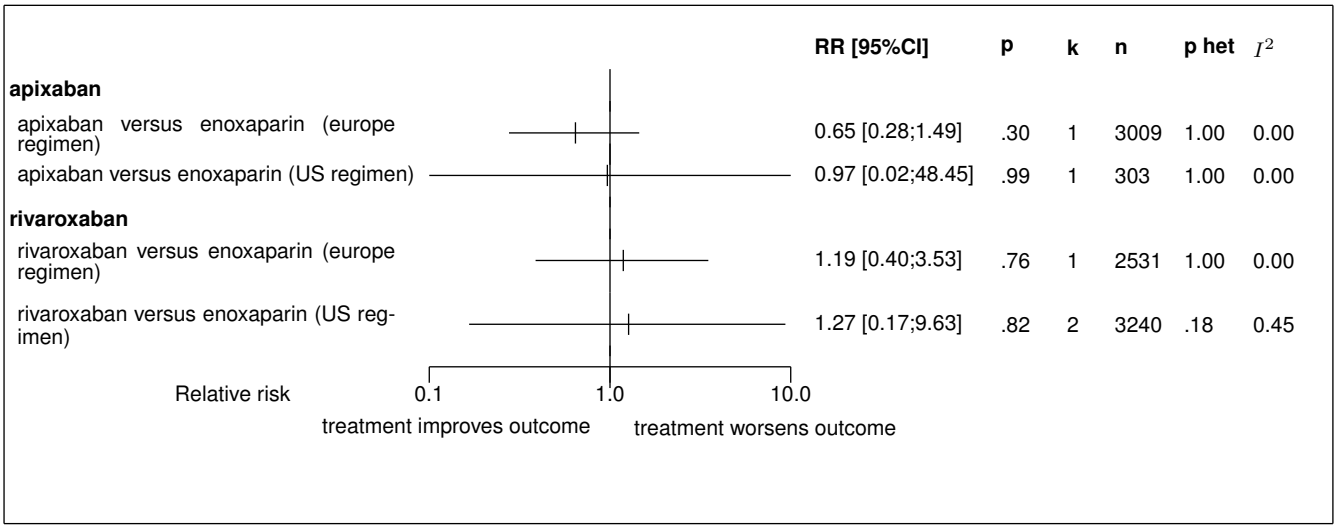
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.14: *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; ᶠ: random effect model used

Figure 2.15: *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; ˡ: random effect model used

3 Detailed results for apixaban

3.1 Available trials

A total of 2 RCTs which randomized 3362 patients were identified: it compared apixaban with enoxaparin (europe regimen) and it compared apixaban with enoxaparin (US regimen).
The average study size was 1681 patients (range 305 to 3057). 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 2 trials; 2 trials reported data on major VTE (fatal and non fatal DVT,PE); 2 trials reported data on symptomatic deep-vein thrombosis; 2 trials reported data on total VTE and all-cause mortality; 2 trials reported data on major bleeding; 2 trials reported data on proximal DVT; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on deep vein thrombosis; 1 trials reported data on symptomatic venous thromboembolism (DVT, PE); 1 trials reported data on asymptomatic DVT; 1 trials reported data on major or clinically relevant non-major bleeding; 1 trials reported data on coronary event; and 1 trials reported data on any bleedings.
Following tables 3.1 (page 33), 3.2 (page 33), 3.4 (page 35), and 3.3 (page 34) 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 (europe regimen)		
ADVANCE 2 (2010) [1] [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) [2] [a]	apixaban 2.5mg BID for 12 days	enoxaparin 30mg twice daily for 12 days began 1224 h after skin woundclosure,

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 (europe regimen)	

continued...

Trial	Patients	
ADVANCE 2 (2010) [1]	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) [2]	Patients undergoing elective total knee replacement surgery	

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

Trial	Design	Duration	Centre	Primary endpoint
Apixaban versus enoxaparin (europe regimen)				
ADVANCE 2, 2010 [1] 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 [2] [(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

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 (europe regimen)		
ADVANCE 2, 2010 [1]	12 days	2-4 (3)
Apixaban versus enoxaparin (US regimen)		
APROPOS 2.5mg, 2007 [2]	12 days	2-4 (3)

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 37). This table is followed by the Forest's plot corresponding to each endpoint.

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 **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 1.00 (95% CI 0.06 to 15.98, p=0.9996).
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)

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 (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.
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 0.58 (95% CI 0.28 to 1.20, p=0.1434).
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 0.39 (95% CI 0.08 to 1.98, p=0.2578).
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 0.63 (95% CI 0.29 to 1.40, p=0.2565).
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 0.33 (95% CI 0.03 to 3.10, p=0.3301).

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 0.97 (95% CI 0.02 to 48.45, p=0.9868).

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
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
myocardial infarction (fatal and non fatal)	RR=1.00	[0.06;15.98]	0.9996	1.0000 (I^2=0.00)	1	3057
coronary event	RR=1.00	[0.06;16.05]	0.9974	1.0000 (I^2=0.00)	1	3009
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
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=0.39	[0.08;1.98]	0.2578	1.0000 (I^2=0.00)	1	220
asymptomatic DVT	RR=0.63	[0.29;1.40]	0.2565	1.0000 (I^2=0.00)	1	220
proximal DVT	RR=0.33	[0.03;3.10]	0.3301	1.0000 (I^2=0.00)	1	220
all cause death	RR=1.96	[0.07;57.94]	0.6959	1.0000 (I^2=0.00)	1	220
major bleeding	RR=0.97	[0.02;48.45]	0.9868	1.0000 (I^2=0.00)	1	303

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*

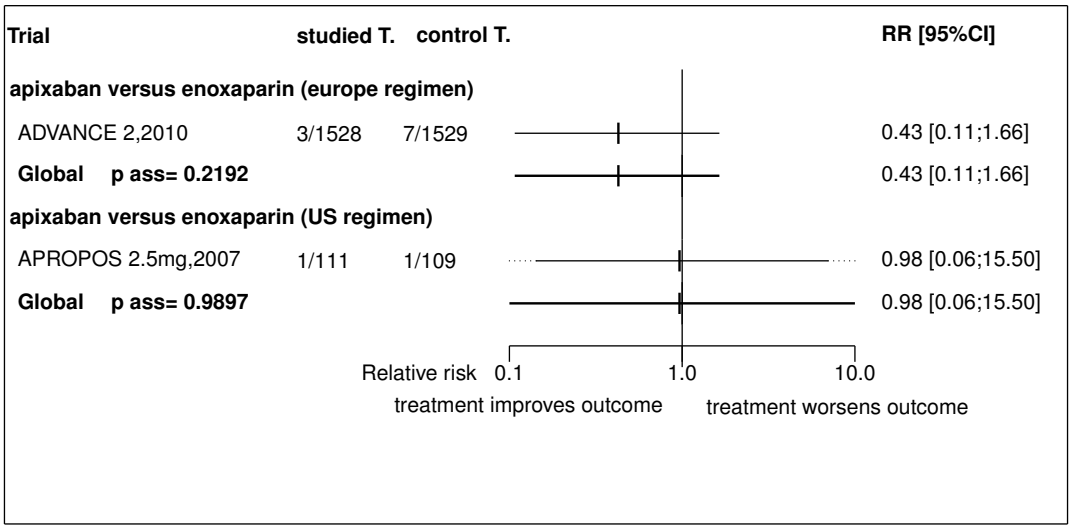


Figure 3.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

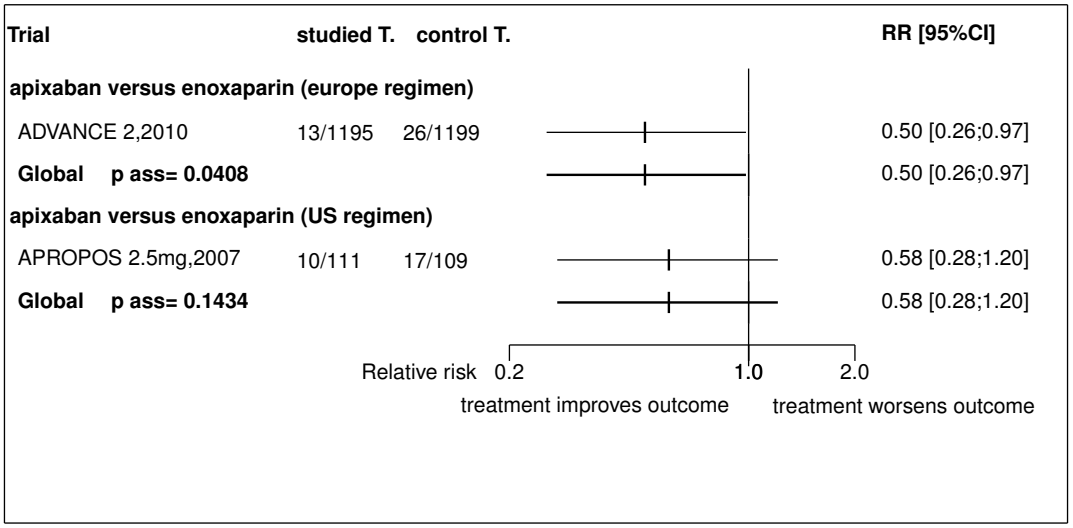


Figure 3.3: *Forest's plot for deep vein thrombosis*

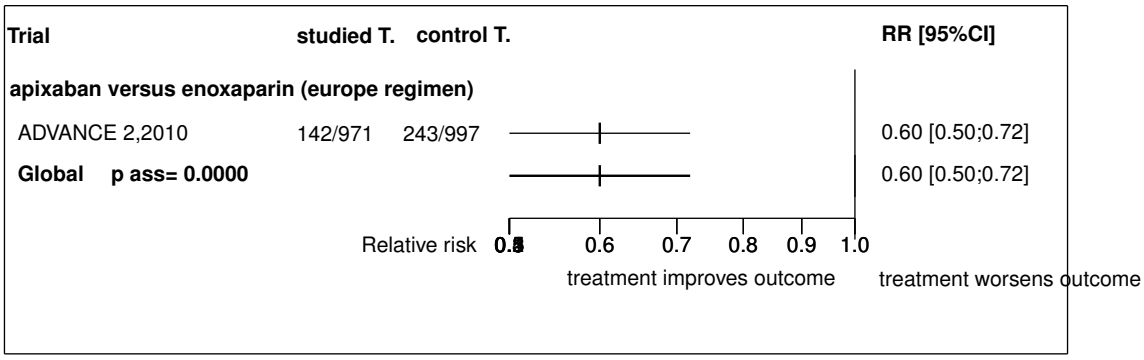


Figure 3.4: *Forest's plot for any bleedings*

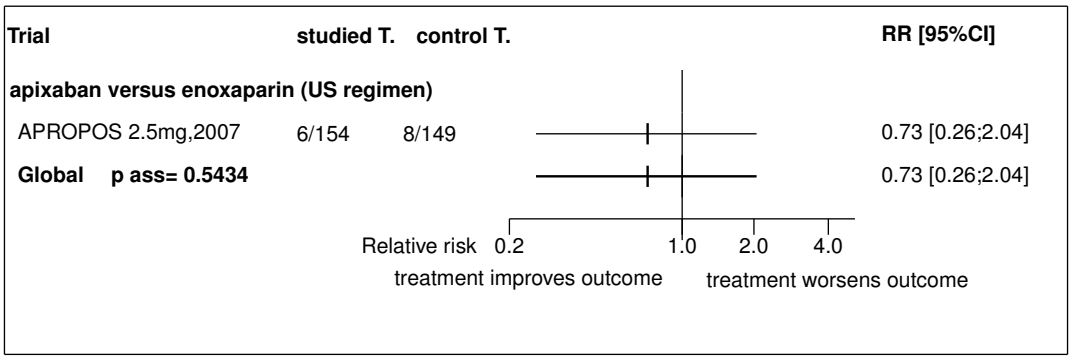


Figure 3.5: *Forest's plot for total VTE and all-cause mortality*

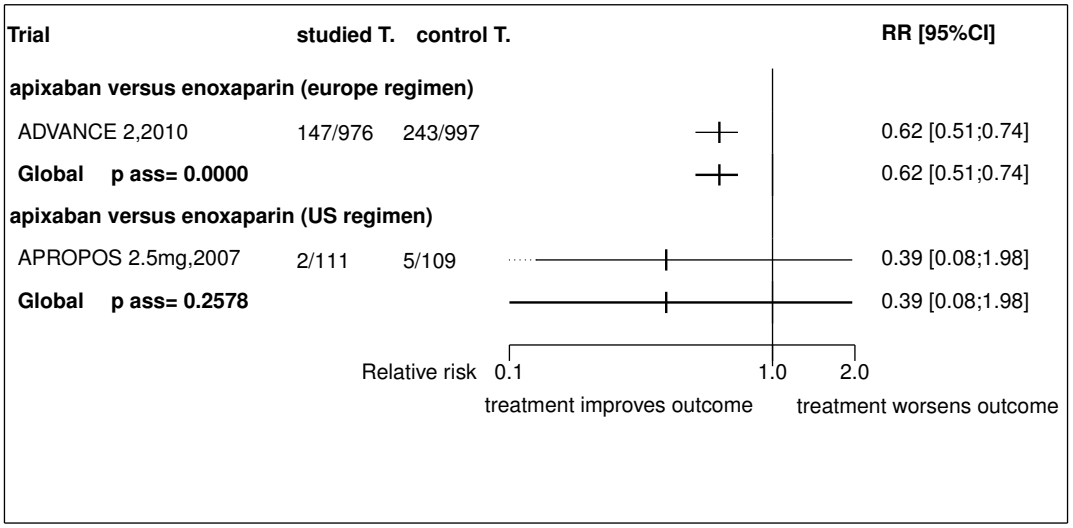


Figure 3.6: *Forest's plot for asymptomatic DVT*

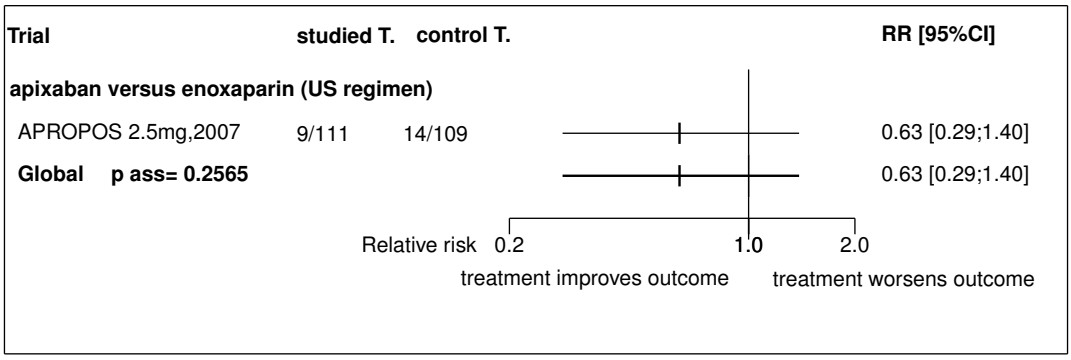


Figure 3.7: *Forest's plot for proximal DVT*

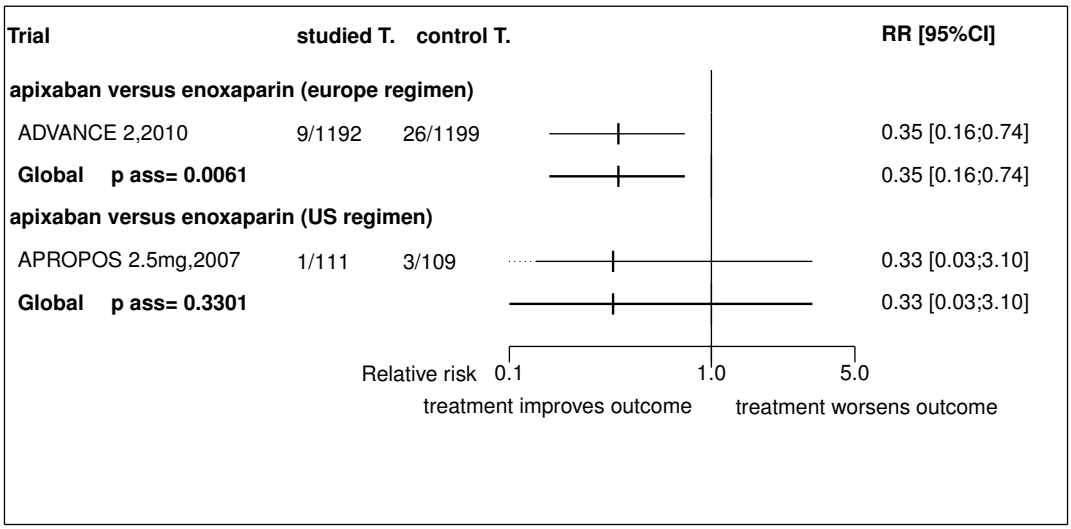


Figure 3.8: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

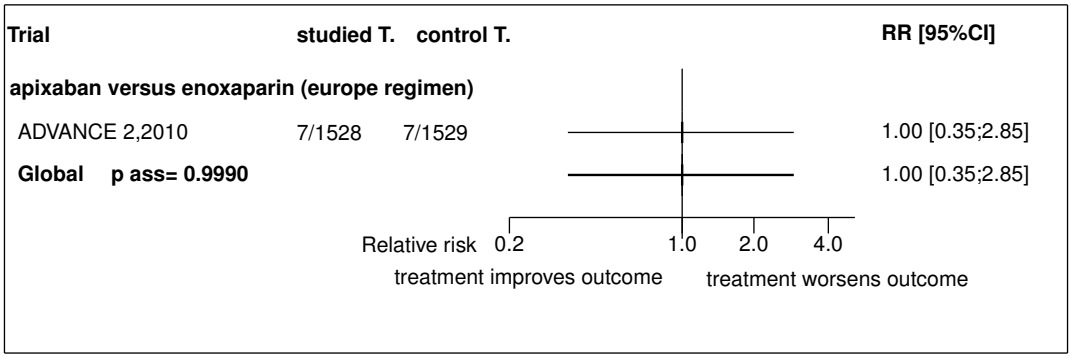


Figure 3.9: *Forest's plot for myocardial infarction (fatal and non fatal)*

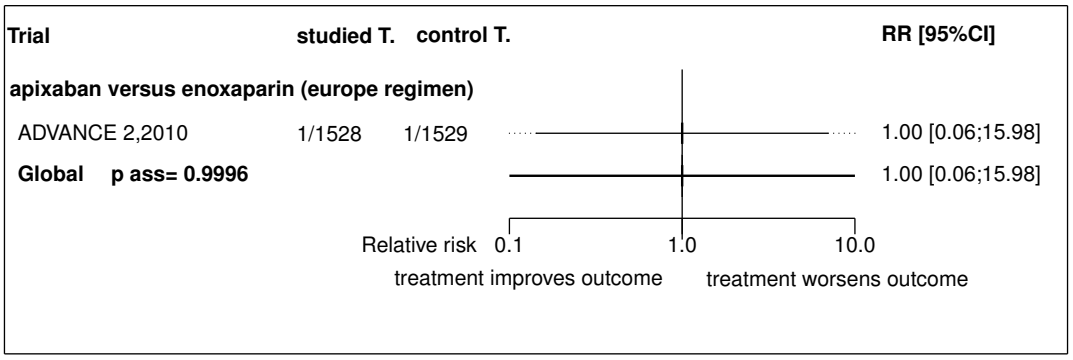


Figure 3.10: *Forest's plot for coronary event*

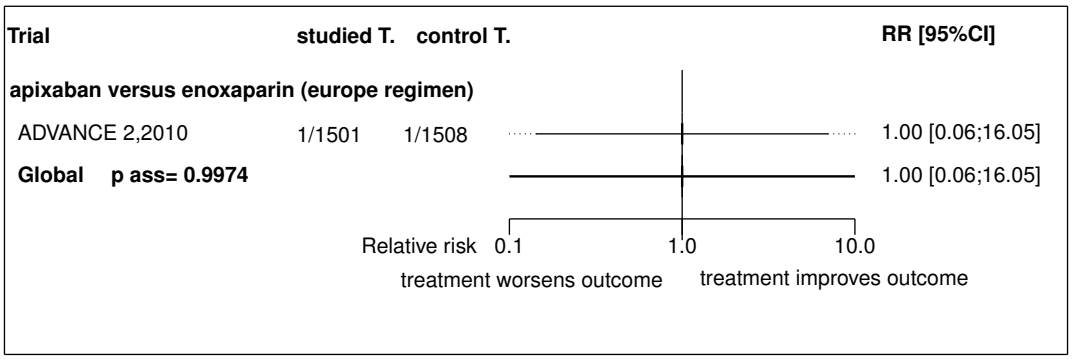


Figure 3.11: *Forest's plot for major or clinically relevant non-major bleeding*

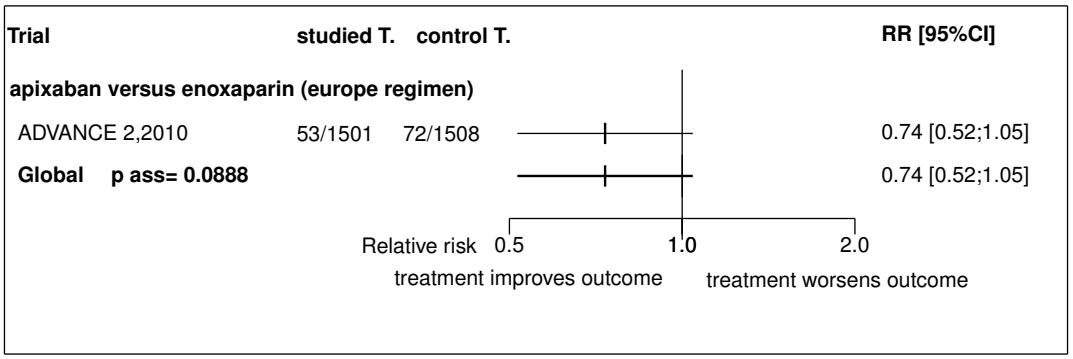


Figure 3.12: *Forest's plot for all cause death*

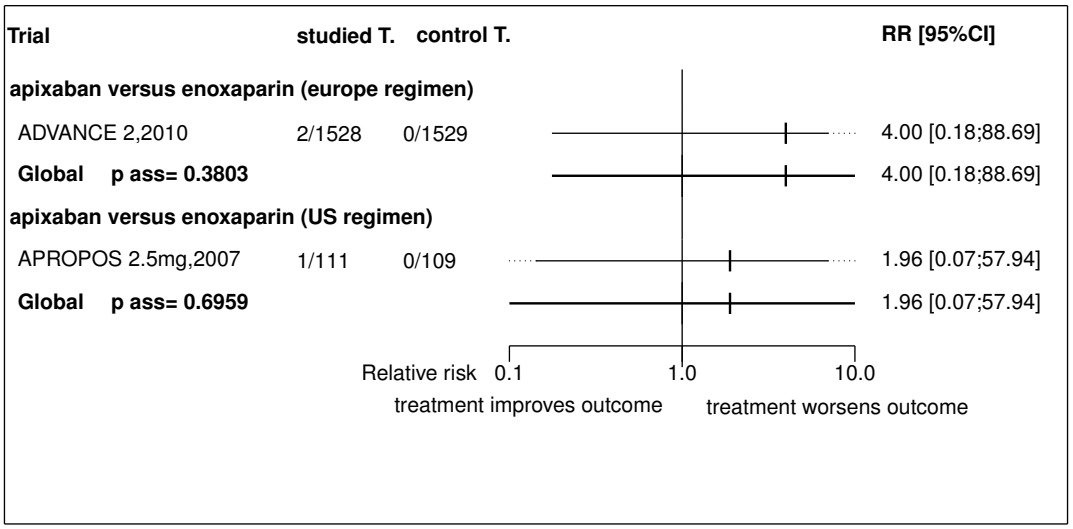
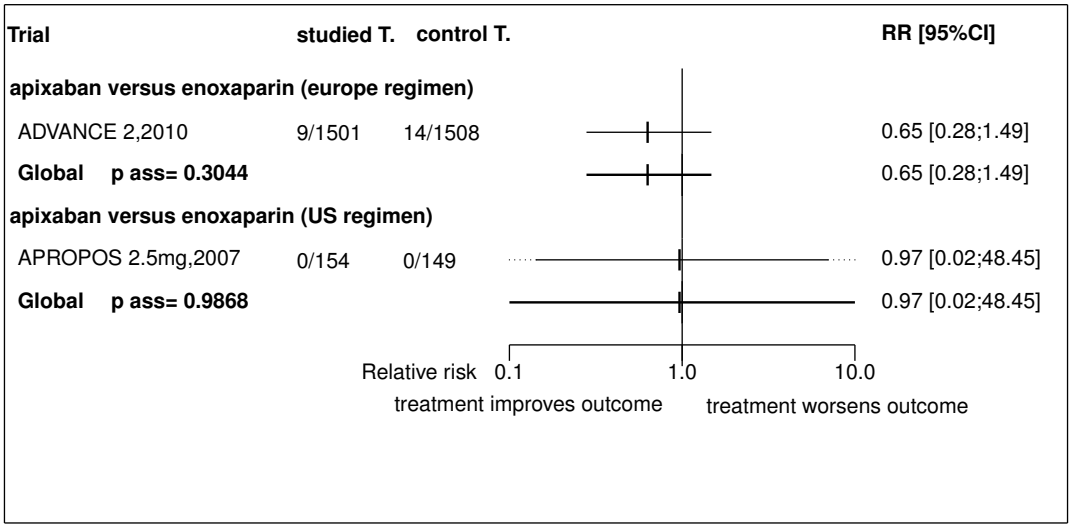


Figure 3.13: *Forest's plot for major bleeding*



References

[1] 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]

[2] 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]

3.3 Individual trial summaries

Table 3.6: *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)

Reference

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]

Table 3.7: *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]

4 Detailed results for rivaroxaban

4.1 Available trials

A total of 3 RCTs which randomized 5886 patients were identified: it compared rivaroxaban with enoxaparin (europe regimen) and 2 trials compared rivaroxaban with enoxaparin (US regimen). The average study size was 1962 patients (range 207 to 3148). 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.
Major bleeding data was reported in 3 trials; 2 trials reported data on myocardial infarction (fatal and non fatal); 2 trials reported data on all cause death; 2 trials reported data on proximal DVT; 2 trials reported data on non-fatal pulmonary embolism; 2 trials reported data on symptomatic venous thromboembolism (DVT, PE); 2 trials reported data on major VTE (fatal and non fatal DVT,PE); 2 trials reported data on distal DVT; 2 trials reported data on total VTE and all-cause mortality; 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on deep vein thrombosis; 1 trials reported data on asymptomatic DVT; 2 trials reported data on coronary event; and 1 trials reported data on major or clinically relevant non-major bleeding.
Following tables 4.1 (page 47), 4.2 (page 47), 4.4 (page 49), and 4.3 (page 48) summarized the main characteristics of the trials including in this systematic review of randomized trials of rivaroxaban.

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

Trial	Studied treatment	Control treatment
Rivaroxaban versus enoxaparin (europe regimen)		
RECORD 3 (2008) [1]	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 (US regimen)		
ODIXa-KNEE (2005) [2] [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) [3]	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 ranging study with doses 2.5, 5, 10, 20, and 30 mg

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

Trial	Patients
Rivaroxaban versus enoxaparin (europe regimen)	

continued...

Trial	Patients	
RECORD 3 (2008) [1]	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 (US regimen)		
ODIXa-KNEE (2005) [2]	Patients undergoing elective total knee replacement	
RECORD 4 (2009) [3]	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 4.3: *Design and methodological quality of trials - direct factor Xa inhibitors - rivaroxaban*

Trial	Design	Duration	Centre	Primary endpoint
Rivaroxaban versus enoxaparin (europe regimen)				
RECORD 3, 2008 [1] 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 (US regimen)				
ODIXa-KNEE, 2005 [2] n=207	Parallel groups double blind exploratory trial	5-9 days inclusion period: Feb 2004 - Nov 2004	North America 43 centres	
RECORD 4, 2009 [3] 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 4.4: *Trial characteristics - direct factor Xa inhibitors - rivaroxaban*

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

4.2 Meta-analysis results

The results are detailed in table 4.5 (page 51). This table is followed by the Forest's plot corresponding to each endpoint.

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 **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.51 (95% CI 0.05 to 5.61, p=0.5814).
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 (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 **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.20 (95% CI 0.02 to 1.69, p=0.1384).
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 4.5: *Results details - direct factor Xa inhibitors - rivaroxaban*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
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
myocardial infarction (fatal and non fatal)	RR=0.51	[0.05;5.61]	0.5814	1.0000 (I^2=0.00)	1	2531
coronary event	RR=0.51	[0.05;5.59]	0.5798	1.0000 (I^2=0.00)	1	2459
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 (US regimen)						

continued...

Comparison 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 (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
myocardial infarction (fatal and non fatal)	RR=0.20	[0.02;1.69]	0.1384	1.0000 (I^2=0.00)	1	3148
coronary event	RR=0.33	[0.03;3.16]	0.3360	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 4.1: *Forest's plot for symptomatic deep-vein thrombosis*

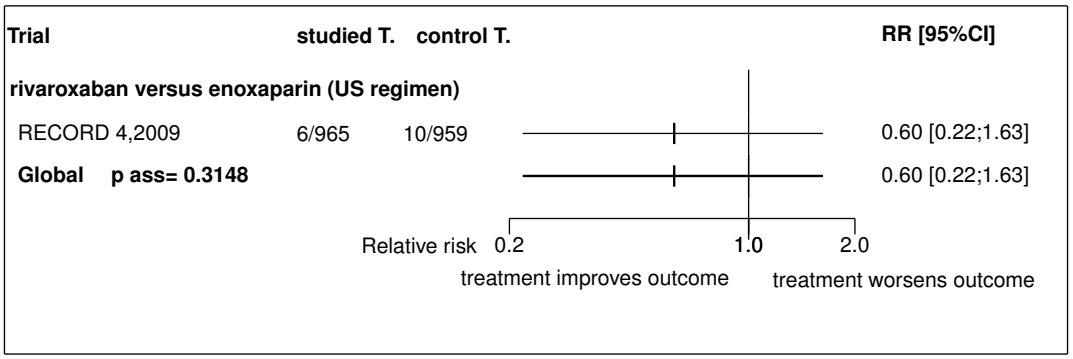


Figure 4.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

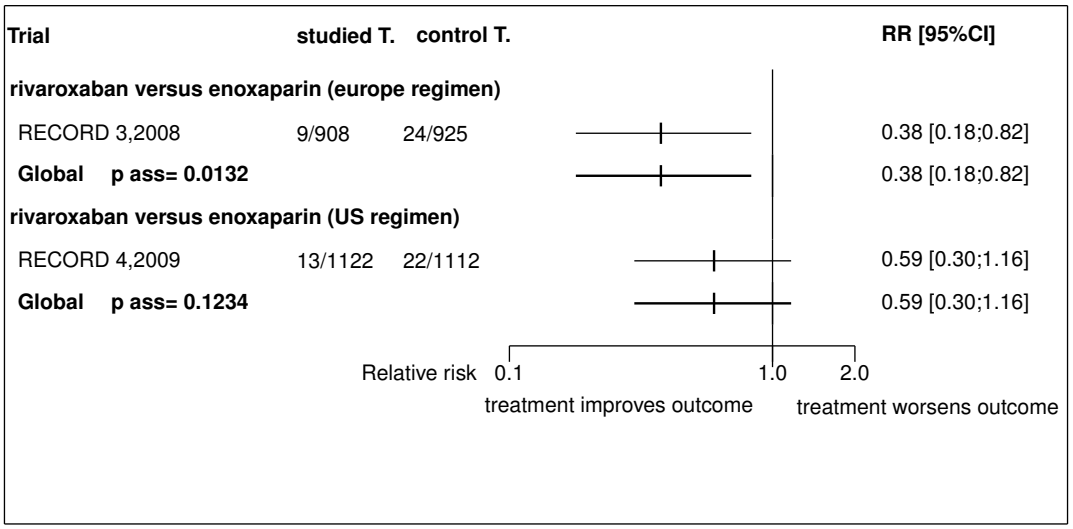


Figure 4.3: *Forest's plot for deep vein thrombosis*

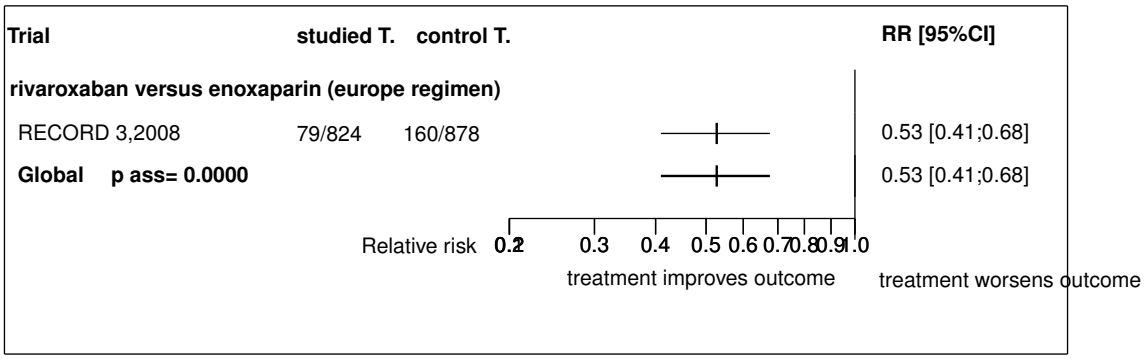


Figure 4.4: *Forest's plot for total VTE and all-cause mortality*

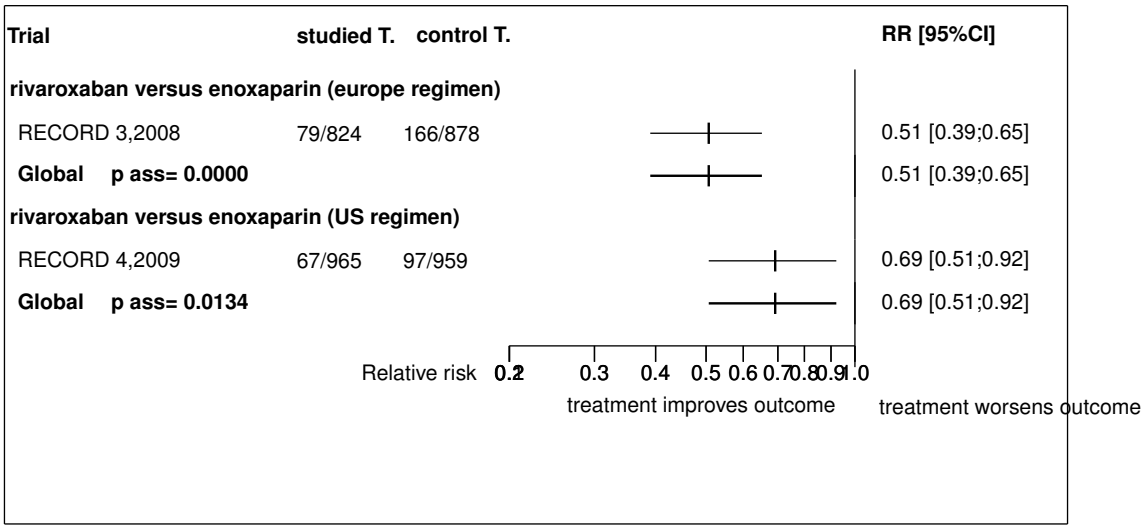


Figure 4.5: *Forest's plot for asymptomatic DVT*

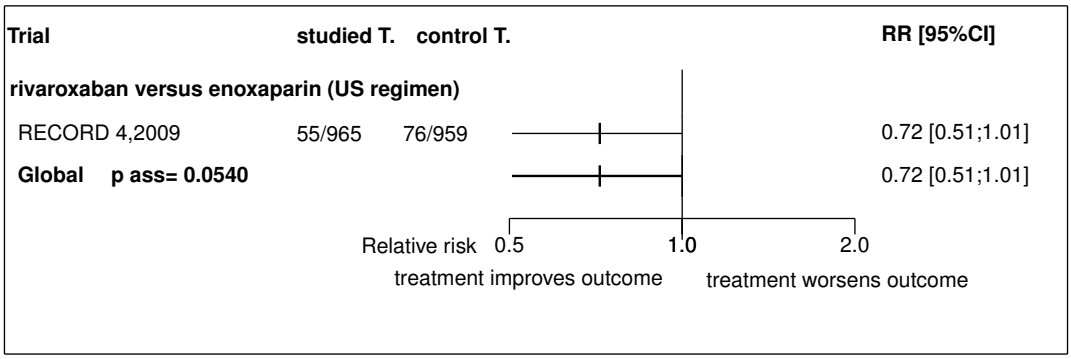


Figure 4.6: *Forest's plot for non-fatal pulmonary embolism*

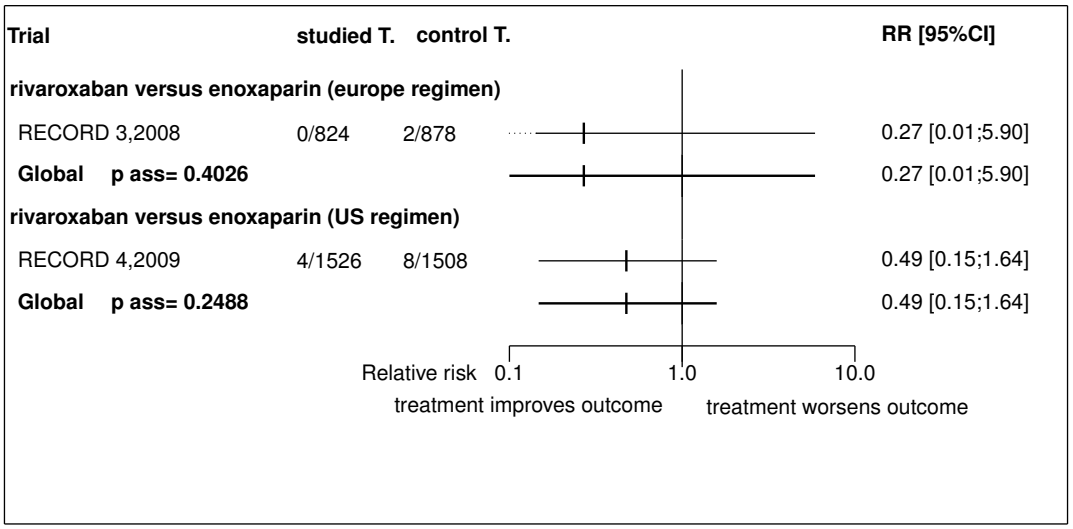


Figure 4.7: *Forest's plot for distal DVT*

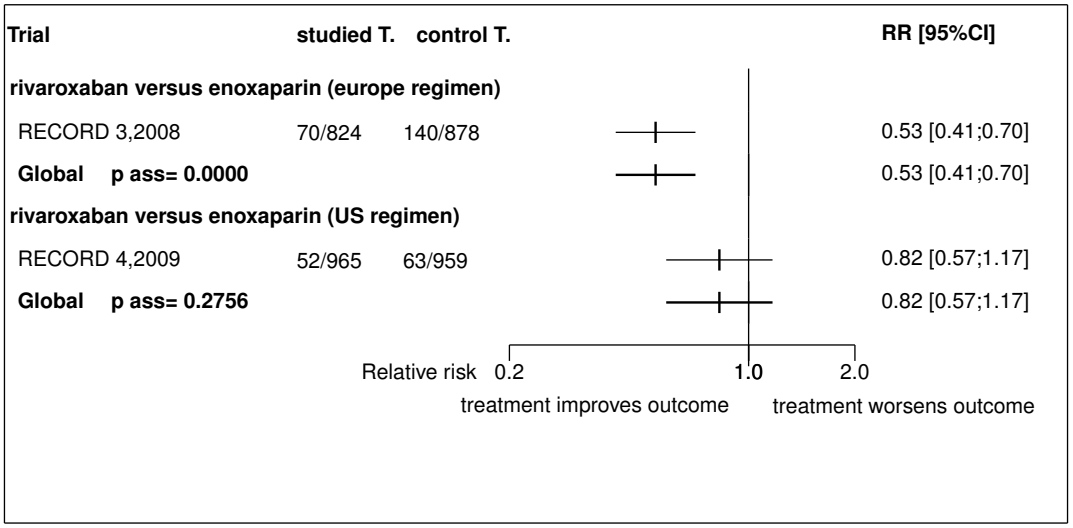


Figure 4.8: *Forest's plot for proximal DVT*

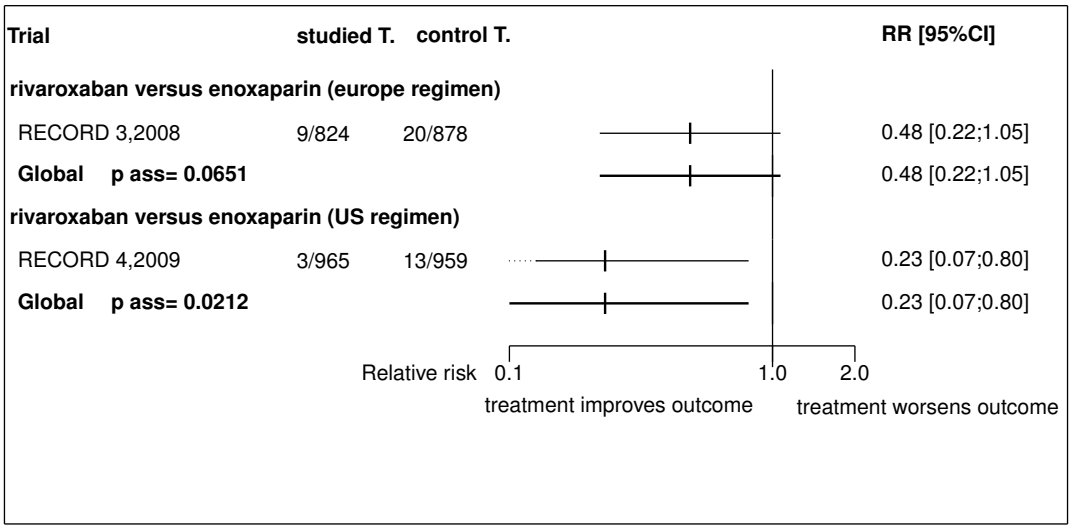


Figure 4.9: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

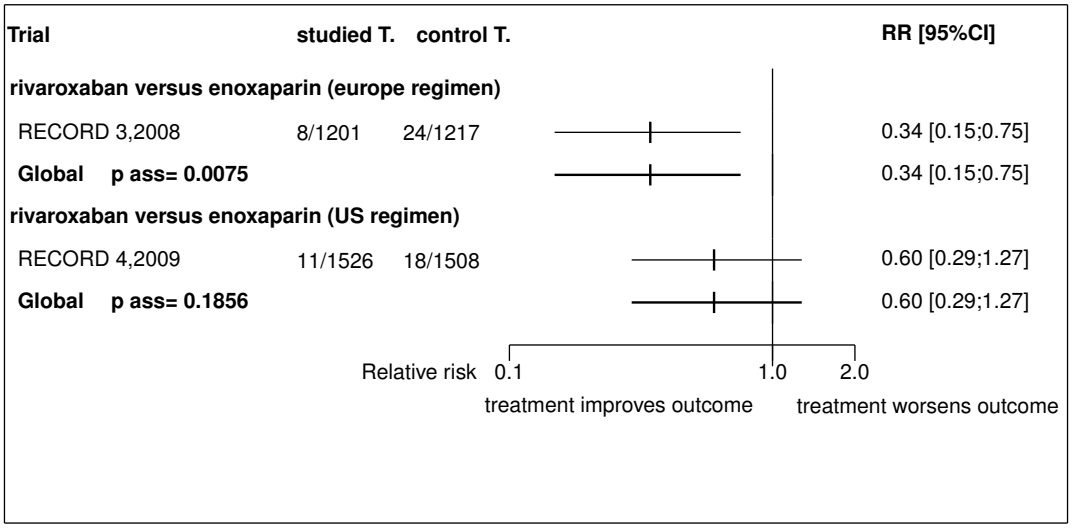


Figure 4.10: *Forest's plot for myocardial infarction (fatal and non fatal)*

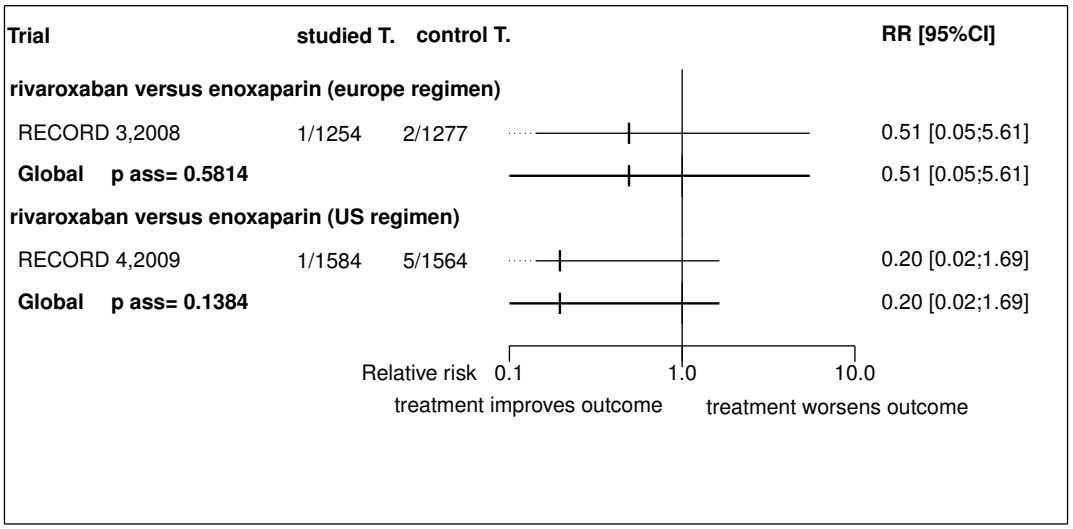


Figure 4.11: *Forest's plot for coronary event*

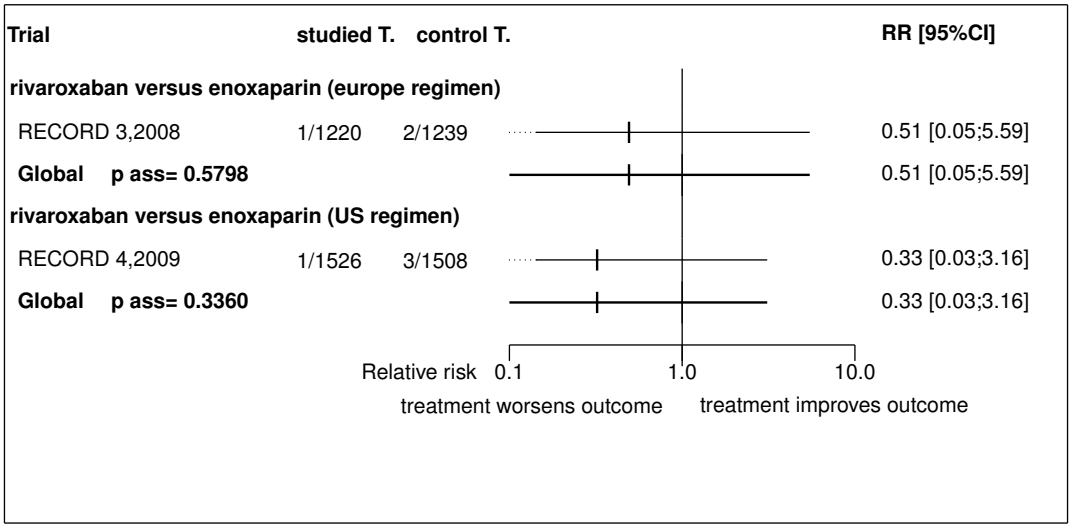


Figure 4.12: *Forest's plot for major or clinically relevant non-major bleeding*

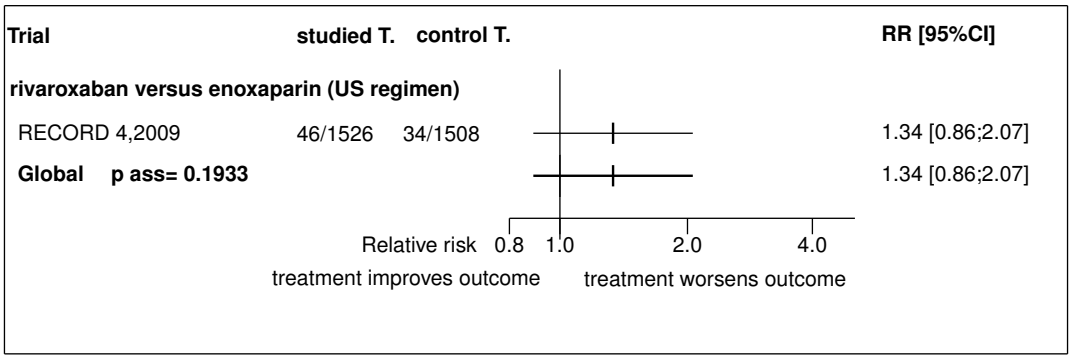


Figure 4.13: *Forest's plot for all cause death*

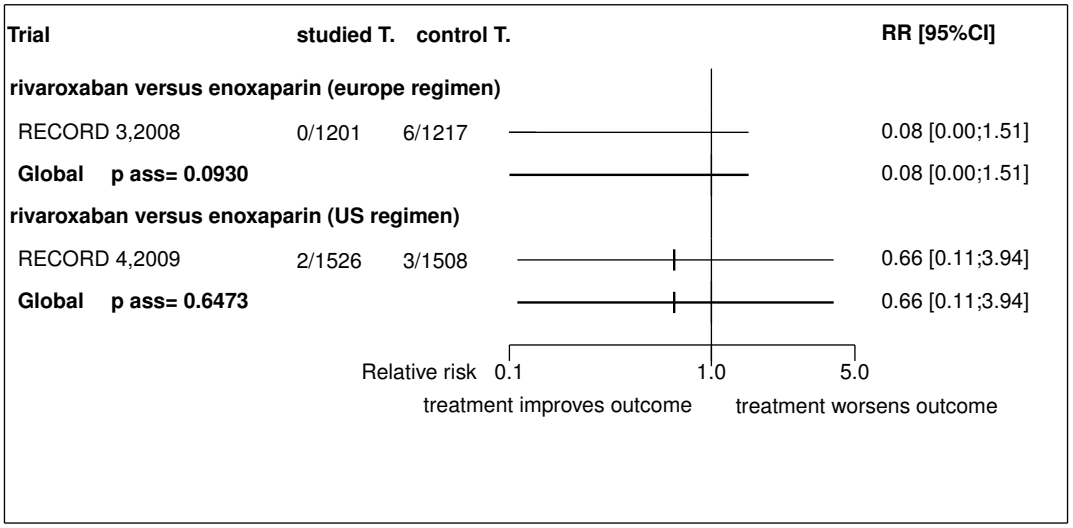
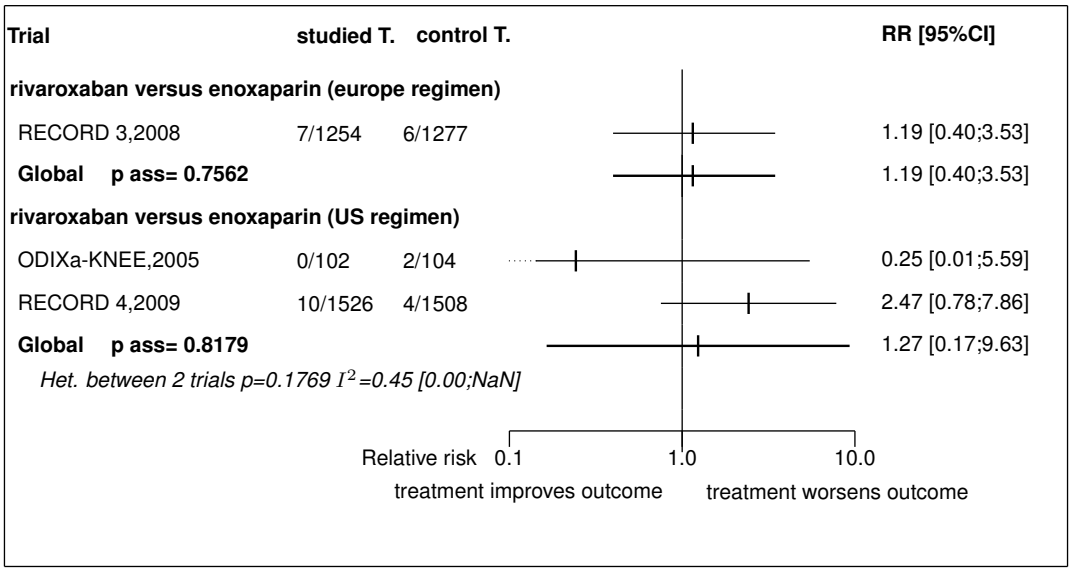


Figure 4.14: *Forest's plot for major bleeding*



References

[1] 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]

[2] 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]

[3] 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]

4.3 Individual trial summaries

Table 4.6: *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]

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 4.7: *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 4.8: *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]

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]

5 Global meta-analysis: all direct factor Xa inhibitors

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

Table 5.1: *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
symptomatic venous thromboembolism (DVT, PE)	RR=0.55	0.19;1.59	0.2689	0.1052 (0.62)	2	5475
myocardial infarction (fatal and non fatal)	RR=0.68	0.11;4.17	0.6770	0.7179 (0.00)	2	5588
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

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

Table 5.2: *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
total VTE and all-cause mortality	RR=0.67	0.50;0.90	0.0084	0.5062 (0.00)	2	2144

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
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
proximal DVT	RR=0.25	0.08;0.74	0.0129	0.7864 (0.00)	2	2144
symptomatic venous thromboembolism (DVT, PE)	RR=0.60	0.29;1.27	0.1856	1.0000 (0.00)	1	3034
myocardial infarction (fatal and non fatal)	RR=0.20	0.02;1.69	0.1384	1.0000 (0.00)	1	3148
major bleeding	RR=1.78	0.63;5.06	0.2783	0.3821 (0.00)	3	3543

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

6 Ongoing studies of direct factor Xa inhibitors

No ongoing trial was identified.

7 Excluded studies for direct factor Xa inhibitors

No trial was excluded.

References

Part II

Low molecular weight heparin

8 Overview of low molecular weight heparin

8.1 Included trials

A total of 2 randomized comparisons which enrolled 375 patients were identified. In all, 1 randomized comparison concerned ardeparin and one enoxaparin.
The detailed descriptions of trials and meta-analysis results is given in section 9 (page 73) for ardeparin and in section 10 (page 79) for enoxaparin.

The average study size was 187 patients (range 129 to 246). The first study was published in 1991, and the last study was published in 1996.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 8.1 (page 70) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

8.2 Summary of meta-analysis results

The meta-analysis of the available trials about low molecular weight heparin provide the results listed in tables 8.2 to 8.3 (page 71) and in the following graphs.

8.2.1 Ardeparin

Ardeparin was superior to **placebo** in terms of deep vein thrombosis (RR=0.50, 95% CI 0.35 to 0.71, p=0.0000, 1 trial).

8.2.2 Enoxaparin

Enoxaparin was superior to **placebo** in terms of deep vein thrombosis (RR=0.29, 95% CI 0.16 to 0.52, p=0.0000, 1 trial).

Table 8.1: *Main study characteristics - Low molecular weight heparin*

Trial	Patients	Treatments	Trial design and method
Ardeparin			
Ardeparin versus placebo			
Levine, 1996 [1] n = 122 vs. 124	knee	ardeparin 50/kgx2 +elastic stockings **versus** placebo+elastic stockings	double blind
Enoxaparin			
Enoxaparin versus placebo			
Leclerc, 1991 [1] n = 65 vs. 64	knee	enoxaparin 3000 x2 **versus** placebo	double blind

Table 8.2: *Summary of all results for ardeparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
ardeparin versus placebo						
deep vein thrombosis	RR=0.50	0.35;0.71	0.0000	1.0000 (1.00)	1	199
bleeding	RR=1.02	0.21;4.94	0.9839	1.0000 (0.00)	1	246

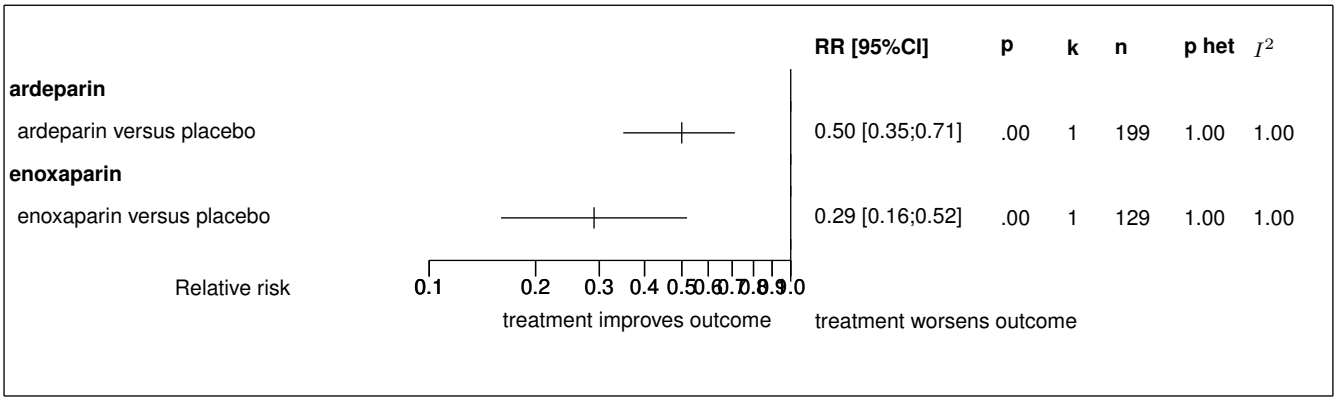
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 8.3: *Summary of all results for enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
enoxaparin versus placebo						
deep vein thrombosis	RR=0.29	0.16;0.52	0.0000	1.0000 (1.00)	1	129
bleeding	RR=0.79	0.22;2.80	0.7128	1.0000 (0.00)	1	131

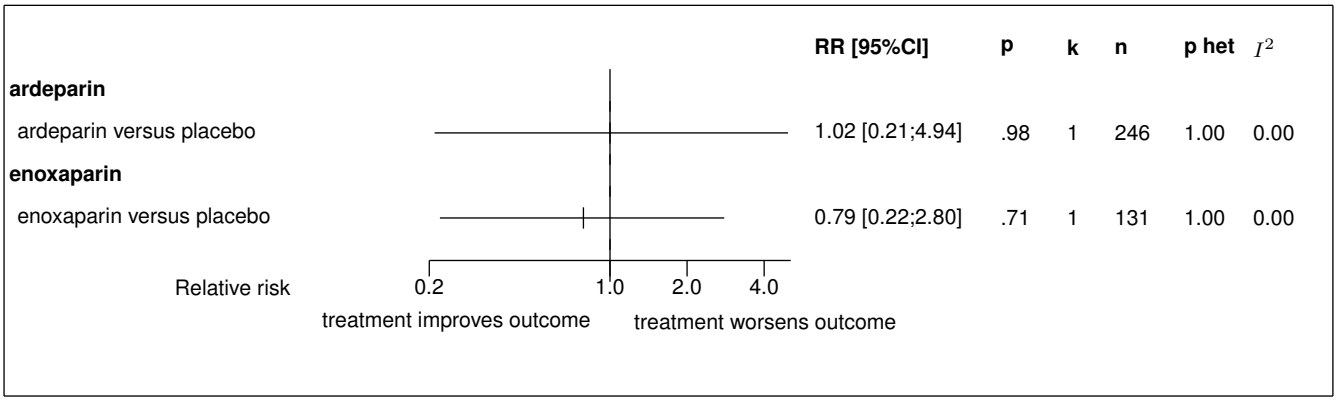
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 8.1: *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 8.2: *Forest's plot for 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

9 Detailed results for ardeparin

9.1 Available trials

Only one trial which randomized 246 patients was identified: it compared ardeparin with placebo.
This trial included 246 patients and was published in 1996.
This trial was double blind in design.
It was reported in English language.
Asymptomatic proximal DVT data was reported in 1 trials; 1 trials reported data on deep vein thrombosis; and 1 trials reported data on bleeding.
Following tables 9.1 (page 73), 9.2 (page 73), 9.4 (page 74), and 9.3 (page 73) summarized the main characteristics of the trial including in this systematic review of randomized trials of ardeparin.

Table 9.1: *Treatment description - Low molecular weight heparin - ardeparin*

Trial	Studied treatment	Control treatment
Ardeparin versus placebo		
Levine (1996) [1]	ardeparin 50/kgx2 +elastic stockings	Placebo+elastic stockings

Table 9.2: *Descriptions of participants - Low molecular weight heparin - ardeparin*

Trial	Patients
Ardeparin versus placebo	
Levine (1996) [1]	Knee

Table 9.3: *Design and methodological quality of trials - Low molecular weight heparin - ardeparin*

Trial	Design	Duration	Centre	Primary endpoint
Ardeparin versus placebo				
Levine, 1996 [1] n=246	double blind	14 days		

Table 9.4: *Trial characteristics - Low molecular weight heparin - ardeparin*

Trial
Ardeparin versus placebo
Levine, 1996 [1]

9.2 Meta-analysis results

The results are detailed in table 9.5 (page 75). This table is followed by the Forest's plot corresponding to each endpoint.

Ardeparin versus placebo

The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of ardeparin in deep vein thrombosis, with a RR of 0.50 (95% CI 0.35 to 0.71, p=0.0000).

Table 9.5: *Results details - Low molecular weight heparin - ardeparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ardeparin versus placebo						
deep vein thrombosis	RR=0.50	[0.35;0.71]	0.0000	1.0000 (I^2=1.00)	1	199
bleeding	RR=1.02	[0.21;4.94]	0.9839	1.0000 (I^2=0.00)	1	246

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 9.1: *Forest's plot for deep vein thrombosis*

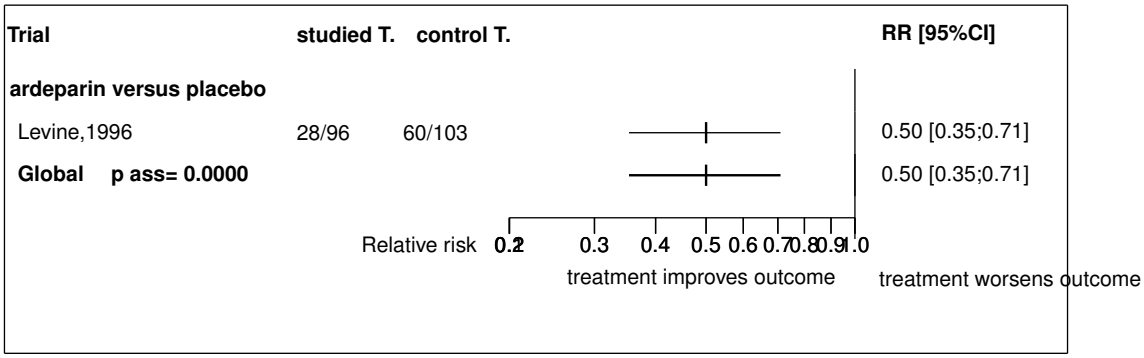
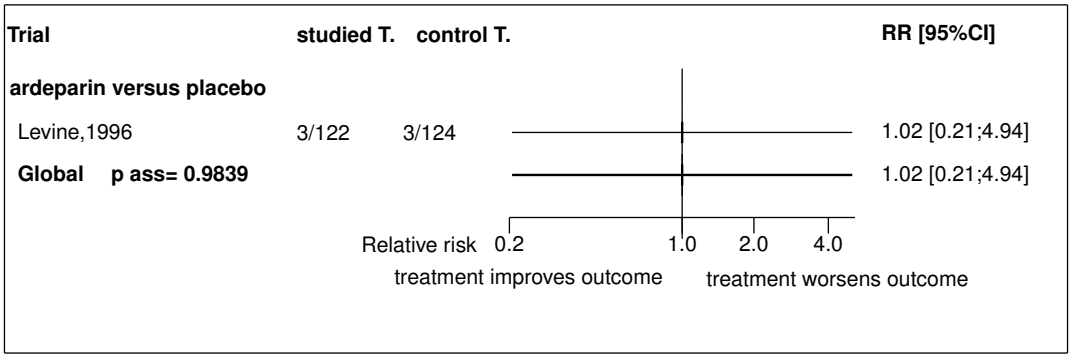


Figure 9.2: *Forest's plot for bleeding*



References

[1] Levine MN, Gent M, Hirsh J, Weitz J, Turpie AG, Powers P, Neemeh J, Willan A, Skingley P. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. Arch Intern Med 1996 Apr 22;156:851-6. [PMID=8774203]

9.3 Individual trial summaries

Table 9.6: *Levine, 1996 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=246 (122 vs. 124) **Follow-up duration:** 14 days **Study design:** Randomized controlled trial Double blind	Knee	**Studied treatment:** ardeparin 50/kgx2 +elastic stockings **Control treatment:** Placebo+elastic stockings	Deep vein thrombosis RR=0.50 [0.35;0.71]

Reference

Levine MN, Gent M, Hirsh J, Weitz J, Turpie AG, Powers P, Neemeh J, Willan A, Skingley P. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. Arch Intern Med 1996 Apr 22;156:851-6 [PMID=8774203]

10 Detailed results for enoxaparin

10.1 Available trials

Only one trial which randomized 129 patients was identified: it compared enoxaparin with placebo.
This trial included 129 patients and was published in 1991.
This trial was double blind in design.
It was reported in English language.
Asymptomatic proximal DVT data was reported in 1 trials; 1 trials reported data on deep vein thrombosis; and 1 trials reported data on bleeding.
Following tables 10.1 (page 79), 10.2 (page 79), 10.4 (page 81), and 10.3 (page 79) summarized the main characteristics of the trial including in this systematic review of randomized trials of enoxaparin.

Table 10.1: *Treatment description - Low molecular weight heparin - enoxaparin*

Trial	Studied treatment	Control treatment
Enoxaparin versus placebo		
Leclerc (1991) [1]	Enoxaparin 3000 x2 2x30mg;12-24h after	Placebo Placebo

Table 10.2: *Descriptions of participants - Low molecular weight heparin - enoxaparin*

Trial	Patients
Enoxaparin versus placebo	
Leclerc (1991) [1]	Knee

Table 10.3: *Design and methodological quality of trials - Low molecular weight heparin - enoxaparin*

Trial	Design	Duration	Centre	Primary endpoint
Enoxaparin versus placebo				
Leclerc, 1991 [1] n=129	double blind	14 days		

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 10.4: *Trial characteristics - Low molecular weight heparin - enoxaparin*

Trial
Enoxaparin versus placebo
Leclerc, 1991 [1]

10.2 Meta-analysis results

The results are detailed in table 10.5 (page 82). This table is followed by the Forest's plot corresponding to each endpoint.

Enoxaparin versus placebo

The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of enoxaparin in deep vein thrombosis, with a RR of 0.29 (95% CI 0.16 to 0.52, p=0.0000).

Table 10.5: *Results details - Low molecular weight heparin - enoxaparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
enoxaparin versus placebo						
deep vein thrombosis	RR=0.29	[0.16;0.52]	0.0000	1.0000 (I^2=1.00)	1	129
bleeding	RR=0.79	[0.22;2.80]	0.7128	1.0000 (I^2=0.00)	1	131

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 10.1: *Forest's plot for deep vein thrombosis*

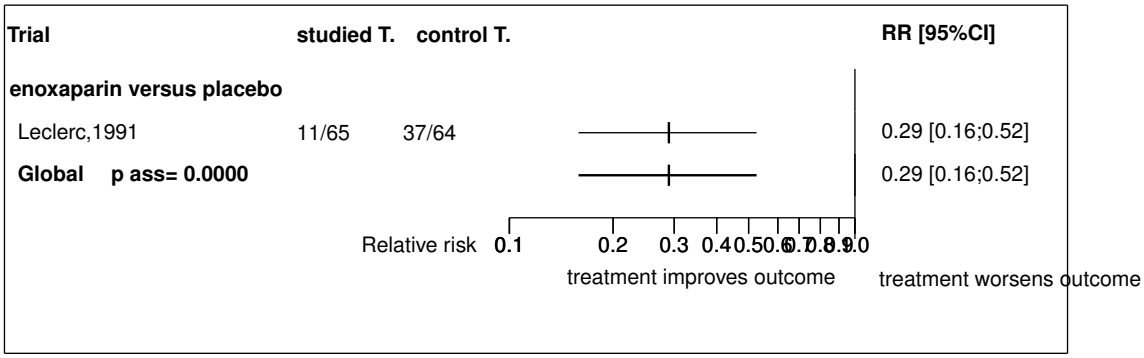
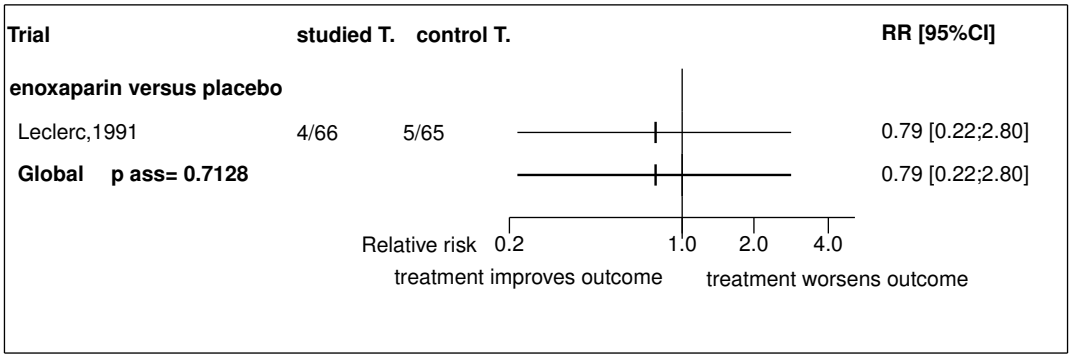


Figure 10.2: *Forest's plot for bleeding*



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[1] Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F, Haviernick S, Atkinson S, Bourgouin J. Prevention of deep vein thrombosis after major knee surgery–a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. Thromb Haemost 1992 Apr 2;67:417-23. [PMID=1321509]

10.3 Individual trial summaries

Table 10.6: *Leclerc, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=129 (65 vs. 64) **Follow-up duration:** 14 days **Study design:** Randomized controlled trial Double blind	Knee	**Studied treatment:** Enoxaparin 3000 x2 2x30mg;12-24h after **Control treatment:** Placebo Placebo	Deep vein thrombosis RR=0.29 [0.16;0.52]

Reference

Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F, Haviernick S, Atkinson S, Bourgouin J. Prevention of deep vein thrombosis after major knee surgery–a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. Thromb Haemost 1992 Apr 2;67:417-23 [PMID=1321509]

11 Global meta-analysis: all Low molecular weight heparin

11.1 Global meta-analysis: all Low molecular weight heparin versus placebo

Table 11.1: *All Low molecular weight heparinversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.40	0.24;0.68	0.0000	0.1200 (0.59)	2	328

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

12 Ongoing studies of Low molecular weight heparin

No ongoing trial was identified.

13 Excluded studies for Low molecular weight heparin

No trial was excluded.

References

Part III

Oral direct thrombin inhibitor

14 Overview of oral direct thrombin inhibitor

14.1 Included trials

A total of 8 randomized comparisons which enrolled 12617 patients were identified. In all, 2 randomized comparisons concerned dabigatran 150mg , two dabigatran 220mg and 4 ximelagatran.
The detailed descriptions of trials and meta-analysis results is given in section 15 (page 102) for dabigatran 150mg, in section 16 (page 117) for dabigatran 220mg and in section 17 (page 131) for ximelagatran.

The average study size was 1577 patients (range 103 to 2835). The first study was published in 2001, and the last study was published in 2008.
A total of 7 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 14.1 (page 91) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

14.2 Summary of meta-analysis results

The meta-analysis of the available trials about oral direct thrombin inhibitor provide the results listed in tables 14.2 to 14.4 (page 94) and in the following graphs.

14.2.1 Dabigatran 150mg

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)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)and major bleeding (RR=0.42, 95% CI 0.15 to 1.17, p=0.0973, 1 trial).

14.2.2 Dabigatran 220mg

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)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).

14.2.3 Ximelagatran

No significant difference was found between **ximelagatran** and **Dalteparin** in terms of venous thromboembolism (RR=0.83, 95% CI 0.25 to 2.76, p=0.7619, 1 trial)and major bleeding (RR=0.97, 95% CI 0.02 to 47.50, p=0.9880, 1 trial).

No significant difference was found between **ximelagatran** and **Enoxaparin** in terms of venous thromboembolism (RR=0.88, 95% CI 0.63 to 1.24, p=0.4703, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0002)(RR=1.44, 95% CI 0.49 to 4.22, p=0.5096, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0120)

Table 14.1: *Main study characteristics - oral direct thrombin inhibitor*

Trial	Patients	Treatments	Trial design and method
Dabigatran 150mg			
Dabigatran 150mg versus enoxaparin (europe regimen)			
RE-MODEL (150mg), 2007 [1] 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 [2] 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 (europe regimen)			
RE-MODEL (220mg), 2007 [1] 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)			

continued...

Trial	Patients	Treatments	Trial design and method
RE-MOBILIZE (220mg), 2008 [2] 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)
Ximelagatran			
Ximelagatran versus Dalteparin			
METHRO I, 2002 [1] n= 103	adults undergoing hip or knee replacement	melagatran 14 mg s.c. immediately before surgery, melagatran at 20.00 hours, then ximelagatran 624 mg orally b.d. for 69 days **versus** dalteparin 5000 IU o.d., started evening before surgery for 69 days	open parallel group 8 centres, Swedish
Ximelagatran versus Enoxaparin			
METHRO III, 2002 [2, 3, 4] n= 2788	hip or knee replacement	melagatran 3 mg s.c. 412h after surgery, then ximelagatran24 mg orally b.d. for 710 days **versus** enoxaparin 40 mg s.c. o.d. 12 h before surgery for 710 days	double-blind Primary endpoint: venous thromboembolism 80 centres, Europe, South Africa
Phase II (Heit), 2001 [5] n= 600	adults (age >18 years and weight at least 40 kg) undergoing knee replacements	ximelagatran 8, 12, 18 or 24 mgorally b.d., at least 12 h after surgery for 612 days **versus** enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 612 days	double-blind parallel group 6 centres, North American

continued...

Trial	Patients	Treatments	Trial design and method
EXPRESS, 2003 [6, 7] n= 2835	hip or knee replacement	melagatran 2 mg s.c. up to 30 min before surgery, then melagatran 3 mg at least 8 hafter surgery, then ximelagatran 24 mg orally b.d. for 811 days **versus** enoxaparin 40 mg s.c. o.d.,starting 12 h before surgery for 811 days	double-blind parallel group Primary endpoint: venous thromboembolism 77 centres, Europe

Table 14.2: *Summary of all results for dabigatran 150mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
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 14.3: *Summary of all results for dabigatran 220mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
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

continued...

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 (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
coronary event	RR=1.26	0.40;3.99	0.6997	1.0000 (0.00)	1	2076
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
coronary event	RR=1.05	0.48;2.31	0.9068	1.0000 (0.00)	1	2586
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

Table 14.4: *Summary of all results for ximelagatran*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
ximelagatran versus Dalteparin						
venous thromboembolism	RR=0.83	0.25;2.76	0.7619	1.0000 (0.00)	1	53
major bleeding	RR=0.97	0.02;47.50	0.9880	1.0000 (0.00)	1	67
ximelagatran versus Enoxaparin						
venous thromboembolism	RR=0.88 [1]	0.63;1.24	0.4703	0.0002 (0.88) †	3	4785
major bleeding	RR=1.44 [2]	0.49;4.22	0.5096	0.0120 (0.77) †	3	5805

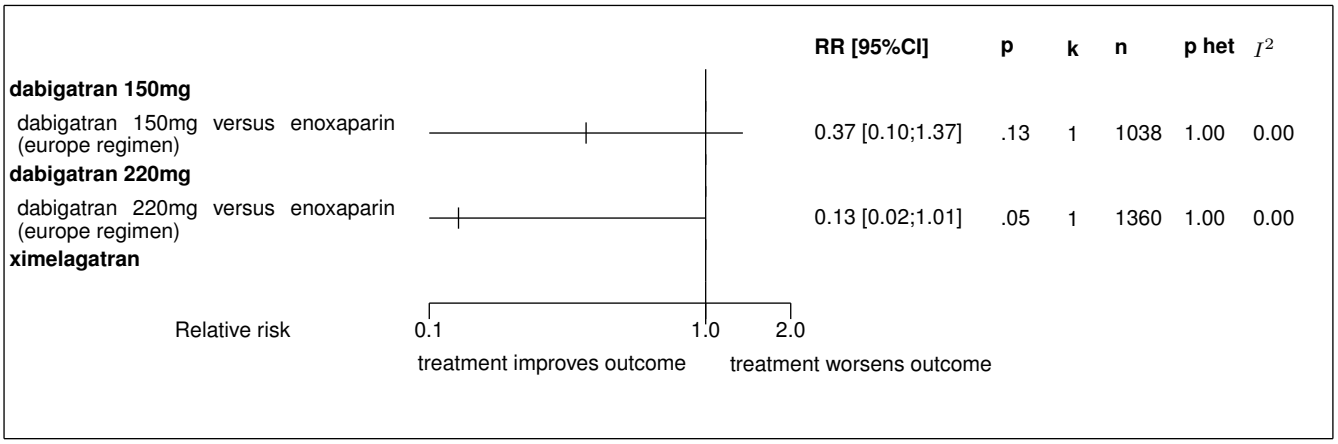
continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.95 95% CI 0.86;1.04
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.60 95% CI 1.07;2.41

Endpoint	Effect	95% CI	p ass	p het	k	n

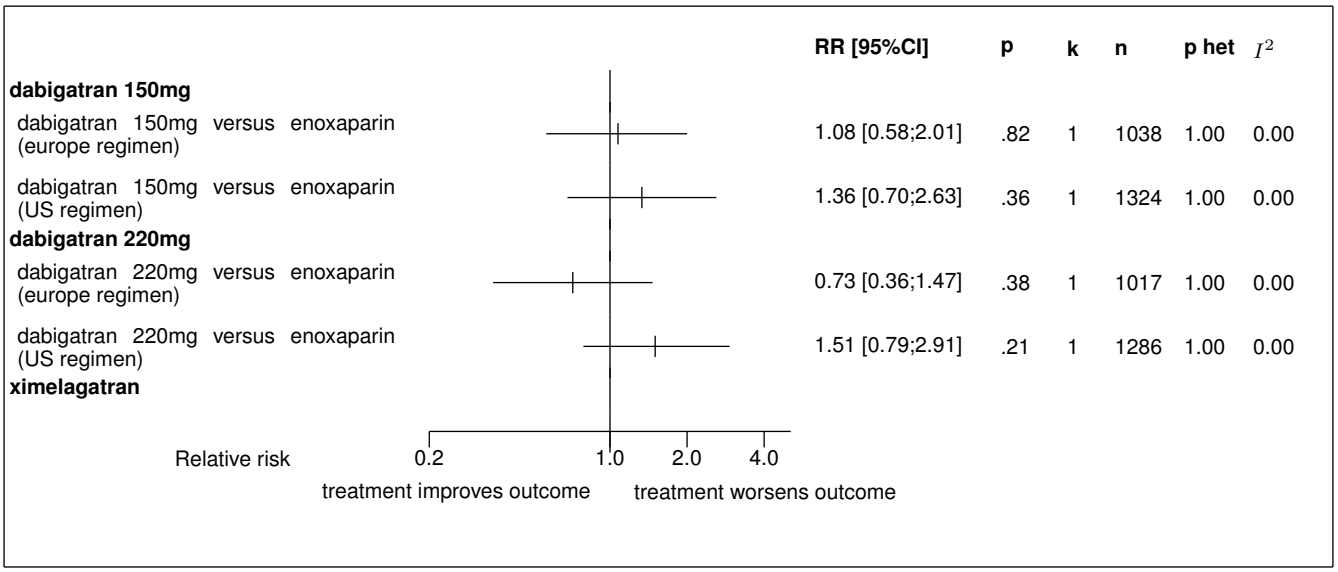
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 14.1: *Forest's plot for symptomatic deep-vein thrombosis*



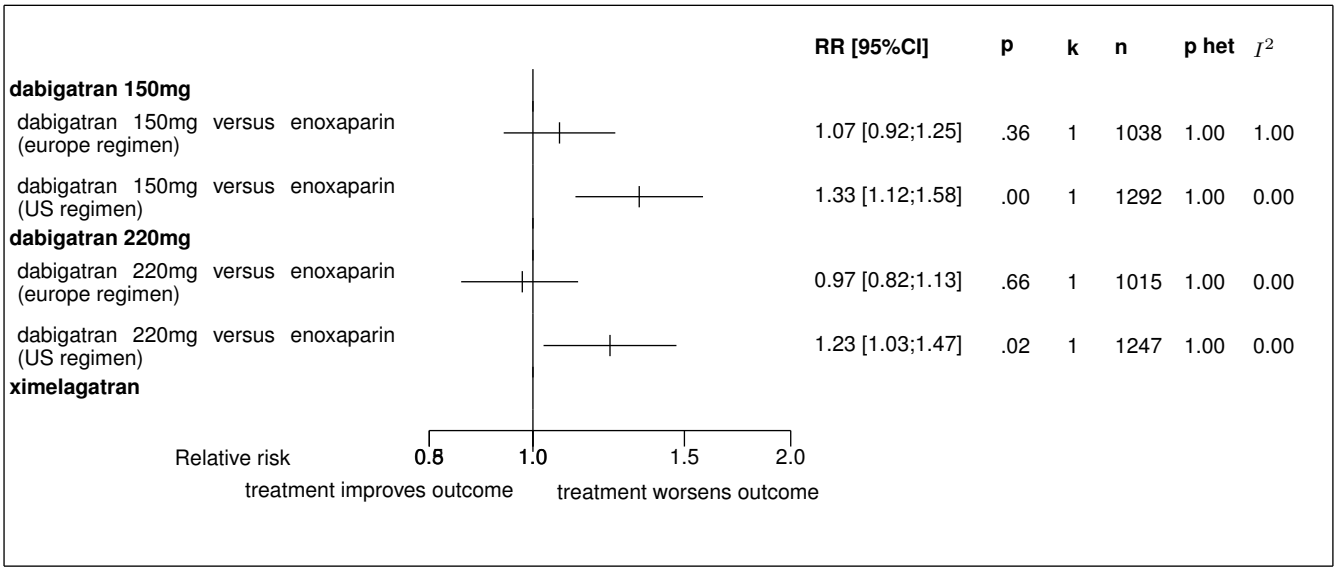
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*



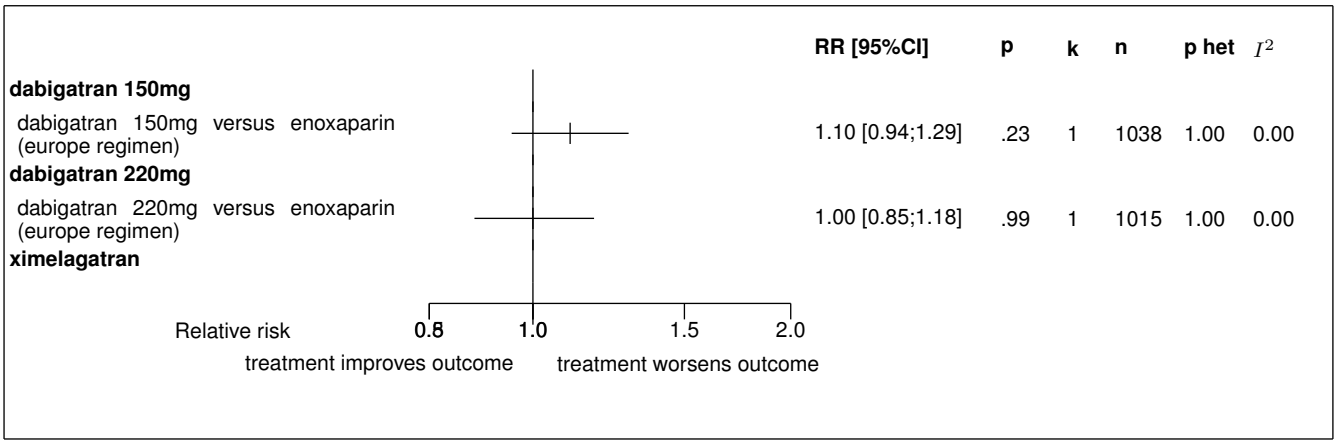
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.3: *Forest's plot for total VTE and all-cause mortality*



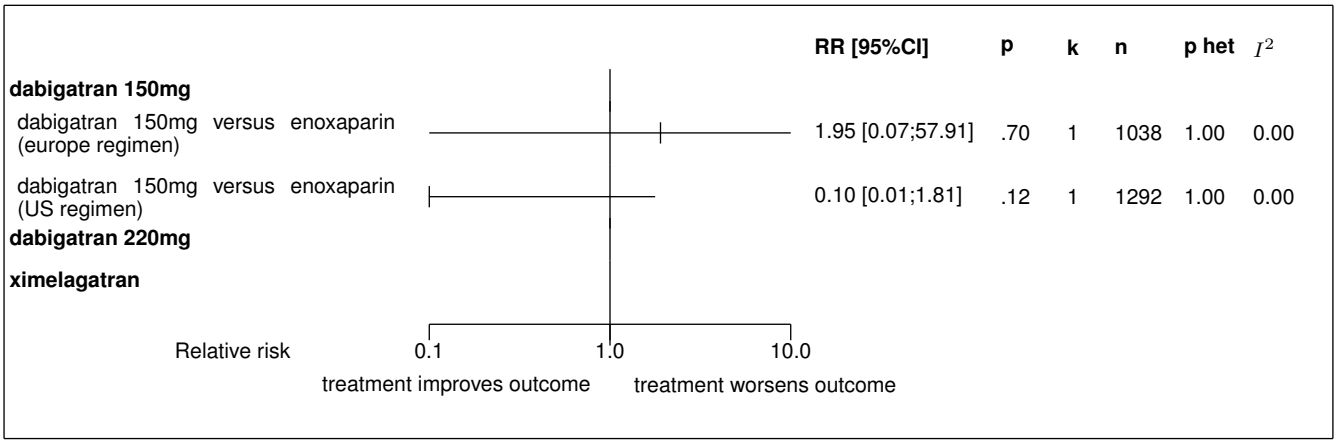
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.4: *Forest's plot for asymptomatic DVT*



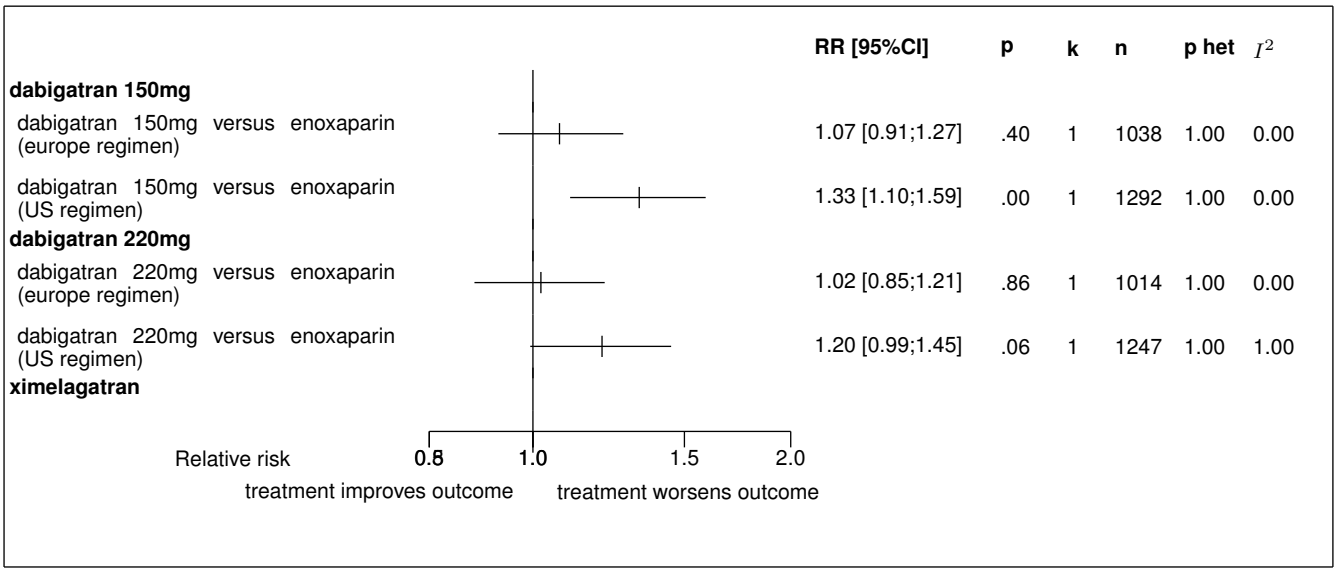
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.5: *Forest's plot for non-fatal pulmonary embolism*



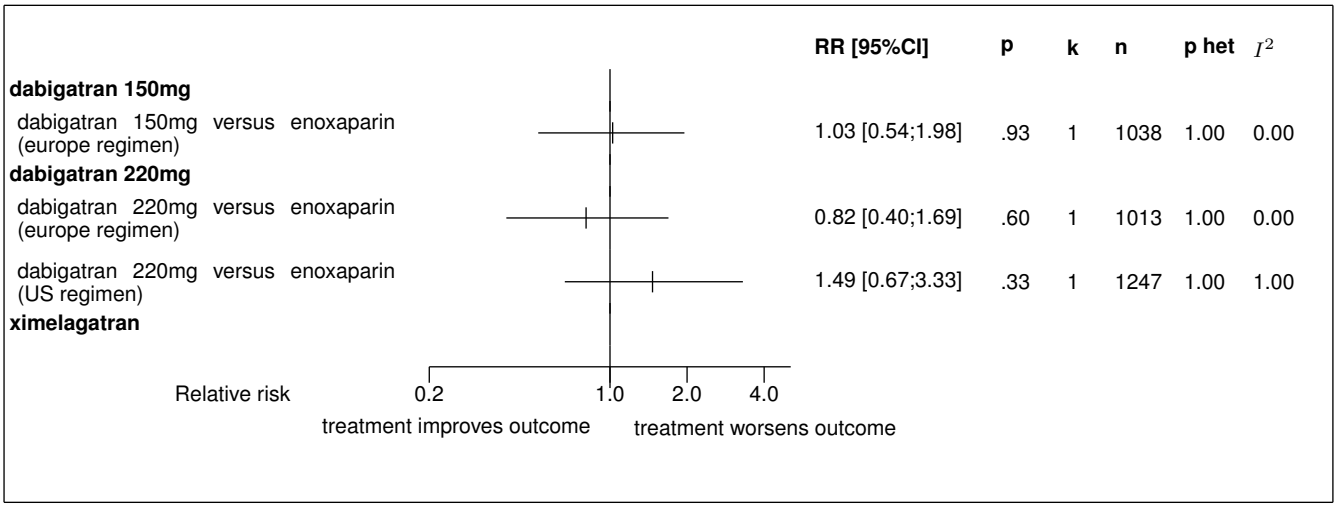
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.6: *Forest's plot for distal DVT*



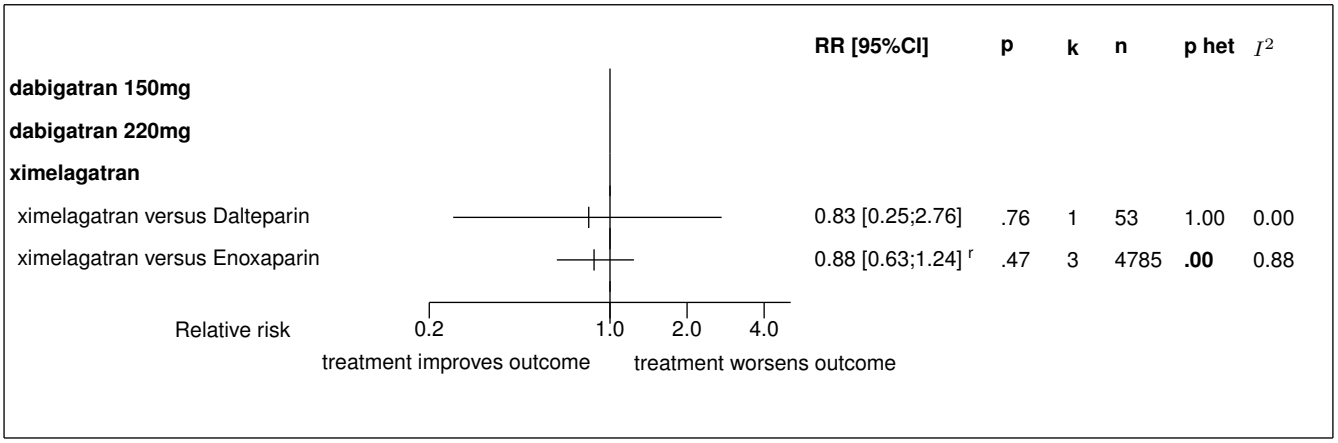
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.7: *Forest's plot for proximal DVT*



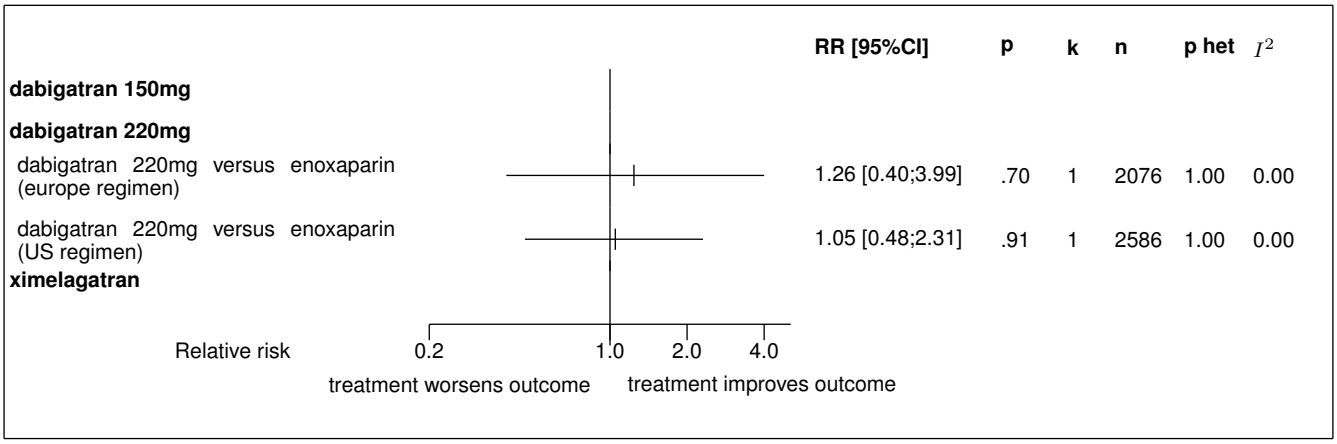
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.8: *Forest's plot for venous thromboembolism*



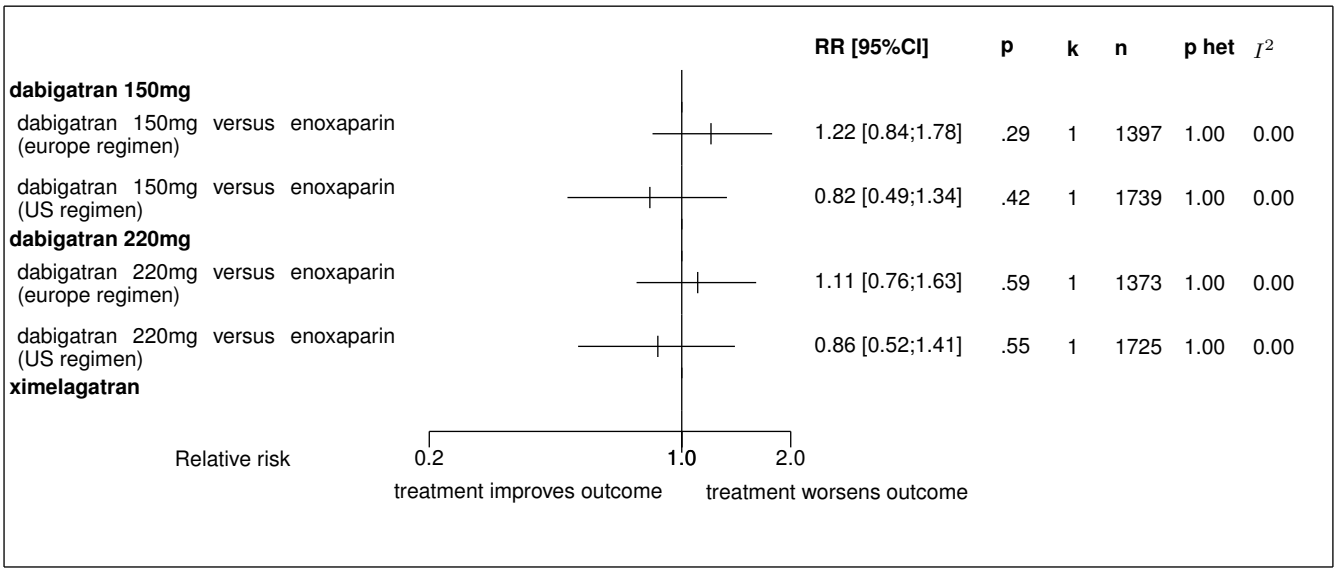
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.9: *Forest's plot for coronary event*



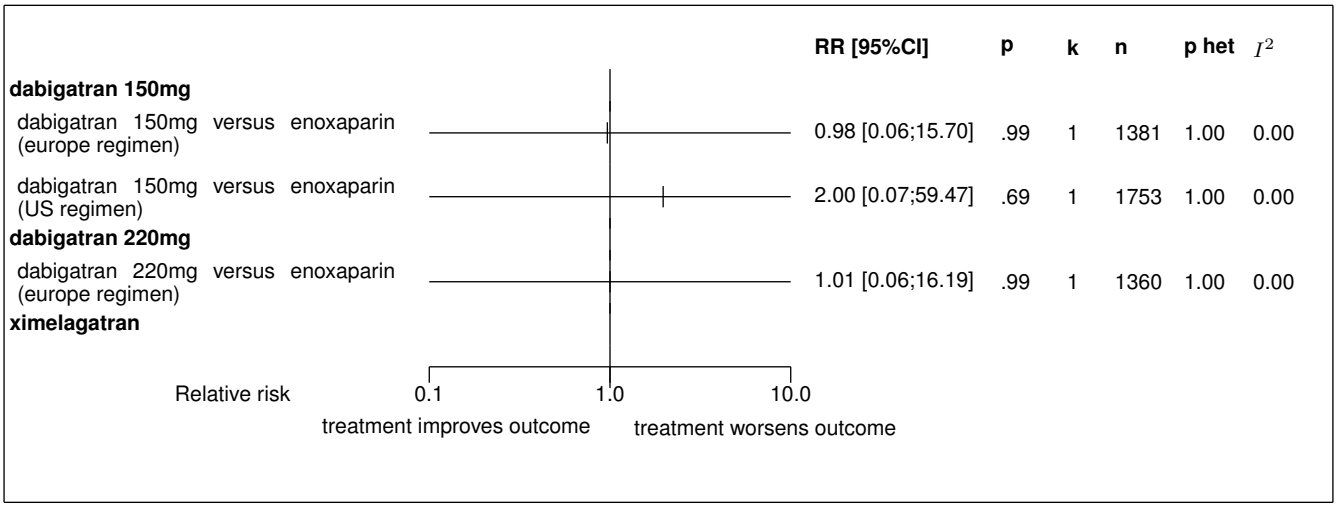
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.10: *Forest's plot for major or clinically relevant non-major bleeding*



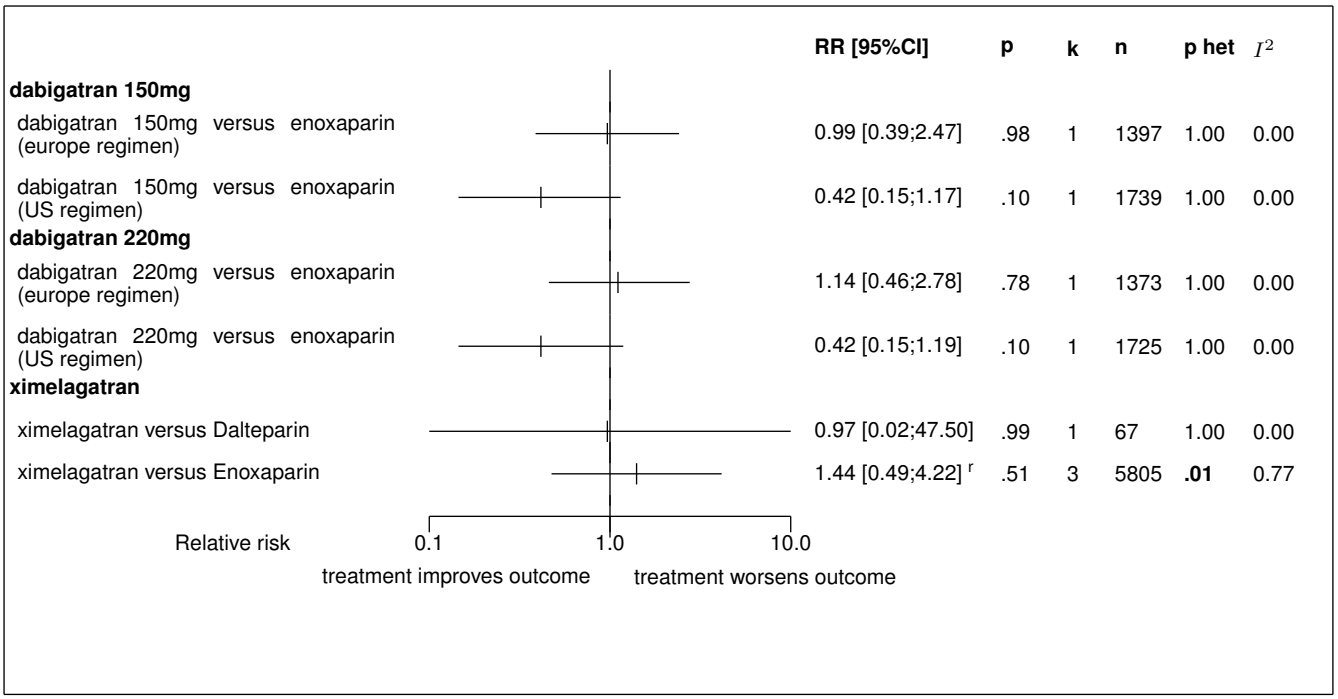
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 14.11: *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 14.12: *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

15 Detailed results for dabigatran 150mg

15.1 Available trials

A total of 2 RCTs which randomized 3160 patients were identified: it compared dabigatran 150mg with enoxaparin (europe regimen) and it compared dabigatran 150mg with enoxaparin (US regimen).
The average study size was 1580 patients (range 1407 to 1753). 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 2 trials; 2 trials reported data on major VTE (fatal and non fatal DVT,PE); 2 trials reported data on distal DVT; 2 trials reported data on total VTE and all-cause mortality; 2 trials reported data on major bleeding; 2 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on proximal DVT; 1 trials reported data on asymptomatic DVT; and 2 trials reported data on major or clinically relevant non-major bleeding.
Following tables 15.1 (page 102), 15.2 (page 102), 15.4 (page 105), and 15.3 (page 103) summarized the main characteristics of the trials including in this systematic review of randomized trials of dabigatran 150mg.

Table 15.1: *Treatment description - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Studied treatment	Control treatment
Dabigatran 150mg versus enoxaparin (europe regimen)		
RE-MODEL (150mg) (2007) [1]	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) [2]	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

Table 15.2: *Descriptions of participants - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Patients
Dabigatran 150mg versus enoxaparin (europe regimen)	

continued...

Trial	Patients	
RE-MODEL (150mg) (2007) [1]	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) [2]	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 15.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 150mg versus enoxaparin (europe regimen)				
RE-MODEL (150mg), 2007 [1] 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)				

continued...

Trial	Design	Duration	Centre	Primary endpoint
RE-MOBILIZE (150mg), 2008 [2] 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 15.4: *Trial characteristics - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	mean follow-up	test intervalle
Dabigatran 150mg versus enoxaparin (europe regimen)		
RE-MODEL (150mg), 2007 [1]	8 days	2-4 (3)
Dabigatran 150mg versus enoxaparin (US regimen)		
RE-MOBILIZE (150mg), 2008 [2]	14 days	2-4 (3)

15.2 Meta-analysis results

The results are detailed in table 15.5 (page 107). This table is followed by the Forest's plot corresponding to each endpoint.

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
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 15.1: *Forest's plot for symptomatic deep-vein thrombosis*

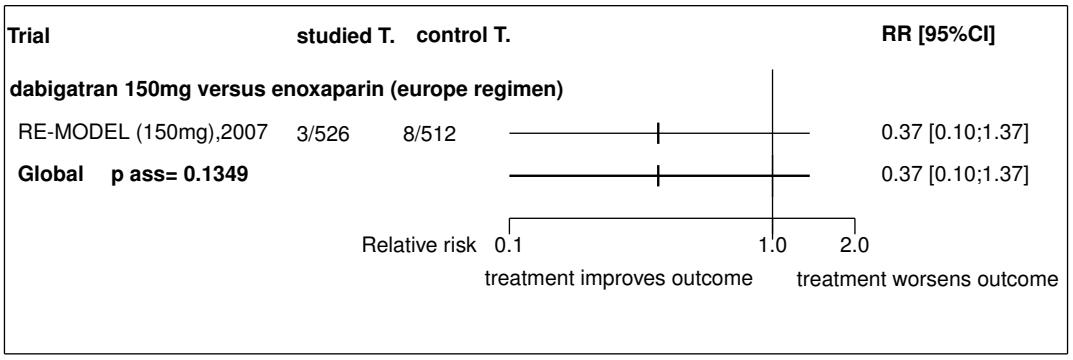


Figure 15.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

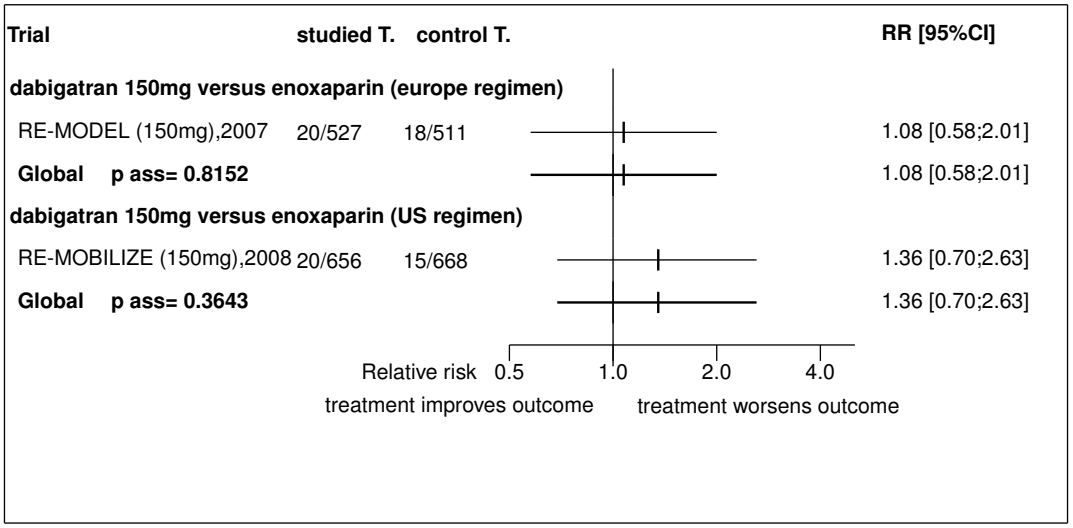


Figure 15.3: *Forest's plot for total VTE and all-cause mortality*

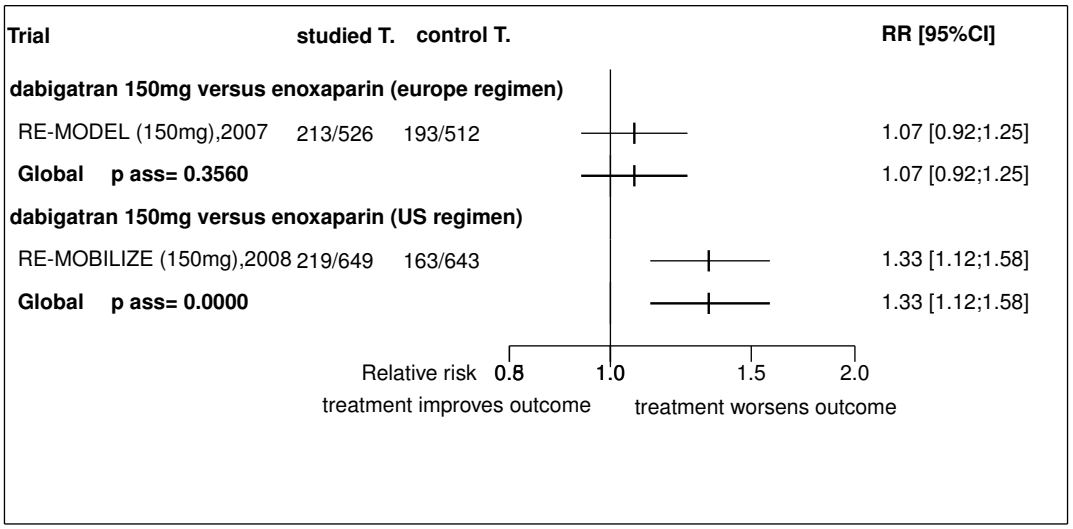


Figure 15.4: *Forest's plot for asymptomatic DVT*

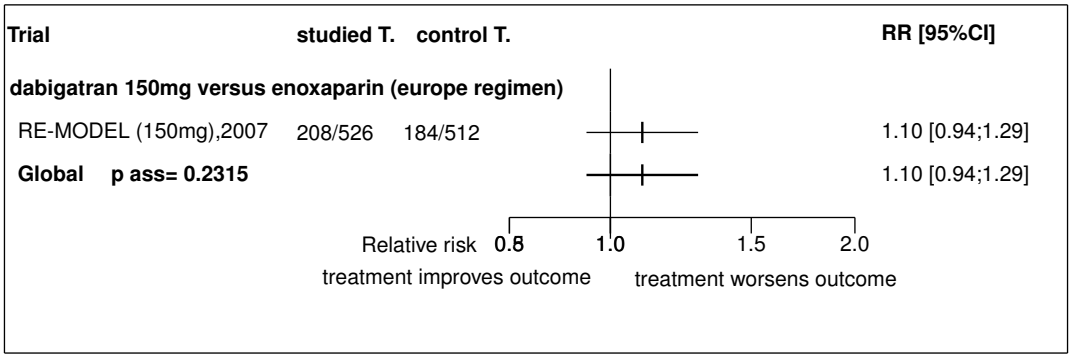


Figure 15.5: *Forest's plot for non-fatal pulmonary embolism*

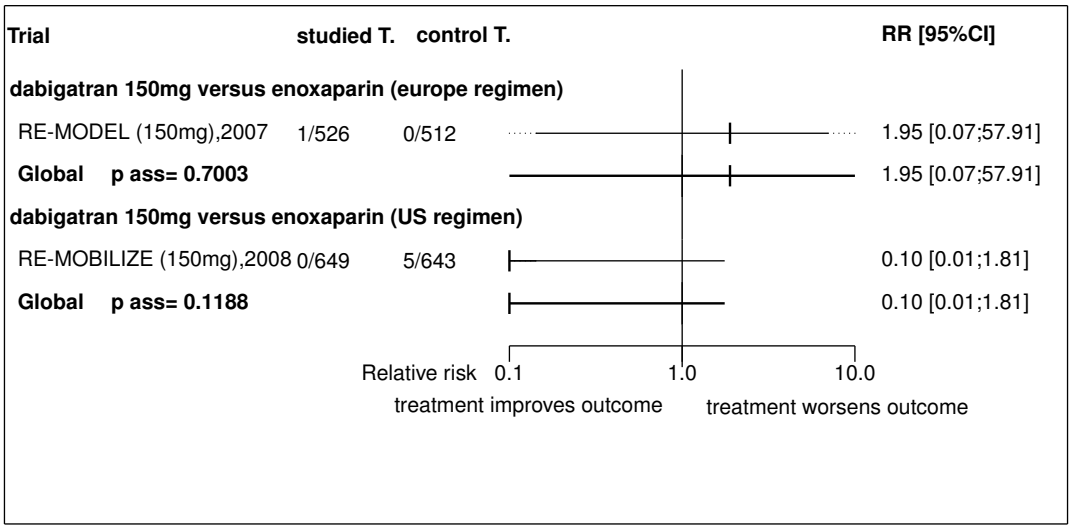


Figure 15.6: *Forest's plot for distal DVT*

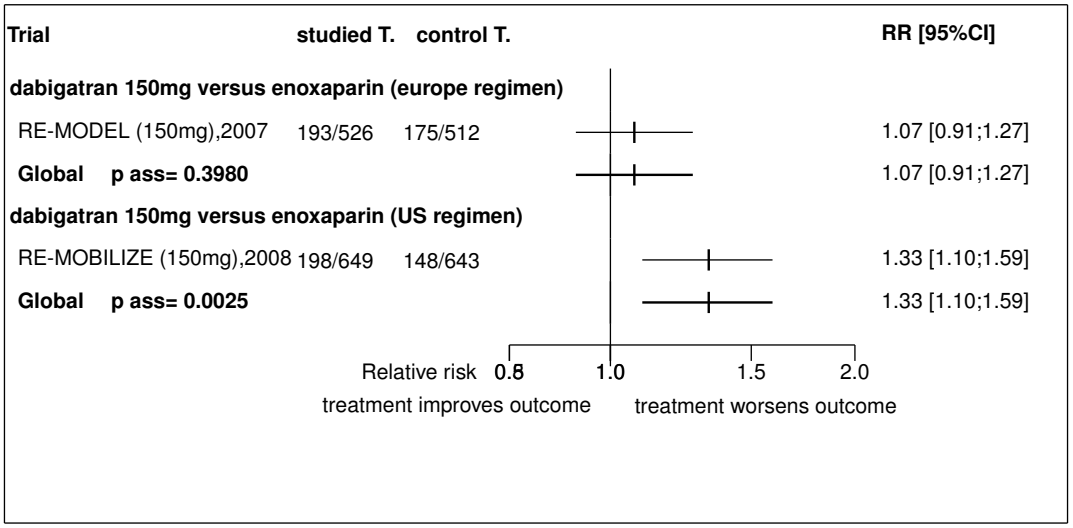


Figure 15.7: *Forest's plot for proximal DVT*

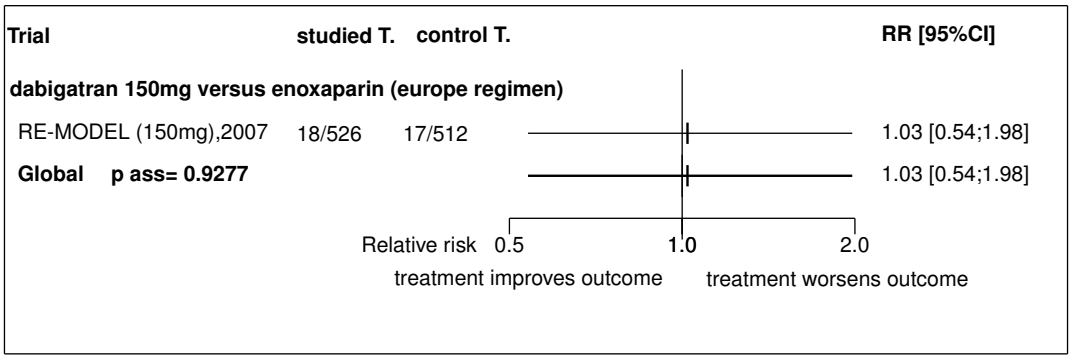


Figure 15.8: *Forest's plot for major or clinically relevant non-major bleeding*

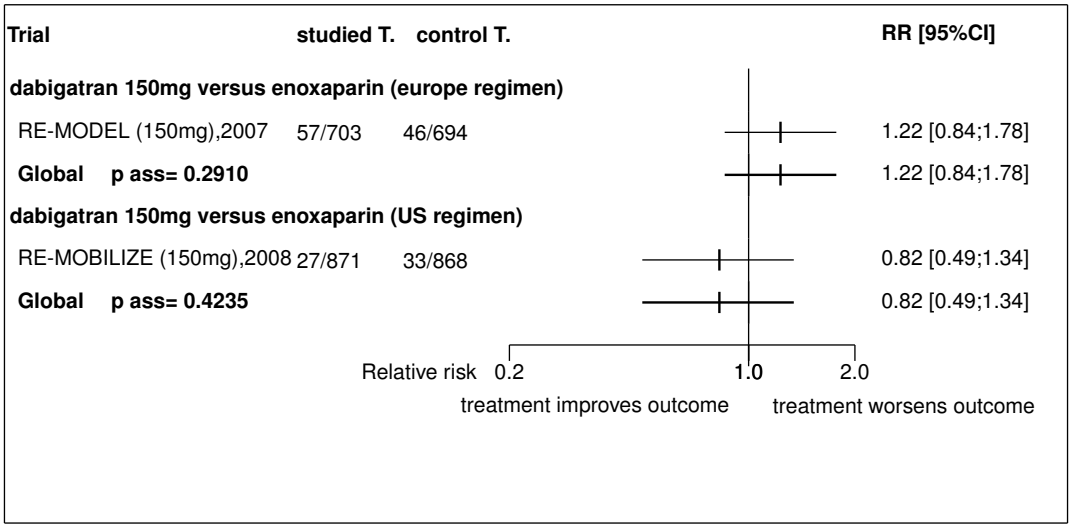


Figure 15.9: *Forest's plot for all cause death*

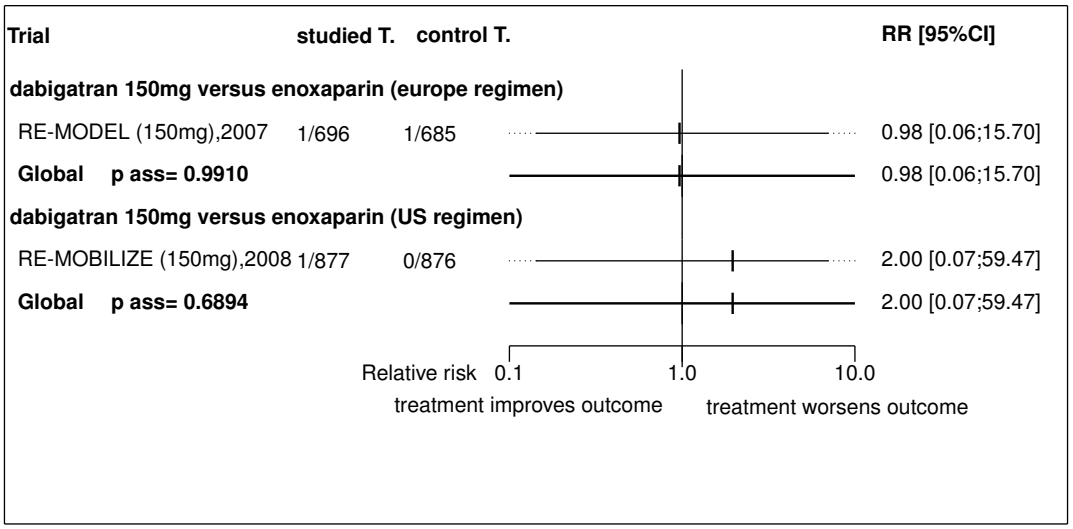
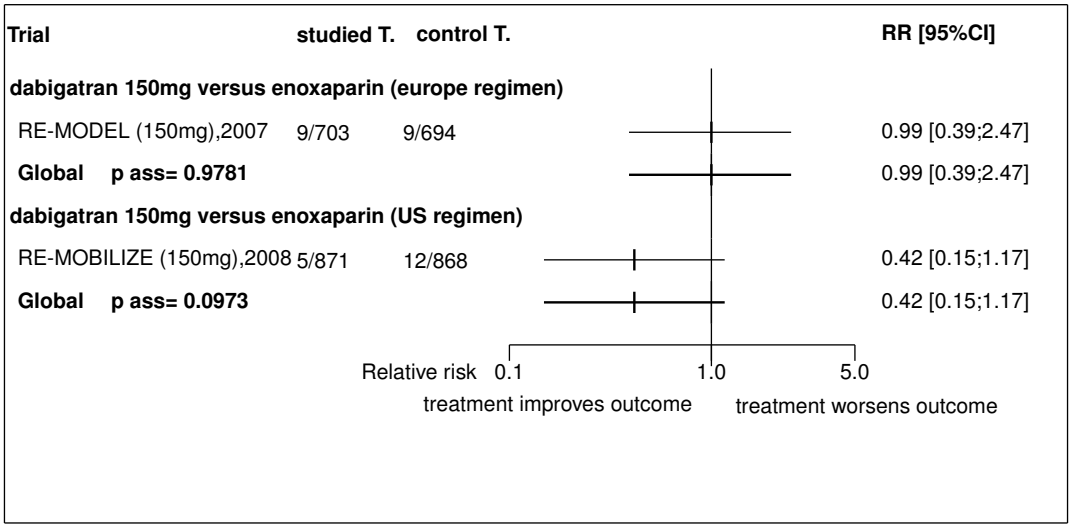


Figure 15.10: *Forest's plot for major bleeding*



References

[1] 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]

[2] 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]

15.3 Individual trial summaries

Table 15.6: *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]

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 15.7: *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]

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]

16 Detailed results for dabigatran 220mg

16.1 Available trials

A total of 2 RCTs which randomized 3131 patients were identified: it compared dabigatran 220mg with enoxaparin (europe regimen) and it compared dabigatran 220mg with enoxaparin (US regimen).
The average study size was 1565 patients (range 1393 to 1738). 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.
Major bleeding data was reported in 2 trials; 2 trials reported data on proximal DVT; 2 trials reported data on total VTE and all-cause mortality; 2 trials reported data on major VTE (fatal and non fatal DVT,PE); 2 trials reported data on distal DVT; 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on all cause death; 1 trials reported data on asymptomatic DVT; 2 trials reported data on coronary event; and 2 trials reported data on major or clinically relevant non-major bleeding.
Following tables 16.1 (page 117), 16.2 (page 117), 16.4 (page 120), and 16.3 (page 118) summarized the main characteristics of the trials including in this systematic review of randomized trials of dabigatran 220mg.

Table 16.1: *Treatment description - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Studied treatment	Control treatment
Dabigatran 220mg versus enoxaparin (europe regimen)		
RE-MODEL (220mg) (2007) [1]	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) [2]	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

Table 16.2: *Descriptions of participants - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Patients
Dabigatran 220mg versus enoxaparin (europe regimen)	

continued...

Trial	Patients	
RE-MODEL (220mg) (2007) [1]	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) [2]	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 16.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 220mg versus enoxaparin (europe regimen)				
RE-MODEL (220mg), 2007 [1] 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)				

continued...

Trial	Design	Duration	Centre	Primary endpoint
RE-MOBILIZE (220mg), 2008 [2] 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 16.4: *Trial characteristics - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	mean follow-up	test intervalle
Dabigatran 220mg versus enoxaparin (europe regimen)		
RE-MODEL (220mg), 2007 [1]	8 days	2-4 (3)
Dabigatran 220mg versus enoxaparin (US regimen)		
RE-MOBILIZE (220mg), 2008 [2]	14 days	2-4 (3)

16.2 Meta-analysis results

The results are detailed in table 16.5 (page 122). This table is followed by the Forest's plot corresponding to each endpoint.

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
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
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
coronary event	RR=1.26	[0.40;3.99]	0.6997	1.0000 (I^2=0.00)	1	2076
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
coronary event	RR=1.05	[0.48;2.31]	0.9068	1.0000 (I^2=0.00)	1	2586
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 16.1: *Forest's plot for symptomatic deep-vein thrombosis*

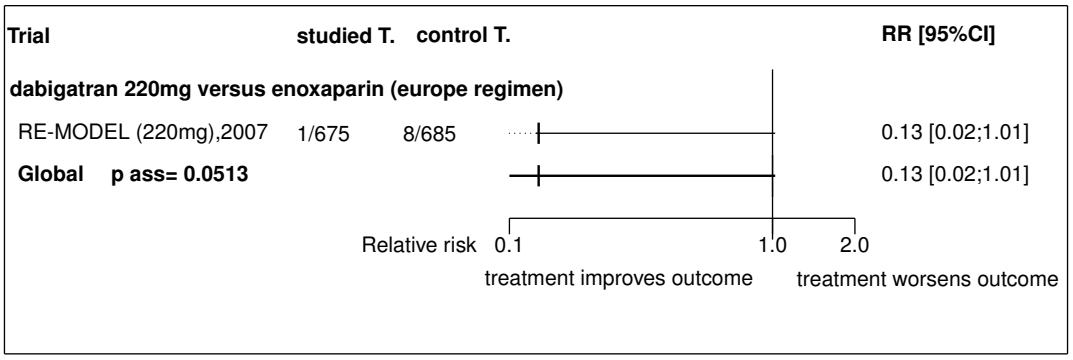


Figure 16.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

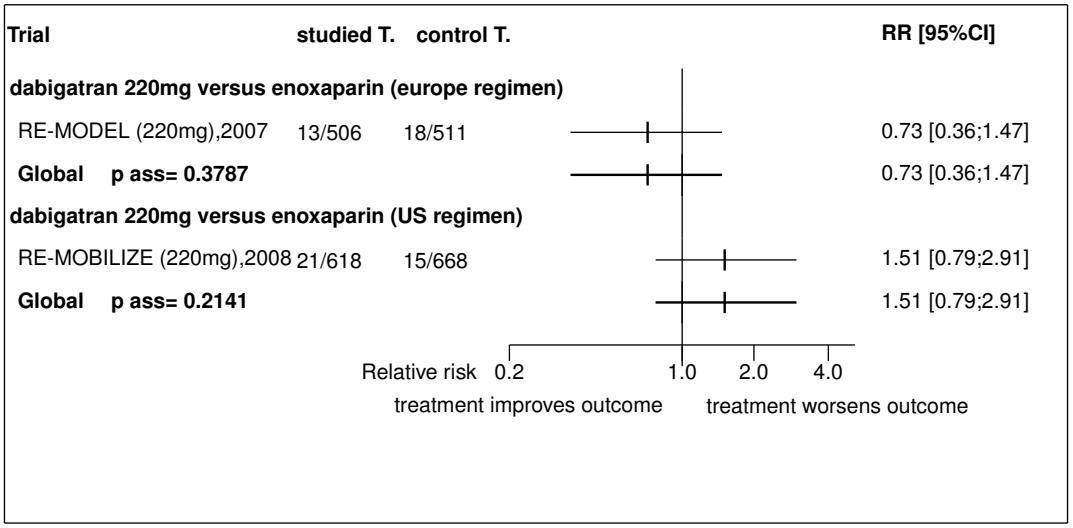


Figure 16.3: *Forest's plot for total VTE and all-cause mortality*

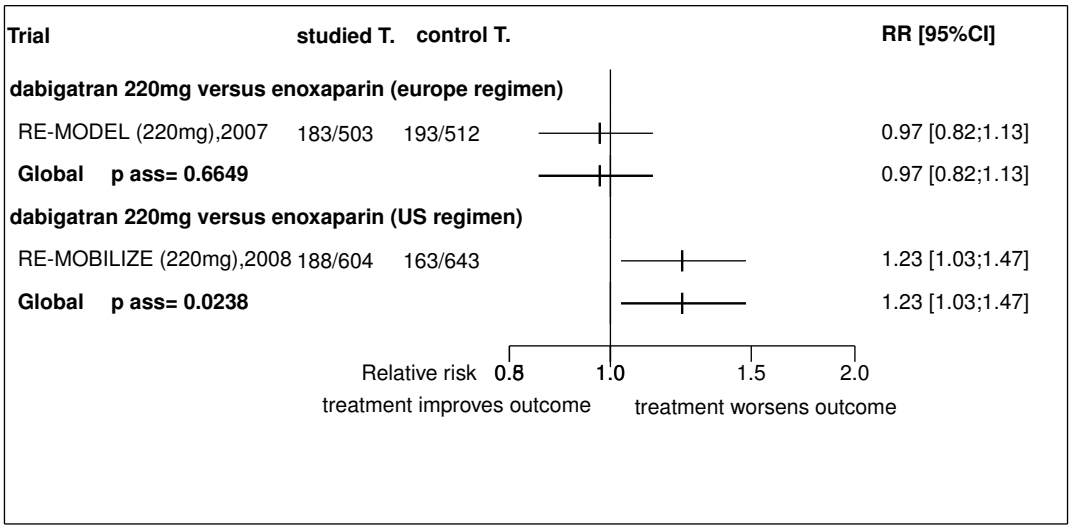


Figure 16.4: *Forest's plot for asymptomatic DVT*

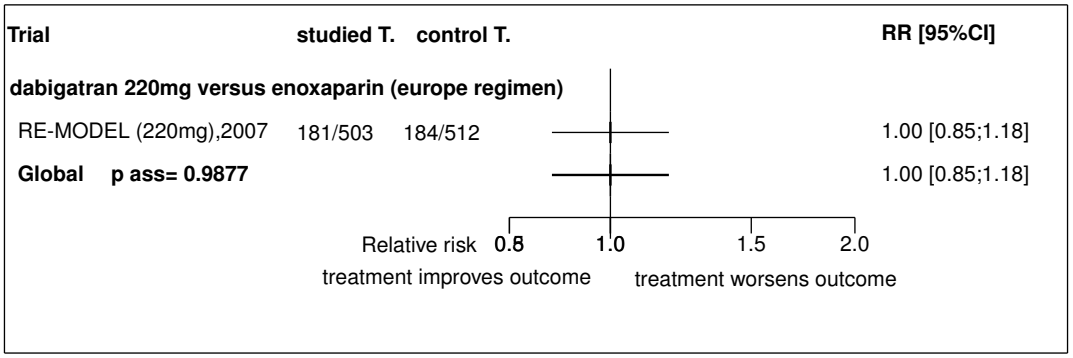


Figure 16.5: *Forest's plot for distal DVT*

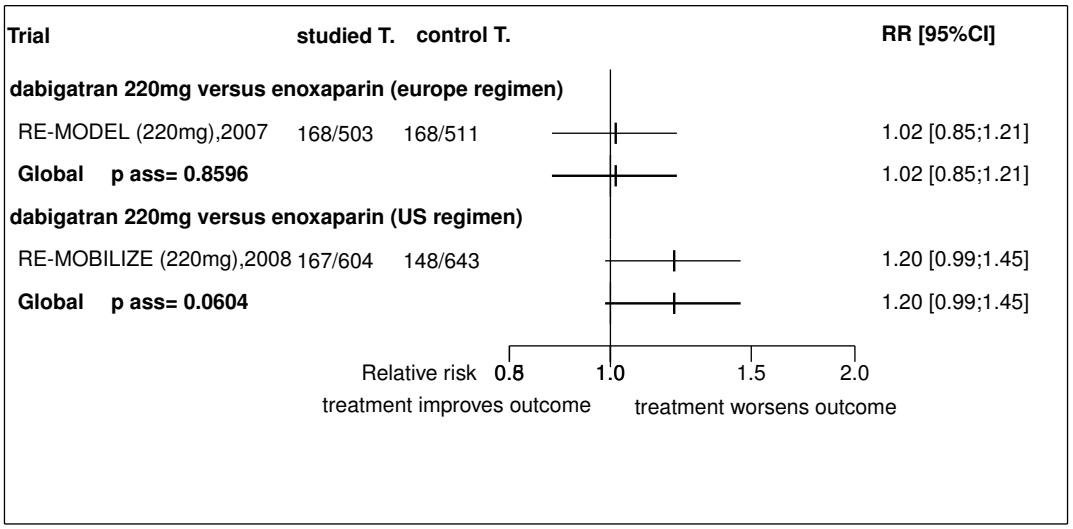


Figure 16.6: *Forest's plot for proximal DVT*

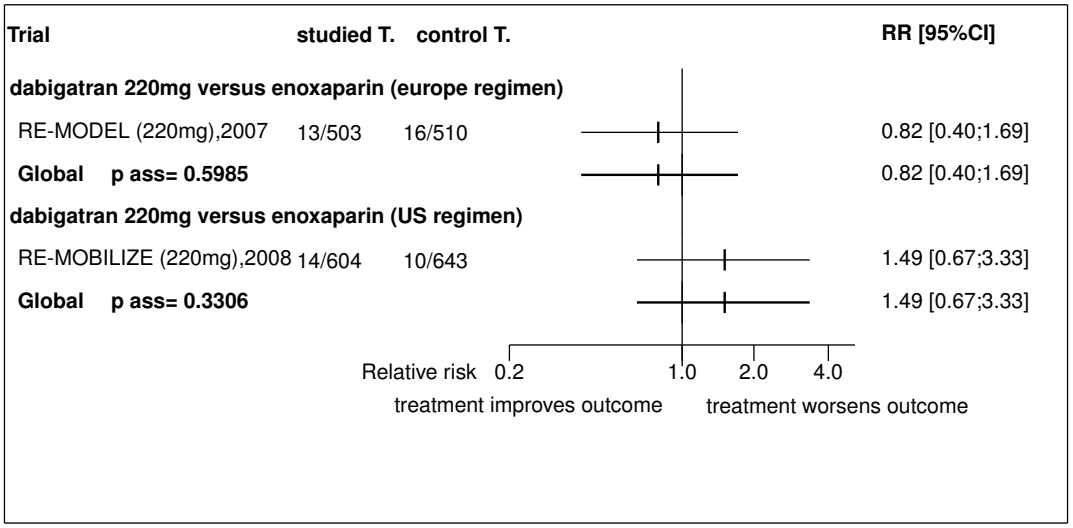


Figure 16.7: *Forest's plot for coronary event*

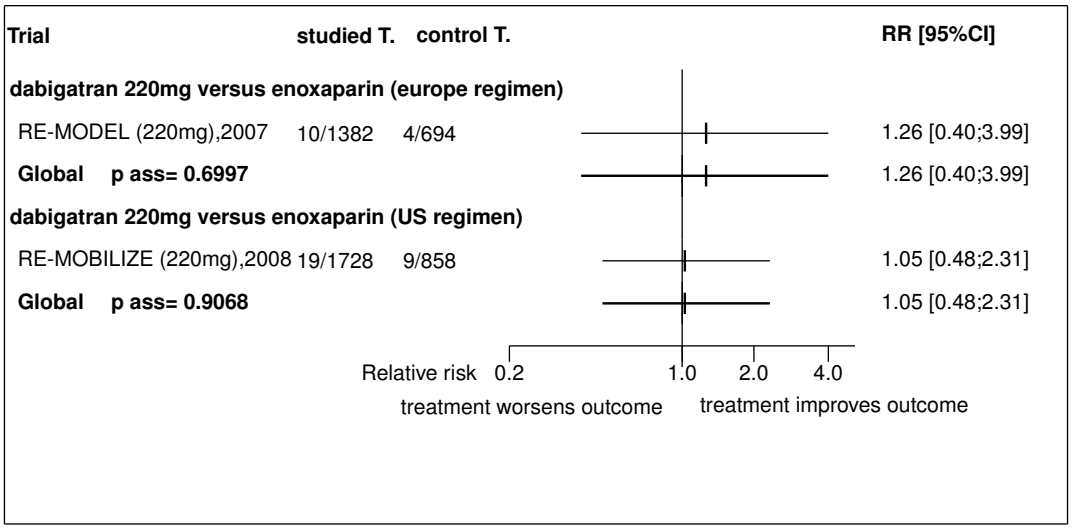


Figure 16.8: *Forest's plot for major or clinically relevant non-major bleeding*

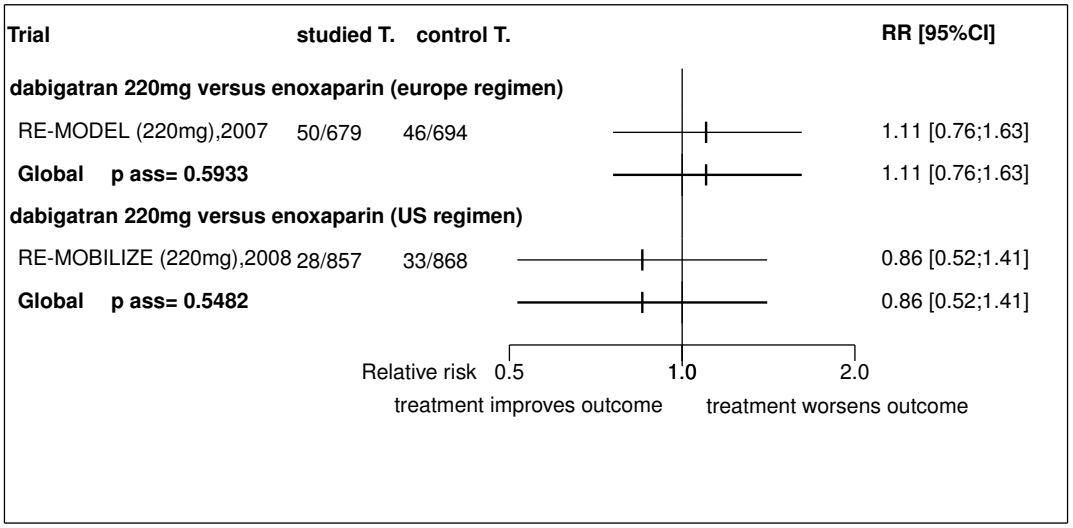


Figure 16.9: *Forest's plot for all cause death*

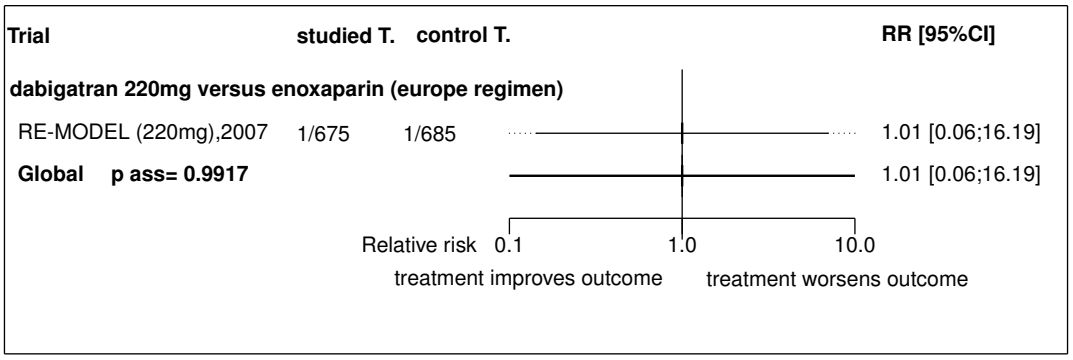
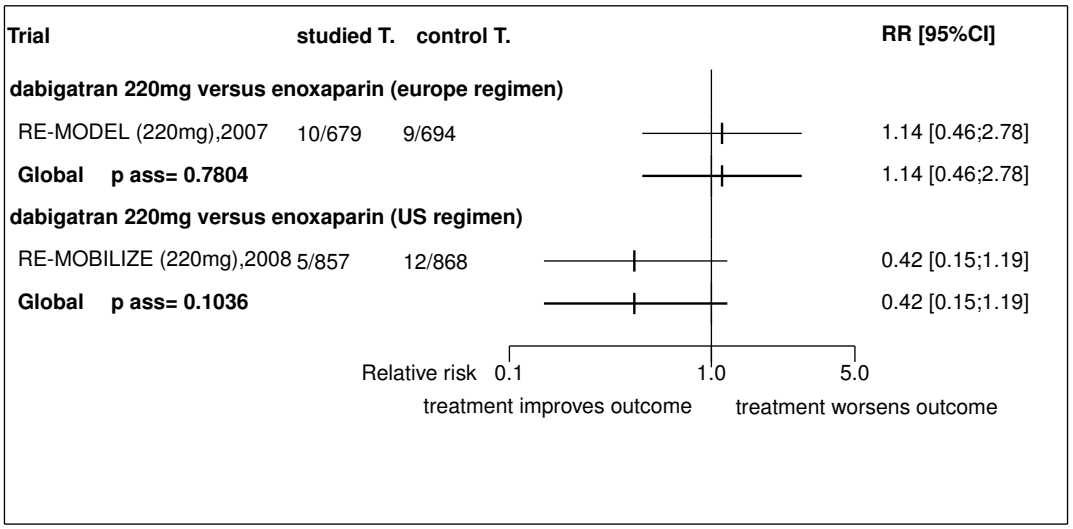


Figure 16.10: *Forest's plot for major bleeding*



References

[1] 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]

[2] . 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]

16.3 Individual trial summaries

Table 16.6: *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]

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 16.7: *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]

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]

17 Detailed results for ximelagatran

17.1 Available trials

A total of 4 RCTs which randomized 6326 patients were identified: it compared ximelagatran with Dalteparin and 3 trials compared ximelagatran with Enoxaparin.
The average study size was 1581 patients (range 103 to 2835). The first study was published in 2001, and the last study was published in 2003.
A total of 3 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Venous thromboembolism data was reported in 4 trials; and 4 trials reported data on major bleeding.
Following tables 17.1 (page 131), 17.2 (page 131), 17.4 (page 133), and 17.3 (page 132) summarized the main characteristics of the trials including in this systematic review of randomized trials of ximelagatran.

Table 17.1: *Treatment description - oral direct thrombin inhibitor - ximelagatran*

Trial	Studied treatment	Control treatment
Ximelagatran versus Dalteparin		
METHRO I (2002) [1]	Melagatran 14 mg s.c. immediately before surgery, melagatran at 20.00 hours, then ximelagatran 624 mg orally b.d. for 69 days	Dalteparin 5000 IU o.d., started evening before surgery for 69 days
Ximelagatran versus Enoxaparin		
METHRO III (2002) [2, 3, 4]	Melagatran 3 mg s.c. 412h after surgery, then ximelagatran24 mg orally b.d. for 710 days	Enoxaparin 40 mg s.c. o.d. 12 h before surgery for 710 days
Phase II (Heit) (2001) [5]	Ximelagatran 8, 12, 18 or 24 mgorally b.d., at least 12 h after surgery for 612 days	Enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 612 days
EXPRESS (2003) [6, 7]	Melagatran 2 mg s.c. up to 30 min before surgery, then melagatran 3 mg at least 8 hafter surgery, then ximelagatran 24 mg orally b.d. for 811 days	Enoxaparin 40 mg s.c. o.d.,starting 12 h before surgery for 811 days

Table 17.2: *Descriptions of participants - oral direct thrombin inhibitor - ximelagatran*

Trial	Patients
Ximelagatran versus Dalteparin	
METHRO I (2002) [1]	Adults undergoing hip or knee replacement

continued...

Trial	Patients
Ximelagatran versus Enoxaparin	
METHRO III (2002) [2, 3, 4]	Hip or knee replacement
Phase II (Heit) (2001) [5]	Adults (age >18 years and weight at least 40 kg) undergoing knee replacements
EXPRESS (2003) [6, 7]	Hip or knee replacement

Table 17.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - ximelagatran*

Trial	Design	Duration	Centre	Primary endpoint
Ximelagatran versus Dalteparin				
METHRO I, 2002 [1] n=103	parallel group open	69 days	Swedish 8 centres	
Ximelagatran versus Enoxaparin				
METHRO III, 2002 [2, 3, 4] n=2788	double-blind	811 days	Europe, South Africa 80 centres	venous thromboembolism
Phase II (Heit), 2001 [5] n=600	parallel group double-blind	612 days	North American 6 centres	
EXPRESS, 2003 [6, 7] n=2835	parallel group double-blind	811 days	Europe 77 centres	venous thromboembolism

Table 17.4: *Trial characteristics - oral direct thrombin inhibitor - ximelagatran*

Trial
Ximelagatran versus Dalteparin
METHRO I, 2002 [1]
Ximelagatran versus Enoxaparin
METHRO III, 2002 [2, 3, 4]
Phase II (Heit), 2001 [5]
EXPRESS, 2003 [6, 7]

17.2 Meta-analysis results

The results are detailed in table 17.5 (page 134). This table is followed by the Forest's plot corresponding to each endpoint.

Ximelagatran versus Dalteparin

The single study eligible for this comparison provided data on **venous thromboembolism**. No statistically significant difference between the groups was found in venous thromboembolism, with a RR of 0.83 (95% CI 0.25 to 2.76, p=0.7619).
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 0.97 (95% CI 0.02 to 47.50, p=0.9880).

Ximelagatran versus Enoxaparin

All the 3 studies had extractable data about the number of participants with **venous thromboembolism**. When pooled together, there was no statistically significant difference between the groups in venous thromboembolism, with a RR of 0.88 (95% CI 0.63 to 1.24, p=0.4703). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0002, I^2 = 0.88%).
All the 3 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 1.44 (95% CI 0.49 to 4.22, p=0.5096). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0120, I^2 = 0.77%).

Table 17.5: *Results details - oral direct thrombin inhibitor - ximelagatran*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ximelagatran versus Dalteparin						
venous thromboembolism	RR=0.83	[0.25;2.76]	0.7619	1.0000 (I^2=0.00)	1	53
major bleeding	RR=0.97	[0.02;47.50]	0.9880	1.0000 (I^2=0.00)	1	67
ximelagatran versus Enoxaparin						
venous thromboembolism	RR=0.88	[0.63;1.24]	0.4703	0.0002 (I^2=0.88)	3	4785
major bleeding	RR=1.44	[0.49;4.22]	0.5096	0.0120 (I^2=0.77)	3	5805

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 17.1: *Forest's plot for venous thromboembolism*

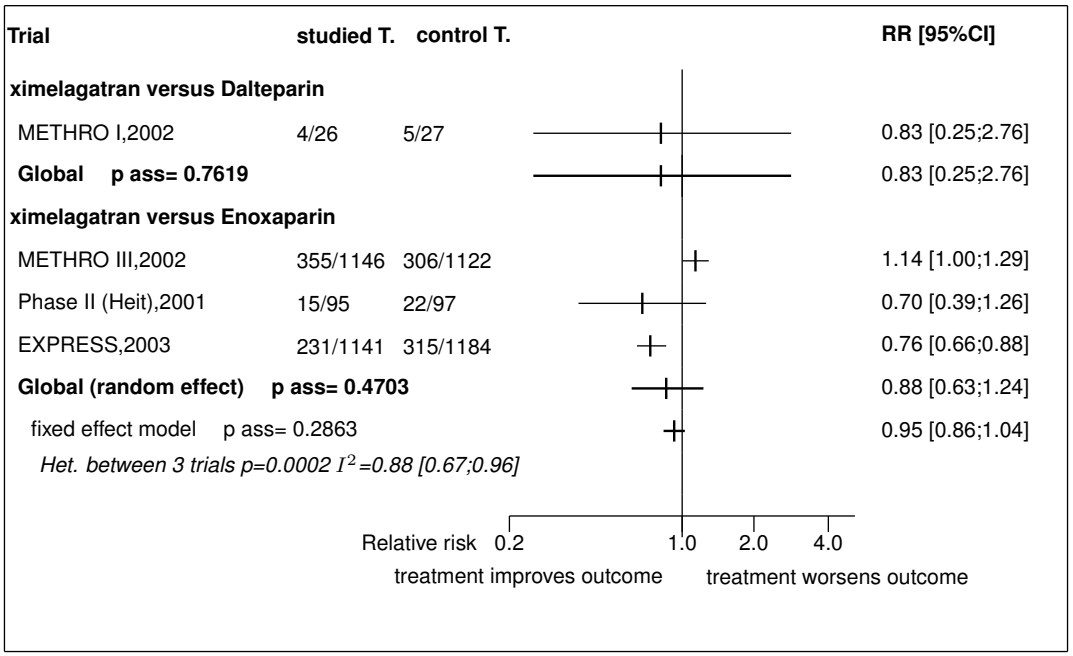
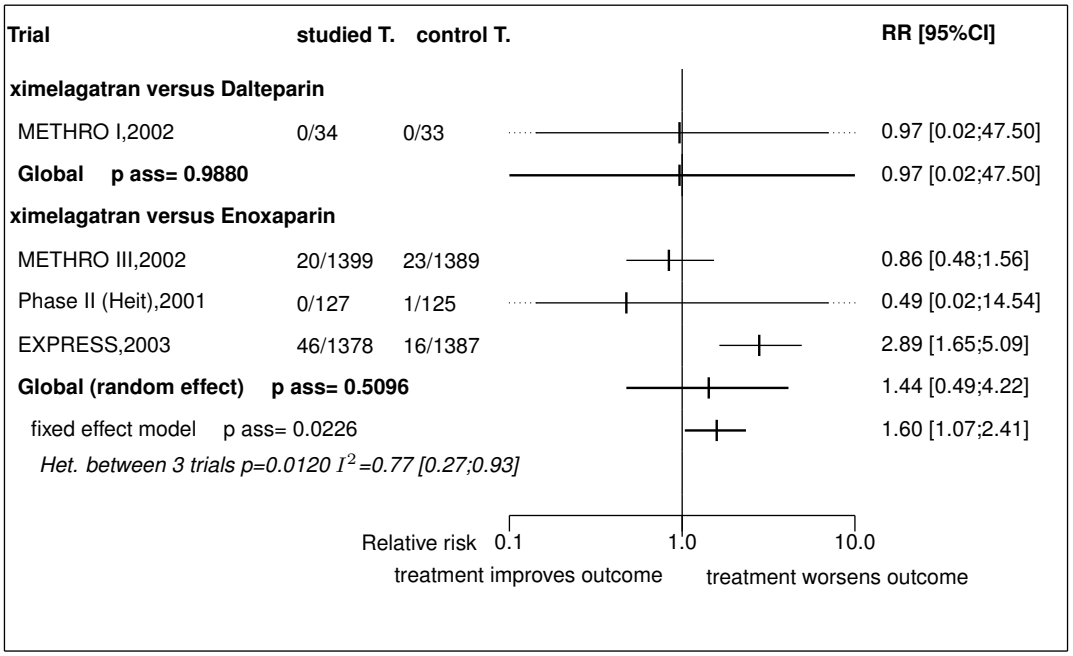


Figure 17.2: *Forest's plot for major bleeding*



References

[1] Eriksson BI, Arfwidsson AC, Frison L, Eriksson UG, Bylock A, Klebo P, Fager G, Gustafsson D. A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I. MElagatran for THRombin inhibition in Orthopaedic surgery. Thromb Haemost 2002;87:231-7. [PMID=11858482]

[2] Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, Eskilson C, Nylander I, Frison L, Ogren M. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. Thromb Haemost 2003;89:288-96. [PMID=12574809]

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[4] Eriksson BI. Clinical experience of melagatran/ximelagatran in major orthopaedic surgery. Thromb Res 2003;109 Suppl 1:S23-9. [PMID=12818631]

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[6] Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, Rosencher N, Klebo P, Panfilov S, Eskilson C, Andersson M, Freij A. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. J Thromb Haemost 2003;1:2490-6. [PMID=14675083]

[7] Glynn O. The express study: preliminary results. Int J Clin Pract 2003;57:57-9. [PMID=12587945]

17.3 Individual trial summaries

Table 17.6: *METHRO I, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (103 vs. 0) **Follow-up duration:** 69 days **Study design:** Randomized controlled trial parallel group Open Swedish, 8 centres	Adults undergoing hip or knee replacement	**Studied treatment:** Melagatran 14 mg s.c. immediately before surgery, melagatran at 20.00 hours, then ximelagatran 624 mg orally b.d. for 69 days **Control treatment:** Dalteparin 5000 IU o.d., started evening before surgery for 69 days	

Reference

Eriksson BI, Arfwidsson AC, Frison L, Eriksson UG, Bylock A, Klebo P, Fager G, Gustafsson D. A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I. MElagatran for THRombin inhibition in Orthopaedic surgery. Thromb Haemost 2002;87:231-7 [PMID=11858482]

Table 17.7: *METHRO III, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (2788 vs. 0) **Follow-up duration:** 811 days **Study design:** Randomized controlled trial Double-blind Europe, South Africa, 80 centres	Hip or knee replacement	**Studied treatment:** Melagatran 3 mg s.c. 412h after surgery, then ximelagatran24 mg orally b.d. for 710 days **Control treatment:** Enoxaparin 40 mg s.c. o.d. 12 h before surgery for 710 days	

References

Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, Eskilson C, Nylander I, Frison L, Ogren M. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. Thromb Haemost 2003;89:288-96 [PMID=12574809]
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Eriksson BI. Clinical experience of melagatran/ximelagatran in major orthopaedic surgery. Thromb Res 2003;109 Suppl 1:S23-9 [PMID=12818631]

Table 17.8: *Phase II (Heit), 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (600 vs. 0) **Follow-up duration:** 612 days **Study design:** Randomized controlled trial parallel group Double-blind North American, 6 centres	Adults (age >18 years and weight at least 40 kg) undergoing knee replacements	**Studied treatment:** Ximelagatran 8, 12, 18 or 24 mgorally b.d., at least 12 h after surgery for 612 days **Control treatment:** Enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 612 days	

Reference

Heit JA, Colwell CW, Francis CW, Ginsberg JS, Berkowitz SD, Whipple J, Peters G. Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: a phase 2 dose-finding study. Arch Intern Med 2001;161:2215-21 [PMID=11575978]

Table 17.9: *EXPRESS, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (2835 vs. 0) **Follow-up duration:** 811 days **Study design:** Randomized controlled trial parallel group Double-blind Europe, 77 centres	Hip or knee replacement	**Studied treatment:** Melagatran 2 mg s.c. up to 30 min before surgery, then melagatran 3 mg at least 8 hafter surgery, then ximelagatran 24 mg orally b.d. for 811 days **Control treatment:** Enoxaparin 40 mg s.c. o.d.,starting 12 h before surgery for 811 days	

References

Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, Rosencher N, Klebo P, Panfilov S, Eskilson C, Andersson M, Freij A. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. J Thromb Haemost 2003;1:2490-6 [PMID=14675083]
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18 Global meta-analysis: all oral direct thrombin inhibitor

18.1 Global meta-analysis: all oral direct thrombin inhibitor versus Dalteparin

Table 18.1: *All oral direct thrombin inhibitorversus Dalteparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
venous thromboembolism	RR=0.83	0.25;2.76	0.7619	1.0000 (0.00)	1	53
major bleeding	RR=0.97	0.02;47.50	0.9880	1.0000 (0.00)	1	67

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

18.2 Global meta-analysis: all oral direct thrombin inhibitor versus Enoxaparin

Table 18.2: *All oral direct thrombin inhibitorversus Enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
venous thromboembolism	RR=0.88 [1]	0.63;1.24	0.4703	0.0002 (0.88) †	3	4785
major bleeding	RR=1.44 [2]	0.49;4.22	0.5096	0.0120 (0.77) †	3	5805

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

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

Table 18.3: *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

continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.95 95% CI 0.86;1.04
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.60 95% CI 1.07;2.41

Endpoint	Effect	95% CI	p ass	p het	k	n
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
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

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

Table 18.4: *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
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

19 Ongoing studies of oral direct thrombin inhibitor

No ongoing trial was identified.

20 Excluded studies for oral direct thrombin inhibitor

No trial was excluded.

References

Part IV

Platelet aggregation inhibitors

21 Overview of platelet aggregation inhibitors

21.1 Included trials

Only one trial which randomized 36 patients was identified. In all, 1 randomized comparison concerned Aspirin.
The detailed descriptions of trials and meta-analysis results is given in section 22 (page 151) for Aspirin.

This trial included 36 patients and was published in 1980.
This trial was double blind in design.
It was reported in English language.
The table 21.1 (page 148) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

21.2 Summary of meta-analysis results

The meta-analysis of the available trials about platelet aggregation inhibitors provide the results listed in tables 21.2 to 21.2 (page 149) and in the following graphs.

21.2.1 Aspirin

Aspirin was superior to **placebo** in terms of deep vein thrombosis (RR=0.44, 95% CI 0.23 to 0.85, p=0.0150, 1 trial). However, no significant difference was found on non-fatal pulmonary embolism (RR=0.38, 95% CI 0.10 to 1.41, p=0.1474, 1 trial), proximal DVT (RR=0.33, 95% CI 0.06 to 1.73, p=0.1918, 1 trial)and fatal pulmonary embolism (RR=0.50, 95% CI 0.01 to 23.69, p=0.7247, 1 trial).

Table 21.1: *Main study characteristics - platelet aggregation inhibitors*

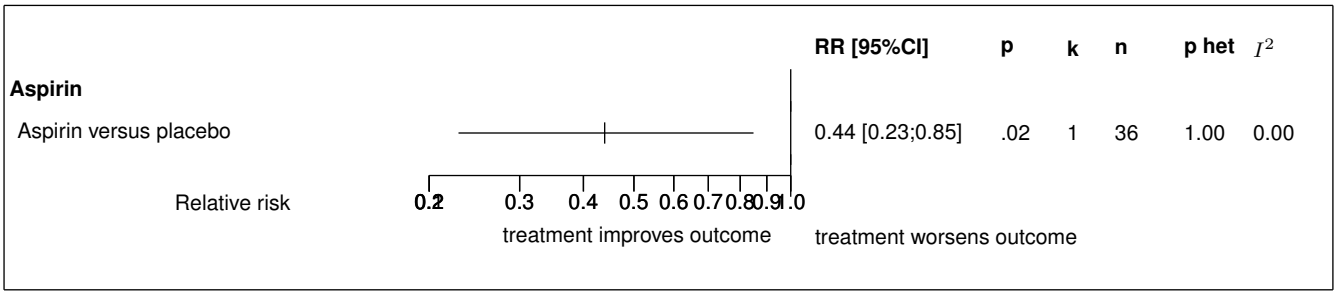
Trial	Patients	Treatments	Trial design and method
Aspirin			
Aspirin versus placebo			
McKenna-I, 1980 [1] n = 24 vs. 12	total knee replacement	aspirin 975mg or 3900mg daily **versus** placebo treatment duration: 2 weeks	double-blind parallel groups

Table 21.2: *Summary of all results for Aspirin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Aspirin versus placebo						
deep vein thrombosis	RR=0.44	0.23;0.85	0.0150	1.0000 (0.00)	1	36
non-fatal pulmonary embolism	RR=0.38	0.10;1.41	0.1474	1.0000 (0.00)	1	36
proximal DVT	RR=0.33	0.06;1.73	0.1918	1.0000 (0.00)	1	36
fatal pulmonary embolism	RR=0.50	0.01;23.69	0.7247	1.0000 (0.00)	1	36
bleeding	RR=1.00	0.04;27.75	1.0000	1.0000 (0.00)	1	36

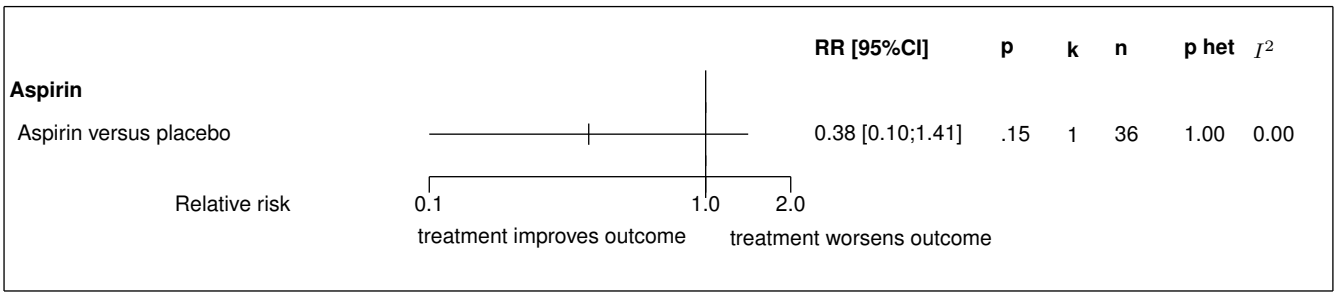
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 21.1: *Forest's plot for deep vein thrombosis*



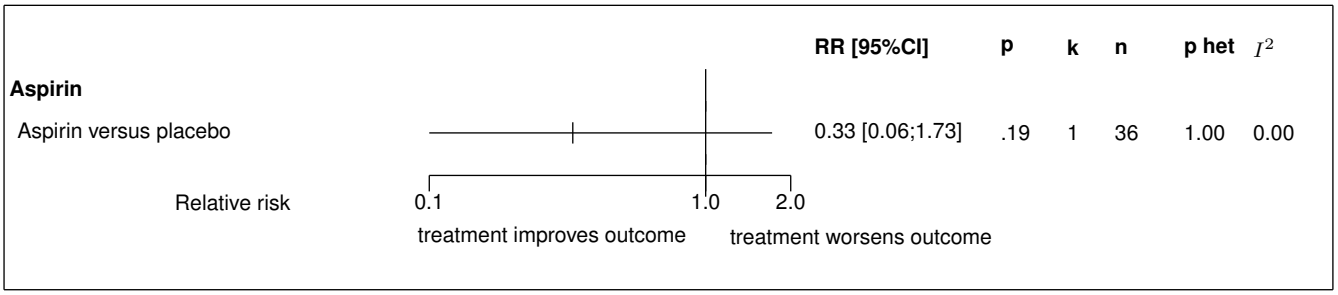
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.2: *Forest's plot for non-fatal pulmonary embolism*



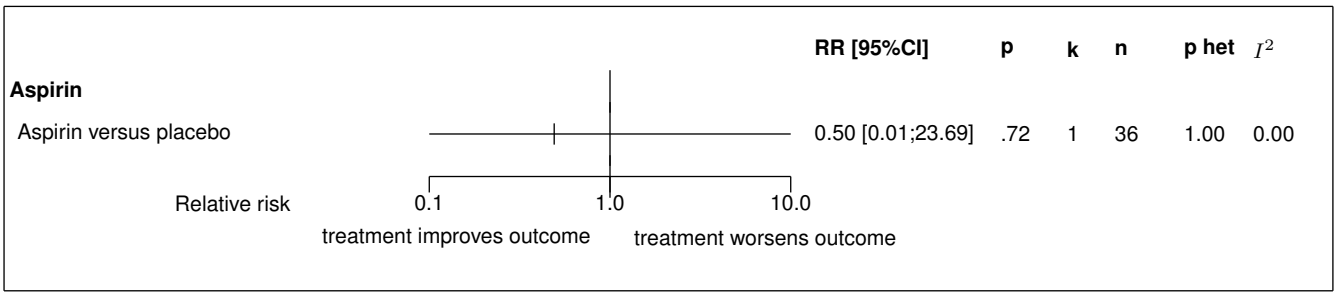
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.3: *Forest's plot for proximal DVT*



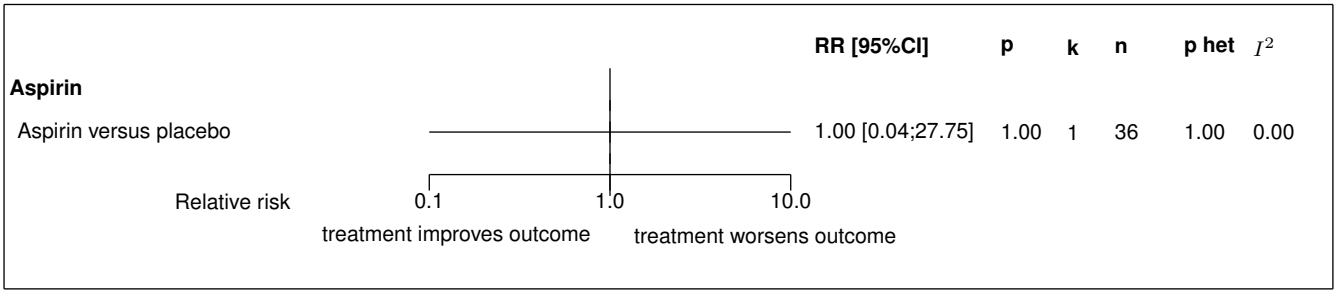
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.4: *Forest's plot for 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 21.5: *Forest's plot for 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

22 Details

22.1 Available trials

Only one trial which randomized 36 patients was identified: it compared Aspirin with placebo.
This trial included 36 patients and was published in 1980.
This trial was double blind in design.
It was reported in English language.
Bleeding data was reported in 1 trials; 1 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on deep vein thrombosis; 1 trials reported data on fatal pulmonary embolism; and 1 trials reported data on proximal DVT.
Following tables 22.1 (page 151), 22.2 (page 151), 22.4 (page 153), and 22.3 (page 151) summarized the main characteristics of the trial including in this systematic review of randomized trials of Aspirin.

Table 22.1: *Treatment description - platelet aggregation inhibitors - Aspirin*

Trial	Studied treatment	Control treatment
Aspirin versus placebo		
McKenna-I (1980) [1]	Aspirin 975mg or 3900mg daily	placebo

Table 22.2: *Descriptions of participants - platelet aggregation inhibitors - Aspirin*

Trial	Patients
Aspirin versus placebo	
McKenna-I (1980) [1]	Total knee replacement

Table 22.3: *Design and methodological quality of trials - platelet aggregation inhibitors - Aspirin*

Trial	Design	Duration	Centre	Primary endpoint
Aspirin versus placebo				
McKenna-I, 1980 [1] n=36	Parallel groups double-blind exploratory trial	2 weeks		

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 22.4: *Trial characteristics - platelet aggregation inhibitors - Aspirin*

Trial	treatment duration
Aspirin versus placebo	
McKenna-I, 1980 [1]	2 weeks

22.2 Meta-analysis results

The results are detailed in table 22.5 (page 154). This table is followed by the Forest's plot corresponding to each endpoint.

Aspirin versus placebo

The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of Aspirin in deep vein thrombosis, with a RR of 0.44 (95% CI 0.23 to 0.85, p=0.0150).
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 0.38 (95% CI 0.10 to 1.41, p=0.1474).
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 0.33 (95% CI 0.06 to 1.73, p=0.1918).
The single study eligible for this comparison provided data on **fatal pulmonary embolism**. No statistically significant difference between the groups was found in fatal pulmonary embolism, with a RR of 0.50 (95% CI 0.01 to 23.69, p=0.7247).

Table 22.5: *Results details - platelet aggregation inhibitors - Aspirin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Aspirin versus placebo						
deep vein thrombosis	RR=0.44	[0.23;0.85]	0.0150	1.0000 (I^2=0.00)	1	36
non-fatal pulmonary embolism	RR=0.38	[0.10;1.41]	0.1474	1.0000 (I^2=0.00)	1	36
proximal DVT	RR=0.33	[0.06;1.73]	0.1918	1.0000 (I^2=0.00)	1	36
fatal pulmonary embolism	RR=0.50	[0.01;23.69]	0.7247	1.0000 (I^2=0.00)	1	36
bleeding	RR=1.00	[0.04;27.75]	1.0000	1.0000 (I^2=0.00)	1	36

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 22.1: *Forest's plot for deep vein thrombosis*

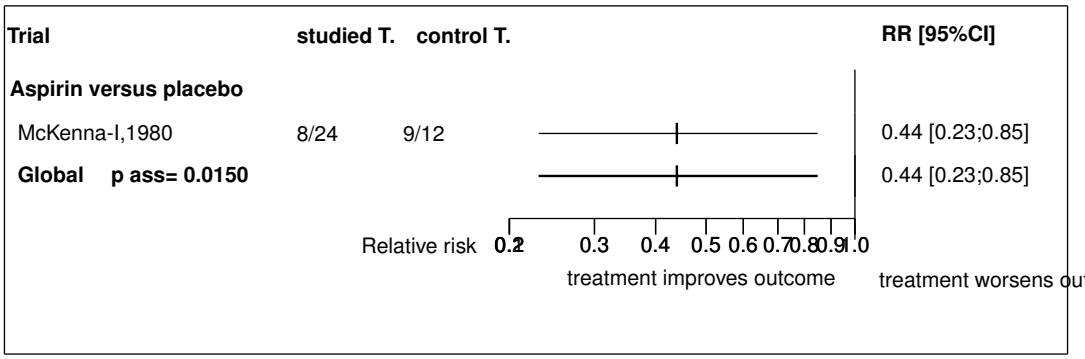


Figure 22.2: *Forest's plot for non-fatal pulmonary embolism*

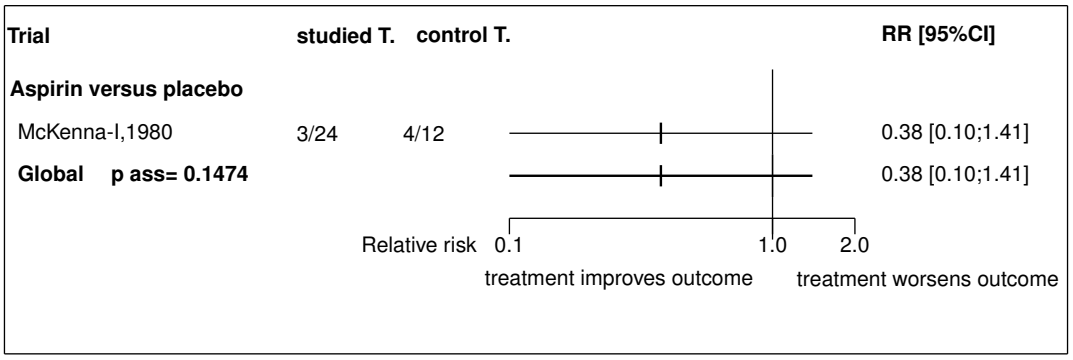


Figure 22.3: *Forest's plot for proximal DVT*

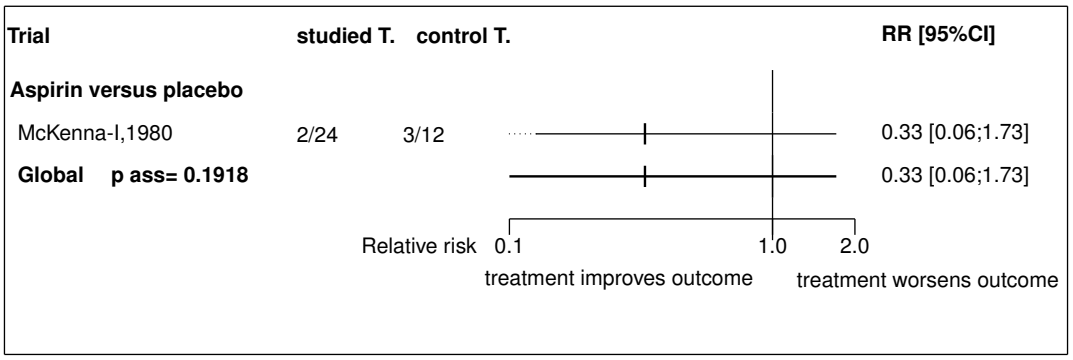


Figure 22.4: *Forest's plot for fatal pulmonary embolism*

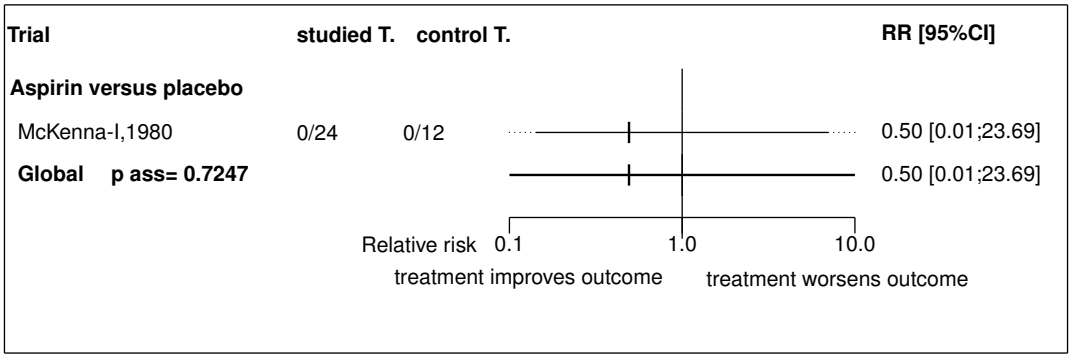
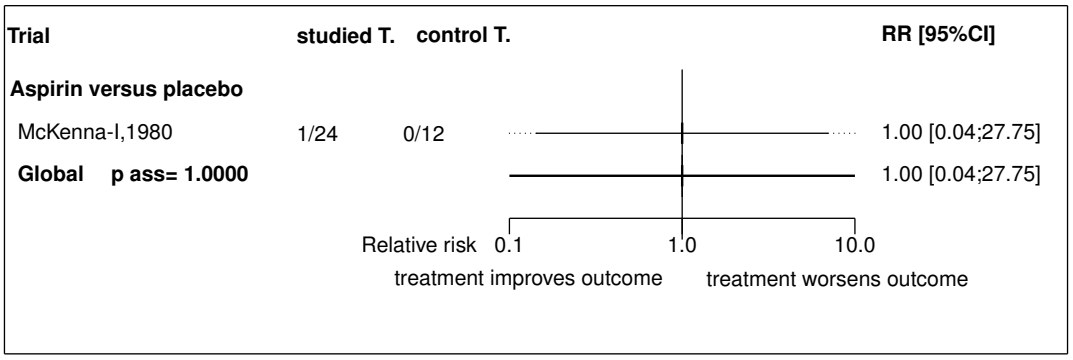


Figure 22.5: *Forest's plot for bleeding*



References

[1] McKenna R, Galante J, Bachmann F, Wallace DL, Kaushal PS, Meredith P. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. Br Med J 1980;280:514-7. [PMID=6989432]

22.3 Individual trial summaries

Table 22.6: *McKenna-I, 1980 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=36 (24 vs. 12) **Follow-up duration:** 2 weeks **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Total knee replacement	**Studied treatment:** Aspirin 975mg or 3900mg daily **Control treatment:** placebo	Deep vein thrombosis RR=0.44 [0.23;0.85] Non-fatal pulmonary embolism RR=0.38 [0.10;1.41] Proximal DVT RR=0.33 [0.06;1.73]

Reference

McKenna R, Galante J, Bachmann F, Wallace DL, Kaushal PS, Meredith P. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. Br Med J 1980;280:514-7 [PMID=6989432]

23 Global meta-analysis: all platelet aggregation inhibitors

23.1 Global meta-analysis: all platelet aggregation inhibitors versus placebo

Table 23.1: *All platelet aggregation inhibitorsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.44	0.23;0.85	0.0150	1.0000 (0.00)	1	36
non-fatal pulmonary embolism	RR=0.38	0.10;1.41	0.1474	1.0000 (0.00)	1	36
proximal DVT	RR=0.33	0.06;1.73	0.1918	1.0000 (0.00)	1	36
fatal pulmonary embolism	RR=0.50	0.01;23.69	0.7247	1.0000 (0.00)	1	36

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

24 Ongoing studies of platelet aggregation inhibitors

No ongoing trial was identified.

25 Excluded studies for platelet aggregation inhibitors

No trial was excluded.

References

Part V

Synthetic oligosaccharide

26 Overview of synthetic oligosaccharide

26.1 Included trials

A total of 2 randomized comparisons which enrolled 1085 patients were identified. In all, 2 randomized comparisons concerned fondaparinux.
The detailed descriptions of trials and meta-analysis results is given in section 27 (page 169) for fondaparinux.

The average study size was 542 patients (range 51 to 1034). The first study was published in 2001, and the last study was published in 2001.
A total of 1 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 26.1 (page 164) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

26.2 Summary of meta-analysis results

The meta-analysis of the available trials about synthetic oligosaccharide provide the results listed in tables 26.2 to 26.2 (page 165) and in the following graphs.

26.2.1 Fondaparinux

Fondaparinux was superior to **enoxaparin** in terms of deep vein thrombosis (RR=0.46, 95% CI 0.33 to 0.63, p=0.0000, 1 trial), proximal DVT (RR=0.45, 95% CI 0.21 to 0.99, p=0.0459, 1 trial)and venous thromboembolism (RR=0.45, 95% CI 0.33 to 0.62, p=0.0000, 2 trials). However, no significant difference was found on symptomatic deep-vein thrombosis (RR=0.75, 95% CI 0.17 to 3.33, p=0.7055, 1 trial), symptomatic pulmonary embolism (RR=0.25, 95% CI 0.03 to 2.23, p=0.2143, 1 trial), non-fatal pulmonary embolism (RR=0.25, 95% CI 0.03 to 2.23, p=0.2143, 1 trial), symptomatic venous thromboembolism (DVT, PE) (RR=0.43, 95% CI 0.11 to 1.65, p=0.2176, 1 trial), fatal pulmonary embolism (RR=1.00, 95% CI 0.02 to 50.30, p=1.0000, 1 trial)and major bleeding (RR=5.19, 95% CI 0.52 to 52.10, p=0.1617, 2 trials).

Table 26.1: *Main study characteristics - synthetic oligosaccharide*

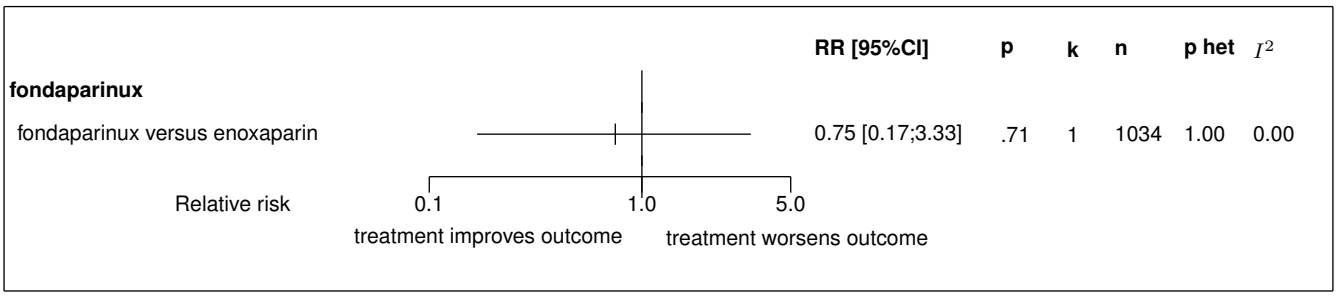
Trial	Patients	Treatments	Trial design and method
Fondaparinux			
Fondaparinux versus enoxaparin			
L8635, 0 n = 28 vs. 23	taiwanese patients undergoing elective knee replacement	fondaparinux 2.5mg once daily subcutaneously for 7 days **versus** enoxaparin 40mg once daily SC for 7 days	open, blind assessment parallel groups Primary endpoint: VTE events 3 centres, Taiwan
PENTAMAKS (Bauer), 2001 [1] n = 517 vs. 517	elective major knee surgery	fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery **versus** enoxaparin 30mg twice daily (North america recommendation)	double blind parallel groups Primary endpoint: venous thromboembolism 64 centres, North america

Table 26.2: *Summary of all results for fondaparinux*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
fondaparinux versus enoxaparin						
symptomatic deep-vein thrombosis	RR=0.75	0.17;3.33	0.7055	1.0000 (0.00)	1	1034
deep vein thrombosis	RR=0.46	0.33;0.63	0.0000	1.0000 (0.00)	1	722
symptomatic pulmonary embolism	RR=0.25	0.03;2.23	0.2143	1.0000 (0.00)	1	1034
non-fatal pulmonary embolism	RR=0.25	0.03;2.23	0.2143	1.0000 (0.00)	1	1034
proximal DVT	RR=0.45	0.21;0.99	0.0459	1.0000 (0.00)	1	740
symptomatic venous thromboembolism (DVT, PE)	RR=0.43	0.11;1.65	0.2176	1.0000 (0.00)	1	1034
venous thromboembolism	RR=0.45	0.33;0.62	0.0000	0.6879 (0.00)	2	765
fatal pulmonary embolism	RR=1.00	0.02;50.30	1.0000	1.0000 (0.00)	1	1034
all cause death	RR=0.67	0.11;3.97	0.6562	1.0000 (0.00)	1	1034
major bleeding	RR=5.19	0.52;52.10	0.1617	0.2463 (0.26)	2	1085

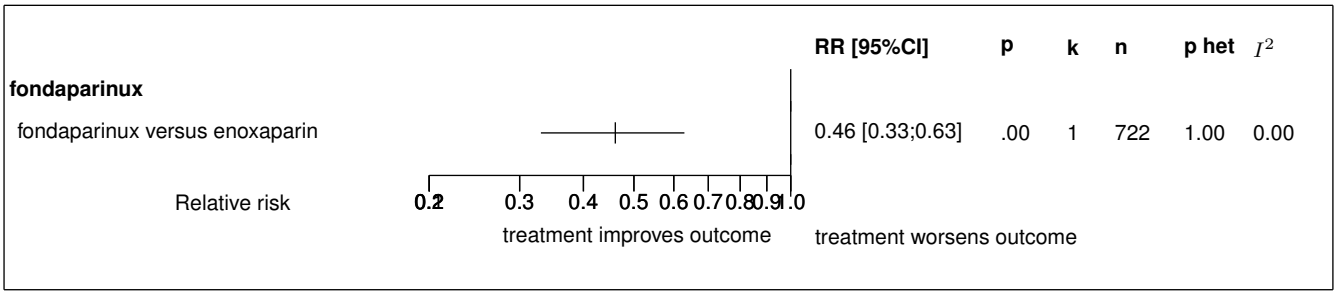
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 26.1: *Forest's plot for symptomatic deep-vein thrombosis*



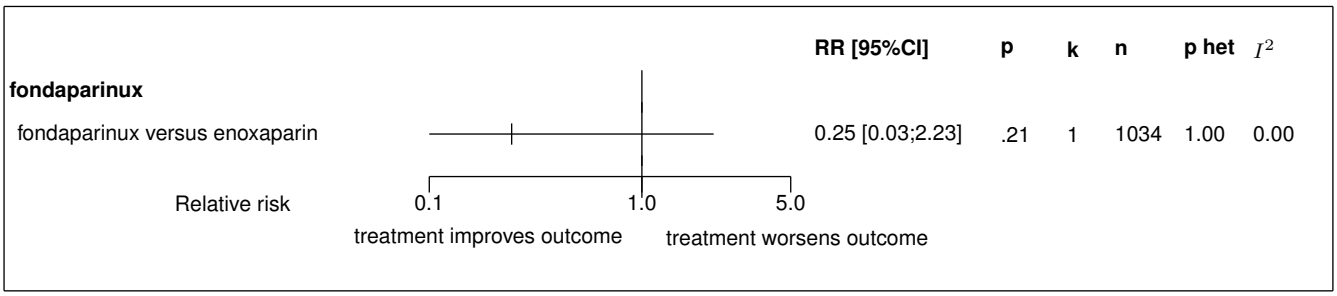
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 26.2: *Forest's plot for deep vein thrombosis*



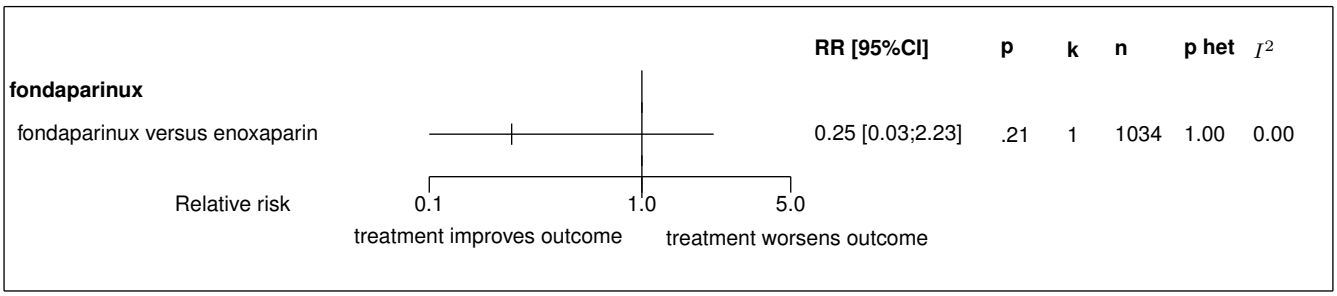
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 26.3: *Forest's plot for symptomatic pulmonary embolism*



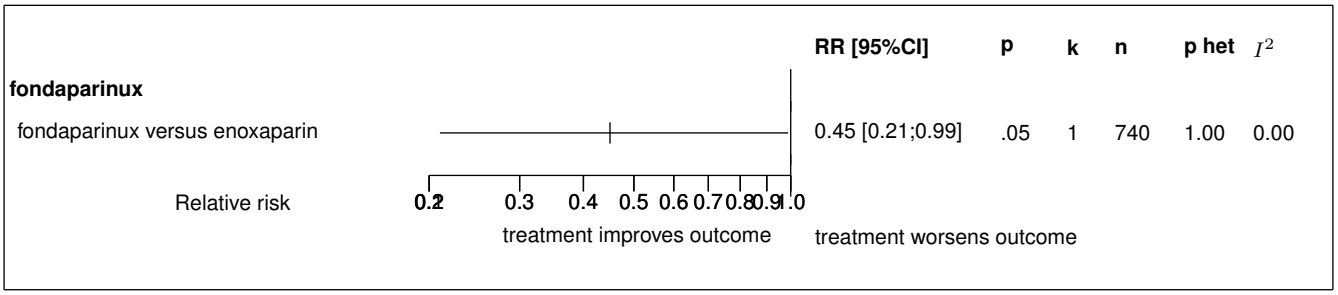
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 26.4: *Forest's plot for non-fatal pulmonary embolism*



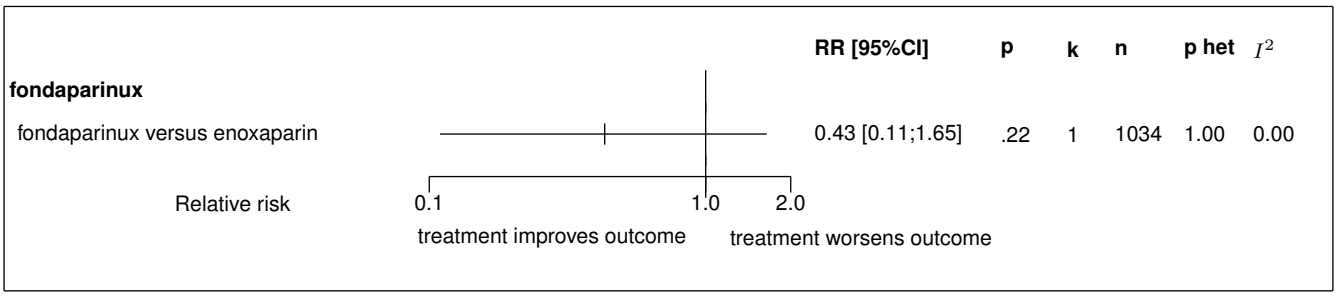
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 26.5: *Forest's plot for proximal DVT*



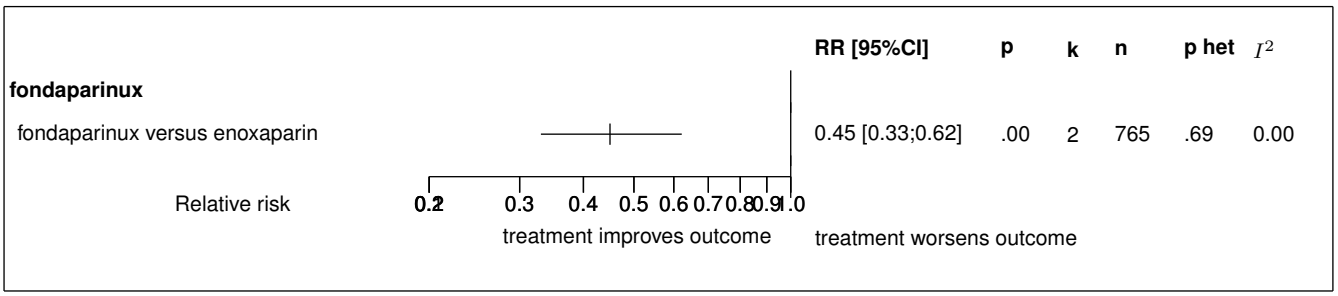
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 26.6: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*



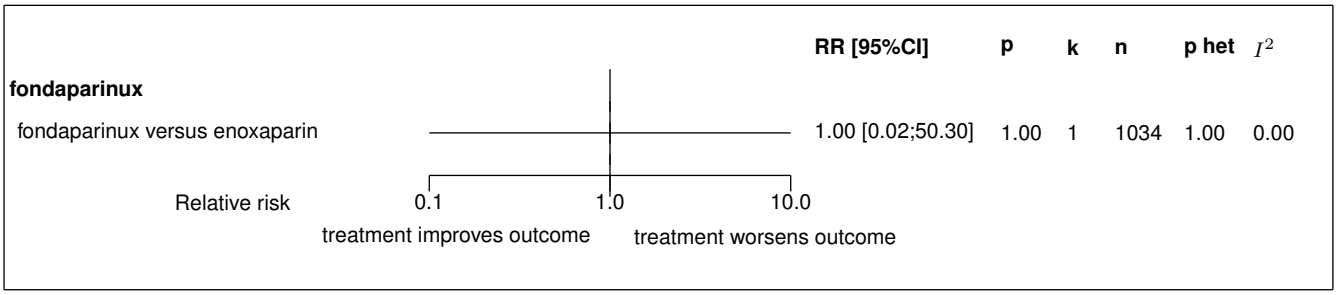
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 26.7: *Forest's plot for venous thromboembolism*



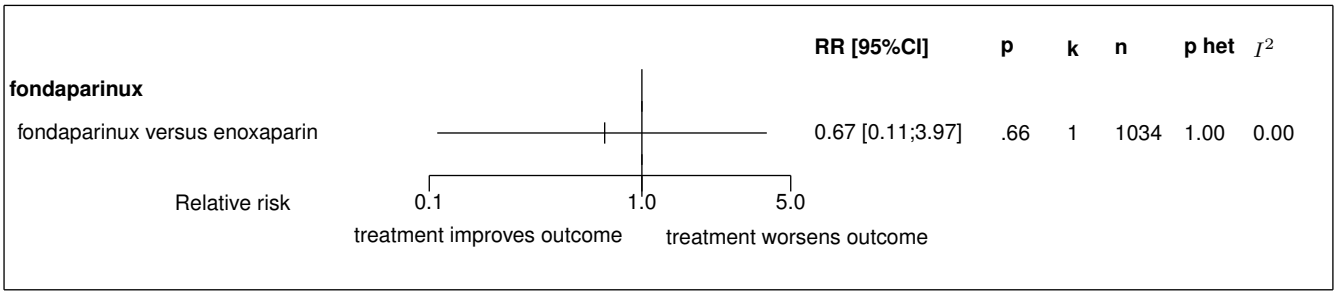
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 26.8: *Forest's plot for fatal pulmonary embolism*



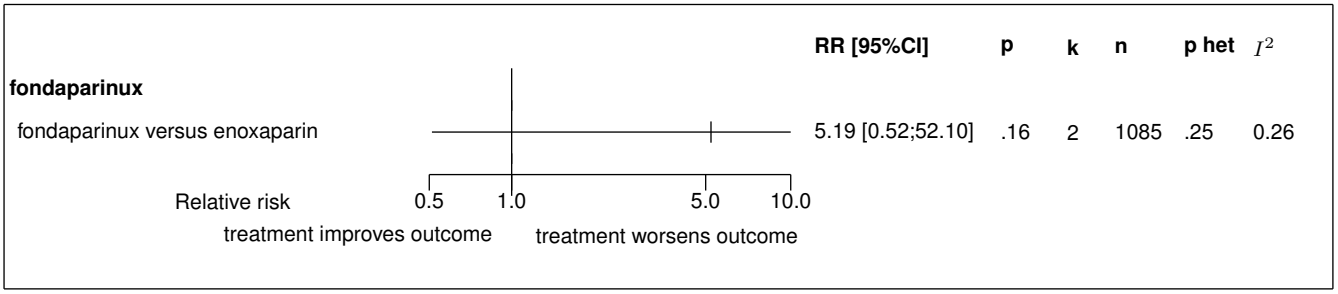
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 26.9: *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 26.10: *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

27 Details

27.1 Available trials

A total of 2 RCTs which randomized 1085 patients were identified: all compared fondaparinux with enoxaparin.
The average study size was 542 patients (range 51 to 1034). The first study was published in 2001, and the last study was published in 2001.
A total of 1 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Venous thromboembolism data was reported in 2 trials; 2 trials reported data on major bleeding; 1 trials reported data on all cause death; 1 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on symptomatic venous thromboembolism (DVT, PE); 1 trials reported data on proximal DVT; 1 trials reported data on fatal pulmonary embolism; 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on symptomatic pulmonary embolism; and 1 trials reported data on deep vein thrombosis.
Following tables 27.1 (page 169), 27.2 (page 169), 27.4 (page 171), and 27.3 (page 170) summarized the main characteristics of the trials including in this systematic review of randomized trials of fondaparinux.

Table 27.1: *Treatment description - synthetic oligosaccharide - fondaparinux*

Trial	Studied treatment	Control treatment
Fondaparinux versus enoxaparin		
L8635 (0)	Fondaparinux 2.5mg once daily subcutaneously for 7 days First post-operative dose given >= 6 hours after closure of the surgical wound and the second dose 18-24 hours after first dose. Thereafter daily at 8pm 2 hours for 5 days	enoxaparin 40mg once daily SC for 7 days first dose given 12 hours before surgery, thereafter daily for 7 days
PENTAMAKS (Bauer) (2001) [1]	fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery	enoxaparin 30mg twice daily (North america recommendation) enoxaparin 30-mg twice-daily starting 12 to 24 hours after surgery

Table 27.2: *Descriptions of participants - synthetic oligosaccharide - fondaparinux*

Trial	Patients
Fondaparinux versus enoxaparin	
L8635 (0)	Taiwanese patients undergoing elective knee replacement

continued...

Trial	Patients	
PENTAMAKS (Bauer) (2001) [1]	Elective major knee surgery	
	Inclusion criteria: at least 18 years of age; undergoing elective major knee surgery (surgery requiring resection of the distal end of the femur or proximal end of the tibia or revision of at least one component of a previously implanted total-knee prosthesis)	**Exclusion criteria:** surgery in the contralateral knee was performed at the same time or within two weeks;active bleeding; documented congenital or acquired bleeding disorder; current ulcerative or angiodysplastic gastrointestinal disease; hemorrhagic stroke or brain, spinal, or ophthalmologic surgery within the previous three months; insertion of an indwelling intrathecal or epidural catheter during the treatment period; unusual difficulty in administering epidural or spinal anesthesia (e.g., more than two attempts); hypersensitivity to heparin, low-molecular-weight heparins, porcine products, or iodinated contrast medium; a contraindication to anticoagulant therapy; current addictive disorder; serum creatinine concentration above 2 mg per deciliter; platelet count below 100,000 per cubic millimeter

Table 27.3: *Design and methodological quality of trials - synthetic oligosaccharide - fondaparinux*

Trial	Design	Duration	Centre	Primary endpoint
Fondaparinux versus enoxaparin				
L8635, 0 n=51	Parallel groups open, blind assessment exploratory trial	10 days inclusion period: dec 2002 - sept 2003	Taiwan 3 centres	VTE events
PENTAMAKS (Bauer), 2001 [1] n=1034	Parallel groups double blind confirmatory trial at low risk of bias	11 days inclusion period: dec 1998 - jan 2000	North america 64 centres	venous thromboembolism

Table 27.4: *Trial characteristics - synthetic oligosaccharide - fondaparinux*

Trial	Use of cement	History of venous thromboembolism
Fondaparinux versus enoxaparin		
L8635, 0		
PENTAMAKS (Bauer), 2001 [1]	93.5%	5%

27.2 Meta-analysis results

The results are detailed in table 27.5 (page 172). This table is followed by the Forest's plot corresponding to each endpoint.

Fondaparinux 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 fondaparinux and enoxaparin, with a RR of 0.75 (95%CI 0.17 to 3.33, p=0.7055) in favour of fondaparinux. In other words, symptomatic deep-vein thrombosis was slightly lower in the fondaparinux group , but this was not statistically significant.
Only one of the 2 studies eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of fondaparinux in deep vein thrombosis, with a RR of 0.46 (95% CI 0.33 to 0.63, p=0.0000).
Only one of the 2 studies eligible for this comparison provided data on **symptomatic pulmonary embolism**. No statistically significant difference between the groups was found in symptomatic pulmonary embolism, with a RR of 0.25 (95% CI 0.03 to 2.23, p=0.2143).
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 0.25 (95% CI 0.03 to 2.23, p=0.2143).
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 fondaparinux in proximal DVT, with a RR of 0.45 (95% CI 0.21 to 0.99, p=0.0459).
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 0.43 (95% CI 0.11 to 1.65, p=0.2176).
All the 2 studies had extractable data about the number of participants with **venous thromboembolism**. The analysis detected a statistically significant difference in favor of fondaparinux in venous thromboembolism, with a RR of 0.45 (95% CI 0.33 to 0.62, p=0.0000). No heterogeneity was detected (p = 0.6879, I^2 = 0.00%).
Only one of the 2 studies eligible for this comparison provided data on **fatal pulmonary embolism**. No statistically significant difference between the groups was found in fatal pulmonary embolism, with a RR of 1.00 (95% CI 0.02 to 50.30, p=1.0000).
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 5.19 (95% CI 0.52 to 52.10, p=0.1617). No heterogeneity was detected (p = 0.2463, I^2 = 0.26%).

Table 27.5: *Results details - synthetic oligosaccharide - fondaparinux*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fondaparinux versus enoxaparin						
symptomatic deep-vein thrombosis	RR=0.75	[0.17;3.33]	0.7055	1.0000 (I^2=0.00)	1	1034
deep vein thrombosis	RR=0.46	[0.33;0.63]	0.0000	1.0000 (I^2=0.00)	1	722
symptomatic pulmonary embolism	RR=0.25	[0.03;2.23]	0.2143	1.0000 (I^2=0.00)	1	1034

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
non-fatal pulmonary embolism	RR=0.25	[0.03;2.23]	0.2143	1.0000 (I^2=0.00)	1	1034
proximal DVT	RR=0.45	[0.21;0.99]	0.0459	1.0000 (I^2=0.00)	1	740
symptomatic venous thromboembolism (DVT, PE)	RR=0.43	[0.11;1.65]	0.2176	1.0000 (I^2=0.00)	1	1034
venous thromboembolism	RR=0.45	[0.33;0.62]	0.0000	0.6879 (I^2=0.00)	2	765
fatal pulmonary embolism	RR=1.00	[0.02;50.30]	1.0000	1.0000 (I^2=0.00)	1	1034
all cause death	RR=0.67	[0.11;3.97]	0.6562	1.0000 (I^2=0.00)	1	1034
major bleeding	RR=5.19	[0.52;52.10]	0.1617	0.2463 (I^2=0.26)	2	1085

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

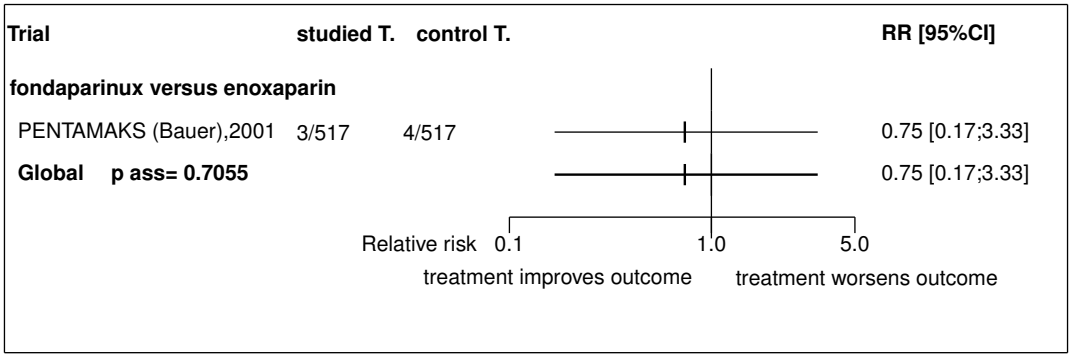


Figure 27.2: *Forest's plot for deep vein thrombosis*

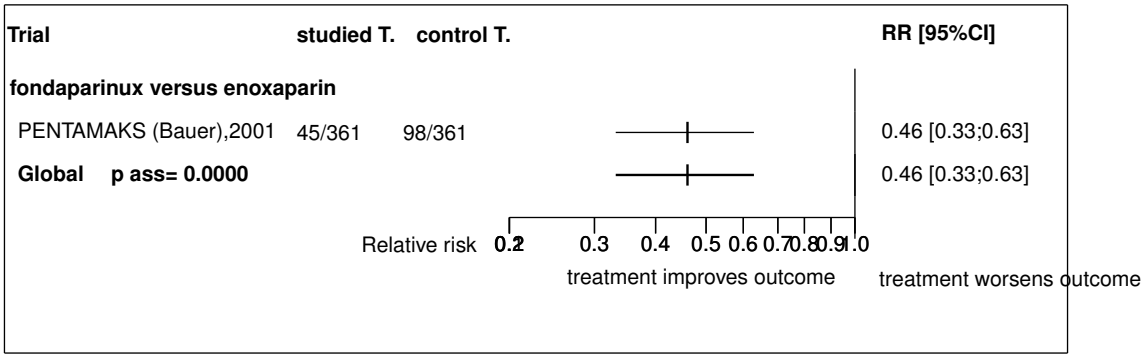


Figure 27.3: *Forest's plot for symptomatic pulmonary embolism*

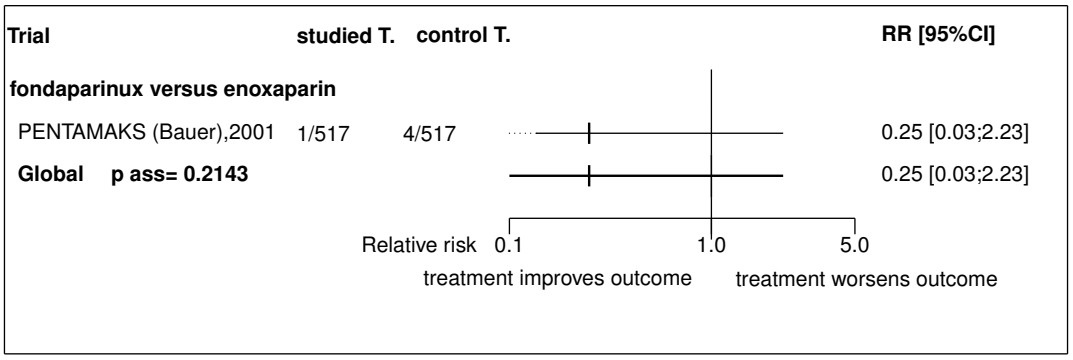


Figure 27.4: *Forest's plot for non-fatal pulmonary embolism*

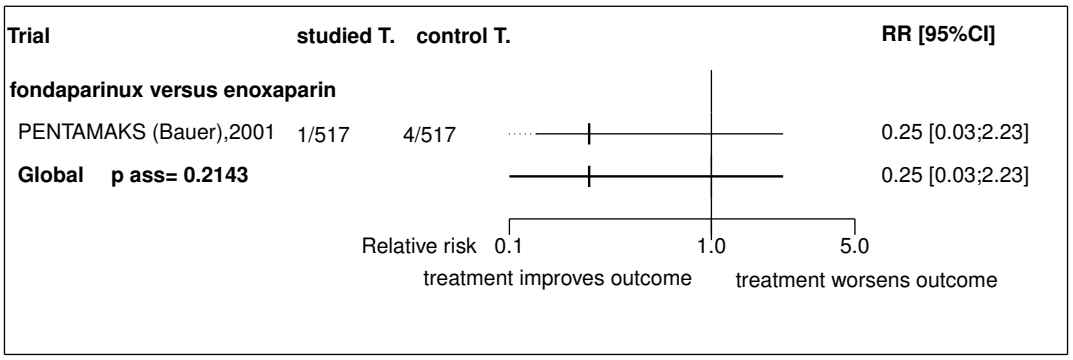


Figure 27.5: *Forest's plot for proximal DVT*

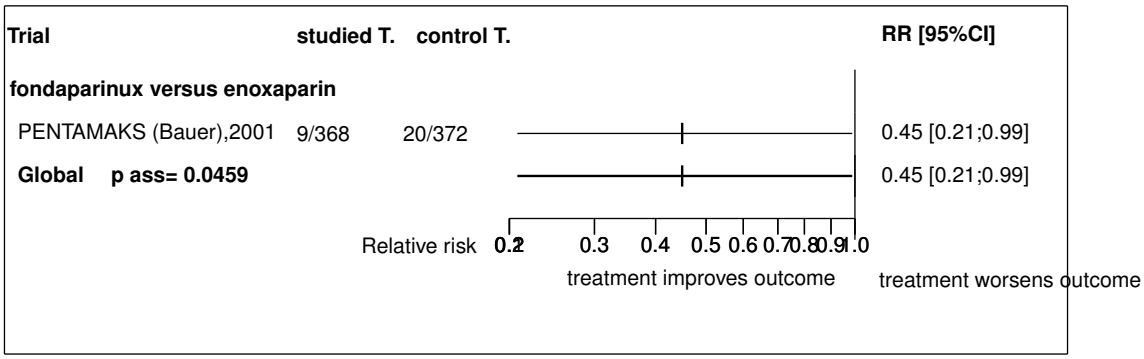


Figure 27.6: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

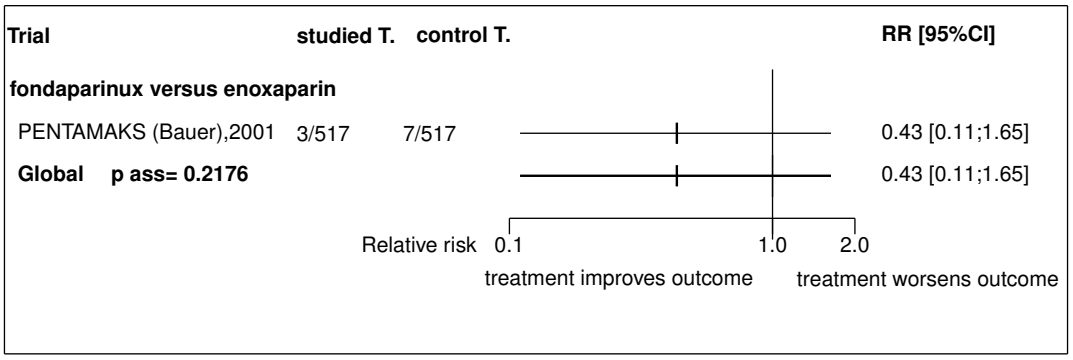


Figure 27.7: *Forest's plot for venous thromboembolism*

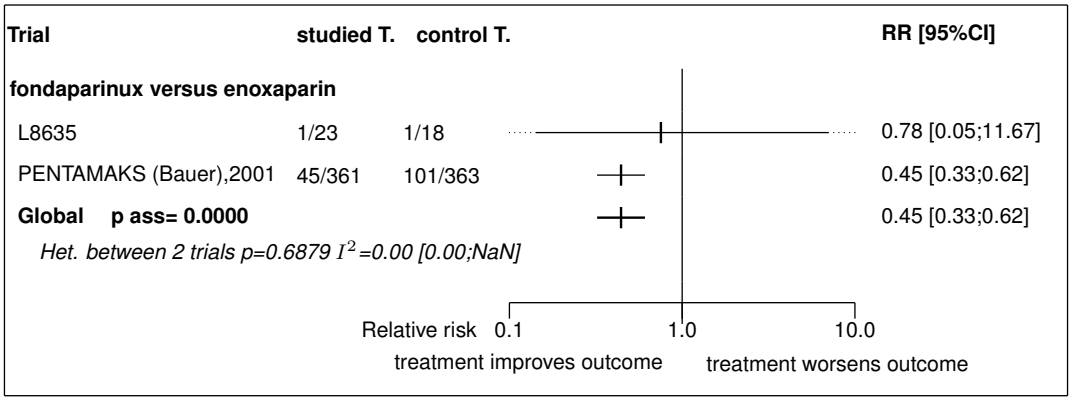


Figure 27.8: *Forest's plot for fatal pulmonary embolism*

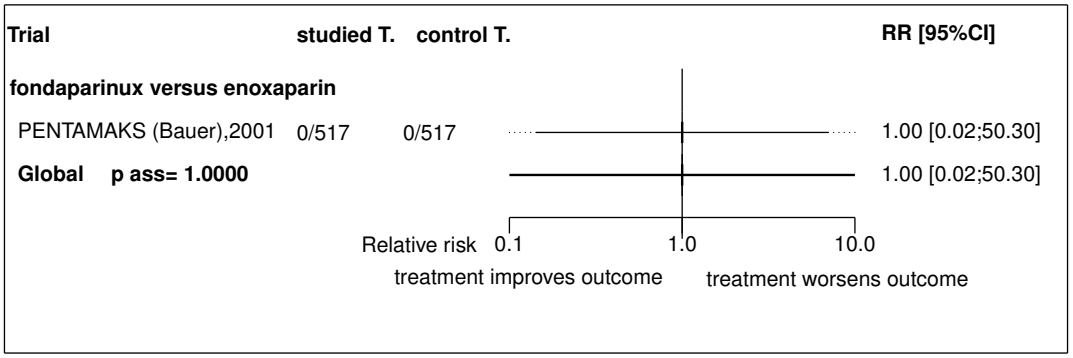


Figure 27.9: *Forest's plot for all cause death*

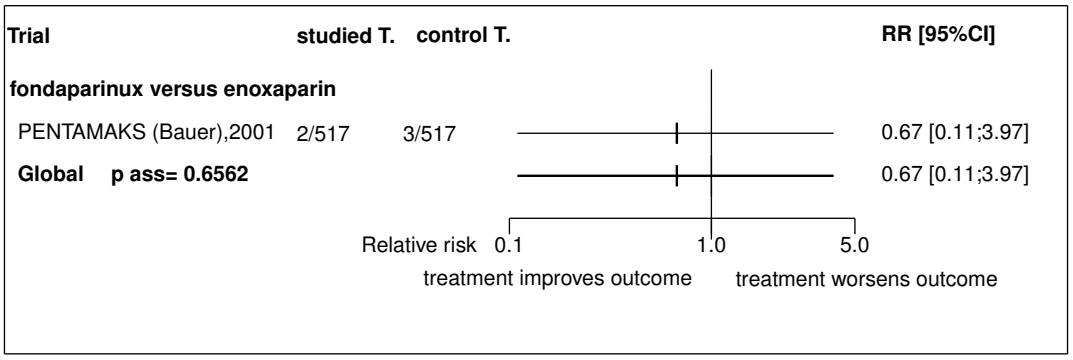
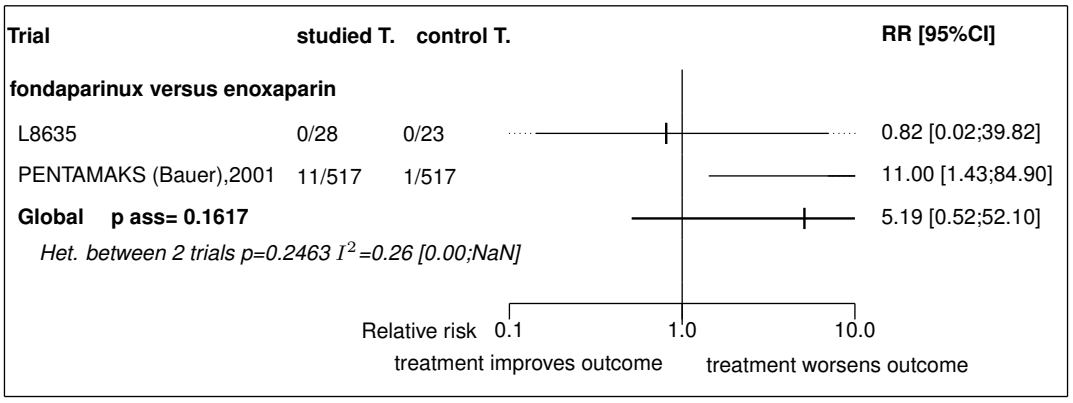


Figure 27.10: *Forest's plot for major bleeding*



References

[1] Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001 Nov 1;345:1305-10. [PMID=11794149]

27.3 Individual trial summaries

Table 27.6: *L8635, 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=51 (28 vs. 23) **Follow-up duration:** 10 days **Study design:** Randomized controlled trial Parallel groups Open, blind assessment Exploratory trial Taiwan, 3 centres **Inclusion period:** dec 2002 - sept 2003	Taiwanese patients undergoing elective knee replacement	**Studied treatment:** Fondaparinux 2.5mg once daily subcutaneously for 7 days First post-operative dose given >= 6 hours after closure of the surgical wound and the second dose 18-24 hours after first dose. Thereafter daily at 8pm 2 hours for 5 days **Control treatment:** enoxaparin 40mg once daily SC for 7 days first dose given 12 hours before surgery, thereafter daily for 7 days	
Reference			

Table 27.7: *PENTAMAKS (Bauer), 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1034 (517 vs. 517) **Follow-up duration:** 11 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias North america, 64 centres **Inclusion period:** dec 1998 - jan 2000	Elective major knee surgery **Inclusion criteria:** at least 18 years of age; undergoing elective major knee surgery (surgery requiring resection of the distal end of the femur or proximal end of the tibia or revision of at least one component of a previously implanted total-knee prosthesis) **Exclusion criteria:** surgery in the contralateral knee was performed at the same time or within two weeks;active bleeding; documented congenital or acquired bleeding disorder; current ulcerative or angiodysplastic gastrointestinal disease; hemorrhagic stroke or brain, spinal, or ophthalmologic surgery within the previous three months; insertion of an indwelling intrathecal or epidural catheter during the treatment period; unusual difficulty in administering epidural or spinal anesthesia (e.g., more than two attempts); hypersensitivity to heparin, low-molecular-weight heparins, porcine products, or iodinated contra	**Studied treatment:** fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery **Control treatment:** enoxaparin 30mg twice daily (North america recommendation) enoxaparin 30-mg twice-daily starting 12 to 24 hours after surgery	Symptomatic deep-vein thrombosis RR=0.75 [0.17;3.33] (at D11) Deep vein thrombosis RR=0.46 [0.33;0.63] Symptomatic pulmonary embolism RR=0.25 [0.03;2.23] Non-fatal pulmonary embolism RR=0.25 [0.03;2.23] (at D11) Proximal DVT RR=0.45 [0.21;0.99]

Reference

Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001 Nov 1;345:1305-10 [PMID=11794149]

28 Global meta-analysis: all synthetic oligosaccharide

28.1 Global meta-analysis: all synthetic oligosaccharide versus enoxaparin

Table 28.1: *All synthetic oligosaccharideversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=0.75	0.17;3.33	0.7055	1.0000 (0.00)	1	1034
deep vein thrombosis	RR=0.46	0.33;0.63	0.0000	1.0000 (0.00)	1	722
symptomatic pulmonary embolism	RR=0.25	0.03;2.23	0.2143	1.0000 (0.00)	1	1034
non-fatal pulmonary embolism	RR=0.25	0.03;2.23	0.2143	1.0000 (0.00)	1	1034
proximal DVT	RR=0.45	0.21;0.99	0.0459	1.0000 (0.00)	1	740
symptomatic venous thromboembolism (DVT, PE)	RR=0.43	0.11;1.65	0.2176	1.0000 (0.00)	1	1034
venous thromboembolism	RR=0.45	0.33;0.62	0.0000	0.6879 (0.00)	2	765
fatal pulmonary embolism	RR=1.00	0.02;50.30	1.0000	1.0000 (0.00)	1	1034
major bleeding	RR=5.19	0.52;52.10	0.1617	0.2463 (0.26)	2	1085

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

29 Ongoing studies of synthetic oligosaccharide

No ongoing trial was identified.

30 Excluded studies for synthetic oligosaccharide

No trial was excluded.

References