Antithrombotics for DVT prophylaxis in elective hip replacement

A systematic review and meta-analysis of randomized clinical trials

2017 - 7 - 1

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

Contents

0.1 Synthesis of the meta-analysis results

In all 48 randomised controlled trials (RCTs) were included. These included 5 studies of **direct factor Xa inhibitors** involving 13,259 patients, 24 studies of **low molecular weight heparin** involving 6,353 patients, 6 studies of **oral direct thrombin inhibitor**
(1 unpublished) involving 14,107 patients, 7 studies of **platelet aggregation inhibitors** involving 528 patients, 3 studies of **recombinant hirudin** involving 1,546 patients and 3 studies of **synthetic oligosaccharide** involving 5,607 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 4 trials (including 13,259 patients) were identified .
Among these comparisons, one trial are about apixaban,one about edoxaban,two about rivaroxaban and one about rivaroxaban (long duration).
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Apixaban

Results obtained with apixaban for all the endpoints with data in at least one trial are summarized table 1.

Table 1: *Results summary - Apixaban*

Benefit	Harmful	No evidence
	Apixaban versus enoxaparin	
↓ major VTE (fatal and non fatal DVT,PE) RR=0.40* [0.19;0.83] k=1 ↓ deep vein thrombosis RR=0.32¶ [0.20;0.51] k=1 ↓ total VTE and all-cause mortality RR=0.36¶ [0.23;0.56] k=1 ↓ asymptomatic DVT RR=0.33¶ [0.20;0.54] k=1 ↓ proximal DVT RR=0.35* [0.15;0.82] k=1		→ symptomatic deep-vein thrombosis RR=0.20^{NS} [0.02;1.71] k=1 → non-fatal pulmonary embolism RR=0.40^{NS} [0.08;2.05] k=1 → symptomatic venous thromboembolism (DVT, PE) RR=0.40^{NS} [0.13;1.27] k=1 → myocardial infarction (fatal and non fatal) RR=2.24^{NS} [0.69;7.27] k=1 → coronary event RR=1.66^{NS} [0.40;6.93] k=1 → major or clinically relevant non-major bleeding RR=0.96^{NS} [0.76;1.21] k=1 → all cause death RR=2.99^{NS} [0.31;28.73] k=1 → major bleeding RR=1.22^{NS} [0.65;2.26] k=1

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

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

Edoxaban

Results obtained with edoxaban for all the endpoints with data in at least one trial are summarized table 2.

Table 2: *Results summary - Edoxaban*

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

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

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

Rivaroxaban

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

Table 3: *Results summary - Rivaroxaban*

Benefit	Harmful	No evidence
	Rivaroxaban versus enoxaparin	
↓ major VTE (fatal and non fatal DVT,PE) RR=0.12¶ [0.04;0.34] k=1 ↓ deep vein thrombosis RR=0.23¶ [0.12;0.43] k=1 ↓ total VTE and all-cause mortality RR=0.30¶ [0.18;0.51] k=1 ↓ proximal DVT RR=0.03¶ [0.00;0.23] k=1		→ non-fatal pulmonary embolism RR=3.91^{NS} [0.44;34.92] k=1 → distal DVT RR=0.49^{NS} [0.24;1.00] k=1 → symptomatic venous thromboembolism (DVT, PE) RR=0.55^{NS} [0.20;1.48] k=1 → coronary event RR=0.49^{NS} [0.12;1.95] k=1 → all cause death RR=0.98^{NS} [0.24;3.90] k=1 → major bleeding RR=3.02^{NS} [0.61;14.95] k=1
	Rivaroxaban versus enoxaparin (short duration)	
↓ deep vein thrombosis RR=0.42† [0.22;0.79] k=1 ↓ total VTE and all-cause mortality RR=0.42† [0.22;0.79] k=1 ↓ distal DVT RR=0.36† [0.17;0.73] k=1		→ non-fatal pulmonary embolism RR=0.95^{NS} [0.02;47.30] k=1 → proximal DVT RR=0.95^{NS} [0.20;4.59] k=1

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

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

Rivaroxaban (long duration)

Results obtained with rivaroxaban (long duration) for all the endpoints with data in at least one trial are summarized table 4.

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

Benefit	Harmful	No evidence
Rivaroxaban (long duration) versus enoxaparin (short duration)		
↓ major VTE (fatal and non fatal DVT,PE) RR=0.12¶ [0.05;0.28] k=1 ↓ deep vein thrombosis RR=0.20¶ [0.11;0.35] k=1 ↓ total VTE and all-cause mortality RR=0.21¶ [0.13;0.35] k=1 ↓ distal DVT RR=0.34† [0.16;0.71] k=1 ↓ proximal DVT RR=0.11¶ [0.05;0.29] k=1 ↓ symptomatic venous thromboembolism (DVT, PE) RR=0.20* [0.06;0.69] k=1		→ non-fatal pulmonary embolism RR=0.25^{NS} [0.03;2.25] k=1 → coronary event RR=1.33^{NS} [0.30;5.95] k=1 → major or clinically relevant non-major bleeding RR=1.20^{NS} [0.93;1.54] k=1 → all cause death RR=0.34^{NS} [0.07;1.66] k=1 → major bleeding RR=1.00^{NS} [0.06;15.98] k=1

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

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

0.1.2 Low molecular weight heparin

Reports of 24 trials (including 6,353 patients) were identified .
Among these comparisons, two trials are about certoparine + DHE,9 about dalteparin,7 about enoxaparin,two about fluxum,two about nadroparin,one about semuloparin and one about tinzaparin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Certoparine + DHE

Results obtained with certoparine + DHE for all the endpoints with data in at least one trial are summarized table 5.

Table 5: *Results summary - Certoparine + DHE*

Benefit	Harmful	No evidence
Certoparine + DHE versus Unfractionated heparin		
		→ deep vein thrombosis RR=1.05^{NS} [0.75;1.47] k=2 → symptomatic pulmonary embolism RR=0.68^{NS} [0.05;8.80] k=2 → all cause death RR=1.02^{NS} [0.06;16.14] k=2 → bleeding RR=1.63^{NS} [0.62;4.31] k=2

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

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

Dalteparin

Results obtained with dalteparin for all the endpoints with data in at least one trial are summarized table 6.

Table 6: *Results summary - Dalteparin*

Benefit	Harmful	No evidence
	Dalteparin versus placebo	
↓ deep vein thrombosis RR=0.44* [0.22;0.89] k=1		→ symptomatic pulmonary embolism RR=0.47^{NS} [0.02;13.60] k=1 → all cause death RR=1.86^{NS} [0.06;54.39] k=1
	Dalteparin versus Dextran	
↓ deep vein thrombosis RR=0.61† [0.44;0.83] k=3		→ symptomatic pulmonary embolism RR=2.01^{NS} [0.43;9.49] k=3 → all cause death RR=1.04^{NS} [0.11;9.87] k=3 → bleeding RR=0.47^{NS} [0.16;1.34] k=3
	Dalteparin versus Unfractionated heparin	
↓ symptomatic pulmonary embolism RR=0.48* [0.23;0.99] k=3		→ deep vein thrombosis RR=0.85^{NS} [0.58;1.23] k=5 → all cause death RR=0.62^{NS} [0.07;5.24] k=3 → bleeding RR=0.90^{NS} [0.34;2.37] k=4

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ 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 7.

Table 7: *Results summary - Enoxaparin*

Benefit	Harmful	No evidence
	Enoxaparin versus no treatment	
		→ deep vein thrombosis RR=0.67^{NS} [0.43;1.03] k=1
	Enoxaparin versus placebo	
↓ deep vein thrombosis RR=0.32¶ [0.21;0.50] k=3		→ symptomatic pulmonary embolism RR=1.00^{NS} [0.02;49.42] k=1 → all cause death RR=0.50^{NS} [0.02;14.57] k=1 → bleeding RR=0.67^{NS} [0.11;4.04] k=2
	Enoxaparin versus Dextran	
↓ deep vein thrombosis RR=0.31† [0.14;0.68] k=1		→ symptomatic pulmonary embolism RR=1.05^{NS} [0.02;52.50] k=1 → all cause death RR=2.10^{NS} [0.07;62.03] k=1
	Enoxaparin versus Unfractionated heparin	

continued...

Benefit	Harmful	No evidence
		→ deep vein thrombosis RR=0.71^{NS} [0.41;1.24] k=2 → symptomatic pulmonary embolism RR=0.33^{NS} [0.03;3.22] k=2 → all cause death RR=0.95^{NS} [0.06;15.18] k=2 → bleeding RR=0.77^{NS} [0.21;2.83] k=2

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

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

Fluxum

Results obtained with fluxum for all the endpoints with data in at least one trial are summarized table 8.

Table 8: *Results summary - Fluxum*

Benefit	Harmful	No evidence
	Fluxum versus Unfractionated heparin	
		→ deep vein thrombosis RR=0.70^{NS} [0.33;1.46] k=2 → symptomatic pulmonary embolism RR=0.66^{NS} [0.05;8.32] k=2 → all cause death RR=0.48^{NS} [0.02;13.66] k=1 → bleeding RR=0.98^{NS} [0.06;15.36] k=2

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

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

Nadroparin

Results obtained with nadroparin for all the endpoints with data in at least one trial are summarized table 9.

Table 9: *Results summary - Nadroparin*

Benefit	Harmful	No evidence
	Nadroparin versus no treatment	
↓ deep vein thrombosis RR=0.13* [0.02;0.96] k=1		
	Nadroparin versus Unfractionated heparin	
		→ deep vein thrombosis RR=0.80^{NS} [0.47;1.35] k=1 → symptomatic pulmonary embolism RR=0.25^{NS} [0.03;2.25] k=1 → all cause death RR=0.51^{NS} [0.05;5.55] k=1 → bleeding RR=0.34^{NS} [0.04;3.23] k=1

continued...

Benefit	Harmful	No evidence

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

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

Semuloparin

Results obtained with semuloparin for all the endpoints with data in at least one trial are summarized table 10.

Table 10: *Results summary - Semuloparin*

Benefit	Harmful	No evidence
	Semuloparin versus enoxaparin	
↓ deep vein thrombosis RR=0.57¶ [0.42;0.78] k=1 ↓ total VTE and all-cause mortality RR=0.57¶ [0.42;0.77] k=1 ↓ major or clinically relevant non-major bleeding RR=0.48* [0.24;0.95] k=1 ↓ bleeding RR=0.29* [0.09;0.87] k=1		→ symptomatic pulmonary embolism RR=1.00^{NS} [0.02;50.45] k=1 → all cause death RR=0.50^{NS} [0.05;5.52] 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)

Tinzaparin

Results obtained with tinzaparin for all the endpoints with data in at least one trial are summarized table 11.

Table 11: *Results summary - Tinzaparin*

Benefit	Harmful	No evidence
	Tinzaparin versus placebo	
↓ deep vein thrombosis RR=0.68* [0.46;1.00] k=1		→ all cause death RR=1.13^{NS} [0.07;17.86] 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 14,107 patients) were identified (including 1 unpublished).

Among these comparisons, one trial are about dabigatran 150mg,two about dabigatran 220mg and 3 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 12.

Table 12: *Results summary - Dabigatran 150mg*

Benefit	Harmful	No evidence
	Dabigatran 150mg versus enoxaparin	
	↑ symptomatic deep-vein thrombosis RR=8.89* [1.13;70.07] k=1	→ major VTE (fatal and non fatal DVT,PE) RR=1.09^{NS} [0.70;1.70] k=1 → total VTE and all-cause mortality RR=1.28^{NS} [0.93;1.78] k=1 → asymptomatic DVT RR=1.15^{NS} [0.82;1.63] k=1 → non-fatal pulmonary embolism RR=0.33^{NS} [0.03;3.16] k=1 → distal DVT RR=1.50^{NS} [0.90;2.50] k=1 → proximal DVT RR=0.90^{NS} [0.55;1.49] k=1 → coronary event RR=0.72^{NS} [0.31;1.68] k=1 → all cause death RR=0.98^{NS} [0.02;49.28] k=1 → major bleeding RR=0.83^{NS} [0.42;1.63] 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 13.

Table 13: *Results summary - Dabigatran 220mg*

Benefit	Harmful	No evidence
	Dabigatran 220mg versus enoxaparin	

continued...

Benefit	Harmful	No evidence
		→ symptomatic deep-vein thrombosis RR=6.03^{NS} [0.73;49.98] k=1 → major VTE (fatal and non fatal DVT,PE) RR=0.78^{NS} [0.48;1.27] k=1 → total VTE and all-cause mortality RR=0.90^{NS} [0.63;1.29] k=1 → asymptomatic DVT RR=0.73^{NS} [0.49;1.08] k=1 → non-fatal pulmonary embolism RR=1.70^{NS} [0.41;7.09] k=1 → distal DVT RR=0.94^{NS} [0.53;1.66] k=1 → proximal DVT RR=0.57^{NS} [0.32;1.00] k=1 → coronary event RR=0.99^{NS} [0.06;15.86] k=1 → all cause death RR=6.03^{NS} [0.30;120.18] k=1 → major bleeding RR=1.29^{NS} [0.70;2.37] k=1

* 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 14.

Table 14: *Results summary - Ximelagatran*

Benefit	Harmful	No evidence
	Ximelagatran versus Enoxaparin	
		→ venous thromboembolism RR=1.09^{NS} [0.76;1.59] H k=3 → major bleeding RR=1.35^{NS} [0.56;3.25] 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

Reports of 7 trials (including 528 patients) were identified .
Among these comparisons, 4 trials are about Aspirin and 3 about Hydroxychloroquine.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Aspirin

Results obtained with aspirin for all the endpoints with data in at least one trial are summarized table 15.

Table 15: *Results summary - Aspirin*

Benefit	Harmful	No evidence
	Aspirin versus no treatment	
↓ deep vein thrombosis RR=0.14¶ [0.04;0.45] k=1		→ non-fatal pulmonary embolism RR=0.25^{NS} [0.01;7.24] k=1 → fatal pulmonary embolism RR=0.50^{NS} [0.01;24.59] k=1 → wound haematoma / infection RR=1.00^{NS} [0.09;10.59] k=1 → bleeding RR=0.50^{NS} [0.01;24.59] k=1
	Aspirin versus placebo	
↓ proximal DVT RR=0.47† [0.29;0.76] k=2		→ deep vein thrombosis RR=0.72^{NS} [0.45;1.15] k=3 → non-fatal pulmonary embolism RR=0.51^{NS} [0.13;1.97] k=3 → fatal pulmonary embolism RR=1.03^{NS} [0.11;9.81] k=3 → wound haematoma / infection RR=1.22^{NS} [0.40;3.69] k=2 → bleeding RR=1.03^{NS} [0.11;9.81] 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)

Hydroxychloroquine

Results obtained with hydroxychloroquine for all the endpoints with data in at least one trial are summarized table 16.

Table 16: *Results summary - Hydroxychloroquine*

Benefit	Harmful	No evidence
	Hydroxychloroquine versus placebo	
		→ deep vein thrombosis RR=0.97^{NS} [0.70;1.34] k=3 → non-fatal pulmonary embolism RR=2.19^{NS} [0.52;9.17] k=2 → fatal pulmonary embolism RR=0.98^{NS} [0.10;9.17] k=3 → wound haematoma / infection RR=1.00^{NS} [0.07;15.12] k=1 → bleeding RR=0.98^{NS} [0.10;9.17] 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)

0.1.5 Recombinant hirudin

Reports of 3 trials (including 1,564 patients) were identified .
Among these comparisons, 3 trials are about desirudin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Results obtained with desirudin for all the endpoints with data in at least one trial are summarized table 17.

Table 17: *Results summary - Desirudin*

Benefit	Harmful	No evidence
	Desirudin versus enoxaparin	
	Desirudin versus UFH	

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

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

0.1.6 Synthetic oligosaccharide

Reports of 3 trials (including 5,607 patients) were identified .
Among these comparisons, two trials are about fondaparinux and one about SR123781A.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. One ongoing trial was identified.

Fondaparinux

Results obtained with fondaparinux for all the endpoints with data in at least one trial are summarized table 18.

Table 18: *Results summary - Fondaparinux*

Benefit	Harmful	No evidence
	Fondaparinux versus enoxaparin	
↓ deep vein thrombosis RR=0.55† [0.35;0.86] k=2 ↓ venous thromboembolism RR=0.57* [0.35;0.95] k=2	↑ symptomatic deep-vein thrombosis RR=5.79* [1.27;26.51] k=2 ↑ major bleeding RR=1.59* [1.08;2.32] k=2	→ symptomatic pulmonary embolism RR=2.10^{NS} [0.43;10.18] k=2 → non-fatal pulmonary embolism RR=2.00^{NS} [0.15;27.38] k=2 → proximal DVT RR=0.62^{NS} [0.12;3.24] H k=2 → symptomatic venous thromboembolism (DVT, PE) RR=3.48^{NS} [0.61;19.75] k=2 → fatal pulmonary embolism RR=0.67^{NS} [0.05;8.74] k=2 → all cause death RR=1.09^{NS} [0.10;12.02] k=2

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

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

SR123781A

Results obtained with SR123781A for all the endpoints with data in at least one trial are summarized table 19.

Table 19: *Results summary - SR123781A*

Benefit	Harmful	No evidence
	SR123781A versus enoxaparin	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ 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 hip replacement. 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. recombinant hirudin
6. 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 hip replacement.

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 proximal DVT, Deep vein thrombosis, distal DVT, total VTE and all-cause mortality, major VTE (fatal and non fatal DVT,PE), non-fatal pulmonary embolism, All cause death, Major bleeding, Symptomatic venous thromboembolism (DVT, PE), Symptomatic deep-vein thrombosis, asymptomatic DVT, myocardial infarction (fatal and non fatal), Coronary event, major or clinically relevant non-major bleeding, .

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, recombinant hirudin, 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 13259 patients were identified. In all, 1 randomized comparison concerned apixaban , one edoxaban , two rivaroxaban and one rivaroxaban (long duration).
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 39) for apixaban, in section 4 (page 51) for edoxaban, in section 5 (page 59) for rivaroxaban and in section 6 (page 71) for rivaroxaban (long duration).

The average study size was 2651 patients (range 299 to 5407). The first study was published in 2006, 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 27) 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 2.5 (page 29) and in the following graphs.

2.2.1 Apixaban

Apixaban was superior to **enoxaparin** in terms of major VTE (fatal and non fatal DVT,PE) (RR=0.40, 95% CI 0.19 to 0.83, p=0.0138, 1 trial), deep vein thrombosis (RR=0.32, 95% CI 0.20 to 0.51, p=0.0000, 1 trial), total VTE and all-cause mortality (RR=0.36, 95% CI 0.23 to 0.56, p=0.0000, 1 trial), asymptomatic DVT (RR=0.33, 95% CI 0.20 to 0.54, p=0.0000, 1 trial)and proximal DVT (RR=0.35, 95% CI 0.15 to 0.82, p=0.0163, 1 trial). However, no significant difference was found on symptomatic deep-vein thrombosis (RR=0.20, 95% CI 0.02 to 1.71, p=0.1408, 1 trial), non-fatal pulmonary embolism (RR=0.40, 95% CI 0.08 to 2.05, p=0.2714, 1 trial), symptomatic venous thromboembolism (DVT, PE) (RR=0.40, 95% CI 0.13 to 1.27, p=0.1197, 1 trial), myocardial infarction (fatal and non fatal) (RR=2.24, 95% CI 0.69 to 7.27, p=0.1785, 1 trial)and major bleeding (RR=1.22, 95% CI 0.65 to 2.26, p=0.5371, 1 trial).

2.2.2 Edoxaban

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

2.2.3 Rivaroxaban

Rivaroxaban was superior to **enoxaparin** in terms of major VTE (fatal and non fatal DVT,PE) (RR=0.12, 95% CI 0.04 to 0.34, p=0.0000, 1 trial), deep vein thrombosis (RR=0.23, 95% CI

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

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

2.2.4 Rivaroxaban (long duration)

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

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

Trial	Patients	Treatments	Trial design and method
Apixaban			
Apixaban versus enoxaparin			
ADVANCE 3, 2010 [1] n = 2708 vs. 2699	patients undergoing elective total hip replacement surgery	apixaban 2.5mg twice daily for 35 days **versus** enoxaparin 40mg once daily for 35 days	double blind parallel groups Primary endpoint: asymptomatic and symptomatic DVT, PE,all-cause death 160 centres, 21 countries mean follow-up: 35 days test intervalle: 2-4 (3)
Edoxaban			
Edoxaban versus enoxaparin (short duration)			
STARS J-V, 0 n = 255 vs. 248	total hip arthroplasty	edoxaban 30 mg once daily for 11 to 14 days **versus** subcutaneous enoxaparin 2,000 IU, equivalent to 20 mg, twice daily (BID) for 11 to 14 days	double-blind parallel groups Primary endpoint: all DVT,PE japan test intervalle: 2-4 (3)
Rivaroxaban			
Rivaroxaban versus enoxaparin			
RECORD 1, 2008 [1] n = 2266 vs. 2275	patients undergoing total hip arthroplasty	rivaroxaban 10mg once daily for 35 days **versus** enoxaparin 40mg subcutaneous once daily for 31-39 days	double blind parallel groups Primary endpoint: DVT, PE, death multicentre, 27 countries worldwide mean follow-up: 46 days test intervalle: 2-4 (3)
Rivaroxaban versus enoxaparin (short duration)			

continued...

Trial	Patients	Treatments	Trial design and method
ODIXa-HIP 10mg, 2006 [2, 3] n = 142 vs. 157	patients undergoing elective total hip replacement	rivaroxaban 10mg daily for 59 days **versus** once-daily subcutaneous enoxaparin dose of 40 mg for 59 days	double blind parallel groups Primary endpoint: any DVT, PE, all cause death 48 centres, Europe, Israel mean follow-up: 7 days test intervalle: 2-4 (3)
Rivaroxaban (long duration)			
Rivaroxaban (long duration) versus enoxaparin (short duration)			
RECORD 2, 2008 [1] n = 1252 vs. 1257	patients undergoing elective total hip replacement	extended thromboprophylaxis with rivaroxaban 10mg once daily for 31-39 days **versus** enoxaparin 40mg subcutaneous once daily for 10-14 days	double blind parallel groups Primary endpoint: DVT, PE , all cause death 123 centres, 21 countries worldwide mean follow-up: 36 days test intervalle: 2-4 (3)

Table 2.2: *Summary of all results for apixaban*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
apixaban versus enoxaparin						
symptomatic deep-vein thrombosis	RR=0.20	0.02;1.71	0.1408	1.0000 (0.00)	1	5407
major VTE (fatal and non fatal DVT,PE)	RR=0.40	0.19;0.83	0.0138	1.0000 (0.00)	1	4394
deep vein thrombosis	RR=0.32	0.20;0.51	0.0000	1.0000 (1.00)	1	3855
total VTE and all-cause mortality	RR=0.36	0.23;0.56	0.0000	1.0000 (0.00)	1	3866
asymptomatic DVT	RR=0.33	0.20;0.54	0.0000	1.0000 (0.00)	1	5407
non-fatal pulmonary embolism	RR=0.40	0.08;2.05	0.2714	1.0000 (0.00)	1	5407
proximal DVT	RR=0.35	0.15;0.82	0.0163	1.0000 (1.00)	1	4386
symptomatic venous thromboembolism (DVT, PE)	RR=0.40	0.13;1.27	0.1197	1.0000 (0.00)	1	5407
myocardial infarction (fatal and non fatal)	RR=2.24	0.69;7.27	0.1785	1.0000 (0.00)	1	5407
coronary event	RR=1.66	0.40;6.93	0.4885	1.0000 (0.00)	1	5332
major or clinically relevant non-major bleeding	RR=0.96	0.76;1.21	0.7190	1.0000 (0.00)	1	5332
all cause death	RR=2.99	0.31;28.73	0.3427	1.0000 (0.00)	1	5407
major bleeding	RR=1.22	0.65;2.26	0.5371	1.0000 (0.00)	1	5332

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

Table 2.3: *Summary of all results for edoxaban*

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

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

Table 2.4: *Summary of all results for rivaroxaban*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
rivaroxaban versus enoxaparin						
major VTE (fatal and non fatal DVT,PE)	RR=0.12	0.04;0.34	0.0000	1.0000 (0.00)	1	3364
deep vein thrombosis	RR=0.23	0.12;0.43	0.0000	1.0000 (0.00)	1	4433
total VTE and all-cause mortality	RR=0.30	0.18;0.51	0.0000	1.0000 (0.00)	1	3153
non-fatal pulmonary embolism	RR=3.91	0.44;34.92	0.2226	1.0000 (0.00)	1	3153
distal DVT	RR=0.49	0.24;1.00	0.0512	1.0000 (0.00)	1	3153
proximal DVT	RR=0.03	0.00;0.23	0.0000	1.0000 (0.00)	1	3153
symptomatic venous thromboembolism (DVT, PE)	RR=0.55	0.20;1.48	0.2361	1.0000 (0.00)	1	4399
coronary event	RR=0.49	0.12;1.95	0.3102	1.0000 (0.00)	1	3153
all cause death	RR=0.98	0.24;3.90	0.9735	1.0000 (0.00)	1	3153
major bleeding	RR=3.02	0.61;14.95	0.1755	1.0000 (0.00)	1	4433
rivaroxaban versus enoxaparin (short duration)						
deep vein thrombosis	RR=0.42	0.22;0.79	0.0068	1.0000 (1.00)	1	220
total VTE and all-cause mortality	RR=0.42	0.22;0.79	0.0068	1.0000 (1.00)	1	220
non-fatal pulmonary embolism	RR=0.95	0.02;47.30	0.9782	1.0000 (0.00)	1	220
distal DVT	RR=0.36	0.17;0.73	0.0048	1.0000 (0.00)	1	220
proximal DVT	RR=0.95	0.20;4.59	0.9460	1.0000 (0.00)	1	220

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

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

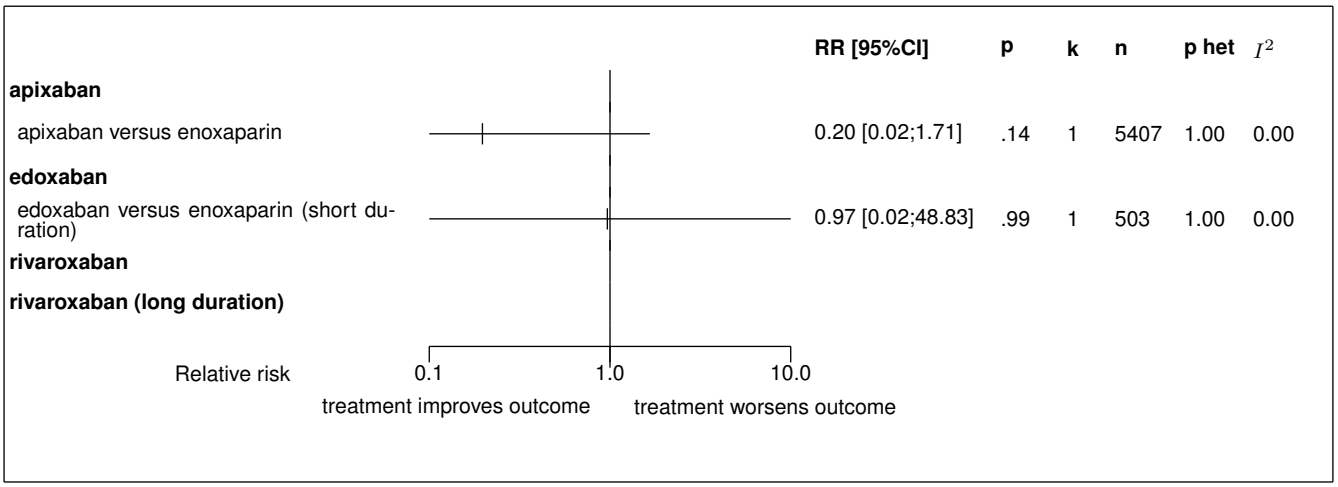
Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
rivaroxaban (long duration) versus enoxaparin (short duration)						
major VTE (fatal and non fatal DVT,PE)	RR=0.12	0.05;0.28	0.0000	1.0000 (0.00)	1	1923
deep vein thrombosis	RR=0.20	0.11;0.35	0.0000	1.0000 (0.00)	1	1733
total VTE and all-cause mortality	RR=0.21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

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
proximal DVT	RR=0.11	0.05;0.29	0.0000	1.0000 (0.00)	1	1733
symptomatic venous thromboembolism (DVT, PE)	RR=0.20	0.06;0.69	0.0106	1.0000 (1.00)	1	2419
coronary event	RR=1.33	0.30;5.95	0.7052	1.0000 (0.00)	1	2457
major or clinically relevant non-major bleeding	RR=1.20	0.93;1.54	0.1582	1.0000 (1.00)	1	2457
all cause death	RR=0.34	0.07;1.66	0.1800	1.0000 (1.00)	1	1733
major bleeding	RR=1.00	0.06;15.98	0.9995	1.0000 (0.00)	1	2457

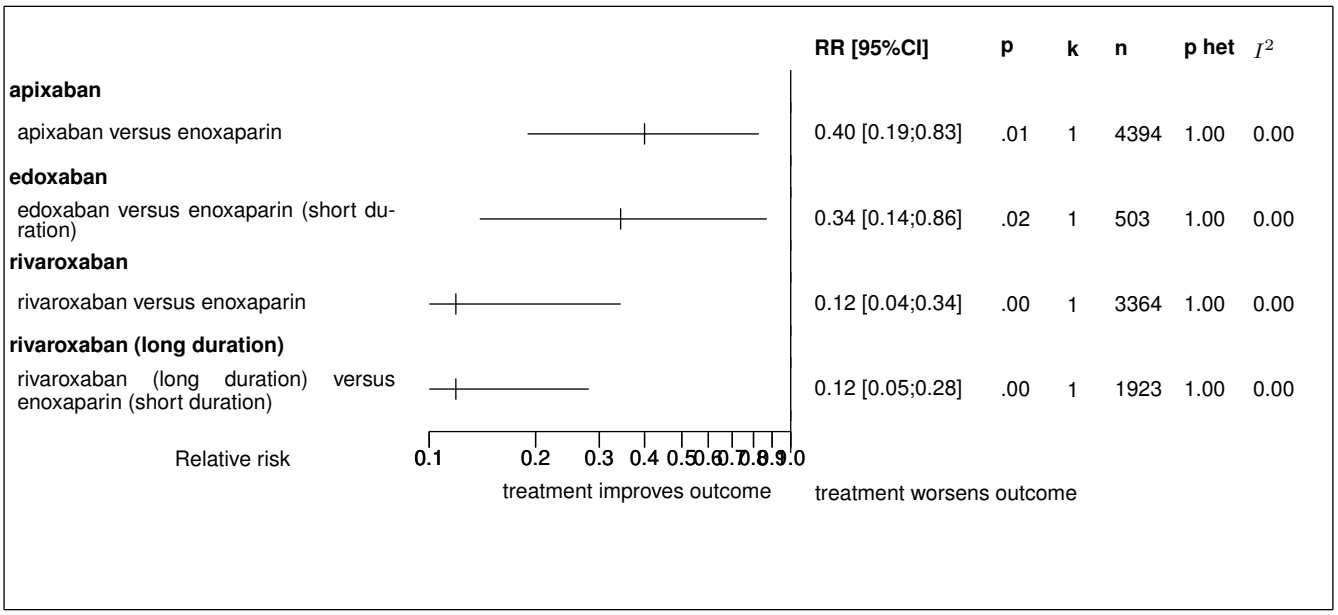
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



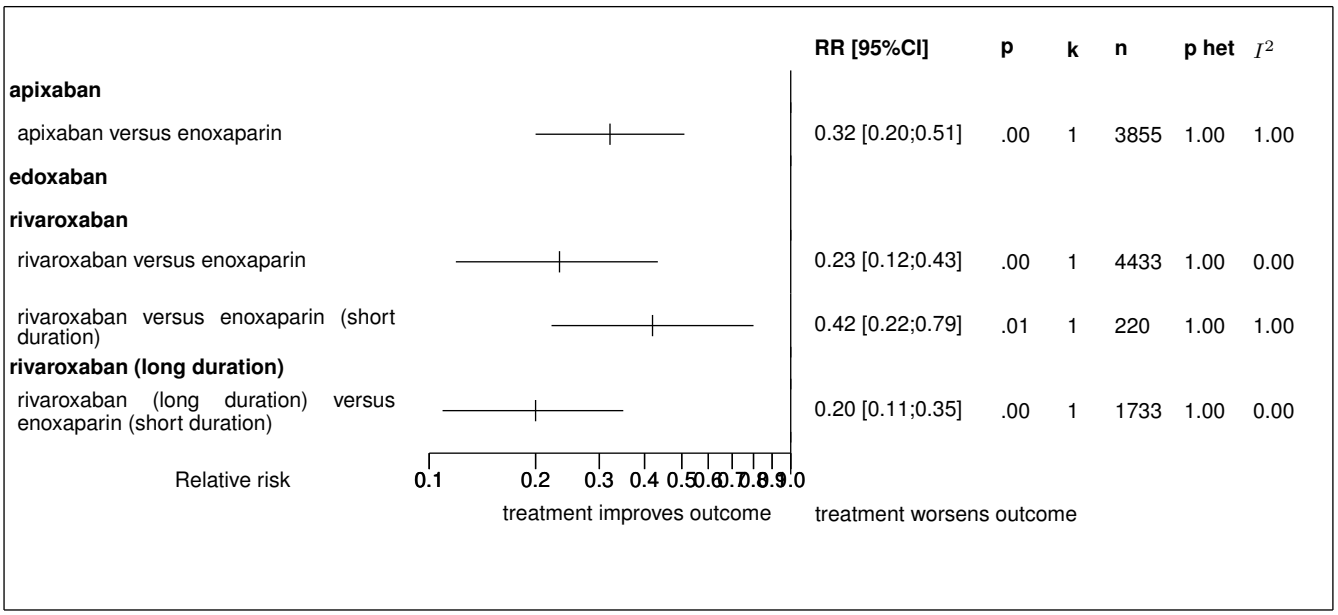
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



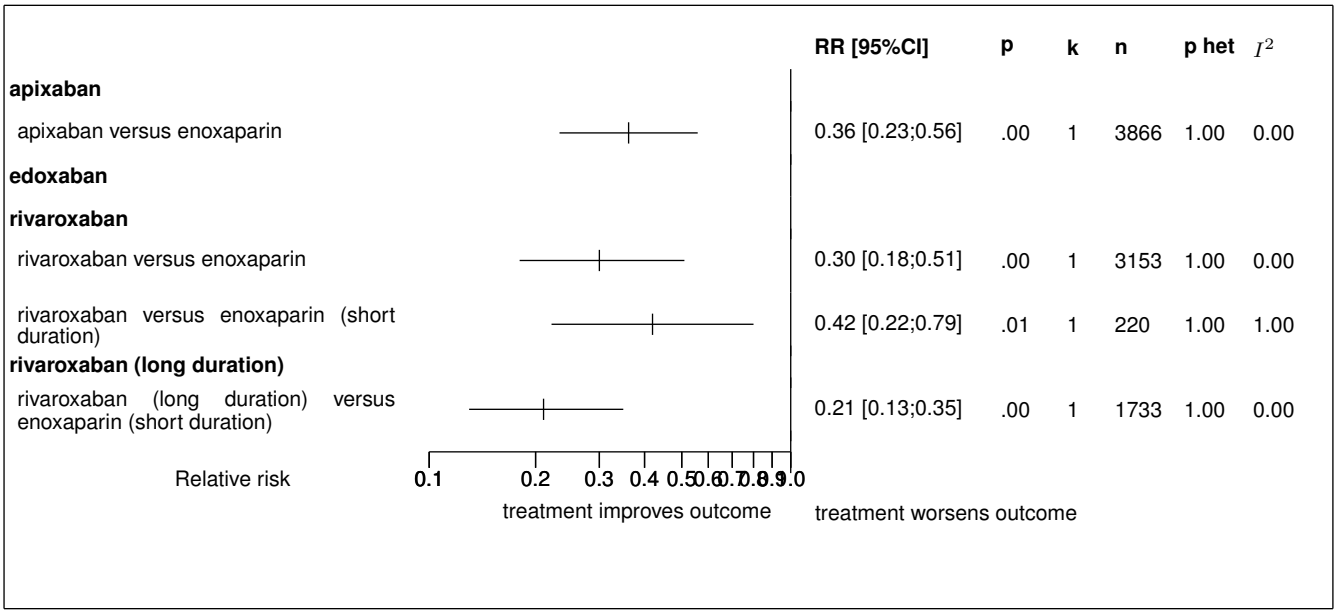
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



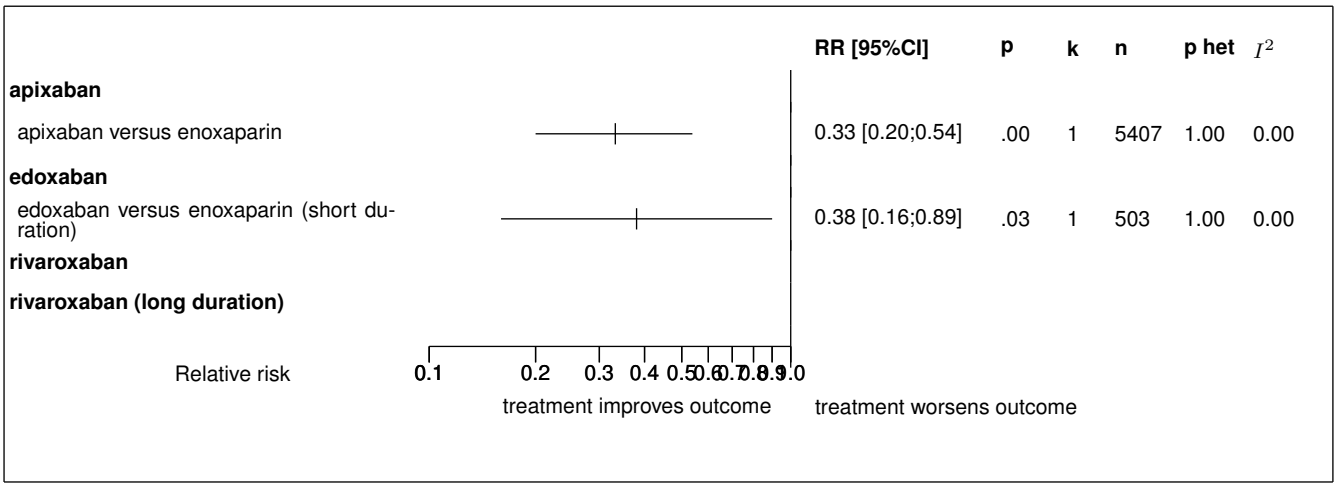
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.4: *Forest's plot for total VTE and all-cause mortality*



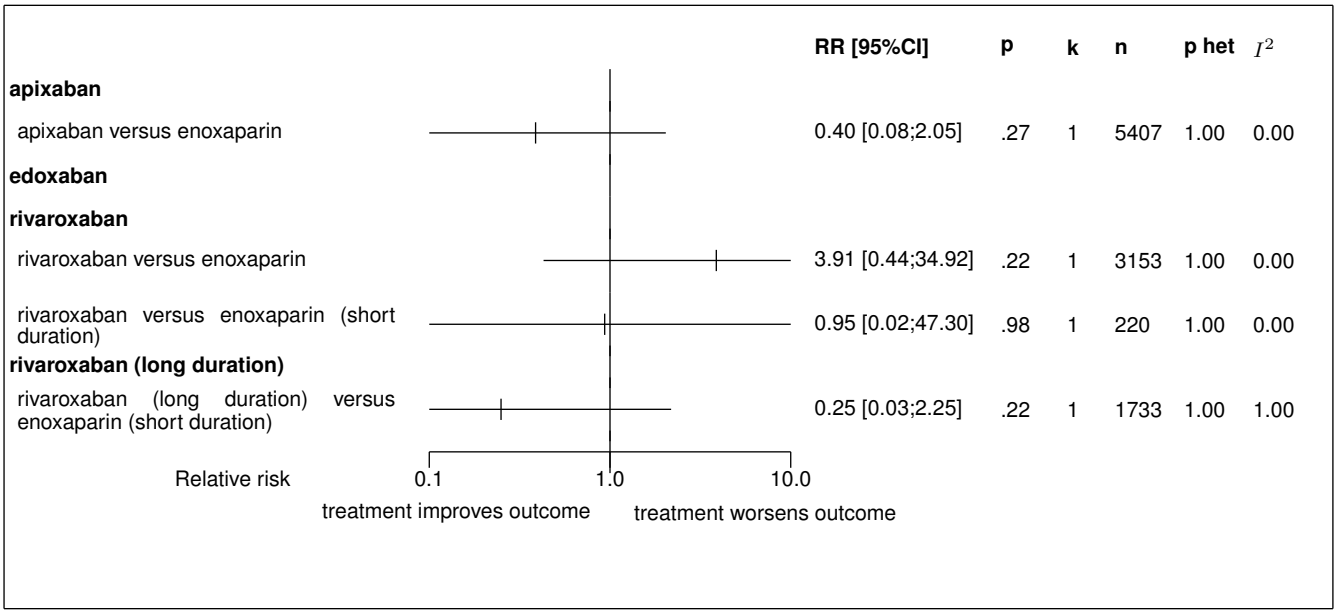
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.5: *Forest's plot for asymptomatic DVT*



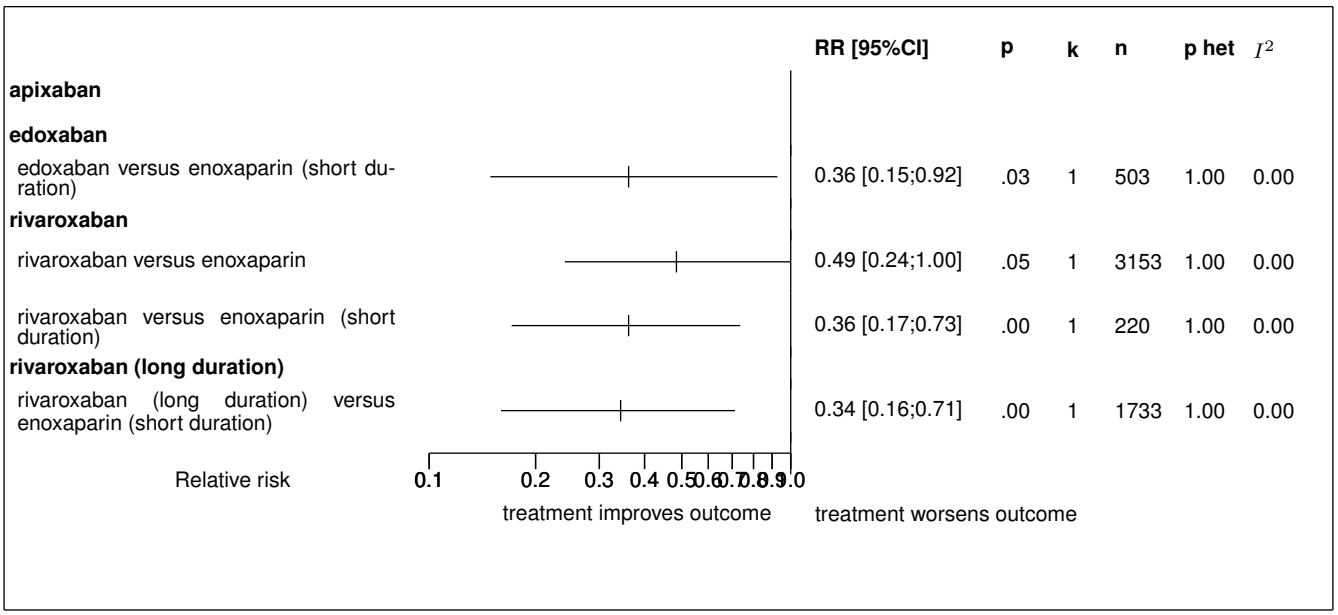
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.6: *Forest's plot for non-fatal pulmonary embolism*



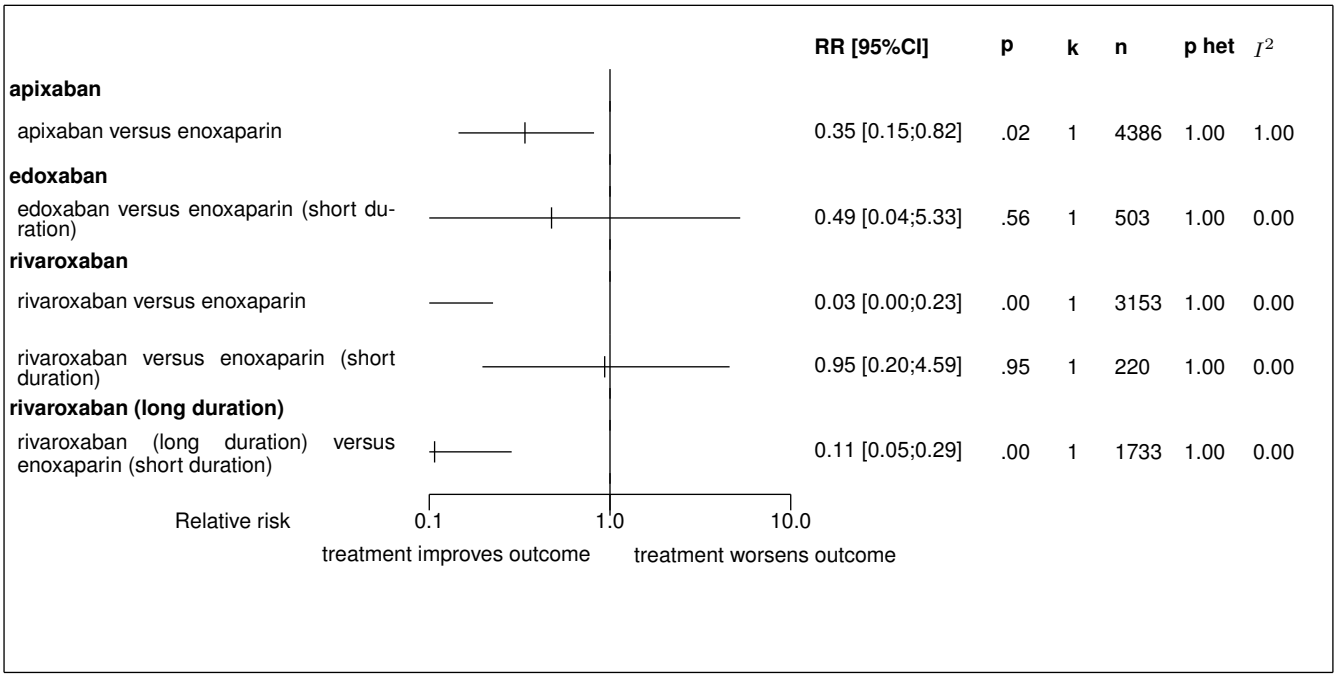
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.7: *Forest's plot for distal DVT*



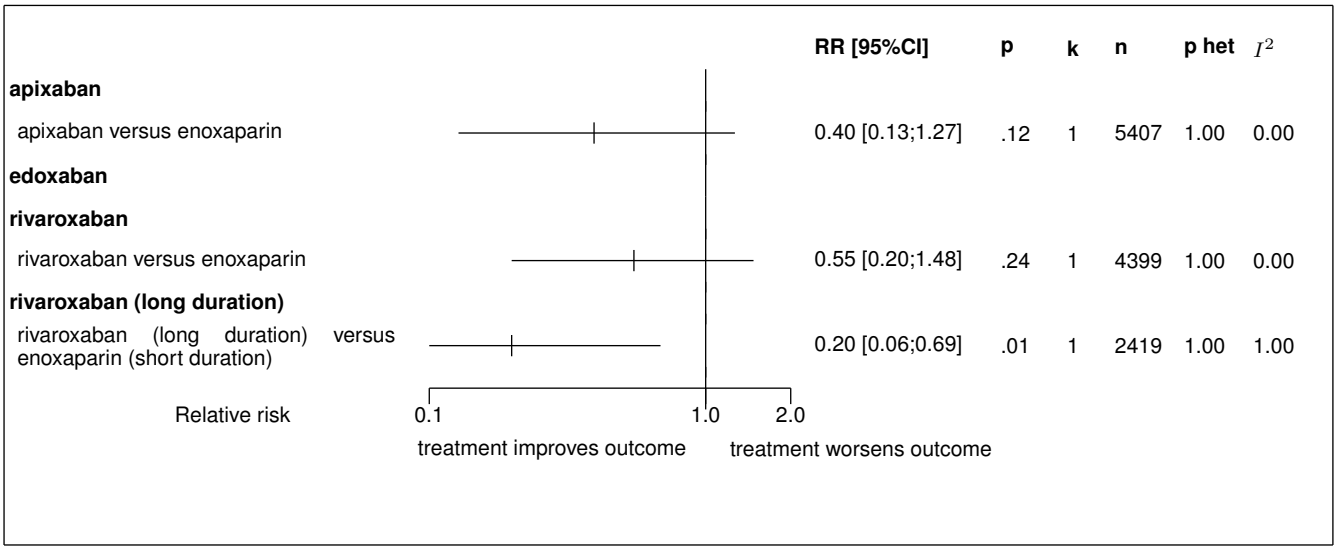
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



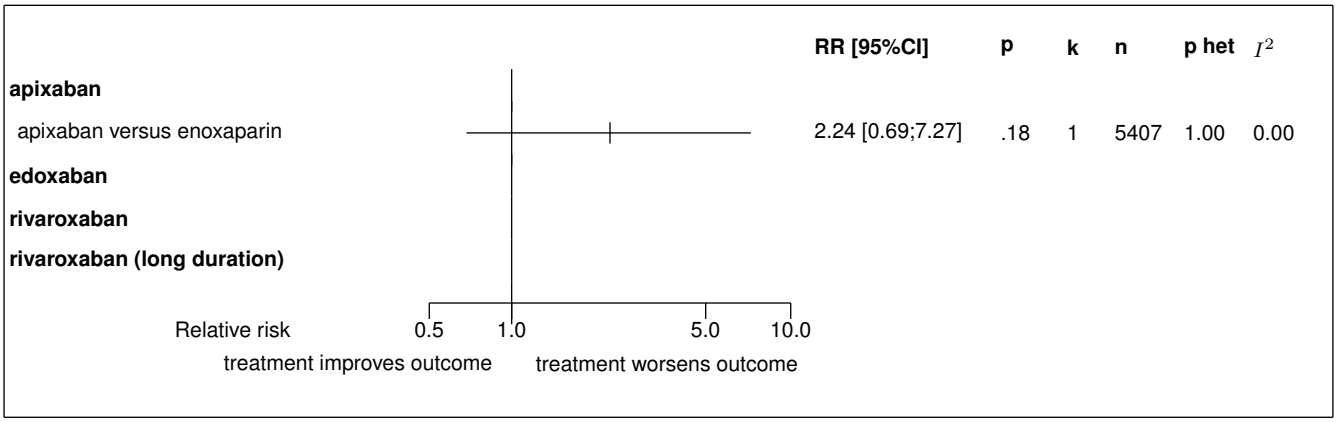
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.9: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*



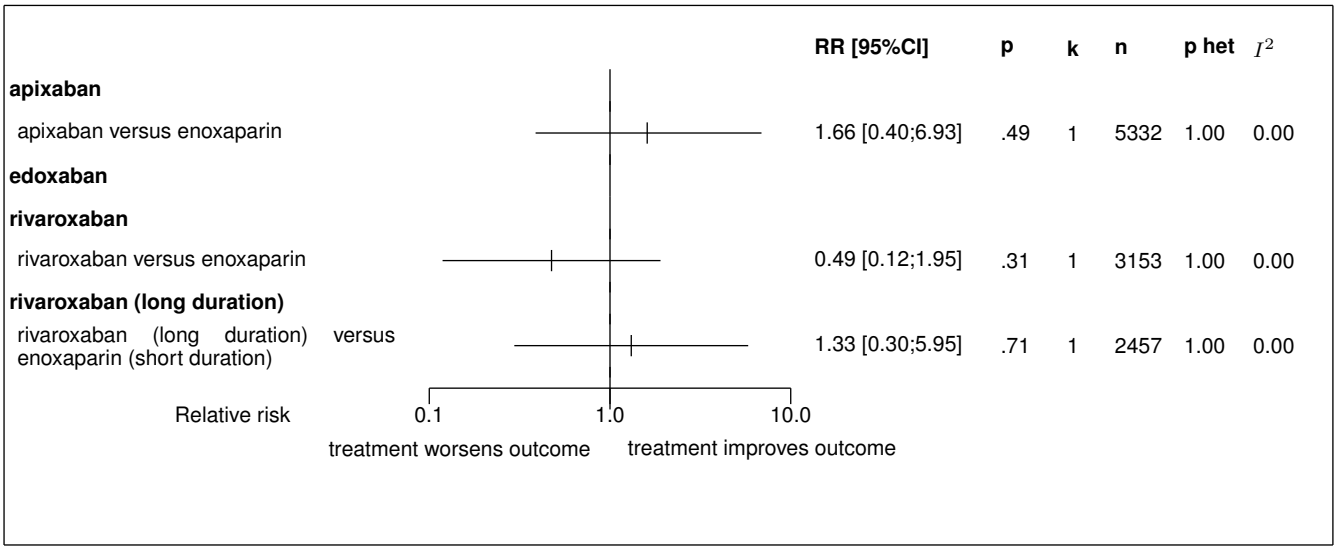
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.10: *Forest's plot for myocardial infarction (fatal and non fatal)*



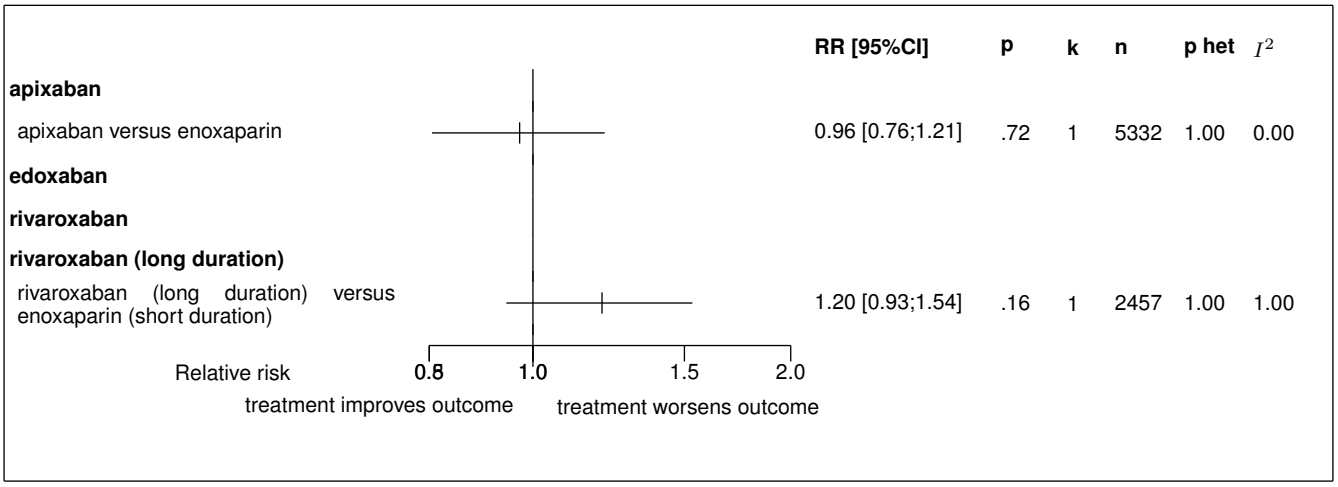
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.11: *Forest's plot for coronary event*



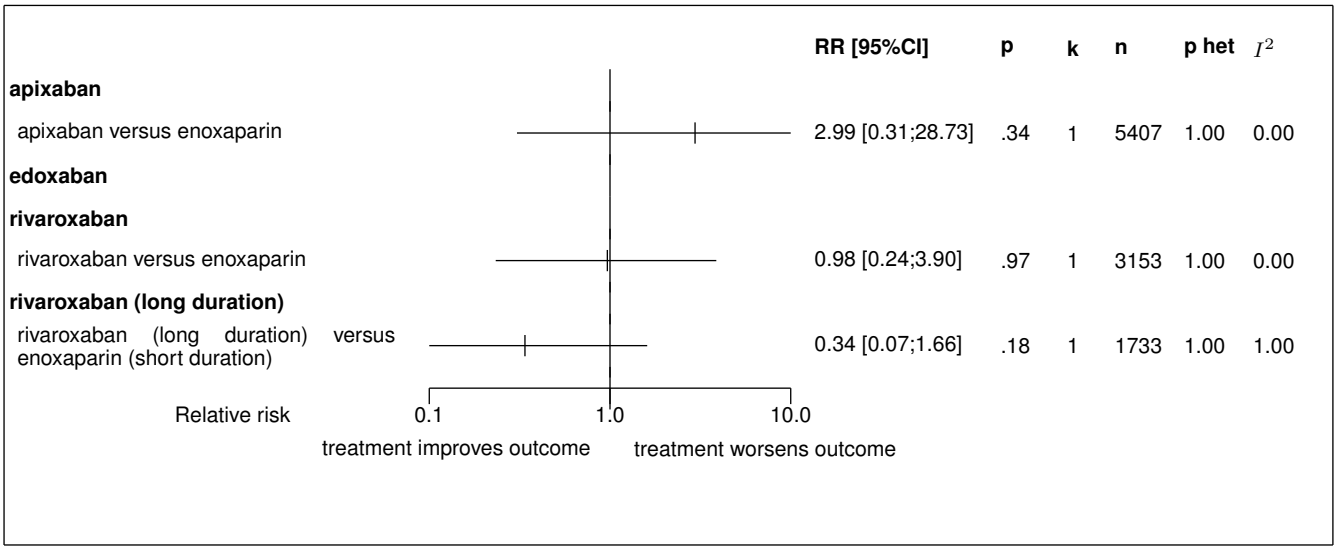
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.12: *Forest's plot for major or clinically relevant non-major bleeding*



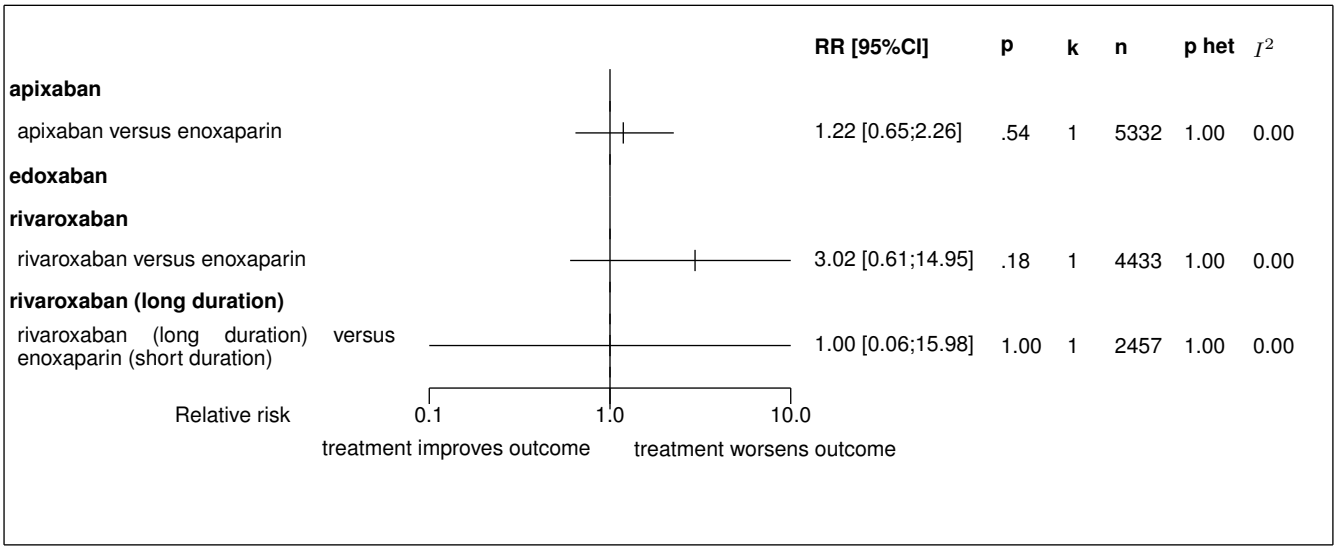
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.13: *Forest's plot for all cause death*



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

Figure 2.14: *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; ᶠ: random effect model used

3 Detailed results for apixaban

3.1 Available trials

Only one trial which randomized 5407 patients was identified: it compared apixaban with enoxaparin.
This trial included 5407 patients and was published in 2010.
This trial was double blind in design.
It was reported in English language.
Myocardial infarction (fatal and non fatal) data was reported in 1 trials; 1 trials reported data on symptomatic venous thromboembolism (DVT, PE); 1 trials reported data on major bleeding; 1 trials reported data on proximal DVT; 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on total VTE and all-cause mortality; 1 trials reported data on all cause death; 1 trials reported data on deep vein thrombosis; 1 trials reported data on major VTE (fatal and non fatal DVT,PE); 1 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on asymptomatic DVT; 1 trials reported data on major or clinically relevant non-major bleeding; and 1 trials reported data on coronary event.
Following tables 3.1 (page 39), 3.2 (page 39), 3.4 (page 41), and 3.3 (page 40) summarized the main characteristics of the trial including in this systematic review of randomized trials of apixaban.

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

Trial	Studied treatment	Control treatment
Apixaban versus enoxaparin		
ADVANCE 3 (2010) [1]	apixaban 2.5mg twice daily for 35 days given 12 to 24 hours following surgery	enoxaparin 40mg once daily for 35 days started the evening before surgery

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

Trial	Patients	
Apixaban versus enoxaparin		
ADVANCE 3 (2010) [1]	Patients undergoing elective total hip replacement surgery	
	Inclusion criteria: scheduled to undergoelective total hip replacement or revision ofa previously inserted hip prosthesis	**Exclusion criteria:** active bleeding; contraindication to anticoagulant prophylaxis; need for ongoing anticoagulant or antiplatelet treatment

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

Trial	Design	Duration	Centre	Primary end-point
Apixaban versus enoxaparin				
ADVANCE 3, 2010 [1] n=5407	Parallel groups double blind confirmatory trial at low risk of bias	35 days (+60) inclusion period: mar 2007 - may 2009	21 countries 160 centres	asymptomatic and symptomatic DVT, PE,all-cause death

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

Trial	mean follow-up	test intervalle
Apixaban versus enoxaparin		
ADVANCE 3, 2010 [1]	35 days	2-4 (3)

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 42). This table is followed by the Forest's plot corresponding to each endpoint.

Apixaban versus enoxaparin

The single study eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. There was no statistically significant difference in symptomatic deep-vein thrombosis between apixaban and enoxaparin, with a RR of 0.20 (95%CI 0.02 to 1.71, p=0.1408) in favour of apixaban. In other words, symptomatic deep-vein thrombosis was slightly lower in the apixaban group , but this was not statistically significant.
The single study eligible for this comparison provided data on **major VTE (fatal and non fatal DVT,PE)**. The analysis detected a statistically significant difference in favor of apixaban in major VTE (fatal and non fatal DVT,PE), with a RR of 0.40 (95% CI 0.19 to 0.83, p=0.0138).
The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of apixaban in deep vein thrombosis, with a RR of 0.32 (95% CI 0.20 to 0.51, p=0.0000).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. The analysis detected a statistically significant difference in favor of apixaban in total VTE and all-cause mortality, with a RR of 0.36 (95% CI 0.23 to 0.56, p=0.0000).
The single study eligible for this comparison provided data on **asymptomatic DVT**. The analysis detected a statistically significant difference in favor of apixaban in asymptomatic DVT, with a RR of 0.33 (95% CI 0.20 to 0.54, p=0.0000).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.40 (95% CI 0.08 to 2.05, p=0.2714).
The single study eligible for this comparison provided data on **proximal DVT**. The analysis detected a statistically significant difference in favor of apixaban in proximal DVT, with a RR of 0.35 (95% CI 0.15 to 0.82, p=0.0163).
The single study eligible for this comparison provided data on **symptomatic venous thromboembolism (DVT, PE)**. No statistically significant difference between the groups was found in symptomatic venous thromboembolism (DVT, PE), with a RR of 0.40 (95% CI 0.13 to 1.27, p=0.1197).
The single study eligible for this comparison provided data on **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 2.24 (95% CI 0.69 to 7.27, p=0.1785).
The single study eligible for this comparison provided data on **major bleeding**. No statistically significant difference between the groups was found in major bleeding, with a RR of 1.22 (95% CI 0.65 to 2.26, p=0.5371).

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
apixaban versus enoxaparin						
symptomatic deep-vein thrombosis	RR=0.20	[0.02;1.71]	0.1408	1.0000 (I^2=0.00)	1	5407
major VTE (fatal and non fatal DVT,PE)	RR=0.40	[0.19;0.83]	0.0138	1.0000 (I^2=0.00)	1	4394

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
deep vein thrombosis	RR=0.32	[0.20;0.51]	0.0000	1.0000 (I^2=1.00)	1	3855
total VTE and all-cause mortality	RR=0.36	[0.23;0.56]	0.0000	1.0000 (I^2=0.00)	1	3866
asymptomatic DVT	RR=0.33	[0.20;0.54]	0.0000	1.0000 (I^2=0.00)	1	5407
non-fatal pulmonary embolism	RR=0.40	[0.08;2.05]	0.2714	1.0000 (I^2=0.00)	1	5407
proximal DVT	RR=0.35	[0.15;0.82]	0.0163	1.0000 (I^2=1.00)	1	4386
symptomatic venous thromboembolism (DVT, PE)	RR=0.40	[0.13;1.27]	0.1197	1.0000 (I^2=0.00)	1	5407
myocardial infarction (fatal and non fatal)	RR=2.24	[0.69;7.27]	0.1785	1.0000 (I^2=0.00)	1	5407
coronary event	RR=1.66	[0.40;6.93]	0.4885	1.0000 (I^2=0.00)	1	5332
major or clinically relevant non-major bleeding	RR=0.96	[0.76;1.21]	0.7190	1.0000 (I^2=0.00)	1	5332
all cause death	RR=2.99	[0.31;28.73]	0.3427	1.0000 (I^2=0.00)	1	5407
major bleeding	RR=1.22	[0.65;2.26]	0.5371	1.0000 (I^2=0.00)	1	5332

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*

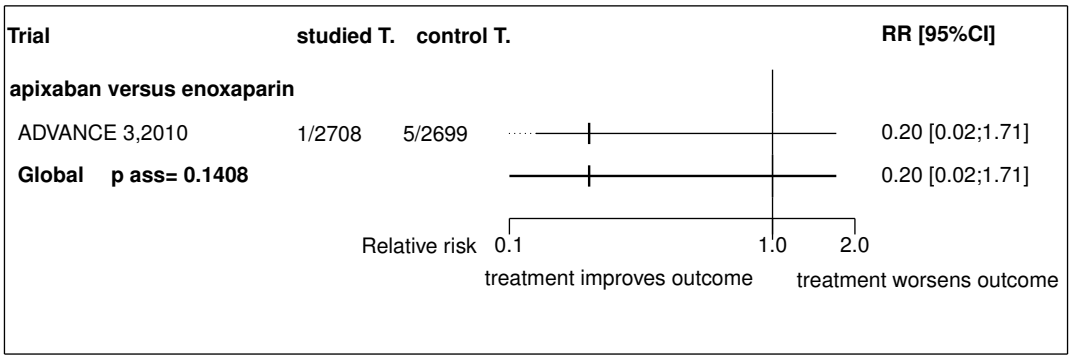


Figure 3.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

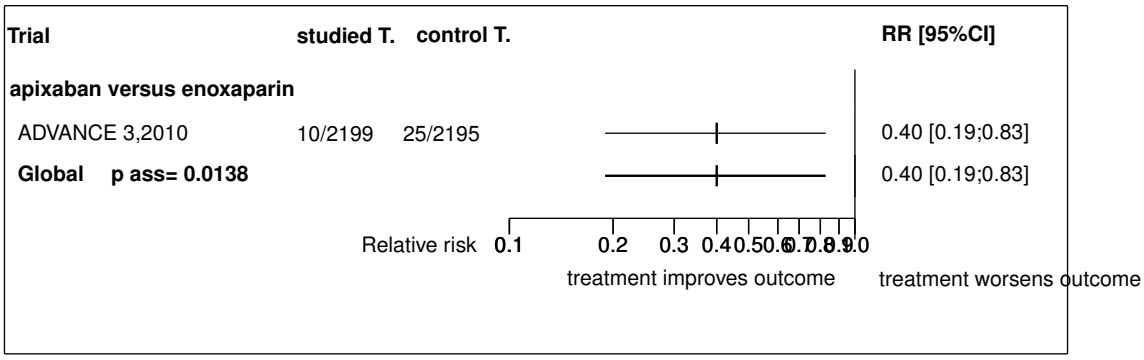


Figure 3.3: *Forest's plot for deep vein thrombosis*

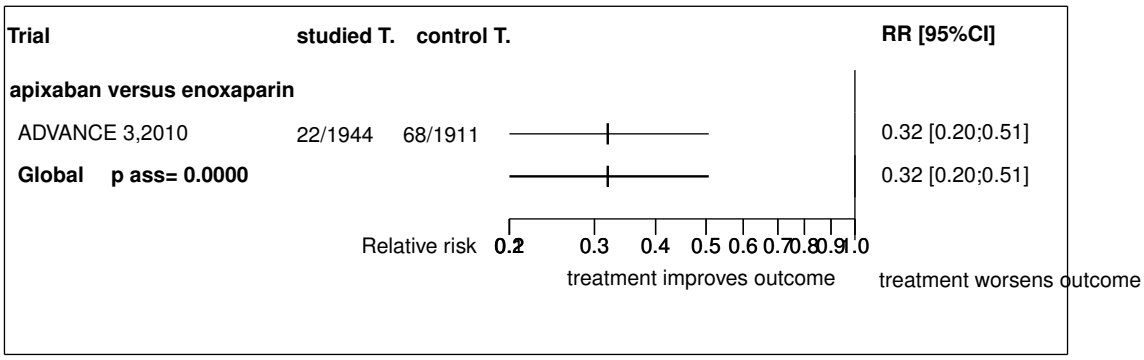


Figure 3.4: *Forest's plot for total VTE and all-cause mortality*

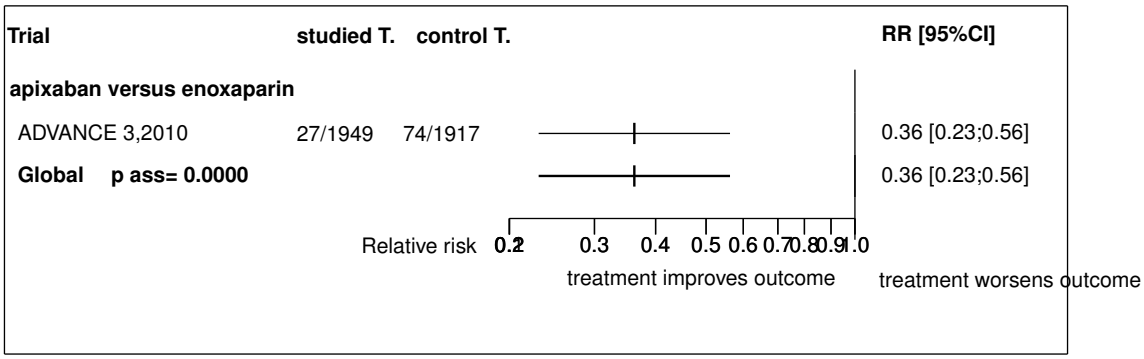


Figure 3.5: *Forest's plot for asymptomatic DVT*

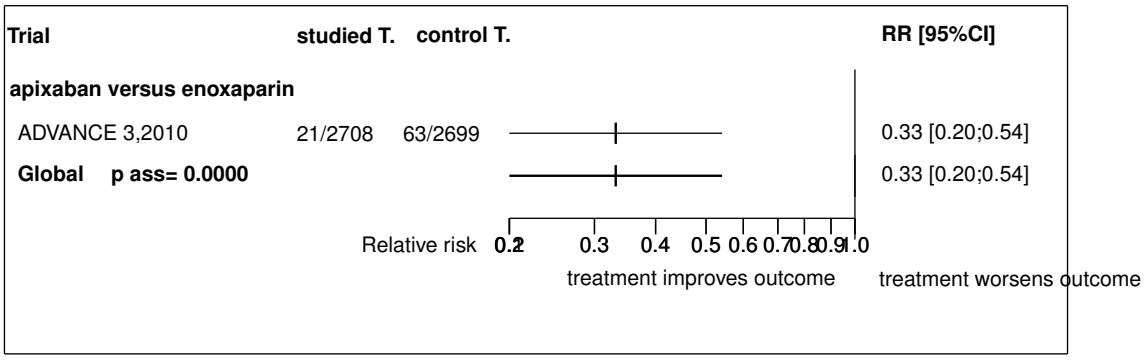


Figure 3.6: *Forest's plot for non-fatal pulmonary embolism*

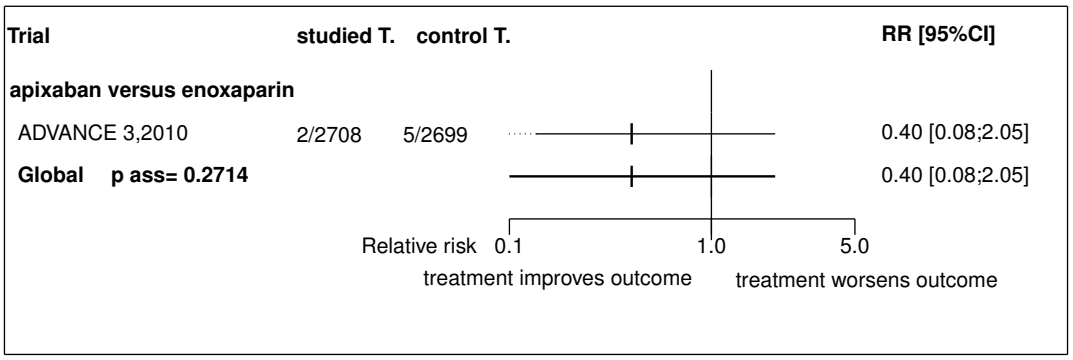


Figure 3.7: *Forest's plot for proximal DVT*

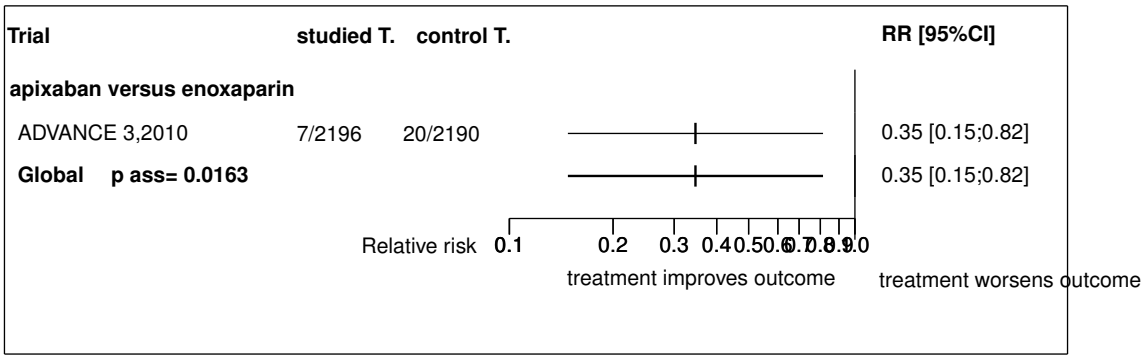


Figure 3.8: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

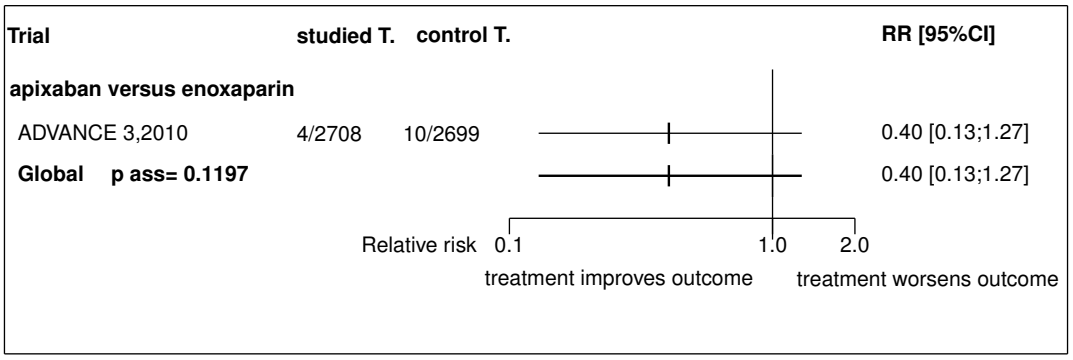


Figure 3.9: *Forest's plot for myocardial infarction (fatal and non fatal)*

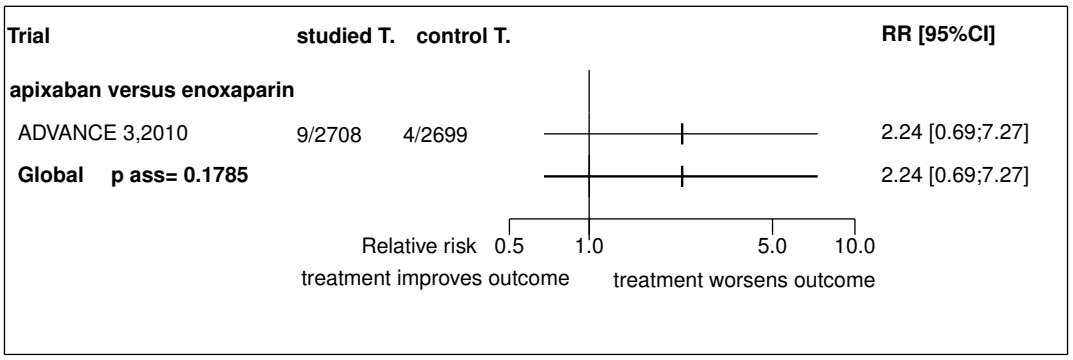


Figure 3.10: *Forest's plot for coronary event*

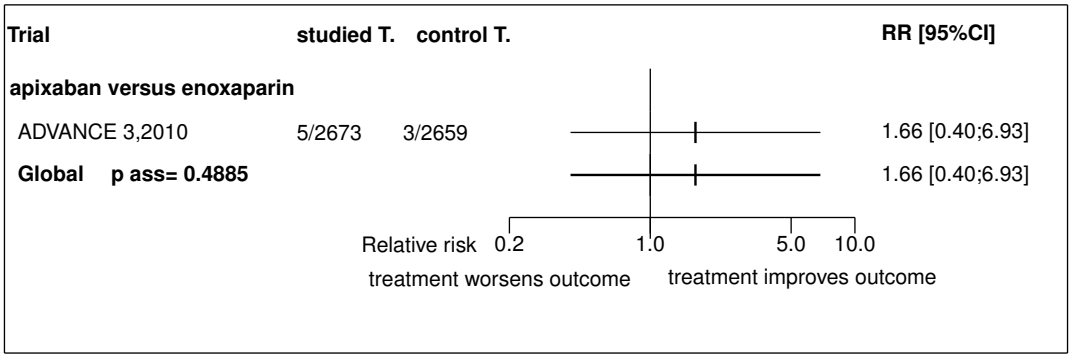


Figure 3.11: *Forest's plot for major or clinically relevant non-major bleeding*

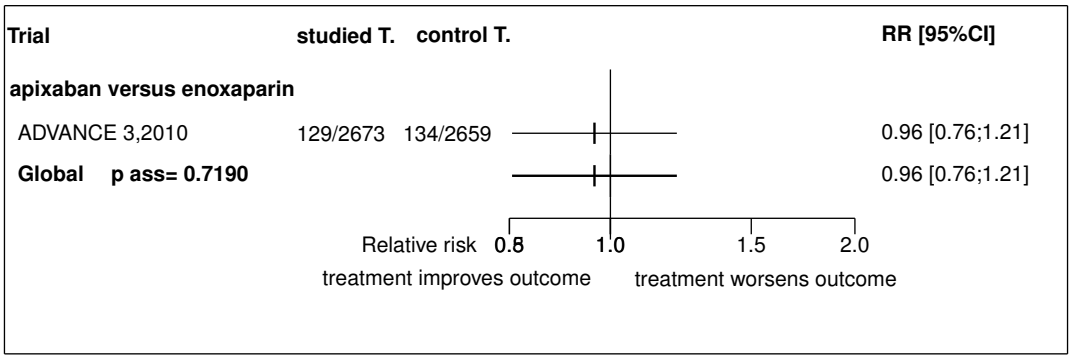


Figure 3.12: *Forest's plot for all cause death*

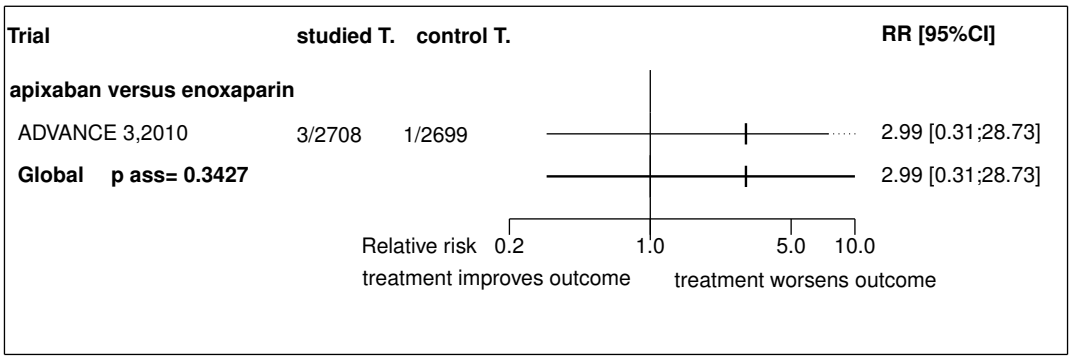
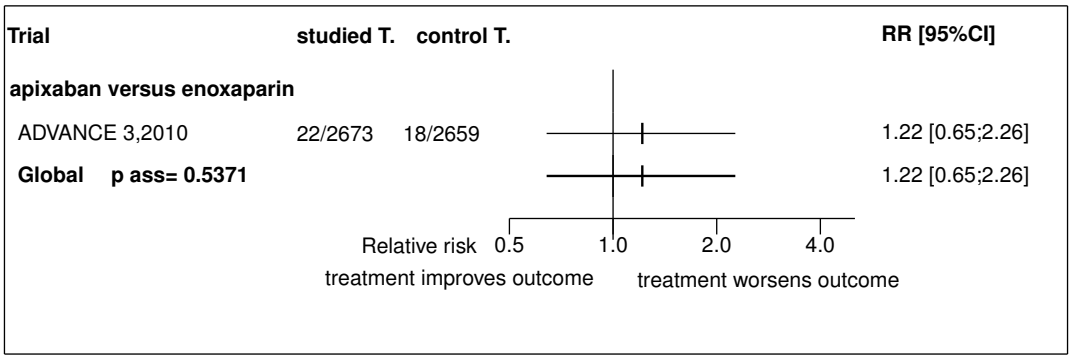


Figure 3.13: *Forest's plot for major bleeding*



References

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

3.3 Individual trial summaries

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

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

Reference

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

4 Detailed results for edoxaban

4.1 Available trials

Only one trial which randomized 503 patients was identified: it compared edoxaban with enoxaparin (short duration).
This trial included 503 patients and was published in .
This trial was double blind in design.
It was reported in English language.
Major VTE (fatal and non fatal DVT,PE) data was reported in 1 trials; 1 trials reported data on distal DVT; 1 trials reported data on asymptomatic DVT; 1 trials reported data on proximal DVT; and 1 trials reported data on symptomatic deep-vein thrombosis.
Following tables 4.1 (page 51), 4.2 (page 51), 4.4 (page 53), and 4.3 (page 51) summarized the main characteristics of the trial including in this systematic review of randomized trials of edoxaban.

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

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

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

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

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

Trial	Design	Duration	Centre	Primary endpoint
Edoxaban versus enoxaparin (short duration)				

continued...

Trial	Design	Duration	Centre	Primary end-point
STARS J-V, 0 n=503	Parallel groups double-blind confirmatory trial at low risk of bias		japan	all DVT,PE

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

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

4.2 Meta-analysis results

The results are detailed in table 4.5 (page 54). This table is followed by the Forest's plot corresponding to each endpoint.

Edoxaban versus enoxaparin (short duration)

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

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

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

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

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

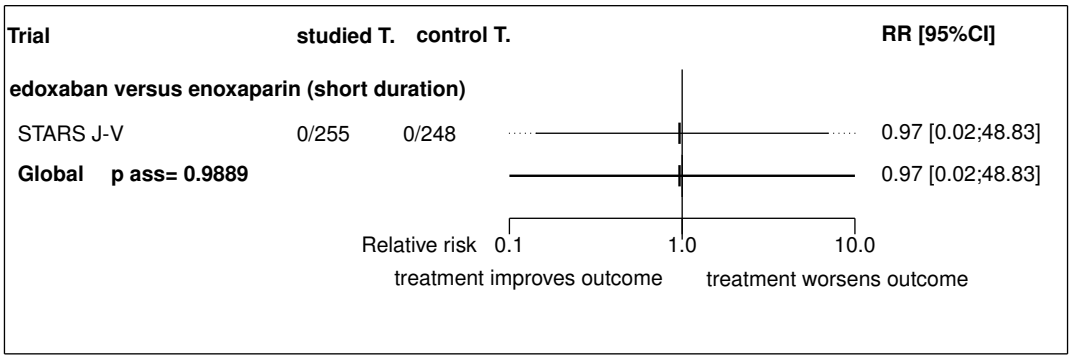


Figure 4.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

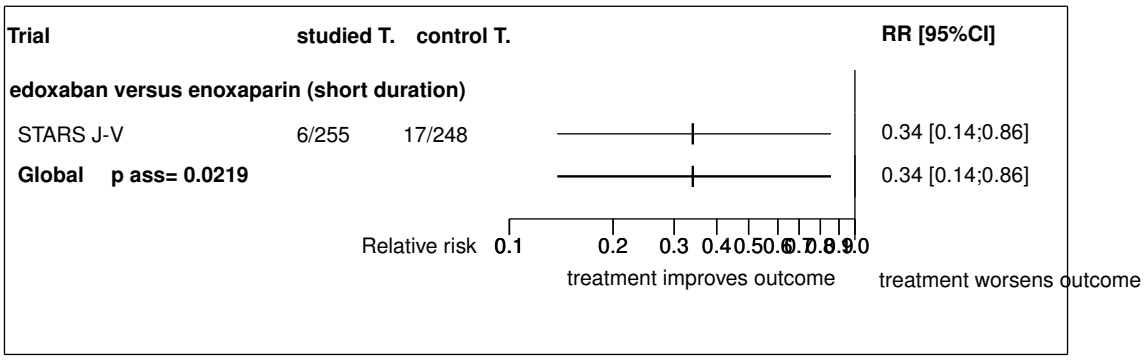


Figure 4.3: *Forest's plot for asymptomatic DVT*

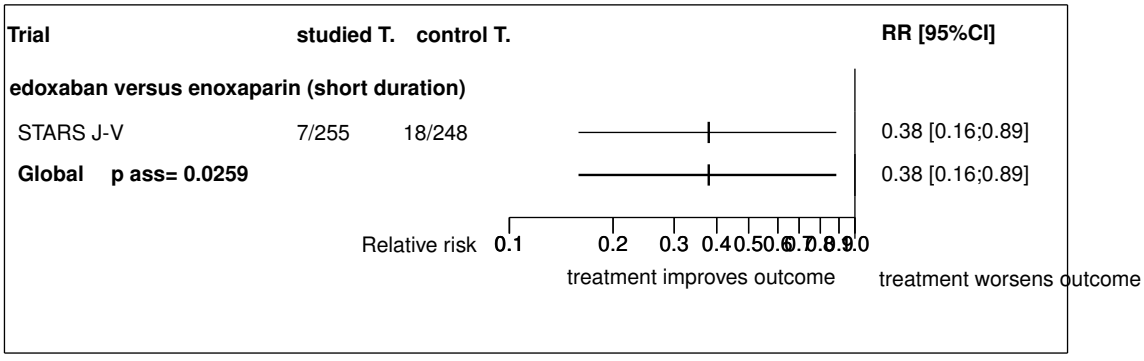


Figure 4.4: *Forest's plot for distal DVT*

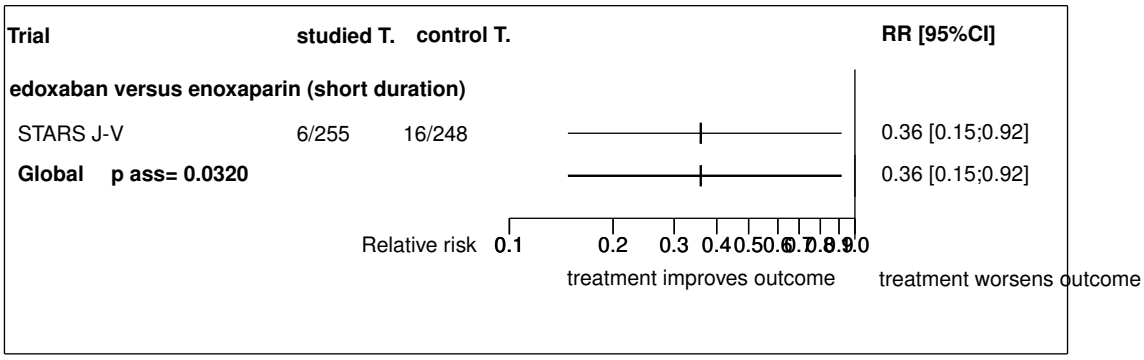
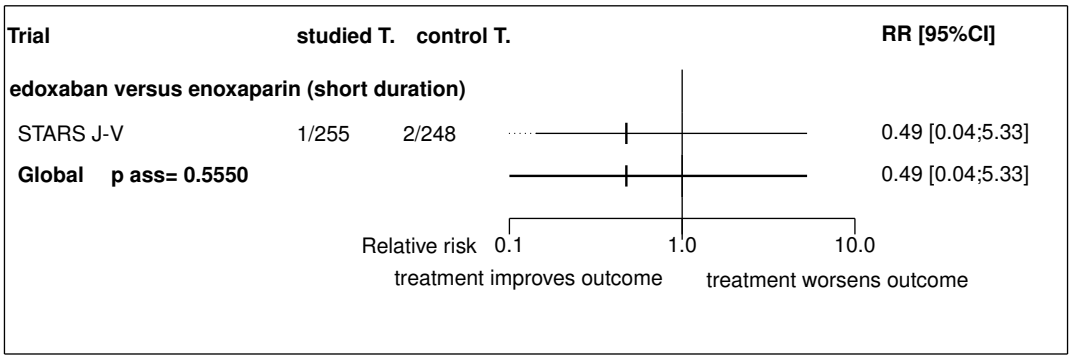


Figure 4.5: *Forest's plot for proximal DVT*



References

4.3 Individual trial summaries

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

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

5 Detailed results for rivaroxaban

5.1 Available trials

A total of 2 RCTs which randomized 4840 patients were identified: it compared rivaroxaban with enoxaparin and it compared rivaroxaban with enoxaparin (short duration).
The average study size was 2420 patients (range 299 to 4541). The first study was published in 2006, 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.
Deep vein thrombosis data was reported in 2 trials; 2 trials reported data on distal DVT; 2 trials reported data on total VTE and all-cause mortality; 2 trials reported data on proximal DVT; 2 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on all cause death; 1 trials reported data on major bleeding; 1 trials reported data on symptomatic venous thromboembolism (DVT, PE); 1 trials reported data on major VTE (fatal and non fatal DVT,PE); and 1 trials reported data on coronary event.
Following tables 5.1 (page 59), 5.2 (page 59), 5.4 (page 61), and 5.3 (page 60) summarized the main characteristics of the trials including in this systematic review of randomized trials of rivaroxaban.

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

Trial	Studied treatment	Control treatment
Rivaroxaban versus enoxaparin		
RECORD 1 (2008) [1]	rivaroxaban 10mg once daily for 35 days started 6 to 8 hours after wound closure	enoxaparin 40mg subcutaneous once daily for 31-39 days initiated 12 hours before surgery and restarted 6 to8 hours after wound closur
Rivaroxaban versus enoxaparin (short duration)		
ODIXa-HIP 10mg (2006) [2, 3] [a]	rivaroxaban 10mg daily for 59 days initiated 6 to 8 hours after surgery	once-daily subcutaneous enoxaparin dose of 40 mg for 59 days started on the evening before surgery and at least 6 to 8 hours after wound closure in accordance with European practice

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

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

Trial	Patients
Rivaroxaban versus enoxaparin	

continued...

Trial	Patients	
RECORD 1 (2008) [1]	Patients undergoing total hip arthroplasty	
	Inclusion criteria: men and women of at least 18 years of age; scheduled to undergo elective total hip arthroplasty	**Exclusion criteria:** staged, bilateral hip arthroplasty; pregnant or breastfeeding; active bleeding or high risk of bleeding;contraindication for prophylaxis with enoxaparin or condition requiring an adjusted dose of enoxaparin; conditions preventing bilateral venography; substantial liver disease; severe renal impairment ; concomitant use of protease inhibitors for the treatment of human immunodeficiency virus infection; planned intermittent pneumatic compression; requirement for anticoagulant therapy that could not be stopped
Rivaroxaban versus enoxaparin (short duration)		
ODIXa-HIP 10mg (2006) [2, 3]	Patients undergoing elective total hip replacement	

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

Trial	Design	Duration	Centre	Primary endpoint
Rivaroxaban versus enoxaparin				
RECORD 1, 2008 [1] n=4541	Parallel groups double blind confirmatory trial at low risk of bias	36 days (range 30-42) inclusion period: Feb 2006 - March 2007	27 countries worldwide multicentre	DVT, PE, death
Rivaroxaban versus enoxaparin (short duration)				
ODIXa-HIP 10mg, 2006 [2, 3] n=299	Parallel groups double blind exploratory trial	5-9 days inclusion period: Nov 2007 - Jul 2007	Europe, Israel 48 centres	any DVT, PE, all cause death

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

Trial	mean follow-up	test intervalle
Rivaroxaban versus enoxaparin		
RECORD 1, 2008 [1]	46 days	2-4 (3)
Rivaroxaban versus enoxaparin (short duration)		
ODIXa-HIP 10mg, 2006 [2, 3]	7 days	2-4 (3)

5.2 Meta-analysis results

The results are detailed in table 5.5 (page 63). This table is followed by the Forest's plot corresponding to each endpoint.

Rivaroxaban versus enoxaparin

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

Rivaroxaban versus enoxaparin (short duration)

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

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
rivaroxaban versus enoxaparin						
major VTE (fatal and non fatal DVT,PE)	RR=0.12	[0.04;0.34]	0.0000	1.0000 (I^2=0.00)	1	3364
deep vein thrombosis	RR=0.23	[0.12;0.43]	0.0000	1.0000 (I^2=0.00)	1	4433
total VTE and all-cause mortality	RR=0.30	[0.18;0.51]	0.0000	1.0000 (I^2=0.00)	1	3153
non-fatal pulmonary embolism	RR=3.91	[0.44;34.92]	0.2226	1.0000 (I^2=0.00)	1	3153
distal DVT	RR=0.49	[0.24;1.00]	0.0512	1.0000 (I^2=0.00)	1	3153
proximal DVT	RR=0.03	[0.00;0.23]	0.0000	1.0000 (I^2=0.00)	1	3153
symptomatic venous thromboembolism (DVT, PE)	RR=0.55	[0.20;1.48]	0.2361	1.0000 (I^2=0.00)	1	4399
coronary event	RR=0.49	[0.12;1.95]	0.3102	1.0000 (I^2=0.00)	1	3153
all cause death	RR=0.98	[0.24;3.90]	0.9735	1.0000 (I^2=0.00)	1	3153
major bleeding	RR=3.02	[0.61;14.95]	0.1755	1.0000 (I^2=0.00)	1	4433
rivaroxaban versus enoxaparin (short duration)						
deep vein thrombosis	RR=0.42	[0.22;0.79]	0.0068	1.0000 (I^2=1.00)	1	220
total VTE and all-cause mortality	RR=0.42	[0.22;0.79]	0.0068	1.0000 (I^2=1.00)	1	220
non-fatal pulmonary embolism	RR=0.95	[0.02;47.30]	0.9782	1.0000 (I^2=0.00)	1	220
distal DVT	RR=0.36	[0.17;0.73]	0.0048	1.0000 (I^2=0.00)	1	220
proximal DVT	RR=0.95	[0.20;4.59]	0.9460	1.0000 (I^2=0.00)	1	220

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

Figure 5.1: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

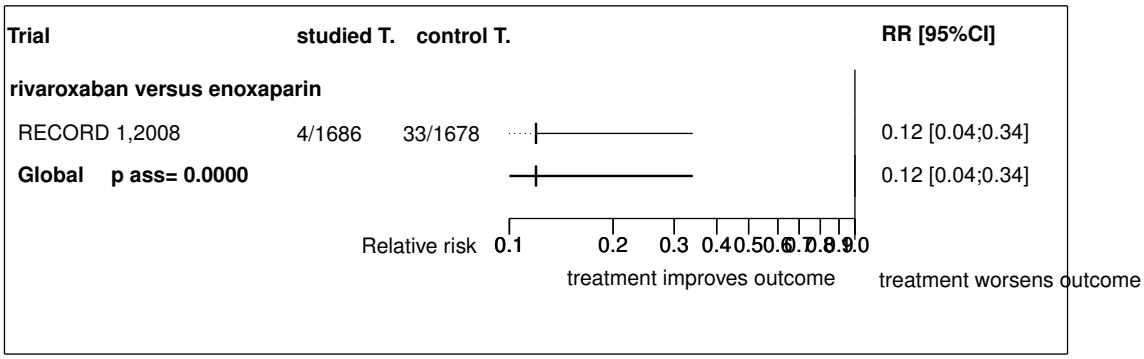


Figure 5.2: *Forest's plot for deep vein thrombosis*

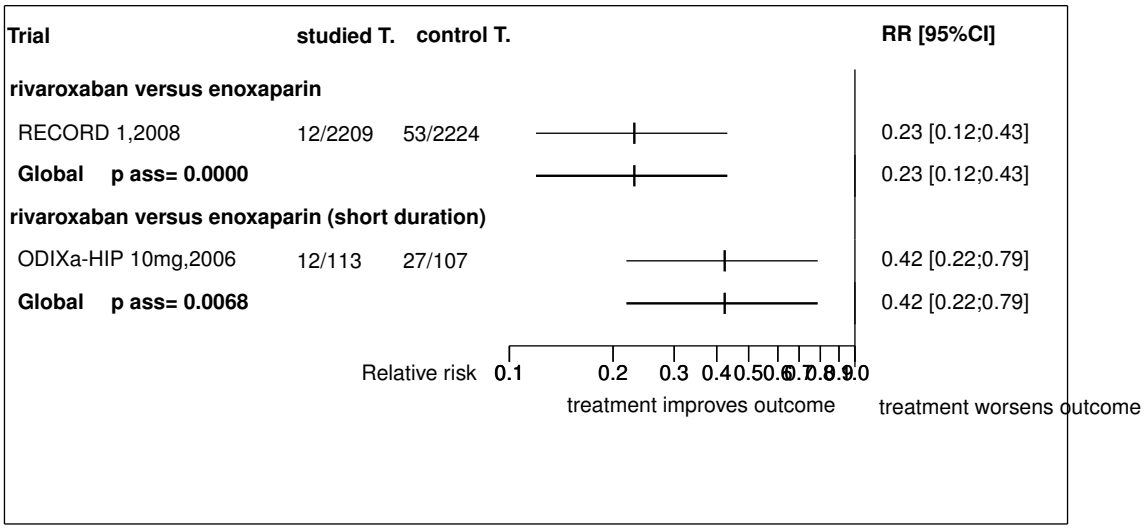


Figure 5.3: *Forest's plot for total VTE and all-cause mortality*

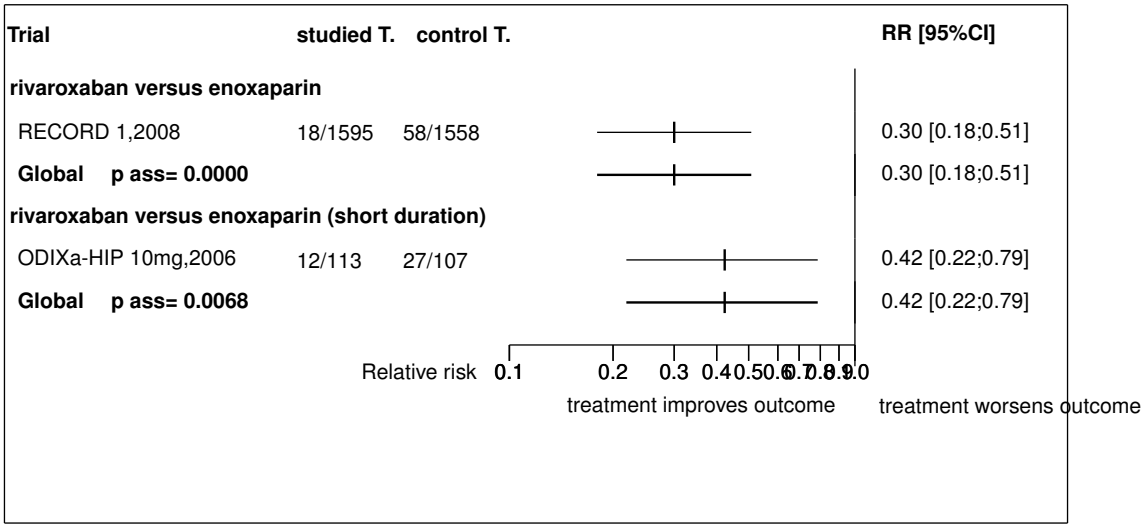


Figure 5.4: *Forest's plot for non-fatal pulmonary embolism*

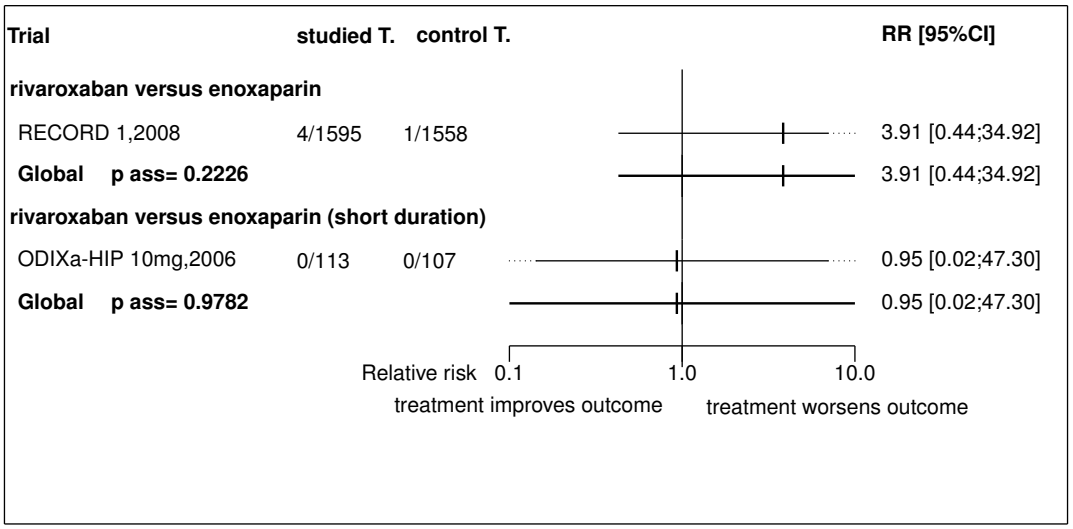


Figure 5.5: *Forest's plot for distal DVT*

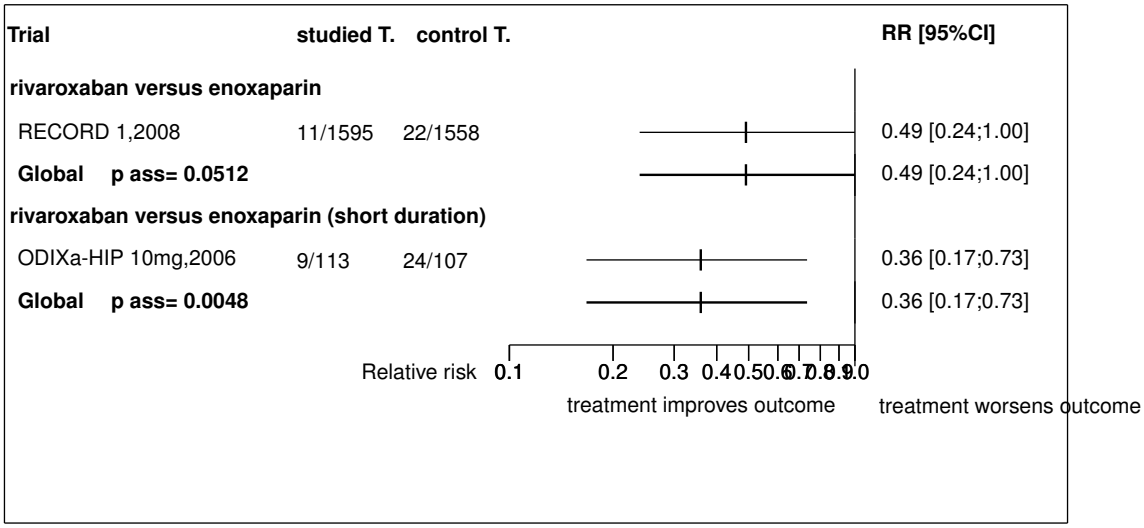


Figure 5.6: *Forest's plot for proximal DVT*

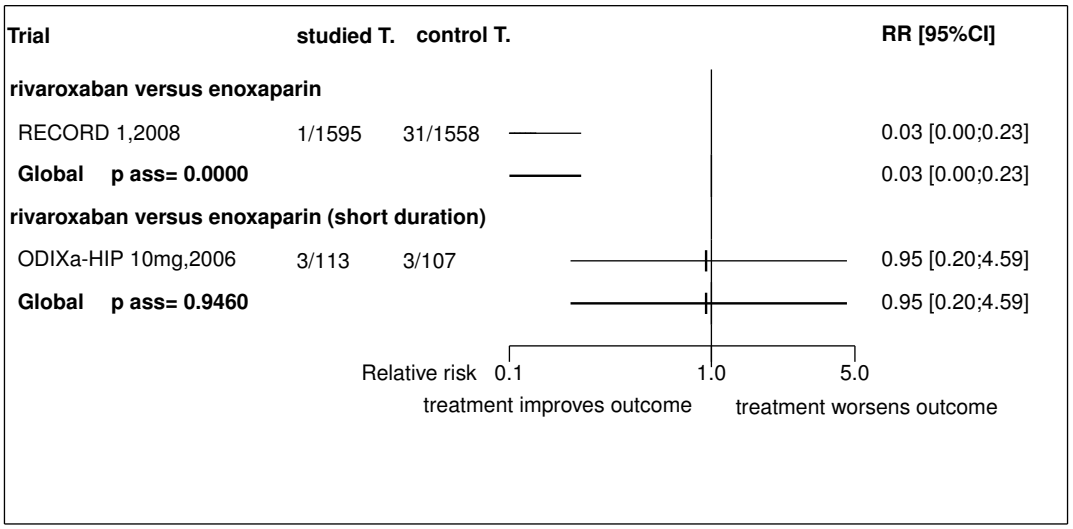


Figure 5.7: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

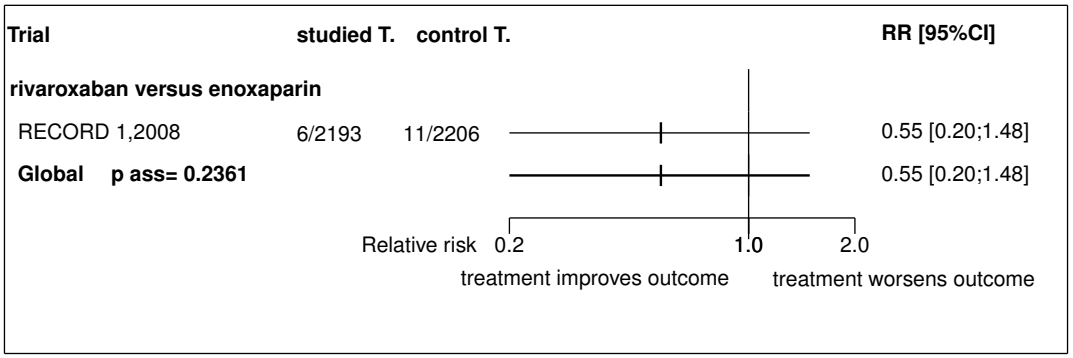


Figure 5.8: *Forest's plot for coronary event*

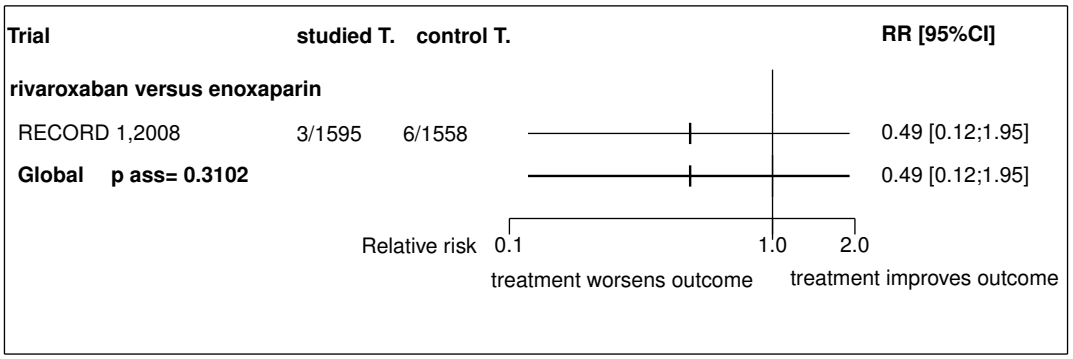


Figure 5.9: *Forest's plot for all cause death*

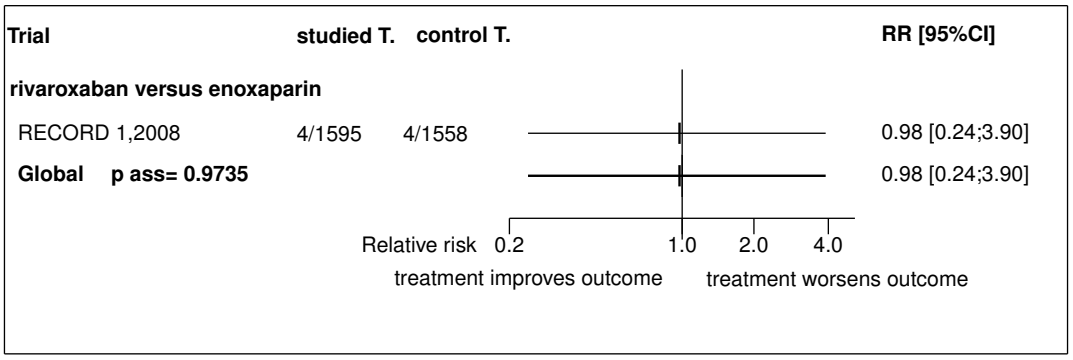
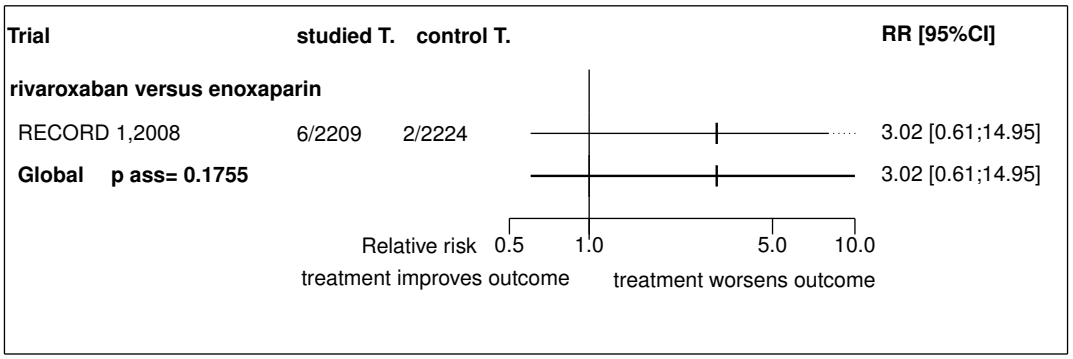


Figure 5.10: *Forest's plot for major bleeding*



References

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

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

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

5.3 Individual trial summaries

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

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

Reference

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

Table 5.7: *ODIXa-HIP 10mg, 2006 - Trial synopsis*

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

References

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

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

6 Detailed results for rivaroxaban (long duration)

6.1 Available trials

Only one trial which randomized 2509 patients was identified: it compared rivaroxaban (long duration) with enoxaparin (short duration).
This trial included 2509 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
All cause death data was reported in 1 trials; 1 trials reported data on deep vein thrombosis; 1 trials reported data on major VTE (fatal and non fatal DVT,PE); 1 trials reported data on distal DVT; 1 trials reported data on total VTE and all-cause mortality; 1 trials reported data on symptomatic venous thromboembolism (DVT, PE); 1 trials reported data on major bleeding; 1 trials reported data on proximal DVT; 1 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on coronary event; and 1 trials reported data on major or clinically relevant non-major bleeding.
Following tables 6.1 (page 71), 6.2 (page 71), 6.4 (page 73), and 6.3 (page 72) summarized the main characteristics of the trial including in this systematic review of randomized trials of rivaroxaban (long duration).

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

Trial	Studied treatment	Control treatment
Rivaroxaban (long duration) versus enoxaparin (short duration)		
RECORD 2 (2008) [1]	extended thromboprophylaxis with rivaroxaban 10mg once daily for 31-39 days started6 to 8 hours after wound closure	enoxaparin 40mg subcutaneous once daily for 10-14 days initiated12 h before surgery and restarted 68 h after woundclosure

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

Trial	Patients	
Rivaroxaban (long duration) versus enoxaparin (short duration)		
RECORD 2 (2008) [1]	Patients undergoing elective total hip replacement	
	Inclusion criteria: male and female patients aged 18 years or above; patients scheduled for elective total hip replacement	**Exclusion criteria:** planned, staged total bilateral hip replacement Active bleeding or high risk of bleeding contraindicating treatment with low molecular weight heparin; Contraindication listed in the labeling or conditions precluding patient treatment with enoxaparin; conditions prohibiting bilateral venography (e.g. amputation of one leg, allergy to contrast media)

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

Trial	Design	Duration	Centre	Primary end-point
Rivaroxaban (long duration) versus enoxaparin (short duration)				
RECORD 2, 2008 [1] n=2509	Parallel groups double blind confirmatory trial at low risk of bias	30-42 days inclusion period: Feb 2006 - Apr 2007	21 countries worldwide 123 centres	DVT, PE , all cause death

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

Trial	mean follow-up	test intervalle
Rivaroxaban (long duration) versus enoxaparin (short duration)		
RECORD 2, 2008 [1]	36 days	2-4 (3)

6.2 Meta-analysis results

The results are detailed in table 6.5 (page 74). This table is followed by the Forest's plot corresponding to each endpoint.

Rivaroxaban (long duration) versus enoxaparin (short duration)

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

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

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

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
symptomatic venous thromboembolism (DVT, PE)	RR=0.20	[0.06;0.69]	0.0106	1.0000 (I^2=1.00)	1	2419
coronary event	RR=1.33	[0.30;5.95]	0.7052	1.0000 (I^2=0.00)	1	2457
major or clinically relevant non-major bleeding	RR=1.20	[0.93;1.54]	0.1582	1.0000 (I^2=1.00)	1	2457
all cause death	RR=0.34	[0.07;1.66]	0.1800	1.0000 (I^2=1.00)	1	1733
major bleeding	RR=1.00	[0.06;15.98]	0.9995	1.0000 (I^2=0.00)	1	2457

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

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

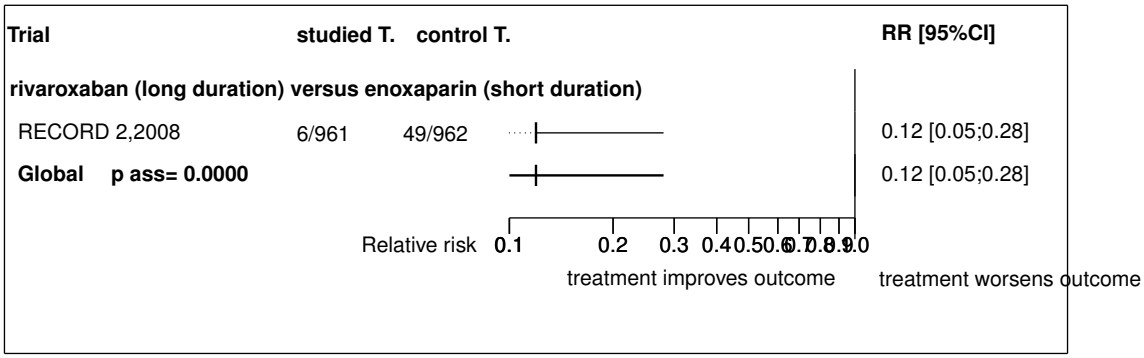


Figure 6.2: *Forest's plot for deep vein thrombosis*

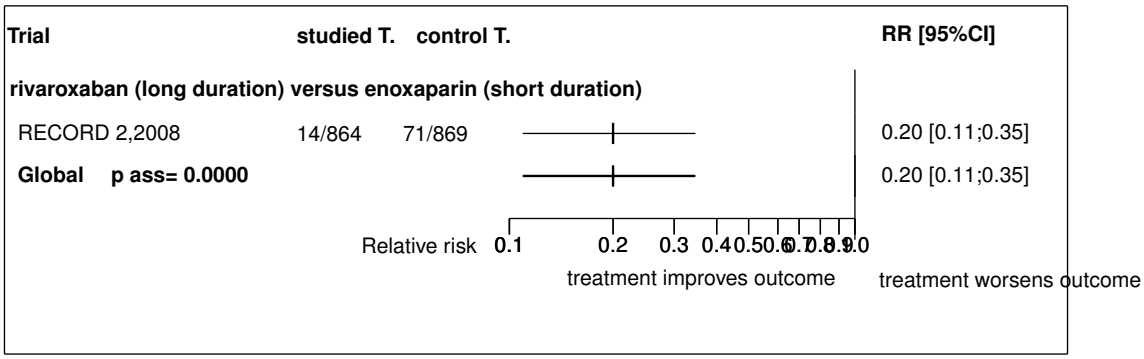


Figure 6.3: *Forest's plot for total VTE and all-cause mortality*

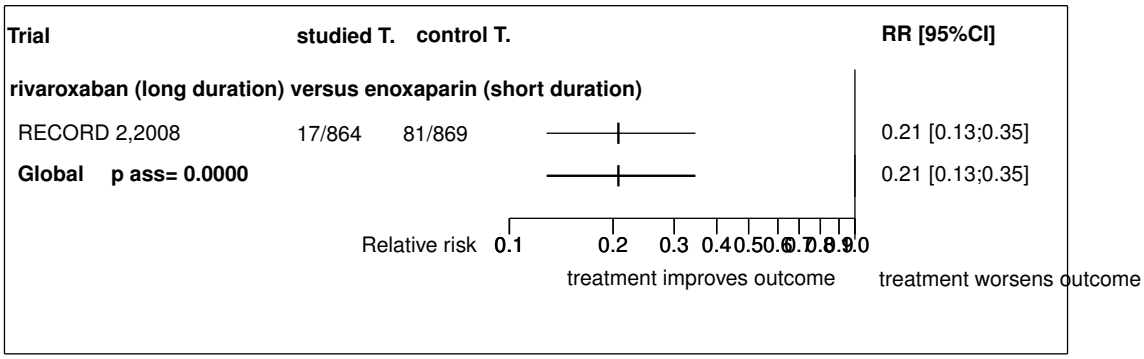


Figure 6.4: *Forest's plot for non-fatal pulmonary embolism*

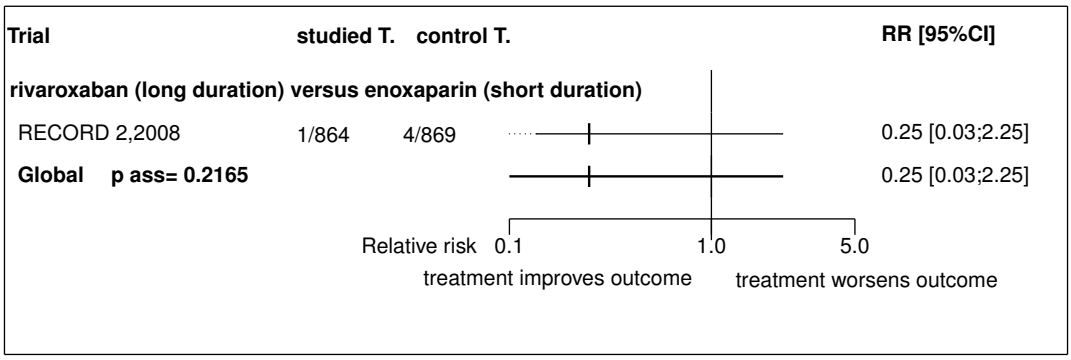


Figure 6.5: *Forest's plot for distal DVT*

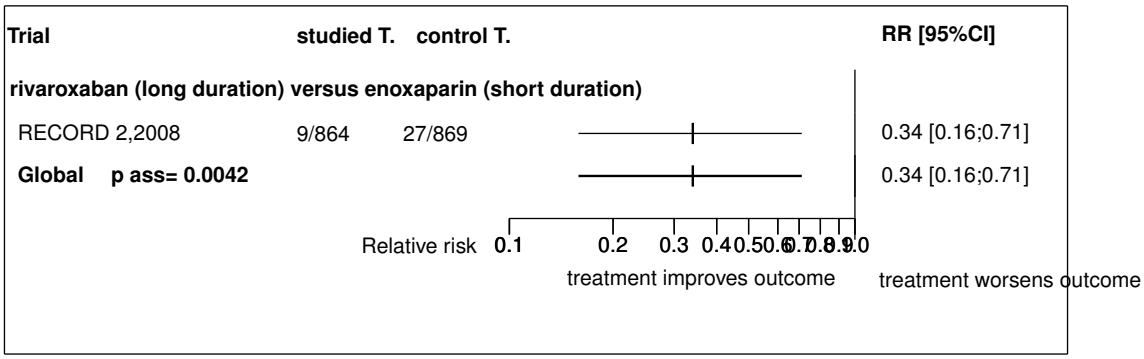


Figure 6.6: *Forest's plot for proximal DVT*

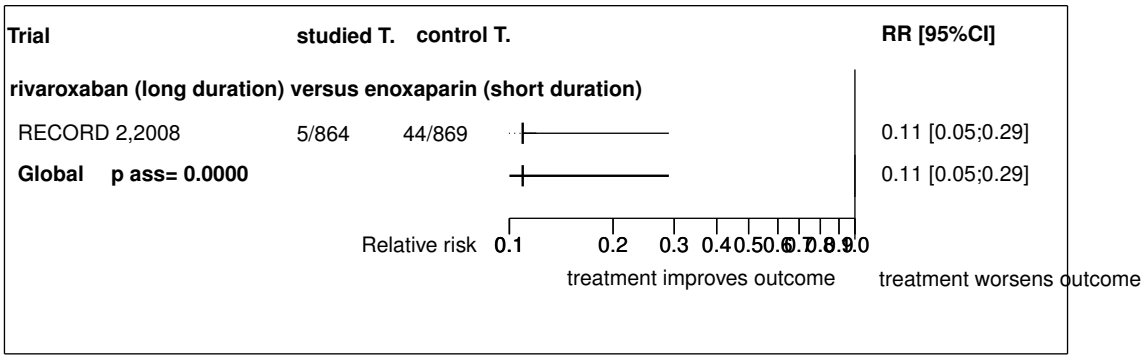


Figure 6.7: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

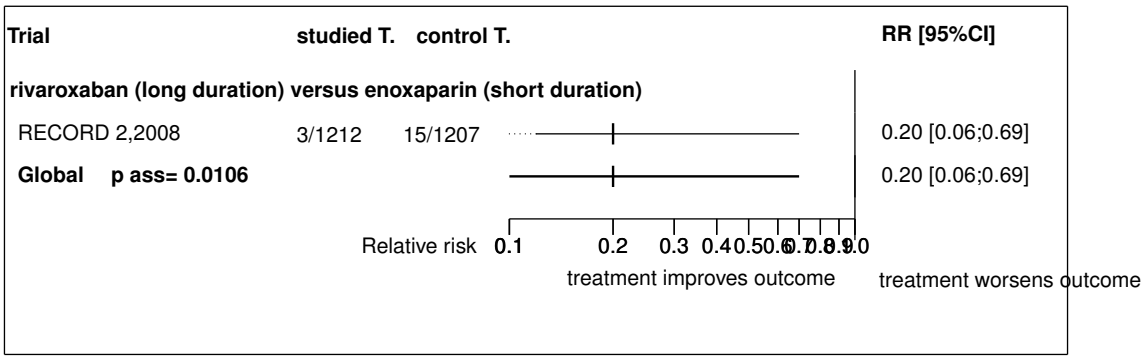


Figure 6.8: *Forest's plot for coronary event*

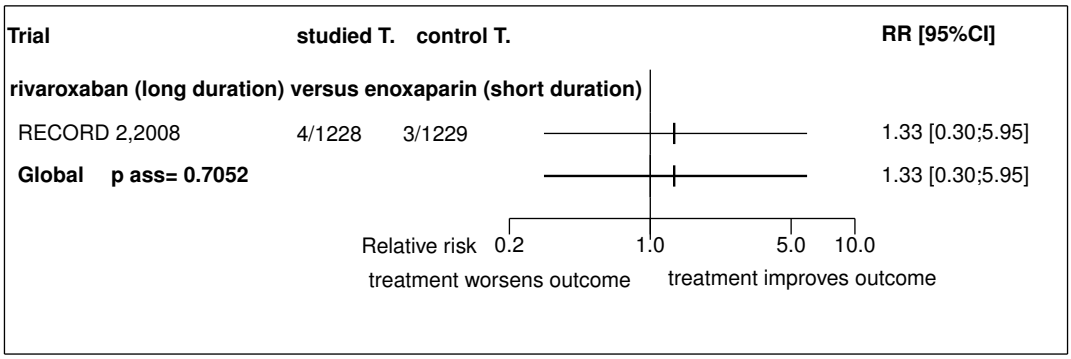


Figure 6.9: *Forest's plot for major or clinically relevant non-major bleeding*

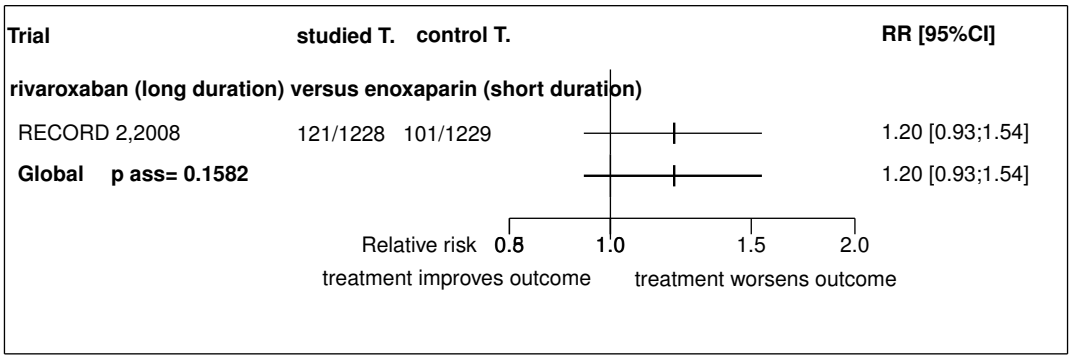


Figure 6.10: *Forest's plot for all cause death*

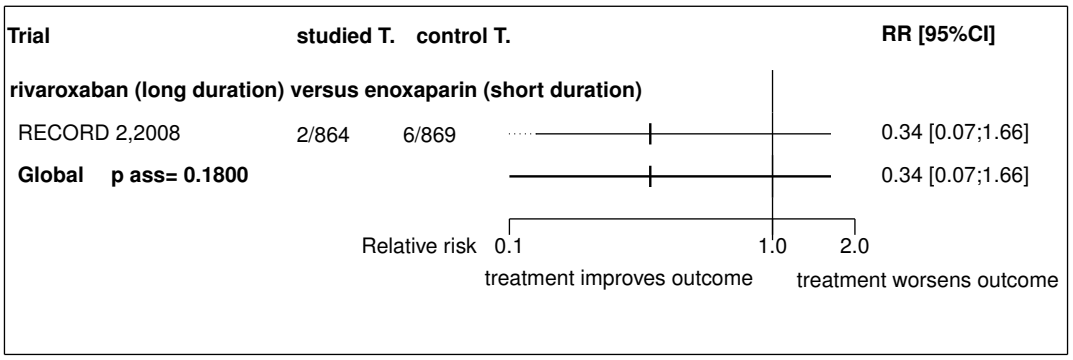
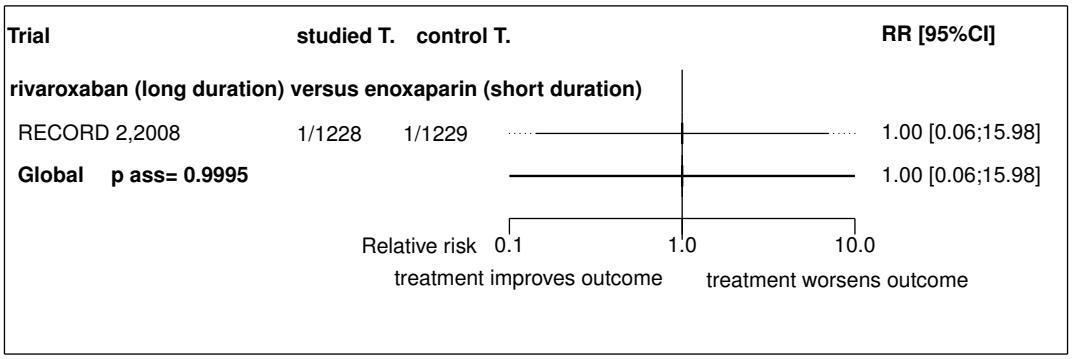


Figure 6.11: *Forest's plot for major bleeding*



References

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

6.3 Individual trial summaries

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

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

Reference

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

7 Global meta-analysis: all direct factor Xa inhibitors

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

Table 7.1: *All direct factor Xa inhibitorsversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=0.20	0.02;1.71	0.1408	1.0000 (0.00)	1	5407
major VTE (fatal and non fatal DVT,PE)	RR=0.23	0.07;0.75	0.0144	0.0642 (0.71)	2	7758
deep vein thrombosis	RR=0.28	0.19;0.41	0.0000	0.4057 (0.00)	2	8288
total VTE and all-cause mortality	RR=0.33	0.24;0.47	0.0000	0.6276 (0.00)	2	7019
asymptomatic DVT	RR=0.33	0.20;0.54	0.0000	1.0000 (0.00)	1	5407
non-fatal pulmonary embolism	RR=1.11	0.12;10.23	0.9289	0.1020 (0.63)	2	8560
distal DVT	RR=0.49	0.24;1.00	0.0512	1.0000 (0.00)	1	3153
proximal DVT	RR=0.12 [1]	0.01;1.29	0.0803	0.0297 (0.79) †	2	7539
symptomatic venous thromboembolism (DVT, PE)	RR=0.48	0.23;1.02	0.0558	0.6816 (0.00)	2	9806
myocardial infarction (fatal and non fatal)	RR=2.24	0.69;7.27	0.1785	1.0000 (0.00)	1	5407
major bleeding	RR=1.40	0.73;2.69	0.3068	0.2985 (0.07)	2	9765

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

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

Table 7.2: *All direct factor Xa inhibitorsversus enoxaparin (short duration)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=0.97	0.02;48.83	0.9889	1.0000 (0.00)	1	503

continued...

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

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

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

8 Ongoing studies of direct factor Xa inhibitors

No ongoing trial was identified.

9 Excluded studies for direct factor Xa inhibitors

No trial was excluded.

References

Part II

Low molecular weight heparin

10 Overview of low molecular weight heparin

10.1 Included trials

A total of 24 randomized comparisons which enrolled 6353 patients were identified. In all, 2 randomized comparisons concerned certoparine + DHE , 9 dalteparin , 7 enoxaparin , two fluxum , two nadroparin , one semuloparin and one tinzaparin.
The detailed descriptions of trials and meta-analysis results is given in section 11 (page 101) for certoparine + DHE, in section 12 (page 110) for dalteparin, in section 13 (page 129) for enoxaparin, in section 14 (page 146) for fluxum, in section 15 (page 155) for nadroparin, in section 16 (page 164) for semuloparin and in section 17 (page 172) for tinzaparin.

The average study size was 264 patients (range 27 to 2326). The first study was published in 1985, and the last study was published in 2012.
A total of 6 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 10.1 (page 89) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

10.2 Summary of meta-analysis results

The meta-analysis of the available trials about low molecular weight heparin provide the results listed in tables 10.2 to 10.8 (page 93) and in the following graphs.

10.2.1 Certoparine + DHE

No significant difference was found between **certoparine + DHE** and **Unfractionated heparin** in terms of deep vein thrombosis (RR=1.05, 95% CI 0.75 to 1.47, p=0.7942, 2 trials)and symptomatic pulmonary embolism (RR=0.68, 95% CI 0.05 to 8.80, p=0.7694, 2 trials).

10.2.2 Dalteparin

Dalteparin was superior to **placebo** in terms of deep vein thrombosis (RR=0.44, 95% CI 0.22 to 0.89, p=0.0221, 1 trial). However, no significant difference was found on symptomatic pulmonary embolism (RR=0.47, 95% CI 0.02 to 13.60, p=0.6570, 1 trial).

Dalteparin was superior to **Dextran** in terms of deep vein thrombosis (RR=0.61, 95% CI 0.44 to 0.83, p=0.0021, 3 trials). However, no significant difference was found on symptomatic pulmonary embolism (RR=2.01, 95% CI 0.43 to 9.49, p=0.3760, 3 trials).

Dalteparin was superior to **Unfractionated heparin** in terms of symptomatic pulmonary embolism (RR=0.48, 95% CI 0.23 to 0.99, p=0.0460, 3 trials). However, no significant difference was found on deep vein thrombosis (RR=0.85, 95% CI 0.58 to 1.23, p=0.3809, 5 trials).

10.2.3 Enoxaparin

No significant difference was found between **enoxaparin** and **no treatment** in terms of deep vein thrombosis (RR=0.67, 95% CI 0.43 to 1.03, p=0.0701, 1 trial).

Enoxaparin was superior to **placebo** in terms of deep vein thrombosis (RR=0.32, 95% CI 0.21 to 0.50, p=0.0000, 3 trials). However, no significant difference was found on symptomatic pulmonary embolism (RR=1.00, 95% CI 0.02 to 49.42, p=1.0000, 1 trial).

Enoxaparin was superior to **Dextran** in terms of deep vein thrombosis (RR=0.31, 95% CI 0.14 to 0.68, p=0.0039, 1 trial). However, no significant difference was found on symptomatic pulmonary embolism (RR=1.05, 95% CI 0.02 to 52.50, p=0.9805, 1 trial).

No significant difference was found between **enoxaparin** and **Unfractionated heparin** in terms of deep vein thrombosis (RR=0.71, 95% CI 0.41 to 1.24, p=0.2309, 2 trials)and symptomatic pulmonary embolism (RR=0.33, 95% CI 0.03 to 3.22, p=0.3389, 2 trials).

10.2.4 Fluxum

No significant difference was found between **fluxum** and **Unfractionated heparin** in terms of deep vein thrombosis (RR=0.70, 95% CI 0.33 to 1.46, p=0.3422, 2 trials)and symptomatic pulmonary embolism (RR=0.66, 95% CI 0.05 to 8.32, p=0.7443, 2 trials).

10.2.5 Nadroparin

Nadroparin was superior to **no treatment** in terms of deep vein thrombosis (RR=0.13, 95% CI 0.02 to 0.96, p=0.0459, 1 trial).

No significant difference was found between **nadroparin** and **Unfractionated heparin** in terms of deep vein thrombosis (RR=0.80, 95% CI 0.47 to 1.35, p=0.3966, 1 trial)and symptomatic pulmonary embolism (RR=0.25, 95% CI 0.03 to 2.25, p=0.2181, 1 trial).

10.2.6 Semuloparin

Semuloparin was superior to **enoxaparin** in terms of deep vein thrombosis (RR=0.57, 95% CI 0.42 to 0.78, p=0.0000, 1 trial)and total VTE and all-cause mortality (RR=0.57, 95% CI 0.42 to 0.77, p=0.0000, 1 trial). However, no significant difference was found on symptomatic pulmonary embolism (RR=1.00, 95% CI 0.02 to 50.45, p=0.9993, 1 trial).
There is a statistically significant difference in favour of semuloparin for major or clinically relevant non-major bleeding (RR=0.48, 95% CI 0.24 to 0.95, p=0.0357, 1 trial)and bleeding (RR=0.29, 95% CI 0.09 to 0.87, p=0.0269, 1 trial).

10.2.7 Tinzaparin

Tinzaparin was superior to **placebo** in terms of deep vein thrombosis (RR=0.68, 95% CI 0.46 to 1.00, p=0.0489, 1 trial).

Table 10.1: *Main study characteristics - Low molecular weight heparin*

Trial	Patients	Treatments	Trial design and method
Certoparine + DHE			
Certoparine + DHE versus Unfractionated heparin			
Haas, 1987 [1] n = 80 vs. 80	elective hip	sandoz +0.5mg DHE **versus** unfractionated heparin	
Lassen, 1988 [2] n = 118 vs. 122	elective hip	certoparin 3000+0.5mg DHE, x1 **versus** placebo	double blind
Dalteparin			
Dalteparin versus placebo			
Torholm, 1991 [1] n = 58 vs. 54	elective hip	dalteparin 5000x1 **versus** placebo	double blind
Dalteparin versus Dextran			
Matzsch, 1991 n = 120 vs. 123	elective hip	dalteparin **versus** dextran	
Eriksson, 1988 [2] n = 50 vs. 50	elective hip	dalteparin **versus** dextran	
Matzsch, 1988 n = 48 vs. 52	elective hip	dalteparin **versus** dextran	
Dalteparin versus Unfractionated heparin			
Binsack, 1986 n = 48 vs. 47	elective hip	dalteparin **versus** unfractionated heparin	

continued...

Trial	Patients	Treatments	Trial design and method
Barre, 1987 n = 40 vs. 40	elective hip	dalteparin **versus** unfractionated heparin	
Dechavanne, 1989 [3] n = 82 vs. 40	elective hip	dalteparin **versus** unfractionated heparin	
Eriksson, 1989 n = 67 vs. 69	elective hip	dalteparin **versus** unfractionated heparin	
Haas, 1985 n = 65 vs. 65	elective hip	dalteparin **versus** unfractionated heparin	
Enoxaparin			
Enoxaparin versus no treatment			
Warwick, 1995 [1] n = 78 vs. 78	elective hip	enoxaparin 4000x1 + elastic stockings **versus** no treatment + elastic stockings	open
Enoxaparin versus placebo			
Kalodiki, 1996 [2] n = 13 vs. 14	elective hip	enoxaparin 4000x1 **versus** placebo	double blind
Samama, 1997 [3] n = 85 vs. 85	elective hip	enoxaparin 4000x1+elastic stockings **versus** placebo+elastic stockings	double blind
Turpie, 1986 [4] n = 50 vs. 50	elective hip	enoxaparin 3000 x2 **versus** placebo	double blind
Enoxaparin versus Dextran			

continued...

Trial	Patients	Treatments	Trial design and method
DES Group, 1991 n = 120 vs. 126	elective hip	enoxaparin **versus** dextran	
Enoxaparin versus Unfractionated heparin			
Levine, 1991 n = 333 vs. 332	elective hip	enoxaparin **versus** unfractionated heparin	
Planes, 1988 [5] n = 124 vs. 113	elective hip	enoxaparin **versus** unfractionated heparin	
Fluxum			
Fluxum versus Unfractionated heparin			
Chiapuzzo, 1988 [1] n = 70 vs. 70	elective hip	fluxum **versus** unfractionated heparin	
Pini, 1989 [2] n = 25 vs. 24	hip	fluxum **versus** unfractionated heparin	
Nadroparin			
Nadroparin versus no treatment			
Yoo, 1997 [1] n = 50 vs. 50	elective hip	nadroparin 41/kgx1 days 1-3, 62/kg x1 days 4-11+elastic stockings **versus** no treatment	open
Nadroparin versus Unfractionated heparin			
Leyvraz, 1991 [2] n = 203 vs. 206	elective hip	fraxiparin **versus** unfractionated heparin	

continued...

Trial	Patients	Treatments	Trial design and method
Semuloparin			
Semuloparin versus enoxaparin			
SAVE-HIP1, 2012 [1] n = 1161 vs. 1165		semuloparin 20 mg once-daily **versus** enoxaparin 40 mg once-daily	
Tinzaparin			
Tinzaparin versus placebo			
Lassen, 1991 [1] n = 105 vs. 105	elective hip	tinzaparin 50/kg x1 +elastic stockings **versus** placebo+elastic stockings	double blind

Table 10.2: *Summary of all results for certoparine + DHE*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
certoparine + DHE versus Unfractionated heparin						
deep vein thrombosis	RR=1.05	0.75;1.47	0.7942	0.8720 (0.00)	2	400
symptomatic pulmonary embolism	RR=0.68	0.05;8.80	0.7694	0.7830 (0.00)	2	400
all cause death	RR=1.02	0.06;16.14	0.9906	0.9906 (0.00)	2	400
bleeding	RR=1.63	0.62;4.31	0.3258	0.2632 (0.20)	2	394

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

Table 10.3: *Summary of all results for dalteparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
dalteparin versus placebo						
deep vein thrombosis	RR=0.44	0.22;0.89	0.0221	1.0000 (1.00)	1	112
symptomatic pulmonary embolism	RR=0.47	0.02;13.60	0.6570	1.0000 (0.00)	1	112
all cause death	RR=1.86	0.06;54.39	0.7180	1.0000 (0.00)	1	112
dalteparin versus Dextran						
deep vein thrombosis	RR=0.61	0.44;0.83	0.0021	0.5335 (0.00)	3	443
symptomatic pulmonary embolism	RR=2.01	0.43;9.49	0.3760	0.3449 (0.06)	3	443
all cause death	RR=1.04	0.11;9.87	0.9758	0.9996 (0.00)	3	443
bleeding	RR=0.47	0.16;1.34	0.1564	0.8286 (0.00)	3	443
dalteparin versus Unfractionated heparin						
deep vein thrombosis	RR=0.85	0.58;1.23	0.3809	0.7540 (0.00)	5	563
symptomatic pulmonary embolism	RR=0.48	0.23;0.99	0.0460	0.6402 (0.00)	3	346
all cause death	RR=0.62	0.07;5.24	0.6593	0.9589 (0.00)	3	338
bleeding	RR=0.90	0.34;2.37	0.8314	0.4461 (0.00)	4	433

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

Table 10.4: *Summary of all results for enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
enoxaparin versus no treatment						
deep vein thrombosis	RR=0.67	0.43;1.03	0.0701	1.0000 (0.00)	1	156
enoxaparin versus placebo						
deep vein thrombosis	RR=0.32	0.21;0.50	0.0000	0.7439 (0.00)	3	280
symptomatic pulmonary embolism	RR=1.00	0.02;49.42	1.0000	1.0000 (0.00)	1	100
all cause death	RR=0.50	0.02;14.57	0.6870	1.0000 (0.00)	1	100
bleeding	RR=0.67	0.11;4.04	0.6635	0.7085 (0.00)	2	270
enoxaparin versus Dextran						
deep vein thrombosis	RR=0.31	0.14;0.68	0.0039	1.0000 (0.00)	1	246
symptomatic pulmonary embolism	RR=1.05	0.02;52.50	0.9805	1.0000 (0.00)	1	246
all cause death	RR=2.10	0.07;62.03	0.6675	1.0000 (0.00)	1	246
enoxaparin versus Unfractionated heparin						
deep vein thrombosis	RR=0.71	0.41;1.24	0.2309	0.0874 (0.66)	2	902
symptomatic pulmonary embolism	RR=0.33	0.03;3.22	0.3389	0.7966 (0.00)	2	902
all cause death	RR=0.95	0.06;15.18	0.9729	0.9746 (0.00)	2	902
bleeding	RR=0.77	0.21;2.83	0.6915	0.2549 (0.23)	2	902

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

Table 10.5: *Summary of all results for fluxum*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
fluxum versus Unfractionated heparin						
deep vein thrombosis	RR=0.70	0.33;1.46	0.3422	0.9571 (0.00)	2	189
symptomatic pulmonary embolism	RR=0.66	0.05;8.32	0.7443	0.7798 (0.00)	2	189
all cause death	RR=0.48	0.02;13.66	0.6675	1.0000 (0.00)	1	49
bleeding	RR=0.98	0.06;15.36	0.9883	0.9884 (0.00)	2	189

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

Table 10.6: *Summary of all results for nadroparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
nadroparin versus no treatment						
deep vein thrombosis	RR=0.13	0.02;0.96	0.0459	1.0000 (0.00)	1	100
nadroparin versus Unfractionated heparin						
deep vein thrombosis	RR=0.80	0.47;1.35	0.3966	1.0000 (0.00)	1	409
symptomatic pulmonary embolism	RR=0.25	0.03;2.25	0.2181	1.0000 (0.00)	1	409
all cause death	RR=0.51	0.05;5.55	0.5784	1.0000 (0.00)	1	409
bleeding	RR=0.34	0.04;3.23	0.3461	1.0000 (0.00)	1	409

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

Table 10.7: *Summary of all results for semuloparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
semuloparin versus enoxaparin						
deep vein thrombosis	RR=0.57	0.42;0.78	0.0000	1.0000 (1.00)	1	1846
symptomatic pulmonary embolism	RR=1.00	0.02;50.45	0.9993	1.0000 (0.00)	1	2302
total VTE and all-cause mortality	RR=0.57	0.42;0.77	0.0000	1.0000 (0.00)	1	1849
major or clinically relevant non-major bleeding	RR=0.48	0.24;0.95	0.0357	1.0000 (1.00)	1	2308
all cause death	RR=0.50	0.05;5.52	0.5722	1.0000 (0.00)	1	2302
bleeding	RR=0.29	0.09;0.87	0.0269	1.0000 (1.00)	1	2308

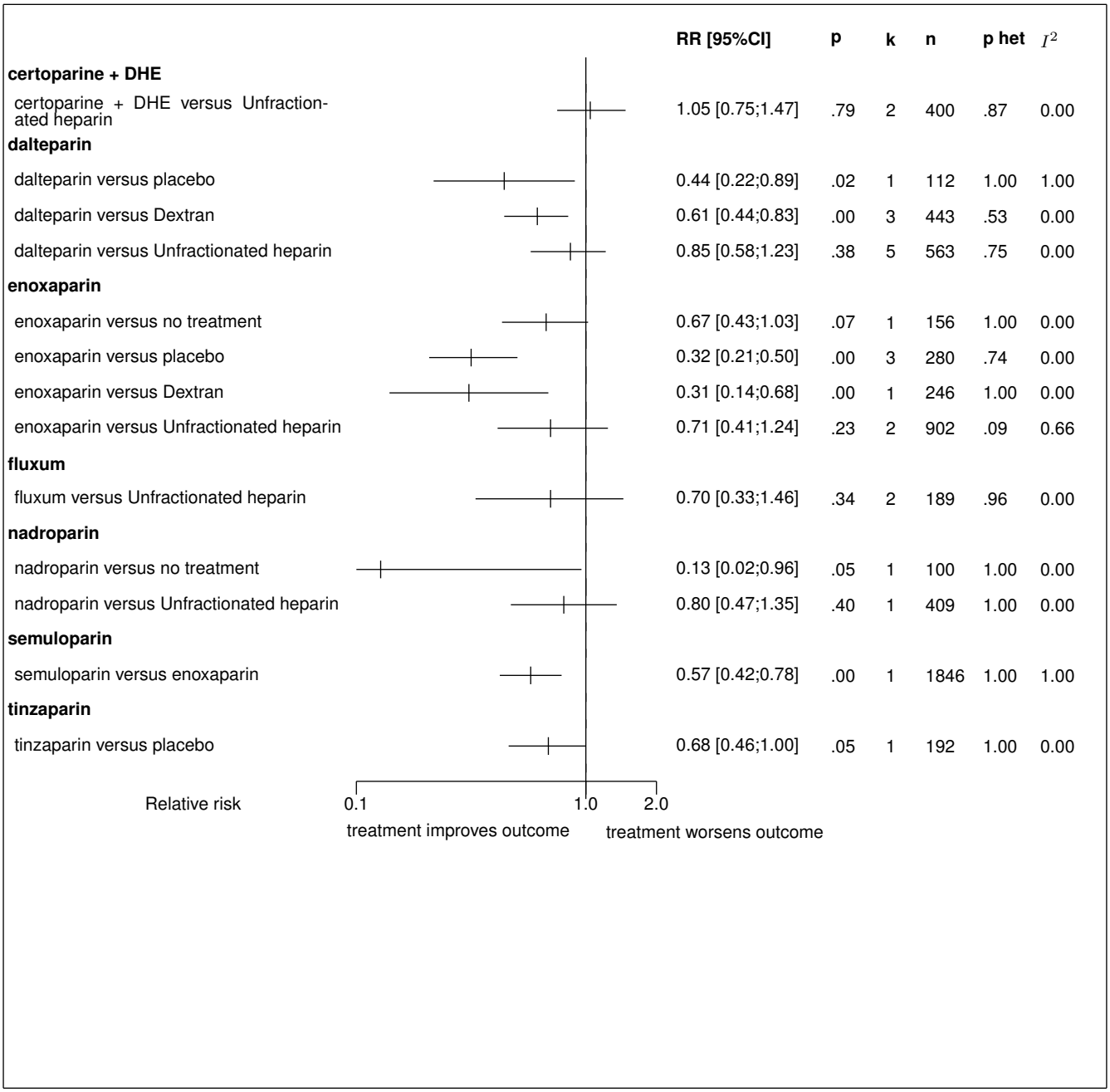
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 10.8: *Summary of all results for tinzaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
tinzaparin versus placebo						
deep vein thrombosis	RR=0.68	0.46;1.00	0.0489	1.0000 (0.00)	1	192
all cause death	RR=1.13	0.07;17.86	0.9291	1.0000 (0.00)	1	192

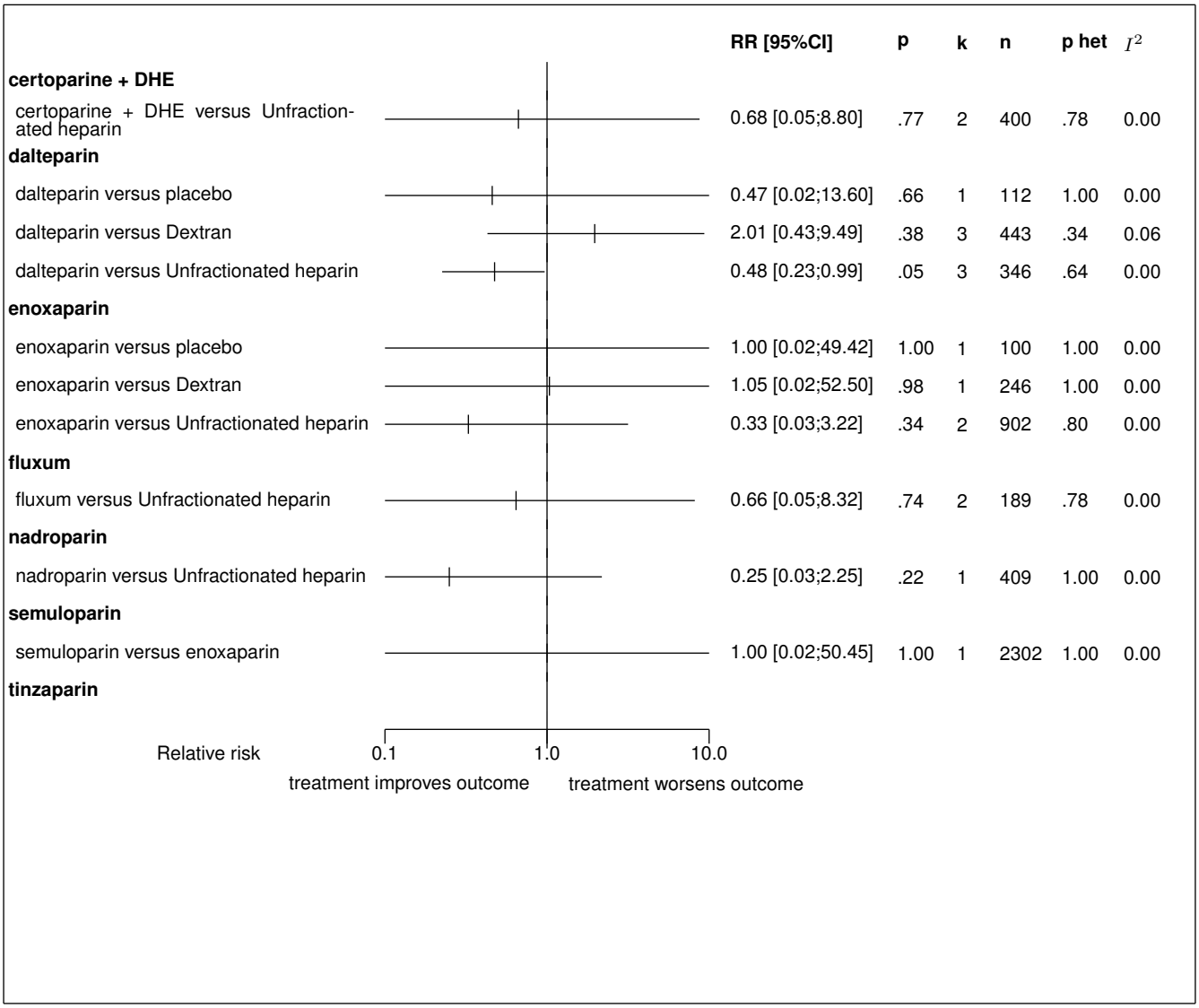
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



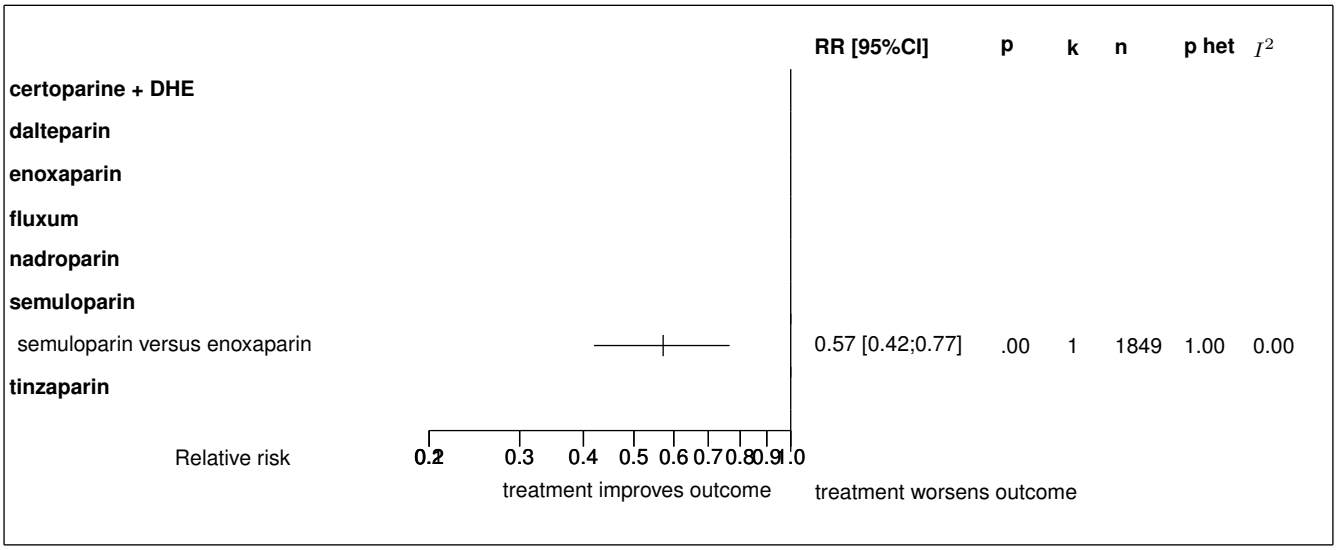
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 10.2: *Forest's plot for symptomatic pulmonary embolism*



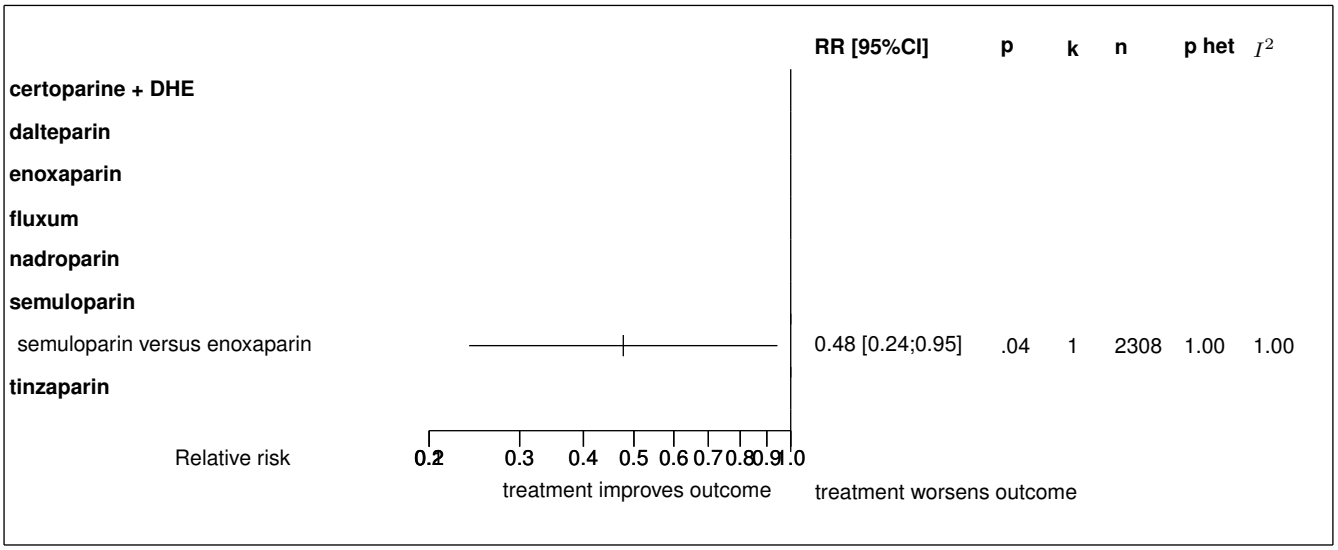
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



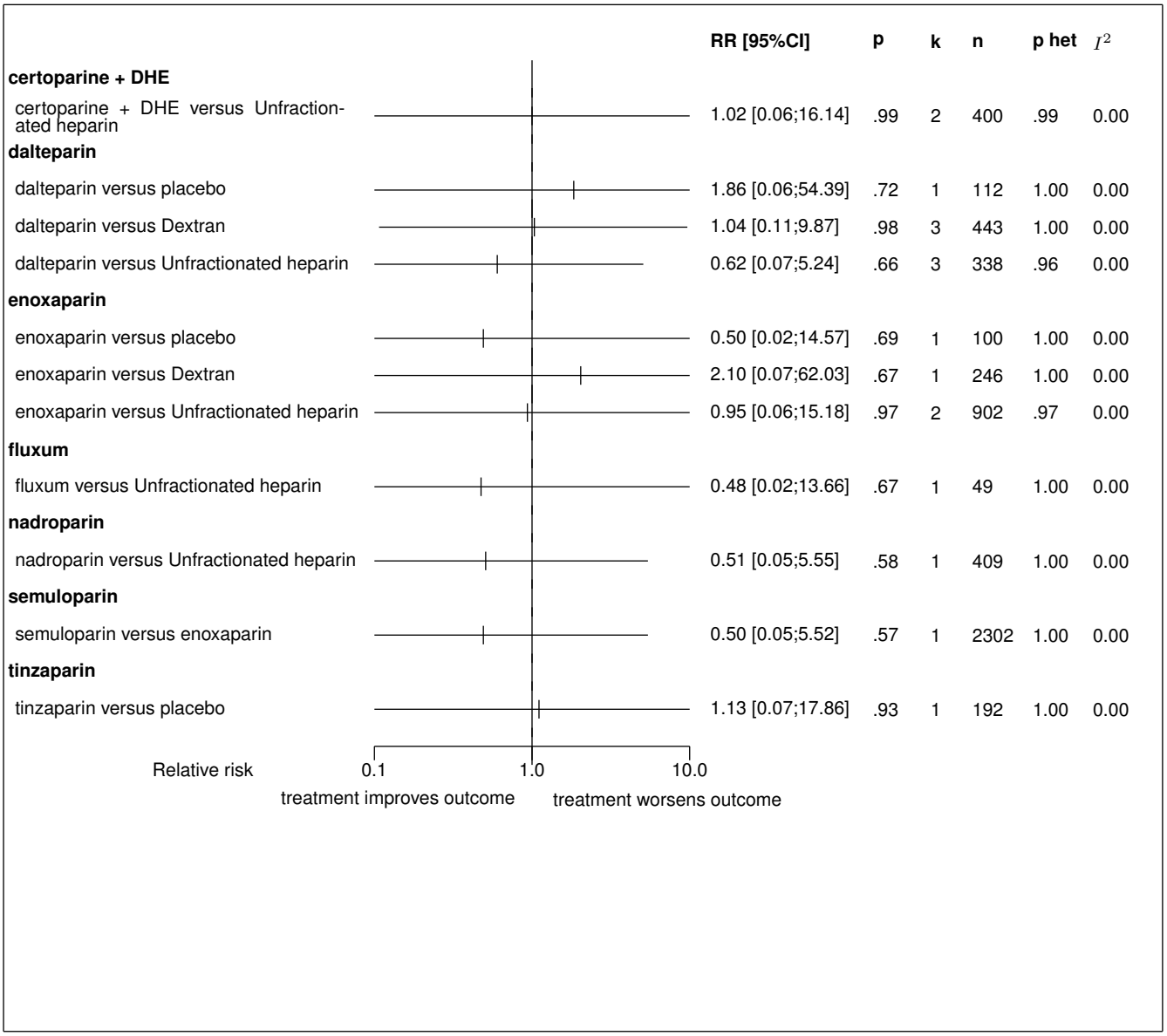
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 10.4: *Forest's plot for major or clinically relevant non-major bleeding*



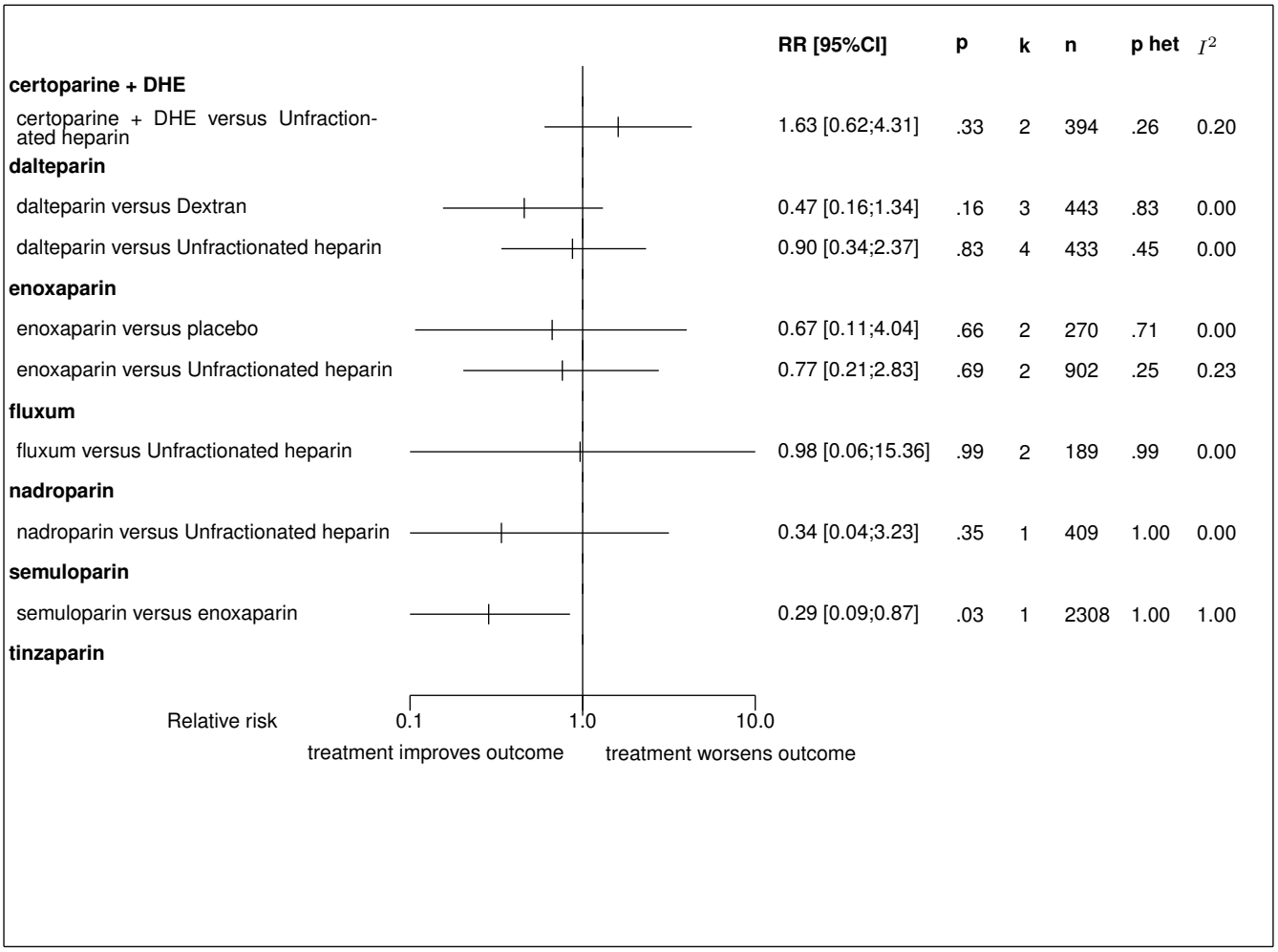
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 10.5: *Forest's plot for all cause death*



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

Figure 10.6: *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

11 Detailed results for certoparine + DHE

11.1 Available trials

A total of 2 RCTs which randomized 400 patients were identified: all compared certoparine + DHE with Unfractionated heparin.
The average study size was 200 patients (range 160 to 240). The first study was published in 1987, and the last study was published in 1988.
This trial was double blind in design.
All included studies were reported in English language. We did not found any unpublished trial.
Symptomatic pulmonary embolism data was reported in 2 trials; 2 trials reported data on deep vein thrombosis; 1 trials reported data on asymptomatic proximal DVT; 2 trials reported data on bleeding; and 2 trials reported data on all cause death.
Following tables 11.1 (page 101), 11.2 (page 101), 11.4 (page 103), and 11.3 (page 102) summarized the main characteristics of the trials including in this systematic review of randomized trials of certoparine + DHE.

Table 11.1: *Treatment description - Low molecular weight heparin - certoparine + DHE*

Trial	Studied treatment	Control treatment
Certoparine + DHE versus Unfractionated heparin		
Haas (1987) [1]	Sandoz +0.5mg DHE 1x6280; 2h before; >=7 days	Unfractionated heparin 2 x 5000; 2h before; >=7 days
Lassen (1988) [2]	certoparin 3000+0.5mg DHE, x1 1 x6000;2h before; 7 days	Placebo 2 x 5000; 2h before; 7 days

Table 11.2: *Descriptions of participants - Low molecular weight heparin - certoparine + DHE*

Trial	Patients
Certoparine + DHE versus Unfractionated heparin	
Haas (1987) [1]	Elective hip
Lassen (1988) [2]	Elective hip

Table 11.3: *Design and methodological quality of trials - Low molecular weight heparin - certoparine + DHE*

Trial	Design	Duration	Centre	Primary endpoint
Certoparine + DHE versus Unfractionated heparin				
Haas, 1987 [1] n=160				
Lassen, 1988 [2] n=240	double blind	6 days		

Table 11.4: *Trial characteristics - Low molecular weight heparin - certoparine + DHE*

Trial
Certoparine + DHE versus Unfractionated heparin
Haas, 1987 [1]
Lassen, 1988 [2]

11.2 Meta-analysis results

The results are detailed in table 11.5 (page 104). This table is followed by the Forest's plot corresponding to each endpoint.

Certoparine + DHE versus Unfractionated heparin

All the 2 studies had extractable data about the number of participants with **deep vein thrombosis**. When pooled together, there was no statistically significant difference between the groups in deep vein thrombosis, with a RR of 1.05 (95% CI 0.75 to 1.47, p=0.7942). No heterogeneity was detected (p = 0.8720, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **symptomatic pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in symptomatic pulmonary embolism, with a RR of 0.68 (95% CI 0.05 to 8.80, p=0.7694). No heterogeneity was detected (p = 0.7830, I^2 = 0.00%).

Table 11.5: *Results details - Low molecular weight heparin - certoparine + DHE*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
certoparine + DHE versus Unfractionated heparin						
deep vein thrombosis	RR=1.05	[0.75;1.47]	0.7942	0.8720 (I^2=0.00)	2	400
symptomatic pulmonary embolism	RR=0.68	[0.05;8.80]	0.7694	0.7830 (I^2=0.00)	2	400
all cause death	RR=1.02	[0.06;16.14]	0.9906	0.9906 (I^2=0.00)	2	400
bleeding	RR=1.63	[0.62;4.31]	0.3258	0.2632 (I^2=0.20)	2	394

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

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

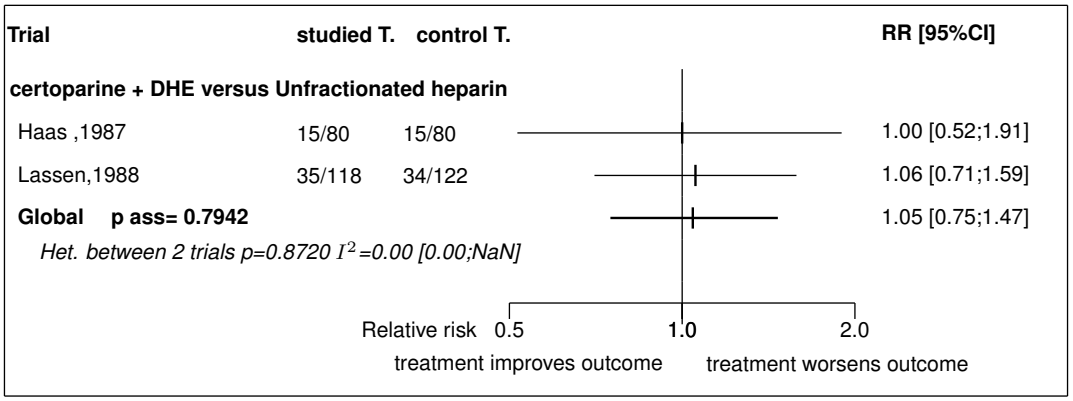


Figure 11.2: *Forest's plot for symptomatic pulmonary embolism*

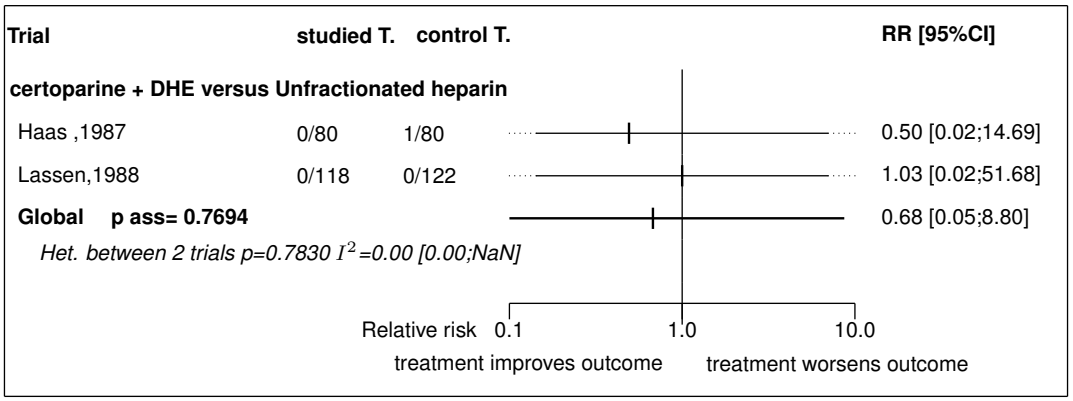


Figure 11.3: *Forest's plot for all cause death*

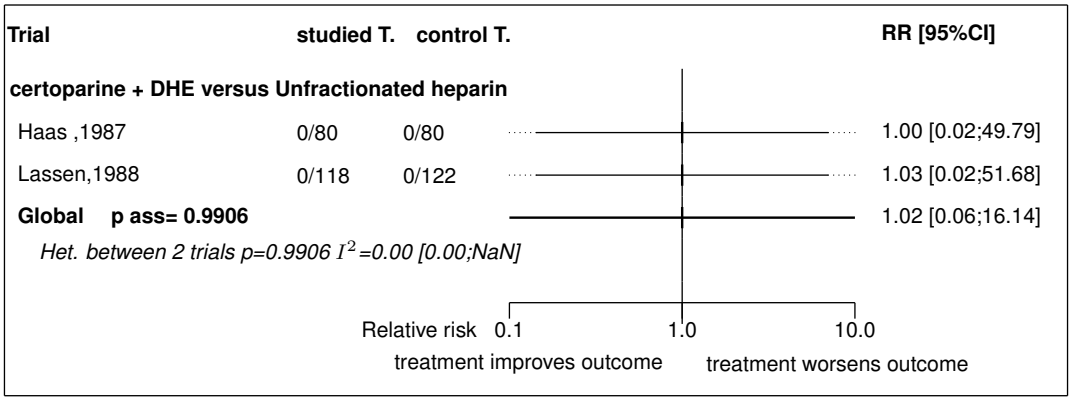
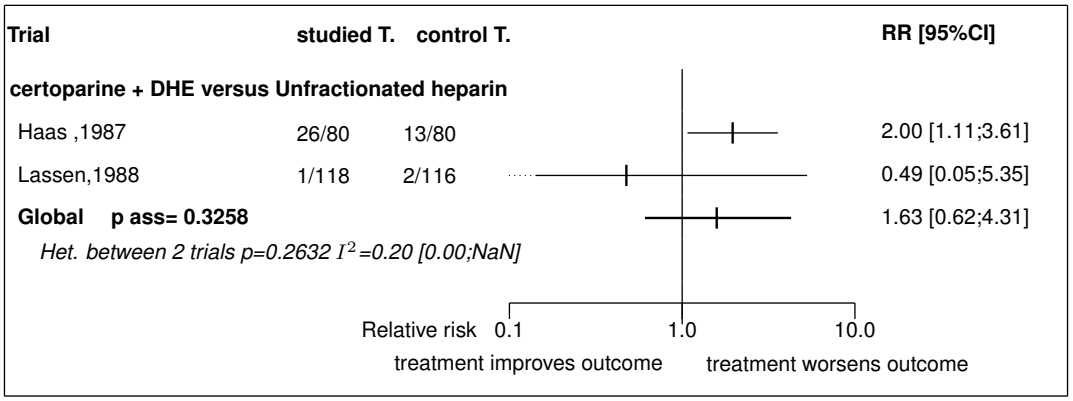


Figure 11.4: *Forest's plot for bleeding*



References

[1] Haas S, Stemberger A, Fritsche HM, Welzel D, Wolf H, Lechner F, Blumel G. Prophylaxis of deep vein thrombosis in high risk patients undergoing total hip replacement with low molecular weight heparin plus dihydroergotamine. Arzneimittelforschung 1987 Jul;37:839-43. [PMID=2823840]

[2] Lassen MR, Borris LC, Christiansen HM, Moller-Larsen F, Knudsen VE, Boris P, Nehen AM, de Carvalho A, Jurik AG, Nielsen BW. Heparin/dihydroergotamine for venous thrombosis prophylaxis: comparison of low-dose heparin and low molecular weight heparin in hip surgery. Br J Surg 1988 Jul;75:686-9. [PMID=2843255]

11.3 Individual trial summaries

Table 11.6: *Haas, 1987 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=160 (80 vs. 80) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** Sandoz +0.5mg DHE 1x6280; 2h before; >=7 days **Control treatment:** Unfractionated heparin 2 x 5000; 2h before; >=7 days	Deep vein thrombosis RR=1.00 [0.52;1.91]

Reference

Haas S, Stemberger A, Fritsche HM, Welzel D, Wolf H, Lechner F, Blumel G. Prophylaxis of deep vein thrombosis in high risk patients undergoing total hip replacement with low molecular weight heparin plus dihydroergotamine. Arzneimittelforschung 1987 Jul;37:839-43 [PMID=2823840]

Table 11.7: *Lassen, 1988 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=240 (118 vs. 122) **Follow-up duration:** 6 days **Study design:** Randomized controlled trial Double blind	Elective hip	**Studied treatment:** certoparin 3000+0.5mg DHE, x1 1 x6000;2h before; 7 days **Control treatment:** Placebo 2 x 5000; 2h before; 7 days	Deep vein thrombosis RR=1.06 [0.71;1.59]

Reference

Lassen MR, Borris LC, Christiansen HM, Moller-Larsen F, Knudsen VE, Boris P, Nehen AM, de Carvalho A, Jurik AG, Nielsen BW. Heparin/dihydroergotamine for venous thrombosis prophylaxis: comparison of low-dose heparin and low molecular weight heparin in hip surgery. Br J Surg 1988 Jul;75:686-9 [PMID=2843255]

12 Detailed results for dalteparin

12.1 Available trials

A total of 9 RCTs which randomized 1118 patients were identified: it compared dalteparin with placebo , 3 trials compared dalteparin with Dextran and 5 trials compared dalteparin with Unfractionated heparin.
The average study size was 124 patients (range 80 to 243). The first study was published in 1985, and the last study was published in 1991.
This trial was double blind in design.
All included studies were reported in English language. We did not found any unpublished trial.
Deep vein thrombosis data was reported in 9 trials; 7 trials reported data on symptomatic pulmonary embolism; 1 trials reported data on asymptomatic proximal DVT; 7 trials reported data on bleeding; and 7 trials reported data on all cause death.
Following tables 12.1 (page 110), 12.2 (page 111), 12.4 (page 113), and 12.3 (page 111) summarized the main characteristics of the trials including in this systematic review of randomized trials of dalteparin.

Table 12.1: *Treatment description - Low molecular weight heparin - dalteparin*

Trial	Studied treatment	Control treatment
Dalteparin versus placebo		
Torholm (1991) [1]	dalteparin 5000x1 2x2500; 2h before to 12h after; 1x5000; 6 days	Placebo Placebo
Dalteparin versus Dextran		
Matzsch (1991)	dalteparin 1 x 50 kg; 2h before; 7 days	Dextran Dextran 70 500 ml before and after surgery and on days 1,3, and 5
Eriksson (1988) [2]	dalteparin 2 x 2500; 2h before; 7 days	Dextran Dextran 70 2 x 500 ml day 0, 1x500 ml days land 3
Matzsch (1988)	dalteparin 1 x 35 kg; 2h before; 7 days	Dextran Dextran 70 500 ml before and after surgery and on days 1, 3, and 5
Dalteparin versus Unfractionated heparin		
Binsack (1986)	dalteparin 2 x 2500 day 0, 1 x 500 ND; 2h before	Unfractionated heparin 3 x 5000; 2h before; ND
Barre (1987)	dalteparin 2x2500; 2h before; 10 days	Unfractionated heparin 3x5000U; day 0, NDdaysl-10;
Dechavanne (1989) [3]	dalteparin 2x2500 for 10-13 days, or 2x2500days 1-2, 1 x 5000 days 3-13; 2h before	Unfractionated heparin 2h before 2 x 5000; days 1-2, ND days 3-13;2h before
Eriksson (1989)	dalteparin 1x5000; 12h before; 10 days	Unfractionated heparin lx 5000; 2h before; 10 days

continued...

Trial	Studied treatment	Control treatment
Haas (1985)	dalteparin 2 x 2500 day 0,1x5000 days 1-15;2h before	Unfractionated heparin 2x5000+ DHE; 2h before; 15 days

Table 12.2: *Descriptions of participants - Low molecular weight heparin - dalteparin*

Trial	Patients
Dalteparin versus placebo	
Torholm (1991) [1]	Elective hip
Dalteparin versus Dextran	
Matzsch (1991)	Elective hip
Eriksson (1988) [2]	Elective hip
Matzsch (1988)	Elective hip
Dalteparin versus Unfractionated heparin	
Binsack (1986)	Elective hip
Barre (1987)	Elective hip
Dechavanne (1989) [3]	Elective hip
Eriksson (1989)	Elective hip
Haas (1985)	Elective hip

Table 12.3: *Design and methodological quality of trials - Low molecular weight heparin - dalteparin*

Trial	Design	Duration	Centre	Primary endpoint
Dalteparin versus placebo				
Torholm, 1991 [1] n=112	double blind	9 days		
Dalteparin versus Dextran				
Matzsch, 1991 n=243				

continued...

Trial	Design	Duration	Centre	Primary end-point
Eriksson, 1988 [2] n=100				
Matzsch, 1988 n=100				
Dalteparin versus Unfractionated heparin				
Binsack, 1986 n=95				
Barre, 1987 n=80				
Dechavanne, 1989 [3] n=122				
Eriksson, 1989 n=136				
Haas, 1985 n=130				

Table 12.4: *Trial characteristics - Low molecular weight heparin - dalteparin*

Trial
Dalteparin versus placebo
Torholm, 1991 [1]
Dalteparin versus Dextran
Matzsch, 1991
Eriksson, 1988 [2]
Matzsch, 1988
Dalteparin versus Unfractionated heparin
Binsack, 1986
Barre, 1987
Dechavanne, 1989 [3]
Eriksson, 1989
Haas, 1985

12.2 Meta-analysis results

The results are detailed in table 12.5 (page 114). This table is followed by the Forest's plot corresponding to each endpoint.

Dalteparin 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 dalteparin in deep vein thrombosis, with a RR of 0.44 (95% CI 0.22 to 0.89, p=0.0221).
The single study 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 0.47 (95% CI 0.02 to 13.60, p=0.6570).

Dalteparin versus Dextran

All the 3 studies had extractable data about the number of participants with **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of dalteparin in deep vein thrombosis, with a RR of 0.61 (95% CI 0.44 to 0.83, p=0.0021). No heterogeneity was detected (p = 0.5335, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **symptomatic pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in symptomatic pulmonary embolism, with a RR of 2.01 (95% CI 0.43 to 9.49, p=0.3760). No heterogeneity was detected (p = 0.3449, I^2 = 0.06%).

Dalteparin versus Unfractionated heparin

All the 5 studies had extractable data about the number of participants with **deep vein thrombosis**. When pooled together, there was no statistically significant difference between the groups in deep vein thrombosis, with a RR of 0.85 (95% CI 0.58 to 1.23, p=0.3809). No heterogeneity was detected (p = 0.7540, I^2 = 0.00%).
A total of 3 of the 5 studies eligible for this comparison provided data on **symptomatic pulmonary embolism**. The analysis detected a statistically significant difference in favor of dalteparin in symptomatic pulmonary embolism, with a RR of 0.48 (95% CI 0.23 to 0.99, p=0.0460). No heterogeneity was detected (p = 0.6402, I^2 = 0.00%).

Table 12.5: *Results details - Low molecular weight heparin - dalteparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dalteparin versus placebo						
deep vein thrombosis	RR=0.44	[0.22;0.89]	0.0221	1.0000 (I^2=1.00)	1	112
symptomatic pulmonary embolism	RR=0.47	[0.02;13.60]	0.6570	1.0000 (I^2=0.00)	1	112
all cause death	RR=1.86	[0.06;54.39]	0.7180	1.0000 (I^2=0.00)	1	112
dalteparin versus Dextran						
deep vein thrombosis	RR=0.61	[0.44;0.83]	0.0021	0.5335 (I^2=0.00)	3	443
symptomatic pulmonary embolism	RR=2.01	[0.43;9.49]	0.3760	0.3449 (I^2=0.06)	3	443

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
all cause death	RR=1.04	[0.11;9.87]	0.9758	0.9996 (I^2=0.00)	3	443
bleeding	RR=0.47	[0.16;1.34]	0.1564	0.8286 (I^2=0.00)	3	443
dalteparin versus Unfractionated heparin						
deep vein thrombosis	RR=0.85	[0.58;1.23]	0.3809	0.7540 (I^2=0.00)	5	563
symptomatic pulmonary embolism	RR=0.48	[0.23;0.99]	0.0460	0.6402 (I^2=0.00)	3	346
all cause death	RR=0.62	[0.07;5.24]	0.6593	0.9589 (I^2=0.00)	3	338
bleeding	RR=0.90	[0.34;2.37]	0.8314	0.4461 (I^2=0.00)	4	433

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

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

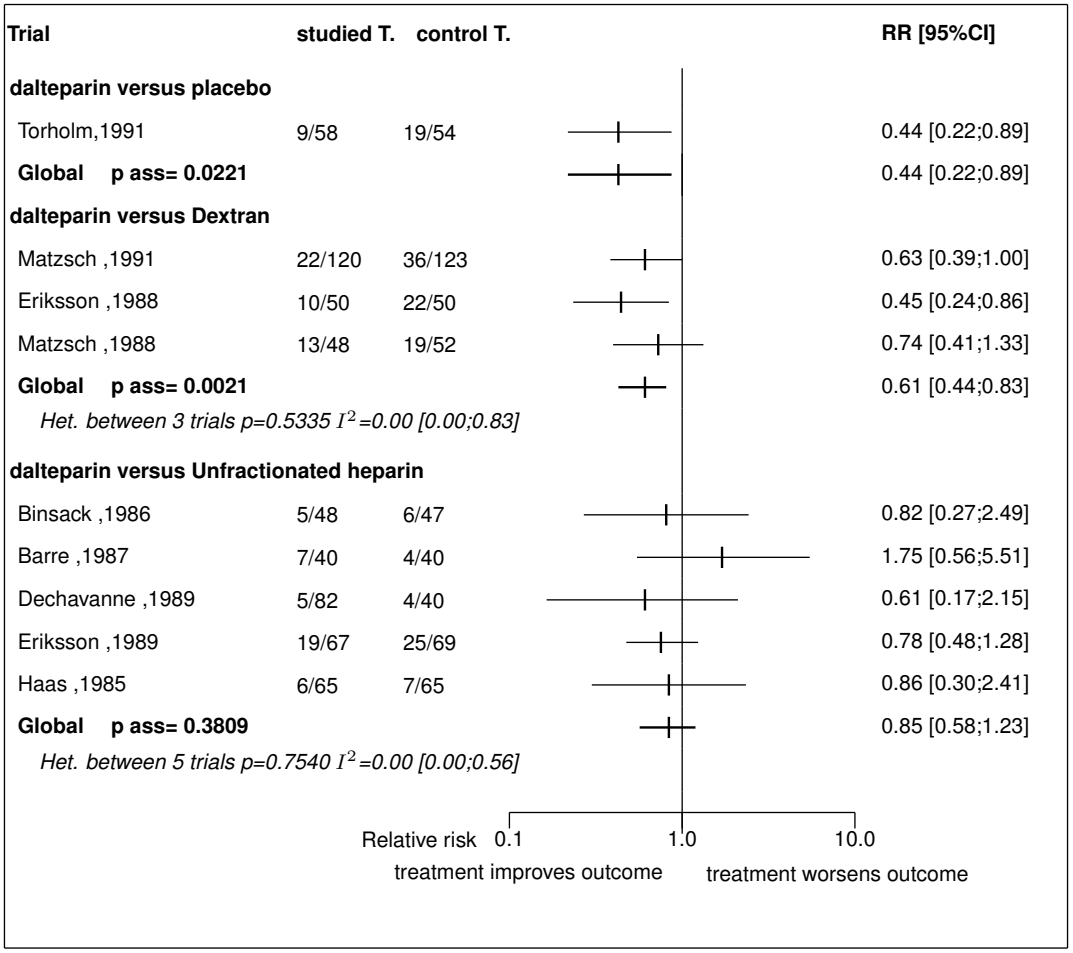


Figure 12.2: *Forest's plot for symptomatic pulmonary embolism*

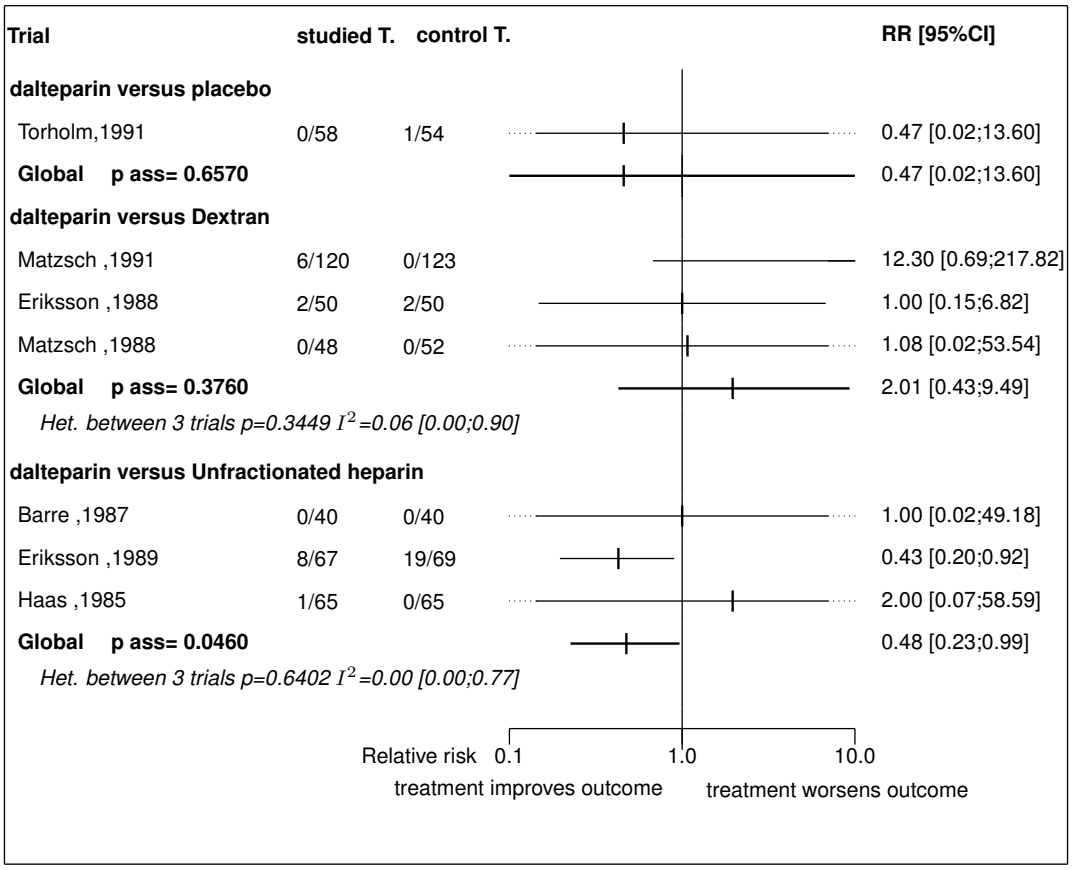


Figure 12.3: *Forest's plot for all cause death*

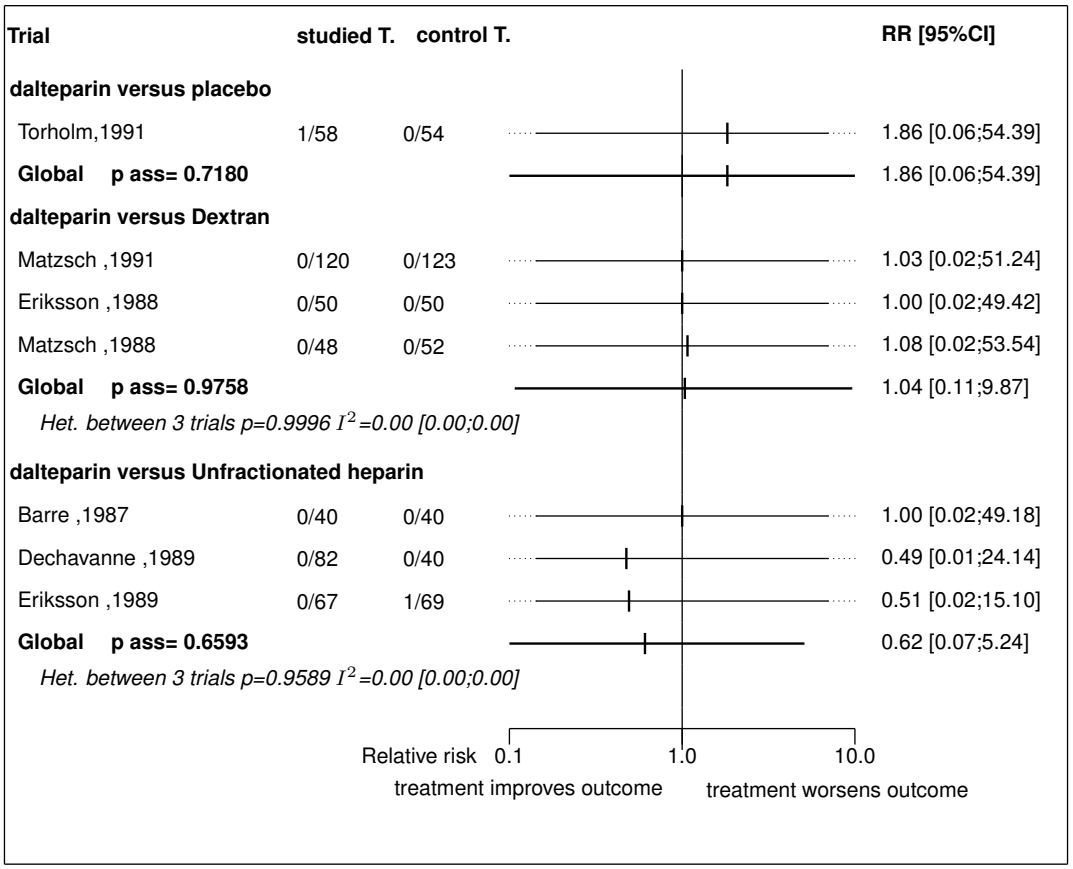
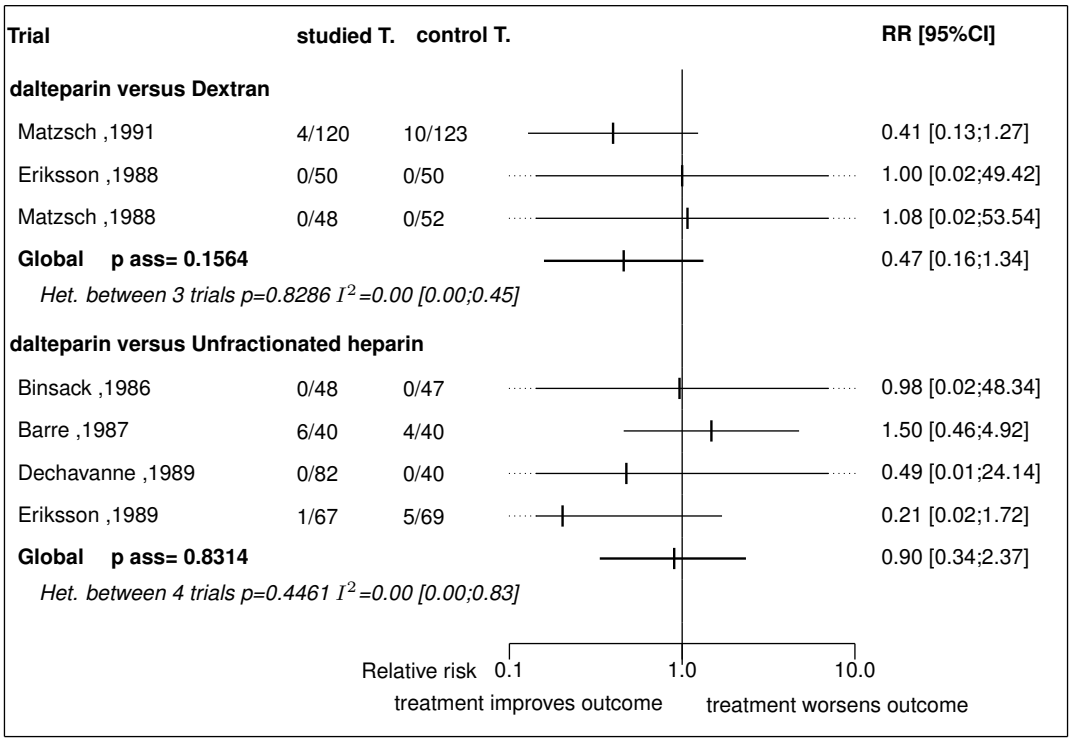


Figure 12.4: *Forest's plot for bleeding*



References

[1] Torholm C, Broeng L, Jorgensen PS, Bjerregaard P, Josephsen L, Jorgensen PK, Hagen K, Knudsen JB. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. J Bone Joint Surg Br 1991 May;73:434-8. [PMID=1670445]

[2] Eriksson BI, Zachrisson BE, Teger-Nilsson AC, Risberg B. Thrombosis prophylaxis with low molecular weight heparin in total hip replacement. Br J Surg 1988 Nov;75:1053-7. [PMID=2463035]

[3] Dechavanne M, Ville D, Berruyer M, Trepo F, Dalery F, Clermont N, Lerat JL, Moyen B, Fischer LP, Kher A. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. Haemostasis 1989;19:5-12. [PMID=2537787]

12.3 Individual trial summaries

Table 12.6: *Torholm, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=112 (58 vs. 54) **Follow-up duration:** 9 days **Study design:** Randomized controlled trial Double blind	Elective hip	**Studied treatment:** dalteparin 5000x1 2x2500; 2h before to 12h after; 1x5000; 6 days **Control treatment:** Placebo Placebo	Deep vein thrombosis RR=0.44 [0.22;0.89]

Reference

Torholm C, Broeng L, Jorgensen PS, Bjerregaard P, Josephsen L, Jorgensen PK, Hagen K, Knudsen JB. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. J Bone Joint Surg Br 1991 May;73:434-8 [PMID=1670445]

Table 12.7: *Matzsch, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=243 (120 vs. 123) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** dalteparin 1 x 50 kg; 2h before; 7 days **Control treatment:** Dextran Dextran 70 500 ml before and after surgery and on days 1,3, and 5	Deep vein thrombosis RR=0.63 [0.39;1.00]
Reference			

Table 12.8: *Eriksson, 1988 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=100 (50 vs. 50) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** dalteparin 2 x 2500; 2h before; 7 days **Control treatment:** Dextran Dextran 70 2 x 500 ml day 0, 1x500 ml days land 3	Deep vein thrombosis RR=0.45 [0.24;0.86] Symptomatic pulmonary embolism RR=1.00 [0.15;6.82]

Reference

Eriksson BI, Zachrisson BE, Teger-Nilsson AC, Risberg B. Thrombosis prophylaxis with low molecular weight heparin in total hip replacement. Br J Surg 1988 Nov;75:1053-7 [PMID=2463035]

Table 12.9: *Matzsch, 1988 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=100 (48 vs. 52) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** dalteparin 1 x 35 kg; 2h before; 7 days **Control treatment:** Dextran Dextran 70 500 ml before and after surgery and on days 1, 3, and 5	Deep vein thrombosis RR=0.74 [0.41;1.33]
Reference			

Table 12.10: *Binsack, 1986 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=95 (48 vs. 47) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** dalteparin 2 x 2500 day 0, 1 x 500 ND; 2h before **Control treatment:** Unfractionated heparin 3 x 5000; 2h before; ND	Deep vein thrombosis RR=0.82 [0.27;2.49]

Reference

Table 12.11: *Barre, 1987 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=80 (40 vs. 40) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** dalteparin 2x2500; 2h before; 10 days **Control treatment:** Unfractionated heparin 3x5000U; day 0, NDdaysI-10;	Deep vein thrombosis RR=1.75 [0.56;5.51]

Reference

Table 12.12: *Dechavanne, 1989 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=122 (82 vs. 40) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** dalteparin 2x2500 for 10-13 days, or 2x2500days 1-2, 1 x 5000 days 3-13; 2h before **Control treatment:** Unfractionated heparin 2h before 2 x 5000; days 1-2, ND days 3-13;2h before	Deep vein thrombosis RR=0.61 [0.17;2.15]

Reference

Dechavanne M, Ville D, Berruyer M, Trepo F, Dalery F, Clermont N, Lerat JL, Moyen B, Fischer LP, Kher A. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. Haemostasis 1989;19:5-12 [PMID=2537787]

Table 12.13: *Eriksson, 1989 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=136 (67 vs. 69) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** dalteparin 1x5000; 12h before; 10 days **Control treatment:** Unfractionated heparin lx 5000; 2h before; 10 days	Deep vein thrombosis RR=0.78 [0.48;1.28] Symptomatic pulmonary embolism RR=0.43 [0.20;0.92]
Reference			

Table 12.14: *Haas, 1985 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=130 (65 vs. 65) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** dalteparin 2 x 2500 day 0,1x5000 days 1-15;2h before **Control treatment:** Unfractionated heparin 2x5000+ DHE; 2h before; 15 days	Deep vein thrombosis RR=0.86 [0.30;2.41]

Reference

13 Detailed results for enoxaparin

13.1 Available trials

A total of 7 RCTs which randomized 1601 patients were identified: it compared enoxaparin with no treatment , 3 trials compared enoxaparin with placebo , it compared enoxaparin with Dextran and 2 trials compared enoxaparin with Unfractionated heparin.
The average study size was 228 patients (range 27 to 665). The first study was published in 1986, and the last study was published in 1997.
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.
Deep vein thrombosis data was reported in 7 trials; 4 trials reported data on symptomatic pulmonary embolism; 3 trials reported data on asymptomatic proximal DVT; 4 trials reported data on bleeding; and 4 trials reported data on all cause death.
Following tables 13.1 (page 129), 13.2 (page 130), 13.4 (page 132), and 13.3 (page 130) summarized the main characteristics of the trials including in this systematic review of randomized trials of enoxaparin.

Table 13.1: *Treatment description - Low molecular weight heparin - enoxaparin*

Trial	Studied treatment	Control treatment
Enoxaparin versus no treatment		
Warwick (1995) [1]	enoxaparin 4000x1 + elastic stockings	no treatment + elastic stockings
Enoxaparin versus placebo		
Kalodiki (1996) [2]	enoxaparin 4000x1	Placebo
Samama (1997) [3]	enoxaparin 4000x1+elastic stockings	Placebo+elastic stockings
Turpie (1986) [4]	Enoxaparin 3000 x2 2x2400; 12-24h after; 14 days	Placebo Placebo
Enoxaparin versus Dextran		
DES Group (1991)	Enoxaparin 1x3900; 12h before; 7 days	Dextran 60 mg/ml; 500 ml; twice on day 0,once on days 1 and 3
Enoxaparin versus Unfractionated heparin		
Levine (1991)	Enoxaparin 2x2400; 12-24h after; >14days	Unfractionated heparin 2x7500U;12or24hbefore; >14days
Planes (1988) [5]	Enoxaparin 1x3200; 12h before; <=14 days	Unfractionated heparin 3 x 5000; 2h before <=14 days

Table 13.2: *Descriptions of participants - Low molecular weight heparin - enoxaparin*

Trial	Patients
Enoxaparin versus no treatment	
Warwick (1995) [1]	Elective hip
Enoxaparin versus placebo	
Kalodiki (1996) [2]	Elective hip
Samama (1997) [3]	Elective hip
Turpie (1986) [4]	Elective hip
Enoxaparin versus Dextran	
DES Group (1991)	Elective hip
Enoxaparin versus Unfractionated heparin	
Levine (1991)	Elective hip
Planes (1988) [5]	Elective hip

Table 13.3: *Design and methodological quality of trials - Low molecular weight heparin - enoxaparin*

Trial	Design	Duration	Centre	Primary endpoint
Enoxaparin versus no treatment				
Warwick, 1995 [1] n=156	open	8-10 days		
Enoxaparin versus placebo				
Kalodiki, 1996 [2] n=27	double blind	discharge (8-12 days)		
Samama, 1997 [3] n=170	double blind	8-12 days		
Turpie, 1986 [4] n=100	double blind	14 days or discharge		
Enoxaparin versus Dextran				

continued...

Trial	Design	Duration	Centre	Primary end-point
DES Group, 1991 n=246				
Enoxaparin versus Unfractionated heparin				
Levine, 1991 n=665				
Planes, 1988 [5] n=237				

Table 13.4: *Trial characteristics - Low molecular weight heparin - enoxaparin*

Trial
Enoxaparin versus no treatment
Warwick, 1995 [1]
Enoxaparin versus placebo
Kalodiki, 1996 [2]
Samama, 1997 [3]
Turpie, 1986 [4]
Enoxaparin versus Dextran
DES Group, 1991
Enoxaparin versus Unfractionated heparin
Levine, 1991
Planes, 1988 [5]

13.2 Meta-analysis results

The results are detailed in table 13.5 (page 133). This table is followed by the Forest's plot corresponding to each endpoint.

Enoxaparin versus no treatment

The single study eligible for this comparison provided data on **deep vein thrombosis**. No statistically significant difference between the groups was found in deep vein thrombosis, with a RR of 0.67 (95% CI 0.43 to 1.03, p=0.0701).

Enoxaparin versus placebo

All the 3 studies had extractable data about the number of participants with **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of enoxaparin in deep vein thrombosis, with a RR of 0.32 (95% CI 0.21 to 0.50, p=0.0000). No heterogeneity was detected (p = 0.7439, I^2 = 0.00%).
Only one of the 3 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 1.00 (95% CI 0.02 to 49.42, p=1.0000).

Enoxaparin versus Dextran

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 0.31 (95% CI 0.14 to 0.68, p=0.0039).
The single study 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 1.05 (95% CI 0.02 to 52.50, p=0.9805).

Enoxaparin versus Unfractionated heparin

All the 2 studies had extractable data about the number of participants with **deep vein thrombosis**. When pooled together, there was no statistically significant difference between the groups in deep vein thrombosis, with a RR of 0.71 (95% CI 0.41 to 1.24, p=0.2309). No heterogeneity was detected (p = 0.0874, I^2 = 0.66%).
All the 2 studies had extractable data about the number of participants with **symptomatic pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in symptomatic pulmonary embolism, with a RR of 0.33 (95% CI 0.03 to 3.22, p=0.3389). No heterogeneity was detected (p = 0.7966, I^2 = 0.00%).

Table 13.5: *Results details - Low molecular weight heparin - enoxaparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
enoxaparin versus no treatment						
deep vein thrombosis	RR=0.67	[0.43;1.03]	0.0701	1.0000 (I^2=0.00)	1	156
enoxaparin versus placebo						
deep vein thrombosis	RR=0.32	[0.21;0.50]	0.0000	0.7439 (I^2=0.00)	3	280
symptomatic pulmonary embolism	RR=1.00	[0.02;49.42]	1.0000	1.0000 (I^2=0.00)	1	100

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
all cause death	RR=0.50	[0.02;14.57]	0.6870	1.0000 (I^2=0.00)	1	100
bleeding	RR=0.67	[0.11;4.04]	0.6635	0.7085 (I^2=0.00)	2	270
enoxaparin versus Dextran						
deep vein thrombosis	RR=0.31	[0.14;0.68]	0.0039	1.0000 (I^2=0.00)	1	246
symptomatic pulmonary embolism	RR=1.05	[0.02;52.50]	0.9805	1.0000 (I^2=0.00)	1	246
all cause death	RR=2.10	[0.07;62.03]	0.6675	1.0000 (I^2=0.00)	1	246
enoxaparin versus Unfractionated heparin						
deep vein thrombosis	RR=0.71	[0.41;1.24]	0.2309	0.0874 (I^2=0.66)	2	902
symptomatic pulmonary embolism	RR=0.33	[0.03;3.22]	0.3389	0.7966 (I^2=0.00)	2	902
all cause death	RR=0.95	[0.06;15.18]	0.9729	0.9746 (I^2=0.00)	2	902
bleeding	RR=0.77	[0.21;2.83]	0.6915	0.2549 (I^2=0.23)	2	902

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

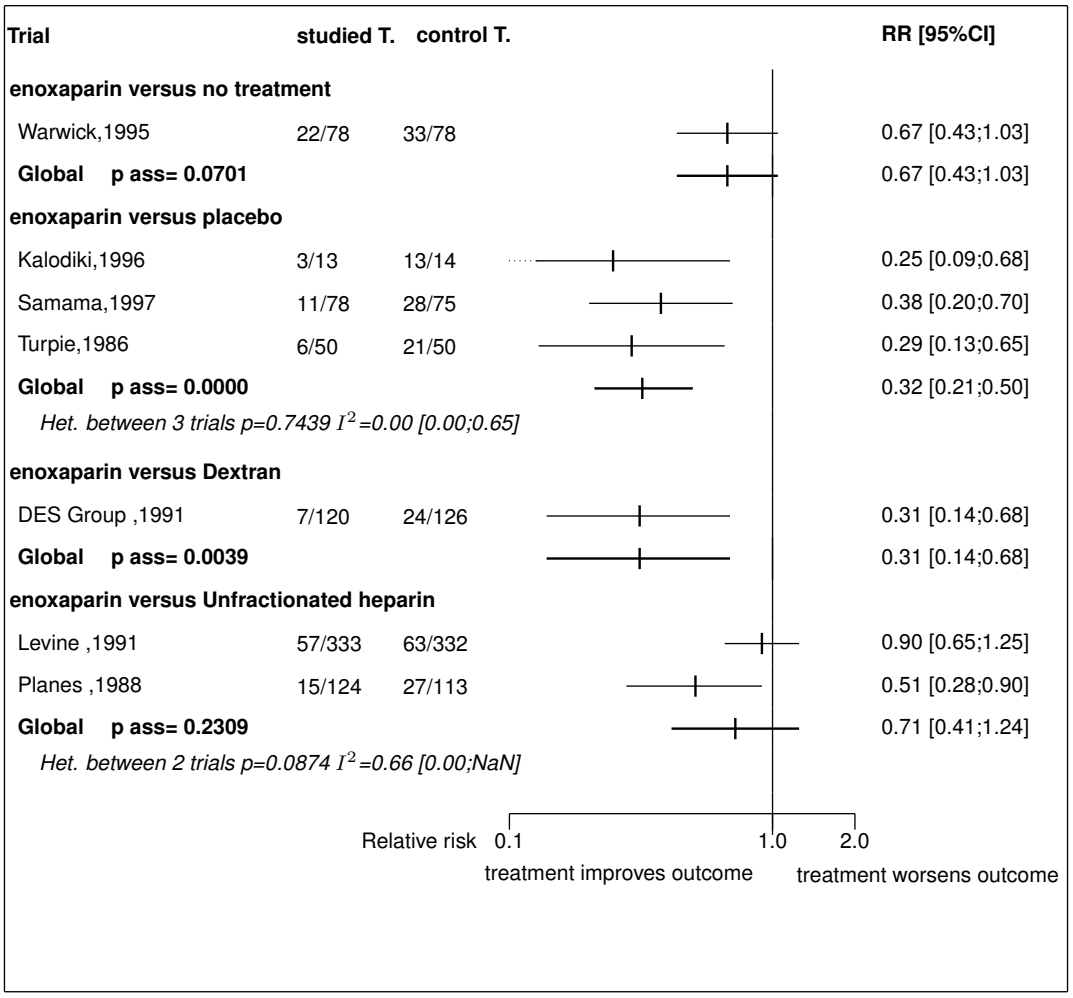


Figure 13.2: *Forest's plot for symptomatic pulmonary embolism*

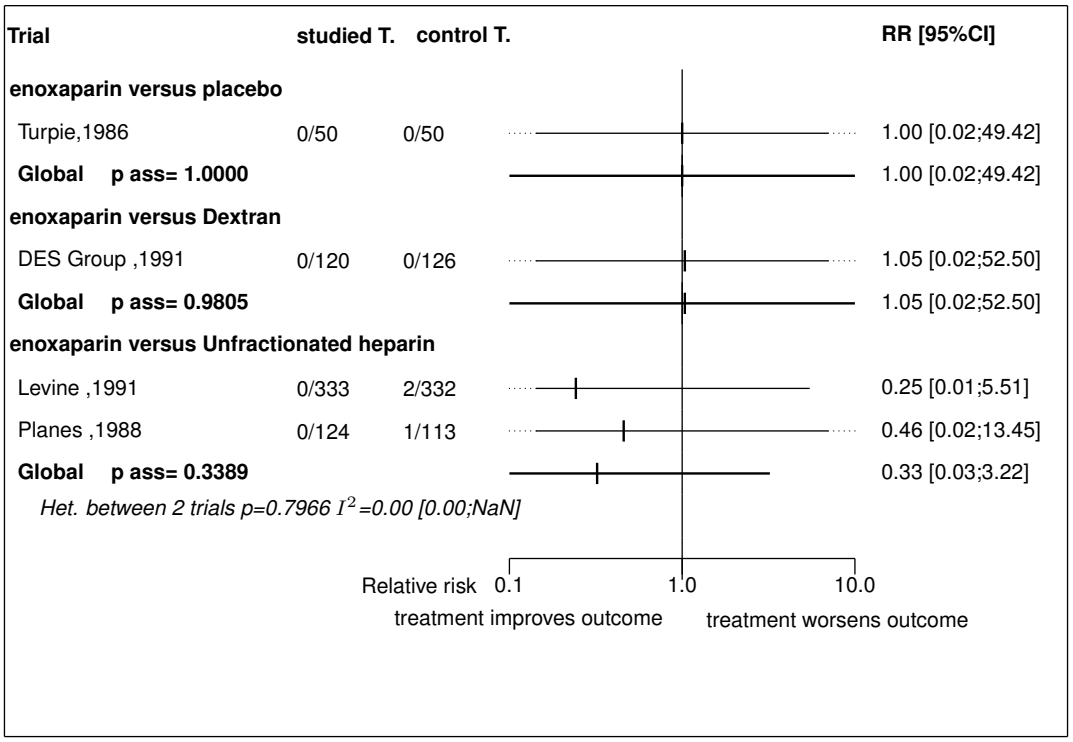


Figure 13.3: *Forest's plot for all cause death*

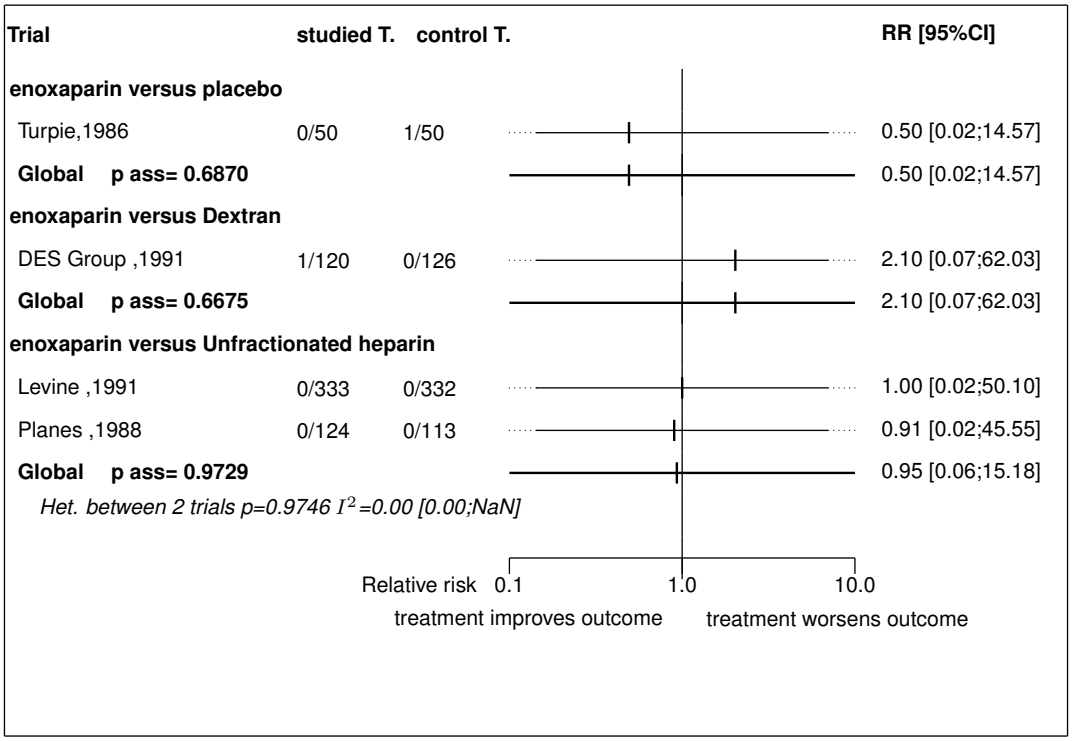
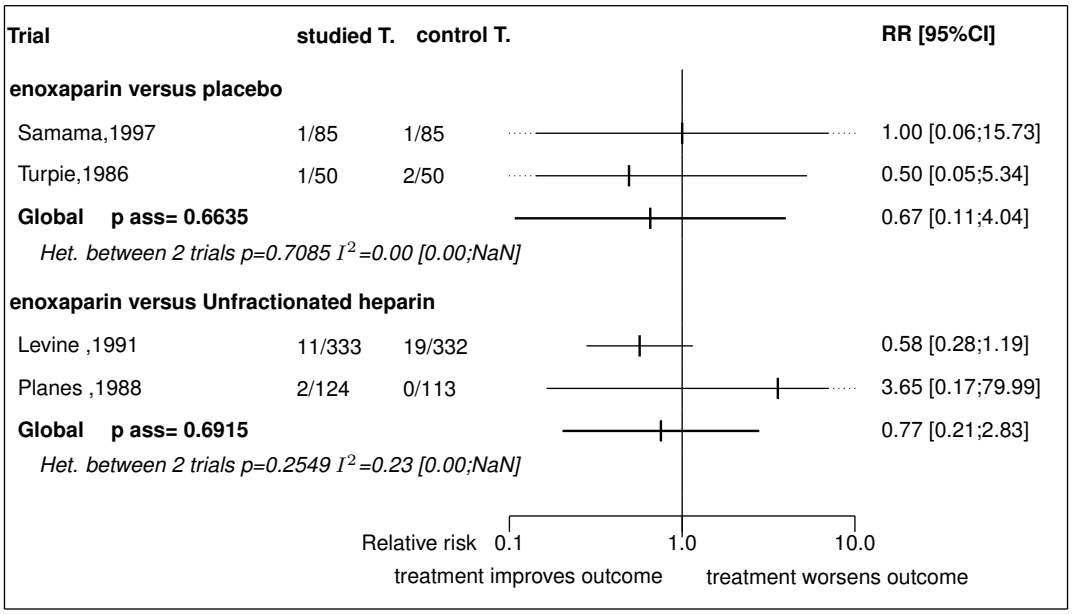


Figure 13.4: *Forest's plot for bleeding*



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[1] Warwick D, Bannister GC, Glew D, Mitchelmore A, Thornton M, Peters TJ, Brookes S. Perioperative low-molecular-weight heparin. Is it effective and safe. J Bone Joint Surg Br 1995 Sep;77:715-9. [PMID=7559695]

[2] Kalodiki EP, Hoppensteadt DA, Nicolaides AN, Fareed J, Gill K, Regan F, al-Kutoubi A, Cunningham DA, Birch R, Harris N, Hunt D, Johnson J, Marx C. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. Int Angiol 1996 Jun;15:162-8. [PMID=8803642]

[3] Samama CM, Clergue F, Barre J, Montefiore A, Ill P, Samii K. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. Arar Study Group. Br J Anaesth 1997 Jun;78:660-5. [PMID=9215015]

[4] Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, Andrew M, Hull RD, Gent M. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med 1986 Oct 9;315:925-9. [PMID=3531851]

[5] Planes A, Vochelle N, Mazas F, Mansat C, Zucman J, Landais A, Pascariello JC, Weill D, Butel J. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. Thromb Haemost 1988 Dec 22;60:407-10. [PMID=2853459]

13.3 Individual trial summaries

Table 13.6: *Warwick, 1995 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=156 (78 vs. 78) **Follow-up duration:** 8-10 days **Study design:** Randomized controlled trial Open	Elective hip	**Studied treatment:** enoxaparin 4000x1 + elastic stockings **Control treatment:** no treatment + elastic stockings	Deep vein thrombosis RR=0.67 [0.43;1.03]

Reference

Warwick D, Bannister GC, Glew D, Mitchelmore A, Thornton M, Peters TJ, Brookes S. Perioperative low-molecular-weight heparin. Is it effective and safe. J Bone Joint Surg Br 1995 Sep;77:715-9 [PMID=7559695]

Table 13.7: *Kalodiki, 1996 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=27 (13 vs. 14) **Follow-up duration:** discharge (8-12 days) **Study design:** Randomized controlled trial Double blind	Elective hip	**Studied treatment:** enoxaparin 4000x1 **Control treatment:** Placebo	Deep vein thrombosis RR=0.25 [0.09;0.68]

Reference

Kalodiki EP, Hoppensteadt DA, Nicolaides AN, Fareed J, Gill K, Regan F, al-Kutoubi A, Cunningham DA, Birch R, Harris N, Hunt D, Johnson J, Marx C. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. Int Angiol 1996 Jun;15:162-8 [PMID=8803642]

Table 13.8: *Samama, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=170 (85 vs. 85) **Follow-up duration:** 8-12 days **Study design:** Randomized controlled trial Double blind	Elective hip	**Studied treatment:** enoxaparin 4000x1+elastic stockings **Control treatment:** Placebo+elastic stockings	Deep vein thrombosis RR=0.38 [0.20;0.70]

Reference

Samama CM, Clergue F, Barre J, Montefiore A, III P, Samii K. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. Arar Study Group. Br J Anaesth 1997 Jun;78:660-5 [PMID=9215015]

Table 13.9: *Turpie, 1986 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=100 (50 vs. 50) **Follow-up duration:** 14 days or discharge **Study design:** Randomized controlled trial Double blind	Elective hip	**Studied treatment:** Enoxaparin 3000 x2 2x2400; 12-24h after; 14 days **Control treatment:** Placebo Placebo	Deep vein thrombosis RR=0.29 [0.13;0.65]

Reference

Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, Andrew M, Hull RD, Gent M. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med 1986 Oct 9;315:925-9 [PMID=3531851]

Table 13.10: *DES Group, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=246 (120 vs. 126) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** Enoxaparin 1x3900; 12h before; 7 days **Control treatment:** Dextran 60 mg/ml; 500 ml; twice on day 0,once on days 1 and 3	Deep vein thrombosis RR=0.31 [0.14;0.68]

Reference

Table 13.11: *Levine, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=665 (333 vs. 332) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** Enoxaparin 2x2400; 12-24h after; >14days **Control treatment:** Unfractionated heparin 2x7500U;12or24hbefore; >14days	Deep vein thrombosis RR=0.90 [0.65;1.25]

Reference

Table 13.12: *Planes, 1988 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=237 (124 vs. 113) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** Enoxaparin 1x3200; 12h before; <=14 days **Control treatment:** Unfractionated heparin 3 x 5000; 2h before <=14 days	Deep vein thrombosis RR=0.51 [0.28;0.90]

Reference

Planes A, Vochelle N, Mazas F, Mansat C, Zucman J, Landais A, Pascariello JC, Weill D, Butel J. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. Thromb Haemost 1988 Dec 22;60:407-10 [PMID=2853459]

14 Detailed results for fluxum

14.1 Available trials

A total of 2 RCTs which randomized 189 patients were identified: all compared fluxum with Unfractionated heparin.
The average study size was 94 patients (range 49 to 140). The first study was published in 1988, and the last study was published in 1989.
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All included studies were reported in English language. We did not found any unpublished trial.
Symptomatic pulmonary embolism data was reported in 2 trials; 2 trials reported data on deep vein thrombosis; 2 trials reported data on bleeding; and 1 trials reported data on all cause death.
Following tables 14.1 (page 146), 14.2 (page 146), 14.4 (page 148), and 14.3 (page 147) summarized the main characteristics of the trials including in this systematic review of randomized trials of fluxum.

Table 14.1: *Treatment description - Low molecular weight heparin - fluxum*

Trial	Studied treatment	Control treatment
Fluxum versus Unfractionated heparin		
Chiapuzzo (1988) [1]	Fluxum 2 x 7500; 2h before; 7 days	Unfractionated heparin 3x5000; 2h before; 7 days
Pini (1989) [2]	Fluxum 2x7500; before; <= 14 days	Unfractionated heparin 3x5000; before; <=14 days

Table 14.2: *Descriptions of participants - Low molecular weight heparin - fluxum*

Trial	Patients
Fluxum versus Unfractionated heparin	
Chiapuzzo (1988) [1]	Elective hip
Pini (1989) [2]	Hip

Table 14.3: *Design and methodological quality of trials - Low molecular weight heparin - fluxum*

Trial	Design	Duration	Centre	Primary end-point
Fluxum versus Unfractionated heparin				
Chiapuzzo, 1988 [1] n=140				
Pini, 1989 [2] n=49				

Table 14.4: *Trial characteristics - Low molecular weight heparin - fluxum*

Trial
Fluxum versus Unfractionated heparin
Chiapuzzo, 1988 [1]
Pini, 1989 [2]

14.2 Meta-analysis results

The results are detailed in table 14.5 (page 149). This table is followed by the Forest's plot corresponding to each endpoint.

Fluxum versus Unfractionated heparin

All the 2 studies had extractable data about the number of participants with **deep vein thrombosis**. When pooled together, there was no statistically significant difference between the groups in deep vein thrombosis, with a RR of 0.70 (95% CI 0.33 to 1.46, p=0.3422). No heterogeneity was detected (p = 0.9571, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **symptomatic pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in symptomatic pulmonary embolism, with a RR of 0.66 (95% CI 0.05 to 8.32, p=0.7443). No heterogeneity was detected (p = 0.7798, I^2 = 0.00%).

Table 14.5: *Results details - Low molecular weight heparin - fluxum*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fluxum versus Unfractionated heparin						
deep vein thrombosis	RR=0.70	[0.33;1.46]	0.3422	0.9571 (I^2=0.00)	2	189
symptomatic pulmonary embolism	RR=0.66	[0.05;8.32]	0.7443	0.7798 (I^2=0.00)	2	189
all cause death	RR=0.48	[0.02;13.66]	0.6675	1.0000 (I^2=0.00)	1	49
bleeding	RR=0.98	[0.06;15.36]	0.9883	0.9884 (I^2=0.00)	2	189

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

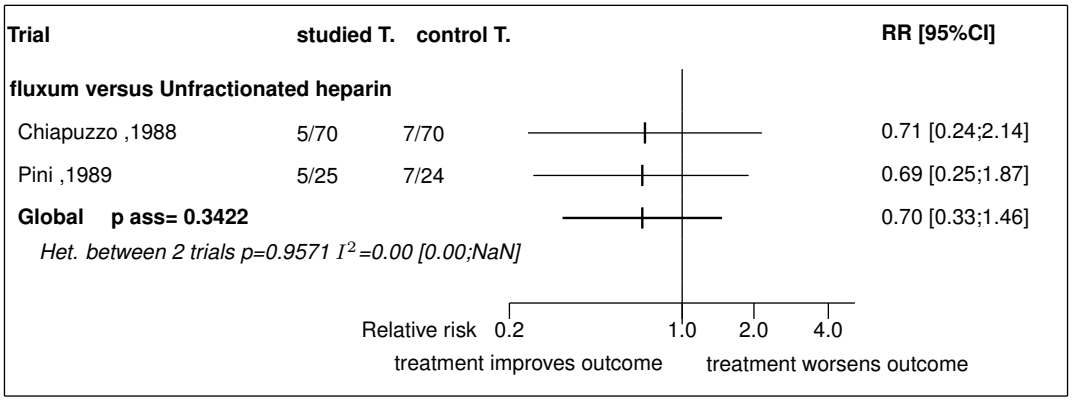


Figure 14.2: *Forest's plot for symptomatic pulmonary embolism*

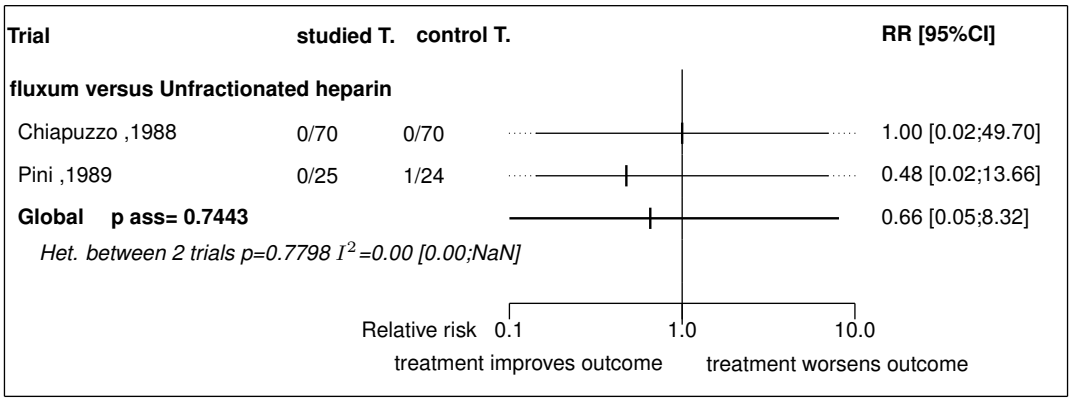


Figure 14.3: *Forest's plot for all cause death*

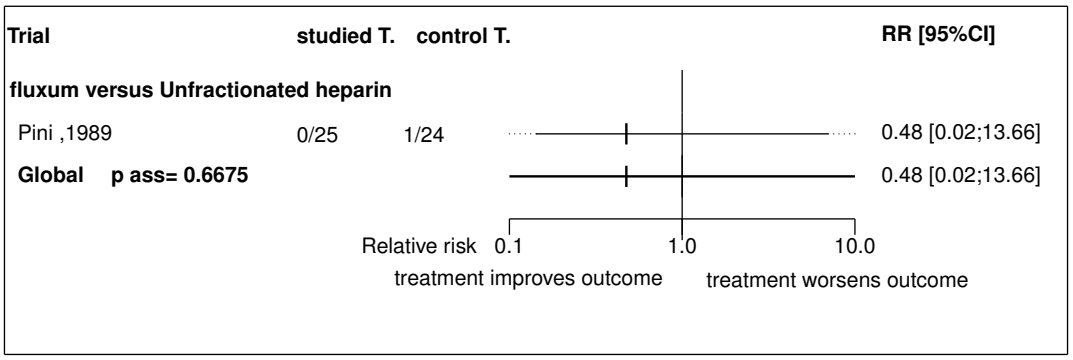
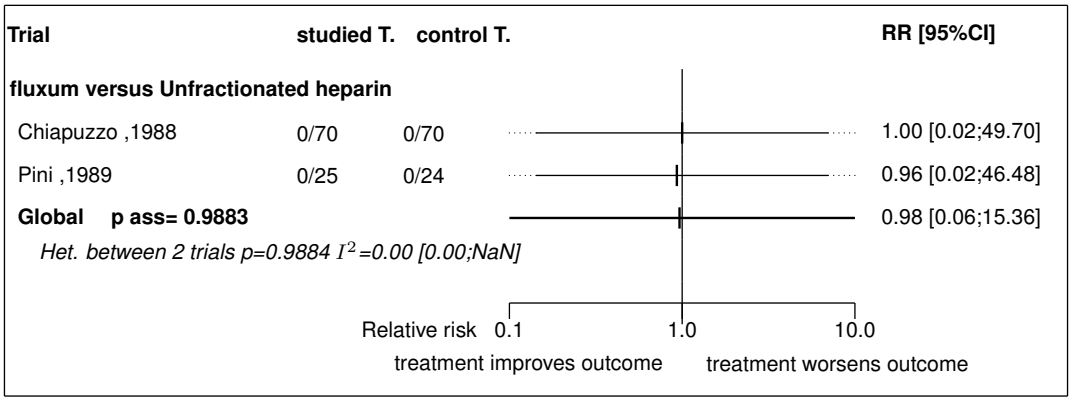


Figure 14.4: *Forest's plot for bleeding*



References

[1] Chiapuzzo E, Orengo GB, Ottria G, Chiapuzzo A, Palazzini E, Fusillo M. The use of low molecular weight heparins for postsurgical deep vein thrombosis prevention in orthopaedic patients. J Int Med Res 1988 Sep-Oct;16:359-66. [PMID=3197913]

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14.3 Individual trial summaries

Table 14.6: *Chiapuzzo, 1988 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=140 (70 vs. 70) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** Fluxum 2 x 7500; 2h before; 7 days **Control treatment:** Unfractionated heparin 3x5000; 2h before; 7 days	Deep vein thrombosis RR=0.71 [0.24;2.14]

Reference

Chiapuzzo E, Orengo GB, Ottria G, Chiapuzzo A, Palazzini E, Fusillo M. The use of low molecular weight heparins for postsurgical deep vein thrombosis prevention in orthopaedic patients. J Int Med Res 1988 Sep-Oct;16:359-66 [PMID=3197913]

Table 14.7: *Pini, 1989 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=49 (25 vs. 24) **Follow-up duration:** **Study design:** Randomized controlled trial	Hip	**Studied treatment:** Fluxum 2x7500; before; <= 14 days **Control treatment:** Unfractionated heparin 3x5000; before; <=14 days	Deep vein thrombosis RR=0.69 [0.25;1.87]

Reference

Pini M, Tagliaferri A, Manotti C, Lasagni F, Rinaldi E, Dettori AG. Low molecular weight heparin (Alfa LHWH) compared with unfractionated heparin in prevention of deep-vein thrombosis after hip fractures. Int Angiol 1989 Jul-Sep;8:134-9 [PMID=2556484]

15 Detailed results for nadroparin

15.1 Available trials

A total of 2 RCTs which randomized 509 patients were identified: it compared nadroparin with no treatment and it compared nadroparin with Unfractionated heparin.
The average study size was 254 patients (range 100 to 409). The first study was published in 1991, and the last study was published in 1997.
This trial was open-label in design.
All included studies were reported in English language. We did not found any unpublished trial.
Deep vein thrombosis data was reported in 2 trials; 1 trials reported data on asymptomatic proximal DVT; 1 trials reported data on symptomatic pulmonary embolism; 1 trials reported data on bleeding; and 1 trials reported data on all cause death.
Following tables 15.1 (page 155), 15.2 (page 155), 15.4 (page 157), and 15.3 (page 156) summarized the main characteristics of the trials including in this systematic review of randomized trials of nadroparin.

Table 15.1: *Treatment description - Low molecular weight heparin - nadroparin*

Trial	Studied treatment	Control treatment
Nadroparin versus no treatment		
Yoo (1997) [1]	nadroparin 41/kgx1 days 1-3, 62/kg x1 days 4-11+elastic stockings	no treatment
Nadroparin versus Unfractionated heparin		
Leyvraz (1991) [2]	Fraxiparin 1 x41/kg days 1-3, 1 x62/kg days 4-10;12h before	Unfractionated heparin ND; 24h Defore; 10 days

Table 15.2: *Descriptions of participants - Low molecular weight heparin - nadroparin*

Trial	Patients
Nadroparin versus no treatment	
Yoo (1997) [1]	Elective hip
Nadroparin versus Unfractionated heparin	
Leyvraz (1991) [2]	Elective hip

Table 15.3: *Design and methodological quality of trials - Low molecular weight heparin - nadroparin*

Trial	Design	Duration	Centre	Primary end-point
Nadroparin versus no treatment				
Yoo, 1997 [1] n=100	open	10 days		
Nadroparin versus Unfractionated heparin				
Leyvraz, 1991 [2] n=409				

Table 15.4: *Trial characteristics - Low molecular weight heparin - nadroparin*

Trial
Nadroparin versus no treatment
Yoo, 1997 [1]
Nadroparin versus Unfractionated heparin
Leyvraz, 1991 [2]

15.2 Meta-analysis results

The results are detailed in table 15.5 (page 158). This table is followed by the Forest's plot corresponding to each endpoint.

Nadroparin versus no treatment

The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of nadroparin in deep vein thrombosis, with a RR of 0.13 (95% CI 0.02 to 0.96, p=0.0459).

Nadroparin versus Unfractionated heparin

The single study eligible for this comparison provided data on **deep vein thrombosis**. No statistically significant difference between the groups was found in deep vein thrombosis, with a RR of 0.80 (95% CI 0.47 to 1.35, p=0.3966).
The single study 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 2.25, p=0.2181).

Table 15.5: *Results details - Low molecular weight heparin - nadroparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nadroparin versus no treatment						
deep vein thrombosis	RR=0.13	[0.02;0.96]	0.0459	1.0000 (I^2=0.00)	1	100
nadroparin versus Unfractionated heparin						
deep vein thrombosis	RR=0.80	[0.47;1.35]	0.3966	1.0000 (I^2=0.00)	1	409
symptomatic pulmonary embolism	RR=0.25	[0.03;2.25]	0.2181	1.0000 (I^2=0.00)	1	409
all cause death	RR=0.51	[0.05;5.55]	0.5784	1.0000 (I^2=0.00)	1	409
bleeding	RR=0.34	[0.04;3.23]	0.3461	1.0000 (I^2=0.00)	1	409

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 deep vein thrombosis*

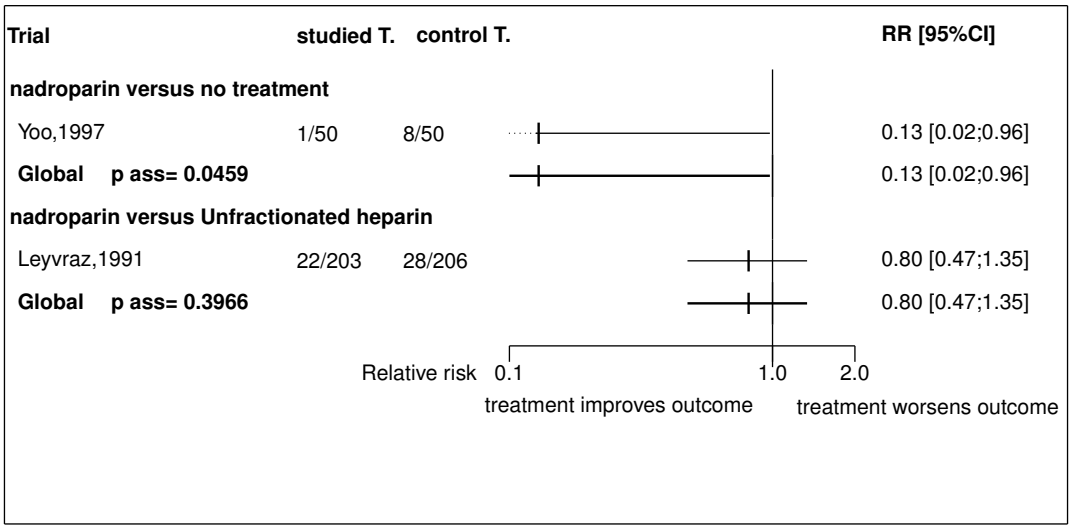


Figure 15.2: *Forest's plot for symptomatic pulmonary embolism*

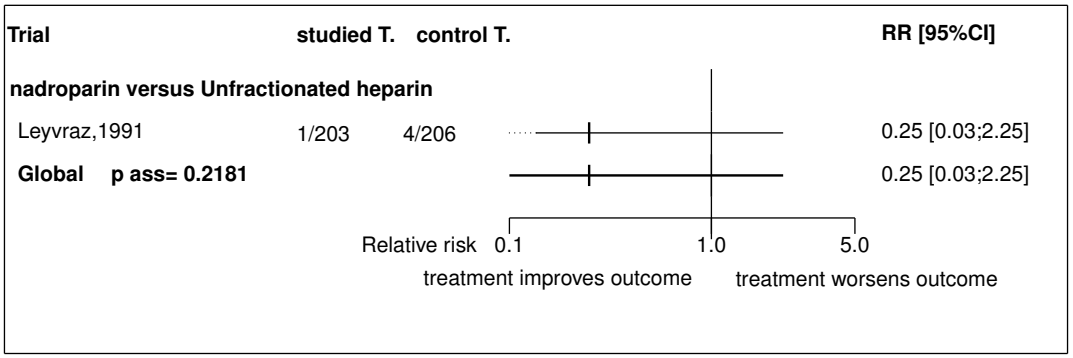


Figure 15.3: *Forest's plot for all cause death*

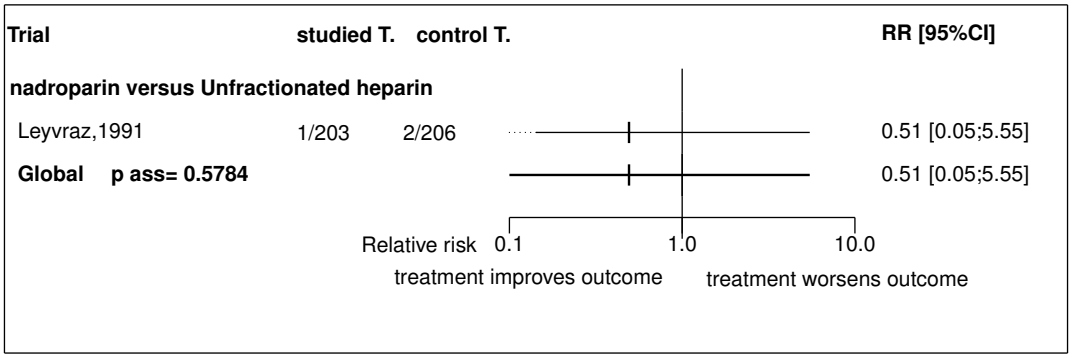
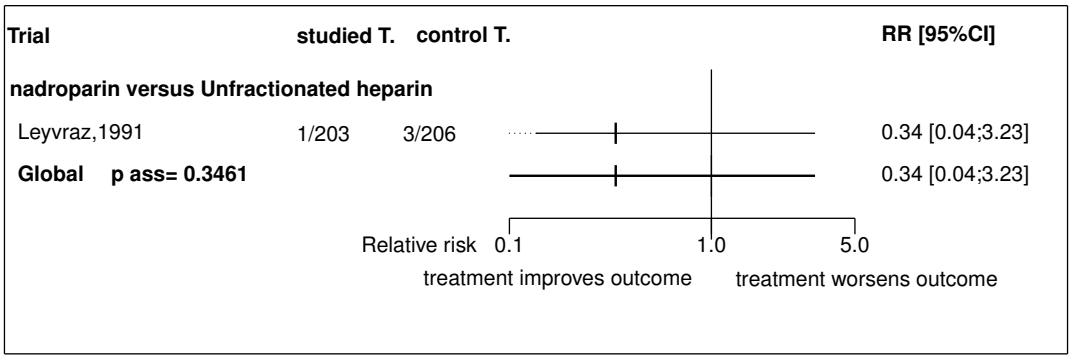


Figure 15.4: *Forest's plot for bleeding*



References

[1] Yoo MC, Kang CS, Kim YH, Kim SK. A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. Int Orthop 1997;21:399-402. [PMID=9498151]

[2] Leyvraz PF, Bachmann F, Hoek J, Buller HR, Postel M, Samama M, Vandenbroek MD. Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. BMJ 1991 Sep 7;303:543-8. [PMID=1655136]

15.3 Individual trial summaries

Table 15.6: *Yoo, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=100 (50 vs. 50) **Follow-up duration:** 10 days **Study design:** Randomized controlled trial Open	Elective hip	**Studied treatment:** nadroparin 41/kgx1 days 1-3, 62/kg x1 days 4-11+elastic stockings **Control treatment:** no treatment	Deep vein thrombosis RR=0.13 [0.02;0.96]

Reference

Yoo MC, Kang CS, Kim YH, Kim SK. A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. Int Orthop 1997;21:399-402 [PMID=9498151]

Table 15.7: *Leyvraz, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=409 (203 vs. 206) **Follow-up duration:** **Study design:** Randomized controlled trial	Elective hip	**Studied treatment:** Fraxiparin 1 x41/kg days 1-3, 1 x62/kg days 4-10;12h before **Control treatment:** Unfractionated heparin ND; 24h Defore; 10 days	Deep vein thrombosis RR=0.80 [0.47;1.35] Symptomatic pulmonary embolism RR=0.25 [0.03;2.25]

Reference

Leyvraz PF, Bachmann F, Hoek J, Buller HR, Postel M, Samama M, Vandenbroek MD. Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. BMJ 1991 Sep 7;303:543-8 [PMID=1655136]

16 Detailed results for semuloparin

16.1 Available trials

Only one trial which randomized 2326 patients was identified: it compared semuloparin with enoxaparin.
This trial included 2326 patients and was published in 2012.
Erreur ??? 0 et 0.
It was reported in English language.
Major or clinically relevant non-major bleeding data was reported in 1 trials; 1 trials reported data on symptomatic pulmonary embolism; 1 trials reported data on deep vein thrombosis; 1 trials reported data on total VTE and all-cause mortality; 1 trials reported data on bleeding; and 1 trials reported data on all cause death.
Following tables 16.1 (page 164), 16.2 (page 164), 16.4 (page 166), and 16.3 (page 164) summarized the main characteristics of the trial including in this systematic review of randomized trials of semuloparin.

Table 16.1: *Treatment description - Low molecular weight heparin - semuloparin*

Trial	Studied treatment	Control treatment
Semuloparin versus enoxaparin		
SAVE-HIP1 (2012) [1]	Semuloparin 20 mg once-daily	Enoxaparin 40 mg once-daily

Table 16.2: *Descriptions of participants - Low molecular weight heparin - semuloparin*

Trial	Patients
Semuloparin versus enoxaparin	
SAVE-HIP1 (2012) [1]	

Table 16.3: *Design and methodological quality of trials - Low molecular weight heparin - semuloparin*

Trial	Design	Duration	Centre	Primary endpoint
Semuloparin versus enoxaparin				

continued...

Trial	Design	Duration	Centre	Primary endpoint
SAVE-HIP1, 2012 [1] n=2326				

Table 16.4: *Trial characteristics - Low molecular weight heparin - semuloparin*

Trial
Semuloparin versus enoxaparin
SAVE-HIP1, 2012 [1]

16.2 Meta-analysis results

The results are detailed in table 16.5 (page 167). This table is followed by the Forest's plot corresponding to each endpoint.

Semuloparin versus enoxaparin

The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of semuloparin in deep vein thrombosis, with a RR of 0.57 (95% CI 0.42 to 0.78, p=0.0000).
The single study 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 1.00 (95% CI 0.02 to 50.45, p=0.9993).
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 semuloparin in total VTE and all-cause mortality, with a RR of 0.57 (95% CI 0.42 to 0.77, p=0.0000).

Table 16.5: *Results details - Low molecular weight heparin - semuloparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
semuloparin versus enoxaparin						
deep vein thrombosis	RR=0.57	[0.42;0.78]	0.0000	1.0000 (I^2=1.00)	1	1846
symptomatic pulmonary embolism	RR=1.00	[0.02;50.45]	0.9993	1.0000 (I^2=0.00)	1	2302
total VTE and all-cause mortality	RR=0.57	[0.42;0.77]	0.0000	1.0000 (I^2=0.00)	1	1849
major or clinically relevant non-major bleeding	RR=0.48	[0.24;0.95]	0.0357	1.0000 (I^2=1.00)	1	2308
all cause death	RR=0.50	[0.05;5.52]	0.5722	1.0000 (I^2=0.00)	1	2302
bleeding	RR=0.29	[0.09;0.87]	0.0269	1.0000 (I^2=1.00)	1	2308

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 deep vein thrombosis*

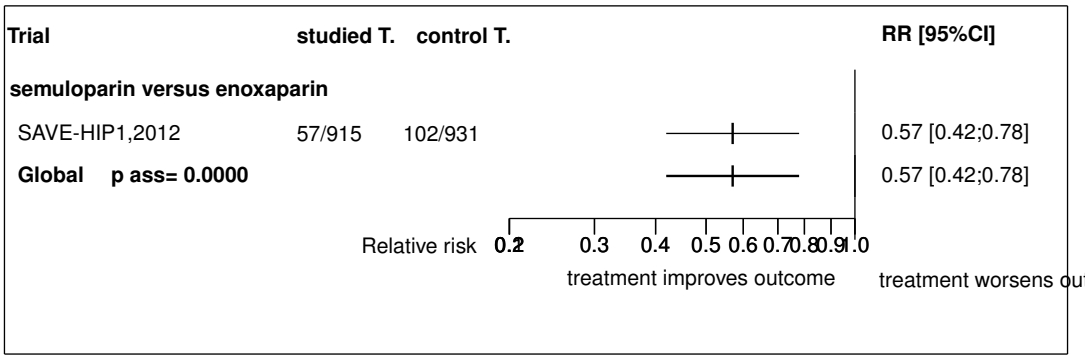


Figure 16.2: *Forest's plot for symptomatic pulmonary embolism*

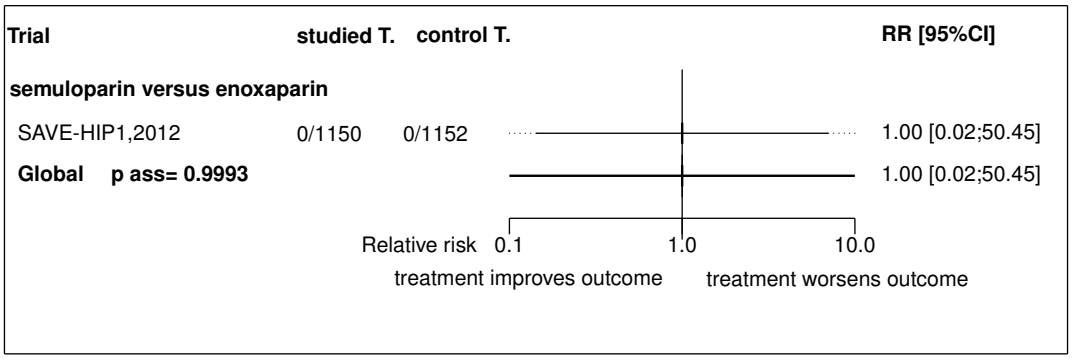


Figure 16.3: *Forest's plot for total VTE and all-cause mortality*

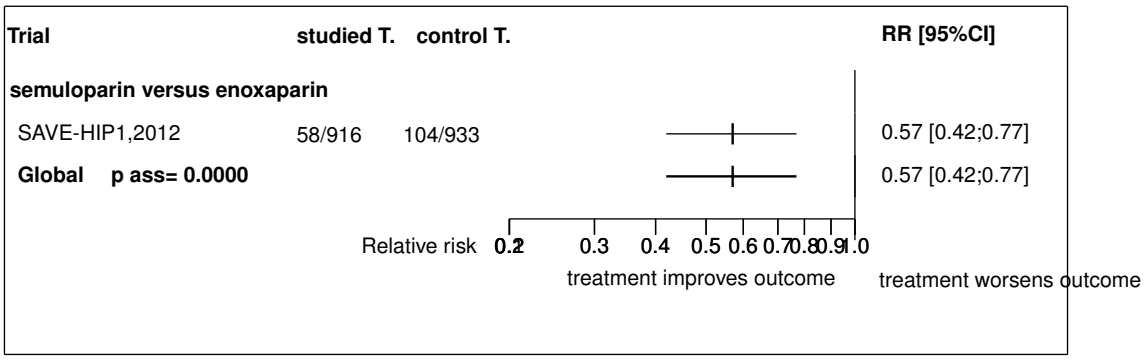


Figure 16.4: *Forest's plot for major or clinically relevant non-major bleeding*

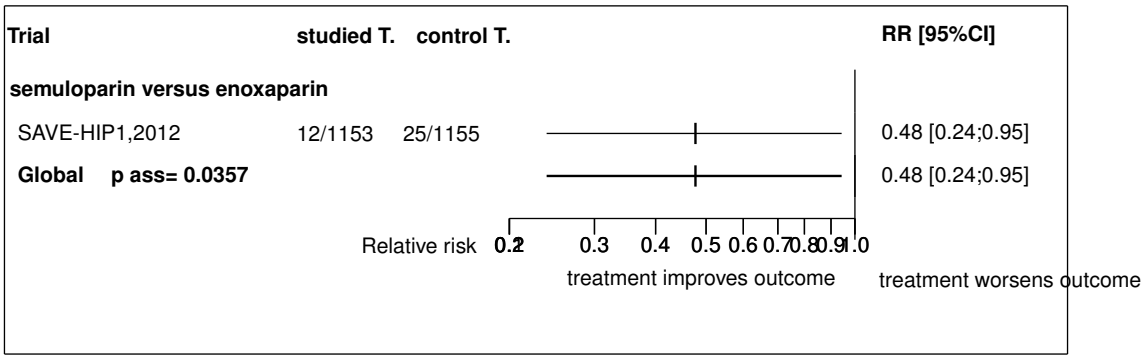


Figure 16.5: *Forest's plot for all cause death*

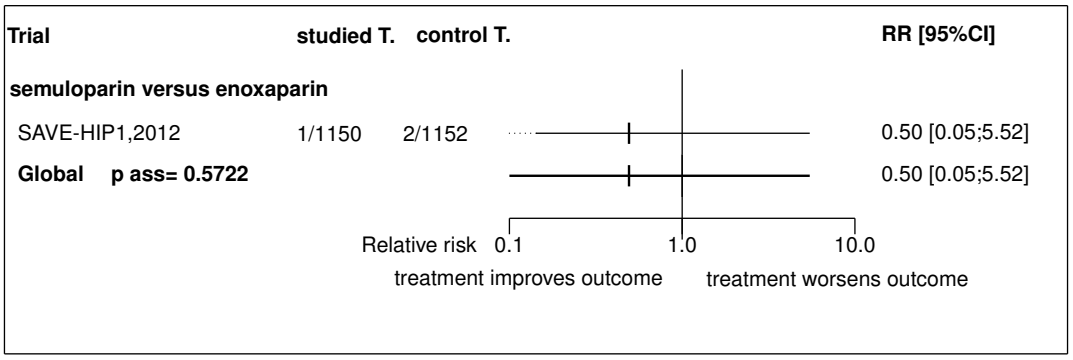
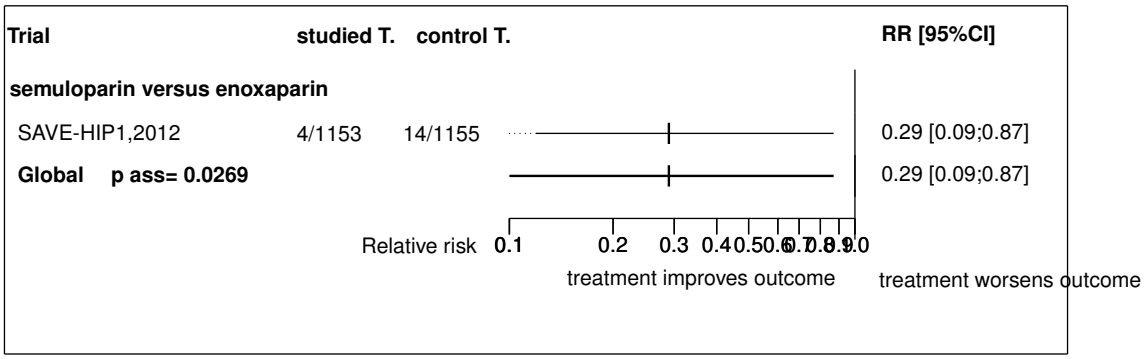


Figure 16.6: *Forest's plot for bleeding*



References

[1] Lassen MR, Fisher W, Mouret P, Agnelli G, George D, Kakkar A, Mismetti P, Turpie AG. Semuloparin for prevention of venous thromboembolism after major orthopedic surgery: results from three randomized clinical trials, SAVE-HIP1, SAVE-HIP2 and SAVE-KNEE. J Thromb Haemost 2012;10:822-32. [PMID=22429800]

16.3 Individual trial summaries

Table 16.6: *SAVE-HIP1, 2012 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2326 (1161 vs. 1165) **Follow-up duration:** **Study design:** Randomized controlled trial		**Studied treatment:** Semuloparin 20 mg once-daily **Control treatment:** Enoxaparin 40 mg once-daily	Deep vein thrombosis RR=0.57 [0.42;0.78] (any DVT) Total VTE and all-cause mortality RR=0.57 [0.42;0.77]

Reference

Lassen MR, Fisher W, Mouret P, Agnelli G, George D, Kakkar A, Mismetti P, Turpie AG. Semuloparin for prevention of venous thromboembolism after major orthopedic surgery: results from three randomized clinical trials, SAVE-HIP1, SAVE-HIP2 and SAVE-KNEE. J Thromb Haemost 2012;10:822-32 [PMID=22429800]

17 Detailed results for tinzaparin

17.1 Available trials

Only one trial which randomized 210 patients was identified: it compared tinzaparin with placebo.
This trial included 210 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 all cause death.
Following tables 17.1 (page 172), 17.2 (page 172), 17.4 (page 173), and 17.3 (page 172) summarized the main characteristics of the trial including in this systematic review of randomized trials of tinzaparin.

Table 17.1: *Treatment description - Low molecular weight heparin - tinzaparin*

Trial	Studied treatment	Control treatment
Tinzaparin versus placebo		
Lassen (1991) [1]	tinzaparin 50/kg x1 +elastic stockings 1 x50U/kg;2h before; ND	Placebo+elastic stockings Placebo

Table 17.2: *Descriptions of participants - Low molecular weight heparin - tinzaparin*

Trial	Patients
Tinzaparin versus placebo	
Lassen (1991) [1]	Elective hip

Table 17.3: *Design and methodological quality of trials - Low molecular weight heparin - tinzaparin*

Trial	Design	Duration	Centre	Primary endpoint
Tinzaparin versus placebo				
Lassen, 1991 [1] n=210	double blind	8-10 days		

Table 17.4: *Trial characteristics - Low molecular weight heparin - tinzaparin*

Trial
Tinzaparin versus placebo
Lassen, 1991 [1]

17.2 Meta-analysis results

The results are detailed in table 17.5 (page 174). This table is followed by the Forest's plot corresponding to each endpoint.

Tinzaparin 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 tinzaparin in deep vein thrombosis, with a RR of 0.68 (95% CI 0.46 to 1.00, p=0.0489).

Table 17.5: *Results details - Low molecular weight heparin - tinzaparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
tinzaparin versus placebo						
deep vein thrombosis	RR=0.68	[0.46;1.00]	0.0489	1.0000 (I^2=0.00)	1	192
all cause death	RR=1.13	[0.07;17.86]	0.9291	1.0000 (I^2=0.00)	1	192

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 deep vein thrombosis*

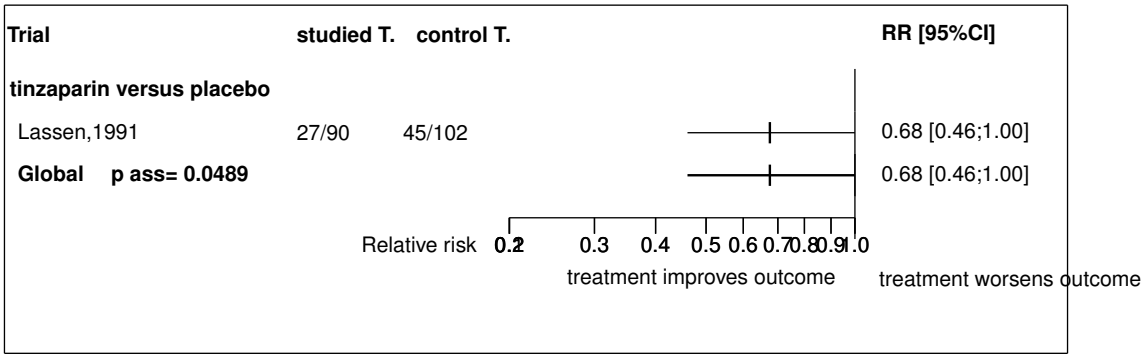
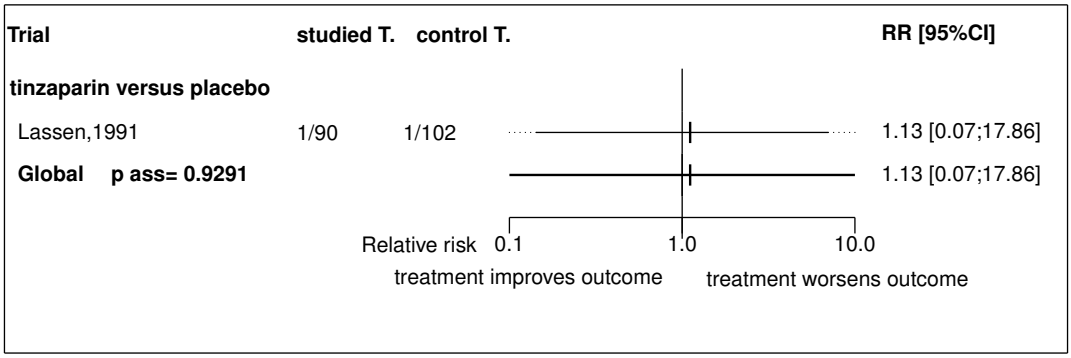


Figure 17.2: *Forest's plot for all cause death*



References

[1] Lassen MR, Borris LC, Christiansen HM, Boll KL, Eiskjaer SP, Nielsen BW, Schtt P, Olsen AD, Rodenberg JC, Lucht U. Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. Acta Orthop Scand 1991;62:33-8. [PMID=1848385]

17.3 Individual trial summaries

Table 17.6: *Lassen, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=210 (105 vs. 105) **Follow-up duration:** 8-10 days **Study design:** Randomized controlled trial Double blind	Elective hip	**Studied treatment:** tinzaparin 50/kg x1 +elastic stockings 1 x50U/kg;2h before; ND **Control treatment:** Placebo+elastic stockings Placebo	Deep vein thrombosis RR=0.68 [0.46;1.00]

Reference

Lassen MR, Borris LC, Christiansen HM, Boll KL, Eiskjaer SP, Nielsen BW, Schtt P, Olsen AD, Rodenberg JC, Lucht U. Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. Acta Orthop Scand 1991;62:33-8 [PMID=1848385]

18 Global meta-analysis: all Low molecular weight heparin

18.1 Global meta-analysis: all Low molecular weight heparin versus Dextran

Table 18.1: *All Low molecular weight heparinversus Dextran*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.55	0.39;0.76	0.0000	0.2991 (0.18)	4	689
symptomatic pulmonary embolism	RR=1.82	0.46;7.24	0.3975	0.5289 (0.00)	4	689

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 Low molecular weight heparin versus enoxaparin

Table 18.2: *All Low molecular weight heparinversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.57	0.42;0.78	0.0000	1.0000 (1.00)	1	1846
symptomatic pulmonary embolism	RR=1.00	0.02;50.45	0.9993	1.0000 (0.00)	1	2302
total VTE and all-cause mortality	RR=0.57	0.42;0.77	0.0000	1.0000 (0.00)	1	1849

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 Low molecular weight heparin versus no treatment

Table 18.3: *All Low molecular weight heparinversus no treatment*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.39	0.09;1.81	0.2302	0.1161 (0.59)	2	256

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 Low molecular weight heparin versus placebo

Table 18.4: *All Low molecular weight heparinversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.43	0.29;0.64	0.0000	0.1367 (0.43)	5	584
symptomatic pulmonary embolism	RR=0.65	0.05;8.29	0.7370	0.7714 (0.00)	2	212

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

18.5 Global meta-analysis: all Low molecular weight heparin versus Unfractionated heparin

Table 18.5: *All Low molecular weight heparinversus Unfractionated heparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.86	0.72;1.02	0.0738	0.8058 (0.00)	12	2463
symptomatic pulmonary embolism	RR=0.46	0.25;0.85	0.0138	0.9958 (0.00)	10	2246

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 Low molecular weight heparin

No ongoing trial was identified.

20 Excluded studies for Low molecular weight heparin

No trial was excluded.

References

Part III

Oral direct thrombin inhibitor

21 Overview of oral direct thrombin inhibitor

21.1 Included trials

A total of 6 randomized comparisons which enrolled 14107 patients were identified. In all, 1 randomized comparison concerned dabigatran 150mg , two dabigatran 220mg and 3 ximelagatran.
The detailed descriptions of trials and meta-analysis results is given in section 22 (page 194) for dabigatran 150mg, in section 23 (page 204) for dabigatran 220mg and in section 24 (page 216) for ximelagatran.

The average study size was 2351 patients (range 1816 to 2835). The first study was published in 2002, and the last study was published in 2007.
All trials were double blind in design. All included studies were reported in English language. We found one unpublished trial.
The table 21.1 (page 185) 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 oral direct thrombin inhibitor provide the results listed in tables 21.2 to 21.4 (page 187) and in the following graphs.

21.2.1 Dabigatran 150mg

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

21.2.2 Dabigatran 220mg

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

21.2.3 Ximelagatran

No significant difference was found between **ximelagatran** and **Enoxaparin** in terms of venous thromboembolism (RR=1.09, 95% CI 0.76 to 1.59, p=0.6323, 3 trials)with a random effect

model in reason of a heterogeneity (Het. p=0.0000)(RR=1.35, 95% CI 0.56 to 3.25, p=0.5029, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0082)

Table 21.1: *Main study characteristics - oral direct thrombin inhibitor*

Trial	Patients	Treatments	Trial design and method
Dabigatran 150mg			
Dabigatran 150mg versus enoxaparin			
RE-NOVATE (150mg), 2007 [1] n = 1174 vs. 1162	total hip replacement	dabigatran etexilate 150 mg q.d. 28-35 days **versus** enoxaparin 40 mg q.d. for 28-25 days	double blind Primary endpoint: total VTE and all-cause mortality 115 centres, Europe, Australia, South Africa mean follow-up: 33 days test intervalle: 2-4 (3)
Dabigatran 220mg			
Dabigatran 220mg versus enoxaparin			
RE-NOVATE 2, 0 n = 1010 vs. 1003	patients undergoing total hip-replacement surgery	dabigatran 220mg once daily for 28-35 Days **versus** enoxaparin 40mg subcutaneous once daily for 28-35 Days	double-blind parallel groups Primary endpoint: venous thromboembolism or death 108 centres, mean follow-up: 32 days test intervalle: 2-4 (3)
RE-NOVATE (220mg), 2007 [1] n = 1157 vs. 1162	total hip replacement	dabigatran etexilate 220 mg q.d. for 28-35 days **versus** enoxaparin 40 mg q.d. for 23-35 days	double blind parallel groups Primary endpoint: total VTE and all-cause mortality 115 centres, Europe, Australia, South Africa mean follow-up: 33 days test intervalle: 2-4 (3)
Ximelagatran			
Ximelagatran versus Enoxaparin			

continued...

Trial	Patients	Treatments	Trial design and method
Platinum (Colwell), 2003 [1] n = 906 vs. 910	adults undergoing hip replacement	ximelagatran 24 mg orally b.d., starting at least 12 h after surgery for 712 days **versus** enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 712 days	double-blind parallel group 126 centres, USA, Canada, Israel, Mexico,Argentina, South Africa
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
EXPRESS, 2003 [5, 6] 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 21.2: *Summary of all results for dabigatran 150mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
dabigatran 150mg versus enoxaparin						
symptomatic deep-vein thrombosis	RR=8.89	1.13;70.07	0.0380	1.0000 (0.00)	1	2298
major VTE (fatal and non fatal DVT,PE)	RR=1.09	0.70;1.70	0.7051	1.0000 (0.00)	1	1805
total VTE and all-cause mortality	RR=1.28	0.93;1.78	0.1347	1.0000 (0.00)	1	1771
asymptomatic DVT	RR=1.15	0.82;1.63	0.4174	1.0000 (1.00)	1	1765
non-fatal pulmonary embolism	RR=0.33	0.03;3.16	0.3357	1.0000 (0.00)	1	2298
distal DVT	RR=1.50	0.90;2.50	0.1218	1.0000 (0.00)	1	1765
proximal DVT	RR=0.90	0.55;1.49	0.6906	1.0000 (0.00)	1	1799
coronary event	RR=0.72	0.31;1.68	0.4508	1.0000 (0.00)	1	3463
all cause death	RR=0.98	0.02;49.28	0.9914	1.0000 (0.00)	1	2309
major bleeding	RR=0.83	0.42;1.63	0.5840	1.0000 (0.00)	1	2317

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 21.3: *Summary of all results for dabigatran 220mg*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
dabigatran 220mg versus enoxaparin						
symptomatic deep-vein thrombosis	RR=6.03	0.73;49.98	0.0961	1.0000 (0.00)	1	2279
major VTE (fatal and non fatal DVT,PE)	RR=0.78	0.48;1.27	0.3273	1.0000 (0.00)	1	1826
total VTE and all-cause mortality	RR=0.90	0.63;1.29	0.5652	1.0000 (0.00)	1	1777
asymptomatic DVT	RR=0.73	0.49;1.08	0.1153	1.0000 (0.00)	1	1777
non-fatal pulmonary embolism	RR=1.70	0.41;7.09	0.4671	1.0000 (0.00)	1	1777
distal DVT	RR=0.94	0.53;1.66	0.8251	1.0000 (0.00)	1	1768
proximal DVT	RR=0.57	0.32;1.00	0.0519	1.0000 (0.00)	1	1819
coronary event	RR=0.99	0.06;15.86	0.9961	1.0000 (0.00)	1	2013
all cause death	RR=6.03	0.30;120.18	0.2395	1.0000 (0.00)	1	2279
major bleeding	RR=1.29	0.70;2.37	0.4190	1.0000 (0.00)	1	2300

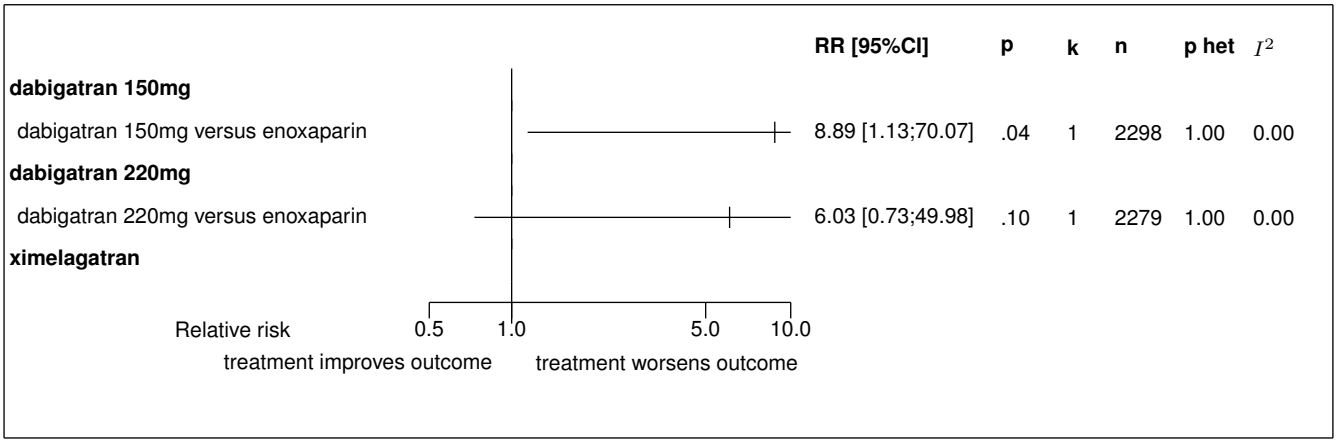
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 21.4: *Summary of all results for ximelagatran*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
ximelagatran versus Enoxaparin						
venous thromboembolism	RR=1.09 [1]	0.76;1.59	0.6323	0.0000 (0.91) †	3	6150
major bleeding	RR=1.35 [2]	0.56;3.25	0.5029	0.0082 (0.79) †	3	7369

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

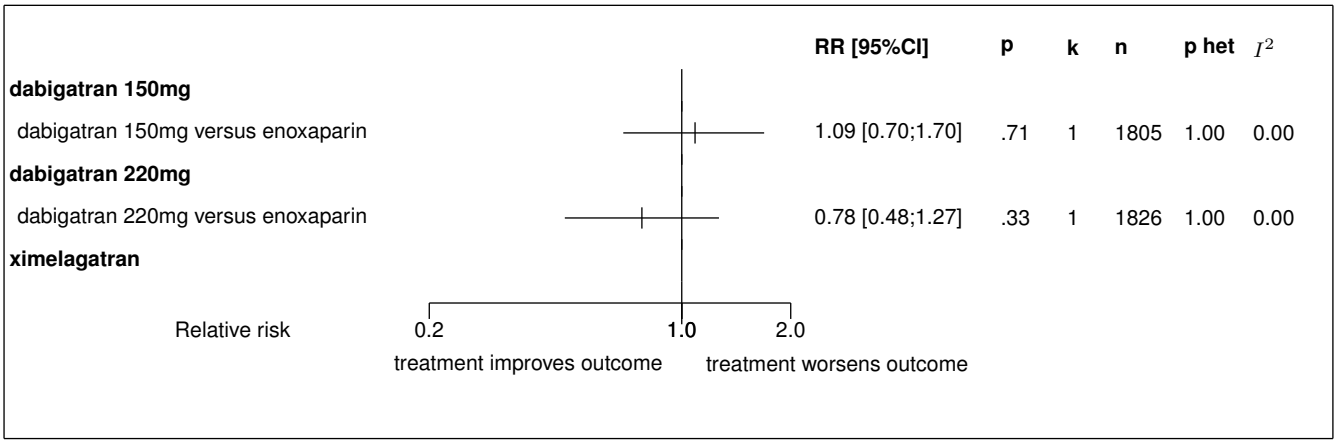
Figure 21.1: *Forest's plot for symptomatic deep-vein thrombosis*



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

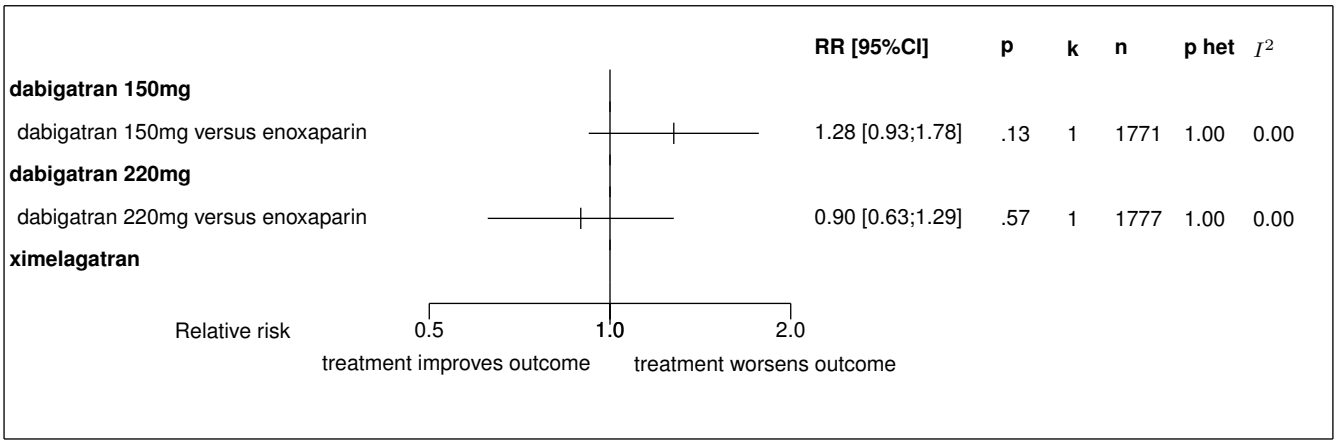
[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.99 95% CI 0.90;1.09
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.50 95% CI 1.02;2.19

Figure 21.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*



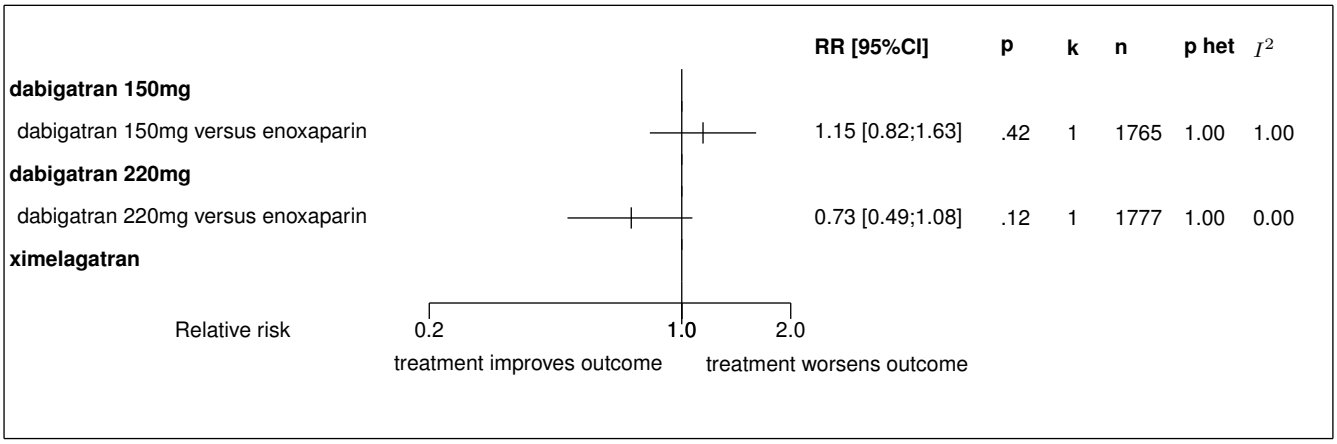
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.3: *Forest's plot for total VTE and all-cause mortality*



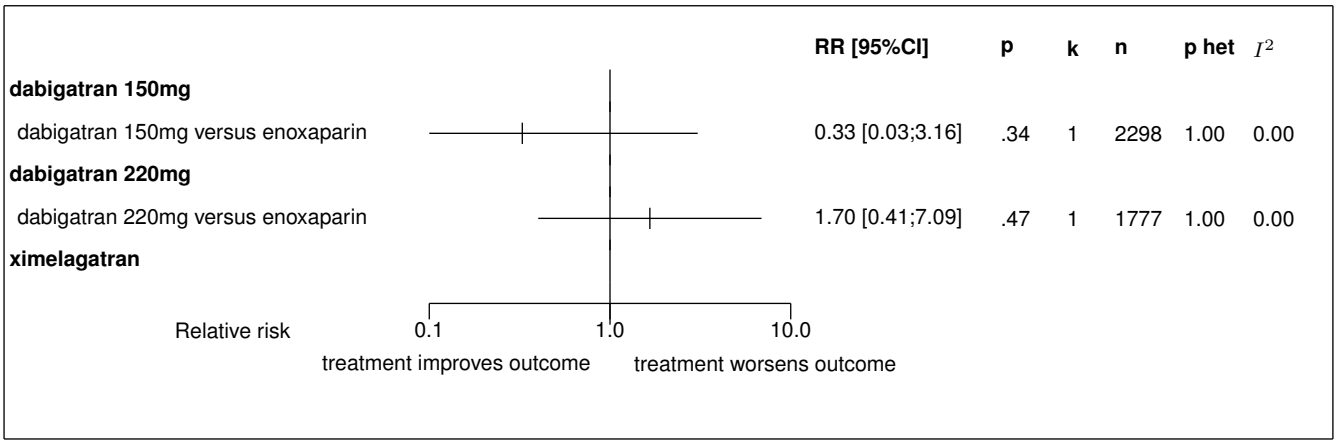
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.4: *Forest's plot for asymptomatic DVT*



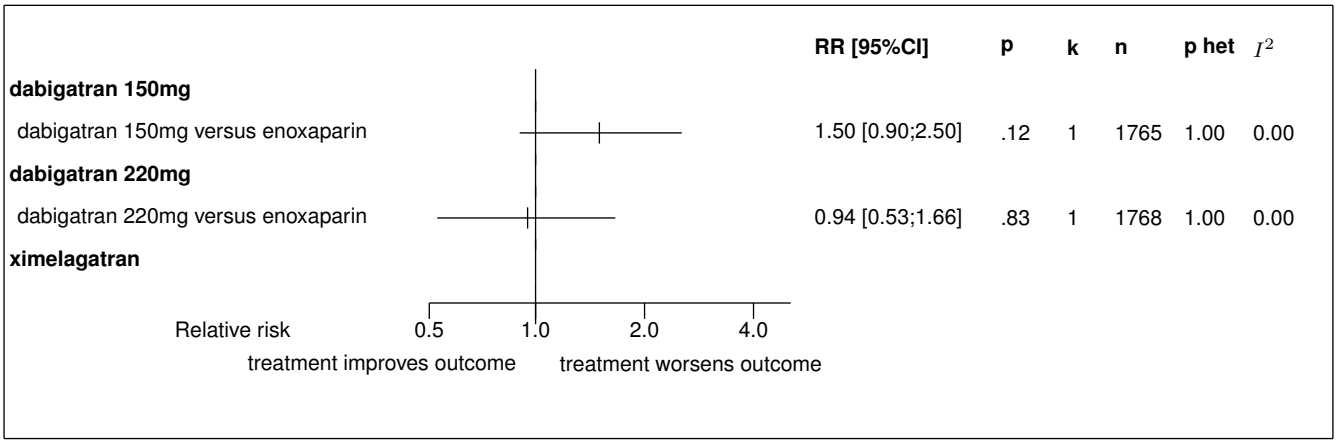
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.5: *Forest's plot for non-fatal pulmonary embolism*



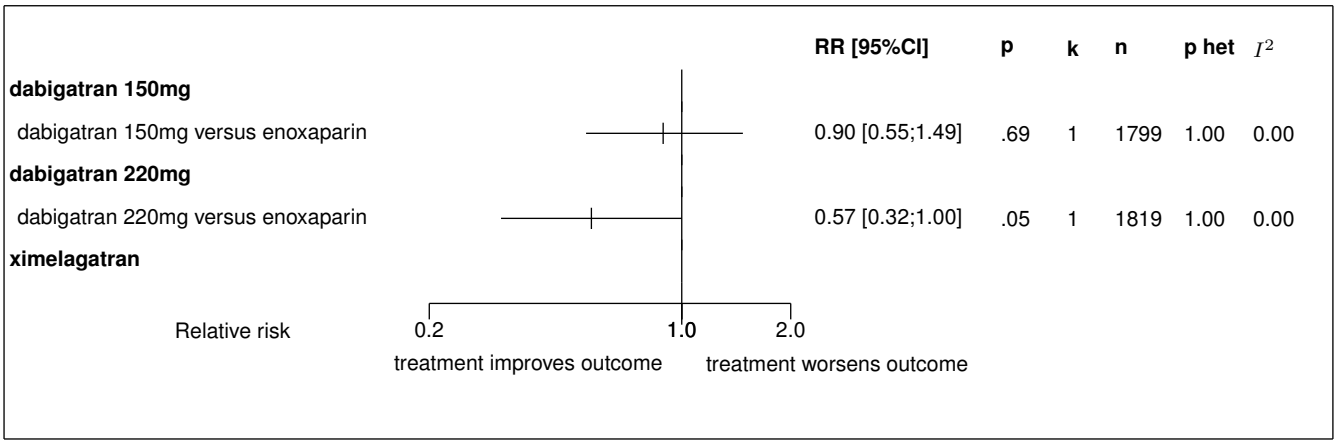
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.6: *Forest's plot for distal DVT*



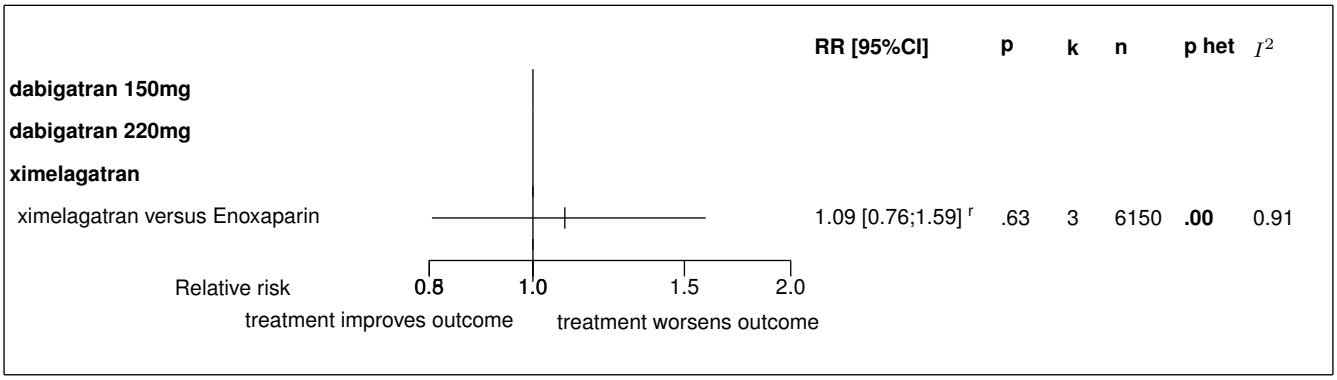
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.7: *Forest's plot for proximal DVT*



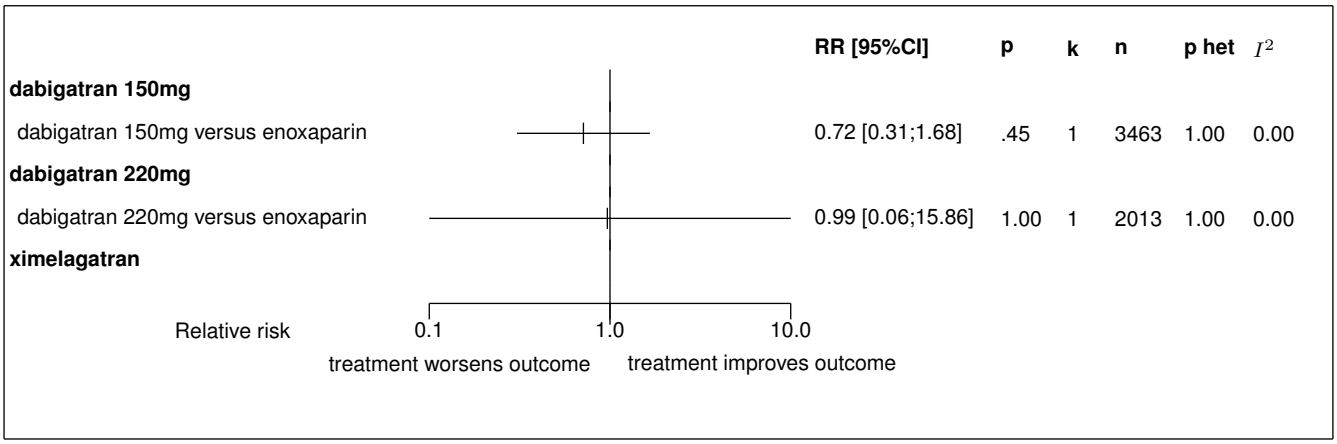
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.8: *Forest's plot for venous thromboembolism*



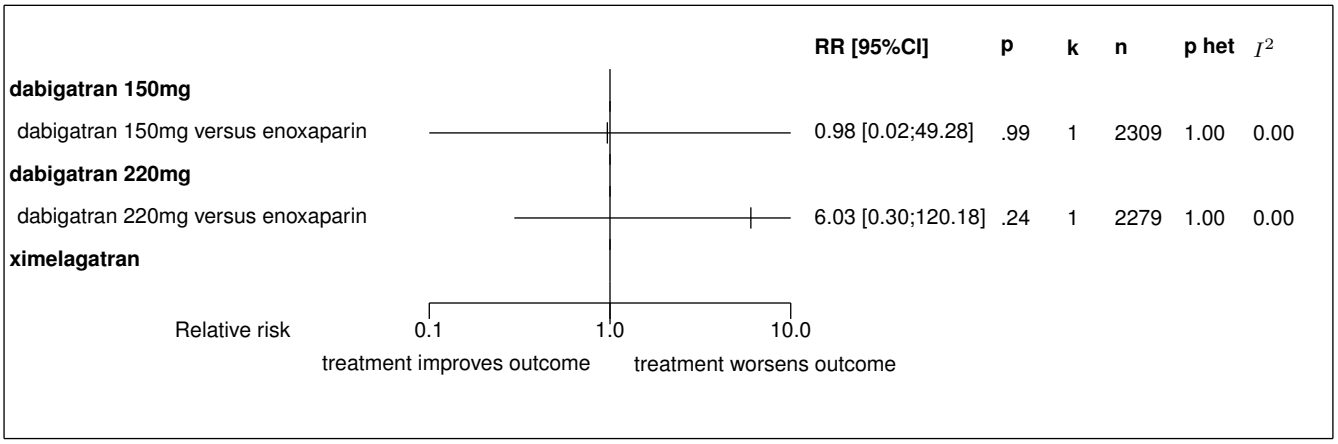
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.9: *Forest's plot for coronary event*



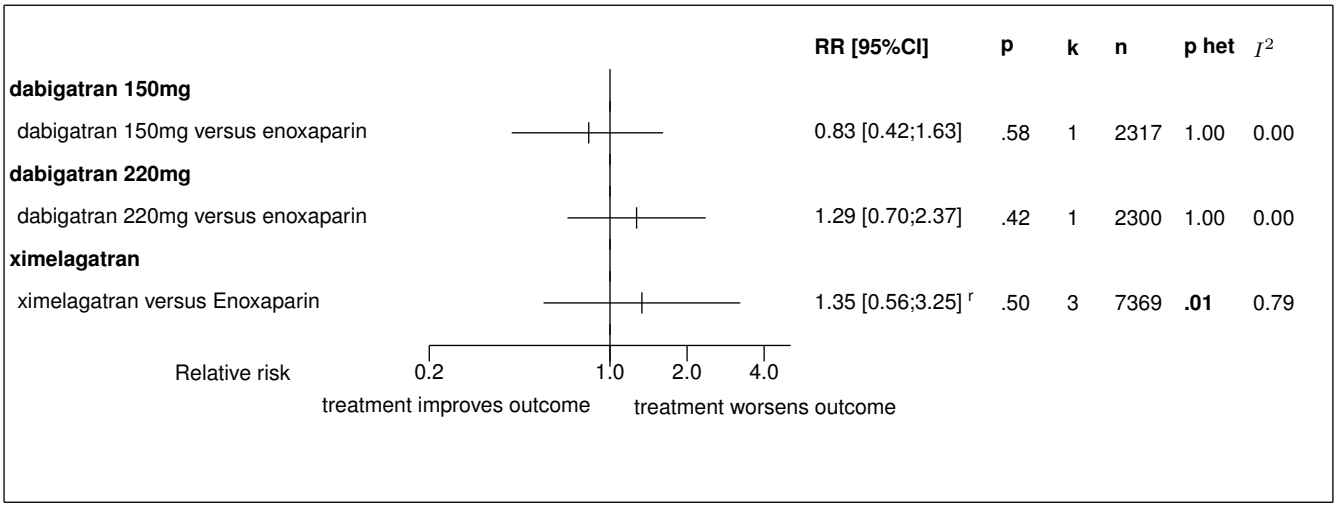
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 21.10: *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 21.11: *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

22 Detailed results for dabigatran 150mg

22.1 Available trials

Only one trial which randomized 2336 patients was identified: it compared dabigatran 150mg with enoxaparin.
This trial included 2336 patients and was published in 2007.
This trial was double blind in design.
It was reported in English language.
All cause death data was reported in 1 trials; 1 trials reported data on major VTE (fatal and non fatal DVT,PE); 1 trials reported data on distal DVT; 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on total VTE and all-cause mortality; 1 trials reported data on major bleeding; 1 trials reported data on proximal DVT; 1 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on asymptomatic DVT; and 1 trials reported data on coronary event.
Following tables 22.1 (page 194), 22.2 (page 194), 22.4 (page 196), and 22.3 (page 195) summarized the main characteristics of the trial including in this systematic review of randomized trials of dabigatran 150mg.

Table 22.1: *Treatment description - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Studied treatment	Control treatment
Dabigatran 150mg versus enoxaparin		
RE-NOVATE (150mg) (2007) [1] [a]	dabigatran etexilate 150 mg q.d. 28-35 days	Enoxaparin 40 mg q.d. for 28-25 days starting the evening before surgery

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

Table 22.2: *Descriptions of participants - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Patients	
Dabigatran 150mg versus enoxaparin		
RE-NOVATE (150mg) (2007) [1]	Total hip replacement **Inclusion criteria:** aged 18 years or older; weight at least 40 kg; scheduled for primary elective unilateral totalhip replacement	**Exclusion criteria:** any bleeding diathesis; history ofacute intracranial disease or haemorrhagic stroke;major surgery, trauma, uncontrolled hypertension, ormyocardial infarction in the past 3 months;gastrointestinal or urogenital bleeding, or ulcer diseasein the past 6 months; severe liver disease; alanine oraspartate aminotransferase concentrations greater thantwo times the upper limit of the normal range in thepast month; severe renal insuffi ciency (creatinineclearance less than 30 mL/min); use of long-actingnon-steroidal antiinfl ammatory drugs

continued...

Trial	Patients

Table 22.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 150mg versus enoxaparin				
RE-NOVATE (150mg), 2007 [1] n=2336	double blind confirmatory trial at low risk of bias	28-35 days, median 33d inclusion period: dec 2004 - apr 2006	Europe, Australia, South Africa 115 centres	total VTE and all-cause mortality

Table 22.4: *Trial characteristics - oral direct thrombin inhibitor - dabigatran 150mg*

Trial	mean follow-up	test intervalle
Dabigatran 150mg versus enoxaparin		
RE-NOVATE (150mg), 2007 [1]	33 days	2-4 (3)

22.2 Meta-analysis results

The results are detailed in table 22.5 (page 197). This table is followed by the Forest's plot corresponding to each endpoint.

Dabigatran 150mg versus enoxaparin

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

Table 22.5: *Results details - oral direct thrombin inhibitor - dabigatran 150mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dabigatran 150mg versus enoxaparin						
symptomatic deep-vein thrombosis	RR=8.89	[1.13;70.07]	0.0380	1.0000 (I^2=0.00)	1	2298
major VTE (fatal and non fatal DVT,PE)	RR=1.09	[0.70;1.70]	0.7051	1.0000 (I^2=0.00)	1	1805
total VTE and all-cause mortality	RR=1.28	[0.93;1.78]	0.1347	1.0000 (I^2=0.00)	1	1771
asymptomatic DVT	RR=1.15	[0.82;1.63]	0.4174	1.0000 (I^2=1.00)	1	1765
non-fatal pulmonary embolism	RR=0.33	[0.03;3.16]	0.3357	1.0000 (I^2=0.00)	1	2298
distal DVT	RR=1.50	[0.90;2.50]	0.1218	1.0000 (I^2=0.00)	1	1765
proximal DVT	RR=0.90	[0.55;1.49]	0.6906	1.0000 (I^2=0.00)	1	1799

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
coronary event	RR=0.72	[0.31;1.68]	0.4508	1.0000 (I^2=0.00)	1	3463
all cause death	RR=0.98	[0.02;49.28]	0.9914	1.0000 (I^2=0.00)	1	2309
major bleeding	RR=0.83	[0.42;1.63]	0.5840	1.0000 (I^2=0.00)	1	2317

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 symptomatic deep-vein thrombosis*

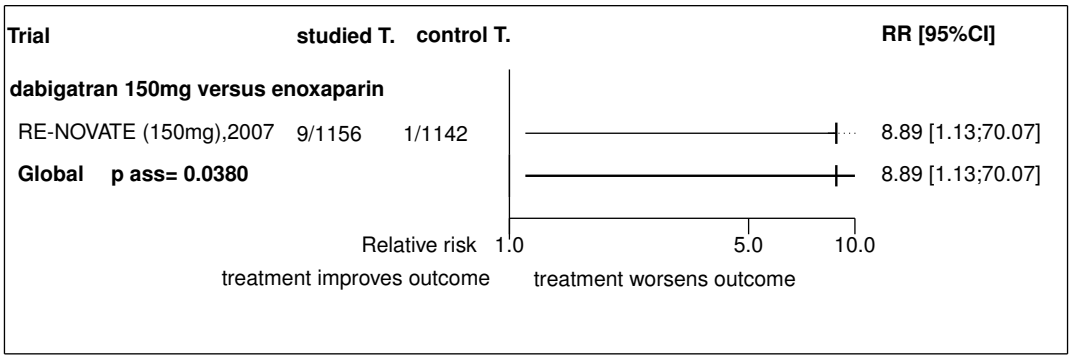


Figure 22.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

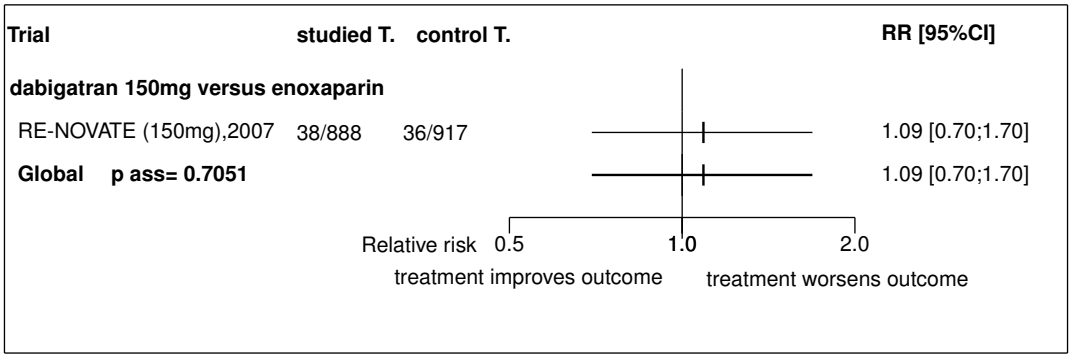


Figure 22.3: *Forest's plot for total VTE and all-cause mortality*

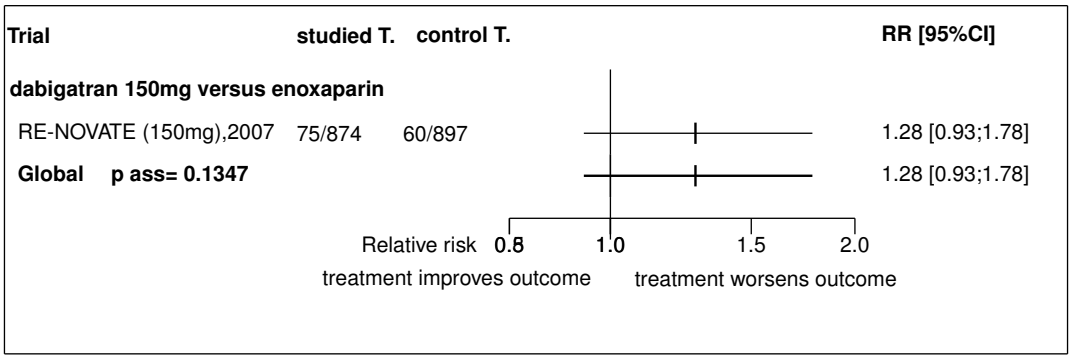


Figure 22.4: *Forest's plot for asymptomatic DVT*

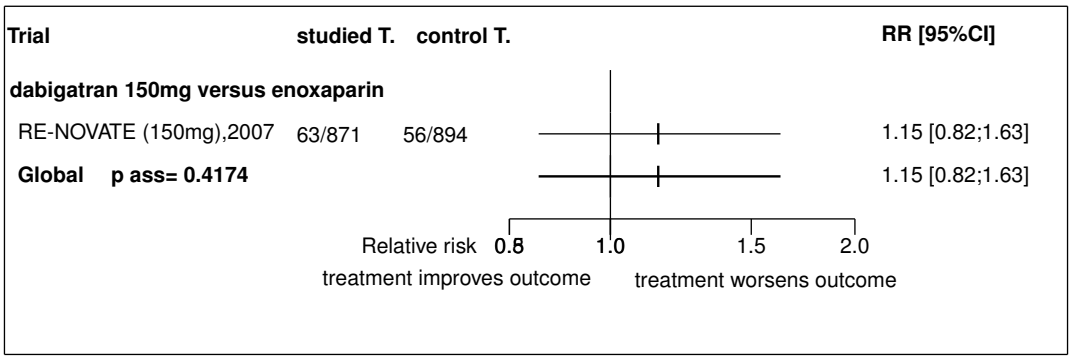


Figure 22.5: *Forest's plot for non-fatal pulmonary embolism*

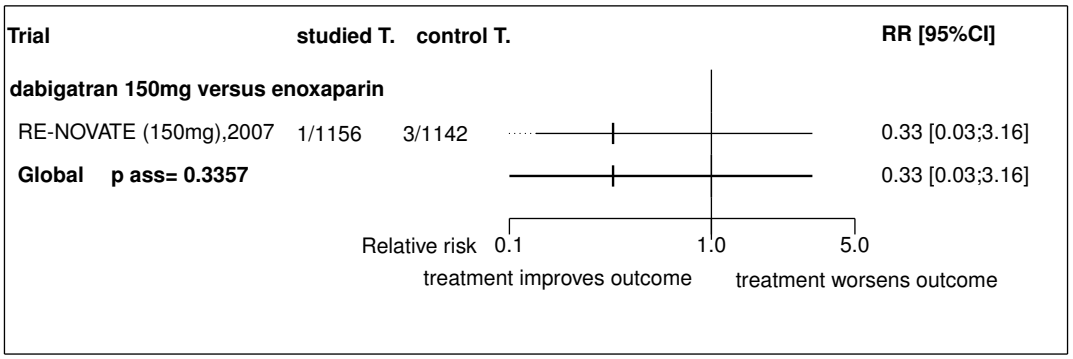


Figure 22.6: *Forest's plot for distal DVT*

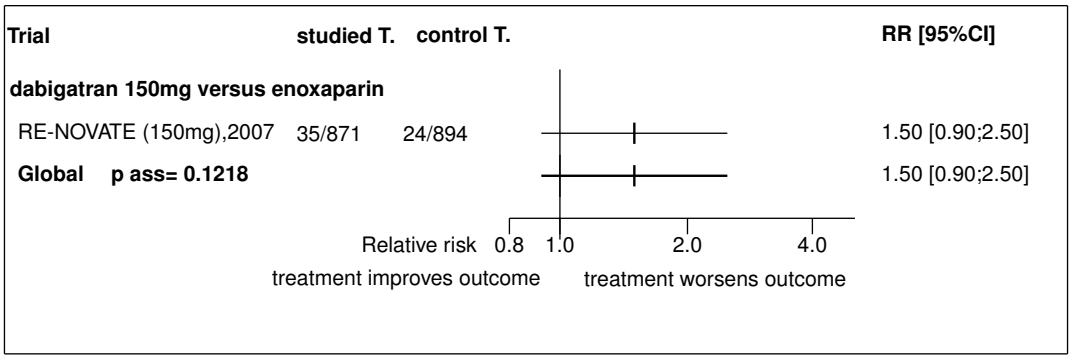


Figure 22.7: *Forest's plot for proximal DVT*

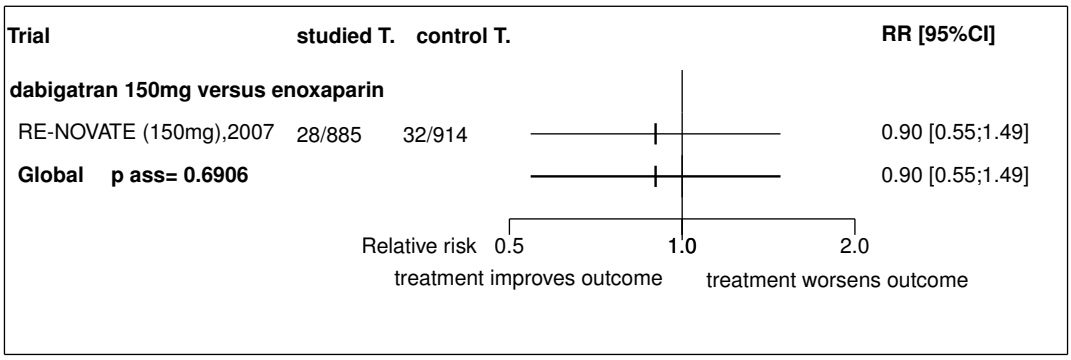


Figure 22.8: *Forest's plot for coronary event*

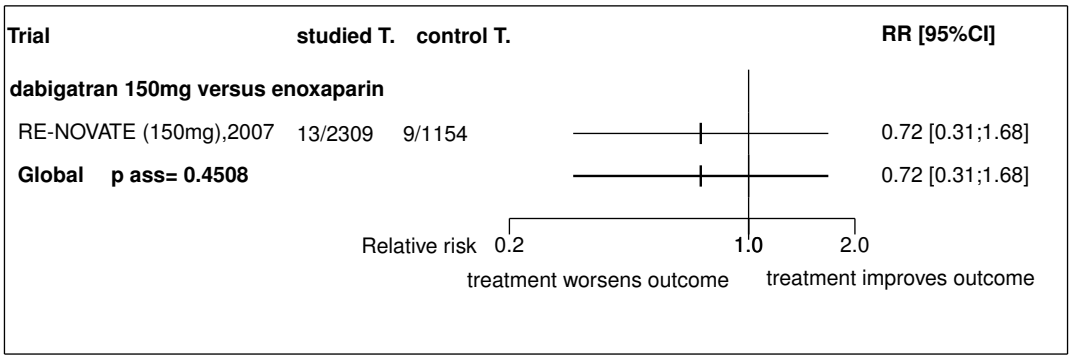


Figure 22.9: *Forest's plot for all cause death*

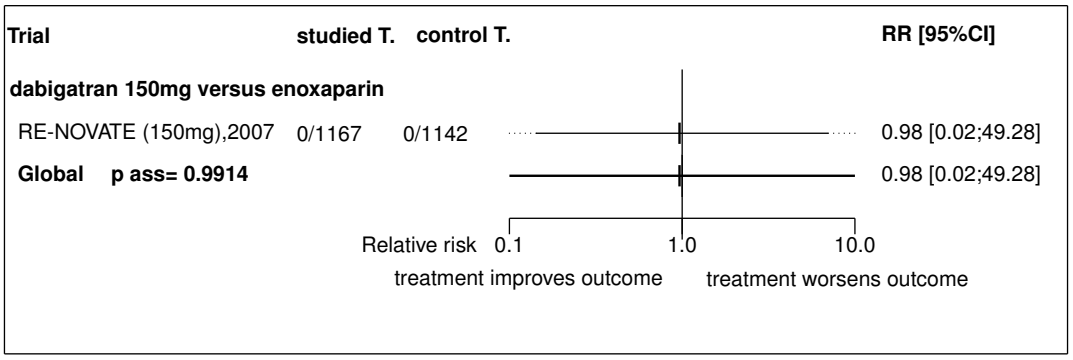
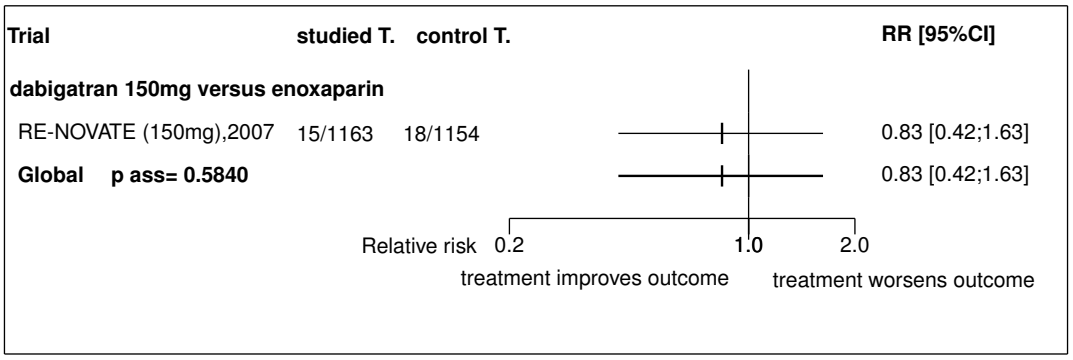


Figure 22.10: *Forest's plot for major bleeding*



References

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

22.3 Individual trial summaries

Table 22.6: *RE-NOVATE (150mg), 2007 - Trial synopsis*

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

Reference

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

23 Detailed results for dabigatran 220mg

23.1 Available trials

A total of 2 RCTs which randomized 4332 patients were identified: all compared dabigatran 220mg with enoxaparin.
The average study size was 2166 patients (range 2013 to 2319). The first study was published in 2007, and the last study was published in 2007.
All trials were double blind in design. All included studies were reported in English language. We found one unpublished trial.
All cause death data was reported in 1 trials; 1 trials reported data on major VTE (fatal and non fatal DVT,PE); 1 trials reported data on distal DVT; 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on total VTE and all-cause mortality; 1 trials reported data on major bleeding; 1 trials reported data on proximal DVT; 1 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on asymptomatic DVT; and 1 trials reported data on coronary event.
Following tables 23.1 (page 204), 23.2 (page 204), 23.4 (page 207), and 23.3 (page 206) summarized the main characteristics of the trials including in this systematic review of randomized trials of dabigatran 220mg.

Table 23.1: *Treatment description - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Studied treatment	Control treatment
Dabigatran 220mg versus enoxaparin		
RE-NOVATE 2 (0)	dabigatran 220mg once daily for 28-35 Days (110 mg administered on the day of surgery)	enoxaparin 40mg subcutaneous once daily for 28-35 Days
RE-NOVATE (220mg) (2007) [1] [b]	dabigatran etexilate 220 mg q.d. for 28-35 days starting the evening before surgery	Enoxaparin 40 mg q.d. for 23-35 days

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

Table 23.2: *Descriptions of participants - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Patients
Dabigatran 220mg versus enoxaparin	

continued...

Trial	Patients	
RE-NOVATE 2 (0)	Patients undergoing total hip-replacement surgery	
	Inclusion criteria: patients scheduled to undergo primary, unilateral, elective total hip arthroplasty; male or female 18 years of age or older.	**Exclusion criteria:** patients weighing less than 40 kg;history of bleeding diathesis;patients who in the investigators judgement are perceived as having an excessive risk of bleeding, for example, constitutional or acquired coagulation disorders or because of anticipated need of quinidine, verapamil or other restricted medication during the treatment period;major surgery or trauma (e.g., hip fracture) within 3 months of enrolment;recent unstable cardiovascular disease (in the investigators opinion) such as uncontrolled hypertension, that is ongoing at the time of enrolment or history of myocardial infarction within 3 months of enrolment;any history of haemorrhagic stroke or any of the following intracranial pathologies: bleeding, neoplasm, AV malformation or aneurysm.ongoing treatment for VTE;clinically relevant bleeding (gastrointestinal, pulmonary, intraocular or urogenital bleeding) within 6 months of enrolment;gastric or duodenal ulcer within one year of enrolment;liver disease expected to have any potential impact on survival (ie, hepatitis B or C, cirrhosis). This does not include Gilberts syndrome or hepatitis A with complete recovery;active liver disease or liver disease decreasing survival (e.g, acute hepatitis, chronic active hepatitis, cirrhosis) or ALT $>$3 x ULN;known severe renal insufficiency (CrCl $<$30 ml/min). Note: CrCl should be calculated only if serum creatinine is elevated or renal insufficiency is suspected;elevated creatinine that, in the investigators opinion, contraindicates venography;treatment with anticoagulants, clopidogrel, ticlopidine, abciximab, aspirin $>$162.5 mg/day or NSAID with t 1/2 $>$12 hours within 7 days prior to hip replacement surgery OR anticipated need while the patient is receiving study medication and prior to 24 hours after the last administration of any blinded study medication (COX-2 selective inhibitors are allowed);anticipated required use of intermittent pneumatic compression and electric stimulation of lower limb;premenopausal women (last menstruation within 1 year prior to signing informed consent) who are pregnant or are nursing. or are of childbearing potential and are NOT practicing acceptable methods of birth control;known allergy to radio opaque contrast media;history of thrombocytopenia, including heparin-induced thrombocytopenia, or a platelet count $<$100,000 cells/microliter at randomisation;allergy to heparins or dabigatran etexilate;active malignant disease or current cytostatic treatment. Patients should be disease free for at least 5 years;leg amputee;known alcohol or drug abuse which would interfere with completion of the study;contraindications to enoxaparin;

continued...

Trial	Patients	
RE-NOVATE (220mg) (2007) [1]	Total hip replacement	
	Inclusion criteria: aged 18 years or older; weight at least 40 kg; scheduled for primary elective unilateral total hip replacement	**Exclusion criteria:** any bleeding diathesis; history of acute intracranial disease or haemorrhagic stroke; major surgery, trauma, uncontrolled hypertension, or myocardial infarction in the past 3 months; gastrointestinal or urogenital bleeding, or ulcer disease in the past 6 months; severe liver disease; alanine or aspartate aminotransferase concentrations greater than two times the upper limit of the normal range in the past month; severe renal insuffi ciency (creatinine clearance less than 30 mL/min); use of long-acting non-steroidal antiinfl ammatory drugs

Table 23.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	Design	Duration	Centre	Primary endpoint
Dabigatran 220mg versus enoxaparin				
RE-NOVATE 2, 0 n=2013	Parallel groups double-blind confirmatory trial at low risk of bias	28-35 days (mean 32d) inclusion period: mar 2008- sept 2009	108 centres	venous thromboembolism or death
RE-NOVATE (220mg), 2007 [1] n=2319	Parallel groups double blind confirmatory trial at low risk of bias	28-35 days, median 33d inclusion period: dec 2004 - apr 2006	Europe, Australia, South Africa 115 centres	total VTE and all-cause mortality

Table 23.4: *Trial characteristics - oral direct thrombin inhibitor - dabigatran 220mg*

Trial	mean follow-up	test intervalle
Dabigatran 220mg versus enoxaparin		
RE-NOVATE 2, 0	32 days	2-4 (3)
RE-NOVATE (220mg), 2007 [1]	33 days	2-4 (3)

23.2 Meta-analysis results

The results are detailed in table 23.5 (page 208). This table is followed by the Forest's plot corresponding to each endpoint.

Dabigatran 220mg versus enoxaparin

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

Table 23.5: *Results details - oral direct thrombin inhibitor - dabigatran 220mg*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
dabigatran 220mg versus enoxaparin						
symptomatic deep-vein thrombosis	RR=6.03	[0.73;49.98]	0.0961	1.0000 (I^2=0.00)	1	2279
major VTE (fatal and non fatal DVT,PE)	RR=0.78	[0.48;1.27]	0.3273	1.0000 (I^2=0.00)	1	1826
total VTE and all-cause mortality	RR=0.90	[0.63;1.29]	0.5652	1.0000 (I^2=0.00)	1	1777
asymptomatic DVT	RR=0.73	[0.49;1.08]	0.1153	1.0000 (I^2=0.00)	1	1777
non-fatal pulmonary embolism	RR=1.70	[0.41;7.09]	0.4671	1.0000 (I^2=0.00)	1	1777

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
distal DVT	RR=0.94	[0.53;1.66]	0.8251	1.0000 (I^2=0.00)	1	1768
proximal DVT	RR=0.57	[0.32;1.00]	0.0519	1.0000 (I^2=0.00)	1	1819
coronary event	RR=0.99	[0.06;15.86]	0.9961	1.0000 (I^2=0.00)	1	2013
all cause death	RR=6.03	[0.30;120.18]	0.2395	1.0000 (I^2=0.00)	1	2279
major bleeding	RR=1.29	[0.70;2.37]	0.4190	1.0000 (I^2=0.00)	1	2300

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

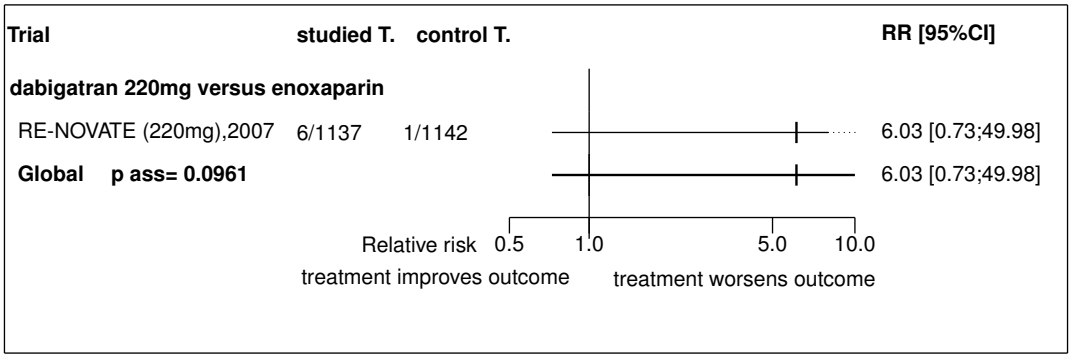


Figure 23.2: *Forest's plot for major VTE (fatal and non fatal DVT,PE)*

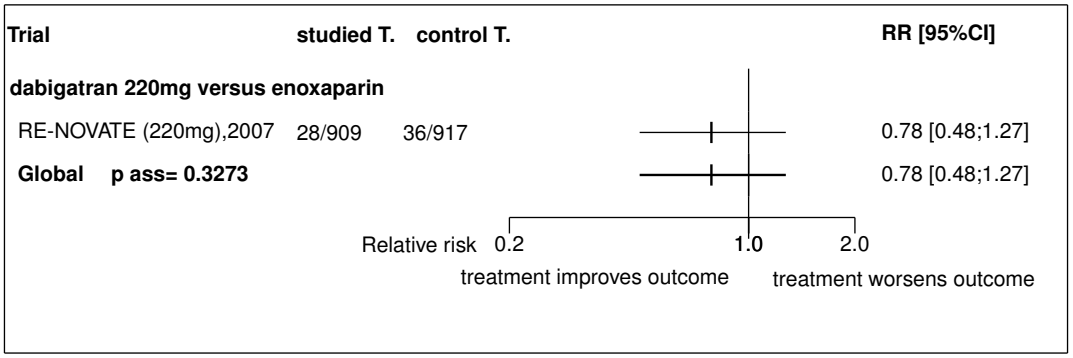


Figure 23.3: *Forest's plot for total VTE and all-cause mortality*

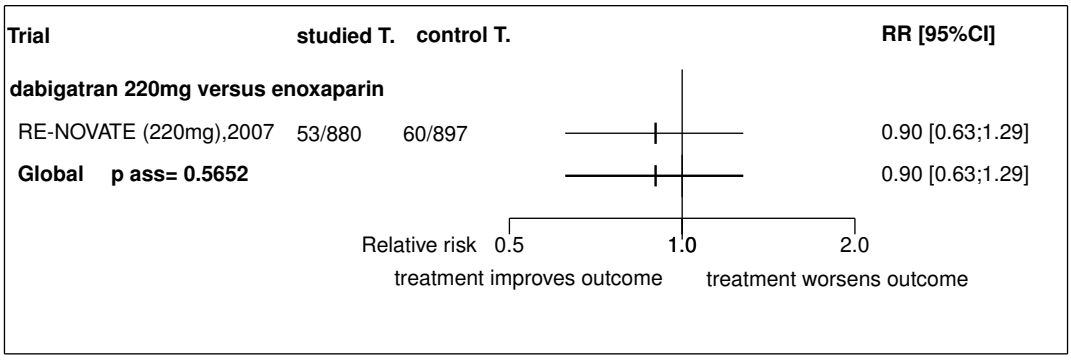


Figure 23.4: *Forest's plot for asymptomatic DVT*

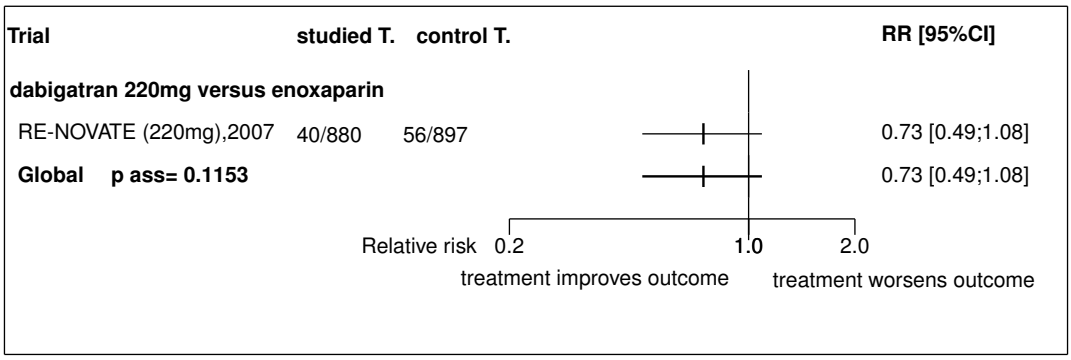


Figure 23.5: *Forest's plot for non-fatal pulmonary embolism*

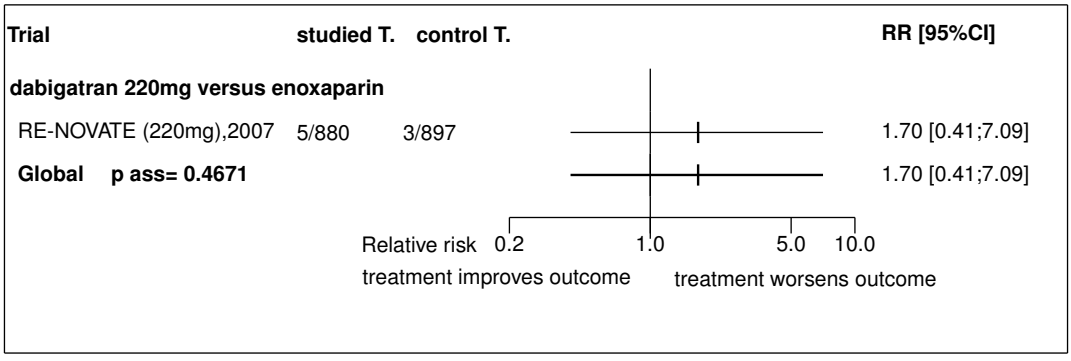


Figure 23.6: *Forest's plot for distal DVT*

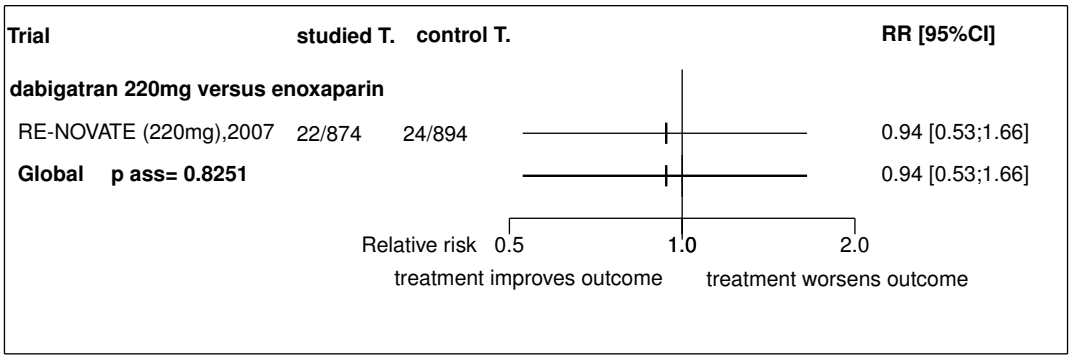


Figure 23.7: *Forest's plot for proximal DVT*

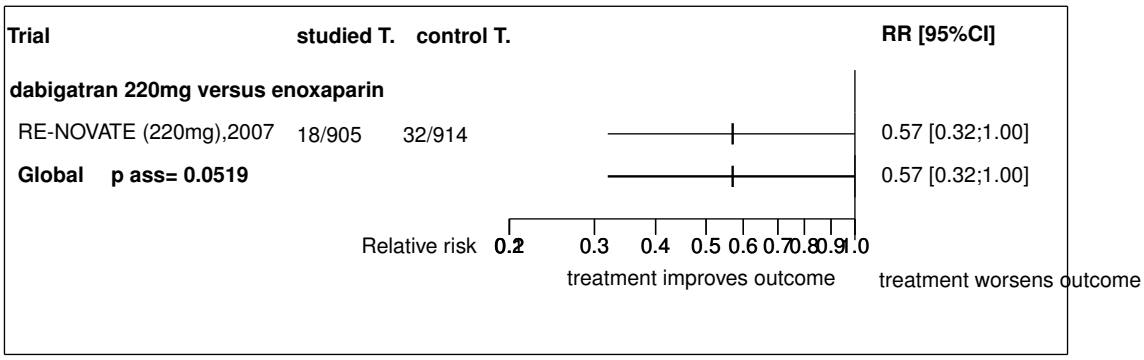


Figure 23.8: *Forest's plot for coronary event*

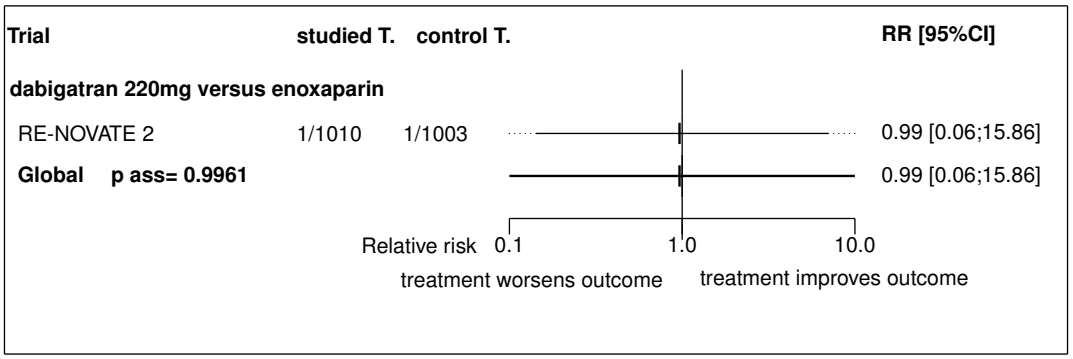


Figure 23.9: *Forest's plot for all cause death*

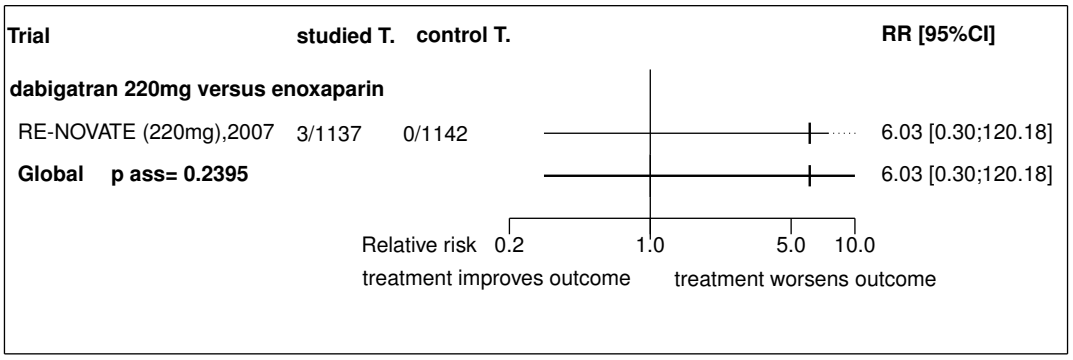
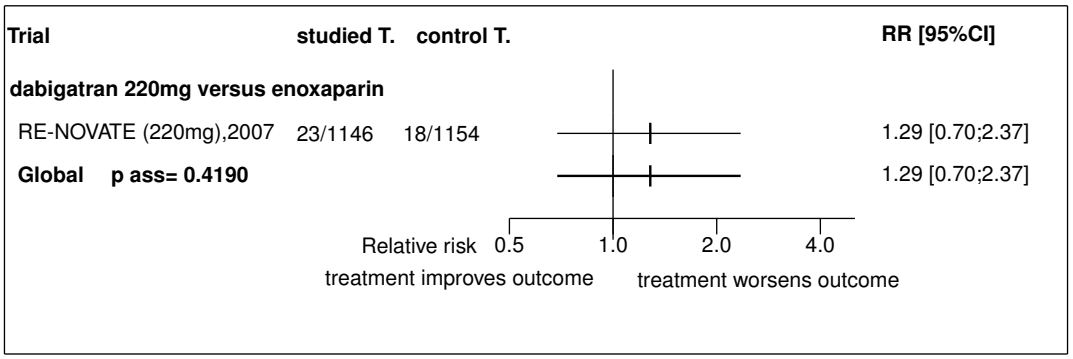


Figure 23.10: *Forest's plot for major bleeding*



References

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

23.3 Individual trial summaries

Table 23.6: *RE-NOVATE 2, 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2013 (1010 vs. 1003) **Follow-up duration:** 28-35 days (mean 32d) **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias 108 centres **Inclusion period:** mar 2008- sept 2009	Patients undergoing total hip-replacement surgery **Inclusion criteria:** patients scheduled to undergo primary, unilateral, elective total hip arthroplasty; male or female 18 years of age or older. **Exclusion criteria:** patients weighing less than 40 kg;history of bleeding diathesis;patients who in the investigators judgement are perceived as having an excessive risk of bleeding, for example, constitutional or acquired coagulation disorders or because of anticipated need of quinidine, verapamil or other restricted medication during the treatment period;major surgery or trauma (e.g., hip fracture) within 3 months of enrolment;recent unstable cardiovascular disease (in the investigators opinion) such as uncontrolled hypertension, that is ongoing at the time of enrolment or history of myocardial infarction withi	**Studied treatment:** dabigatran 220mg once daily for 28-35 Days (110 mg administered on the day of surgery) **Control treatment:** enoxaparin 40mg subcutaneous once daily for 28-35 Days	
Reference			

Table 23.7: *RE-NOVATE (220mg), 2007 - Trial synopsis*

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

Reference

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

24 Detailed results for ximelagatran

24.1 Available trials

A total of 3 RCTs which randomized 7439 patients were identified: all compared ximelagatran with Enoxaparin.
The average study size was 2479 patients (range 1816 to 2835). The first study was published in 2002, and the last study was published in 2003.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Venous thromboembolism data was reported in 3 trials; and 3 trials reported data on major bleeding.
Following tables 24.1 (page 216), 24.2 (page 216), 24.4 (page 218), and 24.3 (page 217) summarized the main characteristics of the trials including in this systematic review of randomized trials of ximelagatran.

Table 24.1: *Treatment description - oral direct thrombin inhibitor - ximelagatran*

Trial	Studied treatment	Control treatment
Ximelagatran versus Enoxaparin		
Platinum (Colwell) (2003) [1]	Ximelagatran 24 mg orally b.d., starting at least 12 h after surgery for 712 days	Enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 712 days
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
EXPRESS (2003) [5, 6]	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 24.2: *Descriptions of participants - oral direct thrombin inhibitor - ximelagatran*

Trial	Patients
Ximelagatran versus Enoxaparin	
Platinum (Colwell) (2003) [1]	Adults undergoing hip replacement
METHRO III (2002) [2, 3, 4]	Hip or knee replacement
EXPRESS (2003) [5, 6]	Hip or knee replacement

continued...

Trial	Patients

Table 24.3: *Design and methodological quality of trials - oral direct thrombin inhibitor - ximelagatran*

Trial	Design	Duration	Centre	Primary endpoint
Ximelagatran versus Enoxaparin				
Platinum (Colwell), 2003 [1] n=1816	parallel group double-blind	712 days	USA, Canada, Israel, Mexico,Argentina, South Africa 126 centres	
METHRO III, 2002 [2, 3, 4] n=2788	double-blind	811 days	Europe, South Africa 80 centres	venous thromboembolism
EXPRESS, 2003 [5, 6] n=2835	parallel group double-blind	811 days	Europe 77 centres	venous thromboembolism

Table 24.4: *Trial characteristics - oral direct thrombin inhibitor - ximelagatran*

Trial
Ximelagatran versus Enoxaparin
Platinum (Colwell), 2003 [1]
METHRO III, 2002 [2, 3, 4]
EXPRESS, 2003 [5, 6]

24.2 Meta-analysis results

The results are detailed in table 24.5 (page 219). This table is followed by the Forest's plot corresponding to each endpoint.

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 1.09 (95% CI 0.76 to 1.59, p=0.6323). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0000, I^2 = 0.91%).
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 1.35 (95% CI 0.56 to 3.25, p=0.5029). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0082, I^2 = 0.79%).

Table 24.5: *Results details - oral direct thrombin inhibitor - ximelagatran*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ximelagatran versus Enoxaparin						
venous thromboembolism	RR=1.09	[0.76;1.59]	0.6323	0.0000 (I^2=0.91)	3	6150
major bleeding	RR=1.35	[0.56;3.25]	0.5029	0.0082 (I^2=0.79)	3	7369

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 24.1: *Forest's plot for venous thromboembolism*

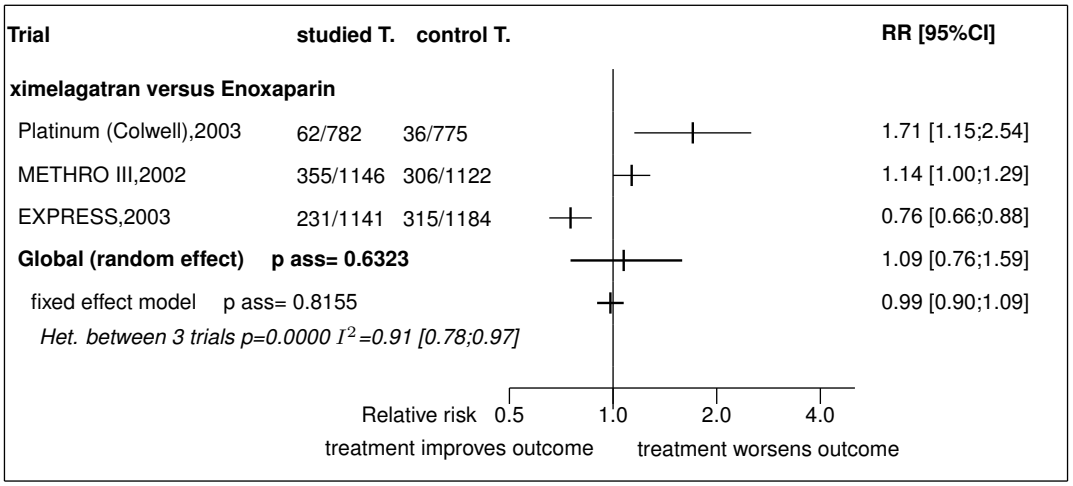
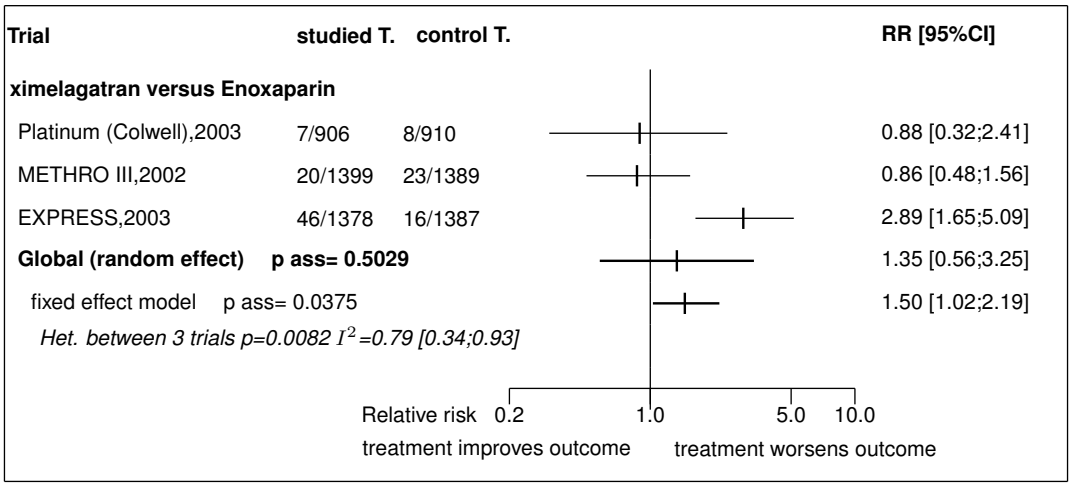


Figure 24.2: *Forest's plot for major bleeding*



References

[1] Colwell CW Jr, Berkowitz SD, Davidson BL, Lotke PA, Ginsberg JS, Lieberman JR, Neubauer J, McElhattan JL, Peters GR, Francis CW. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A randomized, double-blind study. J Thromb Haemost 2003;1:2119-30. [PMID=14521593]

[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]

[3] Mouret P. [The oral direct thrombin inhibitor Ximelagatran Prophylaxis of venous thromboembolism in hip and knee replacement]. Hamostaseologie 2002;22:21-4. [PMID=12215757]

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

[5] 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]

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

24.3 Individual trial summaries

Table 24.6: *Platinum (Colwell), 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1816 (906 vs. 910) **Follow-up duration:** 712 days **Study design:** Randomized controlled trial parallel group Double-blind USA, Canada, Israel, Mexico,Argentina, South Africa, 126 centres	Adults undergoing hip replacement	**Studied treatment:** Ximelagatran 24 mg orally b.d., starting at least 12 h after surgery for 712 days **Control treatment:** Enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 712 days	

Reference

Colwell CW Jr, Berkowitz SD, Davidson BL, Lotke PA, Ginsberg JS, Lieberman JR, Neubauer J, McElhattan JL, Peters GR, Francis CW. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A randomized, double-blind study. J Thromb Haemost 2003;1:2119-30 [PMID=14521593]

Table 24.7: *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]
Mouret P. [The oral direct thrombin inhibitor Ximelagatran Prophylaxis of venous thromboembolism in hip and knee replacement]. Hamostaseologie 2002;22:21-4 [PMID=12215757]
Eriksson BI. Clinical experience of melagatran/ximelagatran in major orthopaedic surgery. Thromb Res 2003;109 Suppl 1:S23-9 [PMID=12818631]

Table 24.8: *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]
Glynn O. The express study: preliminary results. Int J Clin Pract 2003;57:57-9 [PMID=12587945]

25 Global meta-analysis: all oral direct thrombin inhibitor

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

Table 25.1: *All oral direct thrombin inhibitorversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=7.35	1.68;32.23	0.0081	0.7965 (0.00)	2	4577
major VTE (fatal and non fatal DVT,PE)	RR=0.94	0.68;1.30	0.7005	0.3285 (0.00)	2	3631
total VTE and all-cause mortality	RR=1.08	0.77;1.53	0.6513	0.1518 (0.51)	2	3548
asymptomatic DVT	RR=0.93	0.59;1.45	0.7387	0.0858 (0.66)	2	3542
non-fatal pulmonary embolism	RR=0.95	0.21;4.43	0.9527	0.2293 (0.31)	2	4075
distal DVT	RR=1.21	0.76;1.91	0.4212	0.2315 (0.30)	2	3533
proximal DVT	RR=0.73	0.47;1.15	0.1770	0.2297 (0.31)	2	3618
venous thromboembolism	RR=1.09 [1]	0.76;1.59	0.6323	0.0000 (0.91) †	3	6150
major bleeding	RR=1.23 [2]	0.73;2.05	0.4336	0.0187 (0.66) †	5	11986

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

26 Ongoing studies of oral direct thrombin inhibitor

No ongoing trial was identified.

27 Excluded studies for oral direct thrombin inhibitor

No trial was excluded.

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.99 95% CI 0.90;1.09
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.30 95% CI 0.97;1.74

References

Part IV

Platelet aggregation inhibitors

28 Overview of platelet aggregation inhibitors

28.1 Included trials

A total of 7 randomized comparisons which enrolled 528 patients were identified. In all, 4 randomized comparisons concerned Aspirin and 3 Hydroxychloroquine.
The detailed descriptions of trials and meta-analysis results is given in section 29 (page 236) for Aspirin and in section 30 (page 249) for Hydroxychloroquine.

The average study size was 75 patients (range 35 to 145). The first study was published in 1975, and the last study was published in 1986.
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.
The table 28.1 (page 230) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

28.2 Summary of meta-analysis results

The meta-analysis of the available trials about platelet aggregation inhibitors provide the results listed in tables 28.2 to 28.3 (page 232) and in the following graphs.

28.2.1 Aspirin

Aspirin was superior to **no treatment** in terms of deep vein thrombosis (RR=0.14, 95% CI 0.04 to 0.45, p=0.0000, 1 trial). However, no significant difference was found on non-fatal pulmonary embolism (RR=0.25, 95% CI 0.01 to 7.24, p=0.4196, 1 trial), fatal pulmonary embolism (RR=0.50, 95% CI 0.01 to 24.59, p=0.7273, 1 trial)and wound haematoma / infection (RR=1.00, 95% CI 0.09 to 10.59, p=1.0000, 1 trial).

Aspirin was superior to **placebo** in terms of proximal DVT (RR=0.47, 95% CI 0.29 to 0.76, p=0.0021, 2 trials). However, no significant difference was found on deep vein thrombosis (RR=0.72, 95% CI 0.45 to 1.15, p=0.1686, 3 trials), non-fatal pulmonary embolism (RR=0.51, 95% CI 0.13 to 1.97, p=0.3262, 3 trials), fatal pulmonary embolism (RR=1.03, 95% CI 0.11 to 9.81, p=0.9766, 3 trials)and wound haematoma / infection (RR=1.22, 95% CI 0.40 to 3.69, p=0.7243, 2 trials).

28.2.2 Hydroxychloroquine

No significant difference was found between **Hydroxychloroquine** and **placebo** in terms of deep vein thrombosis (RR=0.97, 95% CI 0.70 to 1.34, p=0.8338, 3 trials), non-fatal pulmonary embolism (RR=2.19, 95% CI 0.52 to 9.17, p=0.2847, 2 trials), fatal pulmonary embolism (RR=0.98, 95% CI 0.10 to 9.17, p=0.9866, 3 trials)and wound haematoma / infection (RR=1.00, 95% CI 0.07 to 15.12, p=1.0000, 1 trial).

Table 28.1: *Main study characteristics - platelet aggregation inhibitors*

Trial	Patients	Treatments	Trial design and method
Aspirin			
Aspirin versus no treatment			
Rocha, 1986 [1] n = 60 vs. 30	total hip replacement	aspirin 250mg or 1000mg daily **versus** control (combination of heparin plus dihydroergotamine) treatment duration: 1 weeks	open parallel groups
Aspirin versus placebo			
Stockholm-I, 1975 [2] n = 26 vs. 25	elective surgery of the hip	aspirin 2000mg daily **versus** placebo treatment duration: 2 weeks	double blind
Harris-I, 1977 [3] n = 58 vs. 59	patients over 40 years of age, who had undergone total hip replacement	aspirin 1200mg daily **versus** placebo treatment duration: 1 weeks	double-blind parallel groups Primary endpoint: radiographic phlebography
Sautter, 1983 [4] n = 68 vs. 77	patient with total hip replacement	aspirin 900mg daily + sulfinpyrazone **versus** placebo treatment duration: 3 weeks	parallel groups
Hydroxychloroquine			
Hydroxychloroquine versus placebo			
Cooke, 1977 [1] n = 25 vs. 25	elective surgery on the hip	hydroxychloroquine **versus** placebo treatment duration: 2 weeks	double-blind parallel groups

continued...

Trial	Patients	Treatments	Trial design and method
Hume-A, 1977 [2, 3] n = 20 vs. 20	total hip replacement	hydroxychloroquine **versus** placebo treatment duration: 2 weeks	
Stockholm-II, 1981 [4] n = 18 vs. 17	total hip replacement	hydroxychloroquine **versus** placebo treatment duration: 2 weeks	

Table 28.2: *Summary of all results for Aspirin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Aspirin versus no treatment						
deep vein thrombosis	RR=0.14	0.04;0.45	0.0000	1.0000 (0.00)	1	90
non-fatal pulmonary embolism	RR=0.25	0.01;7.24	0.4196	1.0000 (0.00)	1	90
fatal pulmonary embolism	RR=0.50	0.01;24.59	0.7273	1.0000 (0.00)	1	90
wound haematoma / infection	RR=1.00	0.09;10.59	1.0000	1.0000 (0.00)	1	90
bleeding	RR=0.50	0.01;24.59	0.7273	1.0000 (0.00)	1	90
Aspirin versus placebo						
deep vein thrombosis	RR=0.72	0.45;1.15	0.1686	0.1498 (0.47)	3	313
non-fatal pulmonary embolism	RR=0.51	0.13;1.97	0.3262	0.9402 (0.00)	3	313
proximal DVT	RR=0.47	0.29;0.76	0.0021	0.5549 (0.00)	2	262
fatal pulmonary embolism	RR=1.03	0.11;9.81	0.9766	0.9983 (0.00)	3	313
wound haematoma / infection	RR=1.22	0.40;3.69	0.7243	0.3546 (0.00)	2	262
bleeding	RR=1.03	0.11;9.81	0.9766	0.9983 (0.00)	3	313

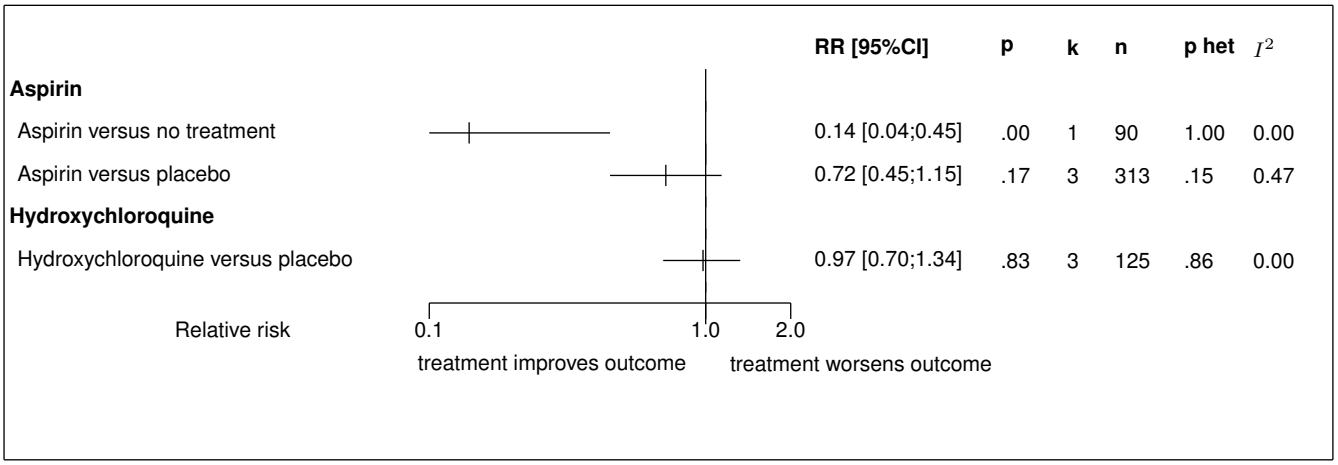
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 28.3: *Summary of all results for Hydroxychloroquine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Hydroxychloroquine versus placebo						
deep vein thrombosis	RR=0.97	0.70;1.34	0.8338	0.8639 (0.00)	3	125
non-fatal pulmonary embolism	RR=2.19	0.52;9.17	0.2847	0.6465 (0.00)	2	85
fatal pulmonary embolism	RR=0.98	0.10;9.17	0.9866	0.9997 (0.00)	3	125
wound haematoma / infection	RR=1.00	0.07;15.12	1.0000	1.0000 (0.00)	1	50
bleeding	RR=0.98	0.10;9.17	0.9866	0.9997 (0.00)	3	125

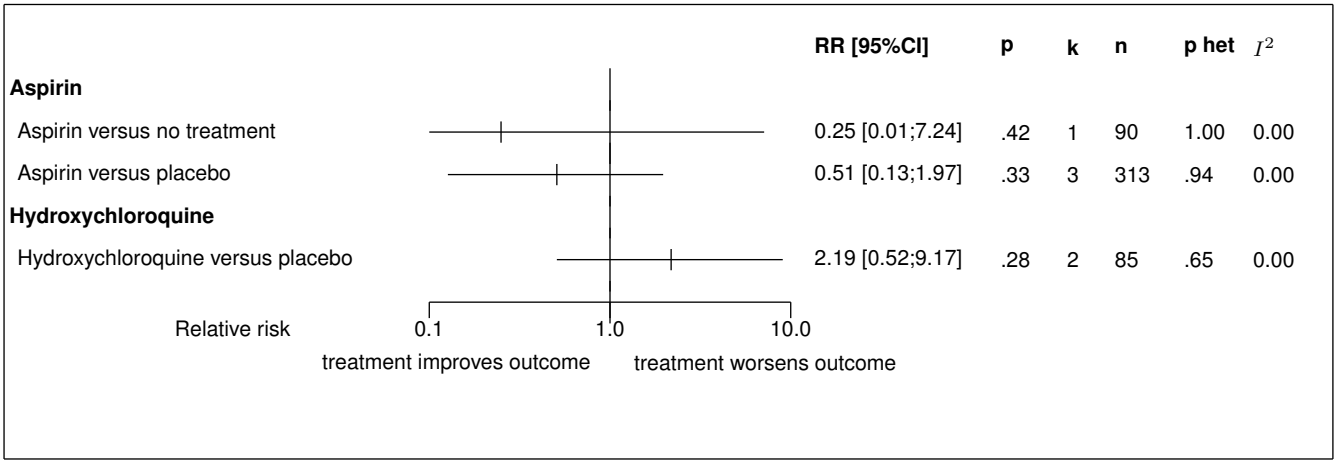
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 28.1: *Forest's plot for deep vein thrombosis*



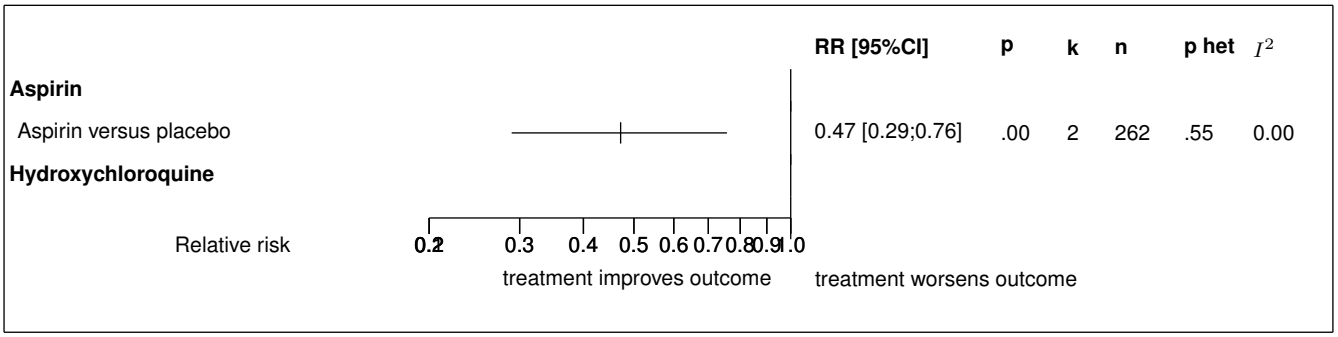
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 28.2: *Forest's plot for non-fatal pulmonary embolism*



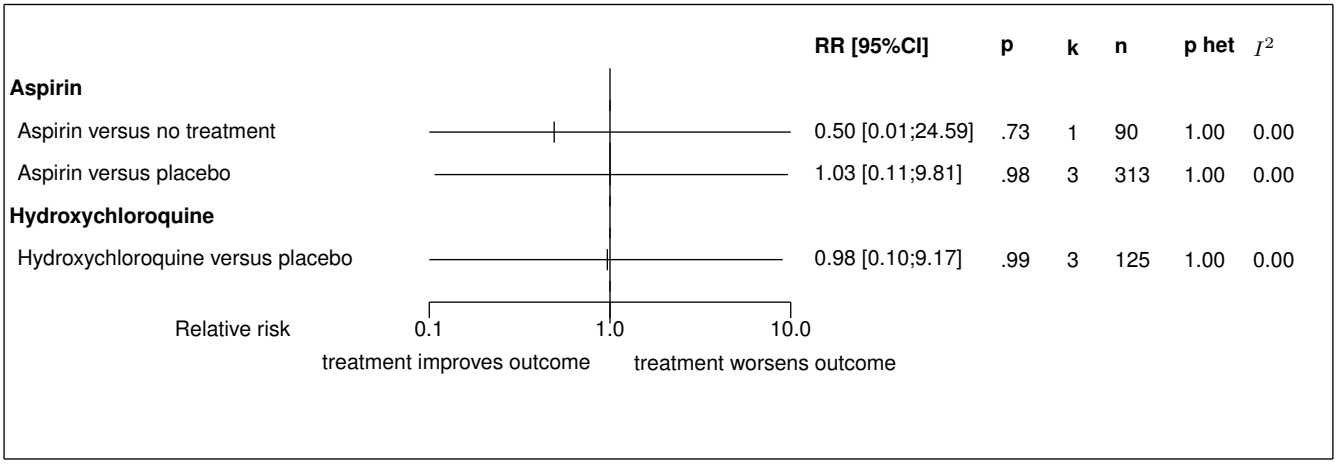
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 28.3: *Forest's plot for proximal DVT*



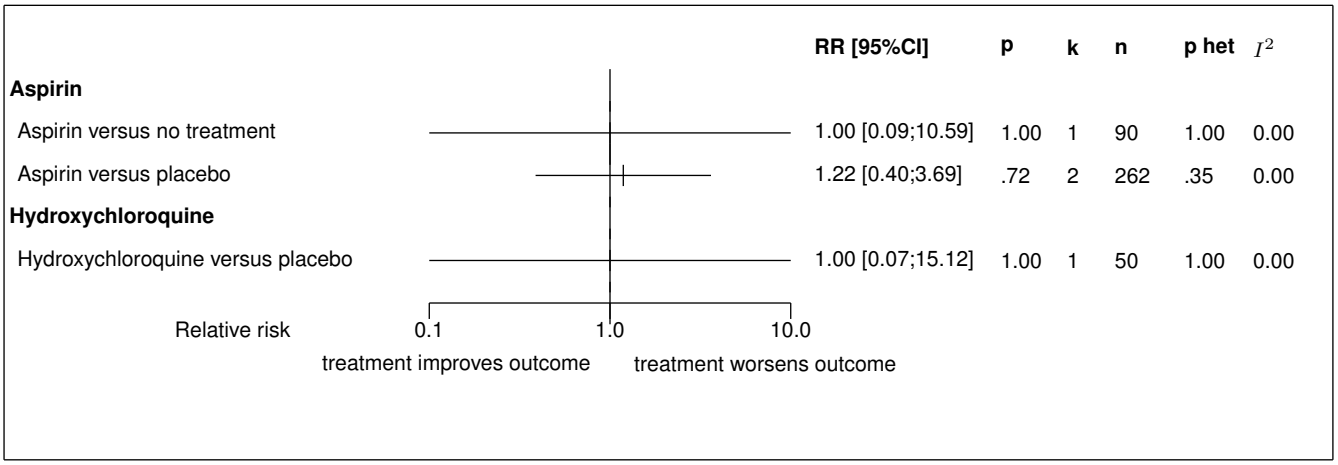
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 28.4: *Forest's plot for fatal pulmonary embolism*



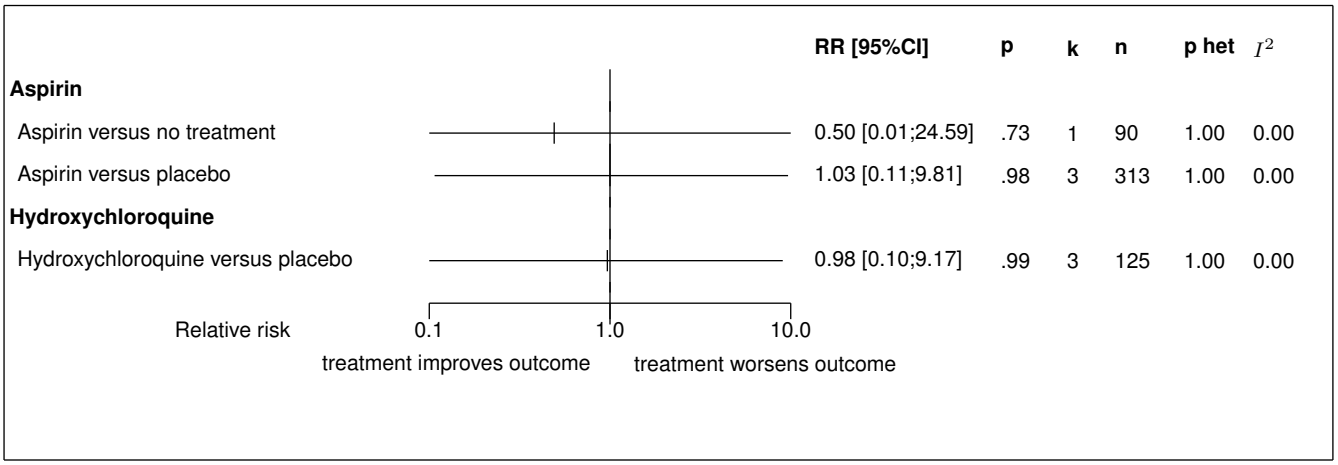
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 28.5: *Forest's plot for wound haematoma / infection*



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 28.6: *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; ᶠ: random effect model used

29 Detailed results for Aspirin

29.1 Available trials

A total of 4 RCTs which randomized 403 patients were identified: it compared Aspirin with no treatment and 3 trials compared Aspirin with placebo.
The average study size was 100 patients (range 51 to 145). The first study was published in 1975, and the last study was published in 1986.
A total of 2 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.
Fatal pulmonary embolism data was reported in 4 trials; 4 trials reported data on deep vein thrombosis; 4 trials reported data on bleeding; 4 trials reported data on non-fatal pulmonary embolism; 3 trials reported data on wound haematoma / infection; and 2 trials reported data on proximal DVT.
Following tables 29.1 (page 236), 29.2 (page 236), 29.4 (page 238), and 29.3 (page 237) summarized the main characteristics of the trials including in this systematic review of randomized trials of Aspirin.

Table 29.1: *Treatment description - platelet aggregation inhibitors - Aspirin*

Trial	Studied treatment	Control treatment
Aspirin versus no treatment		
Rocha (1986) [1]	Aspirin 250mg or 1000mg daily	control (combination of heparin plus dihydroergotamine)
Aspirin versus placebo		
Stockholm-I (1975) [2]	Aspirin 2000mg daily	placebo
Harris-I (1977) [3]	Aspirin 1200mg daily	placebo
Sautter (1983) [4]	Aspirin 900mg daily + sulfinpyrazone	placebo

Table 29.2: *Descriptions of participants - platelet aggregation inhibitors - Aspirin*

Trial	Patients
Aspirin versus no treatment	
Rocha (1986) [1]	Total hip replacement
Aspirin versus placebo	

continued...

Trial	Patients
Stockholm-I (1975) [2]	Elective surgery of the hip
Harris-I (1977) [3]	Patients over 40 years of age, who had undergone total hip replacement
Sautter (1983) [4]	Patient with total hip replacement

Table 29.3: *Design and methodological quality of trials - platelet aggregation inhibitors - Aspirin*

Trial	Design	Duration	Centre	Primary end-point
Aspirin versus no treatment				
Rocha, 1986 [1] n=90	Parallel groups open exploratory trial	1 weeks		
Aspirin versus placebo				
Stockholm-I, 1975 [2] n=51	double blind exploratory trial	2 weeks		
Harris-I, 1977 [3] n=117	Parallel groups double-blind confirmatory trial at low risk of bias	1 weeks		Radiographic phlebography
Sautter, 1983 [4] n=145	Parallel groups exploratory trial	3 weeks		

Table 29.4: *Trial characteristics - platelet aggregation inhibitors - Aspirin*

Trial	treatment duration
Aspirin versus no treatment	
Rocha, 1986 [1]	1 weeks
Aspirin versus placebo	
Stockholm-I, 1975 [2]	2 weeks
Harris-I, 1977 [3]	1 weeks
Sautter, 1983 [4]	3 weeks

29.2 Meta-analysis results

The results are detailed in table 29.5 (page 239). This table is followed by the Forest's plot corresponding to each endpoint.

Aspirin versus no treatment

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 0.14 (95% CI 0.04 to 0.45, p=0.0000).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 0.25 (95% CI 0.01 to 7.24, p=0.4196).
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 24.59, p=0.7273).
The single study eligible for this comparison provided data on **wound haematoma** / **infection**. No statistically significant difference between the groups was found in wound haematoma / infection, with a RR of 1.00 (95% CI 0.09 to 10.59, p=1.0000).

Aspirin versus placebo

All the 3 studies had extractable data about the number of participants with **deep vein thrombosis**. When pooled together, there was no statistically significant difference between the groups in deep vein thrombosis, with a RR of 0.72 (95% CI 0.45 to 1.15, p=0.1686). No heterogeneity was detected (p = 0.1498, I^2 = 0.47%).
All the 3 studies had extractable data about the number of participants with **non-fatal pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in non-fatal pulmonary embolism, with a RR of 0.51 (95% CI 0.13 to 1.97, p=0.3262). No heterogeneity was detected (p = 0.9402, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **proximal DVT**. The analysis detected a statistically significant difference in favor of Aspirin in proximal DVT, with a RR of 0.47 (95% CI 0.29 to 0.76, p=0.0021). No heterogeneity was detected (p = 0.5549, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **fatal pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in fatal pulmonary embolism, with a RR of 1.03 (95% CI 0.11 to 9.81, p=0.9766). No heterogeneity was detected (p = 0.9983, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **wound haematoma** / **infection**. When pooled together, there was no statistically significant difference between the groups in wound haematoma / infection, with a RR of 1.22 (95% CI 0.40 to 3.69, p=0.7243). No heterogeneity was detected (p = 0.3546, I^2 = 0.00%).

Table 29.5: *Results details - platelet aggregation inhibitors - Aspirin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Aspirin versus no treatment						
deep vein thrombosis	RR=0.14	[0.04;0.45]	0.0000	1.0000 (I^2=0.00)	1	90
non-fatal pulmonary embolism	RR=0.25	[0.01;7.24]	0.4196	1.0000 (I^2=0.00)	1	90

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fatal pulmonary embolism	RR=0.50	[0.01;24.59]	0.7273	1.0000 (I^2=0.00)	1	90
wound haematoma / infection	RR=1.00	[0.09;10.59]	1.0000	1.0000 (I^2=0.00)	1	90
bleeding	RR=0.50	[0.01;24.59]	0.7273	1.0000 (I^2=0.00)	1	90
Aspirin versus placebo						
deep vein thrombosis	RR=0.72	[0.45;1.15]	0.1686	0.1498 (I^2=0.47)	3	313
non-fatal pulmonary embolism	RR=0.51	[0.13;1.97]	0.3262	0.9402 (I^2=0.00)	3	313
proximal DVT	RR=0.47	[0.29;0.76]	0.0021	0.5549 (I^2=0.00)	2	262
fatal pulmonary embolism	RR=1.03	[0.11;9.81]	0.9766	0.9983 (I^2=0.00)	3	313
wound haematoma / infection	RR=1.22	[0.40;3.69]	0.7243	0.3546 (I^2=0.00)	2	262
bleeding	RR=1.03	[0.11;9.81]	0.9766	0.9983 (I^2=0.00)	3	313

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

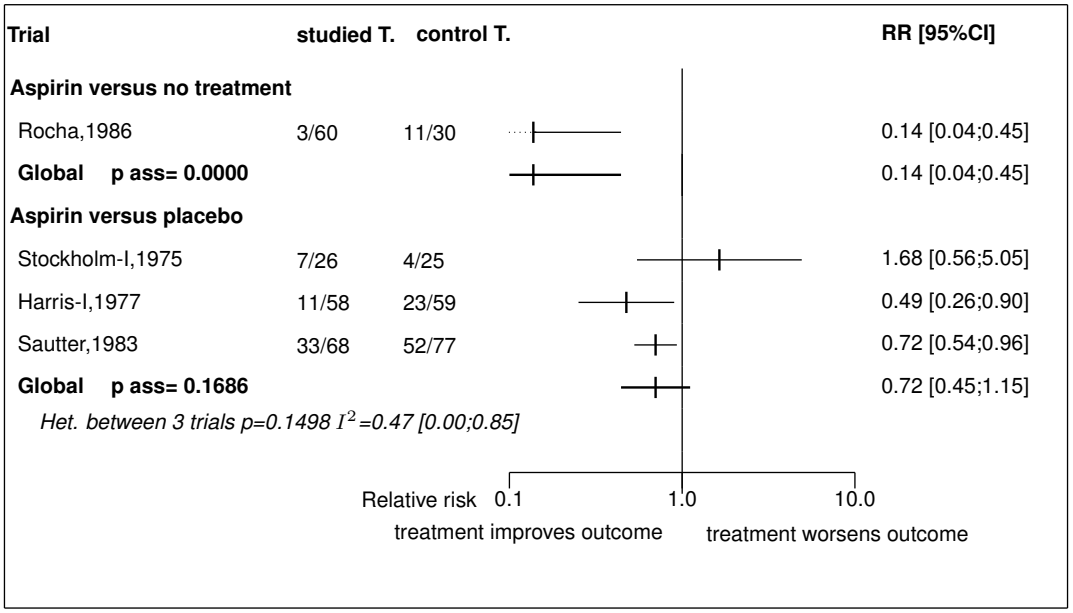


Figure 29.2: *Forest's plot for non-fatal pulmonary embolism*

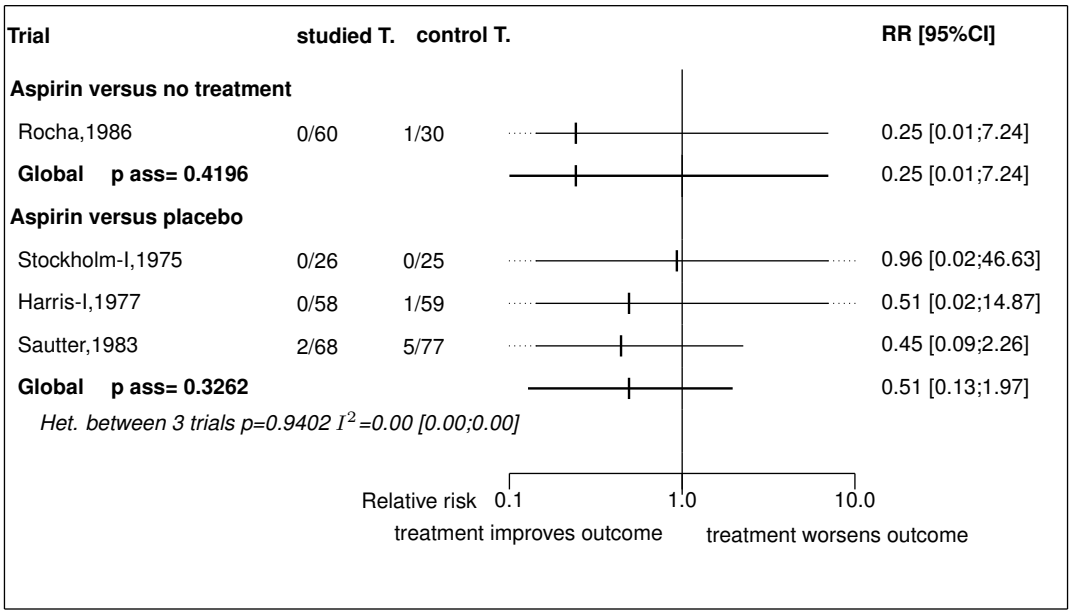


Figure 29.3: *Forest's plot for proximal DVT*

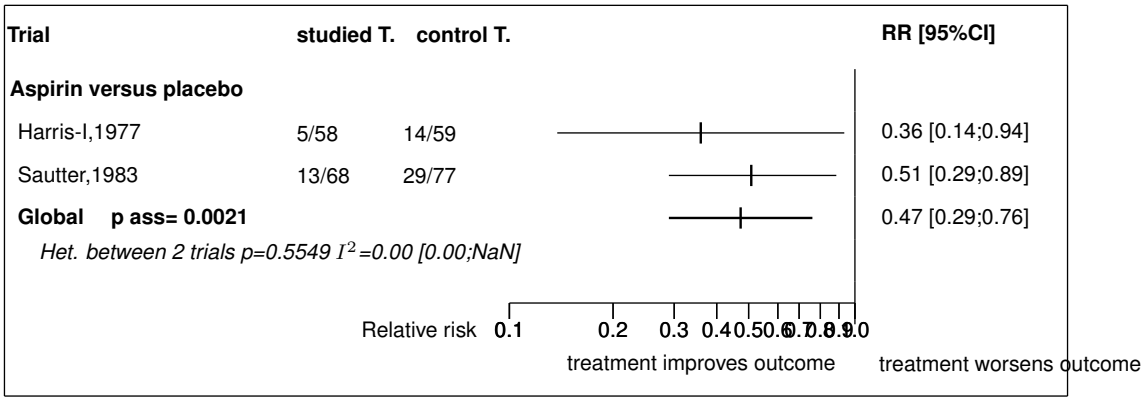


Figure 29.4: *Forest's plot for fatal pulmonary embolism*

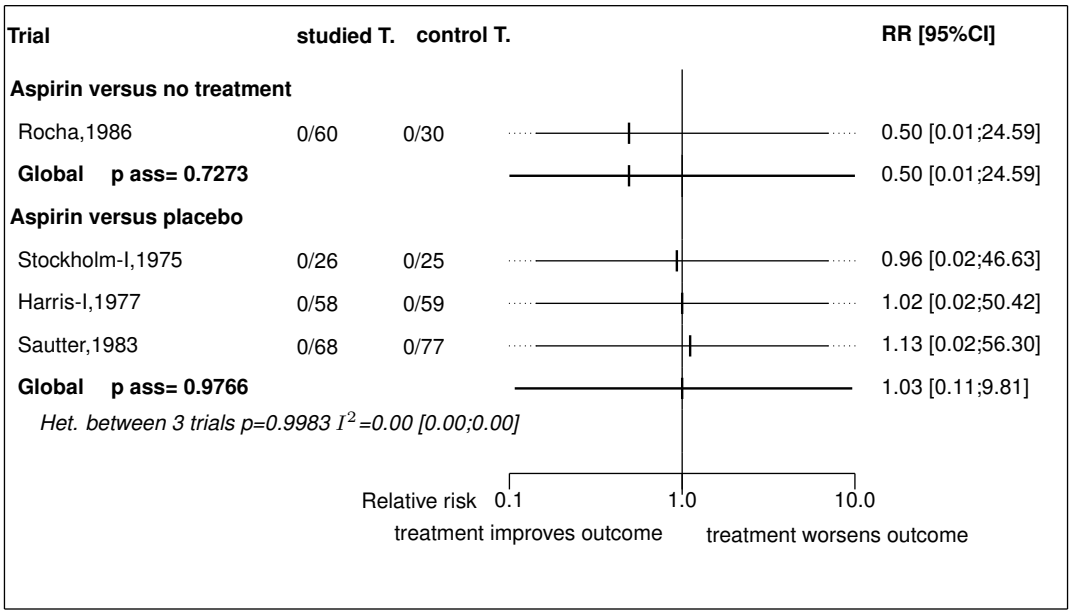


Figure 29.5: *Forest's plot for wound haematoma / infection*

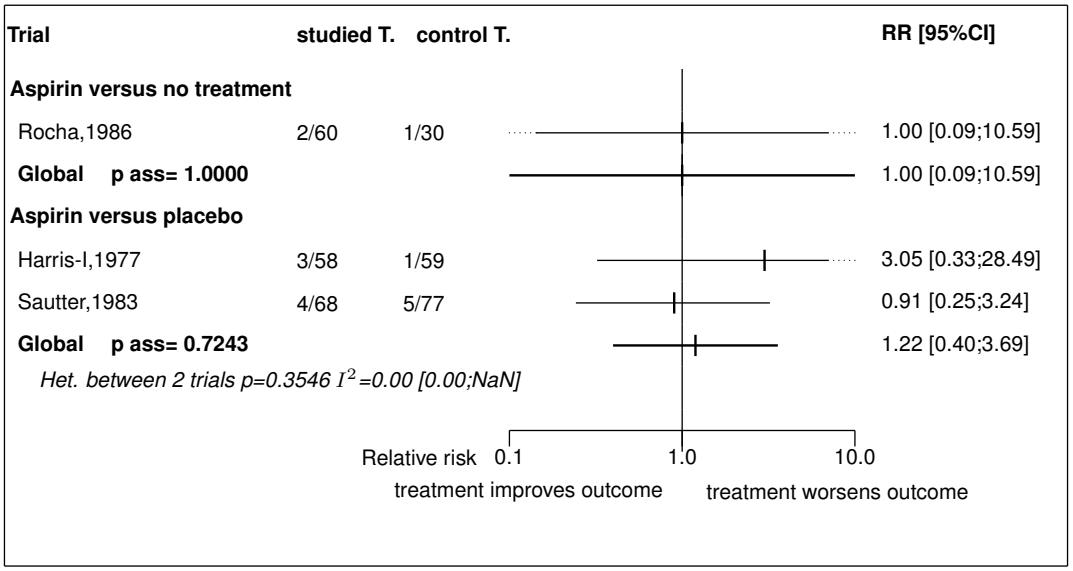
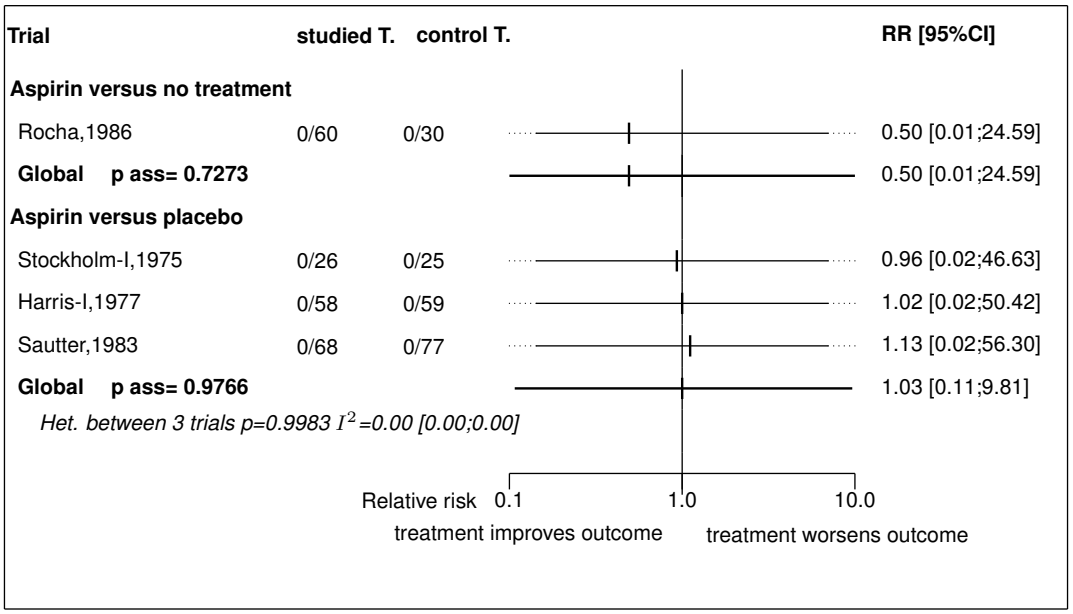


Figure 29.6: *Forest's plot for bleeding*



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[1] Alfaro MJ, Pramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. Thromb Haemost 1986;56:53-6. [PMID=3535158]

[2] Soreff J, Johnsson H, Diener L, Göransson L. Acetylsalicylic acid in a trial to diminish thromboembolic complications after elective hip surgery. Acta Orthop Scand 1975;46:246-55. [PMID=1096521]

[3] Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. N Engl J Med 1977;297:1246-9. [PMID=335247]

[4] Sautter RD, Koch EL, Myers WO, Ray JR 3rd, Mazza JJ, Larson DE, Chen HM, Milbauer JP, Treuhaft PS, Plotka ED. Aspirin-sulfinpyrazone in prophylaxis of deep venous thrombosis in total hip replacement. JAMA 1983;250:2649-54. [PMID=6355542]

29.3 Individual trial summaries

Table 29.6: *Rocha, 1986 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=90 (60 vs. 30) **Follow-up duration:** 1 weeks **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial	Total hip replacement	**Studied treatment:** Aspirin 250mg or 1000mg daily **Control treatment:** control (combination of heparin plus dihydroergotamine)	Deep vein thrombosis RR=0.14 [0.04;0.45]

Reference

Alfaro MJ, Pramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. Thromb Haemost 1986;56:53-6 [PMID=3535158]

Table 29.7: *Stockholm-I, 1975 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=51 (26 vs. 25) **Follow-up duration:** 2 weeks **Study design:** Randomized controlled trial Double blind Exploratory trial	Elective surgery of the hip	**Studied treatment:** Aspirin 2000mg daily **Control treatment:** placebo	Deep vein thrombosis RR=1.68 [0.56;5.05]

Reference

Soreff J, Johnsson H, Diener L, Göransson L. Acetylsalicylic acid in a trial to diminish thromboembolic complications after elective hip surgery. Acta Orthop Scand 1975;46:246-55 [PMID=1096521]

Table 29.8: *Harris-I, 1977 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=117 (58 vs. 59) **Follow-up duration:** 1 weeks **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias	Patients over 40 years of age, who had undergone total hip replacement	**Studied treatment:** Aspirin 1200mg daily **Control treatment:** placebo	Deep vein thrombosis RR=0.49 [0.26;0.90] Proximal DVT RR=0.36 [0.14;0.94]

Reference

Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. N Engl J Med 1977;297:1246-9 [PMID=335247]

Table 29.9: *Sautter, 1983 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=145 (68 vs. 77) **Follow-up duration:** 3 weeks **Study design:** Randomized controlled trial Parallel groups Exploratory trial	Patient with total hip replacement	**Studied treatment:** Aspirin 900mg daily + sulfinpyrazone **Control treatment:** placebo	Deep vein thrombosis RR=0.72 [0.54;0.96] Non-fatal pulmonary embolism RR=0.45 [0.09;2.26] Proximal DVT RR=0.51 [0.29;0.89]

Reference

Sautter RD, Koch EL, Myers WO, Ray JR 3rd, Mazza JJ, Larson DE, Chen HM, Milbauer JP, Treuhaft PS, Plotka ED. Aspirin-sulfinpyrazone in prophylaxis of deep venous thrombosis in total hip replacement. JAMA 1983;250:2649-54 [PMID=6355542]

30 Detailed results for Hydroxychloroquine

30.1 Available trials

A total of 3 RCTs which randomized 125 patients were identified: all compared Hydroxychloroquine with placebo.
The average study size was 41 patients (range 35 to 50). The first study was published in 1977, and the last study was published in 1981.
This trial was double blind in design.
All included studies were reported in English language. We did not found any unpublished trial.
Bleeding data was reported in 3 trials; 3 trials reported data on fatal pulmonary embolism; 3 trials reported data on deep vein thrombosis; 2 trials reported data on non-fatal pulmonary embolism; and 1 trials reported data on wound haematoma / infection.
Following tables 30.1 (page 249), 30.2 (page 249), 30.4 (page 251), and 30.3 (page 250) summarized the main characteristics of the trials including in this systematic review of randomized trials of Hydroxychloroquine.

Table 30.1: *Treatment description - platelet aggregation inhibitors - Hydroxychloroquine*

Trial	Studied treatment	Control treatment
Hydroxychloroquine versus placebo		
Cooke (1977) [1]	Hydroxychloroquine	placebo
Hume-A (1977) [2, 3]	Hydroxychloroquine	placebo
Stockholm-II (1981) [4]	Hydroxychloroquine	placebo

Table 30.2: *Descriptions of participants - platelet aggregation inhibitors - Hydroxychloroquine*

Trial	Patients
Hydroxychloroquine versus placebo	
Cooke (1977) [1]	Elective surgery on the hip
Hume-A (1977) [2, 3]	Total hip replacement
Stockholm-II (1981) [4]	Total hip replacement

Table 30.3: *Design and methodological quality of trials - platelet aggregation inhibitors - Hydroxychloroquine*

Trial	Design	Duration	Centre	Primary endpoint
Hydroxychloroquine versus placebo				
Cooke, 1977 [1] n=50	Parallel groups double-blind exploratory trial	2 weeks		
Hume-A, 1977 [2, 3] n=40	exploratory trial	2 weeks		
Stockholm-II, 1981 [4] n=35	exploratory trial	2 weeks		

Table 30.4: *Trial characteristics - platelet aggregation inhibitors - Hydroxychloroquine*

Trial	treatment duration
Hydroxychloroquine versus placebo	
Cooke, 1977 [1]	2 weeks
Hume-A, 1977 [2, 3]	2 weeks
Stockholm-II, 1981 [4]	2 weeks

30.2 Meta-analysis results

The results are detailed in table 30.5 (page 252). This table is followed by the Forest's plot corresponding to each endpoint.

Hydroxychloroquine versus placebo

All the 3 studies had extractable data about the number of participants with **deep vein thrombosis**. When pooled together, there was no statistically significant difference between the groups in deep vein thrombosis, with a RR of 0.97 (95% CI 0.70 to 1.34, p=0.8338). No heterogeneity was detected (p = 0.8639, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **non-fatal pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in non-fatal pulmonary embolism, with a RR of 2.19 (95% CI 0.52 to 9.17, p=0.2847). No heterogeneity was detected (p = 0.6465, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **fatal pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in fatal pulmonary embolism, with a RR of 0.98 (95% CI 0.10 to 9.17, p=0.9866). No heterogeneity was detected (p = 0.9997, I^2 = 0.00%).
Only one of the 3 studies eligible for this comparison provided data on **wound haematoma / infection**. No statistically significant difference between the groups was found in wound haematoma / infection, with a RR of 1.00 (95% CI 0.07 to 15.12, p=1.0000).

Table 30.5: *Results details - platelet aggregation inhibitors - Hydroxychloroquine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Hydroxychloroquine versus placebo						
deep vein thrombosis	RR=0.97	[0.70;1.34]	0.8338	0.8639 (I^2=0.00)	3	125
non-fatal pulmonary embolism	RR=2.19	[0.52;9.17]	0.2847	0.6465 (I^2=0.00)	2	85
fatal pulmonary embolism	RR=0.98	[0.10;9.17]	0.9866	0.9997 (I^2=0.00)	3	125
wound haematoma / infection	RR=1.00	[0.07;15.12]	1.0000	1.0000 (I^2=0.00)	1	50
bleeding	RR=0.98	[0.10;9.17]	0.9866	0.9997 (I^2=0.00)	3	125

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

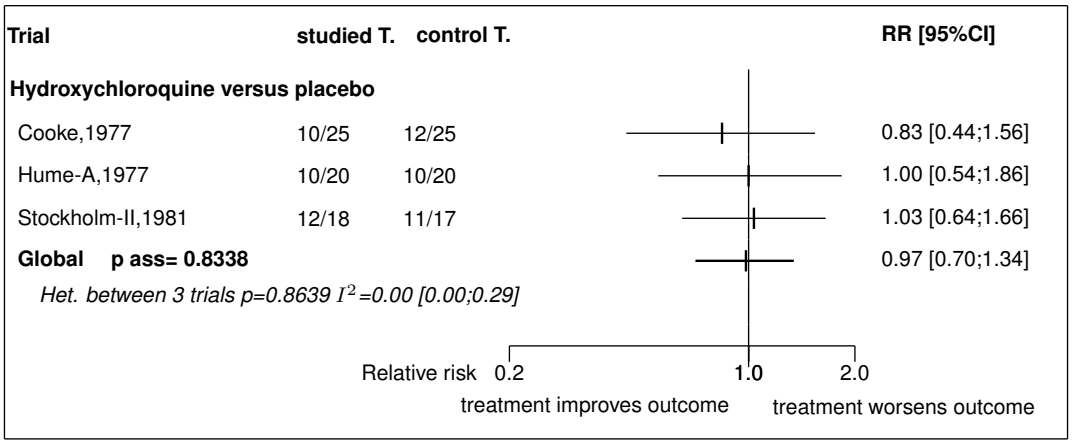


Figure 30.2: *Forest's plot for non-fatal pulmonary embolism*

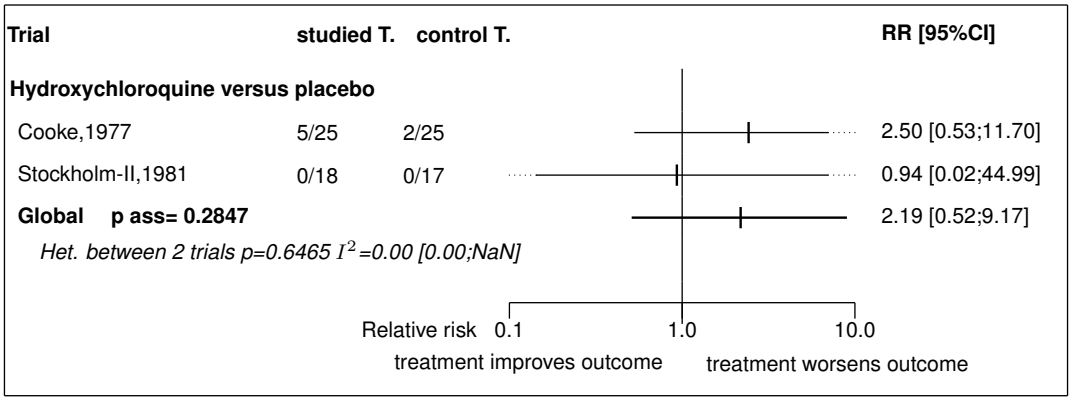


Figure 30.3: *Forest's plot for fatal pulmonary embolism*

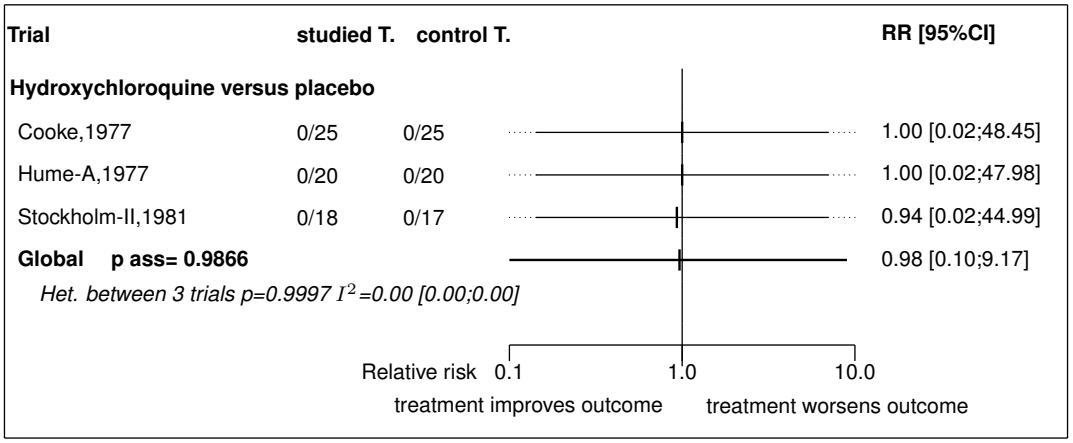


Figure 30.4: *Forest's plot for wound haematoma / infection*

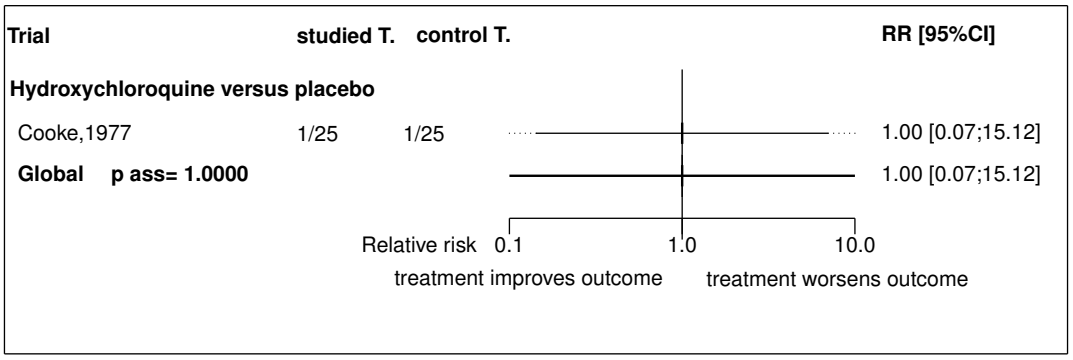
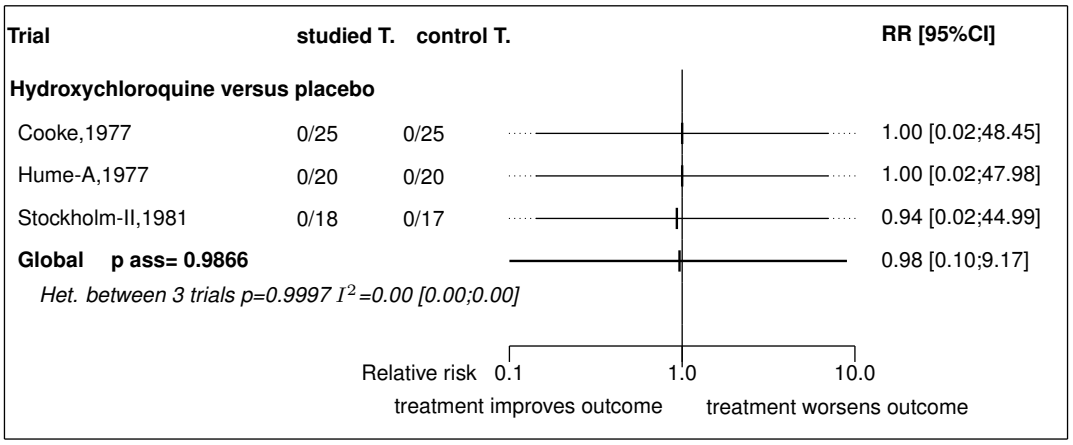


Figure 30.5: *Forest's plot for bleeding*



References

[1] Cooke ED, Dawson MH, Ibbotson RM, Bowcock SA, Ainsworth ME, Pilcher MF. Failure of orally administered hydroxychloroquine sulphate to prevent venous thromboembolism following elective hip operations. J Bone Joint Surg Am 1977;59:496-500. [PMID=325009]

[2] Hume M, Bierbaum B, Kuriakose TX, Surprenant, J. Prevention of postoperative thrombosis by aspirin. Am J Surg 1977;133:420-2. [PMID=322520]

[3] Hume M, Donaldson WR, Suprenant J. Sex, aspirin, and venous thrombosis. Orthop Clin North Am 1978;9:761-7. [PMID=358040]

[4] Johansson E, Forsberg K, Johnsson H. Clinical and experimental evaluation of the thromboprophylactic effect of hydroxychloroquine sulfate after total hip replacement. Haemostasis 1981;10:89-96. [PMID=7007179]

30.3 Individual trial summaries

Table 30.6: *Cooke, 1977 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=50 (25 vs. 25) **Follow-up duration:** 2 weeks **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Elective surgery on the hip	**Studied treatment:** Hydroxychloroquine **Control treatment:** placebo	Deep vein thrombosis RR=0.83 [0.44;1.56] Non-fatal pulmonary embolism RR=2.50 [0.53;11.70]

Reference

Cooke ED, Dawson MH, Ibbotson RM, Bowcock SA, Ainsworth ME, Pilcher MF. Failure of orally administered hydroxychloroquine sulphate to prevent venous thromboembolism following elective hip operations. J Bone Joint Surg Am 1977;59:496-500 [PMID=325009]

Table 30.7: *Hume-A, 1977 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=40 (20 vs. 20) **Follow-up duration:** 2 weeks **Study design:** Randomized controlled trial Exploratory trial	Total hip replacement	**Studied treatment:** Hydroxychloroquine **Control treatment:** placebo	Deep vein thrombosis RR=1.00 [0.54;1.86]

References

Hume M, Bierbaum B, Kuriakose TX, Surprenant, J. Prevention of postoperative thrombosis by aspirin. Am J Surg 1977;133:420-2 [PMID=322520]
Hume M, Donaldson WR, Suprenant J. Sex, aspirin, and venous thrombosis. Orthop Clin North Am 1978;9:761-7 [PMID=358040]

Table 30.8: *Stockholm-II, 1981 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=35 (18 vs. 17) **Follow-up duration:** 2 weeks **Study design:** Randomized controlled trial Exploratory trial	Total hip replacement	**Studied treatment:** Hydroxychloroquine **Control treatment:** placebo	Deep vein thrombosis RR=1.03 [0.64;1.66]

Reference

Johansson E, Forsberg K, Johnsson H. Clinical and experimental evaluation of the thromboprophylactic effect of hydroxychloroquine sulfate after total hip replacement. Haemostasis 1981;10:89-96 [PMID=7007179]

31 Global meta-analysis: all platelet aggregation inhibitors

31.1 Global meta-analysis: all platelet aggregation inhibitors versus no treatment

Table 31.1: *All platelet aggregation inhibitorsversus no treatment*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.14	0.04;0.45	0.0000	1.0000 (0.00)	1	90
non-fatal pulmonary embolism	RR=0.25	0.01;7.24	0.4196	1.0000 (0.00)	1	90
fatal pulmonary embolism	RR=0.50	0.01;24.59	0.7273	1.0000 (0.00)	1	90
wound haematoma / infection	RR=1.00	0.09;10.59	1.0000	1.0000 (0.00)	1	90

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

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

Table 31.2: *All platelet aggregation inhibitorsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.81	0.64;1.04	0.0928	0.2751 (0.21)	6	438
non-fatal pulmonary embolism	RR=1.01	0.38;2.71	0.9811	0.6551 (0.00)	5	398
proximal DVT	RR=0.47	0.29;0.76	0.0021	0.5549 (0.00)	2	262
fatal pulmonary embolism	RR=1.01	0.21;4.92	0.9930	1.0000 (0.00)	6	438
wound haematoma / infection	RR=1.19	0.43;3.31	0.7440	0.6458 (0.00)	3	312

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

32 Ongoing studies of platelet aggregation inhibitors

No ongoing trial was identified.

33 Excluded studies for platelet aggregation inhibitors

No trial was excluded.

References

Part V

Recombinant hirudin

34 Overview of recombinant hirudin

34.1 Included trials

A total of 3 randomized comparisons which enrolled 1564 patients were identified. In all, 3 randomized comparisons concerned desirudin.
The detailed descriptions of trials and meta-analysis results is given in section 35 (page 266) for desirudin.

The average study size was 782 patients (range 445 to 1119). The first study was published in 1996, and the last study was published in 1997.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 34.1 (page 264) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

34.2 Summary of meta-analysis results

The meta-analysis of the available trials about recombinant hirudin provide the results listed in tables 34.2 to 34.2 (page 265) and in the following graphs.

34.2.1 Desirudin

Data were insufficient to compare **desirudin** to **enoxaparin**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Data were insufficient to compare **desirudin** to **UFH**. There were 2 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis.

Table 34.1: *Main study characteristics - recombinant hirudin*

Trial	Patients	Treatments	Trial design and method
Desirudin			
Desirudin versus enoxaparin			
Ericksson, 1997 [1] n = NA vs. NA	patients who undergo total hip replacement	desirudin 15mg SC twice daily for 8-12 days **versus** enoxaparin 40mg once daily for 8-12 days	double blind parallel groups 31 centres, Europe
Desirudin versus UFH			
REVASC, 1997 [2] n = 225 vs. 220	patients having a primary elective total hip replacement	desirudin 15mg twice daily **versus** unfractionated heparin 5000 IU three times a day	parallel groups
Eriksson, 1996 [3] n= 1119	patients undergoing elective hip surgery	recombinant hirudin, desirudin (CGP 39393) 10, 15, or 20 mg twice daily started just before surgery and continued for 8-11 days **versus** unfractionated heparin 5000 IU three times daily started just before surgery and continued for 8-11 days	double blind parallel groups Europe

Table 34.2: *Summary of all results for desirudin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
desirudin versus enoxaparin						
No data were presented in the trial identified						
desirudin versus UFH						
No data were presented in the trial identified						

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

35 Details

35.1 Available trials

A total of 3 RCTs which randomized 1564 patients were identified: it compared desirudin with enoxaparin and 2 trials compared desirudin with UFH.
The average study size was 782 patients (range 445 to 1119). The first study was published in 1996, and the last study was published in 1997.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
data was reported in trials;
Following tables 35.1 (page 266), 35.2 (page 266), 35.4 (page 268), and 35.3 (page 267) summarized the main characteristics of the trials including in this systematic review of randomized trials of desirudin.

Table 35.1: *Treatment description - recombinant hirudin - desirudin*

Trial	Studied treatment	Control treatment
Desirudin versus enoxaparin		
Ericksson (1997) [1]	desirudin 15mg SC twice daily for 8-12 days	enoxaparin 40mg once daily for 8-12 days
Desirudin versus UFH		
REVASC (1997) [2]	desirudin 15mg twice daily	unfractionated heparin 5000 IU three times a day
Eriksson (1996) [3]	recombinant hirudin, desirudin (CGP 39393) 10, 15, or 20 mg twice daily started just before surgery and continued for 8-11 days	unfractionated heparin 5000 IU three times daily started just before surgery and continued for 8-11 days

Table 35.2: *Descriptions of participants - recombinant hirudin - desirudin*

Trial	Patients
Desirudin versus enoxaparin	
Ericksson (1997) [1]	Patients who undergo total hip replacement
Desirudin versus UFH	
REVASC (1997) [2]	Patients having a primary elective total hip replacement
Eriksson (1996) [3]	Patients undergoing elective hip surgery

continued...

Trial	Patients

Table 35.3: *Design and methodological quality of trials - recombinant hirudin - desirudin*

Trial	Design	Duration	Centre	Primary endpoint
Desirudin versus enoxaparin				
Ericksson, 1997 [1] n=NaN	Parallel groups double blind	inclusion period: Apr 1994-Nov 1995	Europe 31 centres	
Desirudin versus UFH				
REVASC, 1997 [2] n=445	Parallel groups			
Eriksson, 1996 [3] n=1119	Parallel groups double blind		Europe	

Table 35.4: *Trial characteristics - recombinant hirudin - desirudin*

Trial
Desirudin versus enoxaparin
Ericksson, 1997 [1]
Desirudin versus UFH
REVASC, 1997 [2]
Eriksson, 1996 [3]

35.2 Meta-analysis results

The results are detailed in table 35.5 (page 269). This table is followed by the Forest's plot corresponding to each endpoint.

Desirudin versus enoxaparin

No data were presented in the 1 trial identified

Desirudin versus UFH

No data were presented in the 2 trials identified

Table 35.5: *Results details - recombinant hirudin - desirudin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
desirudin versus enoxaparin						
No data were presented in the trial identified						
desirudin versus UFH						
No data were presented in the trial identified						

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

References

[1] Eriksson BI, Wille-Jrgensen P, Klebo P, Mouret P, Rosencher N, Bösch P, Baur M, Ekman S, Bach D, Lindbratt S, Close P. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. N Engl J Med 1997;337:1329-35. [PMID=9358126]

[2] Eriksson BI, Ekman S, Lindbratt S, Baur M, Bach D, Torholm C, Klebo P, Close P. Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. J Bone Joint Surg Am 1997;79:326-33. [PMID=9070519]

[3] Eriksson BI, Ekman S, Kalebo P, Zachrisson B, Bach D, Close P. Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. Lancet 1996;347:635-9. [PMID=8596376]

35.3 Individual trial summaries

Table 35.6: *Ericksson, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double blind Europe, 31 centres **Inclusion period:** Apr 1994-Nov 1995	Patients who undergo total hip replacement	**Studied treatment:** desirudin 15mg SC twice daily for 8-12 days **Control treatment:** enoxaparin 40mg once daily for 8-12 days	

Reference

Eriksson BI, Wille-Jrgensen P, Klebo P, Mouret P, Rosencher N, Bösch P, Baur M, Ekman S, Bach D, Lindbratt S, Close P. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. N Engl J Med 1997;337:1329-35 [PMID=9358126]

Table 35.7: *REVASC, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=445 (225 vs. 220) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups	Patients having a primary elective total hip replacement	**Studied treatment:** desirudin 15mg twice daily **Control treatment:** unfractionated heparin 5000 IU three times a day	

Reference

Eriksson BI, Ekman S, Lindbratt S, Baur M, Bach D, Torholm C, Klebo P, Close P. Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. J Bone Joint Surg Am 1997;79:326-33 [PMID=9070519]

Table 35.8: *Eriksson, 1996 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (1119 vs. 0) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double blind Europe	Patients undergoing elective hip surgery	**Studied treatment:** recombinant hirudin, desirudin (CGP 39393) 10, 15, or 20 mg twice daily started just before surgery and continued for 8-11 days **Control treatment:** unfractionated heparin 5000 IU three times daily started just before surgery and continued for 8-11 days	

Reference

Eriksson BI, Ekman S, Kalebo P, Zachrisson B, Bach D, Close P. Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. Lancet 1996;347:635-9 [PMID=8596376]

36 Global meta-analysis: all recombinant hirudin

36.1 Global meta-analysis: all recombinant hirudin versus enoxaparin

Table 36.1: *All recombinant hirudinversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	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; ES: effect size; I^2: inconsistance degree

36.2 Global meta-analysis: all recombinant hirudin versus UFH

Table 36.2: *All recombinant hirudinversus UFH*

Endpoint	Effect	95% CI	p ass	p het (I^2)	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; ES: effect size; I^2: inconsistance degree

37 Ongoing studies of recombinant hirudin

No ongoing trial was identified.

38 Excluded studies for recombinant hirudin

No trial was excluded.

References

Part VI

Synthetic oligosaccharide

39 Overview of synthetic oligosaccharide

39.1 Included trials

A total of 3 randomized comparisons which enrolled 5607 patients were identified. In all, 2 randomized comparisons concerned fondaparinux and one SR123781A.
The detailed descriptions of trials and meta-analysis results is given in section 40 (page 285) for fondaparinux and in section 41 (page 298) for SR123781A.

The average study size was 1869 patients (range 1023 to 2309). The first study was published in 2002, 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.
The table 39.1 (page 278) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

39.2 Summary of meta-analysis results

The meta-analysis of the available trials about synthetic oligosaccharide provide the results listed in tables 39.2 to 39.3 (page 279) and in the following graphs.

39.2.1 Fondaparinux

Fondaparinux was superior to **enoxaparin** in terms of deep vein thrombosis (RR=0.55, 95% CI 0.35 to 0.86, p=0.0083, 2 trials)and venous thromboembolism (RR=0.57, 95% CI 0.35 to 0.95, p=0.0294, 2 trials). But fondaparinux increased the risk of symptomatic deep-vein thrombosis (RR=5.79, 95% CI 1.27 to 26.51, p=0.0235, 2 trials)and major bleeding (RR=1.59, 95% CI 1.08 to 2.32, p=0.0176, 2 trials). However, no significant difference was found on symptomatic pulmonary embolism (RR=2.10, 95% CI 0.43 to 10.18, p=0.3578, 2 trials), non-fatal pulmonary embolism (RR=2.00, 95% CI 0.15 to 27.38, p=0.6023, 2 trials), proximal DVT (RR=0.62, 95% CI 0.12 to 3.24, p=0.5697, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0059)(RR=3.48, 95% CI 0.61 to 19.75, p=0.1589, 2 trials)and fatal pulmonary embolism (RR=0.67, 95% CI 0.05 to 8.74, p=0.7614, 2 trials).

39.2.2 SR123781A

Data were insufficient to compare **SR123781A** to **enoxaparin**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Table 39.1: *Main study characteristics - synthetic oligosaccharide*

Trial	Patients	Treatments	Trial design and method
Fondaparinux			
Fondaparinux versus enoxaparin			
EPHESUS (Lassen), 2002 [1] n = 1155 vs. 1154	elective hip replacement surgery	fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery **versus** enoxaprin 40mg once daily	double blind parallel groups Primary endpoint: venous thromboembolism 73 centres, 16 European countries
PENTATHLON (Turpie), 2002 [2] n = 1138 vs. 1137	elective hip replacement 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 139 centres, USA, Canada, Australia
SR123781A			
SR123781A versus enoxaparin			
DRIVE, 2008 [1] n = 854 vs. 169	patients undergoing total hip replacement surgery	SR123781A for 5-10 days, doses ranging from 0.25 to 4.0 mg daily for 10 days **versus** enoxaparin 40 mg	double blind parallel groups Primary endpoint: VTE 53 centres, 12 countries

Table 39.2: *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=5.79	1.27;26.51	0.0235	0.4372 (0.00)	2	4506
deep vein thrombosis	RR=0.55	0.35;0.86	0.0083	0.0949 (0.64)	2	3408
symptomatic pulmonary embolism	RR=2.10	0.43;10.18	0.3578	0.2754 (0.16)	2	4506
non-fatal pulmonary embolism	RR=2.00	0.15;27.38	0.6023	0.1188 (0.59)	2	4506
proximal DVT	RR=0.62 [1]	0.12;3.24	0.5697	0.0059 (0.87) †	2	3495
symptomatic venous thromboembolism (DVT, PE)	RR=3.48	0.61;19.75	0.1589	0.1588 (0.50)	2	4506
venous thromboembolism	RR=0.57	0.35;0.95	0.0294	0.0522 (0.73)	2	3411
fatal pulmonary embolism	RR=0.67	0.05;8.74	0.7614	0.7954 (0.00)	2	4506
all cause death	RR=1.09	0.10;12.02	0.9429	0.2029 (0.38)	2	4530
major bleeding	RR=1.59	1.08;2.32	0.0176	0.6658 (0.00)	2	4530

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

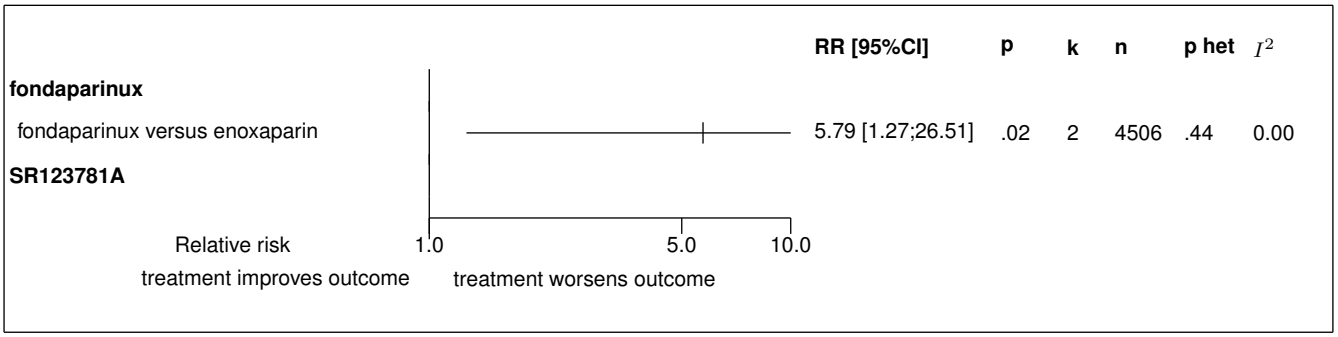
Table 39.3: *Summary of all results for SR123781A*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
SR123781A versus enoxaparin						
No data were presented in the trial identified						

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

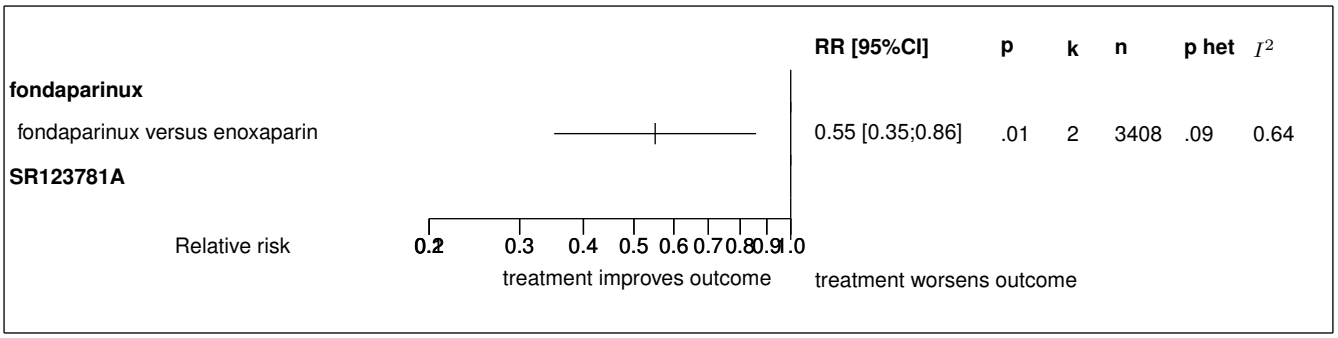
[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.67 95% CI 0.37;1.21

Figure 39.1: *Forest's plot for symptomatic deep-vein thrombosis*



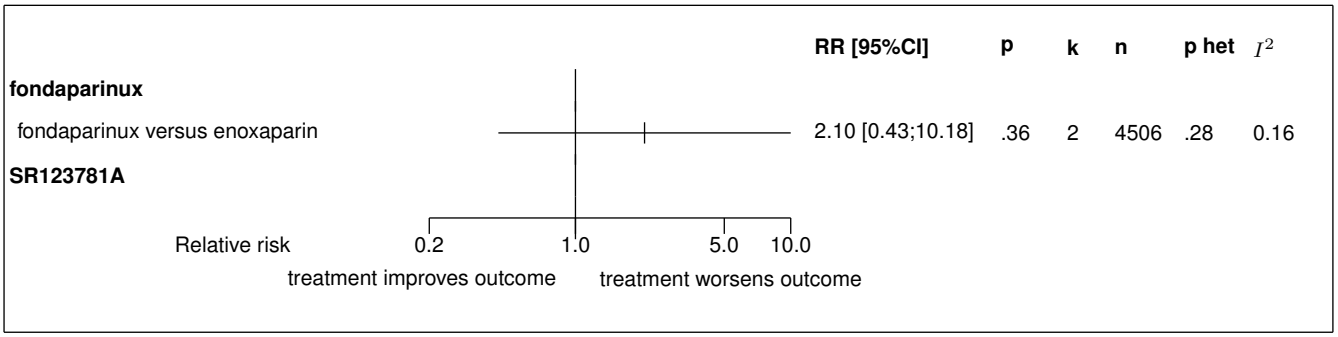
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 39.2: *Forest's plot for deep vein thrombosis*



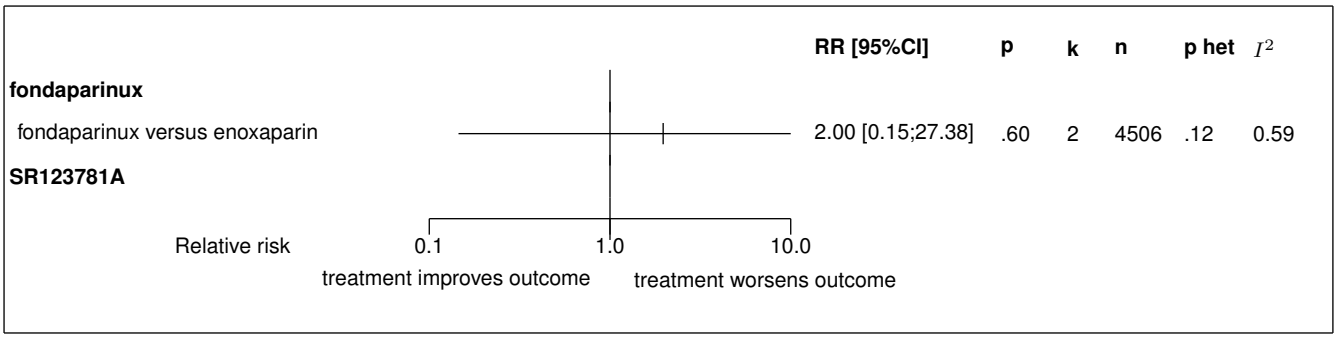
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 39.3: *Forest's plot for symptomatic pulmonary embolism*



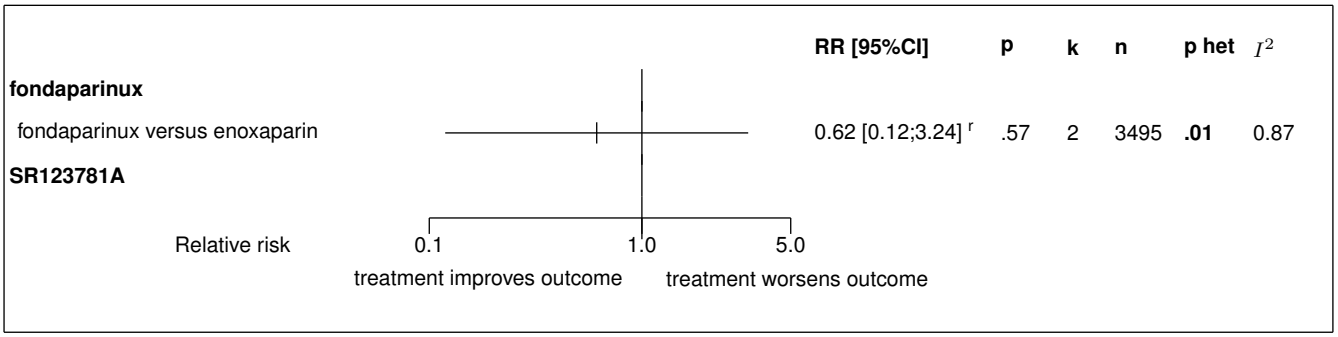
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 39.4: *Forest's plot for non-fatal pulmonary embolism*



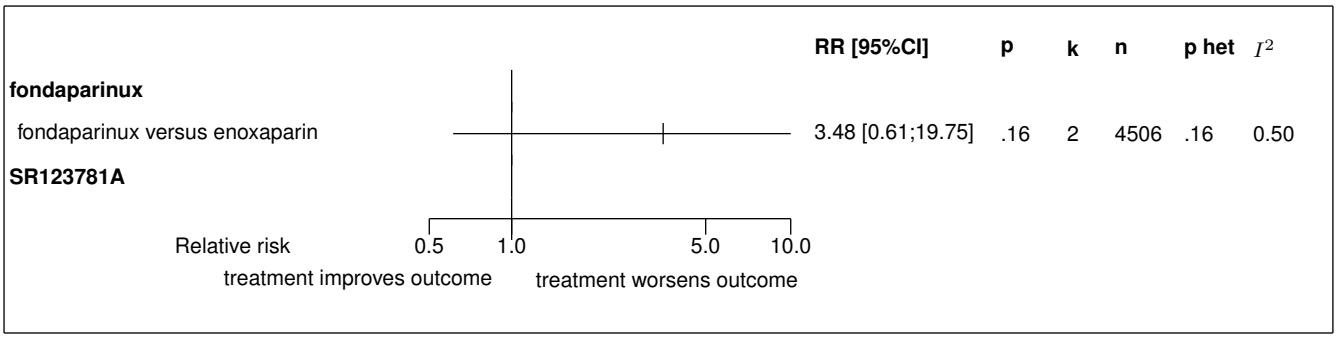
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 39.5: *Forest's plot for proximal DVT*



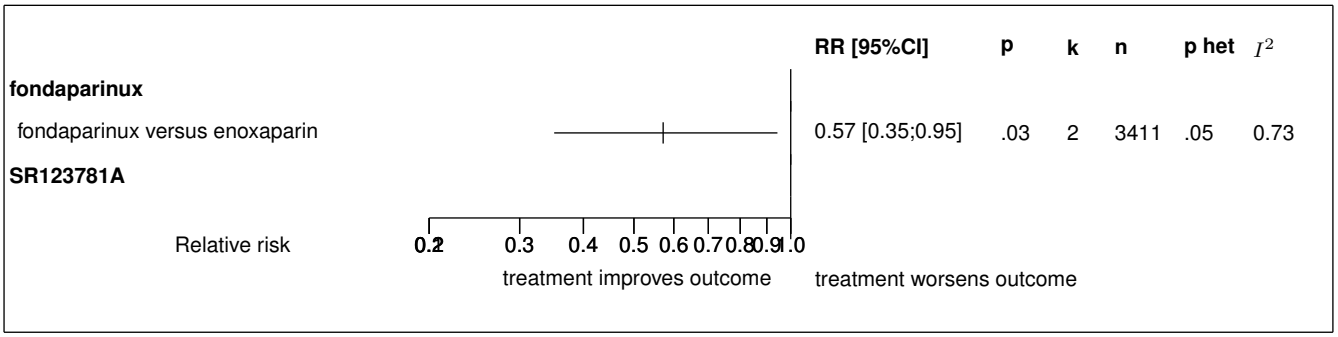
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 39.6: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*



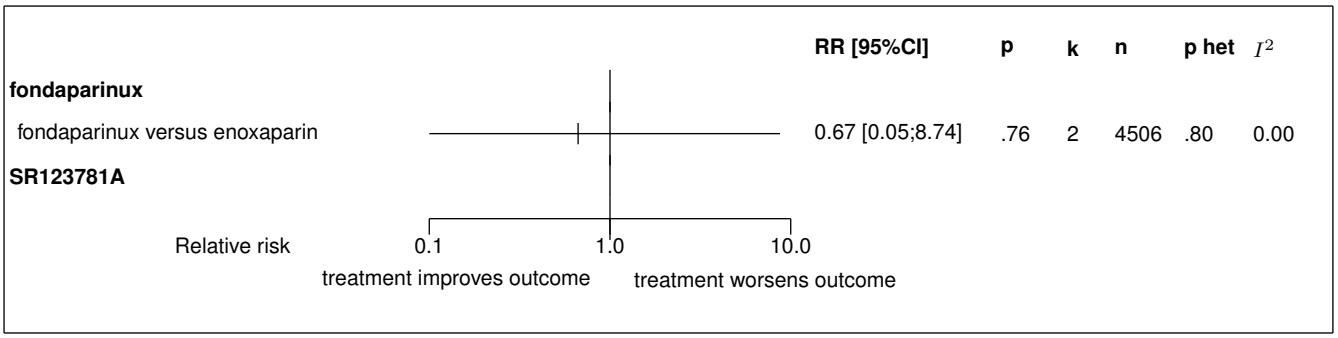
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 39.7: *Forest's plot for venous thromboembolism*



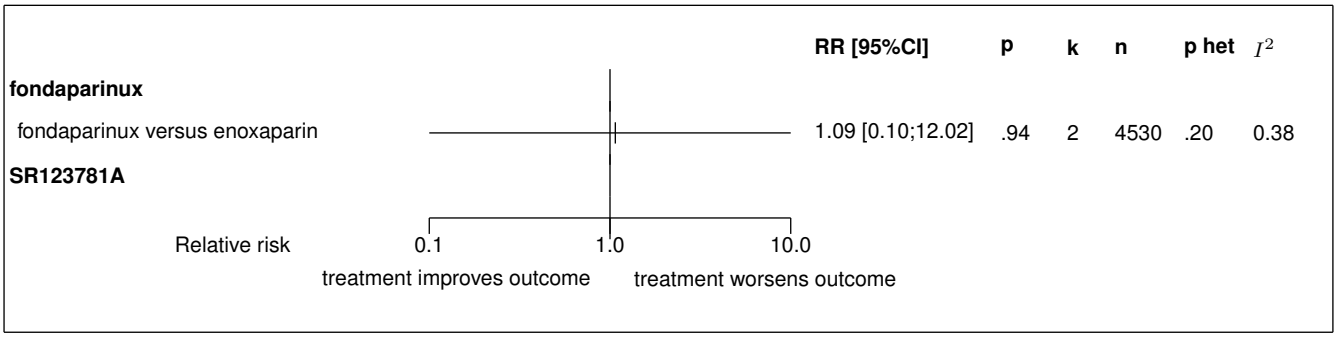
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 39.8: *Forest's plot for fatal pulmonary embolism*



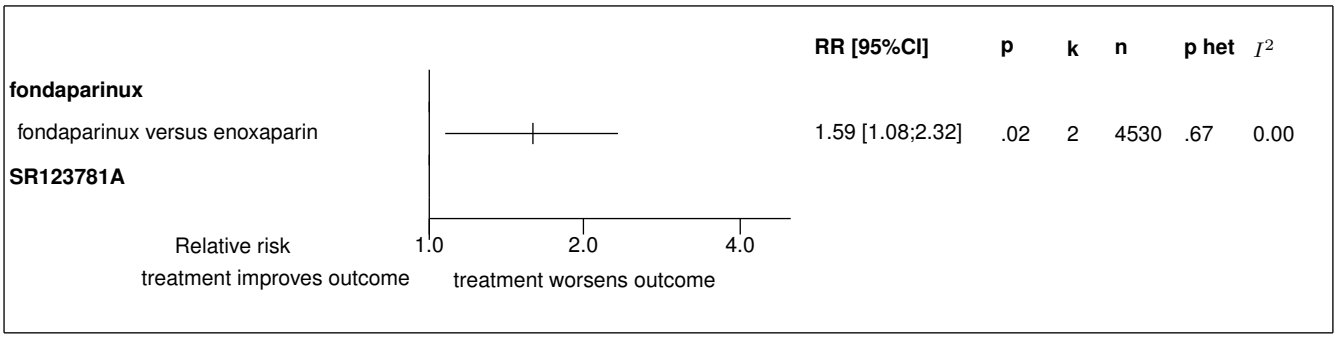
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 39.9: *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; ᶠ: random effect model used

Figure 39.10: *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; ᶠ: random effect model used

40 Detailed results for fondaparinux

40.1 Available trials

A total of 2 RCTs which randomized 4584 patients were identified: all compared fondaparinux with enoxaparin.
The average study size was 2292 patients (range 2275 to 2309). The first study was published in 2002, and the last study was published in 2002.
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 non-fatal pulmonary embolism; 2 trials reported data on symptomatic venous thromboembolism (DVT, PE); 2 trials reported data on proximal DVT; 2 trials reported data on venous thromboembolism; 2 trials reported data on major bleeding; 2 trials reported data on fatal pulmonary embolism; 2 trials reported data on symptomatic deep-vein thrombosis; 2 trials reported data on symptomatic pulmonary embolism; and 2 trials reported data on deep vein thrombosis.
Following tables 40.1 (page 285), 40.2 (page 285), 40.4 (page 288), and 40.3 (page 286) summarized the main characteristics of the trials including in this systematic review of randomized trials of fondaparinux.

Table 40.1: *Treatment description - synthetic oligosaccharide - fondaparinux*

Trial	Studied treatment	Control treatment
Fondaparinux versus enoxaparin		
EPHESUS (Lassen) (2002) [1]	fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery	enoxaprin 40mg once daily enoxaparin 40-mg once-daily starting 12 hours before surgery andfollowed by a second injection 12 to 24 hours after surgery
PENTATHLON (Turpie) (2002) [2]	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 40.2: *Descriptions of participants - synthetic oligosaccharide - fondaparinux*

Trial	Patients
Fondaparinux versus enoxaparin	

continued...

Trial	Patients	
EPHESUS (Lassen) (2002) [1]	Elective hip replacement surgery	
	Inclusion criteria: patients of both sexes; aged 18 years or older; scheduled for primary elective total hip-replacement surgery, or revision of at least one component of a previously implanted total hip prosthesis	**Exclusion criteria:** bilateral hip surgery was planned during the same procedure or within 2 weeks; active bleeding; acute bacterial endocarditis; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; haemorrhagic stroke or brain, spinal, or ophthalmological surgery within the previous 3 months; planned indwelling intrathecal or epidural catheter for more than 6 h after the end of surgery; hypersensitivity to heparin, low-molecular-weight heparins, porcine products, or iodinated contrast media; contraindication to anticoagulant treatment; concomitant intake of any drug that could not be combined with contrast media; addictive disorders;
PENTATHLON (Turpie) (2002) [2]	Elective hip replacement surgery	
	Inclusion criteria: aged 18 years or older; undergoing a first elective total hip-replacement or a revision of at least one component of a previously implanted total hip prosthesis	**Exclusion criteria:** bilateral hip surgery was planned during the same procedure or within 2 weeks; active bleeding; acute bacterial endocarditis; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; haemorrhagic stroke or brain, spinal, or ophthalmological surgery within the previous 3 months; planned indwelling, intrathecal, or epidural catheter during the study treatment period; unusual difficulty in achieving epidural or spinal anaesthesia (eg, more than two attempts); hypersensitivity to heparin, low-molecularweight heparins, porcine products, or iodinated contrast medium; contraindication to anticoagulant treatment; concomitant intake of any drug that could not be combined with contrast medium; addictive disorders; concentration of creatinine in serum that was higher than 180 ˆmicromol/L in a well hydrated patient; platelet count that was lower than 100 109/L

Table 40.3: *Design and methodological quality of trials - synthetic oligosaccharide - fondaparinux*

Trial	Design	Duration	Centre	Primary endpoint
Fondaparinux versus enoxaparin				
EPHESUS (Lassen), 2002 [1] n=2309	Parallel groups double blind	11 days (6 weeks) inclusion period: dec 1998 - jan 2000	16 European countries 73 centres	venous thromboembolism

continued...

Trial	Design	Duration	Centre	Primary endpoint
PENTATHLON (Turpie), 2002 [2] n=2275	Parallel groups double blind confirmatory trial at low risk of bias	11 days inclusion period: dec 1998 - jan 2000	USA, Canada, Australia 139 centres	venous thromboembolism

Table 40.4: *Trial characteristics - synthetic oligosaccharide - fondaparinux*

Trial	Use of cement	History of venous thromboembolism
Fondaparinux versus enoxaparin		
EPHESUS (Lassen), 2002 [1]	60%	4.5%
PENTATHLON (Turpie), 2002 [2]	52%	5.5%

40.2 Meta-analysis results

The results are detailed in table 40.5 (page 290). This table is followed by the Forest's plot corresponding to each endpoint.

Fondaparinux versus enoxaparin

All the 2 studies had extractable data about the number of participants with **symptomatic deep-vein thrombosis**. The analysis detected a statistically significant difference in favor of enoxaparin in symptomatic deep-vein thrombosis, with a RR of 5.79 (95% CI 1.27 to 26.51, p=0.0235). No heterogeneity was detected (p = 0.4372, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of fondaparinux in deep vein thrombosis, with a RR of 0.55 (95% CI 0.35 to 0.86, p=0.0083). No heterogeneity was detected (p = 0.0949, I^2 = 0.64%).
All the 2 studies had extractable data about the number of participants with **symptomatic pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in symptomatic pulmonary embolism, with a RR of 2.10 (95% CI 0.43 to 10.18, p=0.3578). No heterogeneity was detected (p = 0.2754, I^2 = 0.16%).
All the 2 studies had extractable data about the number of participants with **non-fatal pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in non-fatal pulmonary embolism, with a RR of 2.00 (95% CI 0.15 to 27.38, p=0.6023). No heterogeneity was detected (p = 0.1188, I^2 = 0.59%).
All the 2 studies had extractable data about the number of participants with **proximal DVT**. When pooled together, there was no statistically significant difference between the groups in proximal DVT, with a RR of 0.62 (95% CI 0.12 to 3.24, p=0.5697). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0059, I^2 = 0.87%).
All the 2 studies had extractable data about the number of participants with **symptomatic venous thromboembolism (DVT, PE)**. When pooled together, there was no statistically significant difference between the groups in symptomatic venous thromboembolism (DVT, PE), with a RR of 3.48 (95% CI 0.61 to 19.75, p=0.1589). No heterogeneity was detected (p = 0.1588, I^2 = 0.50%).
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 0.57 (95% CI 0.35 to 0.95, p=0.0294). No heterogeneity was detected (p = 0.0522, I^2 = 0.73%).
All the 2 studies had extractable data about the number of participants with **fatal pulmonary embolism**. When pooled together, there was no statistically significant difference between the groups in fatal pulmonary embolism, with a RR of 0.67 (95% CI 0.05 to 8.74, p=0.7614). No heterogeneity was detected (p = 0.7954, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **major bleeding**. The analysis detected a statistically significant difference in favor of enoxaparin in major bleeding, with a RR of 1.59 (95% CI 1.08 to 2.32, p=0.0176). No heterogeneity was detected (p = 0.6658, I^2 = 0.00%).

Table 40.5: *Results details - synthetic oligosaccharide - fondaparinux*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fondaparinux versus enoxaparin						
symptomatic deep-vein thrombosis	RR=5.79	[1.27;26.51]	0.0235	0.4372 (I^2=0.00)	2	4506
deep vein thrombosis	RR=0.55	[0.35;0.86]	0.0083	0.0949 (I^2=0.64)	2	3408
symptomatic pulmonary embolism	RR=2.10	[0.43;10.18]	0.3578	0.2754 (I^2=0.16)	2	4506
non-fatal pulmonary embolism	RR=2.00	[0.15;27.38]	0.6023	0.1188 (I^2=0.59)	2	4506
proximal DVT	RR=0.62	[0.12;3.24]	0.5697	0.0059 (I^2=0.87)	2	3495
symptomatic venous thromboembolism (DVT, PE)	RR=3.48	[0.61;19.75]	0.1589	0.1588 (I^2=0.50)	2	4506
venous thromboembolism	RR=0.57	[0.35;0.95]	0.0294	0.0522 (I^2=0.73)	2	3411
fatal pulmonary embolism	RR=0.67	[0.05;8.74]	0.7614	0.7954 (I^2=0.00)	2	4506
all cause death	RR=1.09	[0.10;12.02]	0.9429	0.2029 (I^2=0.38)	2	4530
major bleeding	RR=1.59	[1.08;2.32]	0.0176	0.6658 (I^2=0.00)	2	4530

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

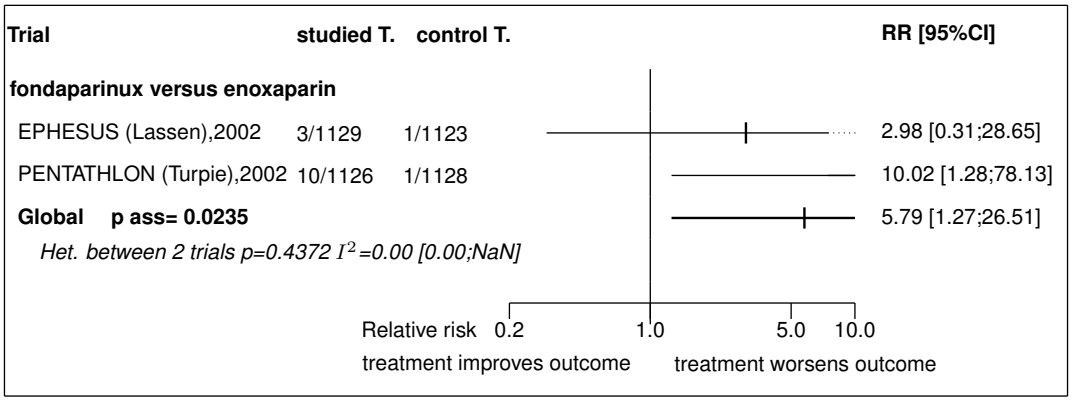


Figure 40.2: *Forest's plot for deep vein thrombosis*

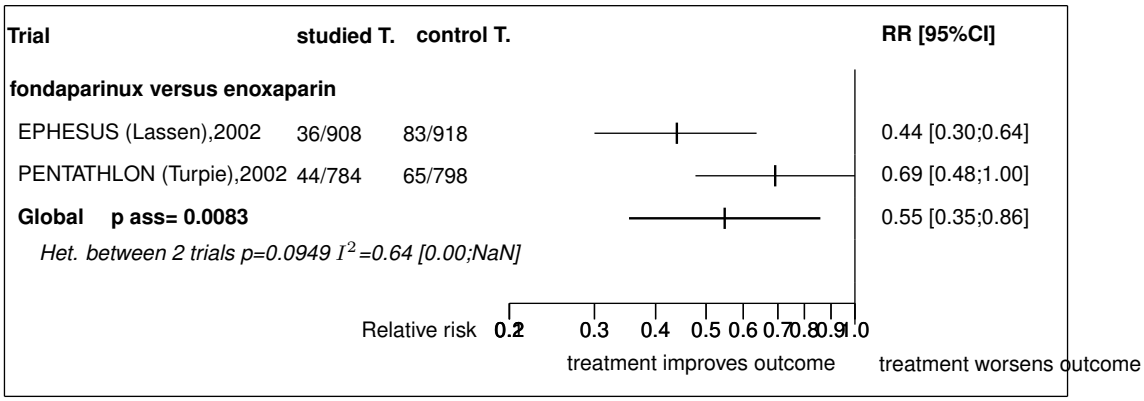


Figure 40.3: *Forest's plot for symptomatic pulmonary embolism*

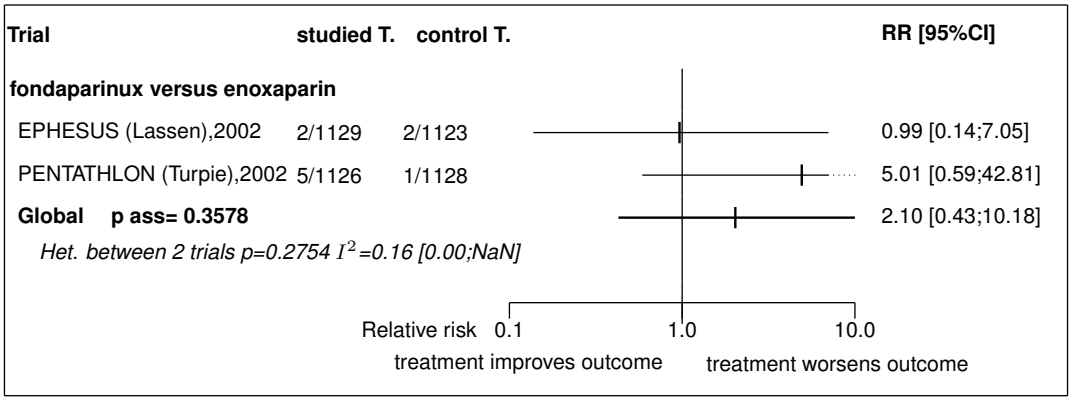


Figure 40.4: *Forest's plot for non-fatal pulmonary embolism*

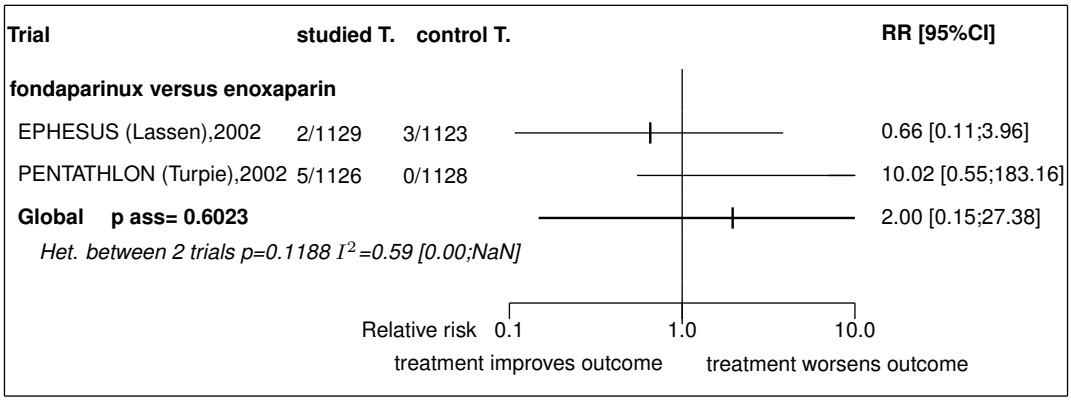


Figure 40.5: *Forest's plot for proximal DVT*

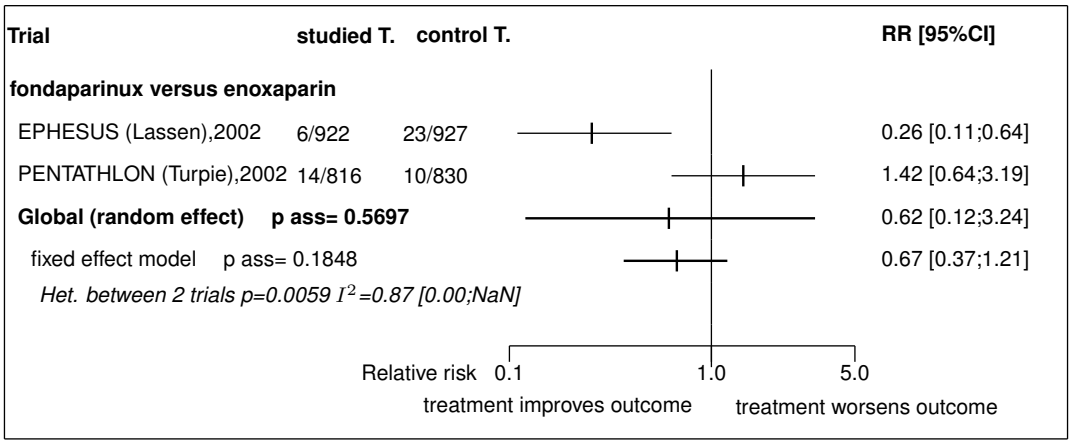


Figure 40.6: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

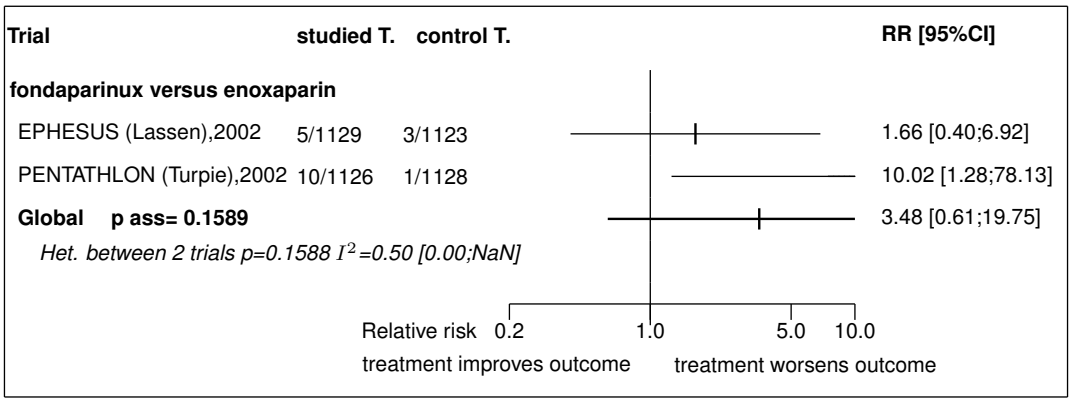


Figure 40.7: *Forest's plot for venous thromboembolism*

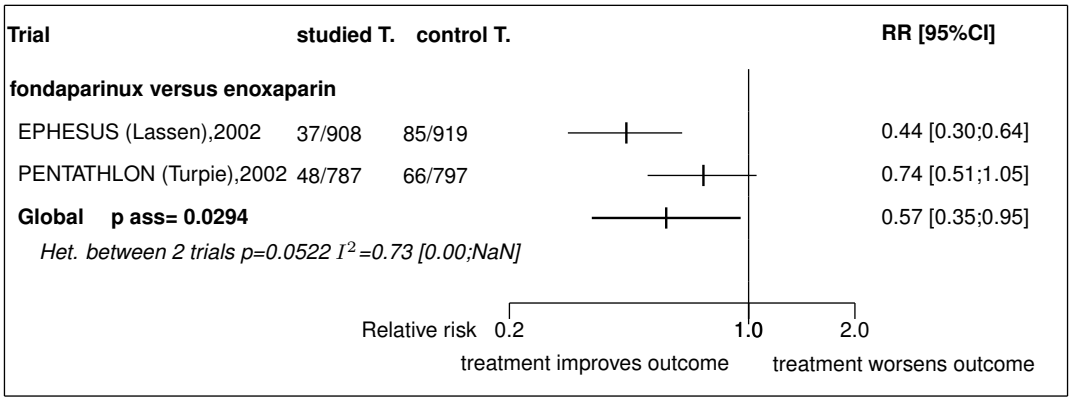


Figure 40.8: *Forest's plot for fatal pulmonary embolism*

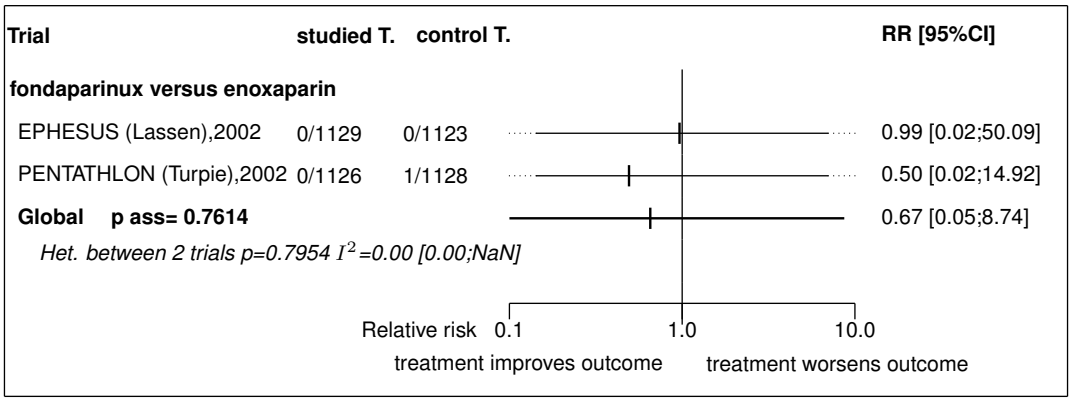


Figure 40.9: *Forest's plot for all cause death*

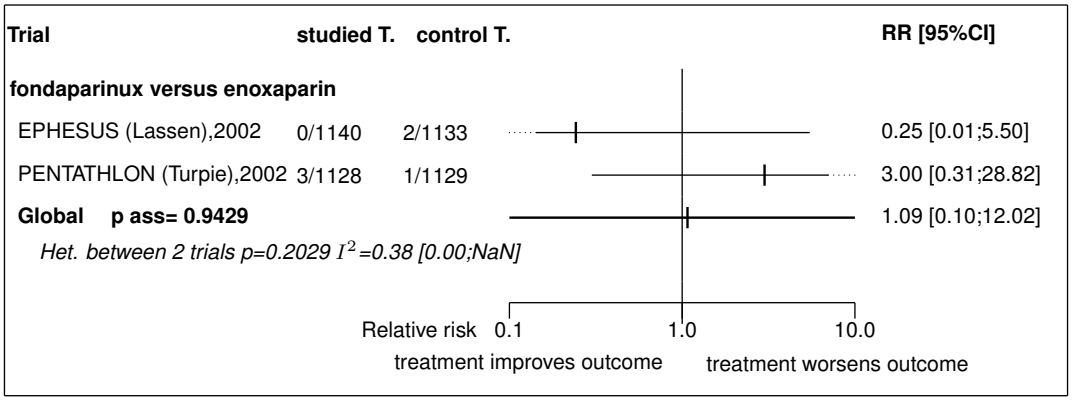
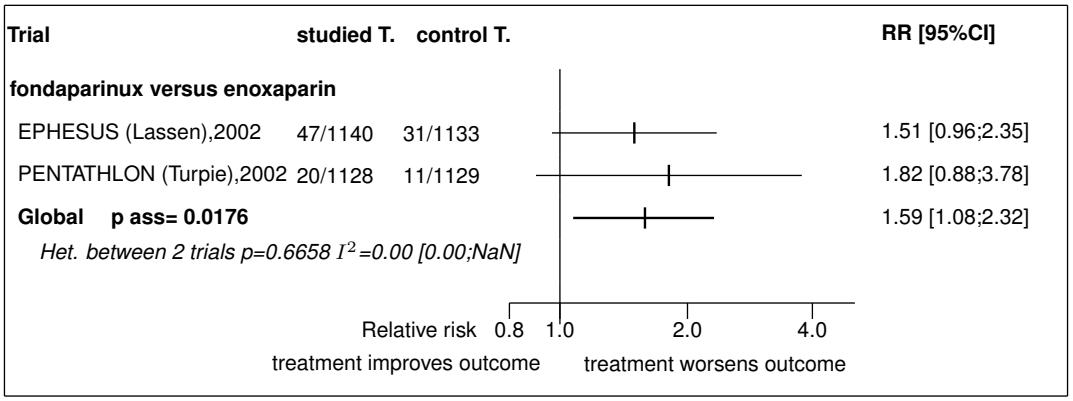


Figure 40.10: *Forest's plot for major bleeding*



References

[1] Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet 2002 May 18;359:1715-20. [PMID=12049858]

[2] Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet 2002 May 18;359:1721-6. [PMID=12049860]

40.3 Individual trial summaries

Table 40.6: *EPHESUS (Lassen), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2309 (1155 vs. 1154) **Follow-up duration:** 11 days (6 weeks) **Study design:** Randomized controlled trial Parallel groups Double blind 16 European countries, 73 centres **Inclusion period:** dec 1998 - jan 2000	Elective hip replacement surgery **Inclusion criteria:** patients of both sexes; aged 18 years or older; scheduled for primary elective total hip-replacement surgery, or revision of at least one component of a previously implanted total hip prosthesis **Exclusion criteria:** bilateral hip surgery was planned during the same procedure or within 2 weeks; active bleeding; acute bacterial endocarditis; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; haemorrhagic stroke or brain, spinal, or ophthalmological surgery within the previous 3 months; planned indwelling intrathecal or epidural catheter for more than 6 h after the end of surgery; hypersensitivity to heparin, low-molecular-weight heparins, porcine products, or iodinated contrast media; contraindication to anticoagulant treatment; concomitant i	**Studied treatment:** fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery **Control treatment:** enoxaprin 40mg once daily enoxaparin 40-mg once-daily starting 12 hours before surgery andfollowed by a second injection 12 to 24 hours after surgery	Symptomatic deep-vein thrombosis RR=2.98 [0.31;28.65] Deep vein thrombosis RR=0.44 [0.30;0.64] Symptomatic pulmonary embolism RR=0.99 [0.14;7.05] Non-fatal pulmonary embolism RR=0.66 [0.11;3.96] Proximal DVT RR=0.26 [0.11;0.64]

Reference
Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet 2002 May 18;359:1715-20 [PMID=12049858]

Table 40.7: *PENTATHLON (Turpie), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2275 (1138 vs. 1137) **Follow-up duration:** 11 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias USA, Canada, Australia, 139 centres **Inclusion period:** dec 1998 - jan 2000	Elective hip replacement surgery **Inclusion criteria:** aged 18 years or older; undergoing a first elective total hip-replacement or a revision of at least one component of a previously implanted total hip prosthesis **Exclusion criteria:** bilateral hip surgery was planned during the same procedure or within 2 weeks; active bleeding; acute bacterial endocarditis; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; haemorrhagic stroke or brain, spinal, or ophthalmological surgery within the previous 3 months; planned indwelling, intrathecal, or epidural catheter during the study treatment period; unusual difficulty in achieving epidural or spinal anaesthesia (eg, more than two attempts); hypersensitivity to heparin, low-molecularweight heparins, porcine products, or	**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=10.02 [1.28;78.13] Deep vein thrombosis RR=0.69 [0.48;1.00] Symptomatic pulmonary embolism RR=5.01 [0.59;42.81] Proximal DVT RR=1.42 [0.64;3.19]

Reference
Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet 2002 May 18;359:1721-6 [PMID=12049860]

41 Detailed results for SR123781A

41.1 Available trials

Only one trial which randomized 1023 patients was identified: it compared SR123781A with enoxaparin.
This trial included 1023 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 41.1 (page 298), 41.2 (page 298), 41.4 (page 299), and 41.3 (page 298) summarized the main characteristics of the trial including in this systematic review of randomized trials of SR123781A.

Table 41.1: *Treatment description - synthetic oligosaccharide - SR123781A*

Trial	Studied treatment	Control treatment
SR123781A versus enoxaparin		
DRIVE (2008) [1] [a]	SR123781A for 5-10 days, doses ranging from 0.25 to 4.0 mg daily for 10 days	enoxaparin 40 mg

a) dose-ranging study: SR123781A 0.25, 0.5, 1.0, 2.0, 4.0 mg and enoxaparin 40 mg daily

Table 41.2: *Descriptions of participants - synthetic oligosaccharide - SR123781A*

Trial	Patients
SR123781A versus enoxaparin	
DRIVE (2008) [1]	Patients undergoing total hip replacement surgery

Table 41.3: *Design and methodological quality of trials - synthetic oligosaccharide - SR123781A*

Trial	Design	Duration	Centre	Primary end-point
SR123781A versus enoxaparin				
DRIVE, 2008 [1] [(a)] n=1023	Parallel groups double blind exploratory trial	5-10 days inclusion period: jun 2006 - apr 2007	12 countries 53 centres	VTE

a) dose-ranging study

Table 41.4: *Trial characteristics - synthetic oligosaccharide - SR123781A*

Trial	Use of cement	History of venous thromboembolism
SR123781A versus enoxaparin		
DRIVE, 2008 [1]		

41.2 Meta-analysis results

The results are detailed in table 41.5 (page 300). This table is followed by the Forest's plot corresponding to each endpoint.

SR123781A versus enoxaparin

No data were presented in the 1 trial identified

Table 41.5: *Results details - synthetic oligosaccharide - SR123781A*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
SR123781A versus enoxaparin						
No data were presented in the trial identified						

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

References

[1] Lassen MR, Dahl O, Mismetti P, Zielske D, Turpie AG. SR123781A: a new once-daily synthetic oligosaccharide anticoagulant for thromboprophylaxis after total hip replacement surgery: the DRIVE (Dose Ranging Study in Elective Total Hip Replacement Surgery) study. J Am Coll Cardiol 2008 Apr 15;51:1498-504. [PMID=18402906]

41.3 Individual trial summaries

Table 41.6: *DRIVE, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1023 (854 vs. 169) **Follow-up duration:** 5-10 days **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial 12 countries, 53 centres **Inclusion period:** jun 2006 - apr 2007	Patients undergoing total hip replacement surgery	**Studied treatment:** SR123781A for 5-10 days, doses ranging from 0.25 to 4.0 mg daily for 10 days **Control treatment:** enoxaparin 40 mg **note:** dose-ranging study: SR123781A 0.25, 0.5, 1.0, 2.0, 4.0 mg and enoxaparin 40 mg daily	

Reference

Lassen MR, Dahl O, Mismetti P, Zielske D, Turpie AG. SR123781A: a new once-daily synthetic oligosaccharide anticoagulant for thromboprophylaxis after total hip replacement surgery: the DRIVE (Dose Ranging Study in Elective Total Hip Replacement Surgery) study. J Am Coll Cardiol 2008 Apr 15;51:1498-504 [PMID=18402906]

42 Global meta-analysis: all synthetic oligosaccharide

42.1 Global meta-analysis: all synthetic oligosaccharide versus enoxaparin

Table 42.1: *All synthetic oligosaccharideversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
symptomatic deep-vein thrombosis	RR=5.79	1.27;26.51	0.0235	0.4372 (0.00)	2	4506
deep vein thrombosis	RR=0.55	0.35;0.86	0.0083	0.0949 (0.64)	2	3408
symptomatic pulmonary embolism	RR=2.10	0.43;10.18	0.3578	0.2754 (0.16)	2	4506
non-fatal pulmonary embolism	RR=2.00	0.15;27.38	0.6023	0.1188 (0.59)	2	4506
proximal DVT	RR=0.62 [1]	0.12;3.24	0.5697	0.0059 (0.87) †	2	3495
symptomatic venous thromboembolism (DVT, PE)	RR=3.48	0.61;19.75	0.1589	0.1588 (0.50)	2	4506
venous thromboembolism	RR=0.57	0.35;0.95	0.0294	0.0522 (0.73)	2	3411
fatal pulmonary embolism	RR=0.67	0.05;8.74	0.7614	0.7954 (0.00)	2	4506
major bleeding	RR=1.59	1.08;2.32	0.0176	0.6658 (0.00)	2	4530

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

43 Ongoing studies of synthetic oligosaccharide

Only one ongoing study was identified. A brief description of this trial is given table 43.1

Table 43.1: *Ongoing studies for synthetic oligosaccharide*

Study	Description
NCT00320398 NCT00320398	Fondaparinux **vs.** patients undergoing either an elective primary total hip replacement (THR) surgery or a revision of a THR

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.67 95% CI 0.37;1.21

44 Excluded studies for synthetic oligosaccharide

No trial was excluded.

References