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Antithrombotics for DVT prophylaxis in hip Fracture

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 hip Fracture.

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0.1 Synthesis of the meta-analysis results

In all 7 randomised controlled trials (RCTs) were included. These included 4 studies of **low molecular weight heparin** involving 1,360 patients, 1 studie of **platelet aggregation inhibitors** involving 13,356 patients and 2 studies of **synthetic oligosaccharide** involving 2,327 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 Low molecular weight heparin

Reports of 4 trials (including 1,360 patients) were identified .
Among these comparisons, one trial are about certoparine + DHE,one about dalteparin,one about nadroparin and one about semuloparin.
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 1.

Table 1: *Results summary - Certoparine + DHE*

Benefit	Harmful	No evidence
	Certoparine + DHE versus Unfractionated heparin	
		→ deep vein thrombosis RR=0.64^{NS} [0.36;1.13] k=1 → symptomatic pulmonary embolism RR=2.09^{NS} [0.07;61.24] k=1 → all cause death RR=2.09^{NS} [0.40;11.03] k=1

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

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

Dalteparin

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

Table 2: *Results summary - Dalteparin*

Benefit	Harmful	No evidence
	Dalteparin versus placebo	
↓ deep vein thrombosis RR=0.52* [0.28;0.95] k=1		→ symptomatic pulmonary embolism RR=0.63^{NS} [0.02;18.25] k=1 → all cause death RR=0.63^{NS} [0.02;18.25] 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)

Nadroparin

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

Table 3: *Results summary - Nadroparin*

Benefit	Harmful	No evidence
Nadroparin versus placebo		
↓ deep vein thrombosis RR=0.46¶ [0.33;0.66] 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)

Semuloparin

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

Table 4: *Results summary - Semuloparin*

Benefit	Harmful	No evidence
Semuloparin versus enoxaparin		
		→ deep vein thrombosis RR=0.77^{NS} [0.57;1.04] k=1 → symptomatic pulmonary embolism RR=2.05^{NS} [0.07;60.82] k=1 → total VTE and all-cause mortality RR=0.81^{NS} [0.60;1.08] k=1 → major or clinically relevant non-major bleeding RR=2.56^{NS} [0.81;8.10] 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 Platelet aggregation inhibitors

Only one trials including 13356 patients was found.
Among these comparisons, one trial are about aspirin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with aspirin for all the endpoints with data in at least one trial are summarized table 5.

Table 5: *Results summary - Aspirin*

Benefit	Harmful	No evidence
	Aspirin versus placebo	
↓ deep vein thrombosis RR=0.71* [0.52;0.97] k=1 ↓ fatal pulmonary embolism RR=0.42† [0.24;0.72] k=1	↑ major bleeding RR=1.25* [1.02;1.54] k=1	→ non pulmonary embolism death RR=1.01^{NS} [0.84;1.22] k=1 → non-fatal pulmonary embolism RR=0.74^{NS} [0.45;1.20] 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 Synthetic oligosaccharide

Reports of 2 trials (including 2,327 patients) were identified .
Among these comparisons, one trial are about extended prophylaxis and one about fondaparinux.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Extended prophylaxis

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

Table 6: *Results summary - Extended prophylaxis*

Benefit	Harmful	No evidence
	Extended prophylaxis versus standard prophylaxis	

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

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

Fondaparinux

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

Table 7: *Results summary - Fondaparinux*

Benefit	Harmful	No evidence
	Fondaparinux versus enoxaparin	

continued...

Benefit	Harmful	No evidence
↓ deep vein thrombosis RR=0.42¶ [0.31;0.57] k=1 ↓ venous thromboembolism RR=0.44¶ [0.32;0.59] k=1 ↓ proximal DVT RR=0.21¶ [0.09;0.51] k=1		→ symptomatic pulmonary embolism RR=2.20^{NS} [0.45;10.87] k=1 → symptomatic deep-vein thrombosis RR=1.01^{NS} [0.06;16.13] k=1 → fatal pulmonary embolism RR=1.01^{NS} [0.14;7.16] k=1 → non-fatal pulmonary embolism RR=1.01^{NS} [0.06;16.13] k=1 → symptomatic venous thromboembolism (DVT, PE) RR=1.01^{NS} [0.25;4.03] k=1 → all cause death RR=0.70^{NS} [0.33;1.49] k=1 → major bleeding RR=0.96^{NS} [0.51;1.82] k=1

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

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

1 Introduction

1.1 Aim of the report

This report review all the randomized clinical trials of antithrombotics for the treatment of DVT prophylaxis in hip Fracture. The following classes of treatment are considered:

1. Low molecular weight heparin
2. platelet aggregation inhibitors
3. 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 hip Fracture.

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 Deep vein thrombosis, Symptomatic pulmonary embolism, total VTE and all-cause mortality, asymptomatic proximal DVT, major or clinically relevant non-major bleeding, Bleeding, All cause death, .

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 Low molecular weight heparin, platelet aggregation inhibitors, synthetic oligosaccharide,
In these sections, studies in which an active intervention was compared with placebo or no treatment are discussed first, by intervention, followed by a discussion of those studies in which two or more active interventions were compared.

Part I

Low molecular weight heparin

2 Overview of low molecular weight heparin

2.1 Included trials

A total of 4 randomized comparisons which enrolled 1360 patients were identified. In all, 1 randomized comparison concerned certoparine + DHE , one dalteparin , one nadroparin and one semuloparin.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 21) for certoparine + DHE, in section 4 (page 28) for dalteparin, in section 5 (page 34) for nadroparin and in section 6 (page 39) for semuloparin.

The average study size was 340 patients (range 68 to 1003). The first study was published in 1989, and the last study was published in 2012.
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 16) 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 low molecular weight heparin provide the results listed in tables 2.2 to 2.5 (page 17) and in the following graphs.

2.2.1 Certoparine + DHE

No significant difference was found between **certoparine + DHE** and **Unfractionated heparin** in terms of deep vein thrombosis (RR=0.64, 95% CI 0.36 to 1.13, p=0.1224, 1 trial)and symptomatic pulmonary embolism (RR=2.09, 95% CI 0.07 to 61.24, p=0.6693, 1 trial).

2.2.2 Dalteparin

Dalteparin was superior to **placebo** in terms of deep vein thrombosis (RR=0.52, 95% CI 0.28 to 0.95, p=0.0347, 1 trial). However, no significant difference was found on symptomatic pulmonary embolism (RR=0.63, 95% CI 0.02 to 18.25, p=0.7900, 1 trial).

2.2.3 Nadroparin

Nadroparin was superior to **placebo** in terms of deep vein thrombosis (RR=0.46, 95% CI 0.33 to 0.66, p=0.0000, 1 trial).

2.2.4 Semuloparin

No significant difference was found between **semuloparin** and **enoxaparin** in terms of deep vein thrombosis (RR=0.77, 95% CI 0.57 to 1.04, p=0.0895, 1 trial), symptomatic pulmonary embolism (RR=2.05, 95% CI 0.07 to 60.82, p=0.6794, 1 trial), total VTE and all-cause mortality (RR=0.81, 95% CI 0.60 to 1.08, p=0.1452, 1 trial)and major or clinically relevant non-major bleeding (RR=2.56, 95% CI 0.81 to 8.10, p=0.1105, 1 trial).

Table 2.1: *Main study characteristics - Low molecular weight heparin*

Trial	Patients	Treatments	Trial design and method
Certoparine + DHE			
Certoparine + DHE versus Unfractionated heparin			
Lassen, 1989 [1] n = 68 vs. 71	hip fracture	certoparin 3000+0.5mg DHE x1 **versus** placebo	double blind
Dalteparin			
Dalteparin versus placebo			
Jorgensen, 1989 n = 30 vs. 38	hip fracture	dalteparin 5000 x1 **versus** placebo	double blind
Nadroparin			
Nadroparin versus placebo			
Sourmelis, 1995 n = 72 vs. 78	hip fracture	nadroparin 3075x1 preop, 6150x1 post op **versus** placebo	double blind
Semuloparin			
Semuloparin versus enoxaparin			
SAVE-HIP 2, 2012 [1] n = 500 vs. 503	hip fracture surgery	semuloparin 20 mg once-daily **versus** enoxaparin 40 mg once-daily	parallel groups

Table 2.2: *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=0.64	0.36;1.13	0.1224	1.0000 (0.00)	1	139
symptomatic pulmonary embolism	RR=2.09	0.07;61.24	0.6693	1.0000 (0.00)	1	139
all cause death	RR=2.09	0.40;11.03	0.3859	1.0000 (0.00)	1	139

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 dalteparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
dalteparin versus placebo						
deep vein thrombosis	RR=0.52	0.28;0.95	0.0347	1.0000 (1.00)	1	68
symptomatic pulmonary embolism	RR=0.63	0.02;18.25	0.7900	1.0000 (0.00)	1	68
all cause death	RR=0.63	0.02;18.25	0.7900	1.0000 (0.00)	1	68

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 nadroparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
nadroparin versus placebo						
deep vein thrombosis	RR=0.46	0.33;0.66	0.0000	1.0000 (0.00)	1	150

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 semuloparin*

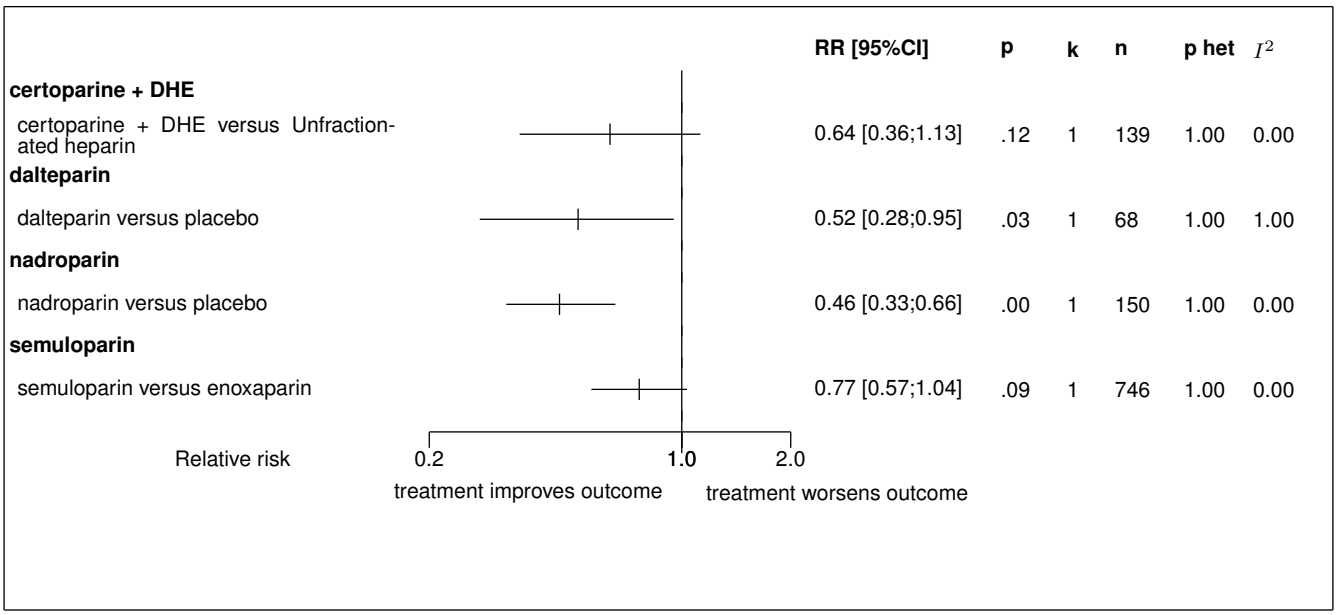
Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
semuloparin versus enoxaparin						
deep vein thrombosis	RR=0.77	0.57;1.04	0.0895	1.0000 (0.00)	1	746
symptomatic pulmonary embolism	RR=2.05	0.07;60.82	0.6794	1.0000 (0.00)	1	987
total VTE and all-cause mortality	RR=0.81	0.60;1.08	0.1452	1.0000 (0.00)	1	753

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
major or clinically relevant non-major bleeding	RR=2.56	0.81;8.10	0.1105	1.0000 (0.00)	1	987

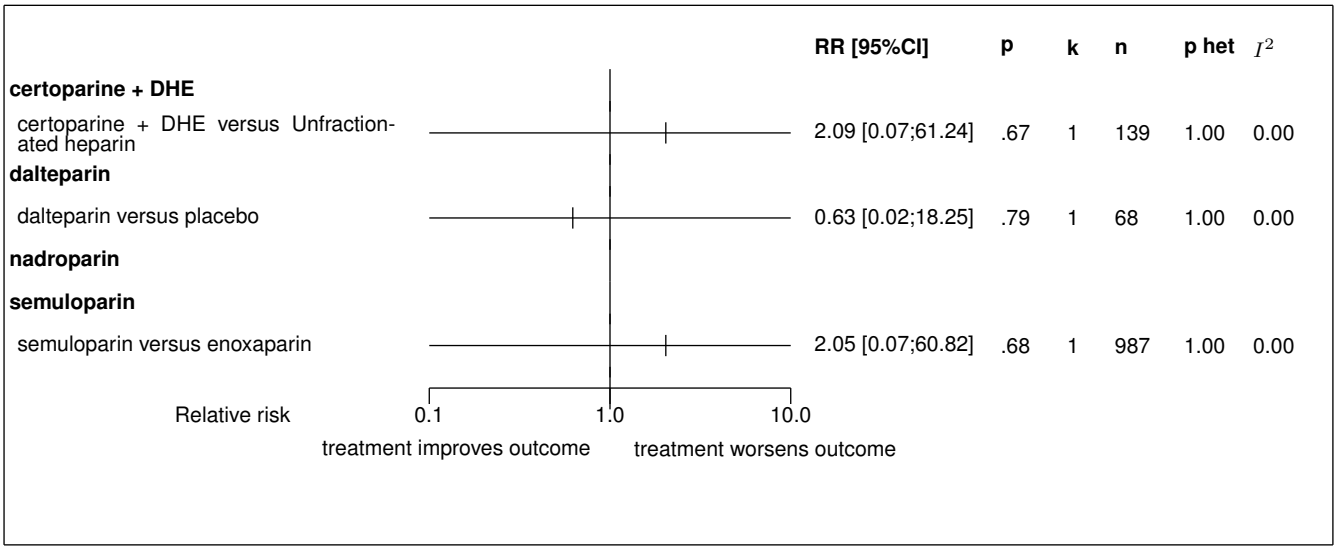
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 2.1: *Forest's plot for 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 symptomatic pulmonary embolism*

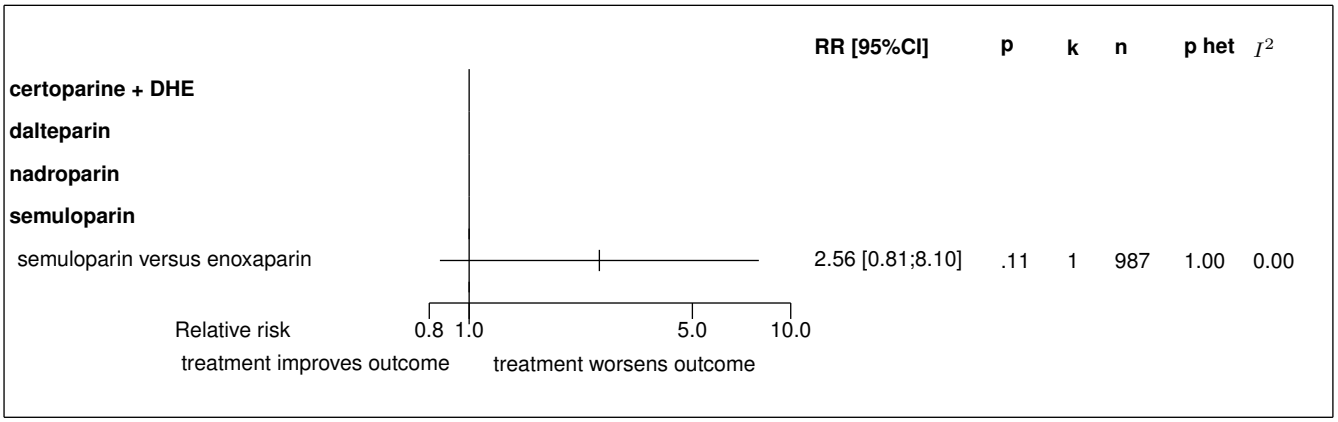


Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.3: *Forest's plot for total VTE and all-cause mortality*

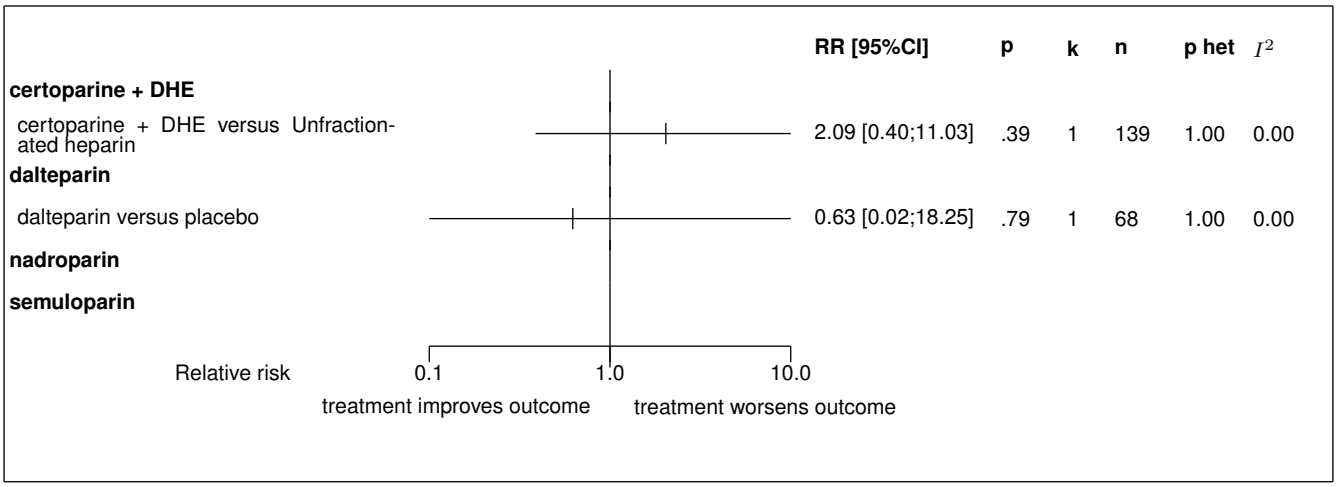
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.4: *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 2.5: *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

3 Detailed results for certoparine + DHE

3.1 Available trials

Only one trial which randomized 139 patients was identified: it compared certoparine + DHE with Unfractionated heparin.
This trial included 139 patients and was published in 1989.
This trial was double blind in design.
It was reported in English language.
Symptomatic pulmonary embolism data was reported in 1 trials; 1 trials reported data on deep vein thrombosis; 1 trials reported data on bleeding; and 1 trials reported data on all cause death.
Following tables 3.1 (page 21), 3.2 (page 21), 3.4 (page 23), and 3.3 (page 21) summarized the main characteristics of the trial including in this systematic review of randomized trials of certoparine + DHE.

Table 3.1: *Treatment description - Low molecular weight heparin - certoparine + DHE*

Trial	Studied treatment	Control treatment
Certoparine + DHE versus Unfractionated heparin		
Lassen (1989) [1]	certoparin 3000+0.5mg DHE x1 1 x6300;2h before; 7 days	placebo 2 x 5000; 2h before; 7 days

Table 3.2: *Descriptions of participants - Low molecular weight heparin - certoparine + DHE*

Trial	Patients
Certoparine + DHE versus Unfractionated heparin	
Lassen (1989) [1]	Hip fracture

Table 3.3: *Design and methodological quality of trials - Low molecular weight heparin - certoparine + DHE*

Trial	Design	Duration	Centre	Primary endpoint
Certoparine + DHE versus Unfractionated heparin				
Lassen, 1989 [1] n=139	double blind	6 days		

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 3.4: *Trial characteristics - Low molecular weight heparin - certoparine + DHE*

Trial
Certoparine + DHE versus Unfractionated heparin
Lassen, 1989 [1]

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 24). This table is followed by the Forest's plot corresponding to each endpoint.

Certoparine + DHE versus Unfractionated heparin

The single study eligible for this comparison provided data on **deep vein thrombosis**. There was no statistically significant difference in deep vein thrombosis between certoparine + DHE and unfractionated heparin, with a RR of 0.64 (95%CI 0.36 to 1.13, p=0.1224) in favour of certoparine + DHE. In other words, deep vein thrombosis was slightly lower in the certoparine + DHE group , but this was not statistically significant.
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 2.09 (95% CI 0.07 to 61.24, p=0.6693).

Table 3.5: *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=0.64	[0.36;1.13]	0.1224	1.0000 (I^2=0.00)	1	139
symptomatic pulmonary embolism	RR=2.09	[0.07;61.24]	0.6693	1.0000 (I^2=0.00)	1	139
all cause death	RR=2.09	[0.40;11.03]	0.3859	1.0000 (I^2=0.00)	1	139

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 deep vein thrombosis*

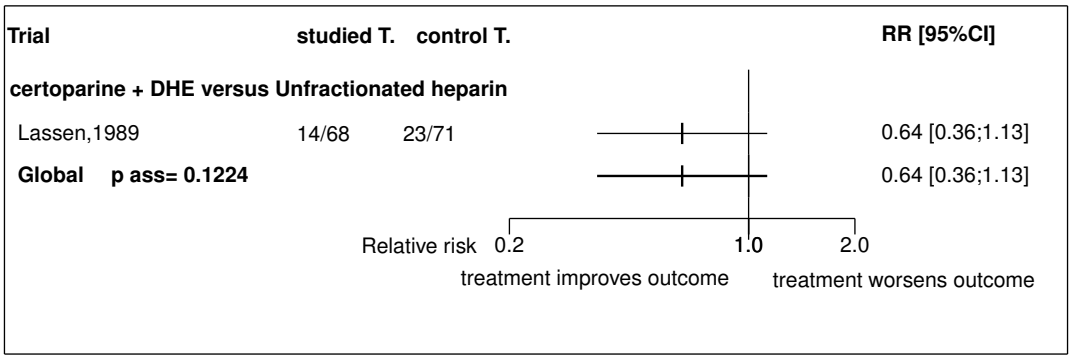


Figure 3.2: *Forest's plot for symptomatic pulmonary embolism*

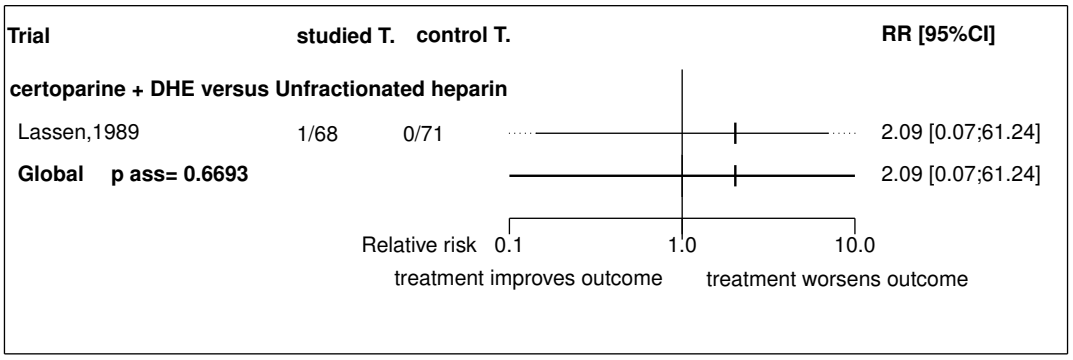
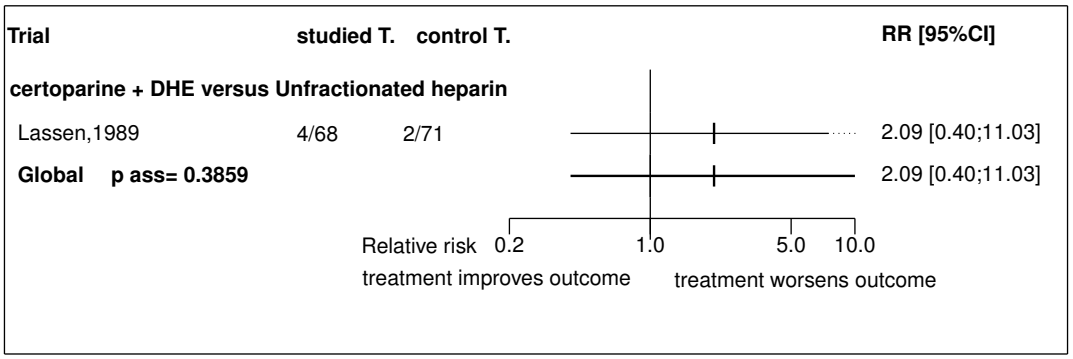


Figure 3.3: *Forest's plot for all cause death*



References

[1] Lassen MR, Borris LC, Christiansen HM, Moller-Larsen F, Knudsen VE, Boris P, Nehen AM, Jurik AG, de Carvalho A, Nielsen BW. Prevention of thromboembolism in hip-fracture patients. Comparison of low-dose heparin and low-molecular-weight heparin combined with dihydroergotamine. Arch Orthop Trauma Surg 1989;108:10-3. [PMID=2913977]

3.3 Individual trial summaries

Table 3.6: *Lassen, 1989 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=139 (68 vs. 71) **Follow-up duration:** 6 days **Study design:** Randomized controlled trial Double blind	Hip fracture	**Studied treatment:** certoparin 3000+0.5mg DHE x1 1 x6300;2h before; 7 days **Control treatment:** placebo 2 x 5000; 2h before; 7 days	Deep vein thrombosis RR=0.64 [0.36;1.13]

Reference

Lassen MR, Borris LC, Christiansen HM, Moller-Larsen F, Knudsen VE, Boris P, Nehen AM, Jurik AG, de Carvalho A, Nielsen BW. Prevention of thromboembolism in hip-fracture patients. Comparison of low-dose heparin and low-molecular-weight heparin combined with dihydroergotamine. Arch Orthop Trauma Surg 1989;108:10-3 [PMID=2913977]

4 Detailed results for dalteparin

4.1 Available trials

Only one trial which randomized 68 patients was identified: it compared dalteparin with placebo.
This trial included 68 patients and was published in 1989.
This trial was double blind in design.
It was reported in English language.
Symptomatic pulmonary embolism data was reported in 1 trials; 1 trials reported data on deep vein thrombosis; 1 trials reported data on bleeding; and 1 trials reported data on all cause death.
Following tables 4.1 (page 28), 4.2 (page 28), 4.4 (page 29), and 4.3 (page 28) summarized the main characteristics of the trial including in this systematic review of randomized trials of dalteparin.

Table 4.1: *Treatment description - Low molecular weight heparin - dalteparin*

Trial	Studied treatment	Control treatment
Dalteparin versus placebo		
Jorgensen (1989)	dalteparin 5000 x1 2x2500; 2h before to 12h after; 1x5000; 6 days	Placebo Placebo

Table 4.2: *Descriptions of participants - Low molecular weight heparin - dalteparin*

Trial	Patients
Dalteparin versus placebo	
Jorgensen (1989)	Hip fracture

Table 4.3: *Design and methodological quality of trials - Low molecular weight heparin - dalteparin*

Trial	Design	Duration	Centre	Primary endpoint
Dalteparin versus placebo				
Jorgensen, 1989 n=68	double blind	9 days		

Table 4.4: *Trial characteristics - Low molecular weight heparin - dalteparin*

Trial
Dalteparin versus placebo
Jorgensen, 1989

4.2 Meta-analysis results

The results are detailed in table 4.5 (page 30). 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 0.52 (95% CI 0.28 to 0.95, p=0.0347).
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 0.63 (95% CI 0.02 to 18.25, p=0.7900).

Table 4.5: *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=0.52	[0.28;0.95]	0.0347	1.0000 (I^2=1.00)	1	68
symptomatic pulmonary embolism	RR=0.63	[0.02;18.25]	0.7900	1.0000 (I^2=0.00)	1	68
all cause death	RR=0.63	[0.02;18.25]	0.7900	1.0000 (I^2=0.00)	1	68

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 deep vein thrombosis*

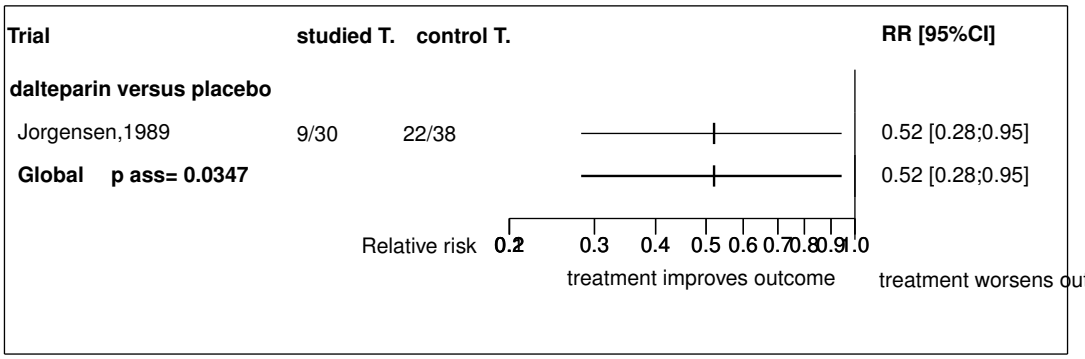


Figure 4.2: *Forest's plot for symptomatic pulmonary embolism*

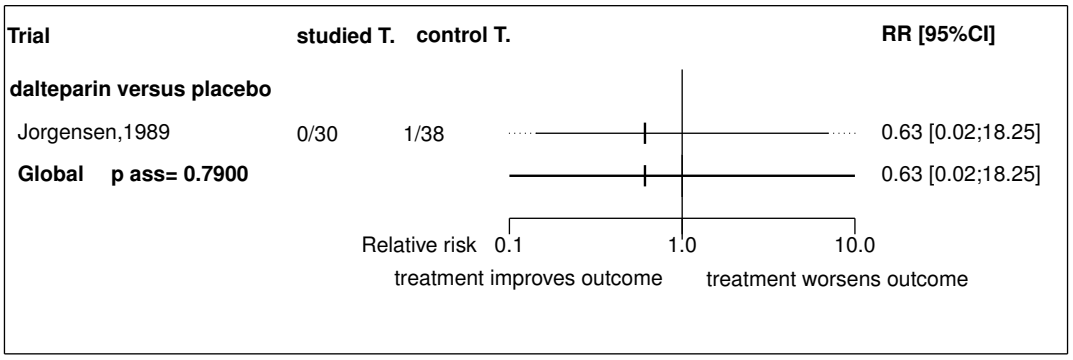
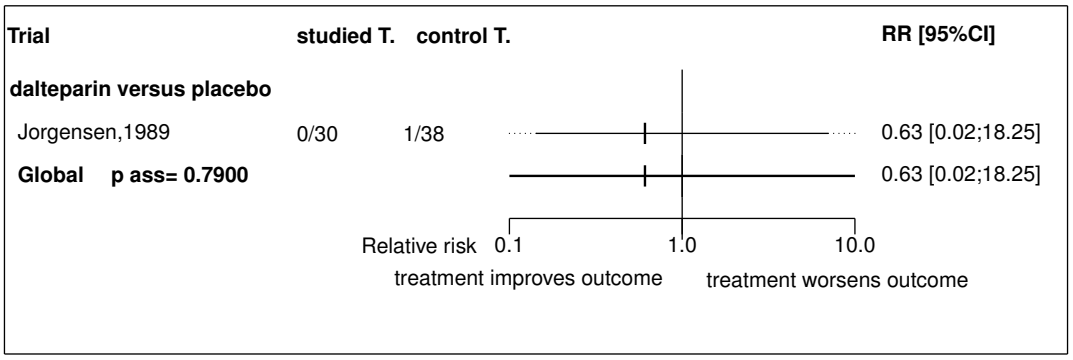


Figure 4.3: *Forest's plot for all cause death*



References

4.3 Individual trial summaries

Table 4.6: *Jorgensen, 1989 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=68 (30 vs. 38) **Follow-up duration:** 9 days **Study design:** Randomized controlled trial Double blind	Hip fracture	**Studied treatment:** dalteparin 5000 x1 2x2500; 2h before to 12h after; 1x5000; 6 days **Control treatment:** Placebo Placebo	Deep vein thrombosis RR=0.52 [0.28;0.95]
Reference			

5 Detailed results for nadroparin

5.1 Available trials

Only one trial which randomized 150 patients was identified: it compared nadroparin with placebo.
This trial included 150 patients and was published in 1995.
This trial was double blind in design.
It was reported in English language.
Deep vein thrombosis data was reported in 1 trials; and 1 trials reported data on asymptomatic proximal DVT.
Following tables 5.1 (page 34), 5.2 (page 34), 5.4 (page 35), and 5.3 (page 34) summarized the main characteristics of the trial including in this systematic review of randomized trials of nadroparin.

Table 5.1: *Treatment description - Low molecular weight heparin - nadroparin*

Trial	Studied treatment	Control treatment
Nadroparin versus placebo		
Sourmelis (1995)	nadroparin 3075x1 preop, 6150x1 post op	Placebo

Table 5.2: *Descriptions of participants - Low molecular weight heparin - nadroparin*

Trial	Patients
Nadroparin versus placebo	
Sourmelis (1995)	Hip fracture

Table 5.3: *Design and methodological quality of trials - Low molecular weight heparin - nadroparin*

Trial	Design	Duration	Centre	Primary end-point
Nadroparin versus placebo				
Sourmelis, 1995 n=150	double blind	10-12 days		

Table 5.4: *Trial characteristics - Low molecular weight heparin - nadroparin*

Trial
Nadroparin versus placebo
Sourmelis, 1995

5.2 Meta-analysis results

The results are detailed in table 5.5 (page 36). This table is followed by the Forest's plot corresponding to each endpoint.

Nadroparin versus placebo

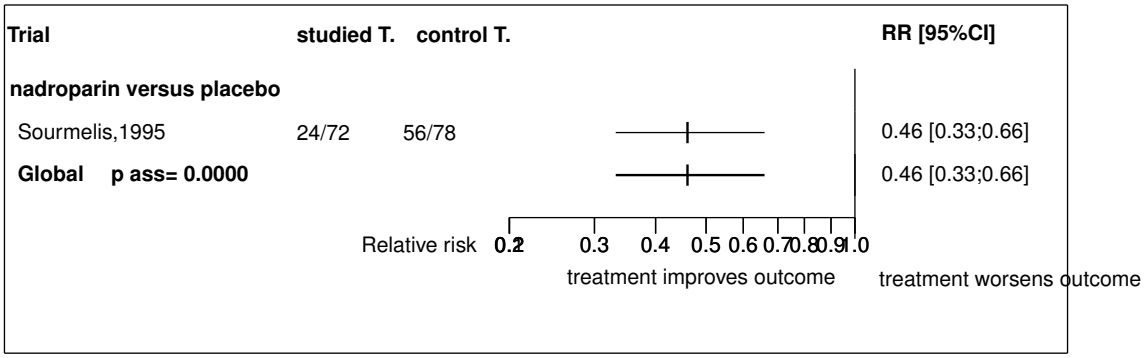
The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of nadroparin in deep vein thrombosis, with a RR of 0.46 (95% CI 0.33 to 0.66, p=0.0000).

Table 5.5: *Results details - Low molecular weight heparin - nadroparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nadroparin versus placebo						
deep vein thrombosis	RR=0.46	[0.33;0.66]	0.0000	1.0000 (I^2=0.00)	1	150

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 deep vein thrombosis*



References

5.3 Individual trial summaries

Table 5.6: *Sourmelis, 1995 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=150 (72 vs. 78) **Follow-up duration:** 10-12 days **Study design:** Randomized controlled trial Double blind	Hip fracture	**Studied treatment:** nadroparin 3075x1 preop, 6150x1 post op **Control treatment:** Placebo	Deep vein thrombosis RR=0.46 [0.33;0.66]
Reference			

6 Detailed results for semuloparin

6.1 Available trials

Only one trial which randomized 1003 patients was identified: it compared semuloparin with enoxaparin.
This trial included 1003 patients and was published in 2012.
Erreur ??? 0 et 0.
It was reported in English language.
Total VTE and all-cause mortality 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 major or clinically relevant non-major bleeding; and 1 trials reported data on bleeding.
Following tables 6.1 (page 39), 6.2 (page 39), 6.4 (page 41), and 6.3 (page 39) summarized the main characteristics of the trial including in this systematic review of randomized trials of semuloparin.

Table 6.1: *Treatment description - Low molecular weight heparin - semuloparin*

Trial	Studied treatment	Control treatment
Semuloparin versus enoxaparin		
SAVE-HIP 2 (2012) [1]	Semuloparin 20 mg once-daily	Enoxaparin 40 mg once-daily

Table 6.2: *Descriptions of participants - Low molecular weight heparin - semuloparin*

Trial	Patients
Semuloparin versus enoxaparin	
SAVE-HIP 2 (2012) [1]	Hip fracture surgery

Table 6.3: *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-HIP 2, 2012 [1] n=1003	Parallel groups			

Table 6.4: *Trial characteristics - Low molecular weight heparin - semuloparin*

Trial
Semuloparin versus enoxaparin
SAVE-HIP 2, 2012 [1]

6.2 Meta-analysis results

The results are detailed in table 6.5 (page 42). 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**. There was no statistically significant difference in deep vein thrombosis between semuloparin and enoxaparin, with a RR of 0.77 (95%CI 0.57 to 1.04, p=0.0895) in favour of semuloparin. In other words, deep vein thrombosis was slightly lower in the semuloparin group , but this was not statistically significant.
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 2.05 (95% CI 0.07 to 60.82, p=0.6794).
The single study eligible for this comparison provided data on **total VTE and all-cause mortality**. No statistically significant difference between the groups was found in total VTE and all-cause mortality, with a RR of 0.81 (95% CI 0.60 to 1.08, p=0.1452).
The single study eligible for this comparison provided data on **major or clinically relevant non-major bleeding**. No statistically significant difference between the groups was found in major or clinically relevant non-major bleeding, with a RR of 2.56 (95% CI 0.81 to 8.10, p=0.1105).

Table 6.5: *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=0.77	[0.57;1.04]	0.0895	1.0000 (I^2=0.00)	1	746
symptomatic pulmonary embolism	RR=2.05	[0.07;60.82]	0.6794	1.0000 (I^2=0.00)	1	987
total VTE and all-cause mortality	RR=0.81	[0.60;1.08]	0.1452	1.0000 (I^2=0.00)	1	753
major or clinically relevant non-major bleeding	RR=2.56	[0.81;8.10]	0.1105	1.0000 (I^2=0.00)	1	987

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 deep vein thrombosis*

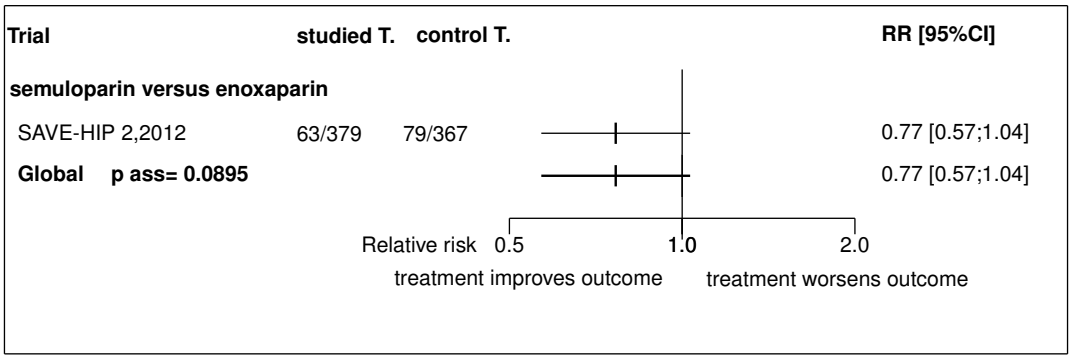


Figure 6.2: *Forest's plot for symptomatic pulmonary embolism*

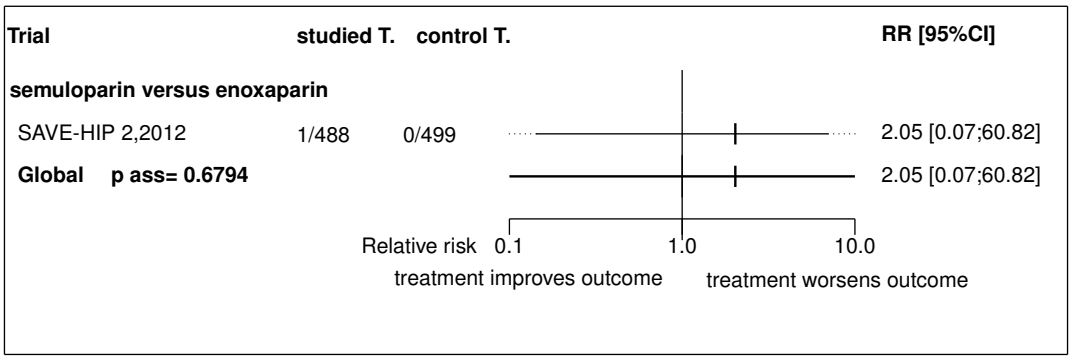


Figure 6.3: *Forest's plot for total VTE and all-cause mortality*

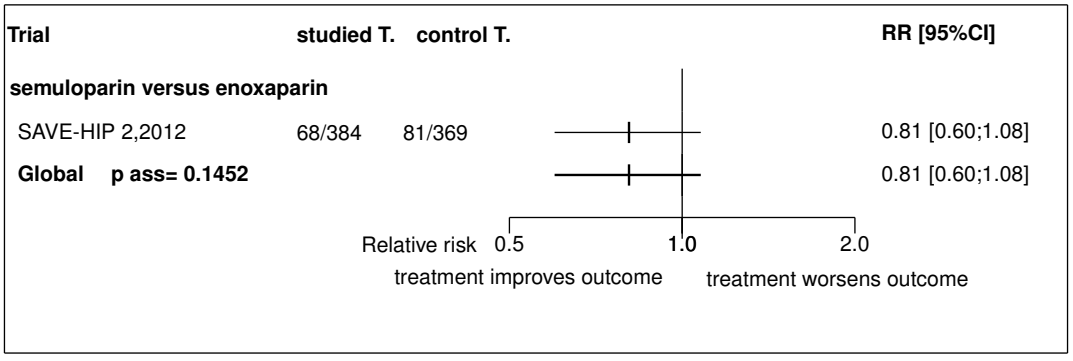
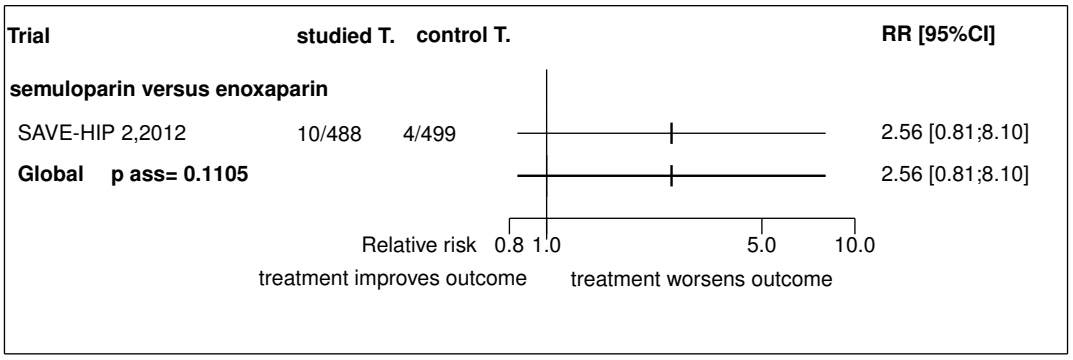


Figure 6.4: *Forest's plot for major or clinically relevant non-major bleeding*



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 May;10:822-32. [PMID=22429800]

6.3 Individual trial summaries

Table 6.6: *SAVE-HIP 2, 2012 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1003 (500 vs. 503) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups	Hip fracture surgery	**Studied treatment:** Semuloparin 20 mg once-daily **Control treatment:** Enoxaparin 40 mg once-daily	Deep vein thrombosis RR=0.77 [0.57;1.04] (any DVT) Total VTE and all-cause mortality RR=0.81 [0.60;1.08] Major or clinically relevant non-major bleeding RR=2.56 [0.81;8.10] (Any clinically relevant bleeding)

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 May;10:822-32 [PMID=22429800]

7 Global meta-analysis: all Low molecular weight heparin

7.1 Global meta-analysis: all Low molecular weight heparin versus enoxaparin

Table 7.1: *All Low molecular weight heparinversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.77	0.57;1.04	0.0895	1.0000 (0.00)	1	746
symptomatic pulmonary embolism	RR=2.05	0.07;60.82	0.6794	1.0000 (0.00)	1	987
total VTE and all-cause mortality	RR=0.81	0.60;1.08	0.1452	1.0000 (0.00)	1	753
major or clinically relevant non-major bleeding	RR=2.56	0.81;8.10	0.1105	1.0000 (0.00)	1	987

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 Low molecular weight heparin versus placebo

Table 7.2: *All Low molecular weight heparinversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.48	0.35;0.65	0.0000	0.7604 (0.00)	2	218
symptomatic pulmonary embolism	RR=0.63	0.02;18.25	0.7900	1.0000 (0.00)	1	68

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

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

Table 7.3: *All Low molecular weight heparinversus Unfractionated heparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.64	0.36;1.13	0.1224	1.0000 (0.00)	1	139
symptomatic pulmonary embolism	RR=2.09	0.07;61.24	0.6693	1.0000 (0.00)	1	139

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 Low molecular weight heparin

No ongoing trial was identified.

9 Excluded studies for Low molecular weight heparin

No trial was excluded.

References

Part II

Platelet aggregation inhibitors

10 Overview of platelet aggregation inhibitors

10.1 Included trials

Only one trial which randomized 13356 patients was identified. In all, 1 randomized comparison concerned aspirin.
The detailed descriptions of trials and meta-analysis results is given in section 11 (page 55) for aspirin.

This trial included 13356 patients and was published in 2000.
This trial was double blind in design.
It was reported in English language.
The table 10.1 (page 52) 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 platelet aggregation inhibitors provide the results listed in tables 10.2 to 10.2 (page 53) and in the following graphs.

10.2.1 Aspirin

Aspirin was superior to **placebo** in terms of deep vein thrombosis (RR=0.71, 95% CI 0.52 to 0.97, p=0.0294, 1 trial)and fatal pulmonary embolism (RR=0.42, 95% CI 0.24 to 0.72, p=0.0019, 1 trial). But aspirin increased the risk of major bleeding (RR=1.25, 95% CI 1.02 to 1.54, p=0.0318, 1 trial). However, no significant difference was found on non pulmonary embolism death (RR=1.01, 95% CI 0.84 to 1.22, p=0.8844, 1 trial)and non-fatal pulmonary embolism (RR=0.74, 95% CI 0.45 to 1.20, p=0.2186, 1 trial).

Table 10.1: *Main study characteristics - platelet aggregation inhibitors*

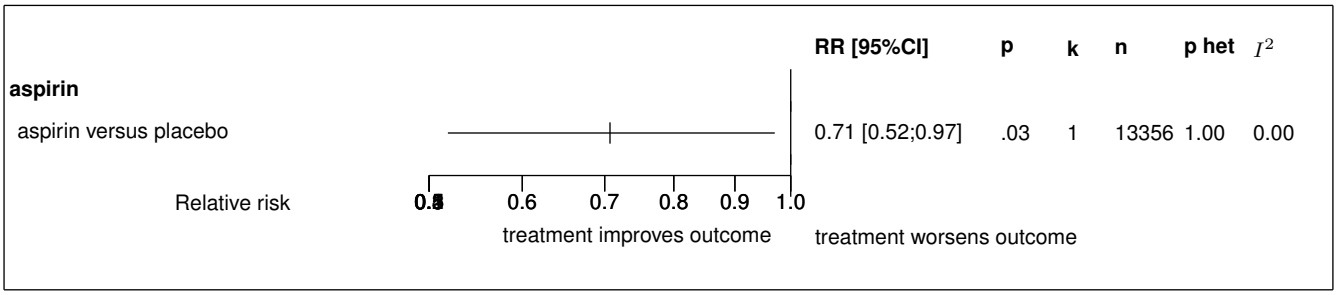
Trial	Patients	Treatments	Trial design and method
Aspirin			
Aspirin versus placebo			
PEP hip-fracture, 2000 [1] n = 6679 vs. 6677	patients undergoing surgery for hip fracture	aspirin 160mg/d started preoperatively and continued for 35 days **versus** placebo	double blind parallel groups 148 centres, Australia, New Zealand, South Africa,

Table 10.2: *Summary of all results for aspirin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
aspirin versus placebo						
deep vein thrombosis	RR=0.71	0.52;0.97	0.0294	1.0000 (0.00)	1	13356
non pulmonary embolism death	RR=1.01	0.84;1.22	0.8844	1.0000 (0.00)	1	13356
fatal pulmonary embolism	RR=0.42	0.24;0.72	0.0019	1.0000 (0.00)	1	13356
non-fatal pulmonary embolism	RR=0.74	0.45;1.20	0.2186	1.0000 (1.00)	1	13356
major bleeding	RR=1.25	1.02;1.54	0.0318	1.0000 (0.00)	1	13356

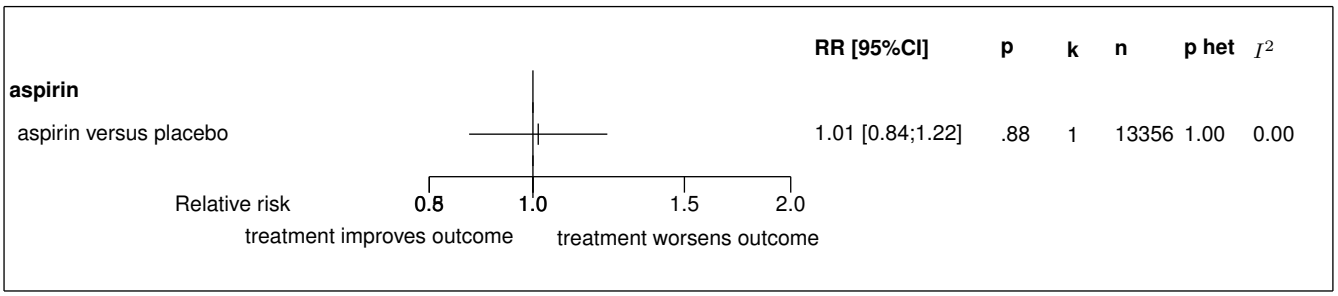
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



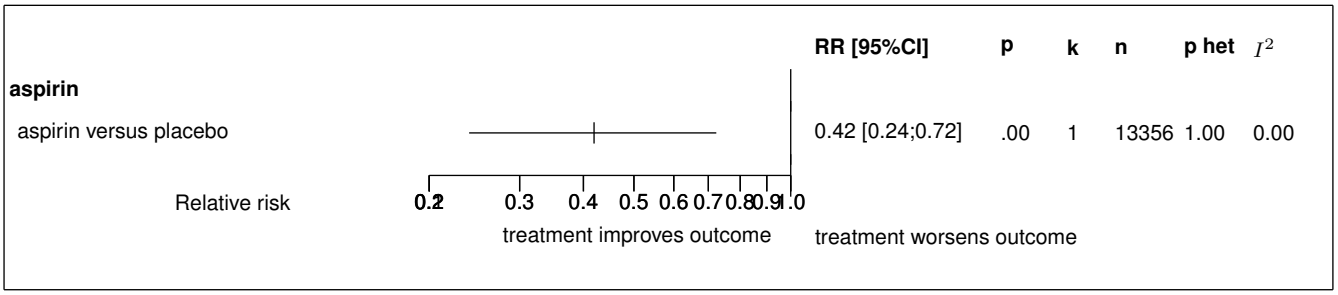
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 10.2: *Forest's plot for non pulmonary embolism death*



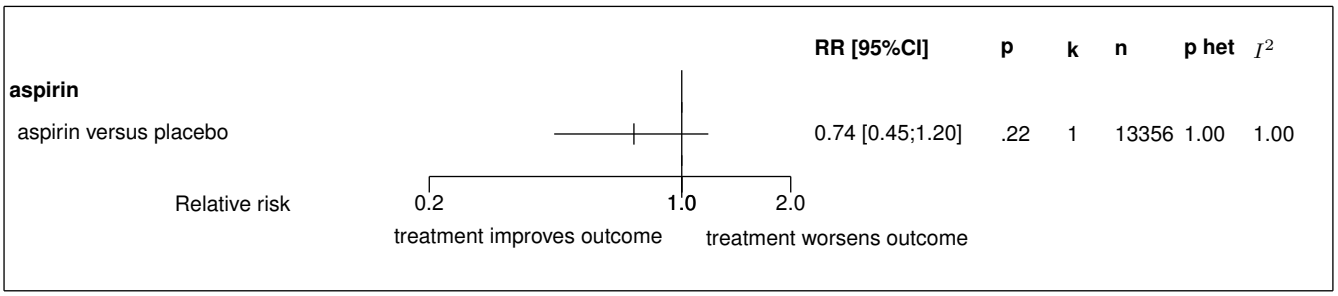
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 10.3: *Forest's plot for fatal pulmonary embolism*



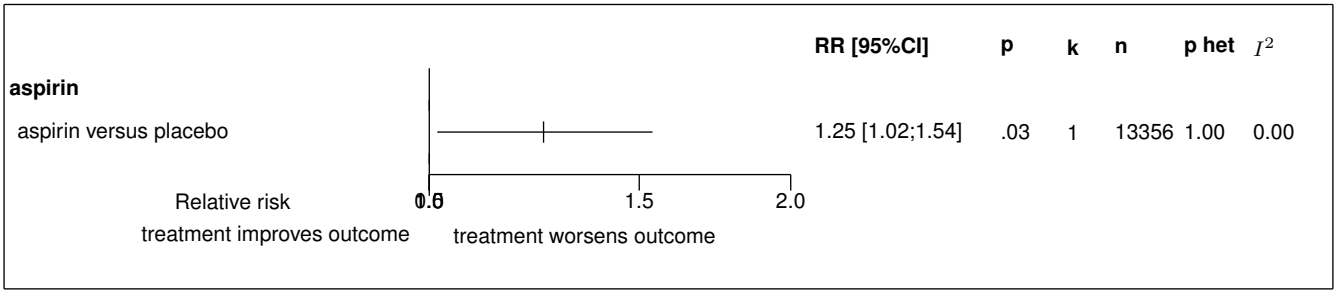
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 10.4: *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 10.5: *Forest's plot for major bleeding*



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

11 Details

11.1 Available trials

Only one trial which randomized 13356 patients was identified: it compared aspirin with placebo.
This trial included 13356 patients and was published in 2000.
This trial was double blind in design.
It was reported in English language.
Major bleeding data was reported in 1 trials; 1 trials reported data on non-fatal pulmonary embolism; 1 trials reported data on deep vein thrombosis; 1 trials reported data on non pulmonary embolism death; and 1 trials reported data on fatal pulmonary embolism.
Following tables 11.1 (page 55), 11.2 (page 55), 11.4 (page 57), and 11.3 (page 56) summarized the main characteristics of the trial including in this systematic review of randomized trials of aspirin.

Table 11.1: *Treatment description - platelet aggregation inhibitors - aspirin*

Trial	Studied treatment	Control treatment
Aspirin versus placebo		
PEP hip-fracture (2000) [1]	aspirin 160mg/d started preoperatively and continued for 35 days	placebo

Table 11.2: *Descriptions of participants - platelet aggregation inhibitors - aspirin*

Trial	Patients	
Aspirin versus placebo		
PEP hip-fracture (2000) [1]	Patients undergoing surgery for hip fracture	
	Inclusion criteria: patients with a femoral-neck fracture or other fracture of theproximal femur	**Exclusion criteria:** clear indication foraspirin (such as a recent myocardial infarction), or a clearcontraindication to aspirin (such as an active peptic ulcer)

Table 11.3: *Design and methodological quality of trials - platelet aggregation inhibitors - aspirin*

Trial	Design	Duration	Centre	Primary end-point
Aspirin versus placebo				
PEP hip-fracture, 2000 [1] n=13356	Parallel groups Double blind confirmatory trial at low risk of bias	35 days inclusion period: mar 1992 - jul 1998	Australia, New Zealand, South Africa, 148 centres	

Table 11.4: *Trial characteristics - platelet aggregation inhibitors - aspirin*

Trial	treatment duration	diagnostic method
Aspirin versus placebo		
PEP hip-fracture, 2000 [1]		

11.2 Meta-analysis results

The results are detailed in table 11.5 (page 58). This table is followed by the Forest's plot corresponding to each endpoint.

Aspirin versus placebo

The single study eligible for this comparison provided data on **deep vein thrombosis**. The analysis detected a statistically significant difference in favor of aspirin in deep vein thrombosis, with a RR of 0.71 (95% CI 0.52 to 0.97, p=0.0294).
The single study eligible for this comparison provided data on **non pulmonary embolism death**. No statistically significant difference between the groups was found in non pulmonary embolism death, with a RR of 1.01 (95% CI 0.84 to 1.22, p=0.8844).
The single study eligible for this comparison provided data on **fatal pulmonary embolism**. The analysis detected a statistically significant difference in favor of aspirin in fatal pulmonary embolism, with a RR of 0.42 (95% CI 0.24 to 0.72, p=0.0019).
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 0.74 (95% CI 0.45 to 1.20, p=0.2186).
The single study eligible for this comparison provided data on **major bleeding**. The analysis detected a statistically significant difference in favor of placebo in major bleeding, with a RR of 1.25 (95% CI 1.02 to 1.54, p=0.0318).

Table 11.5: *Results details - platelet aggregation inhibitors - aspirin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
aspirin versus placebo						
deep vein thrombosis	RR=0.71	[0.52;0.97]	0.0294	1.0000 (I^2=0.00)	1	13356
non pulmonary embolism death	RR=1.01	[0.84;1.22]	0.8844	1.0000 (I^2=0.00)	1	13356
fatal pulmonary embolism	RR=0.42	[0.24;0.72]	0.0019	1.0000 (I^2=0.00)	1	13356
non-fatal pulmonary embolism	RR=0.74	[0.45;1.20]	0.2186	1.0000 (I^2=1.00)	1	13356
major bleeding	RR=1.25	[1.02;1.54]	0.0318	1.0000 (I^2=0.00)	1	13356

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*

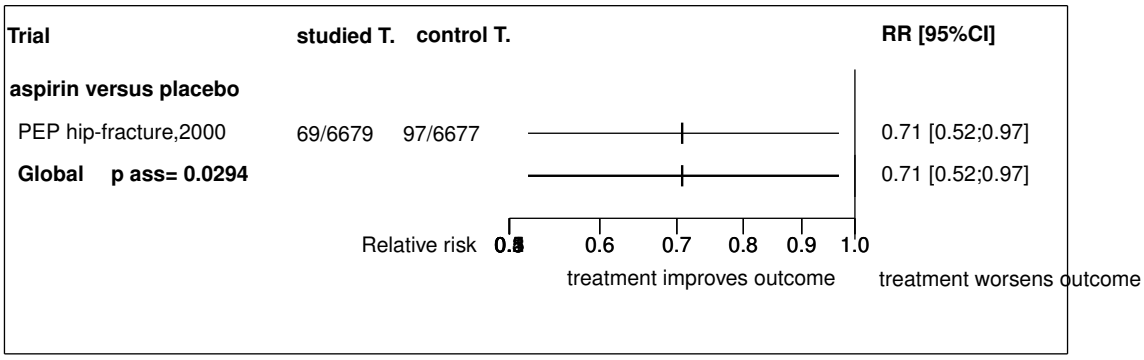


Figure 11.2: *Forest's plot for non pulmonary embolism death*

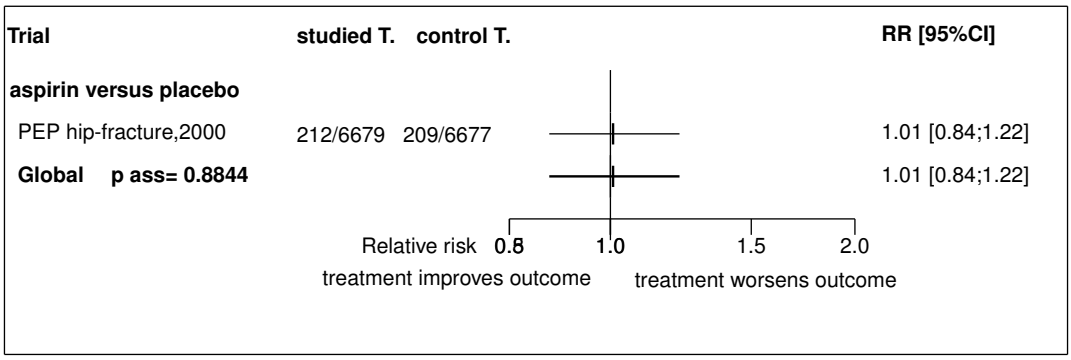


Figure 11.3: *Forest's plot for fatal pulmonary embolism*

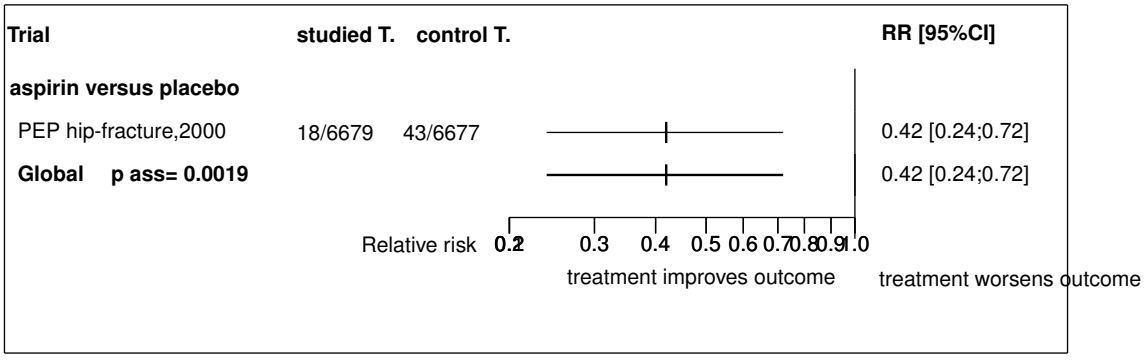


Figure 11.4: *Forest's plot for non-fatal pulmonary embolism*

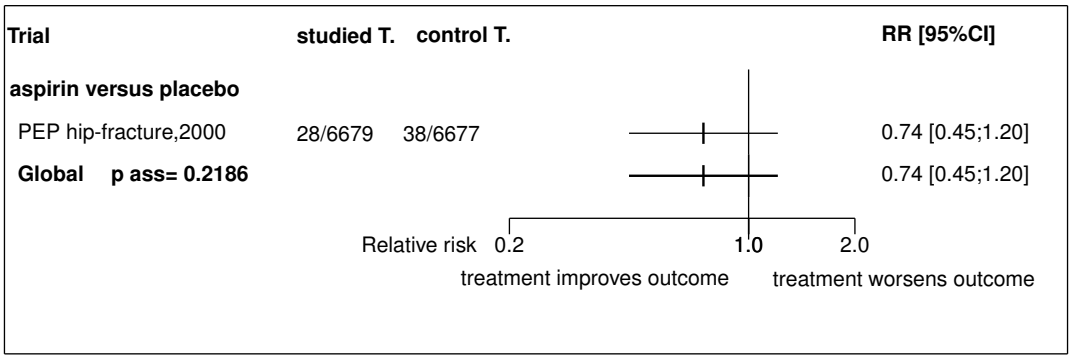
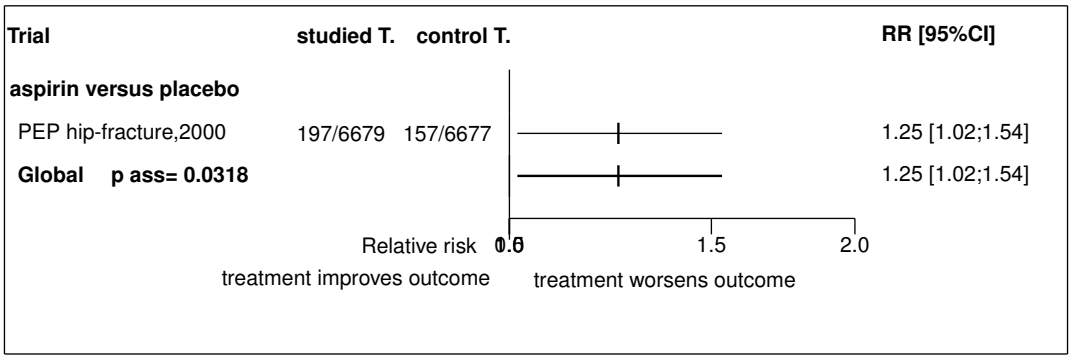


Figure 11.5: *Forest's plot for major bleeding*



References

[1] . Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000 Apr 15;355:1295-302. [PMID=10776741]

11.3 Individual trial summaries

Table 11.6: *PEP hip-fracture, 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=13356 (6679 vs. 6677) **Follow-up duration:** 35 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Australia, New Zealand, South Africa,, 148 centres **Inclusion period:** mar 1992 - jul 1998	Patients undergoing surgery for hip fracture **Inclusion criteria:** Patients with a femoral-neck fracture or other fracture of theproximal femur **Exclusion criteria:** clear indication foraspirin (such as a recent myocardial infarction), or a clearcontraindication to aspirin (such as an active peptic ulcer)	**Studied treatment:** aspirin 160mg/d started preoperatively and continued for 35 days **Control treatment:** placebo	Deep vein thrombosis RR=0.71 [0.52;0.97] Non pulmonary embolism death RR=1.01 [0.84;1.22] Fatal pulmonary embolism RR=0.42 [0.24;0.72] Non-fatal pulmonary embolism RR=0.74 [0.45;1.20]

Reference

. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000 Apr 15;355:1295-302 [PMID=10776741]

12 Global meta-analysis: all platelet aggregation inhibitors

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

Table 12.1: *All platelet aggregation inhibitorsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.71	0.52;0.97	0.0294	1.0000 (0.00)	1	13356
non pulmonary embolism death	RR=1.01	0.84;1.22	0.8844	1.0000 (0.00)	1	13356
fatal pulmonary embolism	RR=0.42	0.24;0.72	0.0019	1.0000 (0.00)	1	13356
non-fatal pulmonary embolism	RR=0.74	0.45;1.20	0.2186	1.0000 (1.00)	1	13356
major bleeding	RR=1.25	1.02;1.54	0.0318	1.0000 (0.00)	1	13356

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

13 Ongoing studies of platelet aggregation inhibitors

No ongoing trial was identified.

14 Excluded studies for platelet aggregation inhibitors

No trial was excluded.

References

Part III

Synthetic oligosaccharide

15 Overview of synthetic oligosaccharide

15.1 Included trials

A total of 2 randomized comparisons which enrolled 2327 patients were identified. In all, 1 randomized comparison concerned extended prophylaxis and one fondaparinux.
The detailed descriptions of trials and meta-analysis results is given in section 16 (page 75) for extended prophylaxis and in section 17 (page 81) for fondaparinux.

The average study size was 1163 patients (range 656 to 1671). The first study was published in 2001, 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.
The table 15.1 (page 68) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

15.2 Summary of meta-analysis results

The meta-analysis of the available trials about synthetic oligosaccharide provide the results listed in tables 15.2 to 15.3 (page 69) and in the following graphs.

15.2.1 Extended prophylaxis

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

15.2.2 Fondaparinux

Fondaparinux was superior to **enoxaparin** in terms of deep vein thrombosis (RR=0.42, 95% CI 0.31 to 0.57, p=0.0000, 1 trial), venous thromboembolism (RR=0.44, 95% CI 0.32 to 0.59, p=0.0000, 1 trial)and proximal DVT (RR=0.21, 95% CI 0.09 to 0.51, p=0.0000, 1 trial). However, no significant difference was found on symptomatic pulmonary embolism (RR=2.20, 95% CI 0.45 to 10.87, p=0.3315, 1 trial), symptomatic deep-vein thrombosis (RR=1.01, 95% CI 0.06 to 16.13, p=0.9939, 1 trial), fatal pulmonary embolism (RR=1.01, 95% CI 0.14 to 7.16, p=0.9914, 1 trial), non-fatal pulmonary embolism (RR=1.01, 95% CI 0.06 to 16.13, p=0.9939, 1 trial), symptomatic venous thromboembolism (DVT, PE) (RR=1.01, 95% CI 0.25 to 4.03, p=0.9878, 1 trial)and major bleeding (RR=0.96, 95% CI 0.51 to 1.82, p=0.8999, 1 trial).

Table 15.1: *Main study characteristics - synthetic oligosaccharide*

Trial	Patients	Treatments	Trial design and method
Extended prophylaxis			
Extended prophylaxis versus standard prophylaxis			
PENTHIFRAPLUS (Eriksson), 2003 [1] n= 656	patients undergoing hip fracture surgery	25-31 days of fondaparinux 2.5-mg once-daily **versus** 6-8 days of fondaparinux 2.5-mg once-daily	double blind parallel groups
Fondaparinux			
Fondaparinux versus enoxaparin			
PENTHIFRA (Eriksson), 2001 [1] n = 831 vs. 840	hip fracture 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 99 centres, 21 countries

Table 15.2: *Summary of all results for extended prophylaxis*

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

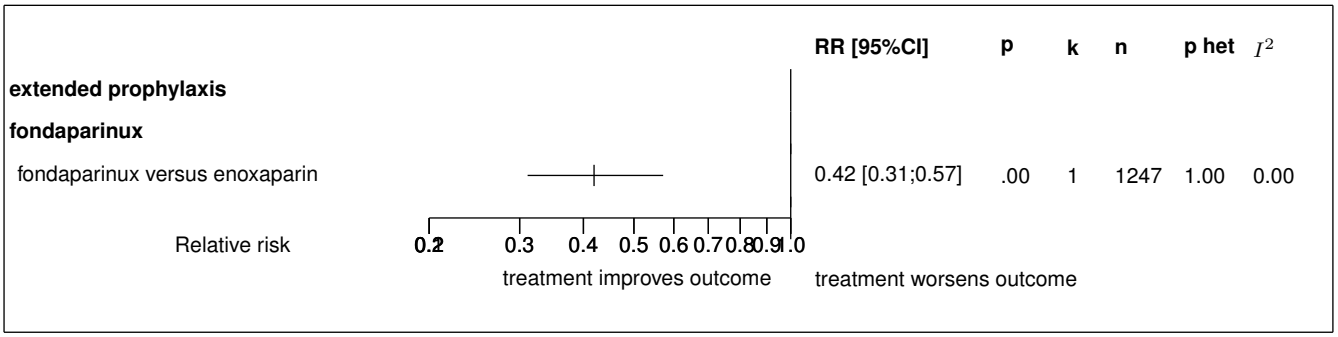
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 15.3: *Summary of all results for fondaparinux*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
fondaparinux versus enoxaparin						
deep vein thrombosis	RR=0.42	0.31;0.57	0.0000	1.0000 (0.00)	1	1247
symptomatic pulmonary embolism	RR=2.20	0.45;10.87	0.3315	1.0000 (1.00)	1	1221
symptomatic deep-vein thrombosis	RR=1.01	0.06;16.13	0.9939	1.0000 (0.00)	1	1671
fatal pulmonary embolism	RR=1.01	0.14;7.16	0.9914	1.0000 (0.00)	1	1671
non-fatal pulmonary embolism	RR=1.01	0.06;16.13	0.9939	1.0000 (0.00)	1	1671
venous thromboembolism	RR=0.44	0.32;0.59	0.0000	1.0000 (0.00)	1	1250
proximal DVT	RR=0.21	0.09;0.51	0.0000	1.0000 (0.00)	1	1296
symptomatic venous thromboembolism (DVT, PE)	RR=1.01	0.25;4.03	0.9878	1.0000 (0.00)	1	1671
all cause death	RR=0.70	0.33;1.49	0.3522	1.0000 (0.00)	1	1673
major bleeding	RR=0.96	0.51;1.82	0.8999	1.0000 (0.00)	1	1673

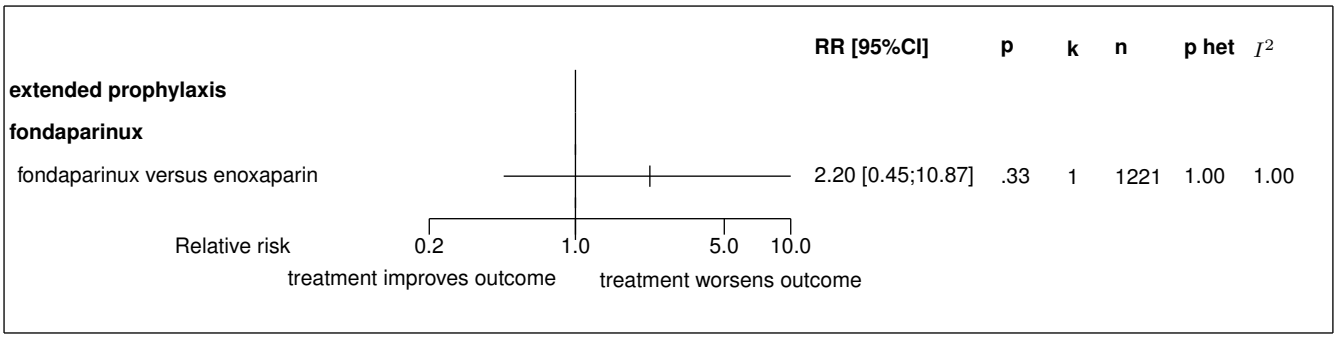
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 15.1: *Forest's plot for deep vein thrombosis*



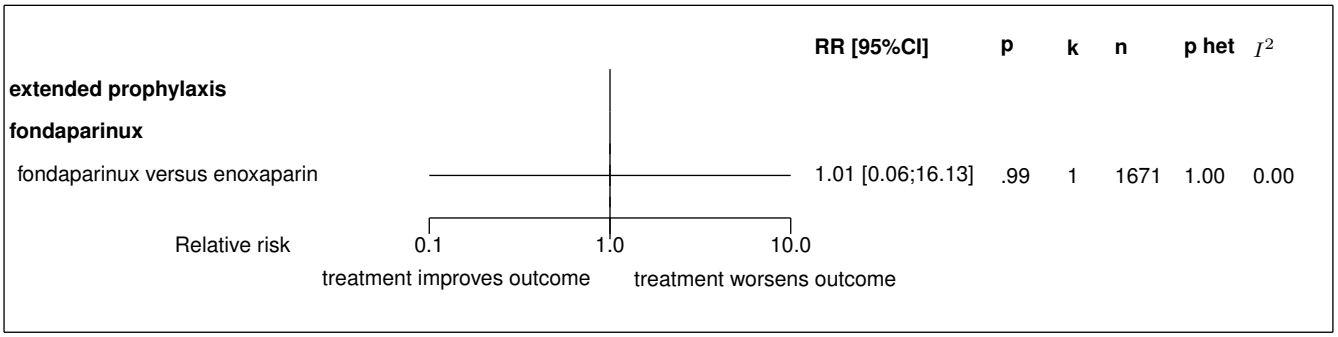
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



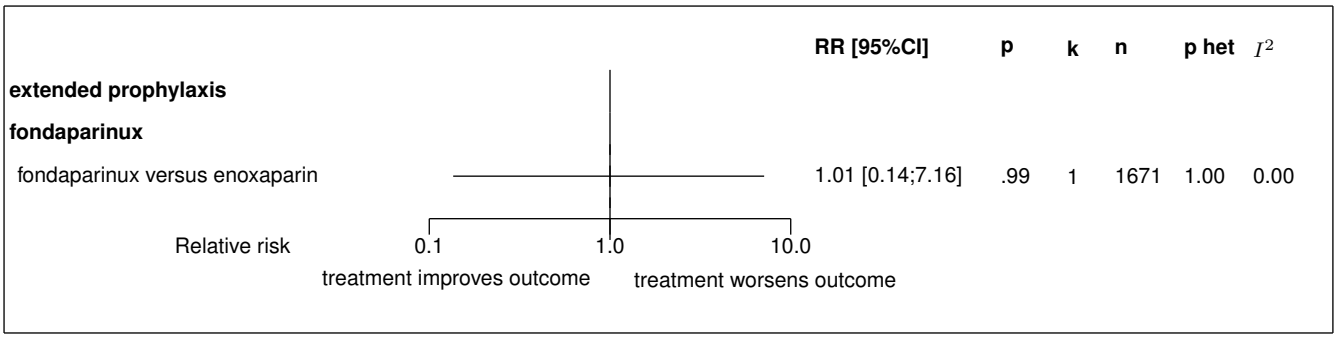
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 15.3: *Forest's plot for symptomatic deep-vein thrombosis*



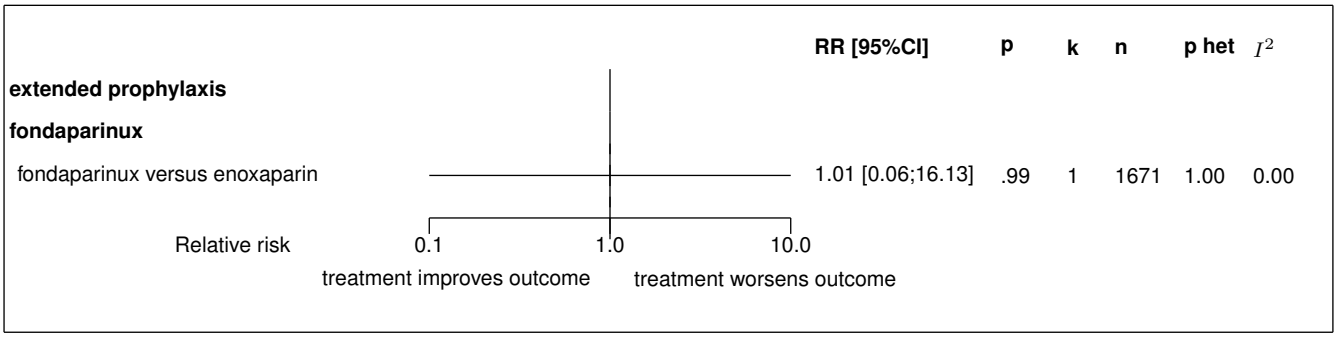
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 15.4: *Forest's plot for fatal pulmonary embolism*



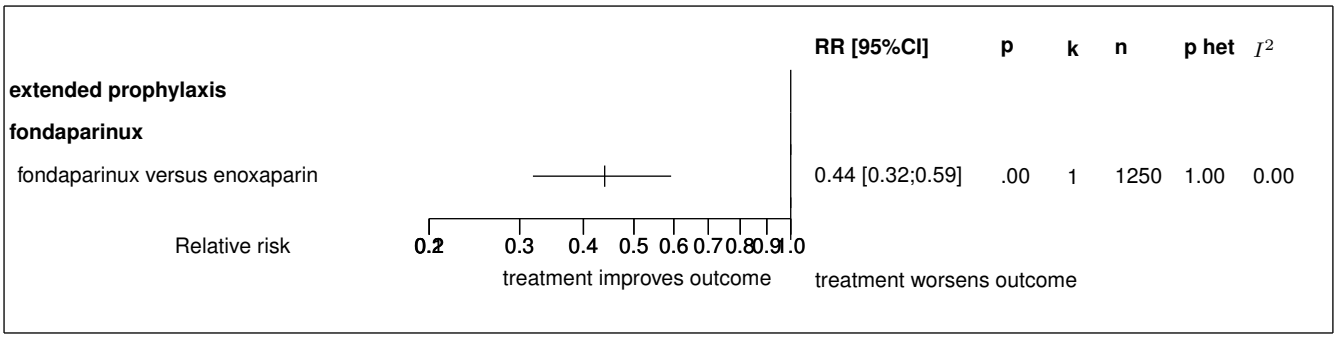
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



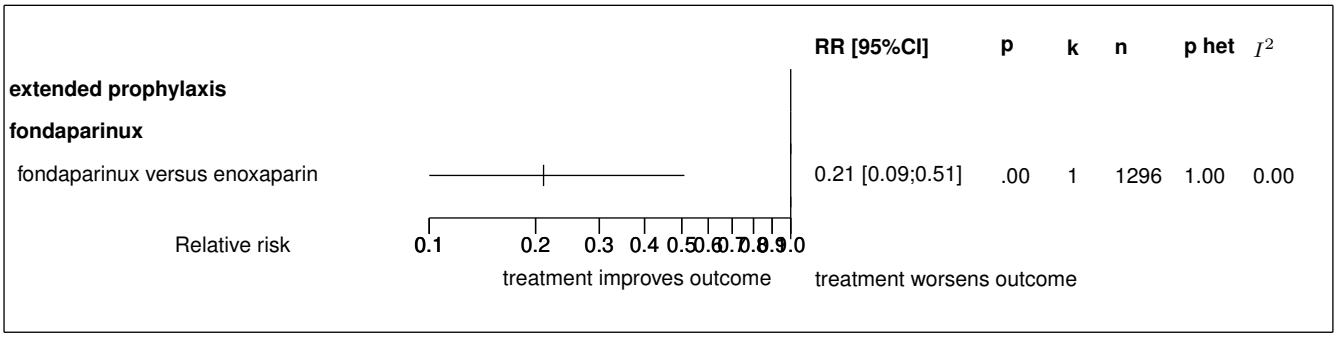
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 15.6: *Forest's plot for venous thromboembolism*



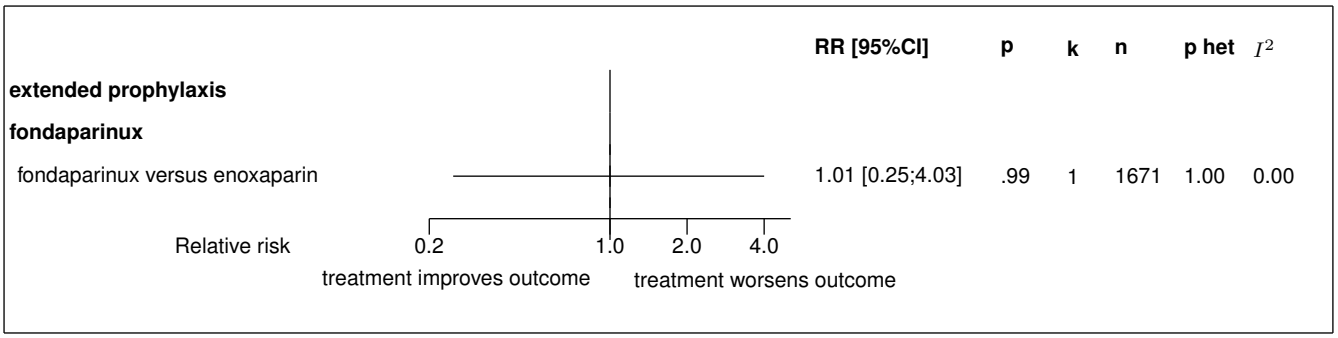
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



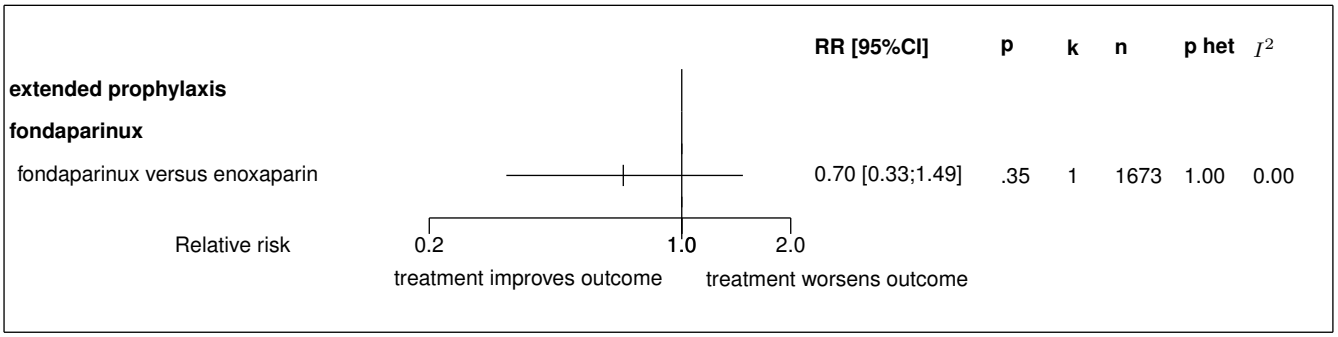
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 15.8: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*



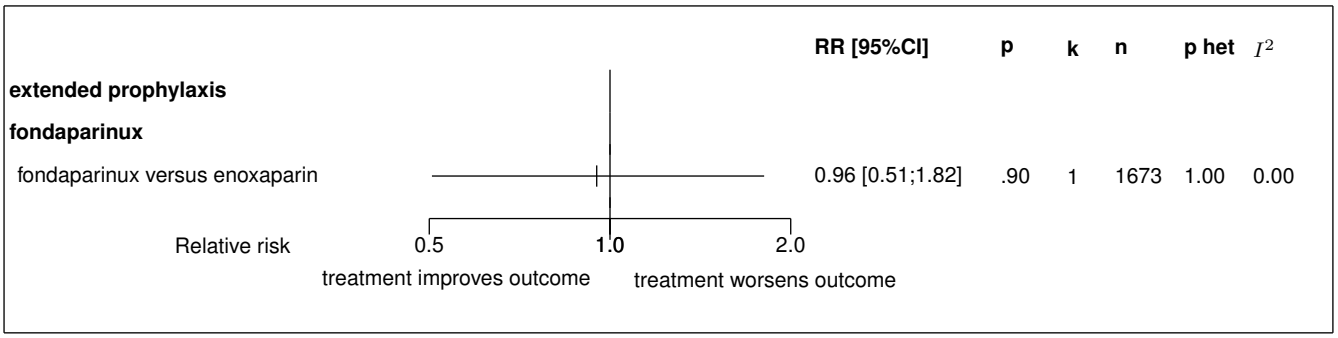
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 15.9: *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 15.10: *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

16 Detailed results for extended prophylaxis

16.1 Available trials

Only one trial which randomized 656 patients was identified: it compared extended prophylaxis with standard prophylaxis.
This trial included 656 patients and was published in 2003.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 16.1 (page 75), 16.2 (page 75), 16.4 (page 77), and 16.3 (page 75) summarized the main characteristics of the trial including in this systematic review of randomized trials of extended prophylaxis.

Table 16.1: *Treatment description - synthetic oligosaccharide - extended prophylaxis*

Trial	Studied treatment	Control treatment
Extended prophylaxis versus standard prophylaxis		
PENTHIFRAPLUS (Eriksson) (2003) [1]	25-31 days of fondaparinux 2.5-mg once-daily	6-8 days of fondaparinux 2.5-mg once-daily

Table 16.2: *Descriptions of participants - synthetic oligosaccharide - extended prophylaxis*

Trial	Patients
Extended prophylaxis versus standard prophylaxis	
PENTHIFRAPLUS (Eriksson) (2003) [1]	Patients undergoing hip fracture surgery

Table 16.3: *Design and methodological quality of trials - synthetic oligosaccharide - extended prophylaxis*

Trial	Design	Duration	Centre	Primary endpoint
Extended prophylaxis versus standard prophylaxis				

continued...

Trial	Design	Duration	Centre	Primary end-point
PENTHIFRAPLUS (Eriksson), 2003 [1] n=656	Parallel groups double blind confirmatory trial at low risk of bias	19-23 days		

Table 16.4: *Trial characteristics - synthetic oligosaccharide - extended prophylaxis*

Trial	Use of cement	History of venous thromboembolism
Extended prophylaxis versus standard prophylaxis		
PENTHIFRAPLUS (Eriksson), 2003 [1]		

16.2 Meta-analysis results

The results are detailed in table 16.5 (page 78). This table is followed by the Forest's plot corresponding to each endpoint.

Extended prophylaxis versus standard prophylaxis

No data were presented in the 1 trial identified

Table 16.5: *Results details - synthetic oligosaccharide - extended prophylaxis*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
extended prophylaxis versus standard prophylaxis						
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, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med 2003 Jun 9;163:1337-42. [PMID=12796070]

16.3 Individual trial summaries

Table 16.6: *PENTHIFRAPLUS (Eriksson), 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (656 vs. 0) **Follow-up duration:** 19-23 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias	Patients undergoing hip fracture surgery	**Studied treatment:** 25-31 days of fondaparinux 2.5-mg once-daily **Control treatment:** 6-8 days of fondaparinux 2.5-mg once-daily	

Reference

Eriksson BI, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med 2003 Jun 9;163:1337-42 [PMID=12796070]

17 Detailed results for fondaparinux

17.1 Available trials

Only one trial which randomized 1671 patients was identified: it compared fondaparinux with enoxaparin.
This trial included 1671 patients and was published in 2001.
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 non-fatal pulmonary embolism; 1 trials reported data on symptomatic venous thromboembolism (DVT, PE); 1 trials reported data on proximal DVT; 1 trials reported data on venous thromboembolism; 1 trials reported data on major bleeding; 1 trials reported data on fatal pulmonary embolism; 1 trials reported data on symptomatic deep-vein thrombosis; 1 trials reported data on symptomatic pulmonary embolism; and 1 trials reported data on deep vein thrombosis.
Following tables 17.1 (page 81), 17.2 (page 81), 17.4 (page 83), and 17.3 (page 82) summarized the main characteristics of the trial including in this systematic review of randomized trials of fondaparinux.

Table 17.1: *Treatment description - synthetic oligosaccharide - fondaparinux*

Trial	Studied treatment	Control treatment
Fondaparinux versus enoxaparin		
PENTHIFRA (Eriksson) (2001) [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

Table 17.2: *Descriptions of participants - synthetic oligosaccharide - fondaparinux*

Trial	Patients
Fondaparinux versus enoxaparin	

continued...

Trial	Patients	
PENTHIFRA (Eriksson) (2001) [1]	Hip fracture surgery	
	Inclusion criteria: at least 18years of age; scheduled to undergo standard surgery forfracture of the upper third of the femur, including the femoralhead and neck	**Exclusion criteria:** multiple trauma affectingmore than one organ system; interval of more than 24 hoursbetween the injury and hospital admission; pregnancy; active bleeding; documented congenital or acquired bleeding disorder; currentulcerative or angiodysplastic gastrointestinal disease; historyof hemorrhagic stroke or brain, spinal, or ophthalmologic surgerywithin the previous three months; planned use of an indwellingintrathecal or epidural catheter for more than six hours after surgery;hypersensitivity to heparin, low-molecular-weight heparins,porcine products, or iodinated contrast medium; contraindicationto anticoagulant therapy; current addictive disorder; serumcreatinine concentration above 2 mg per deciliter in a well-hydrated patient; and a platelet count below 100,000per cubic millimeter

Table 17.3: *Design and methodological quality of trials - synthetic oligosaccharide - fondaparinux*

Trial	Design	Duration	Centre	Primary endpoint
Fondaparinux versus enoxaparin				
PENTHIFRA (Eriksson), 2001 [1] n=1671	Parallel groups double blind confirmatory trial at low risk of bias	11 days inclusion period: nov 1998 - oct 199	21 countries 99 centres	venous thromboembolism

Table 17.4: *Trial characteristics - synthetic oligosaccharide - fondaparinux*

Trial	Use of cement	History of venous thromboembolism
Fondaparinux versus enoxaparin		
PENTHIFRA (Eriksson), 2001 [1]	21.5%	3.7%

17.2 Meta-analysis results

The results are detailed in table 17.5 (page 84). This table is followed by the Forest's plot corresponding to each endpoint.

Fondaparinux 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 fondaparinux in deep vein thrombosis, with a RR of 0.42 (95% CI 0.31 to 0.57, 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 2.20 (95% CI 0.45 to 10.87, p=0.3315).
The single study eligible for this comparison provided data on **symptomatic deep-vein thrombosis**. No statistically significant difference between the groups was found in symptomatic deep-vein thrombosis, with a RR of 1.01 (95% CI 0.06 to 16.13, p=0.9939).
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 1.01 (95% CI 0.14 to 7.16, p=0.9914).
The single study eligible for this comparison provided data on **non-fatal pulmonary embolism**. No statistically significant difference between the groups was found in non-fatal pulmonary embolism, with a RR of 1.01 (95% CI 0.06 to 16.13, p=0.9939).
The single study eligible for this comparison provided data on **venous thromboembolism**. The analysis detected a statistically significant difference in favor of fondaparinux in venous thromboembolism, with a RR of 0.44 (95% CI 0.32 to 0.59, p=0.0000).
The single study eligible for this comparison provided data on **proximal DVT**. The analysis detected a statistically significant difference in favor of fondaparinux in proximal DVT, with a RR of 0.21 (95% CI 0.09 to 0.51, 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 1.01 (95% CI 0.25 to 4.03, p=0.9878).
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 0.96 (95% CI 0.51 to 1.82, p=0.8999).

Table 17.5: *Results details - synthetic oligosaccharide - fondaparinux*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fondaparinux versus enoxaparin						
deep vein thrombosis	RR=0.42	[0.31;0.57]	0.0000	1.0000 (I^2=0.00)	1	1247
symptomatic pulmonary embolism	RR=2.20	[0.45;10.87]	0.3315	1.0000 (I^2=1.00)	1	1221
symptomatic deep-vein thrombosis	RR=1.01	[0.06;16.13]	0.9939	1.0000 (I^2=0.00)	1	1671
fatal pulmonary embolism	RR=1.01	[0.14;7.16]	0.9914	1.0000 (I^2=0.00)	1	1671
non-fatal pulmonary embolism	RR=1.01	[0.06;16.13]	0.9939	1.0000 (I^2=0.00)	1	1671

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
venous thromboembolism	RR=0.44	[0.32;0.59]	0.0000	1.0000 (I^2=0.00)	1	1250
proximal DVT	RR=0.21	[0.09;0.51]	0.0000	1.0000 (I^2=0.00)	1	1296
symptomatic venous thromboembolism (DVT, PE)	RR=1.01	[0.25;4.03]	0.9878	1.0000 (I^2=0.00)	1	1671
all cause death	RR=0.70	[0.33;1.49]	0.3522	1.0000 (I^2=0.00)	1	1673
major bleeding	RR=0.96	[0.51;1.82]	0.8999	1.0000 (I^2=0.00)	1	1673

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*

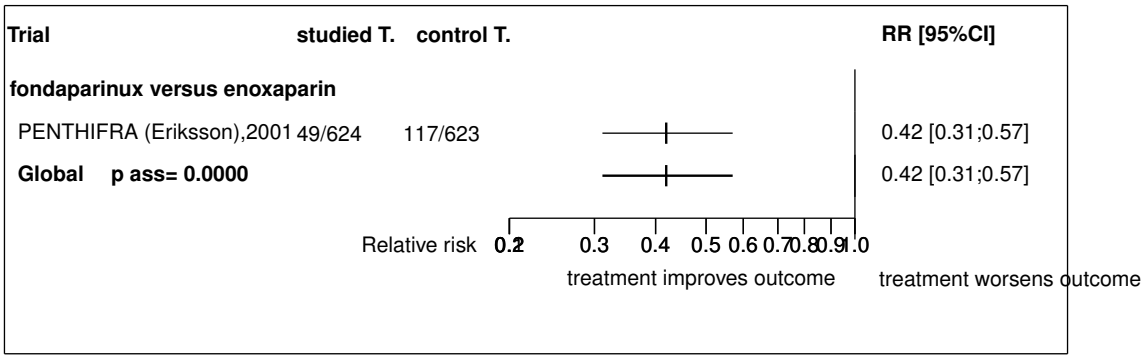


Figure 17.2: *Forest's plot for symptomatic pulmonary embolism*

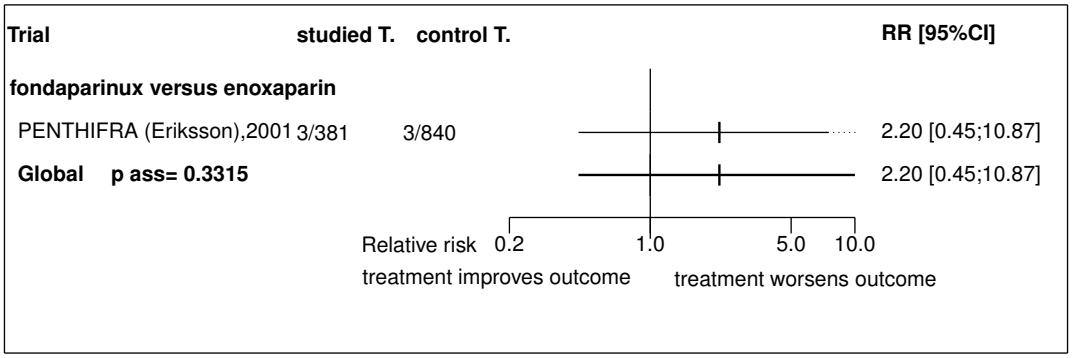


Figure 17.3: *Forest's plot for symptomatic deep-vein thrombosis*

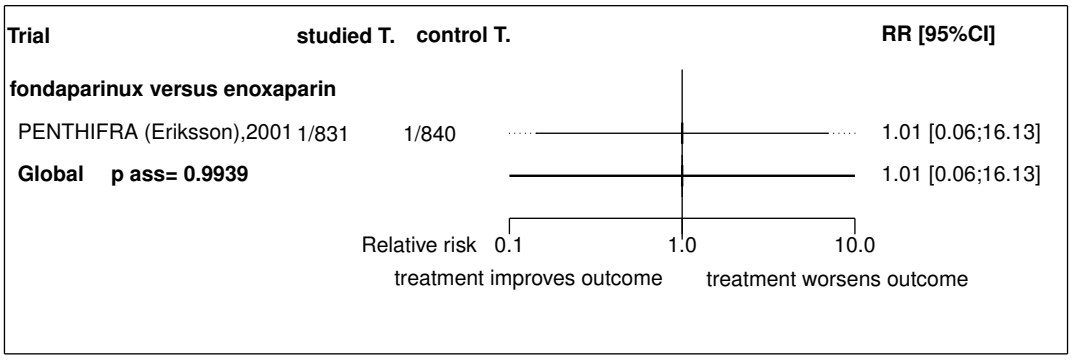


Figure 17.4: *Forest's plot for fatal pulmonary embolism*

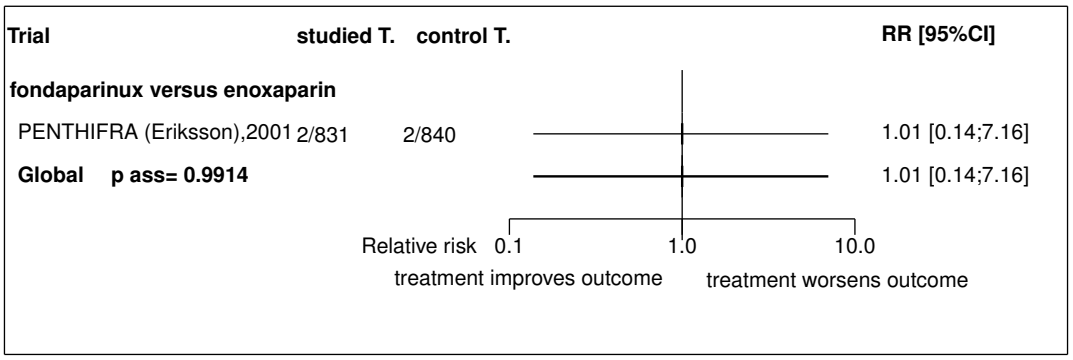


Figure 17.5: *Forest's plot for non-fatal pulmonary embolism*

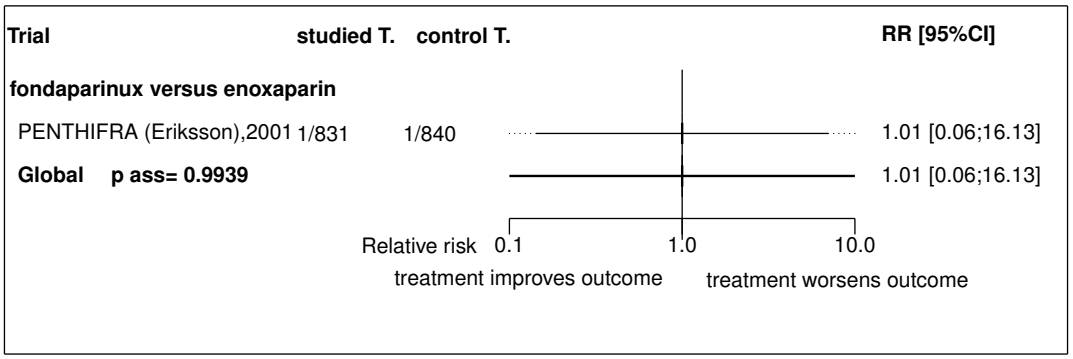


Figure 17.6: *Forest's plot for venous thromboembolism*

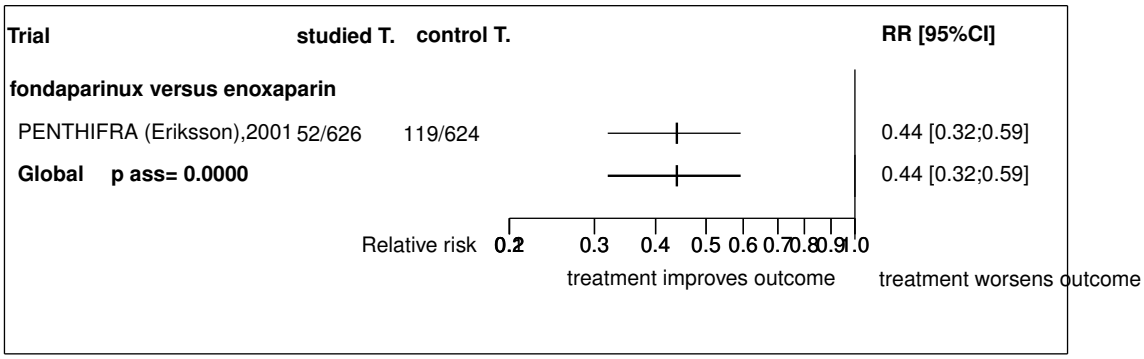


Figure 17.7: *Forest's plot for proximal DVT*

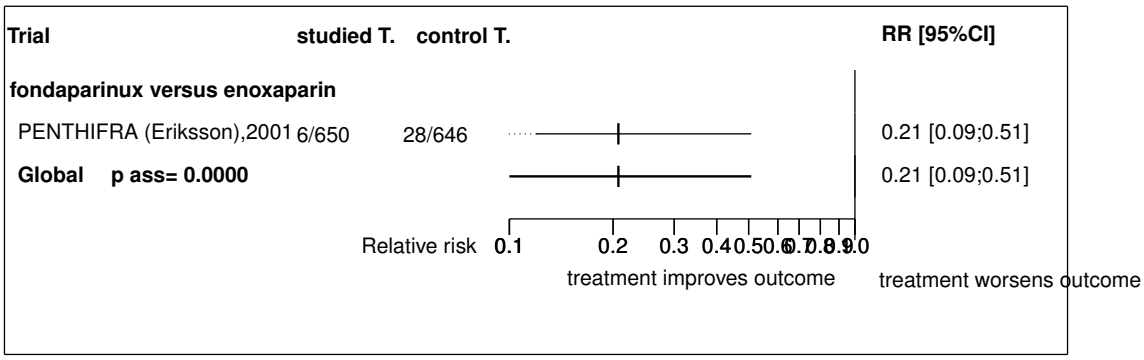


Figure 17.8: *Forest's plot for symptomatic venous thromboembolism (DVT, PE)*

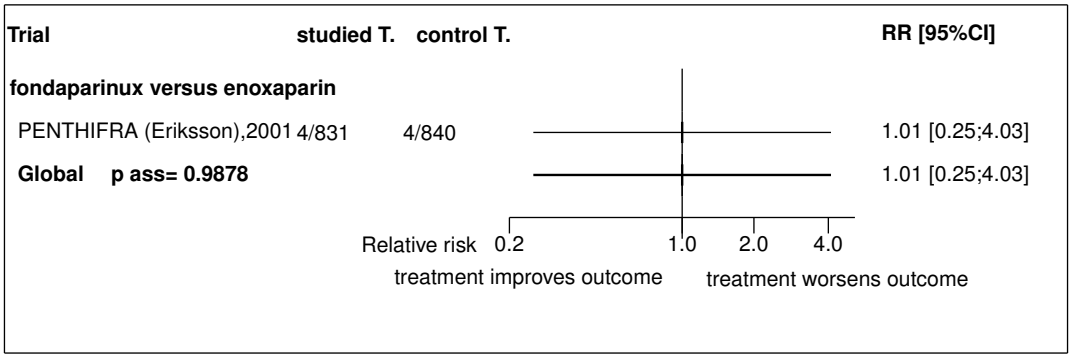


Figure 17.9: *Forest's plot for all cause death*

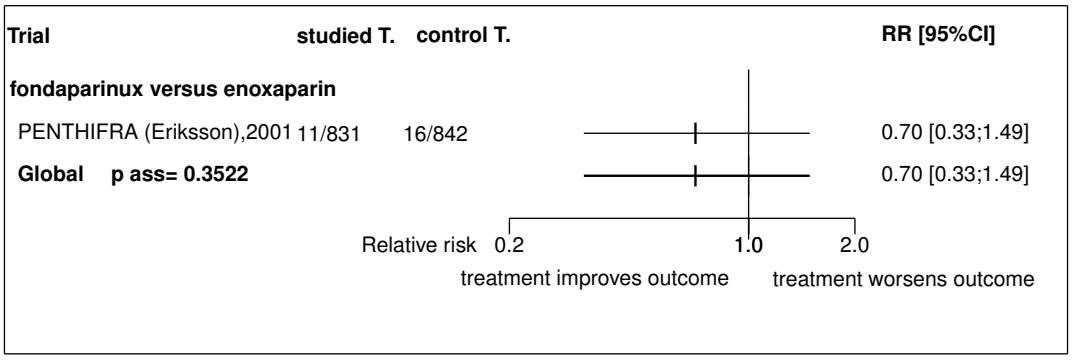
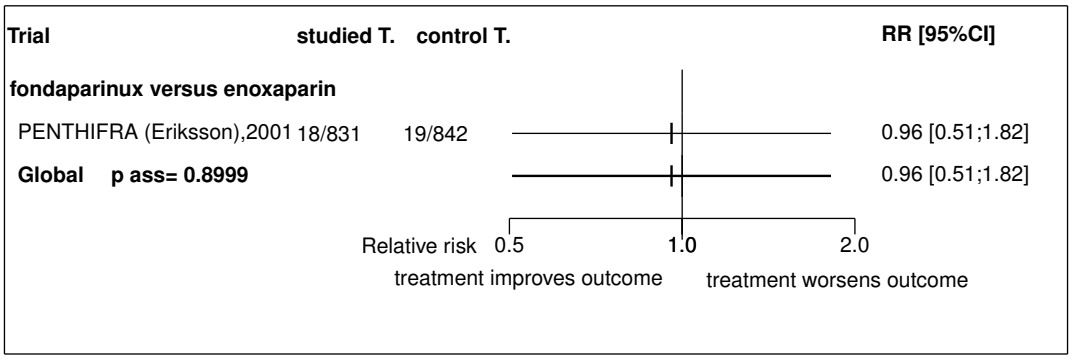


Figure 17.10: *Forest's plot for major bleeding*



References

[1] Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001 Nov 1;345:1298-304. [PMID=11794148]

17.3 Individual trial summaries

Table 17.6: *PENTHIFRA (Eriksson), 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1671 (831 vs. 840) **Follow-up duration:** 11 days **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 21 countries, 99 centres **Inclusion period:** nov 1998 - oct 199	Hip fracture surgery **Inclusion criteria:** at least 18years of age; scheduled to undergo standard surgery forfracture of the upper third of the femur, including the femoralhead and neck **Exclusion criteria:** multiple trauma affectingmore than one organ system; interval of more than 24 hoursbetween the injury and hospital admission; pregnancy; active bleeding; documented congenital or acquired bleeding disorder; currentulcerative or angiodysplastic gastrointestinal disease; historyof hemorrhagic stroke or brain, spinal, or ophthalmologic surgerywithin the previous three months; planned use of an indwellingintrathecal or epidural catheter for more than six hours after surgery;hypersensitivity to heparin, low-molecular-weight heparins,porcine products, or iodinated contrast medium; contraindicationto	**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	Deep vein thrombosis RR=0.42 [0.31;0.57] Symptomatic pulmonary embolism RR=2.20 [0.45;10.87] Symptomatic deep-vein thrombosis RR=1.01 [0.06;16.13] Fatal pulmonary embolism RR=1.01 [0.14;7.16] Non-fatal pulmonary embolism RR=1.01 [0.06;16.13] Venous thromboembolism RR=0.44 [0.32;0.59] Proximal DVT RR=0.21 [0.09;0.51] Symptomatic venous thromboembolism (DVT, PE) RR=1.01 [0.25;4.03]

Reference

Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001 Nov 1;345:1298-304 [PMID=11794148]

18 Global meta-analysis: all synthetic oligosaccharide

18.1 Global meta-analysis: all synthetic oligosaccharide versus enoxaparin

Table 18.1: *All synthetic oligosaccharideversus enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deep vein thrombosis	RR=0.42	0.31;0.57	0.0000	1.0000 (0.00)	1	1247
symptomatic pulmonary embolism	RR=2.20	0.45;10.87	0.3315	1.0000 (1.00)	1	1221
symptomatic deep-vein thrombosis	RR=1.01	0.06;16.13	0.9939	1.0000 (0.00)	1	1671
fatal pulmonary embolism	RR=1.01	0.14;7.16	0.9914	1.0000 (0.00)	1	1671
non-fatal pulmonary embolism	RR=1.01	0.06;16.13	0.9939	1.0000 (0.00)	1	1671
venous thromboembolism	RR=0.44	0.32;0.59	0.0000	1.0000 (0.00)	1	1250
proximal DVT	RR=0.21	0.09;0.51	0.0000	1.0000 (0.00)	1	1296
symptomatic venous thromboembolism (DVT, PE)	RR=1.01	0.25;4.03	0.9878	1.0000 (0.00)	1	1671
major bleeding	RR=0.96	0.51;1.82	0.8999	1.0000 (0.00)	1	1673

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 synthetic oligosaccharide versus standard prophylaxis

Table 18.2: *All synthetic oligosaccharideversus standard prophylaxis*

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

19 Ongoing studies of synthetic oligosaccharide

No ongoing trial was identified.

20 Excluded studies for synthetic oligosaccharide

No trial was excluded.

References