Antithrombotics for acute myocardial infarction

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 acute myocardial infarction.

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0.1 Synthesis of the meta-analysis results

In all 36 randomised controlled trials (RCTs) were included. These included 4 studies of **direct thrombin inhibitor** involving 3,843 patients, 10 studies of **low molecular weight heparin** involving 24,036 patients, 17 studies of **oral anticoagulant** involving 44,643 patients, 1 studie of **pentasccharide** involving 12,092 patients and 4 studies of **unfractionated heparin** involving 1,231 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 thrombin inhibitor

Reports of 4 trials (including 3,861 patients) were identified .
Among these comparisons, one trial are about Argatroban,one about bivalirudin and two about Hirudin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Argatroban

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

Table 1: *Results summary - Argatroban*

Benefit	Harmful	No evidence
	Argatroban versus heparin	

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

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

Bivalirudin

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

Table 2: *Results summary - Bivalirudin*

Benefit	Harmful	No evidence
	Bivalirudin versus heparin	

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

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

Hirudin

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

Table 3: *Results summary - Hirudin*

Benefit	Harmful	No evidence
	Hirudin versus heparin	

* 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 9 trials (including 24,036 patients) were identified .
Among these comparisons, 3 trials are about Dalteparin,6 about Enoxaparin and one about Reviparin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Dalteparin

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

Table 4: *Results summary - Dalteparin*

Benefit	Harmful	No evidence
	Dalteparin versus placebo	
		→ reinfarction RR=0.75^{NS} [0.26;2.14] k=1 → in-hospital death RR=1.00^{NS} [0.57;1.75] k=1 → reinfarction at 30 days RR=3.48^{NS} [0.78;15.59] k=1 → death at 30 days RR=0.58^{NS} [0.17;1.93] k=1
	Dalteparin versus UFH	
↓ reinfarction RR=0.26* [0.07;0.93] k=1		→ in-hospital death RR=0.60^{NS} [0.20;1.81] k=1 → reinfarction at 30 days RR=0.96^{NS} [0.47;1.97] k=1 → death at 30 days RR=0.79^{NS} [0.33;1.86] 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)

Enoxaparin

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

Table 5: *Results summary - Enoxaparin*

Benefit	Harmful	No evidence
	Enoxaparin versus placebo	
↓ reinfarction RR=0.34* [0.13;0.94] k=1 ↓ reinfarction at 30 days RR=0.32* [0.13;0.79] k=1		→ in-hospital death RR=1.25^{NS} [0.56;2.79] k=1 → death at 30 days RR=0.96^{NS} [0.50;1.84] k=1
	Enoxaparin versus UFH	
↓ reinfarction RR=0.61¶ [0.48;0.78] k=5 ↓ reinfarction at 30 days RR=0.62* [0.39;0.97] k=4		→ in-hospital death RR=0.95^{NS} [0.72;1.24] k=5 → death at 30 days RR=0.95^{NS} [0.77;1.17] k=5

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

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

Reviparin

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

Table 6: *Results summary - Reviparin*

Benefit	Harmful	No evidence
	Reviparin versus placebo	
↓ reinfarction RR=0.76* [0.60;0.96] k=1 ↓ in-hospital death RR=0.89* [0.81;0.99] k=1 ↓ reinfarction at 30 days RR=0.77* [0.63;0.95] k=1 ↓ death at 30 days RR=0.87† [0.80;0.96] 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 anticoagulant

Reports of 13 trials (including 44,661 patients) were identified .

Among these comparisons, two trials are about any anticoagulant,3 about coumadin,two about phenprocoumon and 10 about warfarin.

During the selection 8 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Any anticoagulant

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

Table 7: *Results summary - Any anticoagulant*

Benefit	Harmful	No evidence
Any anticoagulant versus placebo		
Any anticoagulant versus aspirin		
		→ myocardial infarction (fatal and non fatal) RR=1.65^{NS} [0.96;2.84] k=1 → all cause death RR=0.90^{NS} [0.66;1.24] 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)

Coumadin

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

Table 8: *Results summary - Coumadin*

Benefit	Harmful	No evidence
Coumadin versus control (on top of aspirin)		
	↑ minor bleeding RR=3.03¶ [1.77;5.20] k=1	→ myocardial infarction (fatal and non fatal) RR=0.69^{NS} [0.31;1.53] k=1 → ischemic stroke RR=0.10^{NS} [0.01;1.77] k=1 → revascularization RR=0.80^{NS} [0.51;1.23] k=1 → all cause death RR=0.58^{NS} [0.26;1.31] k=1 → major bleeding RR=2.26^{NS} [0.59;8.67] k=1
Coumadin versus placebo		
↓ myocardial infarction (fatal and non fatal) RR=0.47¶ [0.38;0.58] k=1 ↓ ischemic stroke RR=0.60* [0.40;0.89] k=1	↑ major bleeding RR=3.85¶ [2.34;6.35] k=1	→ all cause death RR=0.90^{NS} [0.74;1.10] k=1
Coumadin versus aspirin		

continued...

Benefit	Harmful	No evidence
↓ all cause death RR=0.28* [0.09;0.82] k=1		→ all cause death, MI, thrombo-embolic stroke RR=0.57^{NS} [0.32;1.00] k=1 → myocardial infarction (fatal and non fatal) RR=0.96^{NS} [0.46;2.01] k=1 → revascularization RR=0.90^{NS} [0.58;1.39] k=1 → minor bleeding RR=1.68^{NS} [0.92;3.07] k=1 → intracranial hemorrhage RR=1.03^{NS} [0.02;51.95] k=1 → major bleeding RR=1.03^{NS} [0.21;5.09] 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)

Phenprocoumon

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

Table 9: *Results summary - Phenprocoumon*

Benefit	Harmful	No evidence
	Phenprocoumon versus placebo	
		→ coronary event RR=0.81^{NS} [0.52;1.27] k=1 → coronary death RR=1.11^{NS} [0.64;1.92] k=1 → all cause death RR=1.14^{NS} [0.74;1.78] k=1
	Phenprocoumon versus aspirin	
	↑ coronary death RR=1.98* [1.04;3.79] k=1	→ coronary event RR=1.32^{NS} [0.80;2.19] k=1 → all cause death RR=1.43^{NS} [0.90;2.28] 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)

Warfarin

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

Table 10: *Results summary - Warfarin*

Benefit	Harmful	No evidence
	Warfarin versus control (on top of aspirin)	

continued...

Benefit	Harmful	No evidence
↓ all cause death, MI, thrombo-embolic stroke RR=0.71¶ [0.59;0.86] k=1 ↓ stroke (fatal and non fatal) RR=0.67† [0.50;0.88] k=1	↑ minor bleeding RR=3.34¶ [2.29;4.88] H k=5 ↑ major bleeding RR=1.68¶ [1.28;2.21] k=7	→ myocardial infarction (fatal and non fatal) RR=0.81NS [0.61;1.08] H k=5 → ischemic stroke RR=0.90NS [0.61;1.32] H k=6 → revascularization RR=0.56NS [0.21;1.51] H k=2 → all cause death RR=0.95NS [0.86;1.05] k=7 → intracranial hemorrhage RR=1.26NS [0.70;2.25] k=3
Warfarin versus placebo (on top of aspirin)		
		→ myocardial infarction (fatal and non fatal) RR=0.19NS [0.03;1.13] k=1 → ischemic stroke RR=0.83NS [0.02;34.94] k=1 → revascularization RR=1.11NS [0.45;2.77] k=1 → all cause death RR=0.42NS [0.02;10.03] k=1 → minor bleeding RR=3.33NS [0.19;58.37] k=1 → major bleeding RR=1.67NS [0.07;40.10] k=1
Warfarin versus aspirin		
↓ all cause death, MI, thrombo-embolic stroke RR=0.81† [0.69;0.95] k=1 ↓ ischemic stroke RR=0.53* [0.29;0.94] k=1	↑ minor bleeding RR=2.62¶ [1.83;3.75] k=1 ↑ major bleeding RR=4.09¶ [1.90;8.82] k=1	→ all cause death RR=1.03NS [0.79;1.36] k=1 → intracranial hemorrhage RR=4.96NS [0.58;42.38] 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)

0.1.4 Pentasccharide

Only one trials including 12092 patients was found.
Among these comparisons, one trial are about fondaparinux.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with fondaparinux for all the endpoints with data in at least one trial are summarized table 11.

Table 11: *Results summary - Fondaparinux*

Benefit	Harmful	No evidence
Fondaparinux versus placebo		
↓ reinfarction RR=0.68† [0.52;0.88] k=1 ↓ in-hospital death RR=0.87* [0.76;0.99] k=1 ↓ deaths or MI RR=0.87† [0.78;0.96] k=1 ↓ death at 30 days RR=0.87* [0.78;0.98] k=1		→ reinfarction at 30 days RR=0.81NS [0.65;1.01] k=1 → major bleeding RR=0.83NS [0.64;1.06] 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)

0.1.5 Unfractionated heparin

Reports of 4 trials (including 1,231 patients) were identified .
Among these comparisons, 4 trials are about UFH.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with UFH for all the endpoints with data in at least one trial are summarized table 12.

Table 12: *Results summary - UFH*

Benefit	Harmful	No evidence
	UFH versus no heparin	
		→ reinfarction RR=0.77^{NS} [0.07;7.88] k=2 → in-hospital death RR=1.37^{NS} [0.71;2.65] k=2
	UFH versus placebo	
		→ reinfarction RR=1.07^{NS} [0.48;2.41] k=2 → in-hospital death RR=0.72^{NS} [0.32;1.62] k=2

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

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

1 Introduction

1.1 Aim of the report

This report review all the randomized clinical trials of antithrombotics for the treatment of acute myocardial infarction. The following classes of treatment are considered:

1. direct thrombin inhibitor
2. Low molecular weight heparin
3. oral anticoagulant
4. pentasccharide
5. unfractionated heparin

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of antithrombotics for the treatment of acute myocardial infarction in all type of patients.

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 acute myocardial infarction.

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 .

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 thrombin inhibitor, Low molecular weight heparin, oral anticoagulant, pentasccharide, unfractionated heparin,
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 thrombin inhibitor

2 Overview of direct thrombin inhibitor

2.1 Included trials

A total of 4 randomized comparisons which enrolled 3861 patients were identified. In all, 1 randomized comparison concerned Argatroban , one bivalirudin and two Hirudin.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 22) for Argatroban, in section 4 (page 27) for bivalirudin and in section 5 (page 32) for Hirudin.

The average study size was 1287 patients (range 412 to 3002). The first study was published in 1996, and the last study was published in 1999.
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.
The table 2.1 (page 20) 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 thrombin inhibitor provide the results listed in tables 2.2 to 2.4 (page 21) and in the following graphs.

2.2.1 Argatroban

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

2.2.2 Bivalirudin

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

2.2.3 Hirudin

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

Table 2.1: *Main study characteristics - direct thrombin inhibitor*

Trial	Patients	Treatments	Trial design and method
Argatroban			
Argatroban versus heparin			
ARGAMI-2, 1998 [1, 2, 3] n = NA vs. NA	AMI	argatroban 6020 mg/kg bolus; 24 microg /kg/min infusion for 72h **versus** UFH 5000 IU bolus; 1000 IU/h infusion	
Bivalirudin			
Bivalirudin versus heparin			
HERO, 1997 [1] n = 272 vs. 140	AMI (patients presenting within 12 hours with ST-segment elevation)	bivalirudin 0.1250.250 mg/kg bolus; 0.1250.500 mg /kg/min infusion for 72h **versus** UFH 5000 IU bolus; 10001200 IU/h infusion	double blind parallel groups Primary endpoint: TIMI3 of the infarct-related artery at 90 to 120 minutes
Hirudin			
Hirudin versus heparin			
HIT-4, 1999 [1] n= 447	patients with AMI <=6 h were treated with aspirin and streptokinase	hirudin 0.2 mg/kg bolus; 0.5 mg/kg twice daily 0.1 mg/kg 0.1 mg /kg/h infusion for 5-7 days **versus** placebo bolus, UFH 12 500 IU twice daily	double blind parallel groups Primary endpoint: TIMI 3 flow at 90 min
TIMI 9B, 1996 [2] n= 3002	unstable angina or AMI	hirudin 0.1 mg/kg bolus; 0.1 mg /kg/h infusion for 96h **versus** UFH 5000 IU bolus; 1000 IU/h infusion	open parallel groups Primary endpoint: death,MI, HF, cardiogenic shock

Table 2.2: *Summary of all results for Argatroban*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Argatroban versus heparin						
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 2.3: *Summary of all results for bivalirudin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
bivalirudin versus heparin						
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 2.4: *Summary of all results for Hirudin*

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

3 Detailed results for Argatroban

3.1 Available trials

Only one trial which randomized 0 patients was identified: it compared Argatroban with heparin. This trial included NaN patients and was published in 1998.
Erreur ??? 0 et 0.
It was reported in English language.
data was reported in trials;
Following tables 3.1 (page 22), 3.2 (page 22), 3.4 (page 23), and 3.3 (page 22) summarized the main characteristics of the trial including in this systematic review of randomized trials of Argatroban.

Table 3.1: *Treatment description - direct thrombin inhibitor - Argatroban*

Trial	Studied treatment	Control treatment
Argatroban versus heparin		
ARGAMI-2 (1998) [1, 2, 3]	Argatroban 6020 mg/kg bolus; 24 microg /kg/min infusion for 72h	UFH 5000 IU bolus; 1000 IU/h infusion
	Concomittant treatment: tissue-type plasminogen activatoror streptokinase	

Table 3.2: *Descriptions of participants - direct thrombin inhibitor - Argatroban*

Trial	Patients
Argatroban versus heparin	
ARGAMI-2 (1998) [1, 2, 3]	AMI

Table 3.3: *Design and methodological quality of trials - direct thrombin inhibitor - Argatroban*

Trial	Design	Duration	Centre	Primary end-point
Argatroban versus heparin				
ARGAMI-2, 1998 [1, 2, 3] n=NaN		30 days		

Table 3.4: *Trial characteristics - direct thrombin inhibitor - Argatroban*

Trial
Argatroban versus heparin
ARGAMI-2, 1998 [1, 2, 3]

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.

Argatroban versus heparin

No data were presented in the 1 trial identified

Table 3.5: *Results details - direct thrombin inhibitor - Argatroban*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Argatroban versus heparin						
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] Alderman EL. Results from late-breaking clinical trials sessions at ACC '98. American College of Cardiology. J Am Coll Cardiol 1998;32:1-7. [PMID=9669241]

[2] Rott D, Behar S, Hod H, Feinberg MS, Boyko V, Mandelzweig L, Kaplinsky E, Gottlieb S. Improved survival of patients with acute myocardial infarction with significant left ventricular dysfunction undergoing invasive coronary procedures. Am Heart J 2001;141:267-76. [PMID=11174342]

[3] Behar S, Hod H, Kaplinsky E, et al. Argatroban versus heparin as adjuvant therapy for thrombolysis for acute myocardial infarction: safety considerations ARGAMI-2 study [abstract]. Circulation 1998;98(1 Suppl):I453-4.

3.3 Individual trial summaries

Table 3.6: *ARGAMI-2, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** 30 days **Study design:** Randomized controlled trial	AMI	**Studied treatment:** Argatroban 6020 mg/kg bolus; 24 microg /kg/min infusion for 72h **Control treatment:** UFH 5000 IU bolus; 1000 IU/h infusion **Concomittant treat.:**tissue-type plasminogen activatoror streptokinase	

References

Alderman EL. Results from late-breaking clinical trials sessions at ACC '98. American College of Cardiology. J Am Coll Cardiol 1998;32:1-7 [PMID=9669241]
Rott D, Behar S, Hod H, Feinberg MS, Boyko V, Mandelzweig L, Kaplinsky E, Gottlieb S. Improved survival of patients with acute myocardial infarction with significant left ventricular dysfunction undergoing invasive coronary procedures. Am Heart J 2001;141:267-76 [PMID=11174342]
Behar S, Hod H, Kaplinsky E, et al. Argatroban versus heparin as adjuvant therapy for thrombolysis for acute myocardial infarction: safety considerations ARGAMI-2 study [abstract]. Circulation 1998;98(1 Suppl):I453-4

4 Detailed results for bivalirudin

4.1 Available trials

Only one trial which randomized 412 patients was identified: it compared bivalirudin with heparin.
This trial included 412 patients and was published in 1997.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 4.1 (page 27), 4.2 (page 27), 4.4 (page 28), and 4.3 (page 27) summarized the main characteristics of the trial including in this systematic review of randomized trials of bivalirudin.

Table 4.1: *Treatment description - direct thrombin inhibitor - bivalirudin*

Trial	Studied treatment	Control treatment
Bivalirudin versus heparin		
HERO (1997) [1] [a]	Bivalirudin 0.1250.250 mg/kg bolus; 0.1250.500 mg /kg/min infusion for 72h	UFH 5000 IU bolus; 10001200 IU/h infusion

a) 3 arms: low-dose, high dose hirulog and heparin

Table 4.2: *Descriptions of participants - direct thrombin inhibitor - bivalirudin*

Trial	Patients
Bivalirudin versus heparin	
HERO (1997) [1]	AMI (patients presenting within 12 hours with ST-segment elevation)

Table 4.3: *Design and methodological quality of trials - direct thrombin inhibitor - bivalirudin*

Trial	Design	Duration	Centre	Primary endpoint
Bivalirudin versus heparin				
HERO, 1997 [1] [(a)] n=412	Parallel groups double blind exploratory trial	35 days		TIMI3 of the infarct-related artery at 90 to 120 minutes

a) dose-finding study

Table 4.4: *Trial characteristics - direct thrombin inhibitor - bivalirudin*

Trial
Bivalirudin versus heparin
HERO, 1997 [1]

4.2 Meta-analysis results

The results are detailed in table 4.5 (page 29). This table is followed by the Forest's plot corresponding to each endpoint.

Bivalirudin versus heparin

No data were presented in the 1 trial identified

Table 4.5: *Results details - direct thrombin inhibitor - bivalirudin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
bivalirudin versus heparin						
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] White HD, Aylward PE, Frey MJ, Adgey AA, Nair R, Hillis WS, Shalev Y, Brown MA, French JK, Collins R, Maraganore J, Adelman B. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. Circulation 1997 Oct 7;96:2155-61. [PMID=9337184]

4.3 Individual trial summaries

Table 4.6: *HERO, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=412 (272 vs. 140) **Follow-up duration:** 35 days **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	AMI (patients presenting within 12 hours with ST-segment elevation)	**Studied treatment:** Bivalirudin 0.1250.250 mg/kg bolus; 0.1250.500 mg /kg/min infusion for 72h **Control treatment:** UFH 5000 IU bolus; 10001200 IU/h infusion **note:** 3 arms: low-dose, high dose hirulog and heparin	

Reference

White HD, Aylward PE, Frey MJ, Adgey AA, Nair R, Hillis WS, Shalev Y, Brown MA, French JK, Collins R, Maraganore J, Adelman B. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. Circulation 1997 Oct 7;96:2155-61 [PMID=9337184]

5 Detailed results for Hirudin

5.1 Available trials

A total of 2 RCTs which randomized 3449 patients were identified: all compared Hirudin with heparin.
The average study size was 1724 patients (range 447 to 3002). The first study was published in 1996, and the last study was published in 1999.
A total of 1 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
data was reported in trials;
Following tables 5.1 (page 32), 5.2 (page 32), 5.4 (page 34), and 5.3 (page 33) summarized the main characteristics of the trials including in this systematic review of randomized trials of Hirudin.

Table 5.1: *Treatment description - direct thrombin inhibitor - Hirudin*

Trial	Studied treatment	Control treatment
Hirudin versus heparin		
HIT-4 (1999) [1]	Hirudin 0.2 mg/kg bolus; 0.5 mg/kg twice daily 0.1 mg/kg 0.1 mg /kg/h infusion for 5-7 days	Placebo bolus, UFH 12 500 IU twice daily
TIMI 9B (1996) [2]	Hirudin 0.1 mg/kg bolus; 0.1 mg /kg/h infusion for 96h	UFH 5000 IU bolus; 1000 IU/h infusion

Table 5.2: *Descriptions of participants - direct thrombin inhibitor - Hirudin*

Trial	Patients
Hirudin versus heparin	
HIT-4 (1999) [1]	Patients with AMI <=6 h were treated with aspirin and streptokinase
TIMI 9B (1996) [2]	Unstable angina or AMI

Table 5.3: *Design and methodological quality of trials - direct thrombin inhibitor - Hirudin*

Trial	Design	Duration	Centre	Primary end-point
Hirudin versus heparin				
HIT-4, 1999 [1] n=447	Parallel groups double blind exploratory trial	30 days		TIMI 3 flow at 90 min
TIMI 9B, 1996 [2] n=3002	Parallel groups open confirmatory trial at risk of bias	30 days		death,MI, HF, cardiogenic shock

Table 5.4: *Trial characteristics - direct thrombin inhibitor - Hirudin*

Trial
Hirudin versus heparin
HIT-4, 1999 [1]
TIMI 9B, 1996 [2]

5.2 Meta-analysis results

The results are detailed in table 5.5 (page 35). This table is followed by the Forest's plot corresponding to each endpoint.

Hirudin versus heparin

No data were presented in the 2 trials identified

Table 5.5: *Results details - direct thrombin inhibitor - Hirudin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Hirudin versus heparin						
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] Neuhaus KL, Molhoek GP, Zeymer U, Tebbe U, Wegscheider K, Schroder R, Camez A, Laarman GJ, Grollier GM, Lok DJ, Kuckuck H, Lazarus P. Recombinant hirudin (lepirudin) for the improvement of thrombolysis with streptokinase in patients with acute myocardial infarction: results of the HIT-4 trial. J Am Coll Cardiol 1999 Oct;34:966-73. [PMID=10520777]

[2] Antman EM. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. Circulation 1996 Sep 1;94:911-21. [PMID=8790025]

5.3 Individual trial summaries

Table 5.6: *HIT-4, 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (447 vs. 0) **Follow-up duration:** 30 days **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Patients with AMI <=6 h were treated with aspirin and streptokinase	**Studied treatment:** Hirudin 0.2 mg/kg bolus; 0.5 mg/kg twice daily 0.1 mg/kg 0.1 mg /kg/h infusion for 5-7 days **Control treatment:** Placebo bolus, UFH 12 500 IU twice daily	

Reference

Neuhaus KL, Molhoek GP, Zeymer U, Tebbe U, Wegscheider K, Schroder R, Camez A, Laarman GJ, Grollier GM, Lok DJ, Kuckuck H, Lazarus P. Recombinant hirudin (lepirudin) for the improvement of thrombolysis with streptokinase in patients with acute myocardial infarction: results of the HIT-4 trial. J Am Coll Cardiol 1999 Oct;34:966-73 [PMID=10520777]

Table 5.7: *TIMI 9B, 1996 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (3002 vs. 0) **Follow-up duration:** 30 days **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias	Unstable angina or AMI	**Studied treatment:** Hirudin 0.1 mg/kg bolus; 0.1 mg /kg/h infusion for 96h **Control treatment:** UFH 5000 IU bolus; 1000 IU/h infusion	

Reference

Antman EM. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. Circulation 1996 Sep 1;94:911-21 [PMID=8790025]

6 Global meta-analysis: all direct thrombin inhibitor

6.1 Global meta-analysis: all direct thrombin inhibitor versus heparin

Table 6.1: *All direct thrombin inhibitorversus heparin*

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

7 Ongoing studies of direct thrombin inhibitor

No ongoing trial was identified.

8 Excluded studies for direct thrombin inhibitor

No trial was excluded.

References

Part II

Low molecular weight heparin

9 Overview of low molecular weight heparin

9.1 Included trials

A total of 10 randomized comparisons which enrolled 24036 patients were identified. In all, 3 randomized comparisons concerned Dalteparin , 6 Enoxaparin and one Reviparin.
The detailed descriptions of trials and meta-analysis results is given in section 10 (page 51) for Dalteparin, in section 11 (page 62) for Enoxaparin and in section 12 (page 78) for Reviparin.

The average study size was 2403 patients (range 101 to 15570). The first study was published in 1997, and the last study was published in 2005.
A total of 4 trials were double blind and 5 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 9.1 (page 45) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

9.2 Summary of meta-analysis results

The meta-analysis of the available trials about low molecular weight heparin provide the results listed in tables 9.2 to 9.4 (page 47) and in the following graphs.

9.2.1 Dalteparin

No significant difference was found between **Dalteparin** and **placebo** in terms of reinfarction (RR=0.75, 95% CI 0.26 to 2.14, p=0.5910, 1 trial), in-hospital death (RR=1.00, 95% CI 0.57 to 1.75, p=1.0000, 1 trial), reinfarction at 30 days (RR=3.48, 95% CI 0.78 to 15.59, p=0.1030, 1 trial)and death at 30 days (RR=0.58, 95% CI 0.17 to 1.93, p=0.3753, 1 trial).

Dalteparin was superior to **UFH** in terms of reinfarction (RR=0.26, 95% CI 0.07 to 0.93, p=0.0381, 1 trial). However, no significant difference was found on in-hospital death (RR=0.60, 95% CI 0.20 to 1.81, p=0.3671, 1 trial), reinfarction at 30 days (RR=0.96, 95% CI 0.47 to 1.97, p=0.9197, 1 trial)and death at 30 days (RR=0.79, 95% CI 0.33 to 1.86, p=0.5885, 1 trial).

9.2.2 Enoxaparin

Enoxaparin was superior to **placebo** in terms of reinfarction (RR=0.34, 95% CI 0.13 to 0.94, p=0.0371, 1 trial)and reinfarction at 30 days (RR=0.32, 95% CI 0.13 to 0.79, p=0.0138, 1 trial). However, no significant difference was found on in-hospital death (RR=1.25, 95% CI 0.56 to 2.79, p=0.5890, 1 trial)and death at 30 days (RR=0.96, 95% CI 0.50 to 1.84, p=0.9030, 1 trial).

Enoxaparin was superior to **UFH** in terms of reinfarction (RR=0.61, 95% CI 0.48 to 0.78, p=0.0000, 5 trials)and reinfarction at 30 days (RR=0.62, 95% CI 0.39 to 0.97, p=0.0381, 4 trials). However, no significant difference was found on in-hospital death (RR=0.95, 95% CI 0.72 to 1.24, p=0.6840, 5 trials)and death at 30 days (RR=0.95, 95% CI 0.77 to 1.17, p=0.6429, 5 trials).

9.2.3 Reviparin

Reviparin was superior to **placebo** in terms of reinfarction (RR=0.76, 95% CI 0.60 to 0.96, p=0.0207, 1 trial), in-hospital death (RR=0.89, 95% CI 0.81 to 0.99, p=0.0354, 1 trial), reinfarction at 30 days (RR=0.77, 95% CI 0.63 to 0.95, p=0.0162, 1 trial)and death at 30 days (RR=0.87, 95% CI 0.80 to 0.96, p=0.0042, 1 trial).

Table 9.1: *Main study characteristics - Low molecular weight heparin*

Trial	Patients	Treatments	Trial design and method
Dalteparin			
Dalteparin versus placebo			
BIOMACS II, 1999 [1] n = 54 vs. 47	patients with acute myocardial infarction, Age <=80 y, STEMI or new LBBB	dalteparin 100 mg/kg, 2 doses **versus** placebo	double-blind parallel groups Primary endpoint: angiographic TIMI flow in infarct-related vessel
FRAMI, 1997 [2] n = 388 vs. 388	patients with an acute MI, Q wave or STEMI	dalteparin 150 mg/kg BID for 711 d **versus** placebo	Double-blind parallel groups Primary endpoint: echocardiographic LV thrombus, arterial embolism
Dalteparin versus UFH			
ASSENT Plus, 2003 [3] n = 221 vs. 213	patients with AMI treated with alteplase	dalteparin first dose 90 IU/kg, then 120 IU/kg BID, 47 d **versus** UFH 40005000 IU bolus, then 8001000 IU/h for 48 h	open parallel groups Primary endpoint: angiographic 60-min TIMI flow
Enoxaparin			
Enoxaparin versus placebo			
AMI-SK, 2002 [1] n = 253 vs. 243	patients with evolving myocardial infarction, Age >=18 y, STEMI	enoxaparin 30 mg IV bolus, 1 mg/kg for 38 d **versus** placebo	double-blind parallel groups Primary endpoint: angiographic TIMI flow in infarct-related vessel
Enoxaparin versus UFH			
ASSENT 3 Plus, 2003 [2] n = 818 vs. 821	patients with ST-elevation myocardial infarction	enoxaparin 1 mg/kg BID, <=7d **versus** UFH 60 IU/kg, then 12 IU/kg per h for >=3d	open parallel groups Primary endpoint: angiographic TIMI flow

continued...

Trial	Patients	Treatments	Trial design and method
ASSENT 3, 2001 [3] n = 2040 vs. 2038	patients with acute myocardial infarction	enoxaparin 1 mg/kg BID, <=7d **versus** UFH 60 U/kg bolus, then 12 IU/kg per h for 48 h	open parallel groups Primary endpoint: in-hospital MI or RI
Baird, 2002 [4] n = 149 vs. 151	patients receiving fibrinolytic therapy following acute myocardial infarction	enoxaparin 40 mg TID, 4 d **versus** UFH 5000 IU bolus, then 30 000 IU over 24 h for 4d	90-min TIMI flow parallel groups Primary endpoint: death, non-fatal reinfarction, or readmission with unstable angina
ENTIRE-TIMI 2, 2002 [5] n = 160 vs. 82	patients with ST-elevation MI presenting <6 hours from symptom onset were	enoxaparin 1 mg/kg BID, <=8d **versus** UFH 60 IU/kg, then 12 IU/kg per h for >=3d	open parallel groups Primary endpoint: MI, death, readmit for UA
HART II, 2001 [6] n = 200 vs. 200	patients undergoing reperfusion therapy with an accelerated recombinant tissue plasminogen activator regimen and aspirin for AMI	enoxaparin 1 mg/kg BID, <=3d **versus** UFH 40005000 IU bolus, then 15 IU/kg per hour for >=3d	open parallel groups Primary endpoint: infarct-related artery patency
Reviparin			
Reviparin versus placebo			
CREATE, 2005 [1] n = 7780 vs. 7790	patients with acute myocardial infarction, STEMI or new LBBB, <=12 h	reviparin 34366871 IU BID for 7 d (weight adjusted) **versus** placebo	double-blind parallel groups Primary endpoint: death, MI, or stroke; death, MI, stroke, or recurrent ischemia

Table 9.2: *Summary of all results for Dalteparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Dalteparin versus placebo						
reinfarction	RR=0.75	0.26;2.14	0.5910	1.0000 (0.00)	1	776
in-hospital death	RR=1.00	0.57;1.75	1.0000	1.0000 (0.00)	1	776
reinfarction at 30 days	RR=3.48	0.78;15.59	0.1030	1.0000 (0.00)	1	101
death at 30 days	RR=0.58	0.17;1.93	0.3753	1.0000 (1.00)	1	101
Dalteparin versus UFH						
reinfarction	RR=0.26	0.07;0.93	0.0381	1.0000 (0.00)	1	434
in-hospital death	RR=0.60	0.20;1.81	0.3671	1.0000 (0.00)	1	434
reinfarction at 30 days	RR=0.96	0.47;1.97	0.9197	1.0000 (0.00)	1	434
death at 30 days	RR=0.79	0.33;1.86	0.5885	1.0000 (0.00)	1	434

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 9.3: *Summary of all results for Enoxaparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Enoxaparin versus placebo						
reinfarction	RR=0.34	0.13;0.94	0.0371	1.0000 (0.00)	1	496
in-hospital death	RR=1.25	0.56;2.79	0.5890	1.0000 (0.00)	1	496
reinfarction at 30 days	RR=0.32	0.13;0.79	0.0138	1.0000 (0.00)	1	496
death at 30 days	RR=0.96	0.50;1.84	0.9030	1.0000 (0.00)	1	496
Enoxaparin versus UFH						
reinfarction	RR=0.61	0.48;0.78	0.0000	0.4161 (0.00)	5	6659
in-hospital death	RR=0.95	0.72;1.24	0.6840	0.2916 (0.19)	5	6659
reinfarction at 30 days	RR=0.62	0.39;0.97	0.0381	0.1082 (0.51)	4	5020
death at 30 days	RR=0.95	0.77;1.17	0.6429	0.3724 (0.06)	5	6659

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 9.4: *Summary of all results for Reviparin*

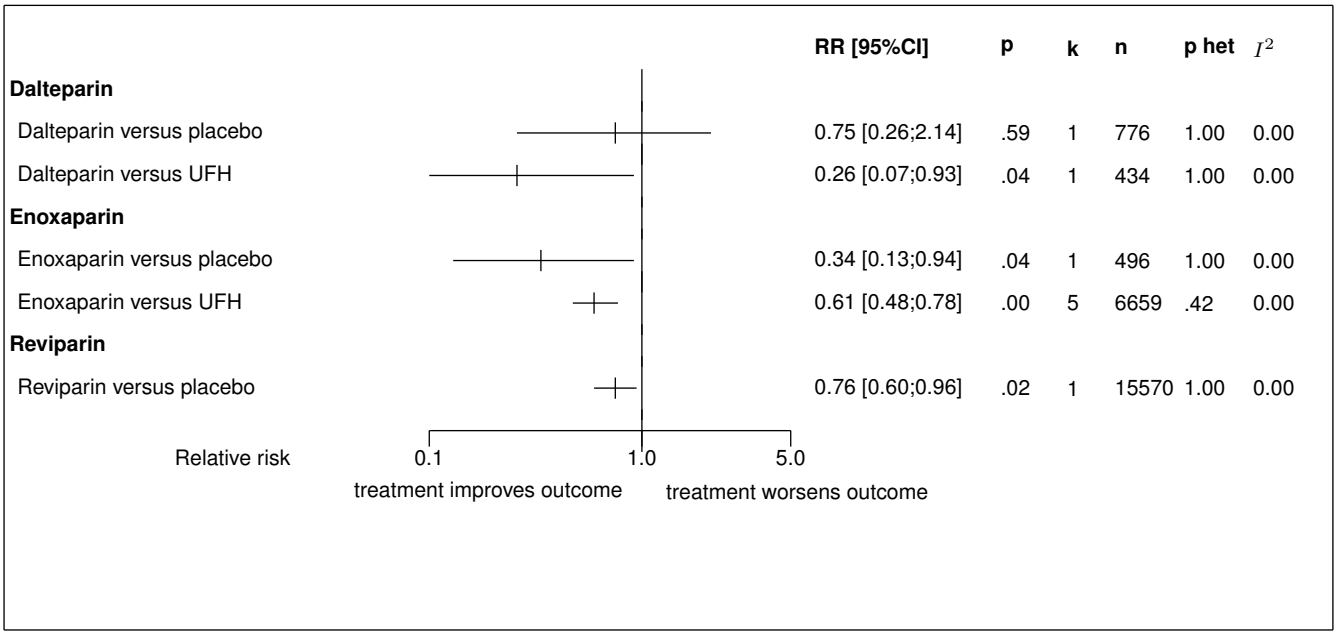
Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Reviparin versus placebo						

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
reinfarction	RR=0.76	0.60;0.96	0.0207	1.0000 (0.00)	1	15570
in-hospital death	RR=0.89	0.81;0.99	0.0354	1.0000 (0.00)	1	15570
reinfarction at 30 days	RR=0.77	0.63;0.95	0.0162	1.0000 (0.00)	1	15570
death at 30 days	RR=0.87	0.80;0.96	0.0042	1.0000 (0.00)	1	15570

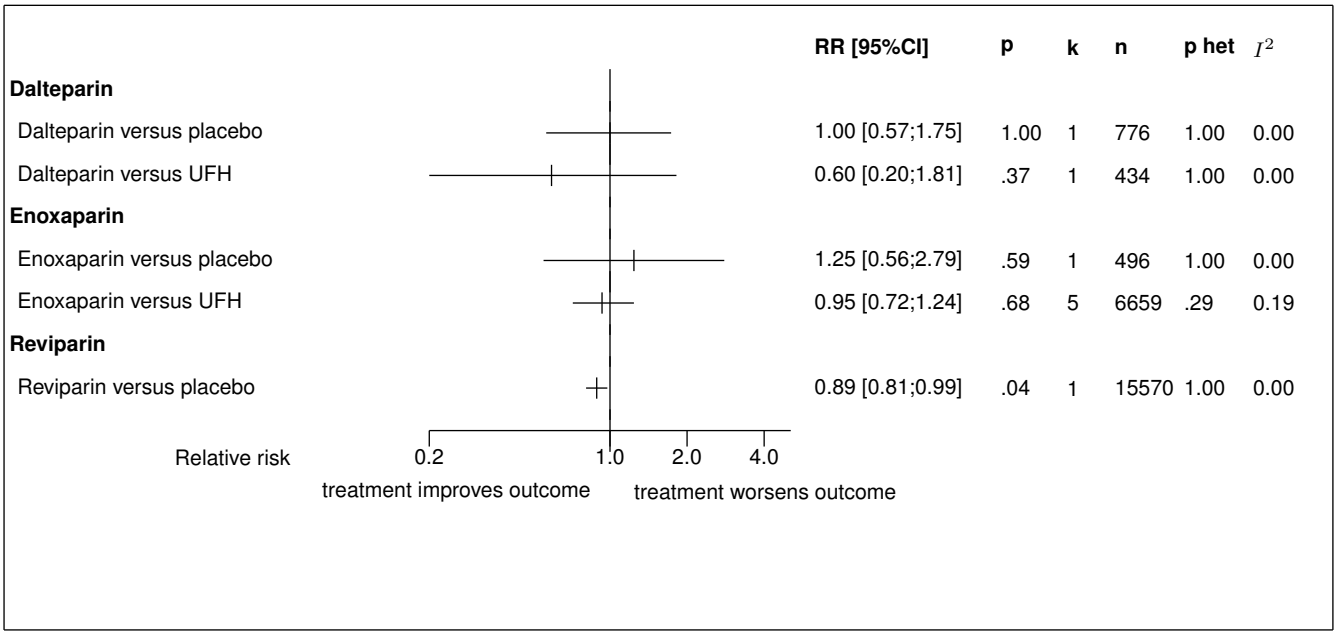
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 9.1: *Forest's plot for reinfarction*



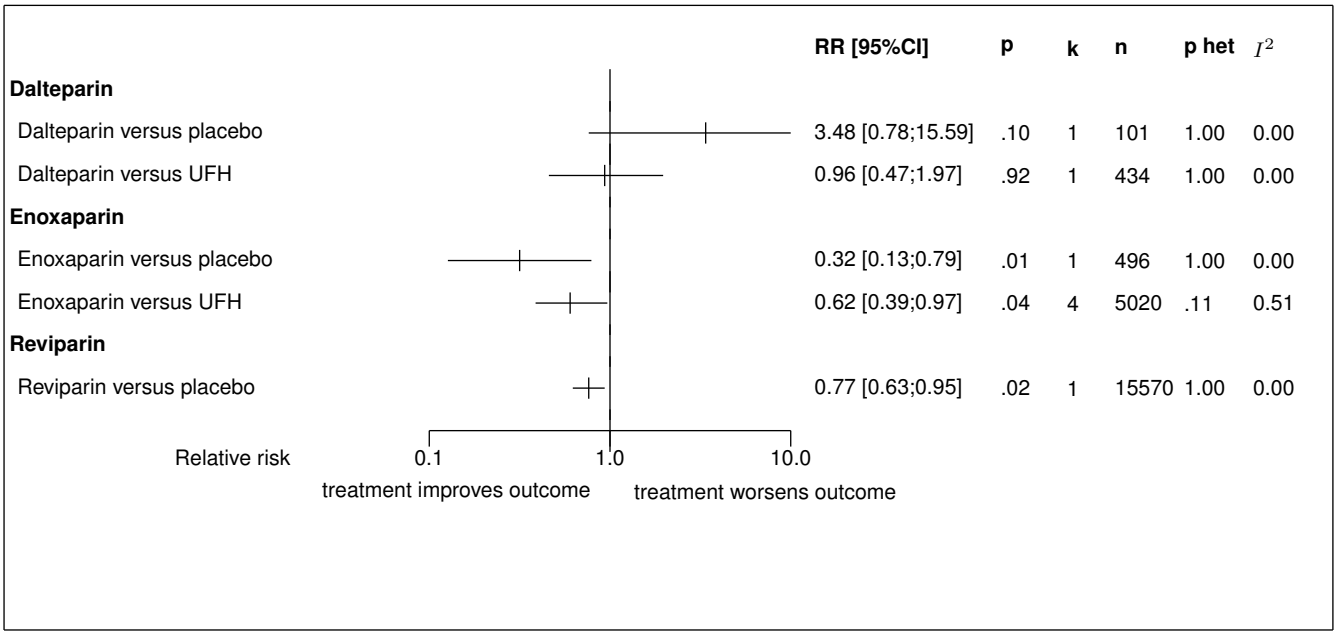
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 9.2: *Forest's plot for in-hospital death*



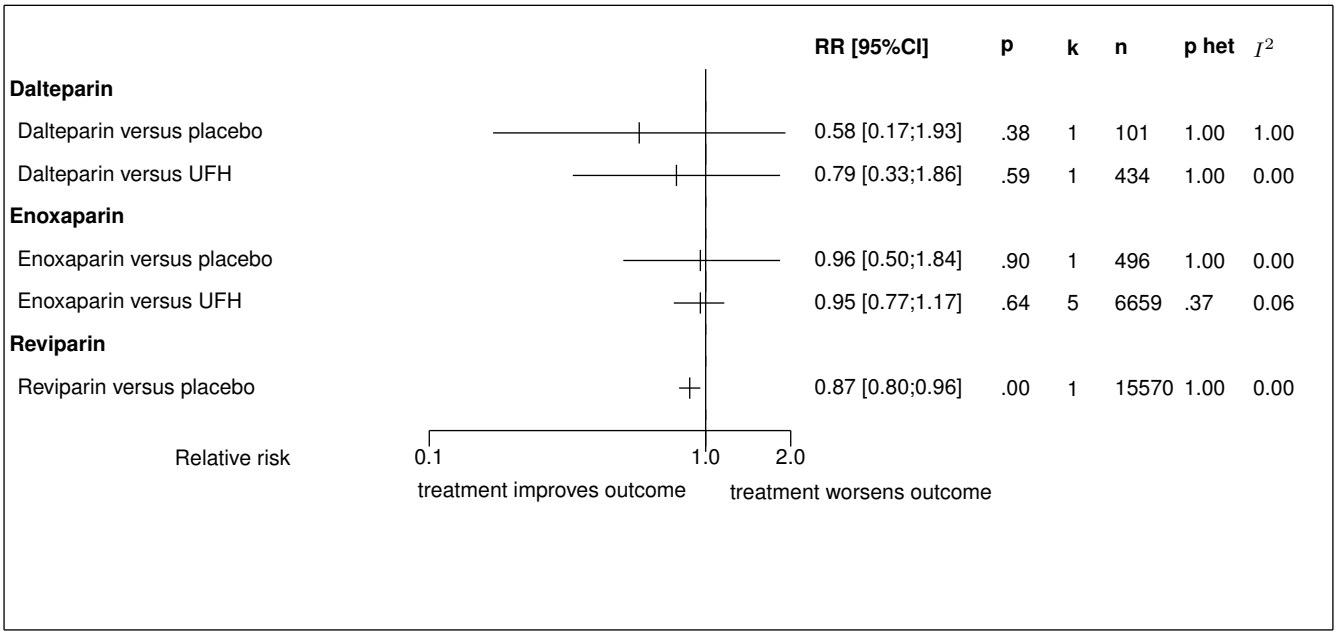
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 9.3: *Forest's plot for reinfarction at 30 days*



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 9.4: *Forest's plot for death at 30 days*



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

10 Detailed results for Dalteparin

10.1 Available trials

A total of 3 RCTs which randomized 1311 patients were identified: 2 trials compared Dalteparin with placebo and it compared Dalteparin with UFH.
The average study size was 437 patients (range 101 to 776). The first study was published in 1997, and the last study was published in 2003.
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.
Reinfarction at 30 days data was reported in 2 trials; 2 trials reported data on reinfarction; 2 trials reported data on death at 30 days; and 2 trials reported data on in-hospital death.
Following tables 10.1 (page 51), 10.2 (page 51), 10.4 (page 53), and 10.3 (page 52) summarized the main characteristics of the trials including in this systematic review of randomized trials of Dalteparin.

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

Trial	Studied treatment	Control treatment
Dalteparin versus placebo		
BIOMACS II (1999) [1]	Dalteparin 100 mg/kg, 2 doses	placebo
FRAMI (1997) [2]	Dalteparin 150 mg/kg BID for 711 d	placebo
Dalteparin versus UFH		
ASSENT Plus (2003) [3]	Dalteparin first dose 90 IU/kg, then 120 IU/kg BID, 47 d	UFH 40005000 IU bolus, then 8001000 IU/h for 48 h
	Concomittant treatment: tPA <=100 mg over 90 min	

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

Trial	Patients
Dalteparin versus placebo	
BIOMACS II (1999) [1]	Patients with acute myocardial infarction, Age <=80 y, STEMI or new LBBB
FRAMI (1997) [2]	Patients with an acute MI, Q wave or STEMI
Dalteparin versus UFH	
ASSENT Plus (2003) [3]	Patients with AMI treated with alteplase

continued...

Trial	Patients

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

Trial	Design	Duration	Centre	Primary endpoint
Dalteparin versus placebo				
BIOMACS II, 1999 [1] n=101	Parallel groups Double-blind	1421 d		Angiographic TIMI flow in infarct-related vessel
FRAMI, 1997 [2] n=776	Parallel groups Double-blind	in hospital		Echocardiographic LV thrombus, arterial embolism
Dalteparin versus UFH				
ASSENT Plus, 2003 [3] n=434	Parallel groups open	30 d		Angiographic 60-min TIMI flow

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

Trial
Dalteparin versus placebo
BIOMACS II, 1999 [1]
FRAMI, 1997 [2]
Dalteparin versus UFH
ASSENT Plus, 2003 [3]

10.2 Meta-analysis results

The results are detailed in table 10.5 (page 54). This table is followed by the Forest's plot corresponding to each endpoint.

Dalteparin versus placebo

Only one of the 2 studies eligible for this comparison provided data on **reinfarction**. No statistically significant difference between the groups was found in reinfarction, with a RR of 0.75 (95% CI 0.26 to 2.14, p=0.5910).
Only one of the 2 studies eligible for this comparison provided data on **in-hospital death**. No statistically significant difference between the groups was found in in-hospital death, with a RR of 1.00 (95% CI 0.57 to 1.75, p=1.0000).
Only one of the 2 studies eligible for this comparison provided data on **reinfarction at 30 days**. No statistically significant difference between the groups was found in reinfarction at 30 days, with a RR of 3.48 (95% CI 0.78 to 15.59, p=0.1030).
Only one of the 2 studies eligible for this comparison provided data on **death at 30 days**. No statistically significant difference between the groups was found in death at 30 days, with a RR of 0.58 (95% CI 0.17 to 1.93, p=0.3753).

Dalteparin versus UFH

The single study eligible for this comparison provided data on **reinfarction**. The analysis detected a statistically significant difference in favor of Dalteparin in reinfarction, with a RR of 0.26 (95% CI 0.07 to 0.93, p=0.0381).
The single study eligible for this comparison provided data on **in-hospital death**. No statistically significant difference between the groups was found in in-hospital death, with a RR of 0.60 (95% CI 0.20 to 1.81, p=0.3671).
The single study eligible for this comparison provided data on **reinfarction at 30 days**. No statistically significant difference between the groups was found in reinfarction at 30 days, with a RR of 0.96 (95% CI 0.47 to 1.97, p=0.9197).
The single study eligible for this comparison provided data on **death at 30 days**. No statistically significant difference between the groups was found in death at 30 days, with a RR of 0.79 (95% CI 0.33 to 1.86, p=0.5885).

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Dalteparin versus placebo						
reinfarction	RR=0.75	[0.26;2.14]	0.5910	1.0000 (I^2=0.00)	1	776
in-hospital death	RR=1.00	[0.57;1.75]	1.0000	1.0000 (I^2=0.00)	1	776
reinfarction at 30 days	RR=3.48	[0.78;15.59]	0.1030	1.0000 (I^2=0.00)	1	101
death at 30 days	RR=0.58	[0.17;1.93]	0.3753	1.0000 (I^2=1.00)	1	101
Dalteparin versus UFH						
reinfarction	RR=0.26	[0.07;0.93]	0.0381	1.0000 (I^2=0.00)	1	434
in-hospital death	RR=0.60	[0.20;1.81]	0.3671	1.0000 (I^2=0.00)	1	434

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
reinfarction at 30 days	RR=0.96	[0.47;1.97]	0.9197	1.0000 (I^2=0.00)	1	434
death at 30 days	RR=0.79	[0.33;1.86]	0.5885	1.0000 (I^2=0.00)	1	434

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

Figure 10.1: *Forest's plot for reinfarction*

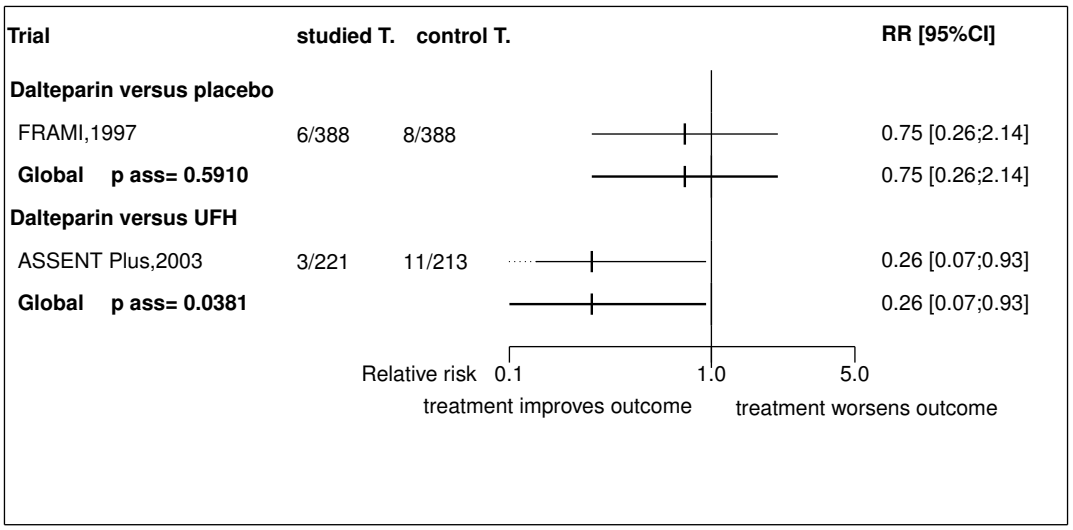


Figure 10.2: *Forest's plot for in-hospital death*

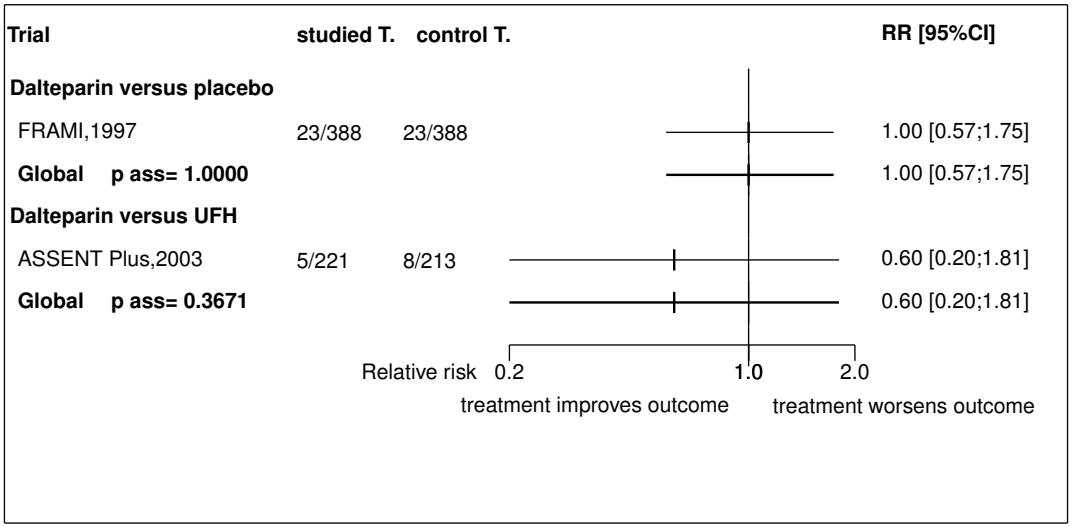


Figure 10.3: *Forest's plot for reinfarction at 30 days*

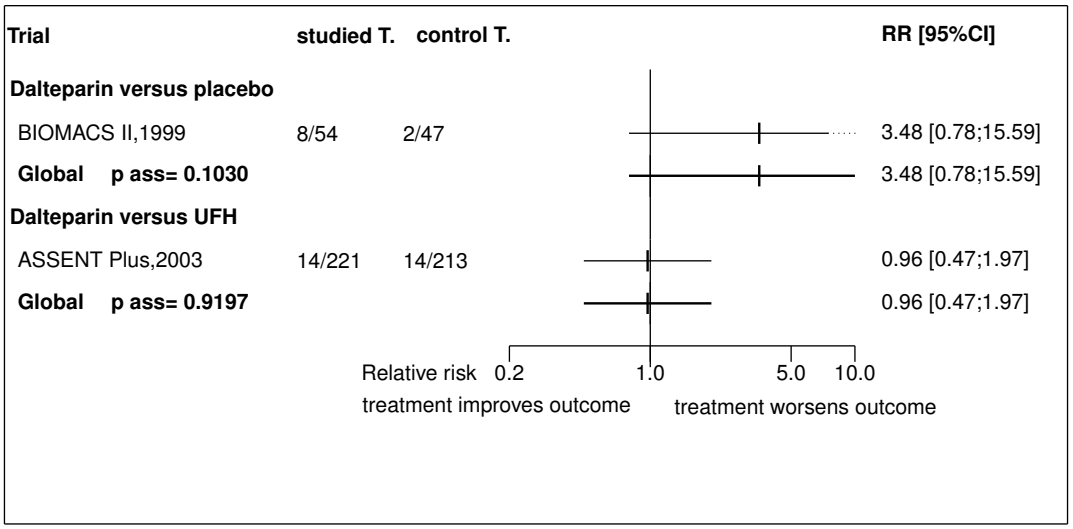
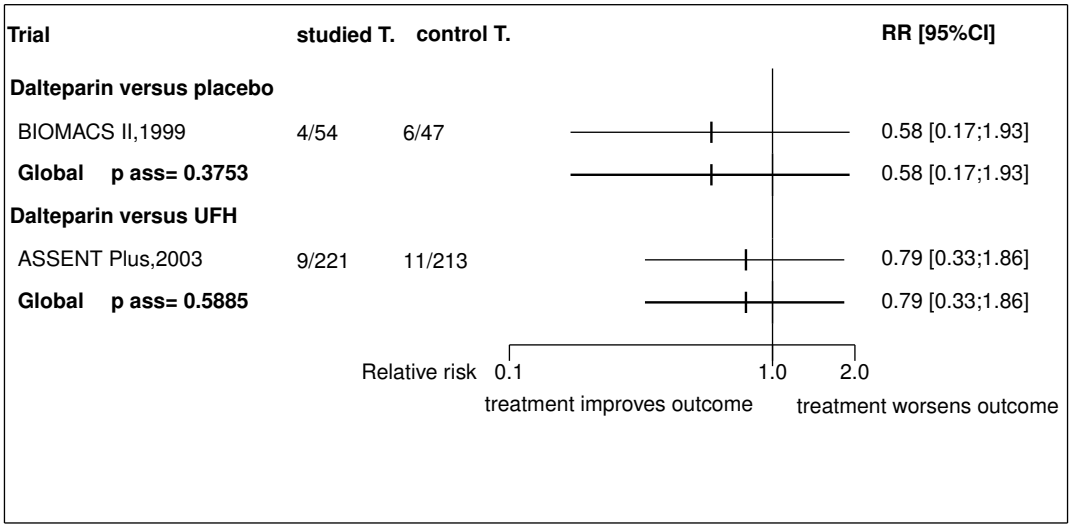


Figure 10.4: *Forest's plot for death at 30 days*



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[1] Frostfeldt G, Ahlberg G, Gustafsson G, Helmius G, Lindahl B, Nygren A, Siegbahn A, Swahn E, Venge P, Wallentin L. Low molecular weight heparin (dalteparin) as adjuvant treatment of thrombolysis in acute myocardial infarction–a pilot study: biochemical markers in acute coronary syndromes (BIOMACS II). J Am Coll Cardiol 1999;33:627-33. [PMID=10080461]

[2] Kontny F, Dale J, Abildgaard U, Pedersen TR. Randomized trial of low molecular weight heparin (dalteparin)

in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) Study. J Am Coll Cardiol 1997;30:962-9. [PMID=9316525]

[3] Wallentin L, Bergstrand L, Dellborg M, Fellenius C, Granger CB, Lindahl B, Lins LE, Nilsson T, Pehrsson K, Siegbahn A, Swahn E. Low molecular weight heparin (dalteparin) compared to unfractionated heparin as an adjunct to rt-PA (alteplase) for improvement of coronary artery patency in acute myocardial infarction-the ASSENT Plus study. Eur Heart J 2003;24:897-908. [PMID=12714021]

10.3 Individual trial summaries

Table 10.6: *BIOMACS II, 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=101 (54 vs. 47) **Follow-up duration:** 1421 d **Study design:** Randomized controlled trial Parallel groups Double-blind	Patients with acute myocardial infarction, Age <=80 y, STEMI or new LBBB	**Studied treatment:** Dalteparin 100 mg/kg, 2 doses **Control treatment:** placebo	Reinfarction at 30 days RR=3.48 [0.78;15.59] Death at 30 days RR=0.58 [0.17;1.93]

Reference

Frostfeldt G, Ahlberg G, Gustafsson G, Helmius G, Lindahl B, Nygren A, Siegbahn A, Swahn E, Venge P, Wallentin L. Low molecular weight heparin (dalteparin) as adjuvant treatment of thrombolysis in acute myocardial infarction–a pilot study: biochemical markers in acute coronary syndromes (BIOMACS II). J Am Coll Cardiol 1999;33:627-33 [PMID=10080461]

Table 10.7: *FRAMI, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=776 (388 vs. 388) **Follow-up duration:** in hospital **Study design:** Randomized controlled trial Parallel groups Double-blind	Patients with an acute MI, Q wave or STEMI	**Studied treatment:** Dalteparin 150 mg/kg BID for 711 d **Control treatment:** placebo	Reinfarction RR=0.75 [0.26;2.14] In-hospital death RR=1.00 [0.57;1.75]

Reference

Kontny F, Dale J, Abildgaard U, Pedersen TR. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) Study. J Am Coll Cardiol 1997;30:962-9 [PMID=9316525]

Table 10.8: *ASSENT Plus, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=434 (221 vs. 213) **Follow-up duration:** 30 d **Study design:** Randomized controlled trial Parallel groups Open	Patients with AMI treated with alteplase	**Studied treatment:** Dalteparin first dose 90 IU/kg, then 120 IU/kg BID, 47 d **Control treatment:** UFH 40005000 IU bolus, then 8001000 IU/h for 48 h **Concomittant treat.:**tPA <=100 mg over 90 min	Reinfarction RR=0.26 [0.07;0.93] In-hospital death RR=0.60 [0.20;1.81] Reinfarction at 30 days RR=0.96 [0.47;1.97] Death at 30 days RR=0.79 [0.33;1.86]

Reference

Wallentin L, Bergstrand L, Dellborg M, Fellenius C, Granger CB, Lindahl B, Lins LE, Nilsson T, Pehrsson K, Siegbahn A, Swahn E. Low molecular weight heparin (dalteparin) compared to unfractionated heparin as an adjunct to rt-PA (alteplase) for improvement of coronary artery patency in acute myocardial infarction-the ASSENT Plus study. Eur Heart J 2003;24:897-908 [PMID=12714021]

11 Detailed results for Enoxaparin

11.1 Available trials

A total of 6 RCTs which randomized 7155 patients were identified: it compared Enoxaparin with placebo and 5 trials compared Enoxaparin with UFH.
The average study size was 1192 patients (range 242 to 4078). The first study was published in 2001, and the last study was published in 2003.
A total of 1 trials were double blind and 4 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Reinfarction data was reported in 6 trials; 6 trials reported data on death at 30 days; 6 trials reported data on in-hospital death; and 5 trials reported data on reinfarction at 30 days.
Following tables 11.1 (page 62), 11.2 (page 63), 11.4 (page 65), and 11.3 (page 63) summarized the main characteristics of the trials including in this systematic review of randomized trials of Enoxaparin.

Table 11.1: *Treatment description - Low molecular weight heparin - Enoxaparin*

Trial	Studied treatment	Control treatment
Enoxaparin versus placebo		
AMI-SK (2002) [1]	Enoxaparin 30 mg IV bolus, 1 mg/kg for 38 d	placebo
Enoxaparin versus UFH		
ASSENT 3 Plus (2003) [2]	Enoxaparin 1 mg/kg BID, <=7d	UFH 60 IU/kg, then 12 IU/kg per h for >=3d
	Concomittant treatment: TNK 3050 mg (weight adjusted)	
ASSENT 3 (2001) [3]	Enoxaparin 1 mg/kg BID, <=7d	UFH 60 U/kg bolus, then 12 IU/kg per h for 48 h
	Concomittant treatment: TNK 3050 mg (weight adjusted)	
Baird (2002) [4]	Enoxaparin 40 mg TID, 4 d	UFH 5000 IU bolus, then 30 000 IU over 24 h for 4d
	Concomittant treatment: SK 1.5 MU or APSAC 30 IU or tPA 100 mg	
ENTIRE-TIMI 2 (2002) [5]	Enoxaparin 1 mg/kg BID, <=8d	UFH 60 IU/kg, then 12 IU/kg per h for >=3d
	Concomittant treatment: TNK 0.53 mg/kg	
HART II (2001) [6]	Enoxaparin 1 mg/kg BID, <=3d	UFH 40005000 IU bolus, then 15 IU/kg per hour for >=3d
	Concomittant treatment: tPA weight adjusted over 90 min	

Table 11.2: *Descriptions of participants - Low molecular weight heparin - Enoxaparin*

Trial	Patients
Enoxaparin versus placebo	
AMI-SK (2002) [1]	Patients with evolving myocardial infarction, Age >=18 y, STEMI
Enoxaparin versus UFH	
ASSENT 3 Plus (2003) [2]	Patients with ST-elevation myocardial infarction
ASSENT 3 (2001) [3]	Patients with acute myocardial infarction
Baird (2002) [4]	Patients receiving fibrinolytic therapy following acute myocardial infarction
ENTIRE-TIMI 2 (2002) [5]	Patients with ST-elevation MI presenting <6 hours from symptom onset were
HART II (2001) [6]	Patients undergoing reperfusion therapy with an accelerated recombinant tissue plasminogen activator regimen and aspirin for AMI

Table 11.3: *Design and methodological quality of trials - Low molecular weight heparin - Enoxaparin*

Trial	Design	Duration	Centre	Primary endpoint
Enoxaparin versus placebo				
AMI-SK, 2002 [1] n=496	Parallel groups Double-blind	30 d		Angiographic TIMI flow in infarct-related vessel
Enoxaparin versus UFH				
ASSENT 3 Plus, 2003 [2] n=1639	Parallel groups open	30 d		Angiographic TIMI flow
ASSENT 3, 2001 [3] n=4078	Parallel groups open	30 d		In-hospital MI or RI
Baird, 2002 [4] n=300	Parallel groups 90-min TIMI flow	90 d		death, non-fatal reinfarction, or readmission with unstable angina

continued...

Trial	Design	Duration	Centre	Primary endpoint
ENTIRE-TIMI 2, 2002 [5] n=242	Parallel groups open	30 d		MI, death, readmit for UA
HART II, 2001 [6] n=400	Parallel groups open	57 d		infarct-related artery patency

Table 11.4: *Trial characteristics - Low molecular weight heparin - Enoxaparin*

Trial
Enoxaparin versus placebo
AMI-SK, 2002 [1]
Enoxaparin versus UFH
ASSENT 3 Plus, 2003 [2]
ASSENT 3, 2001 [3]
Baird, 2002 [4]
ENTIRE-TIMI 2, 2002 [5]
HART II, 2001 [6]

11.2 Meta-analysis results

The results are detailed in table 11.5 (page 66). This table is followed by the Forest's plot corresponding to each endpoint.

Enoxaparin versus placebo

The single study eligible for this comparison provided data on **reinfarction**. The analysis detected a statistically significant difference in favor of Enoxaparin in reinfarction, with a RR of 0.34 (95% CI 0.13 to 0.94, p=0.0371).
The single study eligible for this comparison provided data on **in-hospital death**. No statistically significant difference between the groups was found in in-hospital death, with a RR of 1.25 (95% CI 0.56 to 2.79, p=0.5890).
The single study eligible for this comparison provided data on **reinfarction at 30 days**. The analysis detected a statistically significant difference in favor of Enoxaparin in reinfarction at 30 days, with a RR of 0.32 (95% CI 0.13 to 0.79, p=0.0138).
The single study eligible for this comparison provided data on **death at 30 days**. No statistically significant difference between the groups was found in death at 30 days, with a RR of 0.96 (95% CI 0.50 to 1.84, p=0.9030).

Enoxaparin versus UFH

All the 5 studies had extractable data about the number of participants with **reinfarction**. The analysis detected a statistically significant difference in favor of Enoxaparin in reinfarction, with a RR of 0.61 (95% CI 0.48 to 0.78, p=0.0000). No heterogeneity was detected (p = 0.4161, I^2 = 0.00%).
All the 5 studies had extractable data about the number of participants with **in-hospital death**. When pooled together, there was no statistically significant difference between the groups in in-hospital death, with a RR of 0.95 (95% CI 0.72 to 1.24, p=0.6840). No heterogeneity was detected (p = 0.2916, I^2 = 0.19%).
A total of 4 of the 5 studies eligible for this comparison provided data on **reinfarction at 30 days**. The analysis detected a statistically significant difference in favor of Enoxaparin in reinfarction at 30 days, with a RR of 0.62 (95% CI 0.39 to 0.97, p=0.0381). No heterogeneity was detected (p = 0.1082, I^2 = 0.51%).
All the 5 studies had extractable data about the number of participants with **death at 30 days**. When pooled together, there was no statistically significant difference between the groups in death at 30 days, with a RR of 0.95 (95% CI 0.77 to 1.17, p=0.6429). No heterogeneity was detected (p = 0.3724, I^2 = 0.06%).

Table 11.5: *Results details - Low molecular weight heparin - Enoxaparin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Enoxaparin versus placebo						
reinfarction	RR=0.34	[0.13;0.94]	0.0371	1.0000 (I^2=0.00)	1	496
in-hospital death	RR=1.25	[0.56;2.79]	0.5890	1.0000 (I^2=0.00)	1	496
reinfarction at 30 days	RR=0.32	[0.13;0.79]	0.0138	1.0000 (I^2=0.00)	1	496
death at 30 days	RR=0.96	[0.50;1.84]	0.9030	1.0000 (I^2=0.00)	1	496
Enoxaparin versus UFH						

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
reinfarction	RR=0.61	[0.48;0.78]	0.0000	0.4161 (I^2=0.00)	5	6659
in-hospital death	RR=0.95	[0.72;1.24]	0.6840	0.2916 (I^2=0.19)	5	6659
reinfarction at 30 days	RR=0.62	[0.39;0.97]	0.0381	0.1082 (I^2=0.51)	4	5020
death at 30 days	RR=0.95	[0.77;1.17]	0.6429	0.3724 (I^2=0.06)	5	6659

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 reinfarction*

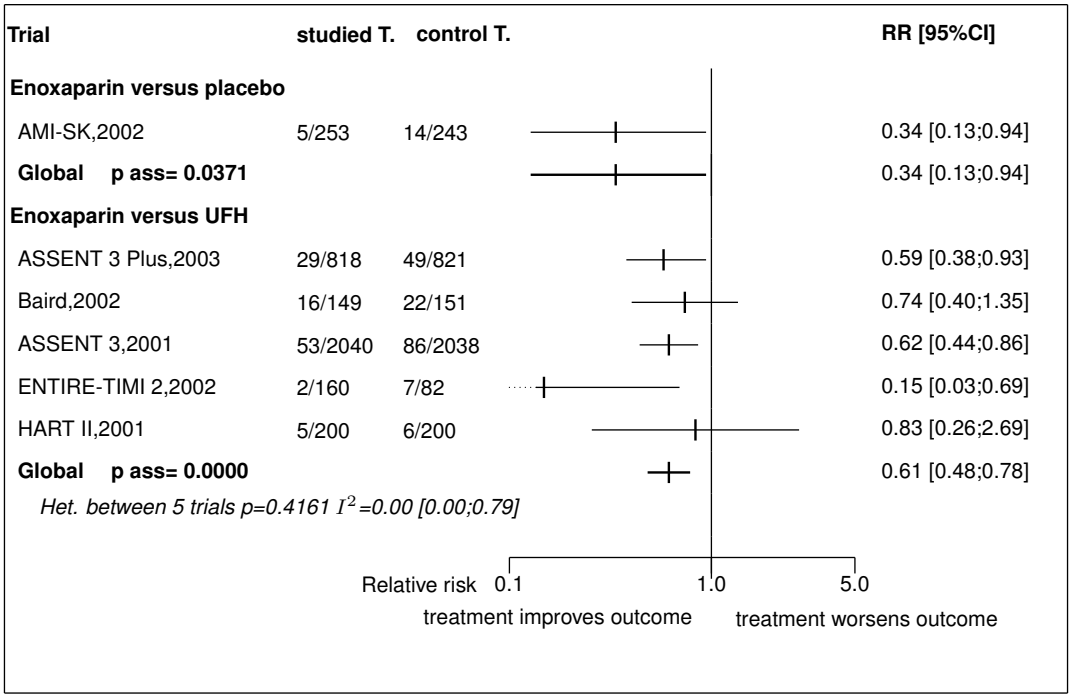


Figure 11.2: *Forest's plot for in-hospital death*

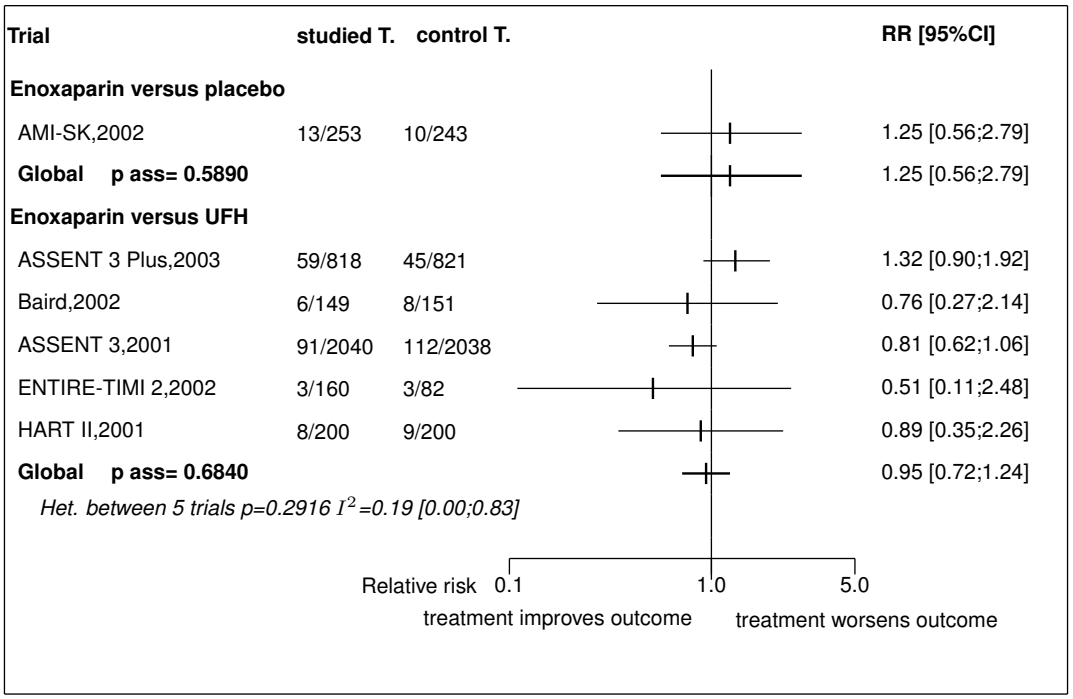


Figure 11.3: *Forest's plot for reinfarction at 30 days*

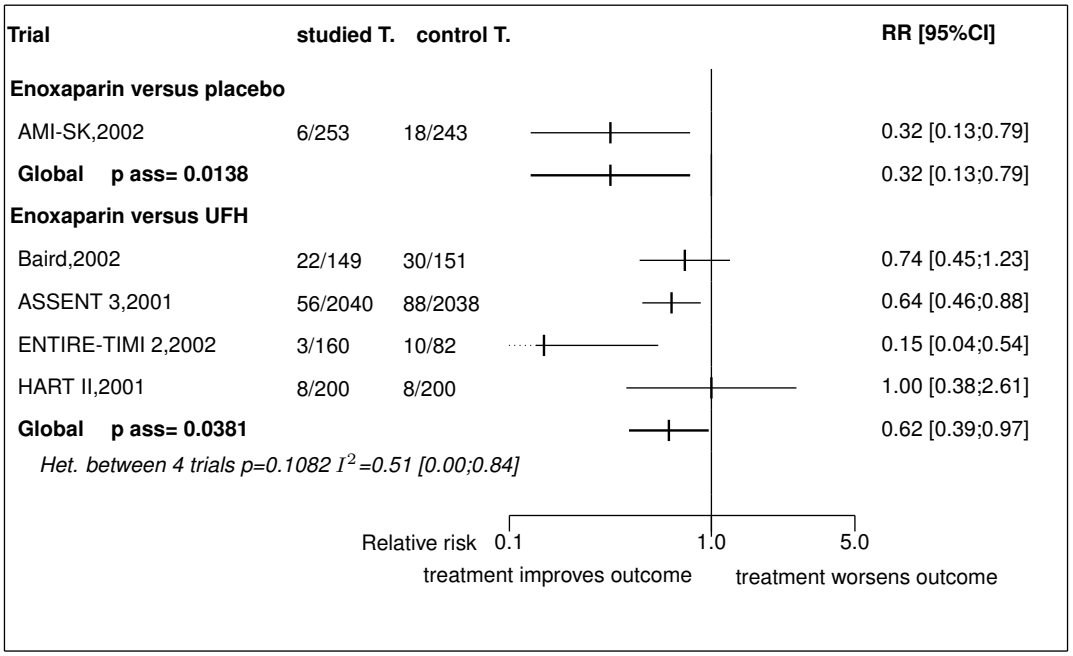
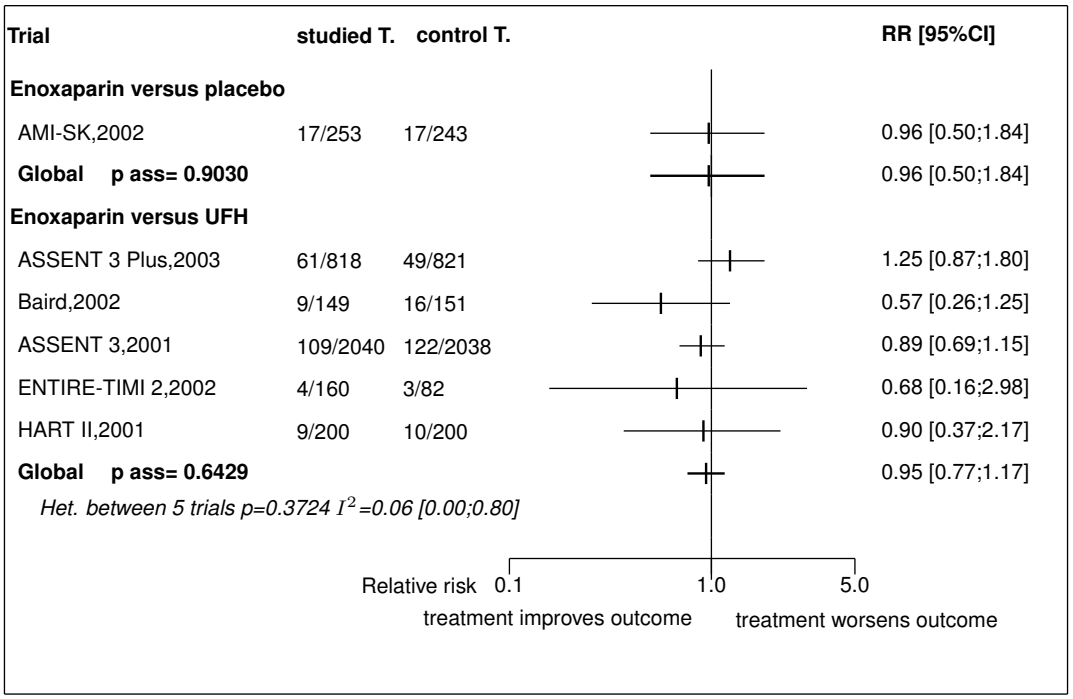


Figure 11.4: *Forest's plot for death at 30 days*



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[1] Simoons M, Krzemiska-Pakula M, Alonso A, Goodman S, Kali A, Loos U, Gosset F, Louer V, Bigonzi F. Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction. The AMI-SK study. Eur Heart J 2002;23:1282-90. [PMID=12175665]

[2] Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Mkijrvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003;108:135-42. [PMID=12847070]

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[4] Baird SH, Menown IB, Mcbride SJ, Trouton TG, Wilson C. Randomized comparison of enoxaparin with unfractionated heparin following fibrinolytic therapy for acute myocardial infarction. Eur Heart J 2002;23:627-32. [PMID=11969277]

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11.3 Individual trial summaries

Table 11.6: *AMI-SK, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=496 (253 vs. 243) **Follow-up duration:** 30 d **Study design:** Randomized controlled trial Parallel groups Double-blind	Patients with evolving myocardial infarction, Age >=18 y, STEMI	**Studied treatment:** Enoxaparin 30 mg IV bolus, 1 mg/kg for 38 d **Control treatment:** placebo	Reinfarction RR=0.34 [0.13;0.94] In-hospital death RR=1.25 [0.56;2.79] Reinfarction at 30 days RR=0.32 [0.13;0.79] Death at 30 days RR=0.96 [0.50;1.84]

Reference

Simoons M, Krzemiska-Pakula M, Alonso A, Goodman S, Kali A, Loos U, Gosset F, Louer V, Bigonzi F. Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction. The AMI-SK study. Eur Heart J 2002;23:1282-90 [PMID=12175665]

Table 11.7: *ASSENT 3 Plus, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1639 (818 vs. 821) **Follow-up duration:** 30 d **Study design:** Randomized controlled trial Parallel groups Open	Patients with ST-elevation myocardial infarction	**Studied treatment:** Enoxaparin 1 mg/kg BID, <=7d **Control treatment:** UFH 60 IU/kg, then 12 IU/kg per h for >=3d **Concomittant treat.:**TNK 3050 mg (weight adjusted)	Reinfarction RR=0.59 [0.38;0.93] In-hospital death RR=1.32 [0.90;1.92] Death at 30 days RR=1.25 [0.87;1.80]

Reference

Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Mk-ijrvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003;108:135-42 [PMID=12847070]

Table 11.8: *ASSENT 3, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4078 (2040 vs. 2038) **Follow-up duration:** 30 d **Study design:** Randomized controlled trial Parallel groups Open	Patients with acute myocardial infarction	**Studied treatment:** Enoxaparin 1 mg/kg BID, <=7d **Control treatment:** UFH 60 U/kg bolus, then 12 IU/kg per h for 48 h **Concomittant treat.:**TNK 3050 mg (weight adjusted)	Reinfarction RR=0.62 [0.44;0.86] In-hospital death RR=0.81 [0.62;1.06] Reinfarction at 30 days RR=0.64 [0.46;0.88] Death at 30 days RR=0.89 [0.69;1.15]

Reference

. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:605-13 [PMID=11530146]

Table 11.9: *Baird, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=300 (149 vs. 151) **Follow-up duration:** 90 d **Study design:** Randomized controlled trial Parallel groups 90-min TIMI flow	Patients receiving fibrinolytic therapy following acute myocardial infarction	**Studied treatment:** Enoxaparin 40 mg TID, 4 d **Control treatment:** UFH 5000 IU bolus, then 30 000 IU over 24 h for 4d **Concomittant treat.:**SK 1.5 MU or APSAC 30 IU or tPA 100 mg	Reinfarction RR=0.74 [0.40;1.35] In-hospital death RR=0.76 [0.27;2.14] Reinfarction at 30 days RR=0.74 [0.45;1.23] Death at 30 days RR=0.57 [0.26;1.25]

Reference

Baird SH, Menown IB, Mcbride SJ, Trouton TG, Wilson C. Randomized comparison of enoxaparin with unfractionated heparin following fibrinolytic therapy for acute myocardial infarction. Eur Heart J 2002;23:627-32 [PMID=11969277]

Table 11.10: *ENTIRE-TIMI 2, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=242 (160 vs. 82) **Follow-up duration:** 30 d **Study design:** Randomized controlled trial Parallel groups Open	Patients with ST-elevation MI presenting <6 hours from symptom onset were	**Studied treatment:** Enoxaparin 1 mg/kg BID, <=8d **Control treatment:** UFH 60 IU/kg, then 12 IU/kg per h for >=3d **Concomittant treat.:**TNK 0.53 mg/kg	Reinfarction RR=0.15 [0.03;0.69] In-hospital death RR=0.51 [0.11;2.48] Reinfarction at 30 days RR=0.15 [0.04;0.54] Death at 30 days RR=0.68 [0.16;2.98]

Reference

Antman EM, Louwerenburg HW, Baars HF, Wesdorp JC, Hamer B, Bassand JP, Bigonzi F, Pisapia G, Gibson CM, Heidbuchel H, Braunwald E, Van de Werf F. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. Circulation 2002;105:1642-9 [PMID=11940541]

Table 11.11: *HART II, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=400 (200 vs. 200) **Follow-up duration:** 57 d **Study design:** Randomized controlled trial Parallel groups Open	Patients undergoing reperfusion therapy with an accelerated recombinant tissue plasminogen activator regimen and aspirin for AMI	**Studied treatment:** Enoxaparin 1 mg/kg BID, <=3d **Control treatment:** UFH 40005000 IU bolus, then 15 IU/kg per hour for >=3d **Concomittant treat.:**tPA weight adjusted over 90 min	Reinfarction RR=0.83 [0.26;2.69] In-hospital death RR=0.89 [0.35;2.26] Reinfarction at 30 days RR=1.00 [0.38;2.61] Death at 30 days RR=0.90 [0.37;2.17]

Reference

Ross AM, Molhoek P, Lundergan C, Knudtson M, Draoui Y, Regalado L, Le Louer V, Bigonzi F, Schwartz W, de Jong E, Coyne K. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). Circulation 2001;104:648-52 [PMID=11489769]

12 Detailed results for Reviparin

12.1 Available trials

Only one trial which randomized 15570 patients was identified: it compared Reviparin with placebo.
This trial included 15570 patients and was published in 2005.
This trial was double blind in design.
It was reported in English language.
Reinfarction at 30 days data was reported in 1 trials; 1 trials reported data on reinfarction; 1 trials reported data on death at 30 days; and 1 trials reported data on in-hospital death.
Following tables 12.1 (page 78), 12.2 (page 78), 12.4 (page 80), and 12.3 (page 78) summarized the main characteristics of the trial including in this systematic review of randomized trials of Reviparin.

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

Trial	Studied treatment	Control treatment
Reviparin versus placebo		
CREATE (2005) [1]	Reviparin 34366871 IU BID for 7 d (weight adjusted)	placebo

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

Trial	Patients
Reviparin versus placebo	
CREATE (2005) [1]	Patients with acute myocardial infarction, STEMI or new LBBB, <=12 h

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

Trial	Design	Duration	Centre	Primary endpoint
Reviparin versus placebo				
CREATE, 2005 [1] n=15570	Parallel groups Double-blind	30 d		Death, MI, or stroke; death, MI, stroke, or recurrent ischemia

continued...

Trial	Design	Duration	Centre	Primary endpoint

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

Trial
Reviparin versus placebo
CREATE, 2005 [1]

12.2 Meta-analysis results

The results are detailed in table 12.5 (page 81). This table is followed by the Forest's plot corresponding to each endpoint.

Reviparin versus placebo

The single study eligible for this comparison provided data on **reinfarction**. The analysis detected a statistically significant difference in favor of Reviparin in reinfarction, with a RR of 0.76 (95% CI 0.60 to 0.96, p=0.0207).
The single study eligible for this comparison provided data on **in-hospital death**. The analysis detected a statistically significant difference in favor of Reviparin in in-hospital death, with a RR of 0.89 (95% CI 0.81 to 0.99, p=0.0354).
The single study eligible for this comparison provided data on **reinfarction at 30 days**. The analysis detected a statistically significant difference in favor of Reviparin in reinfarction at 30 days, with a RR of 0.77 (95% CI 0.63 to 0.95, p=0.0162).
The single study eligible for this comparison provided data on **death at 30 days**. The analysis detected a statistically significant difference in favor of Reviparin in death at 30 days, with a RR of 0.87 (95% CI 0.80 to 0.96, p=0.0042).

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Reviparin versus placebo						
reinfarction	RR=0.76	[0.60;0.96]	0.0207	1.0000 (I^2=0.00)	1	15570
in-hospital death	RR=0.89	[0.81;0.99]	0.0354	1.0000 (I^2=0.00)	1	15570
reinfarction at 30 days	RR=0.77	[0.63;0.95]	0.0162	1.0000 (I^2=0.00)	1	15570
death at 30 days	RR=0.87	[0.80;0.96]	0.0042	1.0000 (I^2=0.00)	1	15570

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 reinfarction*

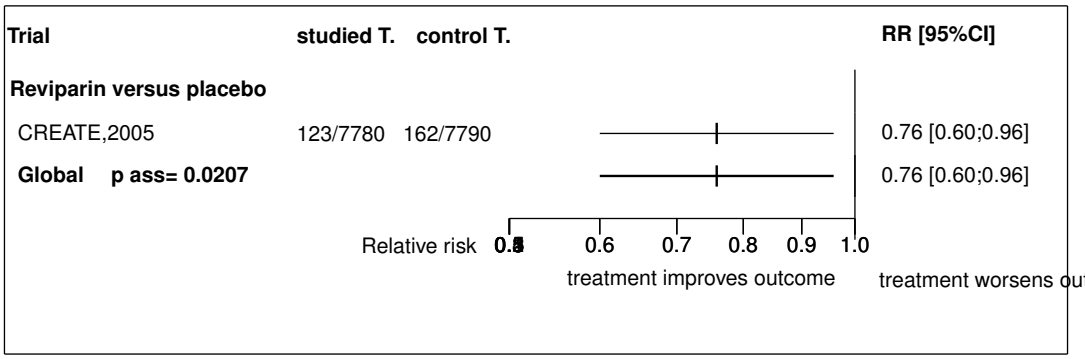


Figure 12.2: *Forest's plot for in-hospital death*

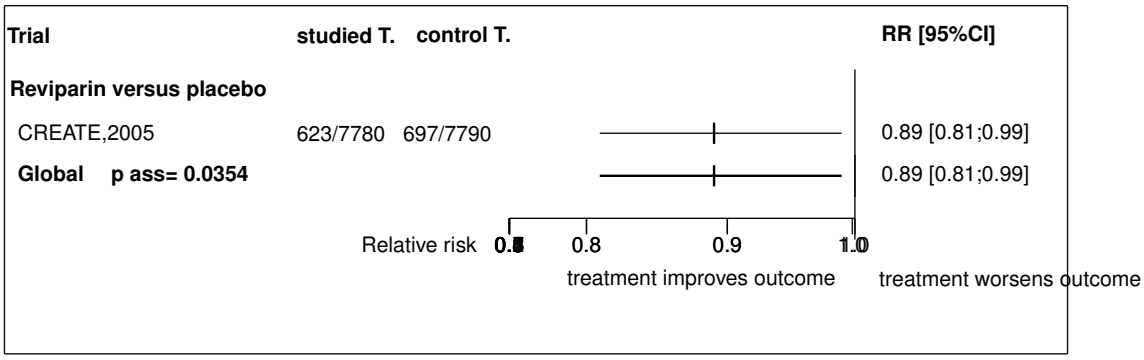


Figure 12.3: *Forest's plot for reinfarction at 30 days*

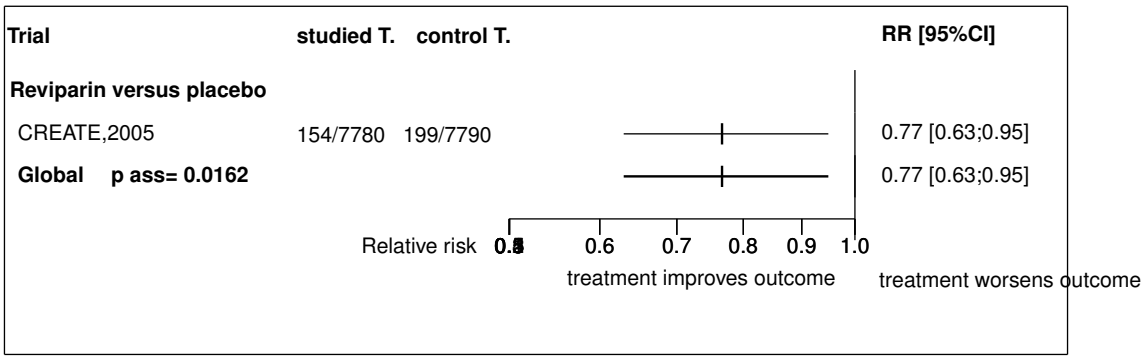
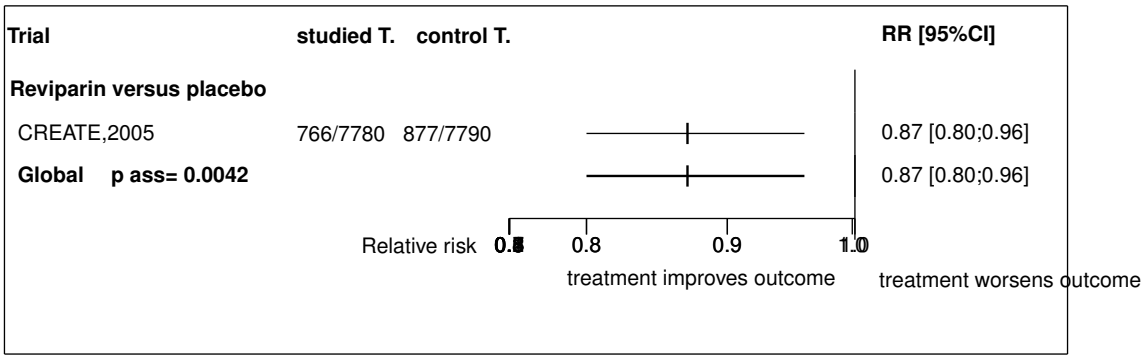


Figure 12.4: *Forest's plot for death at 30 days*



References

[1] Yusuf S, Mehta SR, Xie C, Ahmed RJ, Xavier D, Pais P, Zhu J, Liu L. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. JAMA 2005;293:427-35. [PMID=15671427]

12.3 Individual trial summaries

Table 12.6: *CREATE, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=15570 (7780 vs. 7790) **Follow-up duration:** 30 d **Study design:** Randomized controlled trial Parallel groups Double-blind	Patients with acute myocardial infarction, STEMI or new LBBB, <=12 h	**Studied treatment:** Reviparin 34366871 IU BID for 7 d (weight adjusted) **Control treatment:** placebo	Reinfarction RR=0.76 [0.60;0.96] In-hospital death RR=0.89 [0.81;0.99] Reinfarction at 30 days RR=0.77 [0.63;0.95] Death at 30 days RR=0.87 [0.80;0.96]

Reference

Yusuf S, Mehta SR, Xie C, Ahmed RJ, Xavier D, Pais P, Zhu J, Liu L. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. JAMA 2005;293:427-35 [PMID=15671427]

13 Global meta-analysis: all Low molecular weight heparin

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

Table 13.1: *All Low molecular weight heparinversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
reinfarction	RR=0.70	0.50;0.98	0.0352	0.3190 (0.12)	3	16842
in-hospital death	RR=0.90	0.82;1.00	0.0472	0.6778 (0.00)	3	16842
reinfarction at 30 days	RR=0.80 [1]	0.32;1.98	0.6240	0.0238 (0.73) †	3	16167
death at 30 days	RR=0.87	0.80;0.96	0.0036	0.7685 (0.00)	3	16167

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

13.2 Global meta-analysis: all Low molecular weight heparin versus UFH

Table 13.2: *All Low molecular weight heparinversus UFH*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
reinfarction	RR=0.59	0.45;0.77	0.0000	0.3473 (0.11)	6	7093
in-hospital death	RR=0.92	0.73;1.17	0.5173	0.3527 (0.10)	6	7093
reinfarction at 30 days	RR=0.68	0.46;0.99	0.0440	0.1289 (0.44)	5	5454
death at 30 days	RR=0.94	0.78;1.14	0.5392	0.4893 (0.00)	6	7093

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

14 Ongoing studies of Low molecular weight heparin

No ongoing trial was identified.

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.76 95% CI 0.62;0.93

15 Excluded studies for Low molecular weight heparin

No trial was excluded.

References

Part III

Oral anticoagulant

16 Overview of oral anticoagulant

16.1 Included trials

A total of 17 randomized comparisons which enrolled 44661 patients were identified. In all, 2 randomized comparisons concerned any anticoagulant , 3 coumadin , two phenprocoumon and 10 warfarin.
The detailed descriptions of trials and meta-analysis results is given in section 17 (page 105) for any anticoagulant, in section 18 (page 113) for coumadin, in section 19 (page 127) for phenprocoumon and in section 20 (page 136) for warfarin.

The average study size was 2791 patients (range 11 to 9596). The first study was published in 1980, and the last study was published in 2004.
A total of 8 trials were double blind and 8 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 16.1 (page 93) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

16.2 Summary of meta-analysis results

The meta-analysis of the available trials about oral anticoagulant provide the results listed in tables 16.2 to 16.5 (page 96) and in the following graphs.

16.2.1 Any anticoagulant

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

No significant difference was found between **any anticoagulant** and **aspirin** in terms of myocardial infarction (fatal and non fatal) (RR=1.65, 95% CI 0.96 to 2.84, p=0.0724, 1 trial)and all cause death (RR=0.90, 95% CI 0.66 to 1.24, p=0.5213, 1 trial).

16.2.2 Coumadin

No significant difference was found between **coumadin** and **control (on top of aspirin)** in terms of myocardial infarction (fatal and non fatal) (RR=0.69, 95% CI 0.31 to 1.53, p=0.3655, 1 trial), ischemic stroke (RR=0.10, 95% CI 0.01 to 1.77, p=0.1151, 1 trial), revascularization (RR=0.80, 95% CI 0.51 to 1.23, p=0.3072, 1 trial), all cause death (RR=0.58, 95% CI 0.26 to 1.31, p=0.1903, 1 trial)and major bleeding (RR=2.26, 95% CI 0.59 to 8.67, p=0.2333, 1 trial). Coumadin appear to be associated with significantly greater risk of minor bleeding (RR=3.03, 95% CI 1.77 to 5.20, p=0.0000, 1 trial).

Coumadin was superior to **placebo** in terms of myocardial infarction (fatal and non fatal) (RR=0.47, 95% CI 0.38 to 0.58, p=0.0000, 1 trial)and ischemic stroke (RR=0.60, 95% CI 0.40 to 0.89, p=0.0121, 1 trial). But coumadin increased the risk of major bleeding (RR=3.85, 95% CI 2.34 to 6.35, p=0.0000, 1 trial). However, no significant difference was found on all cause death (RR=0.90, 95% CI 0.74 to 1.10, p=0.3002, 1 trial).

Coumadin was superior to **aspirin** in terms of all cause death (RR=0.28, 95% CI 0.09 to 0.82, p=0.0208, 1 trial). However, no significant difference was found on all cause death, MI,

thrombo-embolic stroke (RR=0.57, 95% CI 0.32 to 1.00, p=0.0516, 1 trial), myocardial infarction (fatal and non fatal) (RR=0.96, 95% CI 0.46 to 2.01, p=0.9138, 1 trial), revascularization (RR=0.90, 95% CI 0.58 to 1.39, p=0.6388, 1 trial), intracranial hemorrhage (RR=1.03, 95% CI 0.02 to 51.95, p=0.9867, 1 trial)and major bleeding (RR=1.03, 95% CI 0.21 to 5.09, p=0.9673, 1 trial).

16.2.3 Phenprocoumon

No significant difference was found between **phenprocoumon** and **placebo** in terms of coronary event (RR=0.81, 95% CI 0.52 to 1.27, p=0.3619, 1 trial), coronary death (RR=1.11, 95% CI 0.64 to 1.92, p=0.7081, 1 trial)and all cause death (RR=1.14, 95% CI 0.74 to 1.78, p=0.5481, 1 trial).

Phenprocoumon was inferior to **aspirin** in terms of coronary death (RR=1.98, 95% CI 1.04 to 3.79, p=0.0385, 1 trial). No significant difference was found on coronary event (RR=1.32, 95% CI 0.80 to 2.19, p=0.2811, 1 trial)and all cause death (RR=1.43, 95% CI 0.90 to 2.28, p=0.1314, 1 trial).

16.2.4 Warfarin

Warfarin was superior to **control (on top of aspirin)** in terms of all cause death, MI, thrombo-embolic stroke (RR=0.71, 95% CI 0.59 to 0.86, p=0.0000, 1 trial)and stroke (fatal and non fatal) (RR=0.67, 95% CI 0.50 to 0.88, p=0.0041, 1 trial). But warfarin increased the risk of major bleeding (RR=1.68, 95% CI 1.28 to 2.21, p=0.0000, 7 trials). However, no significant difference was found on myocardial infarction (fatal and non fatal) (RR=0.81, 95% CI 0.61 to 1.08, p=0.1543, 5 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0009)(RR=0.90, 95% CI 0.61 to 1.32, p=0.5825, 6 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0059)(RR=0.56, 95% CI 0.21 to 1.51, p=0.2529, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0000)(RR=0.95, 95% CI 0.86 to 1.05, p=0.3235, 7 trials)and intracranial hemorrhage (RR=1.26, 95% CI 0.70 to 2.25, p=0.4395, 3 trials). Warfarin appear to be associated with significantly greater risk of minor bleeding (RR=3.34, 95% CI 2.29 to 4.88, p=0.0000, 5 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0160)

No significant difference was found between **warfarin** and **placebo (on top of aspirin)** in terms of myocardial infarction (fatal and non fatal) (RR=0.19, 95% CI 0.03 to 1.13, p=0.0683, 1 trial), ischemic stroke (RR=0.83, 95% CI 0.02 to 34.94, p=0.9238, 1 trial), revascularization (RR=1.11, 95% CI 0.45 to 2.77, p=0.8209, 1 trial), all cause death (RR=0.42, 95% CI 0.02 to 10.03, p=0.5895, 1 trial)and major bleeding (RR=1.67, 95% CI 0.07 to 40.10, p=0.7529, 1 trial).

Warfarin was superior to **aspirin** in terms of all cause death, MI, thrombo-embolic stroke (RR=0.81, 95% CI 0.69 to 0.95, p=0.0098, 1 trial)and ischemic stroke (RR=0.53, 95% CI 0.29 to 0.94, p=0.0312, 1 trial). But warfarin increased the risk of major bleeding (RR=4.09, 95% CI 1.90 to 8.82, p=0.0000, 1 trial). However, no significant difference was found on all cause death (RR=1.03, 95% CI 0.79 to 1.36, p=0.8066, 1 trial)and intracranial hemorrhage (RR=4.96, 95% CI 0.58 to 42.38, p=0.1436, 1 trial). Warfarin appear to be associated with significantly greater risk of minor bleeding (RR=2.62, 95% CI 1.83 to 3.75, p=0.0000, 1 trial).

Table 16.1: *Main study characteristics - oral anticoagulant*

Trial	Patients	Treatments	Trial design and method
Any anticoagulant			
Any anticoagulant versus placebo			
Sixty Plus reinfarction Study, 1980 [1] n = NA vs. NA	over 60 years of age	anticoagulant **versus** placebo	double blind parallel groups
Any anticoagulant versus aspirin			
EPSIM, 1982 [2] n = 652 vs. 651	patients surviving myocardial infarction	anticoagulant **versus** aspirin 500mg three times daily	open parallel groups
Coumadin			
Coumadin versus control (on top of aspirin)			
ASPECT-2 (coumadin+ASA vs ASA), 2002 [1] n = 298 vs. 289	acute MI, unstable angina	coumadin(INR mean 2.4) +aspirin **versus** aspirin	open parallel groups Primary endpoint: death, MI or stroke 53 centres, the Netherlands
Coumadin versus placebo			
ASPECT, 1994 [2] n = 1700 vs. 1704	hospital survivors of myocardial infarction	nicoumalone or phenprocoumon, target INR 2.84.8 **versus** placebo	double blind parallel groups multicentre,
Coumadin versus aspirin			
ASPECT-2 (coumadin alone), 2002 [3] n = 325 vs. 336	acute MI, unstable angina	coumadin (phenprocoumon or acenocoumarol) target INR 3-4 **versus** aspirin 80mg daily	open parallel groups Primary endpoint: death, MI or stroke 53 centres, the Netherlands

continued...

Trial	Patients	Treatments	Trial design and method
Phenprocoumon			
Phenprocoumon versus placebo			
German-Austrian Study Group (oac vs pbo), 1980 [1] n = 320 vs. 309	patients who had survived a myocardial infarction for 30-42 days	phenprocoumon **versus** placebo	double blind parallel groups
Phenprocoumon versus aspirin			
German-Austrian Study Group (oac vs asp), 1980 [2] n = 320 vs. 317	patients who had survived a myocardial infarction for 30-42 days	phenprocoumon **versus** aspirin 1.5 g daily	double blind parallel groups
Warfarin			
Warfarin versus control (on top of aspirin)			
WARIS, 1999 [1] n = 1208 vs. 1206	survivors of acute myocardial infarction	warfarin 2.84.8 **versus** placebo	double blind parallel groups
APRICOT-2, 2002 [2] n = 135 vs. 139	acute MI after thrombolytics	moderate-intensity coumarin target INR 2-3 (+aspirin) **versus** aspirin	open parallel groups Primary endpoint: reocclusion of the infarct-related artery 7 centres, the Netherlands
CARS (warafrin 3mg), 1997 [3] n = 5410 vs. 3393	AMI	warfarin fixed dose 3mg/d + 80 mg ASA **versus** aspirin 160 mg/d	double blind parallel groups Primary endpoint: reinfarction, non-fatal ischaemic stroke, or cardiovascular death 293 centres, North America
CARS (warfarin 1mg), 1997 [4] n = 2028 vs. 3393	patients who had had myocardial infarction	warfarin 1mg/d + aspirin 80mg/d **versus** aspirin 160 mg/d	double blind parallel groups Primary endpoint: reinfarction, non-fatal ischaemic stroke, or cardiovascular death 293 centres, North America

continued...

Trial	Patients	Treatments	Trial design and method
CHAMP, 2002 [5] n = 2522 vs. 2537	AMI (patients enrolled within 14 days of infarction)	warfarin target INR 1.5-2.5 + aspirin 81 mg daily **versus** aspirin 162 mg/d	open parallel groups Primary endpoint: all cause mortality 78 centres, US
LoWASA, 2004 [6] n = 1659 vs. 1641	AMI	warfarin fixed dose 1.25mg/d + ASA 75mg/d **versus** aspirin alone	open parallel groups Primary endpoint: cardiovascular event and CV death 31 centres, Sweden
WARIS II (warfarin+ASA), 2002 [7] n = 4927 vs. 4669	patients hospitalized for acute myocardialinfarction	warfarin target INR 2-2.5 +ASA 75mg/d **versus** ASA 160mg/d	open parallel groups Primary endpoint: death, MI, ischaemic stroke 20 centres, Norway
Zibaeenezhad, 2004 [8] n = 70 vs. 70	acute MI	warfarin target INR 23 +aspirin **versus** aspirin 100 mg/day	open parallel groups
Warfarin versus placebo (on top of aspirin)			
Williams, 1997 [9] n = 6 vs. 5	acute MI, unstable angina	warfarin target INR 22.5 +aspirin **versus** placebo +aspirin	double blind parallel groups Primary endpoint: quantitative angiography
Warfarin versus aspirin			
WARIS II (warfarin alone), 2002 [10] n = 1216 vs. 1206	patients hospitalized for acute myocardialinfarction	warfarin target INR 2.8-4.2 **versus** ASA 160mg/d	NA parallel groups Primary endpoint: death, MI, ischaemic stroke 20 centres, Norway

Table 16.2: *Summary of all results for any anticoagulant*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
any anticoagulant versus placebo						
No data were presented in the trial identified						
any anticoagulant versus aspirin						
myocardial infarction (fatal and non fatal)	RR=1.65	0.96;2.84	0.0724	1.0000 (1.00)	1	1303
all cause death	RR=0.90	0.66;1.24	0.5213	1.0000 (0.00)	1	1303

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 16.3: *Summary of all results for coumadin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
coumadin versus control (on top of aspirin)						
myocardial infarction (fatal and non fatal)	RR=0.69	0.31;1.53	0.3655	1.0000 (1.00)	1	587
ischemic stroke	RR=0.10	0.01;1.77	0.1151	1.0000 (0.00)	1	587
revascularization	RR=0.80	0.51;1.23	0.3072	1.0000 (0.00)	1	587
all cause death	RR=0.58	0.26;1.31	0.1903	1.0000 (0.00)	1	587
minor bleeding	RR=3.03	1.77;5.20	0.0000	1.0000 (0.00)	1	587
major bleeding	RR=2.26	0.59;8.67	0.2333	1.0000 (0.00)	1	587
coumadin versus placebo						
myocardial infarction (fatal and non fatal)	RR=0.47	0.38;0.58	0.0000	1.0000 (0.00)	1	3404
ischemic stroke	RR=0.60	0.40;0.89	0.0121	1.0000 (0.00)	1	3404
all cause death	RR=0.90	0.74;1.10	0.3002	1.0000 (0.00)	1	3404
major bleeding	RR=3.85	2.34;6.35	0.0000	1.0000 (0.00)	1	3404
coumadin versus aspirin						
all cause death, MI, thrombo-embolic stroke	RR=0.57	0.32;1.00	0.0516	1.0000 (0.00)	1	661
myocardial infarction (fatal and non fatal)	RR=0.96	0.46;2.01	0.9138	1.0000 (0.00)	1	661
revascularization	RR=0.90	0.58;1.39	0.6388	1.0000 (0.00)	1	661
all cause death	RR=0.28	0.09;0.82	0.0208	1.0000 (0.00)	1	661
minor bleeding	RR=1.68	0.92;3.07	0.0922	1.0000 (0.00)	1	661

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
intracranial hemorrhage	RR=1.03	0.02;51.95	0.9867	1.0000 (0.00)	1	661
major bleeding	RR=1.03	0.21;5.09	0.9673	1.0000 (0.00)	1	661

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 16.4: *Summary of all results for phenprocoumon*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
phenprocoumon versus placebo						
coronary event	RR=0.81	0.52;1.27	0.3619	1.0000 (0.00)	1	638
coronary death	RR=1.11	0.64;1.92	0.7081	1.0000 (0.00)	1	638
all cause death	RR=1.14	0.74;1.78	0.5481	1.0000 (0.00)	1	638
phenprocoumon versus aspirin						
coronary event	RR=1.32	0.80;2.19	0.2811	1.0000 (0.00)	1	637
coronary death	RR=1.98	1.04;3.79	0.0385	1.0000 (0.00)	1	637
all cause death	RR=1.43	0.90;2.28	0.1314	1.0000 (1.00)	1	637

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 16.5: *Summary of all results for warfarin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
warfarin versus control (on top of aspirin)						
all cause death, MI, thrombo-embolic stroke	RR=0.71	0.59;0.86	0.0000	1.0000 (0.00)	1	9596
myocardial infarction (fatal and non fatal)	RR=0.81 [1]	0.61;1.08	0.1543	0.0009 (0.79) †	5	18369
stroke (fatal and non fatal)	RR=0.67	0.50;0.88	0.0041	1.0000 (0.00)	1	3300
ischemic stroke	RR=0.90 [2]	0.61;1.32	0.5825	0.0059 (0.69) †	6	32319
revascularization	RR=0.56 [3]	0.21;1.51	0.2529	0.0000 (0.92) †	2	9870
all cause death	RR=0.95	0.86;1.05	0.3235	0.2712 (0.21)	7	32593
minor bleeding	RR=3.34 [4]	2.29;4.88	0.0000	0.0160 (0.67) †	5	18369
intracranial hemorrhage	RR=1.26	0.70;2.25	0.4395	0.4049 (0.00)	3	17955

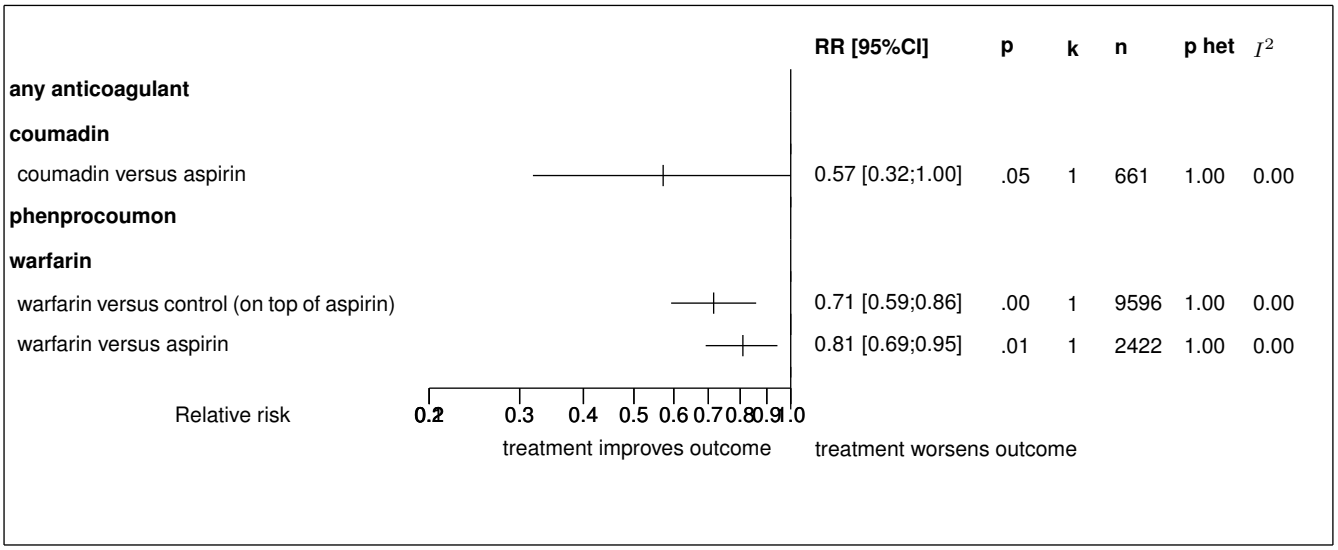
continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.95 95% CI 0.86;1.05
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.86 95% CI 0.71;1.03
[3] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.85 95% CI 0.76;0.97
[4] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=3.54 95% CI 2.99;4.21

Endpoint	Effect	95% CI	p ass	p het	k	n
major bleeding	RR=1.68	1.28;2.21	0.0000	0.2224 (0.27)	7	32593
warfarin versus placebo (on top of aspirin)						
myocardial infarction (fatal and non fatal)	RR=0.19	0.03;1.13	0.0683	1.0000 (0.00)	1	11
ischemic stroke	RR=0.83	0.02;34.94	0.9238	1.0000 (0.00)	1	11
revascularization	RR=1.11	0.45;2.77	0.8209	1.0000 (0.00)	1	11
all cause death	RR=0.42	0.02;10.03	0.5895	1.0000 (0.00)	1	11
minor bleeding	RR=3.33	0.19;58.37	0.4098	1.0000 (0.00)	1	11
major bleeding	RR=1.67	0.07;40.10	0.7529	1.0000 (0.00)	1	11
warfarin versus aspirin						
all cause death, MI, thrombo-embolic stroke	RR=0.81	0.69;0.95	0.0098	1.0000 (0.00)	1	2422
ischemic stroke	RR=0.53	0.29;0.94	0.0312	1.0000 (0.00)	1	2422
all cause death	RR=1.03	0.79;1.36	0.8066	1.0000 (0.00)	1	2422
minor bleeding	RR=2.62	1.83;3.75	0.0000	1.0000 (0.00)	1	2422
intracranial hemorrhage	RR=4.96	0.58;42.38	0.1436	1.0000 (0.00)	1	2422
major bleeding	RR=4.09	1.90;8.82	0.0000	1.0000 (0.00)	1	2422

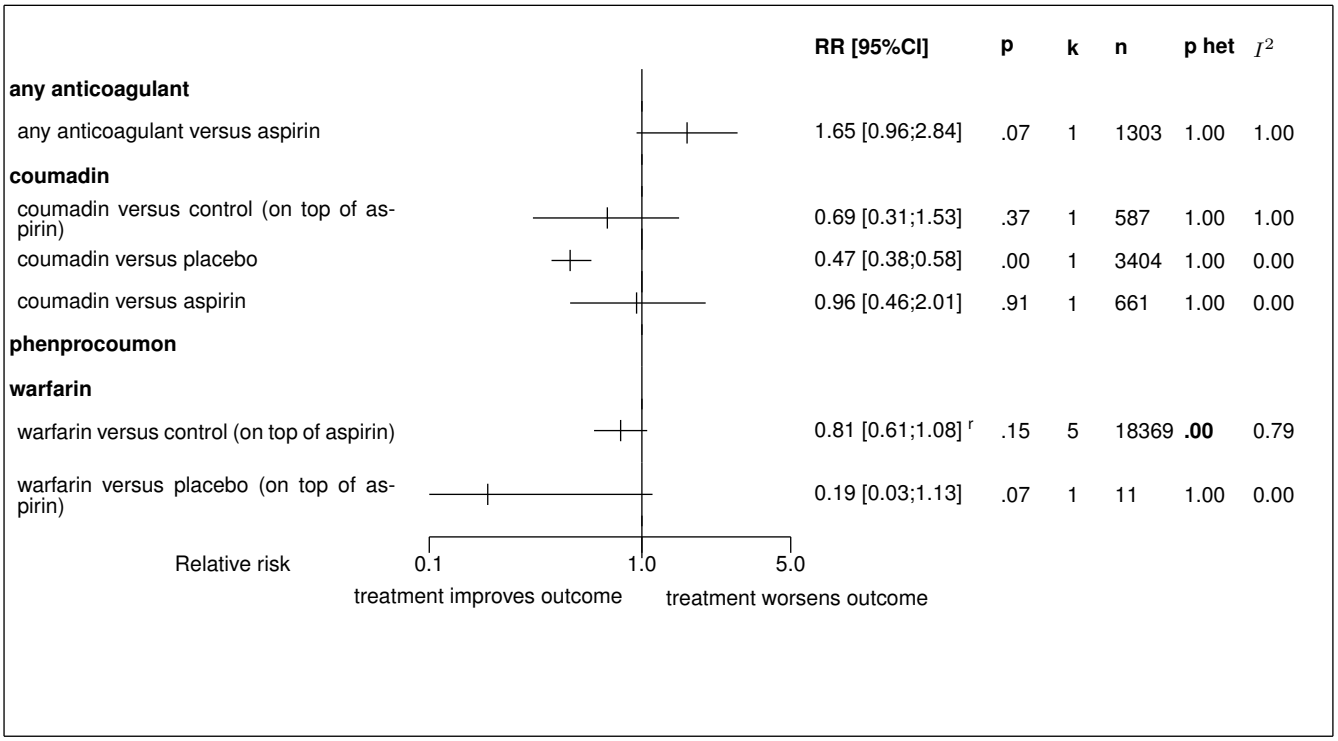
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 16.1: *Forest's plot for all cause death, MI, thrombo-embolic stroke*



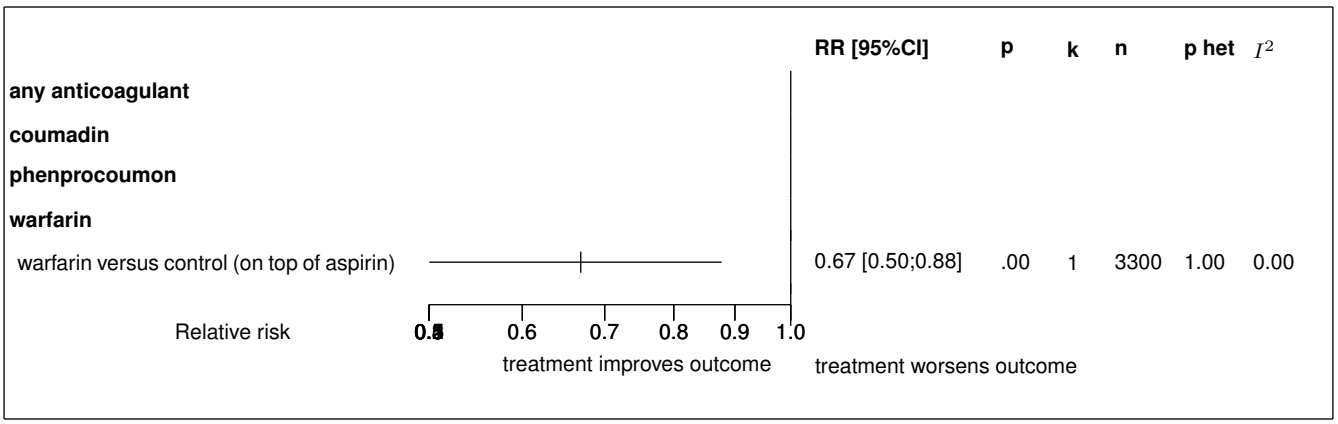
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.2: *Forest's plot for myocardial infarction (fatal and non fatal)*



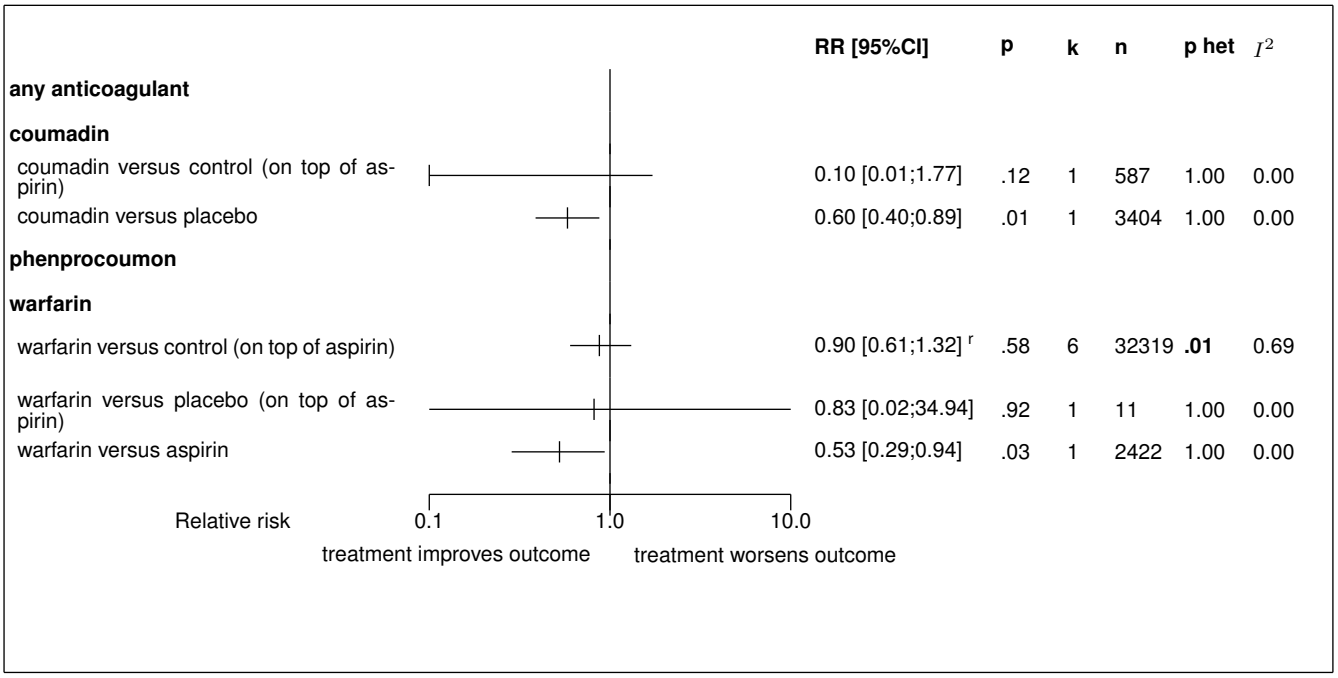
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.3: *Forest's plot for stroke (fatal and non fatal)*



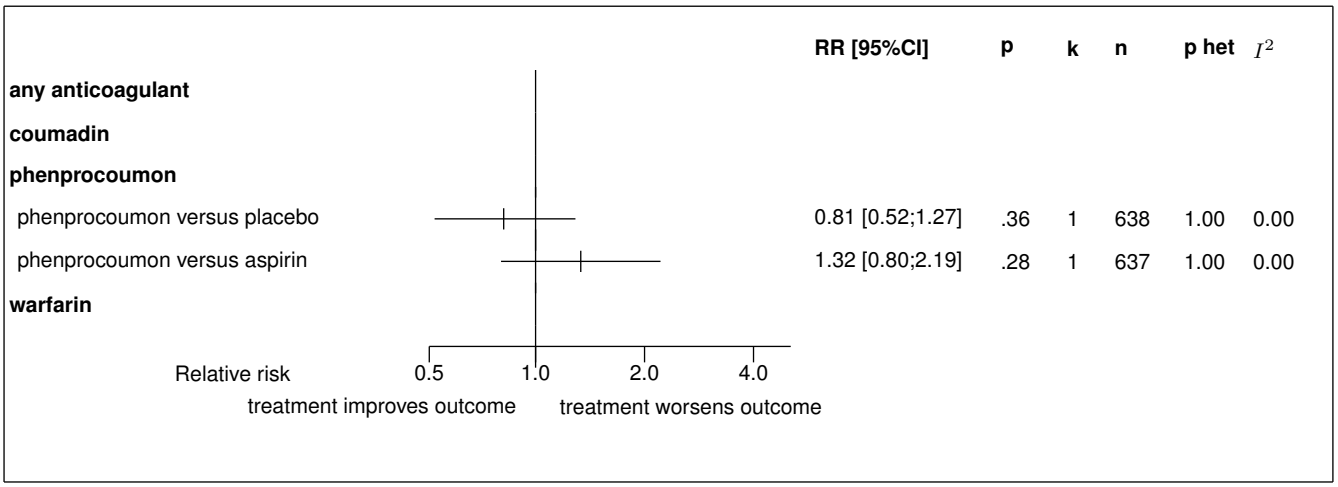
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.4: *Forest's plot for ischemic stroke*



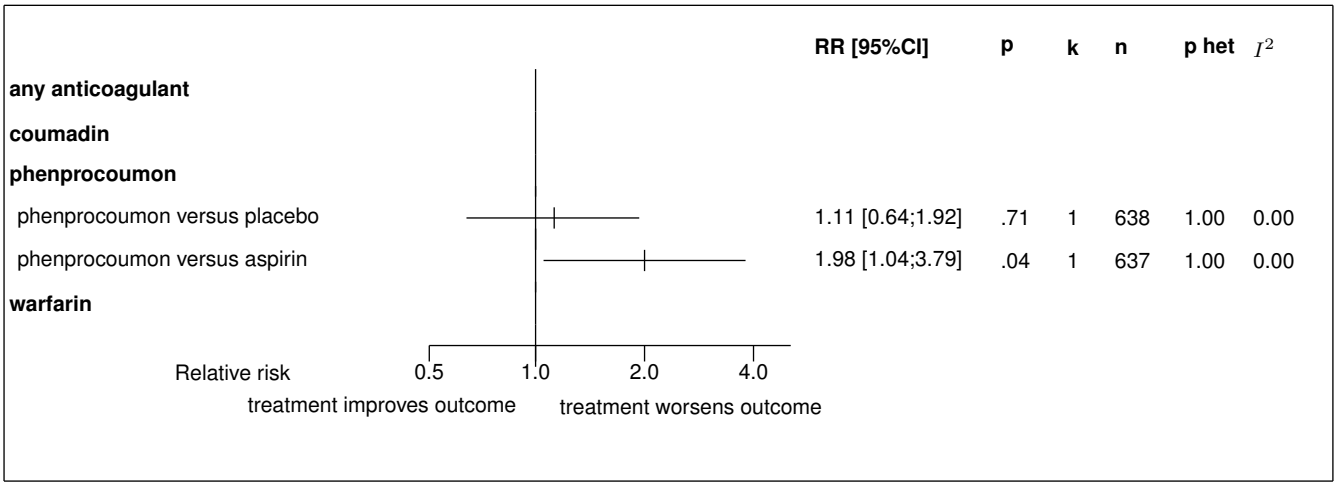
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.5: *Forest's plot for coronary event*



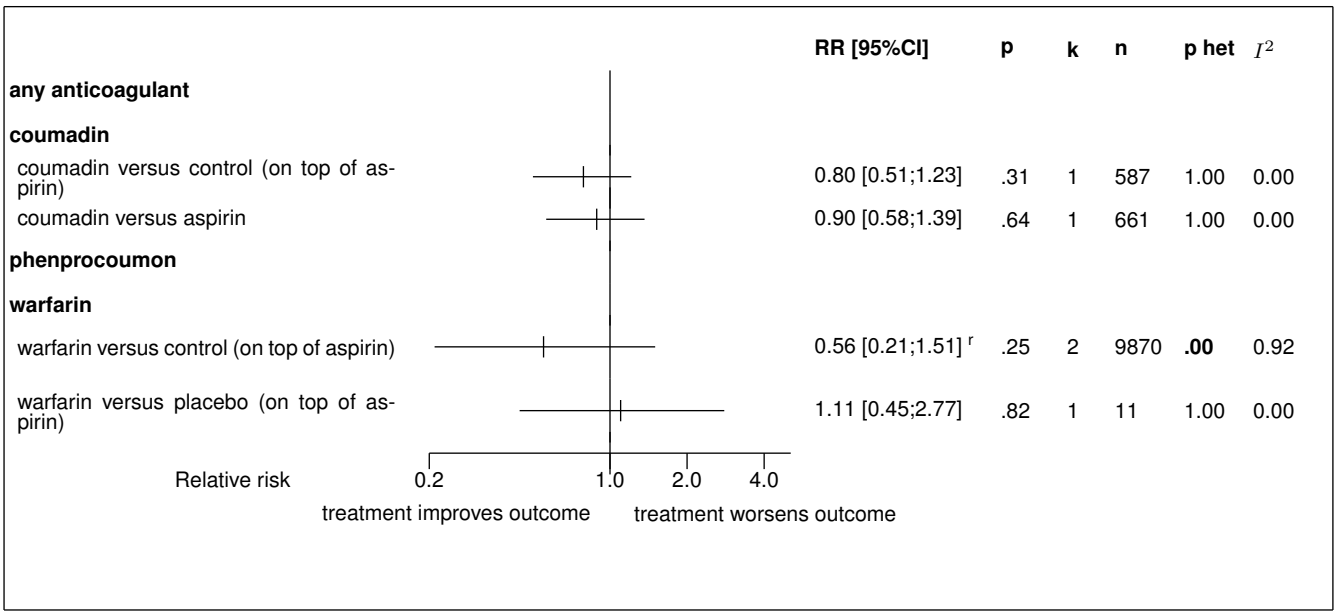
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.6: *Forest's plot for coronary death*



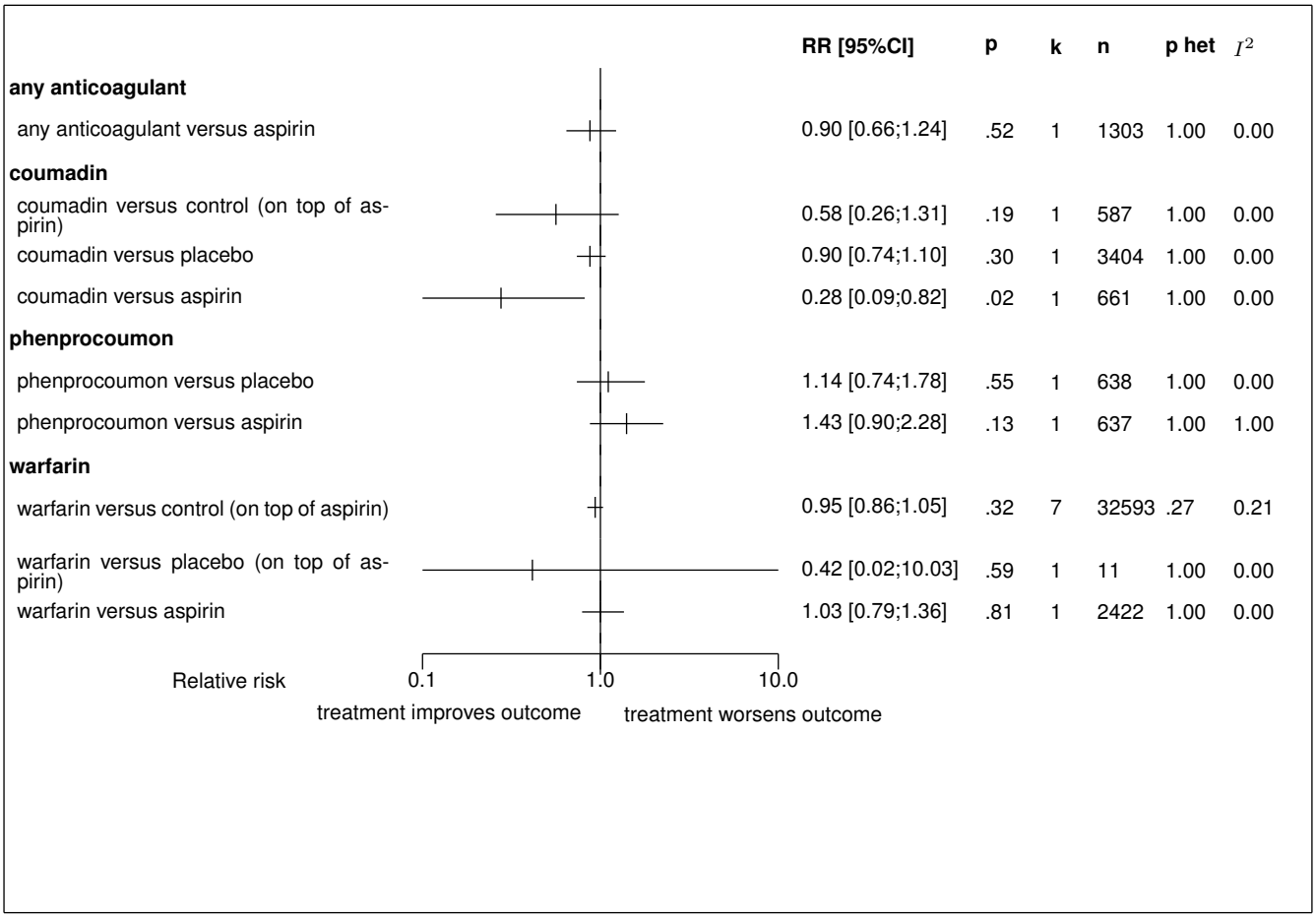
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.7: *Forest's plot for revascularization*



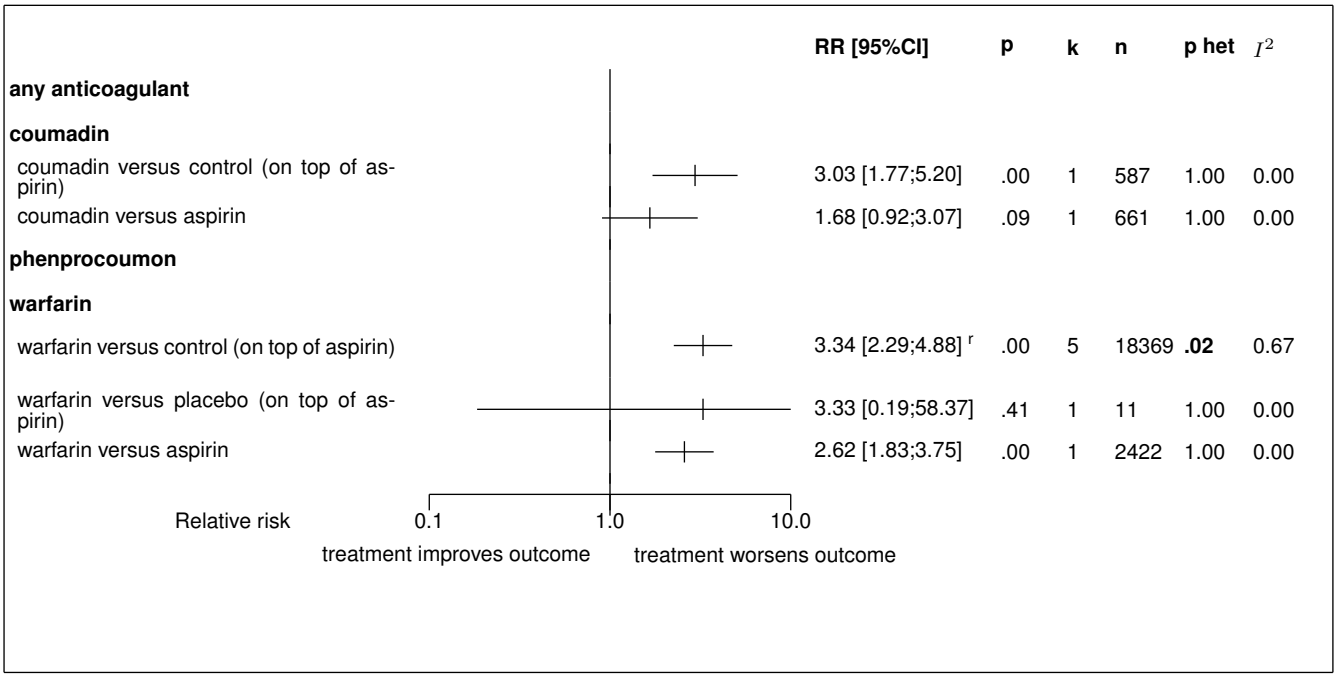
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.8: *Forest's plot for all cause death*



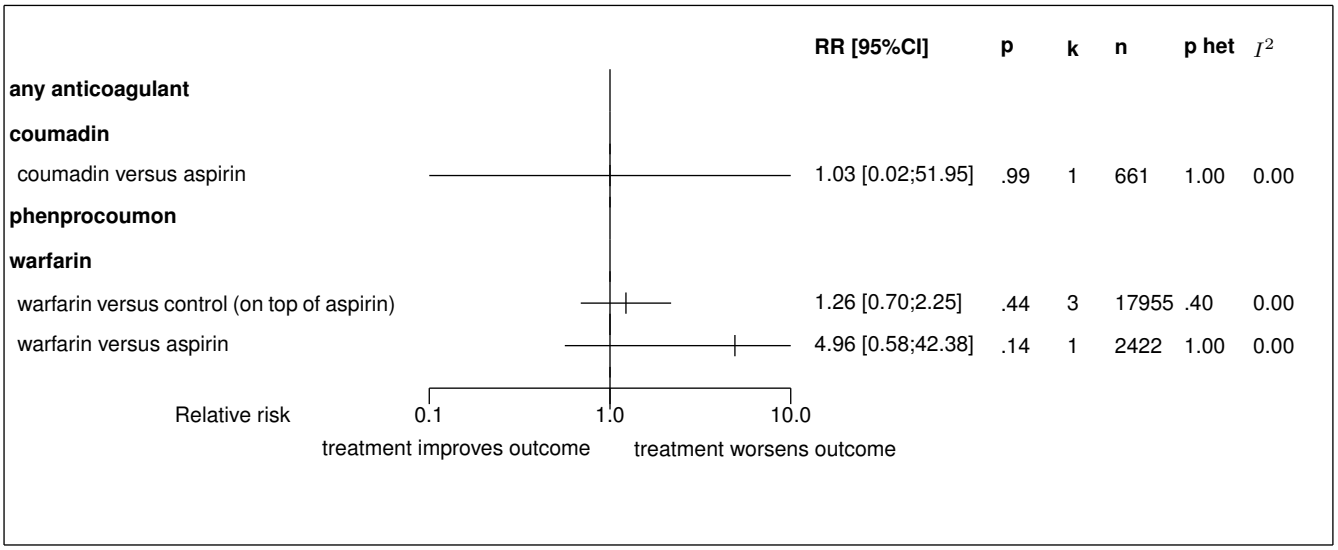
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.9: *Forest's plot for minor bleeding*



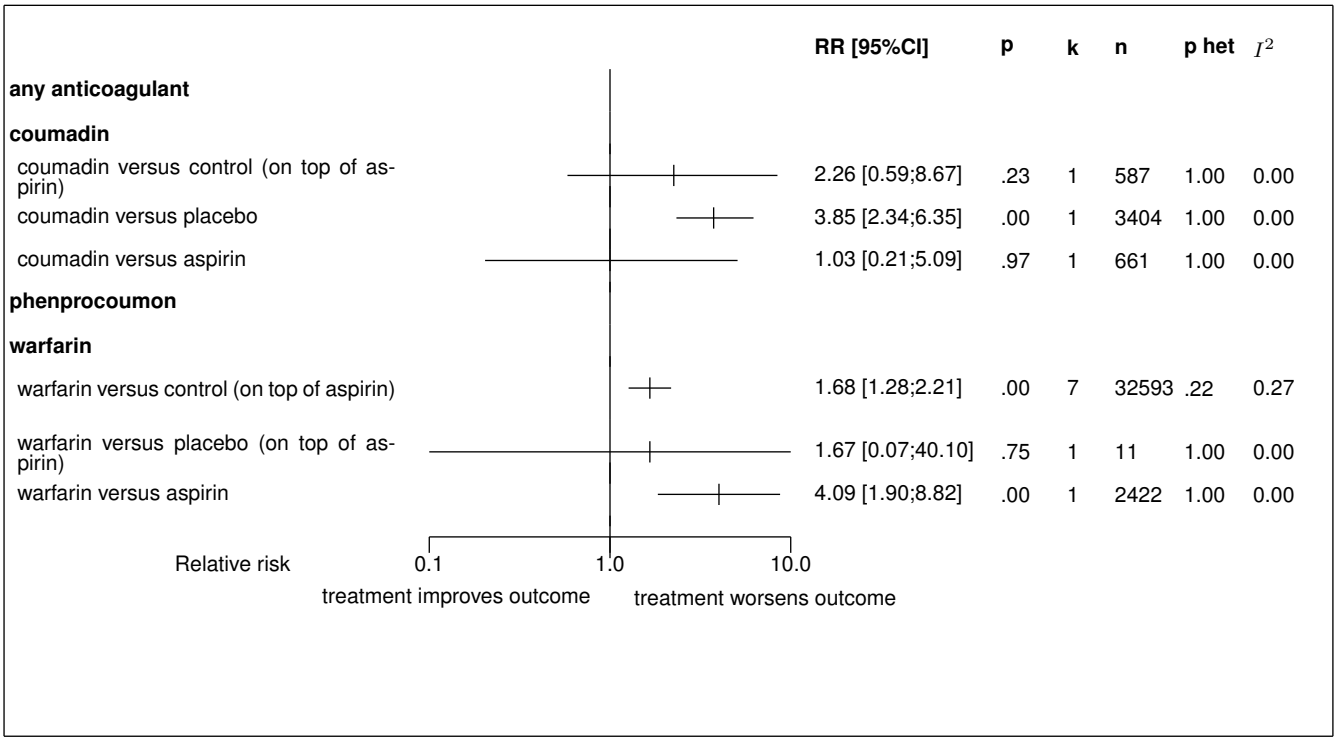
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 16.10: *Forest's plot for intracranial hemorrhage*



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 16.11: *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

17 Detailed results for any anticoagulant

17.1 Available trials

A total of 2 RCTs which randomized 1303 patients were identified: it compared any anticoagulant with placebo and it compared any anticoagulant with aspirin.
The average study size was 1303 patients (range 1303 to 1303). The first study was published in 1980, and the last study was published in 1982.
A total of 1 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Myocardial infarction (fatal and non fatal) data was reported in 2 trials; 1 trials reported data on all cause death; 1 trials reported data on major bleeding; 1 trials reported data on minor bleeding; and 1 trials reported data on ischemic stroke.
Following tables 17.1 (page 105), 17.2 (page 105), 17.4 (page 107), and 17.3 (page 106) summarized the main characteristics of the trials including in this systematic review of randomized trials of any anticoagulant.

Table 17.1: *Treatment description - oral anticoagulant - any anticoagulant*

Trial	Studied treatment	Control treatment
Any anticoagulant versus placebo		
Sixty Plus reinfarction Study (1980) [1]	anticoagulant	placebo
Any anticoagulant versus aspirin		
EPSIM (1982) [2]	anticoagulant	aspirin 500mg three times daily

Table 17.2: *Descriptions of participants - oral anticoagulant - any anticoagulant*

Trial	Patients
Any anticoagulant versus placebo	
Sixty Plus reinfarction Study (1980) [1]	Over 60 years of age
Any anticoagulant versus aspirin	
EPSIM (1982) [2]	Patients surviving myocardial infarction

Table 17.3: *Design and methodological quality of trials - oral anticoagulant - any anticoagulant*

Trial	Design	Duration	Centre	Primary end-point
Any anticoagulant versus placebo				
Sixty Plus reinfarction Study, 1980 [1] n=NaN	Parallel groups double blind	2 years		
Any anticoagulant versus aspirin				
EPSIM, 1982 [2] n=1303	Parallel groups open	29 months (range 6-59)		

Table 17.4: *Trial characteristics - oral anticoagulant - any anticoagulant*

Trial
Any anticoagulant versus placebo
Sixty Plus reinfarction Study, 1980 [1]
Any anticoagulant versus aspirin
EPSIM, 1982 [2]

17.2 Meta-analysis results

The results are detailed in table 17.5 (page 108). This table is followed by the Forest's plot corresponding to each endpoint.

Any anticoagulant versus placebo

No data were presented in the 1 trial identified

Any anticoagulant versus aspirin

The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 1.65 (95% CI 0.96 to 2.84, p=0.0724).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.90 (95% CI 0.66 to 1.24, p=0.5213).

Table 17.5: *Results details - oral anticoagulant - any anticoagulant*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
any anticoagulant versus placebo						
No data were presented in the trial identified						
any anticoagulant versus aspirin						
myocardial infarction (fatal and non fatal)	RR=1.65	[0.96;2.84]	0.0724	1.0000 (I^2=1.00)	1	1303
all cause death	RR=0.90	[0.66;1.24]	0.5213	1.0000 (I^2=0.00)	1	1303

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 myocardial infarction (fatal and non fatal)*

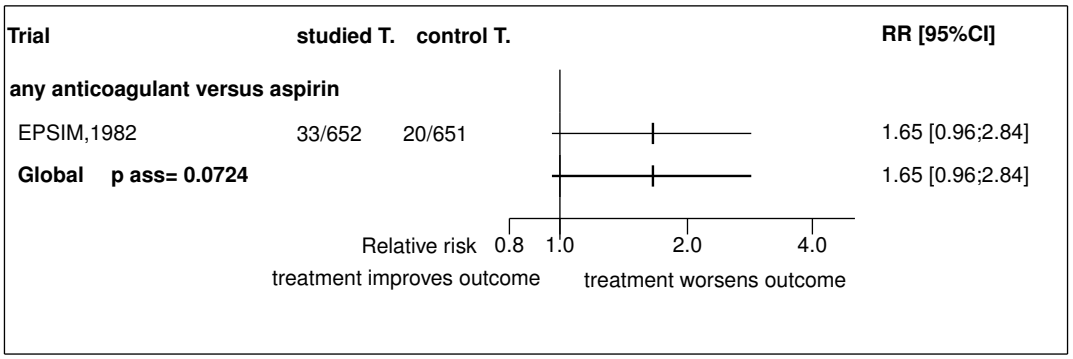
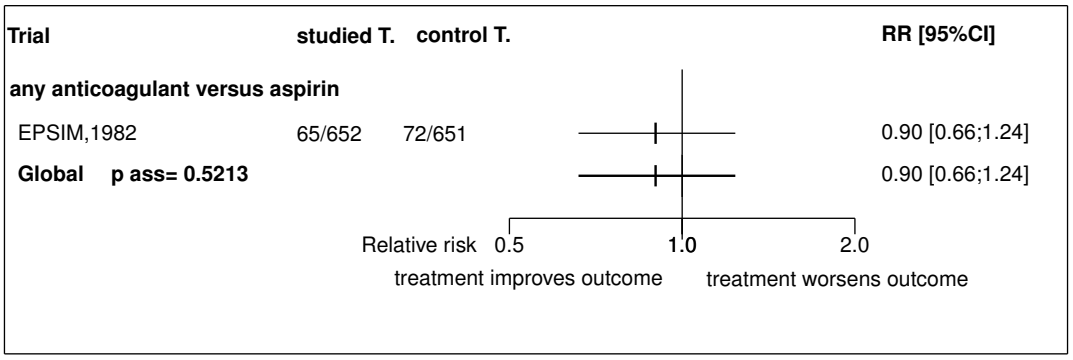


Figure 17.2: *Forest's plot for all cause death*



References

[1] . A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. Report of the Sixty Plus Reinfarction Study Research Group. Lancet 1980;2:989-94. [PMID=6107674]

[2] . A controlled comparison of aspirin and oral anticoagulants in prevention of death after myocardial infarction. N Engl J Med 1982;307:701-8. [PMID=7050710]

17.3 Individual trial summaries

Table 17.6: *Sixty Plus reinfarction Study, 1980 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Double blind	Over 60 years of age	**Studied treatment:** anticoagulant **Control treatment:** placebo	

Reference

. A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. Report of the Sixty Plus Reinfarction Study Research Group. Lancet 1980;2:989-94 [PMID=6107674]

Table 17.7: *EPSIM, 1982 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1303 (652 vs. 651) **Follow-up duration:** 29 months (range 6-59) **Study design:** Randomized controlled trial Parallel groups Open	Patients surviving myocardial infarction	**Studied treatment:** anticoagulant **Control treatment:** aspirin 500mg three times daily	Myocardial infarction (fatal and non fatal) RR=1.65 [0.96;2.84]

Reference

. A controlled comparison of aspirin and oral anticoagulants in prevention of death after myocardial infarction. N Engl J Med 1982;307:701-8 [PMID=7050710]

18 Detailed results for coumadin

18.1 Available trials

A total of 3 RCTs which randomized 4652 patients were identified: it compared coumadin with control (on top of aspirin) , it compared coumadin with placebo and it compared coumadin with aspirin.
The average study size was 1550 patients (range 587 to 3404). The first study was published in 1994, and the last study was published in 2002.
A total of 1 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.
Major bleeding data was reported in 3 trials; 3 trials reported data on myocardial infarction (fatal and non fatal); 3 trials reported data on all cause death; 2 trials reported data on revascularization; 2 trials reported data on ischemic stroke; 2 trials reported data on minor bleeding; 1 trials reported data on intracranial hemorrhage; and 1 trials reported data on all cause death, MI, thrombo-embolic stroke.
Following tables 18.1 (page 113), 18.2 (page 114), 18.4 (page 115), and 18.3 (page 114) summarized the main characteristics of the trials including in this systematic review of randomized trials of coumadin.

Table 18.1: *Treatment description - oral anticoagulant - coumadin*

Trial	Studied treatment	Control treatment
Coumadin versus control (on top of aspirin)		
ASPECT-2 (coumadin+ASA vs ASA) (2002) [1]	coumadin(INR mean 2.4) +aspirin **Concomittant treatment:** aspirin 80 mg daily	aspirin
Coumadin versus placebo		
ASPECT (1994) [2]	nicoumalone or phenprocoumon, target INR 2.84.8	placebo
Coumadin versus aspirin		
ASPECT-2 (coumadin alone) (2002) [3]	coumadin (phenprocoumon or acenocoumarol) target INR 3-4	aspirin 80mg daily

Table 18.2: *Descriptions of participants - oral anticoagulant - coumadin*

Trial	Patients
Coumadin versus control (on top of aspirin)	
ASPECT-2 (coumadin+ASA vs ASA) (2002) [1]	Acute MI, unstable angina
Coumadin versus placebo	
ASPECT (1994) [2]	Hospital survivors of myocardial infarction
Coumadin versus aspirin	
ASPECT-2 (coumadin alone) (2002) [3]	Acute MI, unstable angina

Table 18.3: *Design and methodological quality of trials - oral anticoagulant - coumadin*

Trial	Design	Duration	Centre	Primary end-point
Coumadin versus control (on top of aspirin)				
ASPECT-2 (coumadin+ASA vs ASA), 2002 [1] n=587	Parallel groups open	1 year	the Netherlands 53 centres	death, MI or stroke
Coumadin versus placebo				
ASPECT, 1994 [2] n=3404	Parallel groups double blind	37 months (range 6-76)	multicentre	
Coumadin versus aspirin				
ASPECT-2 (coumadin alone), 2002 [3] n=661	Parallel groups open	1 year (range 0-26 months) inclusion period: -feb 1999	the Netherlands 53 centres	death, MI or stroke

Table 18.4: *Trial characteristics - oral anticoagulant - coumadin*

Trial
Coumadin versus control (on top of aspirin)
ASPECT-2 (coumadin+ASA vs ASA), 2002 [1]
Coumadin versus placebo
ASPECT, 1994 [2]
Coumadin versus aspirin
ASPECT-2 (coumadin alone), 2002 [3]

18.2 Meta-analysis results

The results are detailed in table 18.5 (page 117). This table is followed by the Forest's plot corresponding to each endpoint.

Coumadin versus control (on top of aspirin)

The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.69 (95% CI 0.31 to 1.53, p=0.3655).
The single study eligible for this comparison provided data on **ischemic stroke**. No statistically significant difference between the groups was found in ischemic stroke, with a RR of 0.10 (95% CI 0.01 to 1.77, p=0.1151).
The single study eligible for this comparison provided data on **revascularization**. No statistically significant difference between the groups was found in revascularization, with a RR of 0.80 (95% CI 0.51 to 1.23, p=0.3072).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.58 (95% CI 0.26 to 1.31, p=0.1903).
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 2.26 (95% CI 0.59 to 8.67, p=0.2333).

Coumadin versus placebo

The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of coumadin in myocardial infarction (fatal and non fatal), with a RR of 0.47 (95% CI 0.38 to 0.58, p=0.0000).
The single study eligible for this comparison provided data on **ischemic stroke**. The analysis detected a statistically significant difference in favor of coumadin in ischemic stroke, with a RR of 0.60 (95% CI 0.40 to 0.89, p=0.0121).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.90 (95% CI 0.74 to 1.10, p=0.3002).
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 3.85 (95% CI 2.34 to 6.35, p=0.0000).

Coumadin versus aspirin

The single study eligible for this comparison provided data on **all cause death, MI, thrombo-embolic stroke**. No statistically significant difference between the groups was found in all cause death, MI, thrombo-embolic stroke, with a RR of 0.57 (95% CI 0.32 to 1.00, p=0.0516).
The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.96 (95% CI 0.46 to 2.01, p=0.9138).
The single study eligible for this comparison provided data on **revascularization**. No statistically significant difference between the groups was found in revascularization, with a RR of 0.90 (95% CI 0.58 to 1.39, p=0.6388).
The single study eligible for this comparison provided data on **all cause death**. The analysis detected a statistically significant difference in favor of coumadin in all cause death, with a RR of 0.28 (95% CI 0.09 to 0.82, p=0.0208).

The single study eligible for this comparison provided data on **intracranial hemorrhage**. No statistically significant difference between the groups was found in intracranial hemorrhage, with a RR of 1.03 (95% CI 0.02 to 51.95, p=0.9867).
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 1.03 (95% CI 0.21 to 5.09, p=0.9673).

Table 18.5: *Results details - oral anticoagulant - coumadin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
coumadin versus control (on top of aspirin)						
myocardial infarction (fatal and non fatal)	RR=0.69	[0.31;1.53]	0.3655	1.0000 (I^2=1.00)	1	587
ischemic stroke	RR=0.10	[0.01;1.77]	0.1151	1.0000 (I^2=0.00)	1	587
revascularization	RR=0.80	[0.51;1.23]	0.3072	1.0000 (I^2=0.00)	1	587
all cause death	RR=0.58	[0.26;1.31]	0.1903	1.0000 (I^2=0.00)	1	587
minor bleeding	RR=3.03	[1.77;5.20]	0.0000	1.0000 (I^2=0.00)	1	587
major bleeding	RR=2.26	[0.59;8.67]	0.2333	1.0000 (I^2=0.00)	1	587
coumadin versus placebo						
myocardial infarction (fatal and non fatal)	RR=0.47	[0.38;0.58]	0.0000	1.0000 (I^2=0.00)	1	3404
ischemic stroke	RR=0.60	[0.40;0.89]	0.0121	1.0000 (I^2=0.00)	1	3404
all cause death	RR=0.90	[0.74;1.10]	0.3002	1.0000 (I^2=0.00)	1	3404
major bleeding	RR=3.85	[2.34;6.35]	0.0000	1.0000 (I^2=0.00)	1	3404
coumadin versus aspirin						
all cause death, MI, thrombo-embolic stroke	RR=0.57	[0.32;1.00]	0.0516	1.0000 (I^2=0.00)	1	661
myocardial infarction (fatal and non fatal)	RR=0.96	[0.46;2.01]	0.9138	1.0000 (I^2=0.00)	1	661
revascularization	RR=0.90	[0.58;1.39]	0.6388	1.0000 (I^2=0.00)	1	661
all cause death	RR=0.28	[0.09;0.82]	0.0208	1.0000 (I^2=0.00)	1	661
minor bleeding	RR=1.68	[0.92;3.07]	0.0922	1.0000 (I^2=0.00)	1	661
intracranial hemorrhage	RR=1.03	[0.02;51.95]	0.9867	1.0000 (I^2=0.00)	1	661
major bleeding	RR=1.03	[0.21;5.09]	0.9673	1.0000 (I^2=0.00)	1	661

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 18.1: *Forest's plot for all cause death, MI, thrombo-embolic stroke*

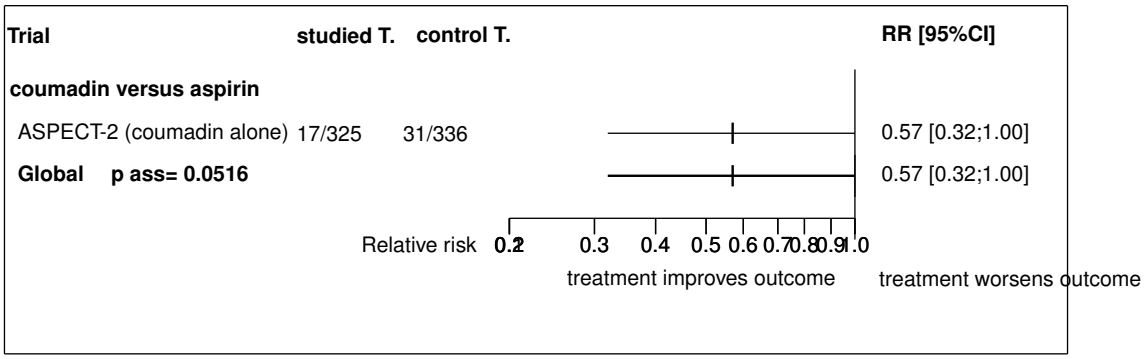


Figure 18.2: *Forest's plot for myocardial infarction (fatal and non fatal)*

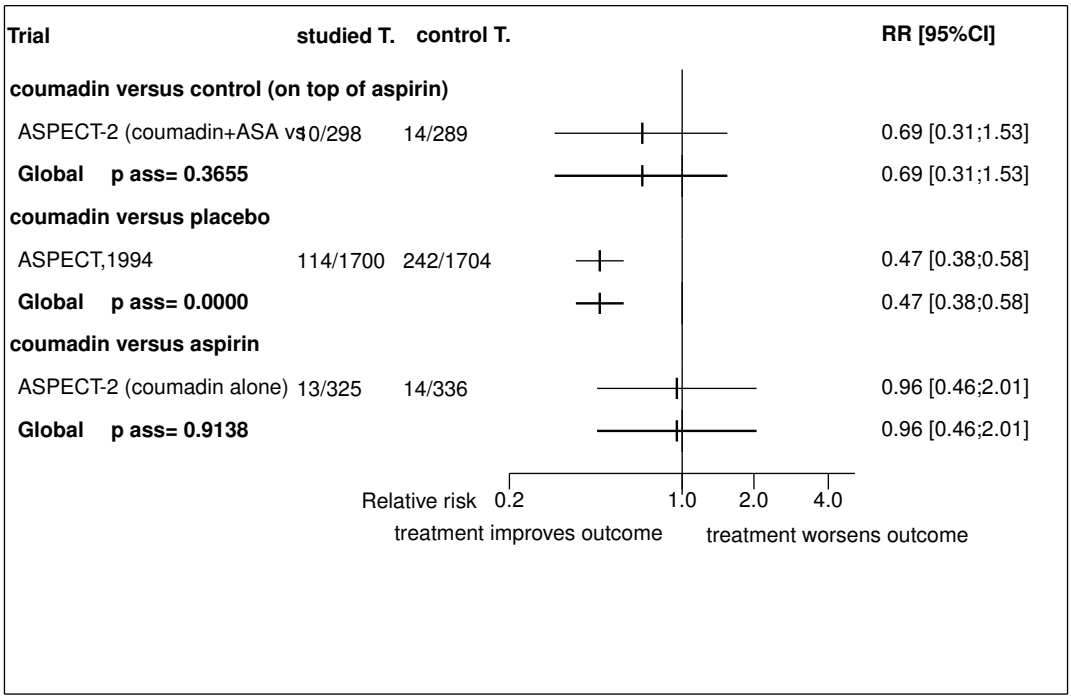


Figure 18.3: *Forest's plot for ischemic stroke*

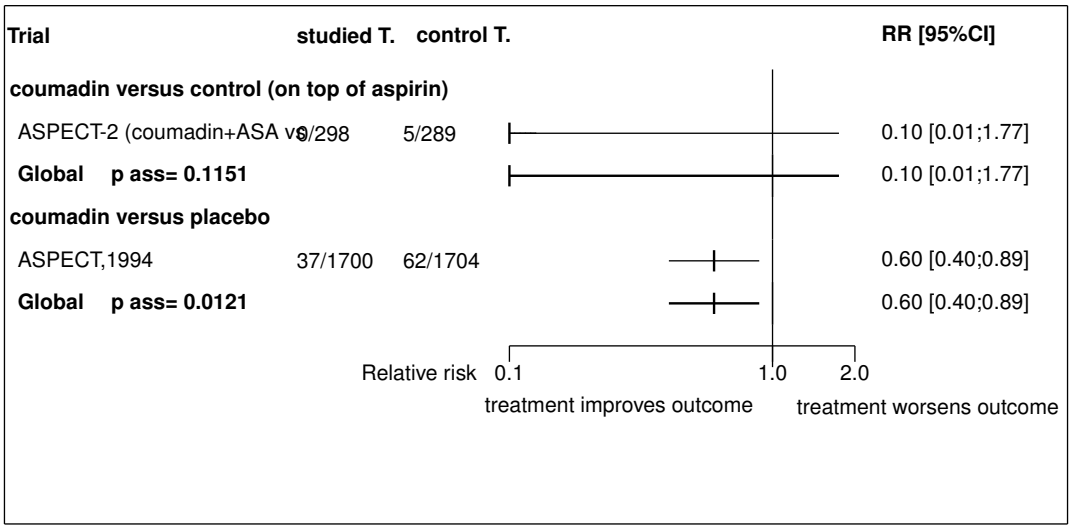


Figure 18.4: *Forest's plot for revascularization*

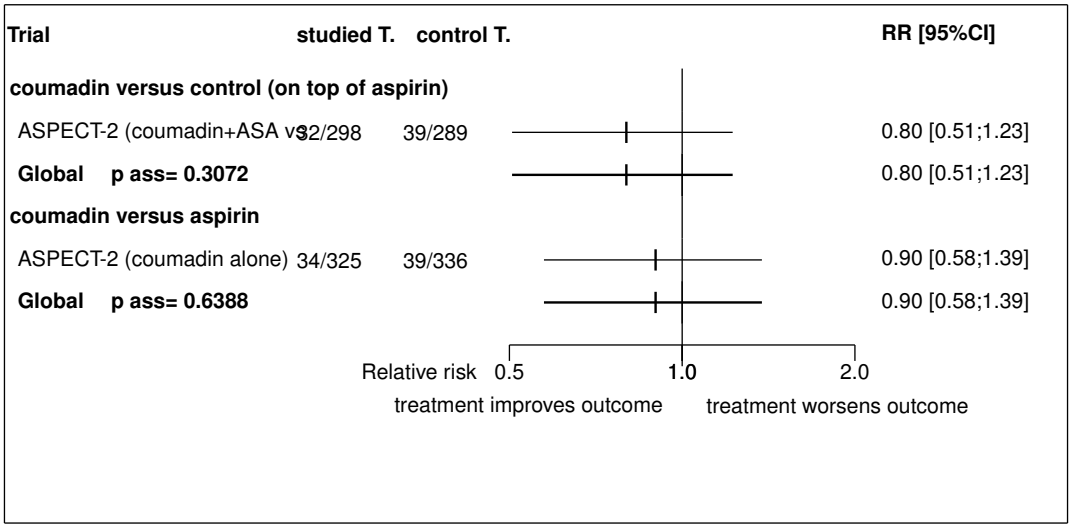


Figure 18.5: *Forest's plot for all cause death*

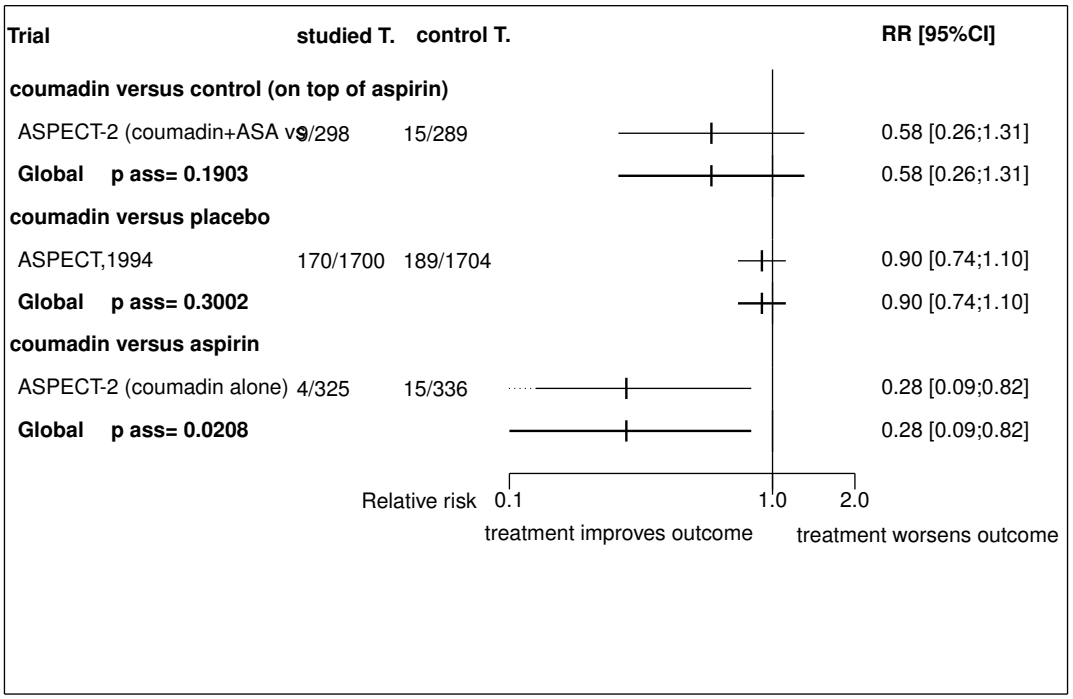


Figure 18.6: *Forest's plot for minor bleeding*

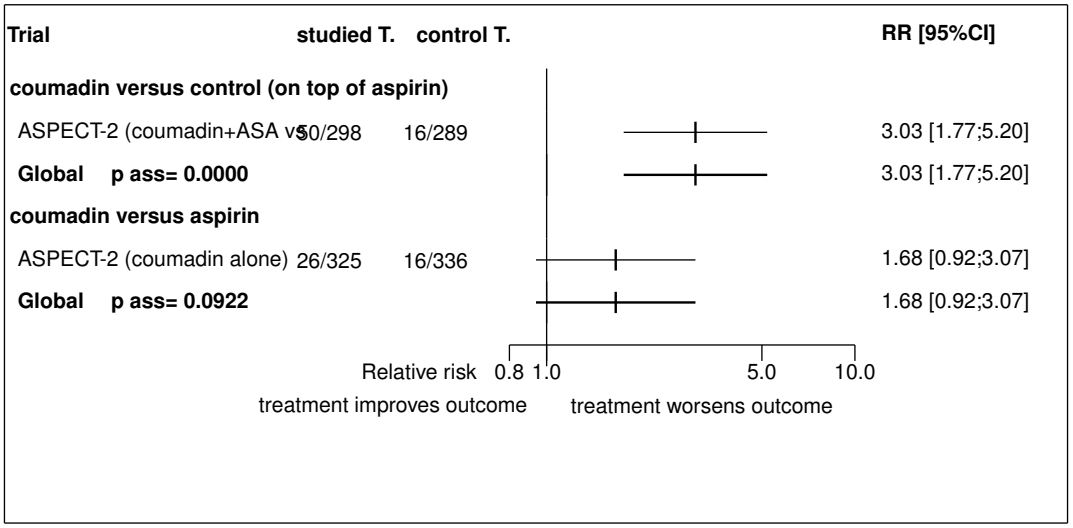


Figure 18.7: *Forest's plot for intracranial hemorrhage*

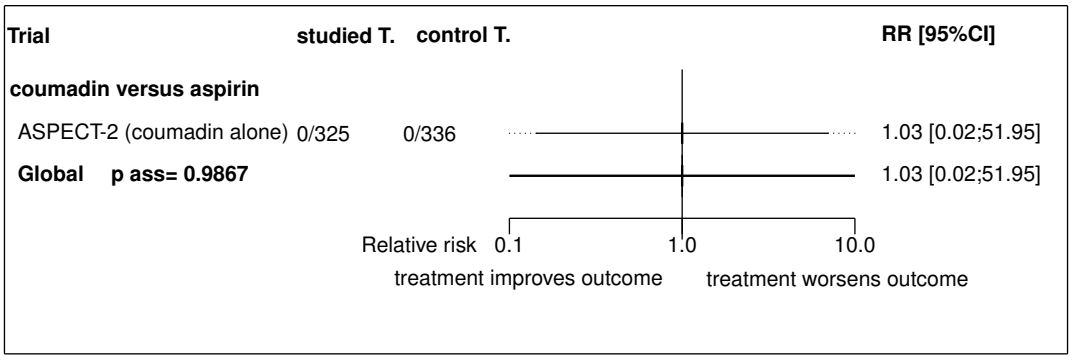
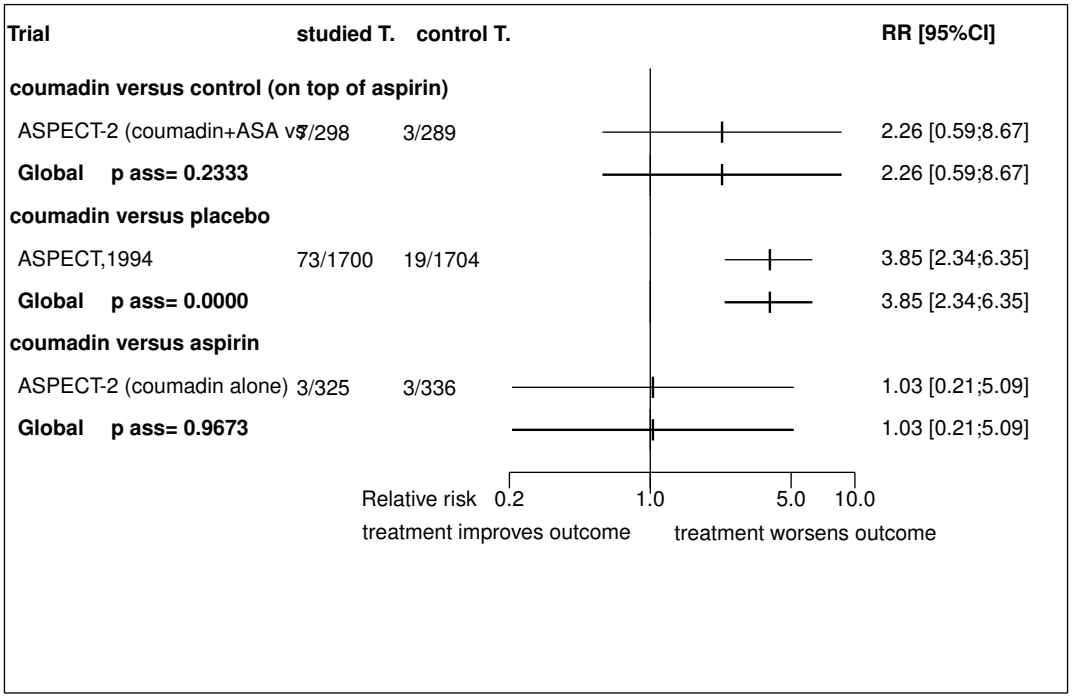


Figure 18.8: *Forest's plot for major bleeding*



References

[1] van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109-13. [PMID=12126819]

[2] . Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Lancet 1994;343:499-503. [PMID=7906757]

[3] van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109-13. [PMID=12126819]

18.3 Individual trial summaries

Table 18.6: *ASPECT-2 (coumadin+ASA vs ASA), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=587 (298 vs. 289) **Follow-up duration:** 1 year **Study design:** Randomized controlled trial Parallel groups Open the Netherlands, 53 centres	Acute MI, unstable angina	**Studied treatment:** coumadin(INR mean 2.4) +aspirin **Control treatment:** aspirin **Concomittant treat.:**aspirin 80 mg daily	Myocardial infarction (fatal and non fatal) RR=0.69 [0.31;1.53]

Reference

van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109-13 [PMID=12126819]

Table 18.7: *ASPECT, 1994 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3404 (1700 vs. 1704) **Follow-up duration:** 37 months (range 6-76) **Study design:** Randomized controlled trial Parallel groups Double blind multicentre	Hospital survivors of myocardial infarction	**Studied treatment:** nicoumalone or phenprocoumon, target INR 2.84.8 **Control treatment:** placebo	Myocardial infarction (fatal and non fatal) RR=0.47 [0.38;0.58] Ischemic stroke RR=0.60 [0.40;0.89] (cerebrovascular events)

Reference

. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Lancet 1994;343:499-503 [PMID=7906757]

Table 18.8: *ASPECT-2 (coumadin alone), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=661 (325 vs. 336) **Follow-up duration:** 1 year (range 0-26 months) **Study design:** Randomized controlled trial Parallel groups Open the Netherlands, 53 centres **Inclusion period:** -feb 1999	Acute MI, unstable angina	**Studied treatment:** coumadin (phenprocoumon or acenocoumarol) target INR 3-4 **Control treatment:** aspirin 80mg daily	All cause death, MI, thrombo-embolic stroke RR=0.57 [0.32;1.00] Myocardial infarction (fatal and non fatal) RR=0.96 [0.46;2.01]

Reference

van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109-13 [PMID=12126819]

19 Detailed results for phenprocoumon

19.1 Available trials

A total of 2 RCTs which randomized 1266 patients were identified: it compared phenprocoumon with placebo and it compared phenprocoumon with aspirin.
The average study size was 633 patients (range 629 to 637). The first study was published in 1980, and the last study was published in 1980.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Coronary event data was reported in 2 trials; 2 trials reported data on all cause death; and 2 trials reported data on coronary death.
Following tables 19.1 (page 127), 19.2 (page 127), 19.4 (page 129), and 19.3 (page 128) summarized the main characteristics of the trials including in this systematic review of randomized trials of phenprocoumon.

Table 19.1: *Treatment description - oral anticoagulant - phenprocoumon*

Trial	Studied treatment	Control treatment
Phenprocoumon versus placebo		
German-Austrian Study Group (oac vs pbo) (1980) [1]	phenprocoumon	placebo
Phenprocoumon versus aspirin		
German-Austrian Study Group (oac vs asp) (1980) [2]	phenprocoumon	aspirin 1.5 g daily

Table 19.2: *Descriptions of participants - oral anticoagulant - phenprocoumon*

Trial	Patients
Phenprocoumon versus placebo	
German-Austrian Study Group (oac vs pbo) (1980) [1]	Patients who had survived a myocardial infarction for 30-42 days
Phenprocoumon versus aspirin	

continued...

Trial	Patients
German-Austrian Study Group (oac vs asp) (1980) [2]	Patients who had survived a myocardial infarction for 30-42 days

Table 19.3: *Design and methodological quality of trials - oral anticoagulant - phenprocoumon*

Trial	Design	Duration	Centre	Primary end-point
Phenprocoumon versus placebo				
German-Austrian Study Group (oac vs pbo), 1980 [1] n=629	Parallel groups double blind	2 years		
Phenprocoumon versus aspirin				
German-Austrian Study Group (oac vs asp), 1980 [2] n=637	Parallel groups double blind	2 years		

Table 19.4: *Trial characteristics - oral anticoagulant - phenprocoumon*

Trial
Phenprocoumon versus placebo
German-Austrian Study Group (oac vs pbo), 1980 [1]
Phenprocoumon versus aspirin
German-Austrian Study Group (oac vs asp), 1980 [2]

19.2 Meta-analysis results

The results are detailed in table 19.5 (page 130). This table is followed by the Forest's plot corresponding to each endpoint.

Phenprocoumon versus placebo

The single study eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 0.81 (95% CI 0.52 to 1.27, p=0.3619).
The single study eligible for this comparison provided data on **coronary death**. No statistically significant difference between the groups was found in coronary death, with a RR of 1.11 (95% CI 0.64 to 1.92, p=0.7081).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.14 (95% CI 0.74 to 1.78, p=0.5481).

Phenprocoumon versus aspirin

The single study eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 1.32 (95% CI 0.80 to 2.19, p=0.2811).
The single study eligible for this comparison provided data on **coronary death**. The analysis detected a statistically significant difference in favor of aspirin in coronary death, with a RR of 1.98 (95% CI 1.04 to 3.79, p=0.0385).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.43 (95% CI 0.90 to 2.28, p=0.1314).

Table 19.5: *Results details - oral anticoagulant - phenprocoumon*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
phenprocoumon versus placebo						
coronary event	RR=0.81	[0.52;1.27]	0.3619	1.0000 (I^2=0.00)	1	638
coronary death	RR=1.11	[0.64;1.92]	0.7081	1.0000 (I^2=0.00)	1	638
all cause death	RR=1.14	[0.74;1.78]	0.5481	1.0000 (I^2=0.00)	1	638
phenprocoumon versus aspirin						
coronary event	RR=1.32	[0.80;2.19]	0.2811	1.0000 (I^2=0.00)	1	637
coronary death	RR=1.98	[1.04;3.79]	0.0385	1.0000 (I^2=0.00)	1	637
all cause death	RR=1.43	[0.90;2.28]	0.1314	1.0000 (I^2=1.00)	1	637

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 19.1: *Forest's plot for coronary event*

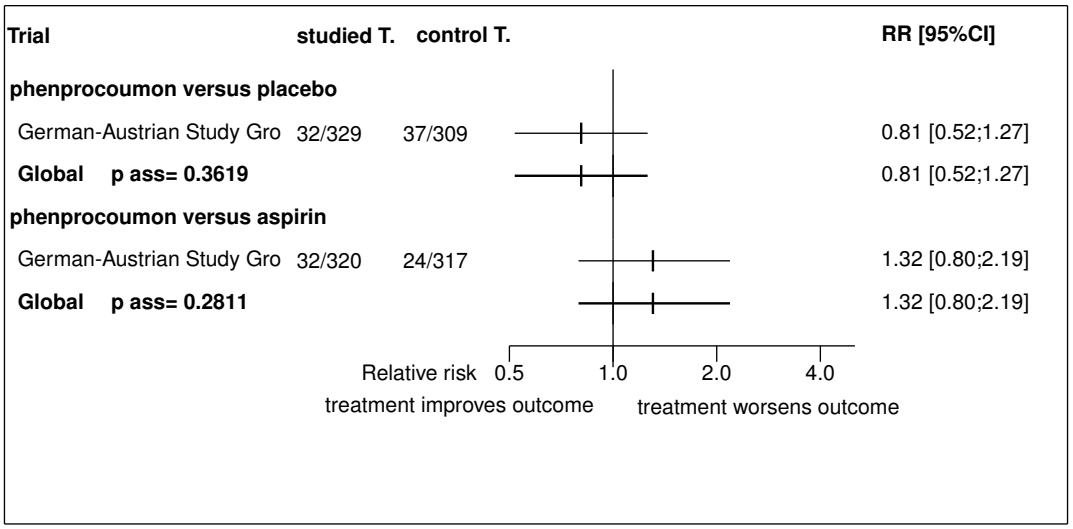


Figure 19.2: *Forest's plot for coronary death*

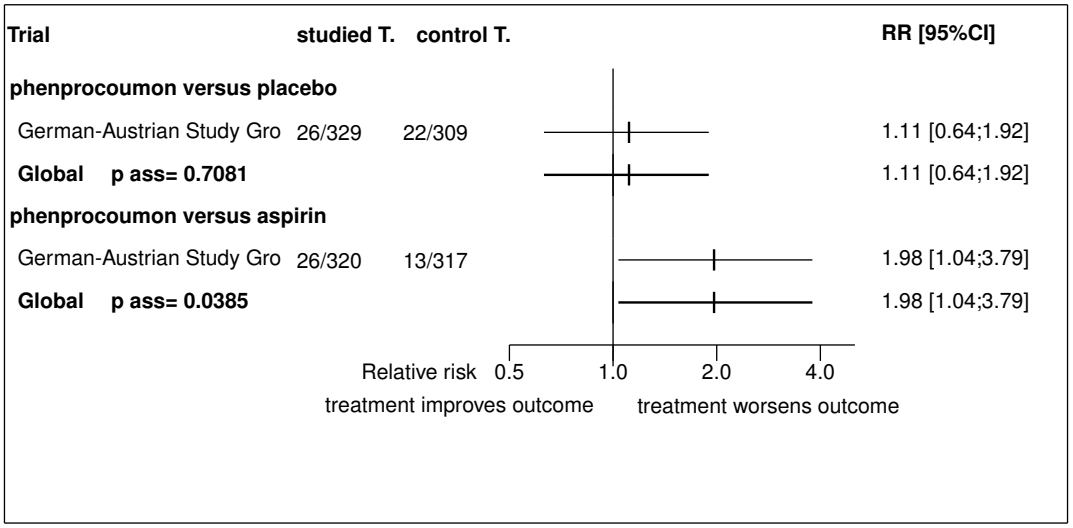
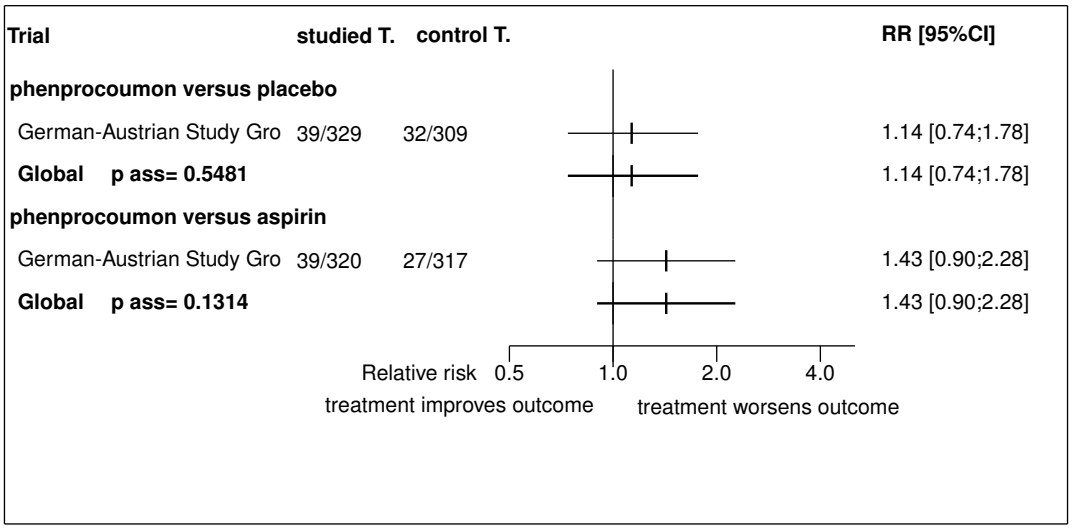


Figure 19.3: *Forest's plot for all cause death*



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[1] Breddin K, Loew D, Lechner K, Oberla K, Walter E. The German-Austrian aspirin trial: a comparison of acetylsalicylic acid, placebo and phenprocoumon in secondary prevention of myocardial infarction. On behalf of the German-Austrian Study Group. Circulation 1980 Dec;62:V63-72. [PMID=6777073]

[2] Breddin K, Loew D, Lechner K, Oberla K, Walter E. The German-Austrian aspirin trial: a comparison of acetylsalicylic acid, placebo and phenprocoumon in secondary prevention of myocardial infarction. On behalf of the German-Austrian Study Group. Circulation 1980;62:V63-72. [PMID=6777073]

19.3 Individual trial summaries

Table 19.6: *German-Austrian Study Group (oac vs pbo), 1980 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=629 (320 vs. 309) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Double blind	Patients who had survived a myocardial infarction for 30-42 days	**Studied treatment:** phenprocoumon **Control treatment:** placebo	Coronary event RR=0.81 [0.52;1.27]

Reference

Breddin K, Loew D, Lechner K, Oberla K, Walter E. The German-Austrian aspirin trial: a comparison of acetylsalicylic acid, placebo and phenprocoumon in secondary prevention of myocardial infarction. On behalf of the German-Austrian Study Group. Circulation 1980 Dec;62:V63-72 [PMID=6777073]

Table 19.7: *German-Austrian Study Group (oac vs asp), 1980 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=637 (320 vs. 317) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Double blind	Patients who had survived a myocardial infarction for 30-42 days	**Studied treatment:** phenprocoumon **Control treatment:** aspirin 1.5 g daily	Coronary event RR=1.32 [0.80;2.19]

Reference

Breddin K, Loew D, Lechner K, Oberla K, Walter E. The German-Austrian aspirin trial: a comparison of acetylsalicylic acid, placebo and phenprocoumon in secondary prevention of myocardial infarction. On behalf of the German-Austrian Study Group. Circulation 1980;62:V63-72 [PMID=6777073]

20 Detailed results for warfarin

20.1 Available trials

A total of 10 RCTs which randomized 37440 patients were identified: 8 trials compared warfarin with control (on top of aspirin) , it compared warfarin with placebo (on top of aspirin) and it compared warfarin with aspirin.
The average study size was 3744 patients (range 11 to 9596). The first study was published in 1997, and the last study was published in 2004.
A total of 4 trials were double blind and 5 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Major bleeding data was reported in 9 trials; 9 trials reported data on all cause death; 8 trials reported data on ischemic stroke; 7 trials reported data on minor bleeding; 6 trials reported data on myocardial infarction (fatal and non fatal); 4 trials reported data on intracranial hemorrhage; 3 trials reported data on revascularization; 1 trials reported data on all cause death, MI, thrombo-embolic stroke; and 1 trials reported data on stroke (fatal and non fatal).
Following tables 20.1 (page 136), 20.2 (page 137), 20.4 (page 141), and 20.3 (page 138) summarized the main characteristics of the trials including in this systematic review of randomized trials of warfarin.

Table 20.1: *Treatment description - oral anticoagulant - warfarin*

Trial	Studied treatment	Control treatment
Warfarin versus control (on top of aspirin)		
WARIS (1999) [1]	warfarin 2.84.8	placebo
APRICOT-2 (2002) [2]	moderate-intensity coumarin target INR 2-3 (+aspirin) **Concomittant treatment:** aspirin 80 mg daily	aspirin
CARS (warafrin 3mg) (1997) [3]	warfarin fixed dose 3mg/d + 80 mg ASA	aspirin 160 mg/d
CARS (warfarin 1mg) (1997) [4]	warfarin 1mg/d + aspirin 80mg/d	aspirin 160 mg/d
CHAMP (2002) [5]	warfarin target INR 1.5-2.5 + aspirin 81 mg daily	aspirin 162 mg/d
LoWASA (2004) [6]	warfarin fixed dose 1.25mg/d + ASA 75mg/d **Concomittant treatment:** aspirin 75 mg daily	aspirin alone
WARIS II (warfarin+ASA) (2002) [7]	warfarin target INR 2-2.5 +ASA 75mg/d	ASA 160mg/d

continued...

Trial	Studied treatment	Control treatment
Zibaeenezhad (2004) [8]	Warfarin target INR 23 +aspirin	aspirin 100 mg/day
	Concomittant treatment: aspirin 100 mg daily	
Warfarin versus placebo (on top of aspirin)		
Williams (1997) [9]	warfarin target INR 22.5 +aspirin	placebo +aspirin
	Concomittant treatment: aspirin 150 mg daily	
Warfarin versus aspirin		
WARIS II (warfarin alone) (2002) [10]	warfarin target INR 2.8-4.2	ASA 160mg/d

Table 20.2: *Descriptions of participants - oral anticoagulant - warfarin*

Trial	Patients
Warfarin versus control (on top of aspirin)	
WARIS (1999) [1]	Survivors of acute myocardial infarction
APRICOT-2 (2002) [2]	Acute MI after thrombolytics
CARS (warafrin 3mg) (1997) [3]	AMI
CARS (warfarin 1mg) (1997) [4]	Patients who had had myocardial infarction
CHAMP (2002) [5]	AMI (patients enrolled within 14 days of infarction)
LoWASA (2004) [6]	AMI
WARIS II (warfarin+ASA) (2002) [7]	Patients hospitalized for acute myocardialinfarction
Zibaeenezhad (2004) [8]	Acute MI
Warfarin versus placebo (on top of aspirin)	
Williams (1997) [9]	Acute MI, unstable angina

continued...

Trial	Patients
Warfarin versus aspirin	
WARIS II (warfarin alone) (2002) [10]	Patients hospitalized for acute myocardialinfarction

Table 20.3: *Design and methodological quality of trials - oral anticoagulant - warfarin*

Trial	Design	Duration	Centre	Primary endpoint
Warfarin versus control (on top of aspirin)				
WARIS, 1999 [1] n=2414	Parallel groups double blind	37 months		
APRICOT-2, 2002 [2] n=274	Parallel groups open	3 months inclusion period: 1994 -	the Netherlands 7 centres	reocclusion of the infarct-related artery
CARS (warafrin 3mg), 1997 [3] n=8803	Parallel groups double blind	14 months	North America 293 centres	reinfarction, non-fatal ischaemic stroke, or cardiovascular death
CARS (warfarin 1mg), 1997 [4] n=5421	Parallel groups double blind	14 months	North America 293 centres	reinfarction, non-fatal ischaemic stroke, or cardiovascular death
CHAMP, 2002 [5] n=5059	Parallel groups open	2.7 years	US 78 centres	all cause mortality
LoWASA, 2004 [6] n=3300	Parallel groups open confirmatory trial at risk of bias	5 years inclusion period: feb 1994 - feb 1999	Sweden 31 centres	Cardiovascular event and CV death
WARIS II (warfarin+ASA), 2002 [7] n=9596	Parallel groups open	4 years inclusion period: jan 1994 - jun 1998	Norway 20 centres	death, MI, ischaemic stroke
Zibaeenezhad, 2004 [8] n=140	Parallel groups open	1 year		
Warfarin versus placebo (on top of aspirin)				

continued...

Trial	Design	Duration	Centre	Primary endpoint
Williams, 1997 [9] n=11	Parallel groups double blind	2.5 months		quantitative angiography
Warfarin versus aspirin				
WARIS II (warfarin alone), 2002 [10] n=2422	Parallel groups NA	48 months inclusion period: jan 1994 - jun 1998	Norway 20 centres	death, MI, ischaemic stroke

Table 20.4: *Trial characteristics - oral anticoagulant - warfarin*

Trial
Warfarin versus control (on top of aspirin)
WARIS, 1999 [1]
APRICOT-2, 2002 [2]
CARS (warafrin 3mg), 1997 [3]
CARS (warfarin 1mg), 1997 [4]
CHAMP, 2002 [5]
LoWASA, 2004 [6]
WARIS II (warfarin+ASA), 2002 [7]
Zibaeenezhad, 2004 [8]
Warfarin versus placebo (on top of aspirin)
Williams, 1997 [9]
Warfarin versus aspirin
WARIS II (warfarin alone), 2002 [10]

20.2 Meta-analysis results

The results are detailed in table 20.5 (page 143). This table is followed by the Forest's plot corresponding to each endpoint.

Warfarin versus control (on top of aspirin)

Only one of the 8 studies eligible for this comparison provided data on **all cause death, MI, thrombo-embolic stroke**. The analysis detected a statistically significant difference in favor of warfarin in all cause death, MI, thrombo-embolic stroke, with a RR of 0.71 (95% CI 0.59 to 0.86, p=0.0000).
A total of 5 of the 8 studies eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in myocardial infarction (fatal and non fatal), with a RR of 0.81 (95% CI 0.61 to 1.08, p=0.1543). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0009, I^2 = 0.79%).
Only one of the 8 studies eligible for this comparison provided data on **stroke (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of warfarin in stroke (fatal and non fatal), with a RR of 0.67 (95% CI 0.50 to 0.88, p=0.0041).
A total of 6 of the 8 studies eligible for this comparison provided data on **ischemic stroke**. When pooled together, there was no statistically significant difference between the groups in ischemic stroke, with a RR of 0.90 (95% CI 0.61 to 1.32, p=0.5825). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0059, I^2 = 0.69%).
A total of 2 of the 8 studies eligible for this comparison provided data on **revascularization**. When pooled together, there was no statistically significant difference between the groups in revascularization, with a RR of 0.56 (95% CI 0.21 to 1.51, p=0.2529). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0000, I^2 = 0.92%).
A total of 7 of the 8 studies eligible for this comparison provided data on **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 0.95 (95% CI 0.86 to 1.05, p=0.3235). No heterogeneity was detected (p = 0.2712, I^2 = 0.21%).
A total of 3 of the 8 studies eligible for this comparison provided data on **intracranial hemorrhage**. When pooled together, there was no statistically significant difference between the groups in intracranial hemorrhage, with a RR of 1.26 (95% CI 0.70 to 2.25, p=0.4395). No heterogeneity was detected (p = 0.4049, I^2 = 0.00%).
A total of 7 of the 8 studies eligible for this comparison provided data on **major bleeding**. The analysis detected a statistically significant difference in favor of control (on top of aspirin) in major bleeding, with a RR of 1.68 (95% CI 1.28 to 2.21, p=0.0000). No heterogeneity was detected (p = 0.2224, I^2 = 0.27%).

Warfarin versus placebo (on top of aspirin)

The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.19 (95% CI 0.03 to 1.13, p=0.0683).
The single study eligible for this comparison provided data on **ischemic stroke**. No statistically significant difference between the groups was found in ischemic stroke, with a RR of 0.83 (95% CI 0.02 to 34.94, p=0.9238).
The single study eligible for this comparison provided data on **revascularization**. No statistically significant difference between the groups was found in revascularization, with a RR of 1.11 (95% CI 0.45 to 2.77, p=0.8209).

The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.42 (95% CI 0.02 to 10.03, p=0.5895).
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 1.67 (95% CI 0.07 to 40.10, p=0.7529).

Warfarin versus aspirin

The single study eligible for this comparison provided data on **all cause death, MI, thrombo-embolic stroke**. The analysis detected a statistically significant difference in favor of warfarin in all cause death, MI, thrombo-embolic stroke, with a RR of 0.81 (95% CI 0.69 to 0.95, p=0.0098).
The single study eligible for this comparison provided data on **ischemic stroke**. The analysis detected a statistically significant difference in favor of warfarin in ischemic stroke, with a RR of 0.53 (95% CI 0.29 to 0.94, p=0.0312).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.03 (95% CI 0.79 to 1.36, p=0.8066).
The single study eligible for this comparison provided data on **intracranial hemorrhage**. No statistically significant difference between the groups was found in intracranial hemorrhage, with a RR of 4.96 (95% CI 0.58 to 42.38, p=0.1436).
The single study eligible for this comparison provided data on **major bleeding**. The analysis detected a statistically significant difference in favor of aspirin in major bleeding, with a RR of 4.09 (95% CI 1.90 to 8.82, p=0.0000).

Table 20.5: *Results details - oral anticoagulant - warfarin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
warfarin versus control (on top of aspirin)						
all cause death, MI, thrombo-embolic stroke	RR=0.71	[0.59;0.86]	0.0000	1.0000 (I^2=0.00)	1	9596
myocardial infarction (fatal and non fatal)	RR=0.81	[0.61;1.08]	0.1543	0.0009 (I^2=0.79)	5	18369
stroke (fatal and non fatal)	RR=0.67	[0.50;0.88]	0.0041	1.0000 (I^2=0.00)	1	3300
ischemic stroke	RR=0.90	[0.61;1.32]	0.5825	0.0059 (I^2=0.69)	6	32319
revascularization	RR=0.56	[0.21;1.51]	0.2529	0.0000 (I^2=0.92)	2	9870
all cause death	RR=0.95	[0.86;1.05]	0.3235	0.2712 (I^2=0.21)	7	32593
minor bleeding	RR=3.34	[2.29;4.88]	0.0000	0.0160 (I^2=0.67)	5	18369
intracranial hemorrhage	RR=1.26	[0.70;2.25]	0.4395	0.4049 (I^2=0.00)	3	17955
major bleeding	RR=1.68	[1.28;2.21]	0.0000	0.2224 (I^2=0.27)	7	32593
warfarin versus placebo (on top of aspirin)						
myocardial infarction (fatal and non fatal)	RR=0.19	[0.03;1.13]	0.0683	1.0000 (I^2=0.00)	1	11
ischemic stroke	RR=0.83	[0.02;34.94]	0.9238	1.0000 (I^2=0.00)	1	11

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
revascularization	RR=1.11	[0.45;2.77]	0.8209	1.0000 (I^2=0.00)	1	11
all cause death	RR=0.42	[0.02;10.03]	0.5895	1.0000 (I^2=0.00)	1	11
minor bleeding	RR=3.33	[0.19;58.37]	0.4098	1.0000 (I^2=0.00)	1	11
major bleeding	RR=1.67	[0.07;40.10]	0.7529	1.0000 (I^2=0.00)	1	11
warfarin versus aspirin						
all cause death, MI, thrombo-embolic stroke	RR=0.81	[0.69;0.95]	0.0098	1.0000 (I^2=0.00)	1	2422
ischemic stroke	RR=0.53	[0.29;0.94]	0.0312	1.0000 (I^2=0.00)	1	2422
all cause death	RR=1.03	[0.79;1.36]	0.8066	1.0000 (I^2=0.00)	1	2422
minor bleeding	RR=2.62	[1.83;3.75]	0.0000	1.0000 (I^2=0.00)	1	2422
intracranial hemorrhage	RR=4.96	[0.58;42.38]	0.1436	1.0000 (I^2=0.00)	1	2422
major bleeding	RR=4.09	[1.90;8.82]	0.0000	1.0000 (I^2=0.00)	1	2422

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 20.1: *Forest's plot for all cause death, MI, thrombo-embolic stroke*

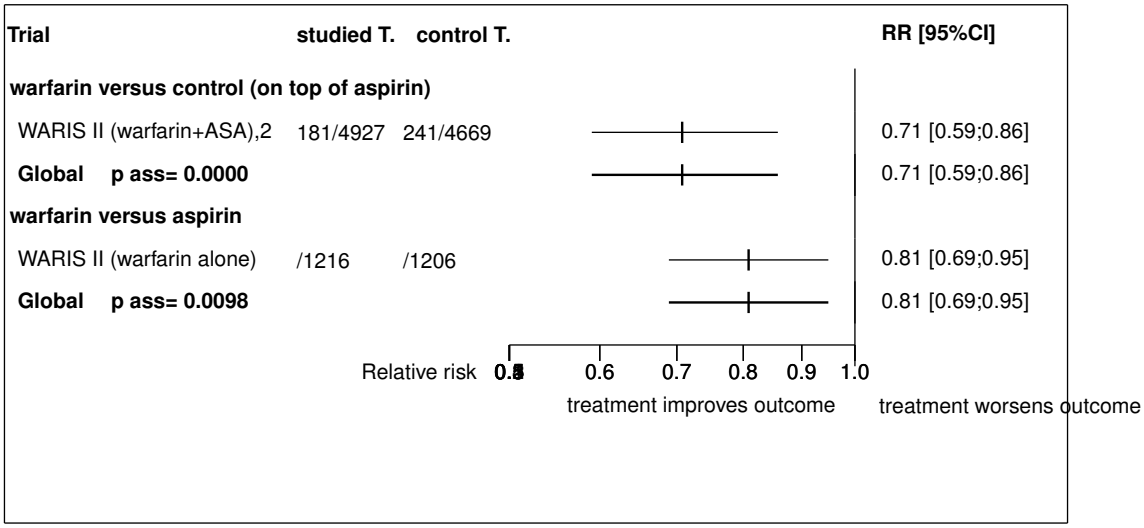


Figure 20.2: *Forest's plot for myocardial infarction (fatal and non fatal)*

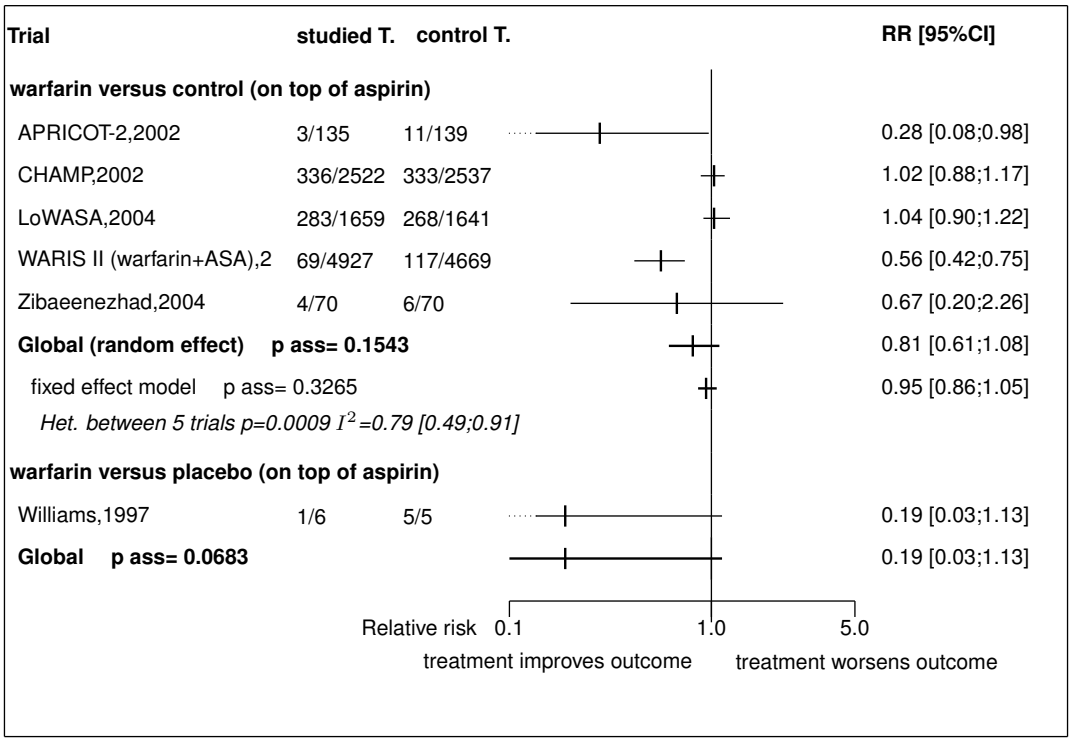


Figure 20.3: *Forest's plot for stroke (fatal and non fatal)*

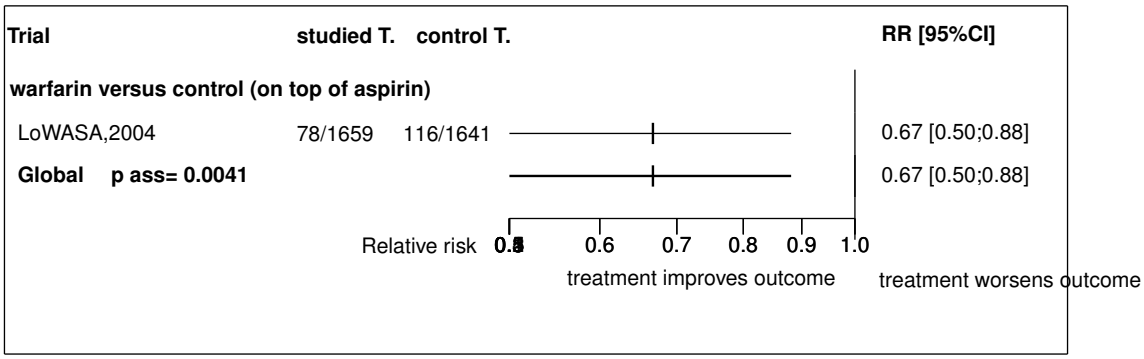


Figure 20.4: *Forest's plot for ischemic stroke*

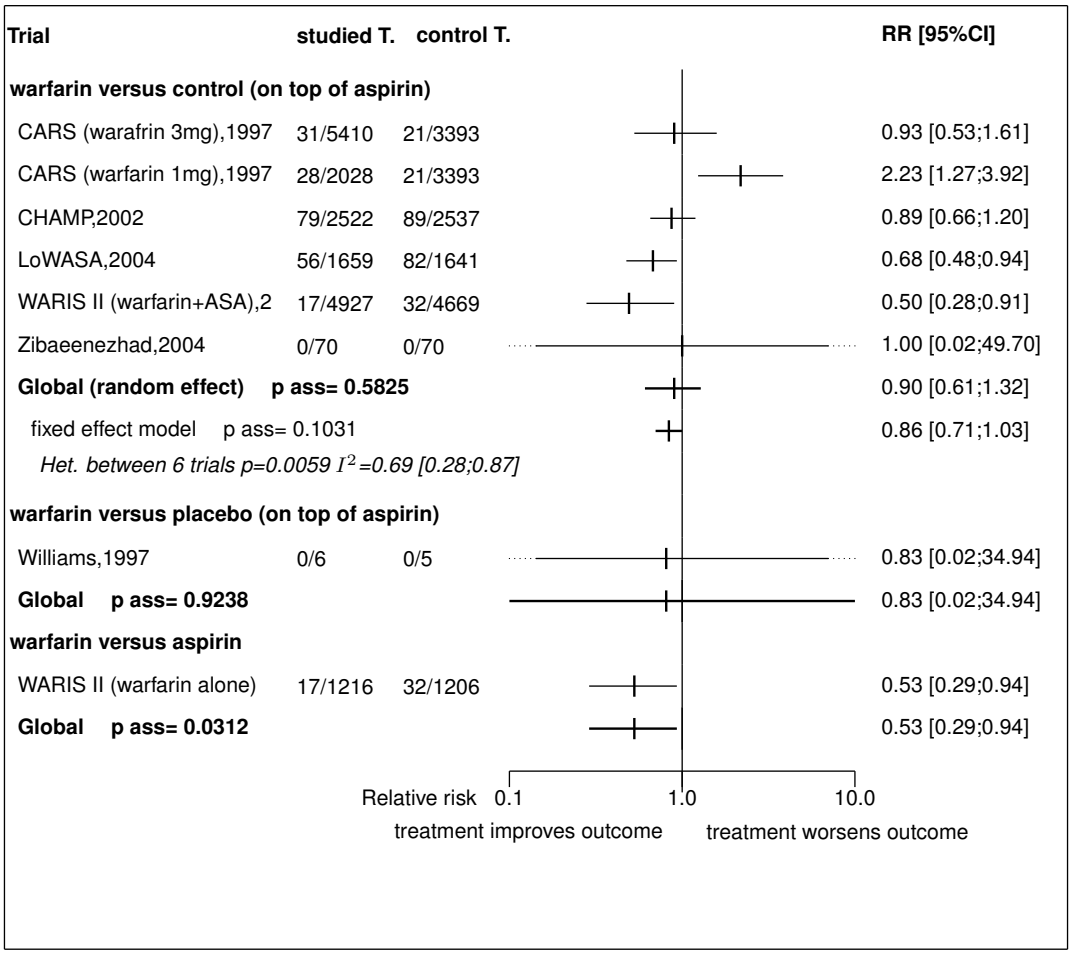


Figure 20.5: *Forest's plot for revascularization*

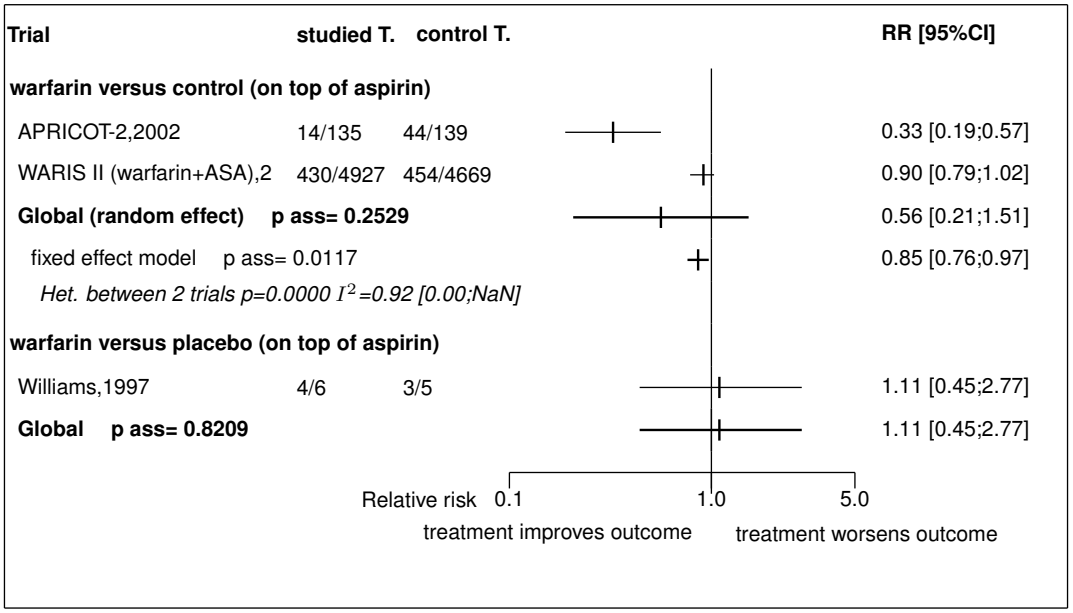


Figure 20.6: *Forest's plot for all cause death*

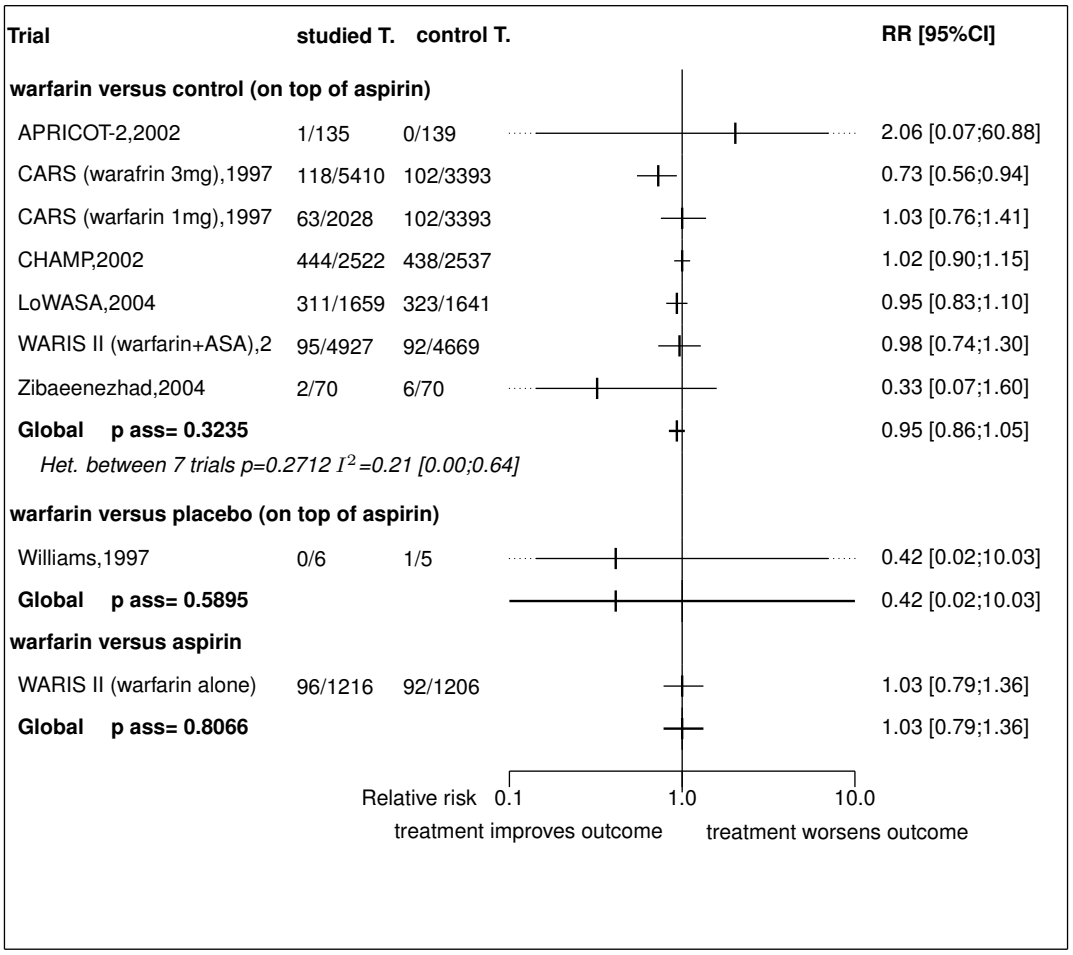


Figure 20.7: *Forest's plot for minor bleeding*

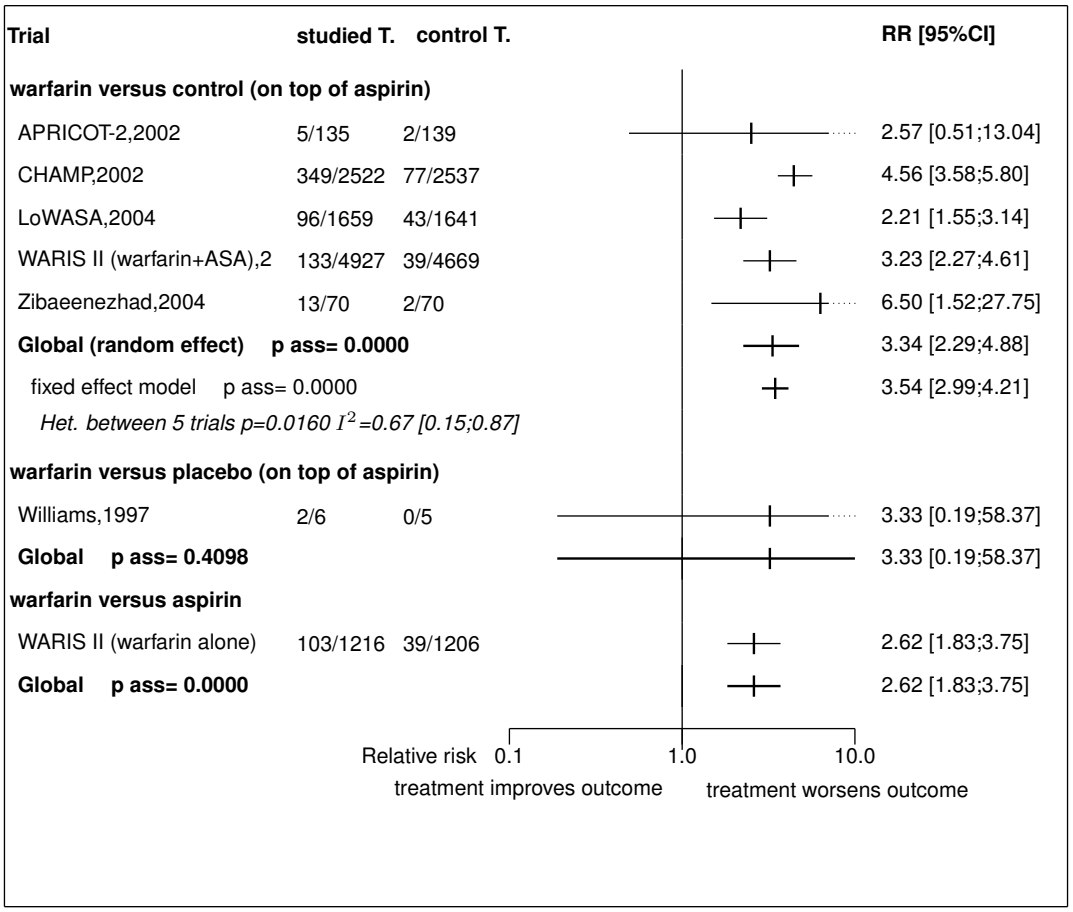


Figure 20.8: *Forest's plot for intracranial hemorrhage*

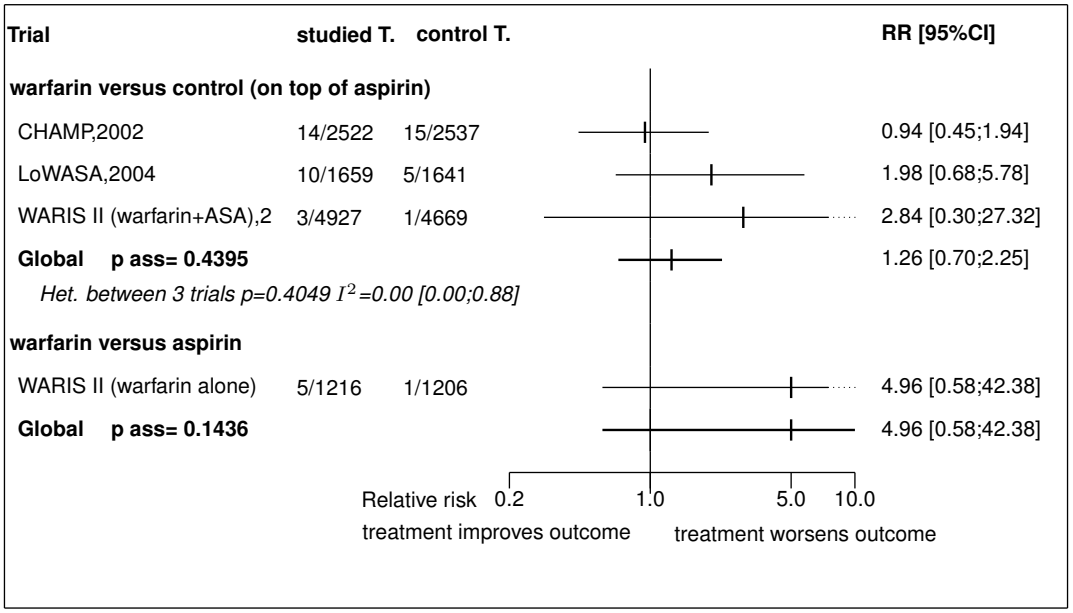
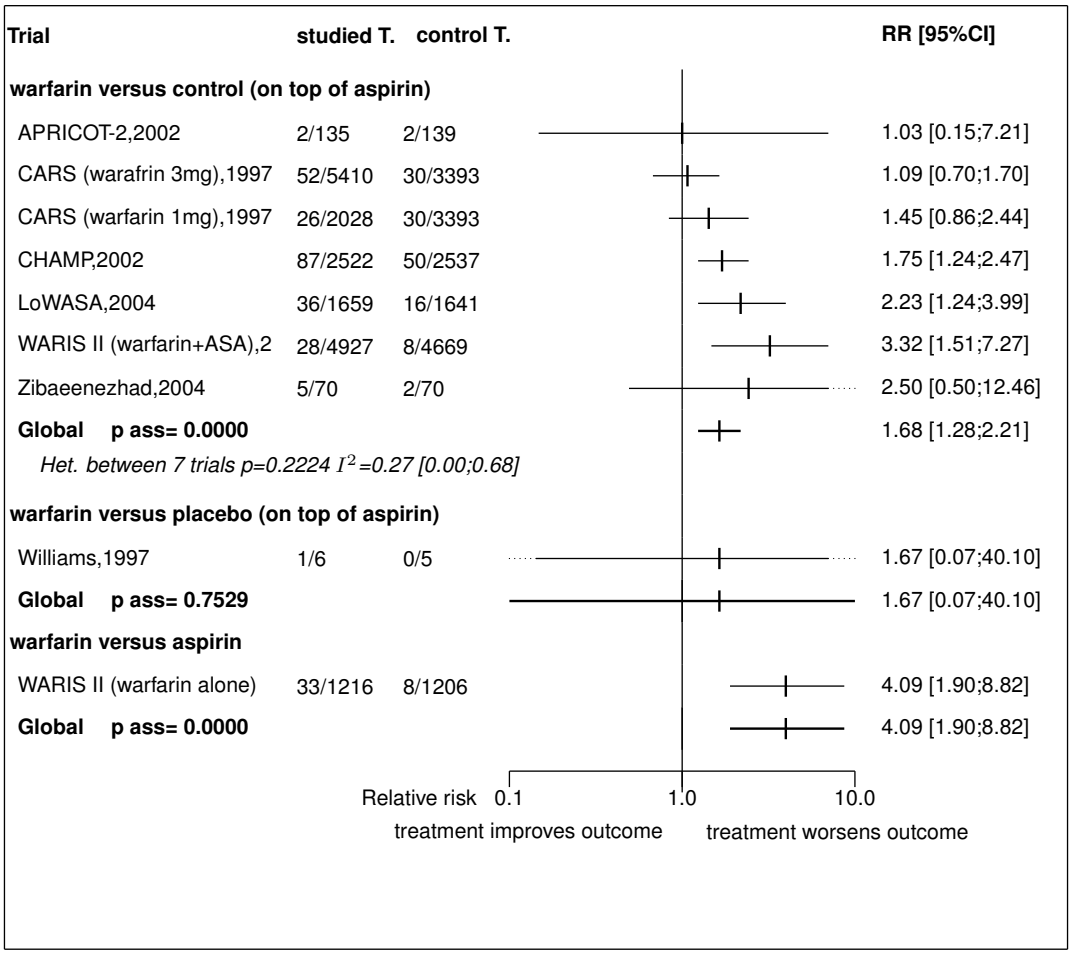


Figure 20.9: *Forest's plot for major bleeding*



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[2] Brouwer MA, van den Bergh PJ, Aengevaeren WR, Veen G, Luijten HE, Hertzberger DP, van Boven AJ, Vromans RP, Uijen GJ, Verheugt FW. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. Circulation 2002;106:659-65. [PMID=12163424]

[3] . Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Lancet 1997;350:389-96. [PMID=9259652]

[4] . Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Lancet 1997;350:389-96. [PMID=9259652]

[5] Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation 2002;105:557-63. [PMID=11827919]

[6] Herlitz J, Holm J, Peterson M, Karlson BW, Haglid Evander M, Erhardt L. Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction; the LoWASA Study. Eur Heart J 2004;25:232-9. [PMID=14972424]

[7] Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74. [PMID=12324552]

[8] Zibaeenezhad MJ, Mowla A, Sorbi MH. Warfarin and aspirin versus aspirin alone in patients with acute myocardial infarction: a pilot study. Angiology 2004;55:17-20. [PMID=14759085]

[9] Williams MJ, Morison IM, Parker JH, Stewart RA. Progression of the culprit lesion in unstable coronary artery disease with warfarin and aspirin versus aspirin alone: preliminary study. J Am Coll Cardiol 1997;30:364-9. [PMID=9247506]

[10] Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74. [PMID=12324552]

20.3 Individual trial summaries

Table 20.6: *WARIS, 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2414 (1208 vs. 1206) **Follow-up duration:** 37 months **Study design:** Randomized controlled trial Parallel groups Double blind	Survivors of acute myocardial infarction	**Studied treatment:** warfarin 2.84.8 **Control treatment:** placebo	

Reference

Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. N Engl J Med 1990;323:147-52 [PMID=2194126]

Table 20.7: *APRICOT-2, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=274 (135 vs. 139) **Follow-up duration:** 3 months **Study design:** Randomized controlled trial Parallel groups Open the Netherlands, 7 centres **Inclusion period:** 1994 -	Acute MI after thrombolytics	**Studied treatment:** moderate-intensity coumarin target INR 2-3 (+aspirin) **Control treatment:** aspirin **Concomittant treat.:**aspirin 80 mg daily	Myocardial infarction (fatal and non fatal) RR=0.28 [0.08;0.98]

Reference

Brouwer MA, van den Bergh PJ, Aengevaeren WR, Veen G, Luijten HE, Hertzberger DP, van Boven AJ, Vromans RP, Uijen GJ, Verheugt FW. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. Circulation 2002;106:659-65 [PMID=12163424]

Table 20.8: *CARS (warafrin 3mg), 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=8803 (5410 vs. 3393) **Follow-up duration:** 14 months **Study design:** Randomized controlled trial Parallel groups Double blind North America, 293 centres	AMI	**Studied treatment:** warfarin fixed dose 3mg/d + 80 mg ASA **Control treatment:** aspirin 160 mg/d	Ischemic stroke RR=0.93 [0.53;1.61] (Ischaemic stroke)

Reference

. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Lancet 1997;350:389-96 [PMID=9259652]

Table 20.9: *CARS (warfarin 1mg), 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=5421 (2028 vs. 3393) **Follow-up duration:** 14 months **Study design:** Randomized controlled trial Parallel groups Double blind North America, 293 centres	Patients who had had myocardial infarction	**Studied treatment:** warfarin 1mg/d + aspirin 80mg/d **Control treatment:** aspirin 160 mg/d	Ischemic stroke RR=2.23 [1.27;3.92]

Reference

. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Lancet 1997;350:389-96 [PMID=9259652]

Table 20.10: *CHAMP, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=5059 (2522 vs. 2537) **Follow-up duration:** 2.7 years **Study design:** Randomized controlled trial Parallel groups Open US, 78 centres	AMI (patients enrolled within 14 days of infarction)	**Studied treatment:** warfarin target INR 1.5-2.5 + aspirin 81 mg daily **Control treatment:** aspirin 162 mg/d	Myocardial infarction (fatal and non fatal) RR=1.02 [0.88;1.17] Ischemic stroke RR=0.89 [0.66;1.20] (stroke)

Reference

Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation 2002;105:557-63 [PMID=11827919]

Table 20.11: *LoWASA, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3300 (1659 vs. 1641) **Follow-up duration:** 5 years **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Sweden, 31 centres **Inclusion period:** feb 1994 - feb 1999	AMI	**Studied treatment:** warfarin fixed dose 1.25mg/d + ASA 75mg/d **Control treatment:** aspirin alone **Concomittant treat.:**aspirin 75 mg daily	Myocardial infarction (fatal and non fatal) RR=1.04 [0.90;1.22] (Reinfarction) Stroke (fatal and non fatal) RR=0.67 [0.50;0.88] (Stroke) Ischemic stroke RR=0.68 [0.48;0.94] (Non-haemorrhagic)

Reference

Herlitz J, Holm J, Peterson M, Karlson BW, Haglid Evander M, Erhardt L. Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction; the LoWASA Study. Eur Heart J 2004;25:232-9 [PMID=14972424]

Table 20.12: *WARIS II (warfarin+ASA), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=9596 (4927 vs. 4669) **Follow-up duration:** 4 years **Study design:** Randomized controlled trial Parallel groups Open Norway, 20 centres **Inclusion period:** jan 1994 - jun 1998	Patients hospitalized for acute myocardialinfarction	**Studied treatment:** warfarin target INR 2-2.5 +ASA 75mg/d **Control treatment:** ASA 160mg/d	All cause death, MI, thrombo-embolic stroke RR=0.71 [0.59;0.86] Myocardial infarction (fatal and non fatal) RR=0.56 [0.42;0.75] Ischemic stroke RR=0.50 [0.28;0.91]

Reference

Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74 [PMID=12324552]

Table 20.13: *Zibaeenezhad, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=140 (70 vs. 70) **Follow-up duration:** 1 year **Study design:** Randomized controlled trial Parallel groups Open	Acute MI	**Studied treatment:** Warfarin target INR 23 +aspirin **Control treatment:** aspirin 100 mg/day **Concomittant treat.:**aspirin 100 mg daily	Myocardial infarction (fatal and non fatal) RR=0.67 [0.20;2.26]

Reference

Zibaeenezhad MJ, Mowla A, Sorbi MH. Warfarin and aspirin versus aspirin alone in patients with acute myocardial infarction: a pilot study. Angiology 2004;55:17-20 [PMID=14759085]

Table 20.14: *Williams, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=11 (6 vs. 5) **Follow-up duration:** 2.5 months **Study design:** Randomized controlled trial Parallel groups Double blind	Acute MI, unstable angina	**Studied treatment:** warfarin target INR 22.5 +aspirin **Control treatment:** placebo +aspirin **Concomittant treat.:**aspirin 150 mg daily	Myocardial infarction (fatal and non fatal) RR=0.19 [0.03;1.13]

Reference

Williams MJ, Morison IM, Parker JH, Stewart RA. Progression of the culprit lesion in unstable coronary artery disease with warfarin and aspirin versus aspirin alone: preliminary study. J Am Coll Cardiol 1997;30:364-9 [PMID=9247506]

Table 20.15: *WARIS II (warfarin alone), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2422 (1216 vs. 1206) **Follow-up duration:** 48 months **Study design:** Randomized controlled trial Parallel groups NA Norway, 20 centres **Inclusion period:** jan 1994 - jun 1998	Patients hospitalized for acute myocardialinfarction	**Studied treatment:** warfarin target INR 2.8-4.2 **Control treatment:** ASA 160mg/d	Ischemic stroke RR=0.53 [0.29;0.94] (Thromboembolic stroke)

Reference

Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74 [PMID=12324552]

21 Global meta-analysis: all oral anticoagulant

21.1 Global meta-analysis: all oral anticoagulant versus aspirin

Table 21.1: *All oral anticoagulantversus aspirin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
all cause death, MI, thrombo-embolic stroke	RR=0.76	0.57;1.00	0.0469	0.2387 (0.28)	2	3083
myocardial infarction (fatal and non fatal)	RR=1.34	0.80;2.24	0.2715	0.2491 (0.25)	2	1964
ischemic stroke	RR=0.53	0.29;0.94	0.0312	1.0000 (0.00)	1	2422
coronary event	RR=1.32	0.80;2.19	0.2811	1.0000 (0.00)	1	637
coronary death	RR=1.98	1.04;3.79	0.0385	1.0000 (0.00)	1	637
revascularization	RR=0.90	0.58;1.39	0.6388	1.0000 (0.00)	1	661
all cause death	RR=0.96 [1]	0.68;1.36	0.8216	0.0441 (0.63) †	4	5023
intracranial hemorrhage	RR=3.45	0.53;22.67	0.1968	0.4914 (0.00)	2	3083
major bleeding	RR=2.47	0.67;9.06	0.1718	0.1274 (0.57)	2	3083

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

21.2 Global meta-analysis: all oral anticoagulant versus control (on top of aspirin)

Table 21.2: *All oral anticoagulantversus control (on top of aspirin)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
all cause death, MI, thrombo-embolic stroke	RR=0.71	0.59;0.86	0.0000	1.0000 (0.00)	1	9596
myocardial infarction (fatal and non fatal)	RR=0.80 [2]	0.62;1.05	0.1103	0.0017 (0.74) †	6	18956
stroke (fatal and non fatal)	RR=0.67	0.50;0.88	0.0041	1.0000 (0.00)	1	3300
ischemic stroke	RR=0.87 [3]	0.58;1.28	0.4706	0.0051 (0.68) †	7	32906

continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.00 95% CI 0.83;1.21
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.95 95% CI 0.86;1.04
[3] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.85 95% CI 0.71;1.02

Endpoint	Effect	95% CI	p ass	p het	k	n
revascularization	RR=0.65 [4]	0.39;1.10	0.1067	0.0022 (0.84) †	3	10457
all cause death	RR=0.94	0.85;1.05	0.2537	0.2501 (0.23)	8	33180
intracranial hemorrhage	RR=1.26	0.70;2.25	0.4395	0.4049 (0.00)	3	17955
major bleeding	RR=1.69	1.32;2.16	0.0000	0.2963 (0.17)	8	33180

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

21.3 Global meta-analysis: all oral anticoagulant versus placebo

Table 21.3: *All oral anticoagulantversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
myocardial infarction (fatal and non fatal)	RR=0.47	0.38;0.58	0.0000	1.0000 (0.00)	1	3404
ischemic stroke	RR=0.60	0.40;0.89	0.0121	1.0000 (0.00)	1	3404
coronary event	RR=0.81	0.52;1.27	0.3619	1.0000 (0.00)	1	638
coronary death	RR=1.11	0.64;1.92	0.7081	1.0000 (0.00)	1	638
all cause death	RR=0.94	0.78;1.12	0.4821	0.3323 (0.00)	2	4042
major bleeding	RR=3.85	2.34;6.35	0.0000	1.0000 (0.00)	1	3404

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

21.4 Global meta-analysis: all oral anticoagulant versus placebo (on top of aspirin)

Table 21.4: *All oral anticoagulantversus placebo (on top of aspirin)*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
myocardial infarction (fatal and non fatal)	RR=0.19	0.03;1.13	0.0683	1.0000 (0.00)	1	11
ischemic stroke	RR=0.83	0.02;34.94	0.9238	1.0000 (0.00)	1	11
revascularization	RR=1.11	0.45;2.77	0.8209	1.0000 (0.00)	1	11
all cause death	RR=0.42	0.02;10.03	0.5895	1.0000 (0.00)	1	11
major bleeding	RR=1.67	0.07;40.10	0.7529	1.0000 (0.00)	1	11

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

[4] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.85 95% CI 0.76;0.96

22 Ongoing studies of oral anticoagulant

No ongoing trial was identified.

23 Excluded studies for oral anticoagulant

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table 23.1.

Table 23.1: *Excluded studies of oral anticoagulant*

Study	Exclusion reason
OASIS pilot (1998) [1]	
LoWASA (copie de 8025) (0)	
ATACS main (1994) [2]	
ATACS pilot (1990) [3]	
Horizons (2008) [4, 5]	
Huynh (2001) [6]	
OASIS main (2001) [7]	
OASIS pilot phase 2 (0)	

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[1] Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: organization to assess strategies for ischemic syndromes (OASIS) pilot study results. Circulation 1998;98:1064-70. [PMID=9736592]

[2] Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wieczorek I, Fox KA, Chesebro JH, Strain J, Keller C. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. Circulation 1994;89:81-8. [PMID=8281698]

[3] Cohen M, Adams PC, Hawkins L, Bach M, Fuster V. Usefulness of antithrombotic therapy in resting angina pectoris or non-Q-wave myocardial infarction in preventing death and myocardial infarction (a pilot study from the Antithrombotic Therapy in Acute Coronary Syndromes Study Group). Am J Cardiol 1990;66:1287-92. [PMID=2244556]

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[5] Mehran R, Lansky AJ, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Wong SC, Nikolsky E, Gambone L, Vandertie L, Parise H, Dangas GD, Stone GW. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet 2009;374:1149-59. [PMID=19717185]

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[7] . Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. J Am Coll Cardiol 2001;37:475-84. [PMID=11216966]

Part IV

Pentasccharide

24 Overview of pentasccharide

24.1 Included trials

Only one trial which randomized 12092 patients was identified. In all, 1 randomized comparison concerned fondaparinux.
The detailed descriptions of trials and meta-analysis results is given in section 25 (page 174) for fondaparinux.

This trial included 12092 patients and was published in 2006.
This trial was double blind in design.
It was reported in English language.
The table 24.1 (page 170) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

24.2 Summary of meta-analysis results

The meta-analysis of the available trials about pentasccharide provide the results listed in tables 24.2 to 24.2 (page 171) and in the following graphs.

24.2.1 Fondaparinux

Fondaparinux was superior to **placebo** in terms of reinfarction (RR=0.68, 95% CI 0.52 to 0.88, p=0.0038, 1 trial), in-hospital death (RR=0.87, 95% CI 0.76 to 0.99, p=0.0410, 1 trial), deaths or MI (RR=0.87, 95% CI 0.78 to 0.96, p=0.0076, 1 trial)and death at 30 days (RR=0.87, 95% CI 0.78 to 0.98, p=0.0249, 1 trial). However, no significant difference was found on reinfarction at 30 days (RR=0.81, 95% CI 0.65 to 1.01, p=0.0651, 1 trial)and major bleeding (RR=0.83, 95% CI 0.64 to 1.06, p=0.1387, 1 trial).

Table 24.1: *Main study characteristics - pentasccharide*

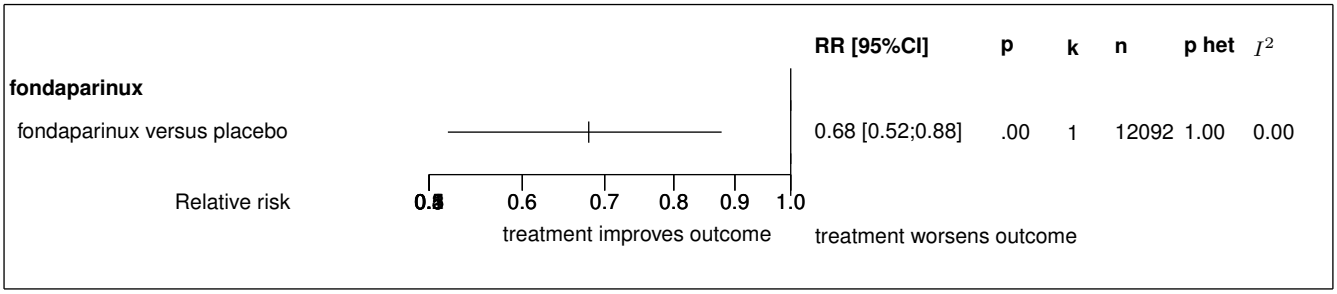
Trial	Patients	Treatments	Trial design and method
Fondaparinux			
Fondaparinux versus placebo			
MICHELANGELO OASIS-6, 2006 [1] n = 6036 vs. 6056	patients with STEMI	fondaparinux 2.5 mg once daily up to 8 days **versus** control (UFH or placebo)	double-blind factorial plan Primary endpoint: death or reinfarction 447 centres, 41 countries

Table 24.2: *Summary of all results for fondaparinux*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
fondaparinux versus placebo						
reinfarction	RR=0.68	0.52;0.88	0.0038	1.0000 (0.00)	1	12092
in-hospital death	RR=0.87	0.76;0.99	0.0410	1.0000 (0.00)	1	12092
deaths or MI	RR=0.87	0.78;0.96	0.0076	1.0000 (0.00)	1	12092
reinfarction at 30 days	RR=0.81	0.65;1.01	0.0651	1.0000 (0.00)	1	12092
death at 30 days	RR=0.87	0.78;0.98	0.0249	1.0000 (0.00)	1	12092
major bleeding	RR=0.83	0.64;1.06	0.1387	1.0000 (0.00)	1	12092

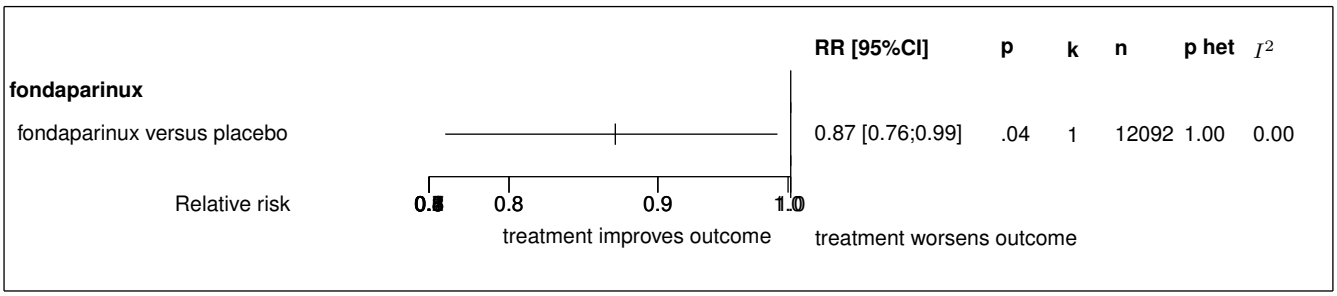
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 24.1: *Forest's plot for reinfarction*



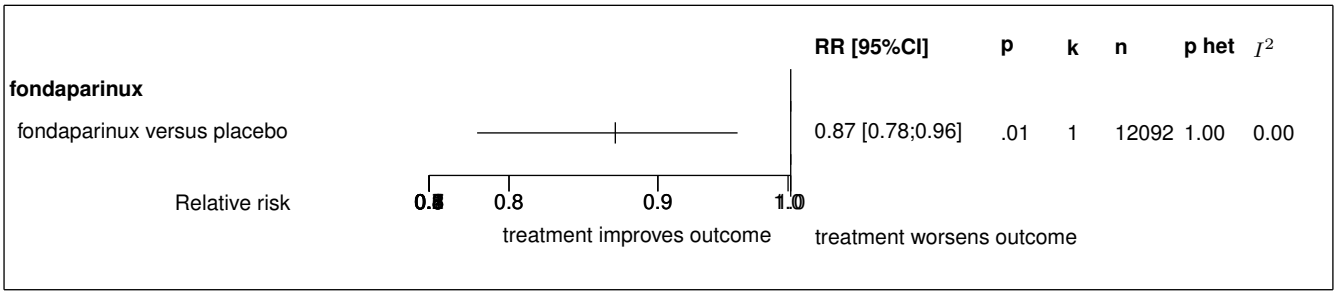
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 24.2: *Forest's plot for in-hospital death*



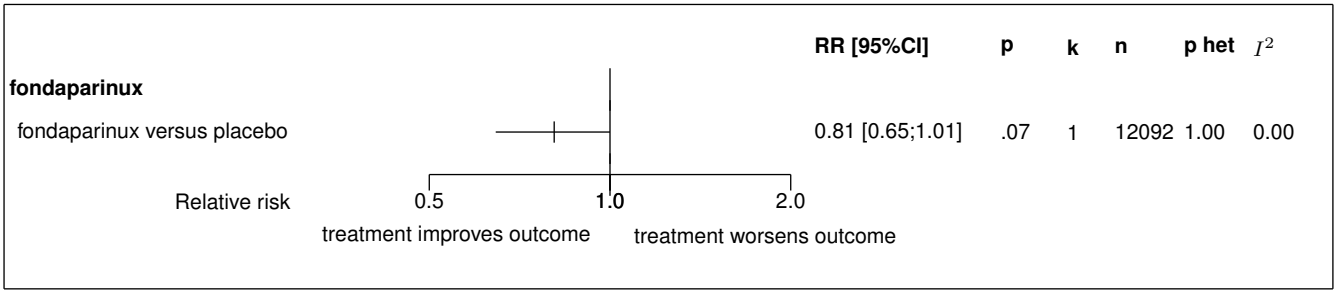
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 24.3: *Forest's plot for deaths or MI*



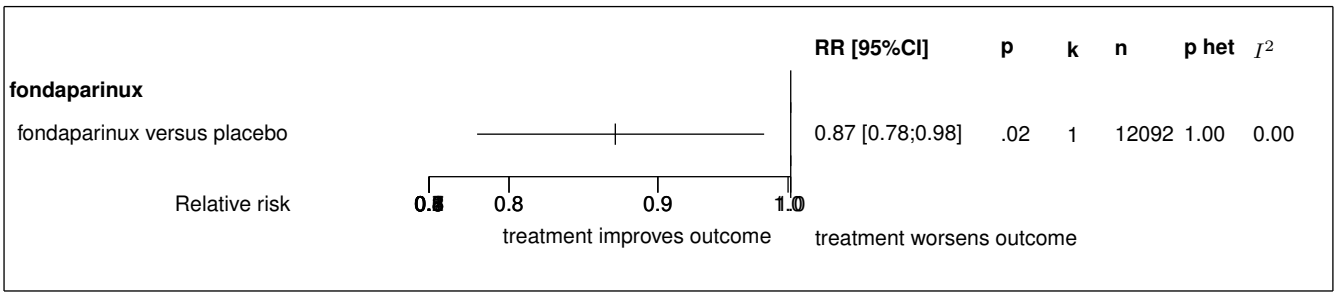
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 24.4: *Forest's plot for reinfarction at 30 days*



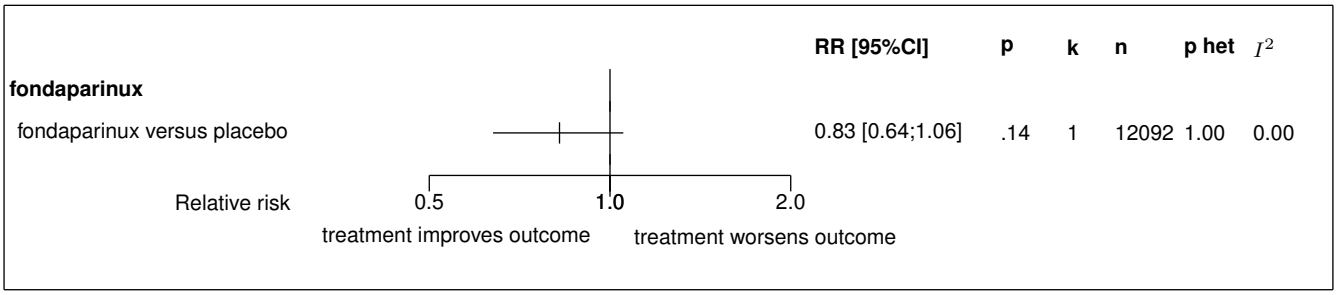
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 24.5: *Forest's plot for death at 30 days*



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 24.6: *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

25 Details

25.1 Available trials

Only one trial which randomized 12092 patients was identified: it compared fondaparinux with placebo.
This trial included 12092 patients and was published in 2006.
This trial was double blind in design.
It was reported in English language.
Death at 30 days data was reported in 1 trials; 1 trials reported data on major bleeding; 1 trials reported data on reinfarction; 1 trials reported data on deaths or MI; 1 trials reported data on reinfarction at 30 days; and 1 trials reported data on in-hospital death.
Following tables 25.1 (page 174), 25.2 (page 174), 25.4 (page 176), and 25.3 (page 175) summarized the main characteristics of the trial including in this systematic review of randomized trials of fondaparinux.

Table 25.1: *Treatment description - pentasccharide - fondaparinux*

Trial	Studied treatment	Control treatment
Fondaparinux versus placebo		
MICHELANGELO OASIS-6 (2006) [1] [a]	fondaparinux 2.5 mg once daily up to 8 days	control (UFH or placebo) placebo in patients in whom unfractionated heparin is not indicated [stratum 1] or unfractionated heparin for up to 48 hours followed by placebo for up to 8 days [stratum 2]

a) from day 3 through day 9, all patients received either fondaparinux or placebo

Table 25.2: *Descriptions of participants - pentasccharide - fondaparinux*

Trial	Patients
Fondaparinux versus placebo	
MICHELANGELO OASIS-6 (2006) [1]	Patients with STEMI

Table 25.3: *Design and methodological quality of trials - pentasccharide - fondaparinux*

Trial	Design	Duration	Centre	Primary endpoint
Fondaparinux versus placebo				
MICHELANGELO OASIS-6, 2006 [1] n=12092	Factorial plan double-blind confirmatory trial at low risk of bias	30 days inclusion period: sep 2003 - jan 2006	41 countries 447 centres	death or reinfarction

Table 25.4: *Trial characteristics - pentasccharide - fondaparinux*

Trial
Fondaparinux versus placebo
MICHELANGELO OASIS-6, 2006 [1]

25.2 Meta-analysis results

The results are detailed in table 25.5 (page 177). This table is followed by the Forest's plot corresponding to each endpoint.

Fondaparinux versus placebo

The single study eligible for this comparison provided data on **reinfarction**. The analysis detected a statistically significant difference in favor of fondaparinux in reinfarction, with a RR of 0.68 (95% CI 0.52 to 0.88, p=0.0038).
The single study eligible for this comparison provided data on **in-hospital death**. The analysis detected a statistically significant difference in favor of fondaparinux in in-hospital death, with a RR of 0.87 (95% CI 0.76 to 0.99, p=0.0410).
The single study eligible for this comparison provided data on **deaths or MI**. The analysis detected a statistically significant difference in favor of fondaparinux in deaths or MI, with a RR of 0.87 (95% CI 0.78 to 0.96, p=0.0076).
The single study eligible for this comparison provided data on **reinfarction at 30 days**. No statistically significant difference between the groups was found in reinfarction at 30 days, with a RR of 0.81 (95% CI 0.65 to 1.01, p=0.0651).
The single study eligible for this comparison provided data on **death at 30 days**. The analysis detected a statistically significant difference in favor of fondaparinux in death at 30 days, with a RR of 0.87 (95% CI 0.78 to 0.98, p=0.0249).
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 0.64 to 1.06, p=0.1387).

Table 25.5: *Results details - pentasccharide - fondaparinux*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fondaparinux versus placebo						
reinfarction	RR=0.68	[0.52;0.88]	0.0038	1.0000 (I^2=0.00)	1	12092
in-hospital death	RR=0.87	[0.76;0.99]	0.0410	1.0000 (I^2=0.00)	1	12092
deaths or MI	RR=0.87	[0.78;0.96]	0.0076	1.0000 (I^2=0.00)	1	12092
reinfarction at 30 days	RR=0.81	[0.65;1.01]	0.0651	1.0000 (I^2=0.00)	1	12092
death at 30 days	RR=0.87	[0.78;0.98]	0.0249	1.0000 (I^2=0.00)	1	12092
major bleeding	RR=0.83	[0.64;1.06]	0.1387	1.0000 (I^2=0.00)	1	12092

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 25.1: *Forest's plot for reinfarction*

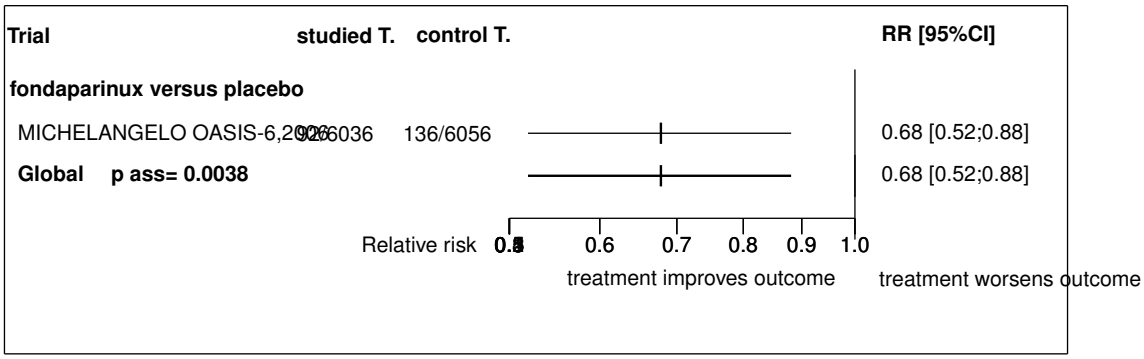


Figure 25.2: *Forest's plot for in-hospital death*

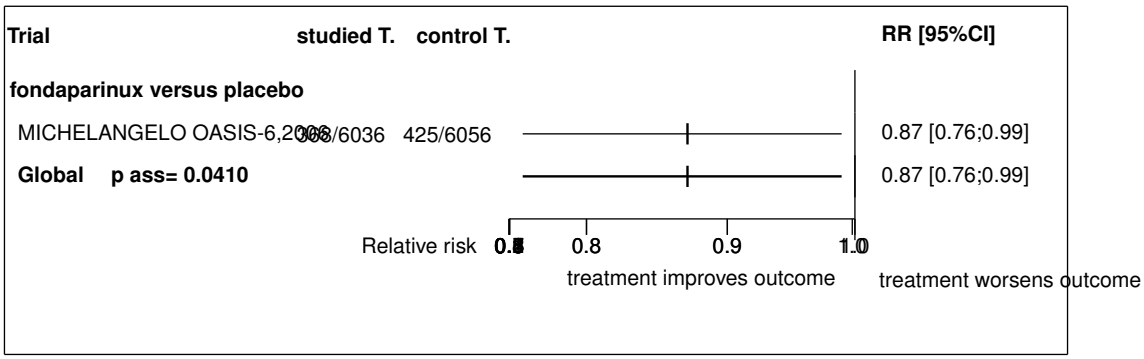


Figure 25.3: *Forest's plot for deaths or MI*

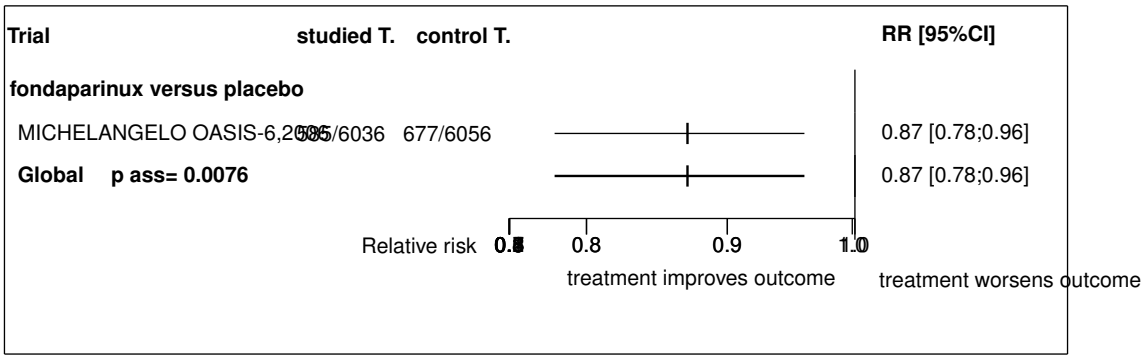


Figure 25.4: *Forest's plot for reinfarction at 30 days*

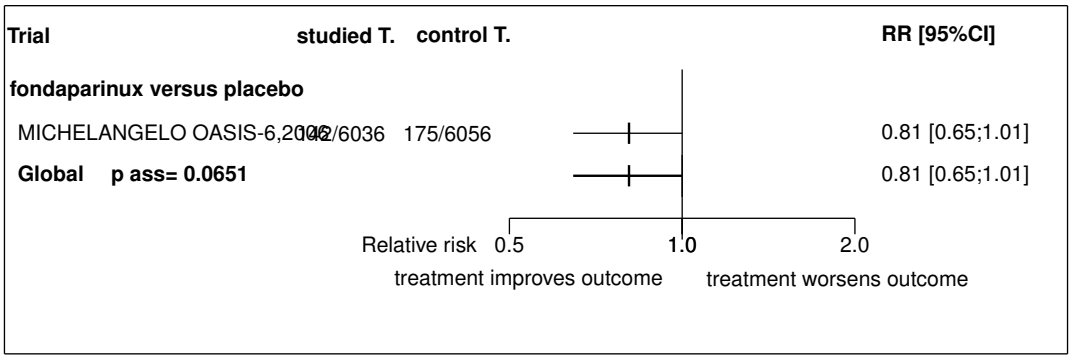


Figure 25.5: *Forest's plot for death at 30 days*

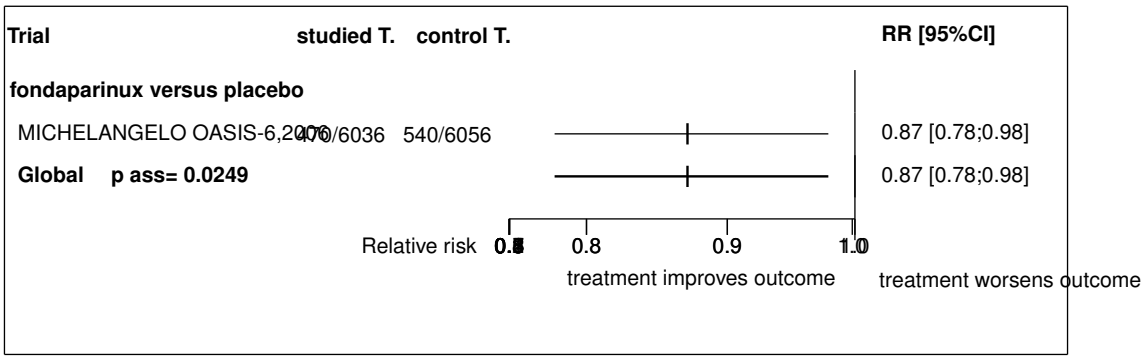
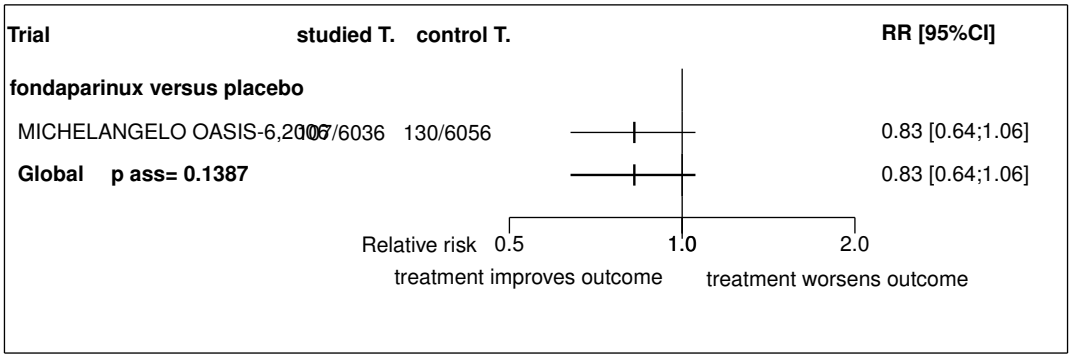


Figure 25.6: *Forest's plot for major bleeding*



References

[1] Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA 2006;295:1519-30. [PMID=16537725]

25.3 Individual trial summaries

Table 25.6: *MICHELANGELO OASIS-6, 2006 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=12092 (6036 vs. 6056) **Follow-up duration:** 30 days **Study design:** Randomized controlled trial Factorial plan Double-blind Confirmatory trial at low risk of bias 41 countries, 447 centres **Inclusion period:** sep 2003 - jan 2006	Patients with STEMI	**Studied treatment:** fondaparinux 2.5 mg once daily up to 8 days **Control treatment:** control (UFH or placebo) placebo in patients in whom unfractionated heparin is not indicated [stratum 1] or unfractionated heparin for up to 48 hours followed by placebo for up to 8 days [stratum 2] **note:** from day 3 through day 9, all patients received either fondaparinux or placebo	Reinfarction RR=0.68 [0.52;0.88] (at 9 days) In-hospital death RR=0.87 [0.76;0.99] (at 9 days) Deaths or MI RR=0.87 [0.78;0.96] Reinfarction at 30 days RR=0.81 [0.65;1.01] Death at 30 days RR=0.87 [0.78;0.98]

Reference

Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA 2006;295:1519-30 [PMID=16537725]

26 Global meta-analysis: all pentasccharide

26.1 Global meta-analysis: all pentasccharide versus placebo

Table 26.1: *All pentasccharideversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
reinfarction	RR=0.68	0.52;0.88	0.0038	1.0000 (0.00)	1	12092
in-hospital death	RR=0.87	0.76;0.99	0.0410	1.0000 (0.00)	1	12092
deaths or MI	RR=0.87	0.78;0.96	0.0076	1.0000 (0.00)	1	12092
reinfarction at 30 days	RR=0.81	0.65;1.01	0.0651	1.0000 (0.00)	1	12092
death at 30 days	RR=0.87	0.78;0.98	0.0249	1.0000 (0.00)	1	12092
major bleeding	RR=0.83	0.64;1.06	0.1387	1.0000 (0.00)	1	12092

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

27 Ongoing studies of pentasccharide

No ongoing trial was identified.

28 Excluded studies for pentasccharide

No trial was excluded.

References

Part V

Unfractionated heparin

29 Overview of unfractionated heparin

29.1 Included trials

A total of 4 randomized comparisons which enrolled 1231 patients were identified. In all, 4 randomized comparisons concerned UFH.
The detailed descriptions of trials and meta-analysis results is given in section 30 (page 190) for UFH.

The average study size was 307 patients (range 128 to 644). The first study was published in 1987, and the last study was published in 1994.
A total of 2 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 29.1 (page 188) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

29.2 Summary of meta-analysis results

The meta-analysis of the available trials about unfractionated heparin provide the results listed in tables 29.2 to 29.2 (page 189) and in the following graphs.

29.2.1 UFH

No significant difference was found between **UFH** and **no heparin** in terms of reinfarction (RR=0.77, 95% CI 0.07 to 7.88, p=0.8244, 2 trials)and in-hospital death (RR=1.37, 95% CI 0.71 to 2.65, p=0.3456, 2 trials).

No significant difference was found between **UFH** and **placebo** in terms of reinfarction (RR=1.07, 95% CI 0.48 to 2.41, p=0.8660, 2 trials)and in-hospital death (RR=0.72, 95% CI 0.32 to 1.62, p=0.4254, 2 trials).

Table 29.1: *Main study characteristics - unfractionated heparin*

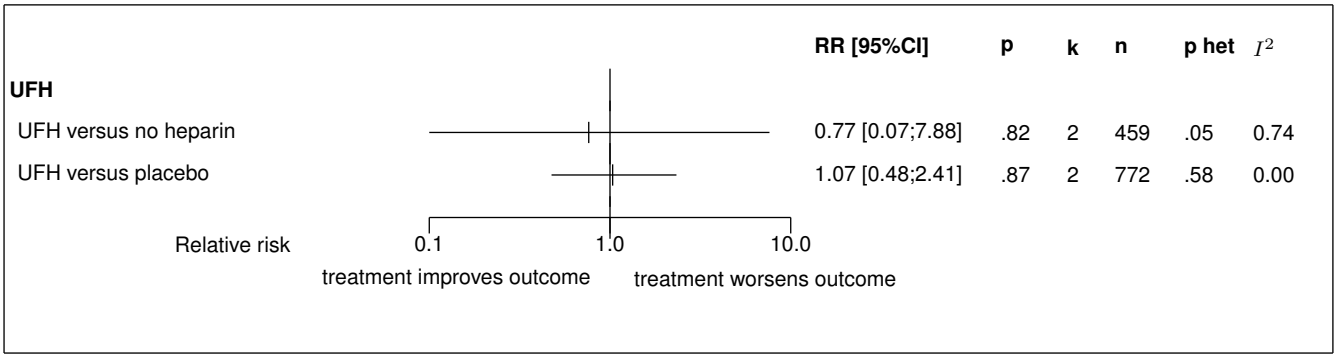
Trial	Patients	Treatments	Trial design and method
UFH			
UFH versus no heparin			
ISIS-2 Pilot, 1987 [1] n = 106 vs. 103	patients with suspected MI <=24 h	UFH nNo bolus, 1000 IU/h for 48 h **versus** no heparin	open parallel groups Primary endpoint: new MI, death
DUCCS, 1994 [2] n = 128 vs. 122	patients with acute myocardial infarction four hours after APSAC administration, age <=85 y STEMI <=12 h	UFH no bolus, 15 IU/kg per h for 4 d; target aPTT 5090 s **versus** no heparin	open parallel groups Primary endpoint: death, recurrent MI, recurrent ischemia, angiographic patency
UFH versus placebo			
ECSG, 1992 [3] n = 324 vs. 320	patients treated with alteplase thrombolysis for acute myocardial infarction, Age 2170 y STEMI <=6h	UFH 5000 IU bolus, UFH 1000 IU/h for 48120 h **versus** placebo	double-blind parallel groups Primary endpoint: angiographic patency
OSIRIS, 1992 [4] n = 64 vs. 64	STEMI w=6 h	UFH 10 000 IU bolus, 1000 IU/h for 24 h **versus** placebo	double-blind parallel groups Primary endpoint: reperfusion, angiographic patency, LVEF

Table 29.2: *Summary of all results for UFH*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
UFH versus no heparin						
reinfarction	RR=0.77	0.07;7.88	0.8244	0.0519 (0.74)	2	459
in-hospital death	RR=1.37	0.71;2.65	0.3456	0.8852 (0.00)	2	459
UFH versus placebo						
reinfarction	RR=1.07	0.48;2.41	0.8660	0.5842 (0.00)	2	772
in-hospital death	RR=0.72	0.32;1.62	0.4254	0.4694 (0.00)	2	772

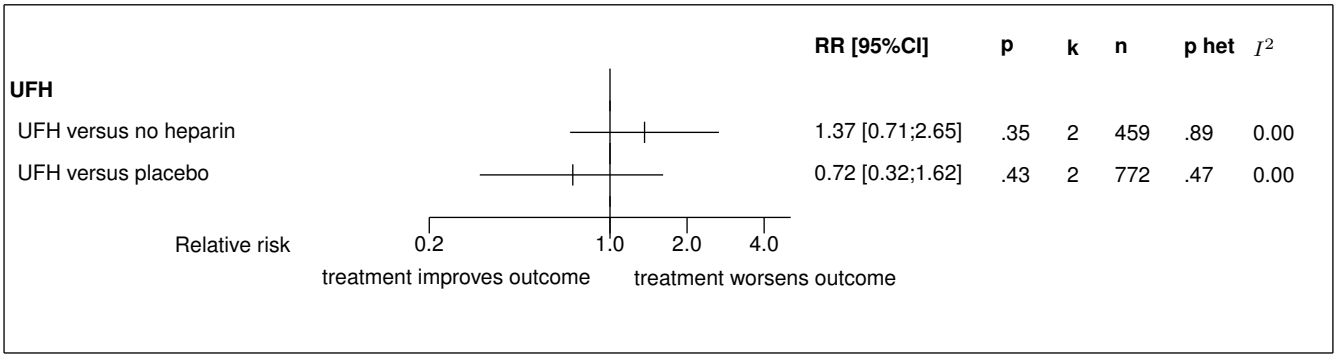
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 29.1: *Forest's plot for reinfarction*



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 29.2: *Forest's plot for in-hospital 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

30 Details

30.1 Available trials

A total of 4 RCTs which randomized 1231 patients were identified: 2 trials compared UFH with no heparin and 2 trials compared UFH with placebo.
The average study size was 307 patients (range 128 to 644). The first study was published in 1987, and the last study was published in 1994.
A total of 2 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.
Reinfarction data was reported in 4 trials; and 4 trials reported data on in-hospital death.
Following tables 30.1 (page 190), 30.2 (page 190), 30.4 (page 192), and 30.3 (page 191) summarized the main characteristics of the trials including in this systematic review of randomized trials of UFH.

Table 30.1: *Treatment description - unfractionated heparin - UFH*

Trial	Studied treatment	Control treatment
UFH versus no heparin		
ISIS-2 Pilot (1987) [1]	UFH nNo bolus, 1000 IU/h for 48 h **Concomittant treatment:** SK 1.5 MU over 1 h	No heparin
DUCCS (1994) [2]	UFH no bolus, 15 IU/kg per h for 4 d; target aPTT 5090 s **Concomittant treatment:** APSAC 30 U over 25 min	No heparin
UFH versus placebo		
ECSG (1992) [3]	UFH 5000 IU bolus, UFH 1000 IU/h for 48120 h **Concomittant treatment:** tPA 100 mg over 3 h	Placebo
OSIRIS (1992) [4]	UFH 10 000 IU bolus, 1000 IU/h for 24 h **Concomittant treatment:** SK 1.5 MU over 1 h	Placebo

Table 30.2: *Descriptions of participants - unfractionated heparin - UFH*

Trial	Patients
UFH versus no heparin	
ISIS-2 Pilot (1987) [1]	Patients with suspected MI <=24 h

continued...

Trial	Patients
DUCCS (1994) [2]	Patients with acute myocardial infarction four hours after APSAC administration, age <=85 y STEMI <=12 h
UFH versus placebo	
ECSG (1992) [3]	Patients treated with alteplase thrombolysis for acute myocardial infarction, Age 2170 y STEMI <=6h
OSIRIS (1992) [4]	STEMI w=6 h

Table 30.3: *Design and methodological quality of trials - unfractionated heparin - UFH*

Trial	Design	Duration	Centre	Primary endpoint
UFH versus no heparin				
ISIS-2 Pilot, 1987 [1] n=209	Parallel groups open	In-hospital, 1 y (deat		New MI, death
DUCCS, 1994 [2] n=250	Parallel groups open	14 d		Death, recurrent MI, recurrent ischemia, angiographic patency
UFH versus placebo				
ECSG, 1992 [3] n=644	Parallel groups Double-blind	In-hospital		Angiographic patency
OSIRIS, 1992 [4] n=128	Parallel groups Double-blind	In-hospital		Reperfusion, angiographic patency, LVEF

Table 30.4: *Trial characteristics - unfractionated heparin - UFH*

Trial
UFH versus no heparin
ISIS-2 Pilot, 1987 [1]
DUCCS, 1994 [2]
UFH versus placebo
ECSG, 1992 [3]
OSIRIS, 1992 [4]

30.2 Meta-analysis results

The results are detailed in table 30.5 (page 193). This table is followed by the Forest's plot corresponding to each endpoint.

UFH versus no heparin

All the 2 studies had extractable data about the number of participants with **reinfarction**. When pooled together, there was no statistically significant difference between the groups in reinfarction, with a RR of 0.77 (95% CI 0.07 to 7.88, p=0.8244). No heterogeneity was detected (p = 0.0519, I^2 = 0.74%).
All the 2 studies had extractable data about the number of participants with **in-hospital death**. When pooled together, there was no statistically significant difference between the groups in in-hospital death, with a RR of 1.37 (95% CI 0.71 to 2.65, p=0.3456). No heterogeneity was detected (p = 0.8852, I^2 = 0.00%).

UFH versus placebo

All the 2 studies had extractable data about the number of participants with **reinfarction**. When pooled together, there was no statistically significant difference between the groups in reinfarction, with a RR of 1.07 (95% CI 0.48 to 2.41, p=0.8660). No heterogeneity was detected (p = 0.5842, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **in-hospital death**. When pooled together, there was no statistically significant difference between the groups in in-hospital death, with a RR of 0.72 (95% CI 0.32 to 1.62, p=0.4254). No heterogeneity was detected (p = 0.4694, I^2 = 0.00%).

Table 30.5: *Results details - unfractionated heparin - UFH*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
UFH versus no heparin						
reinfarction	RR=0.77	[0.07;7.88]	0.8244	0.0519 (I^2=0.74)	2	459
in-hospital death	RR=1.37	[0.71;2.65]	0.3456	0.8852 (I^2=0.00)	2	459
UFH versus placebo						
reinfarction	RR=1.07	[0.48;2.41]	0.8660	0.5842 (I^2=0.00)	2	772
in-hospital death	RR=0.72	[0.32;1.62]	0.4254	0.4694 (I^2=0.00)	2	772

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 reinfarction*

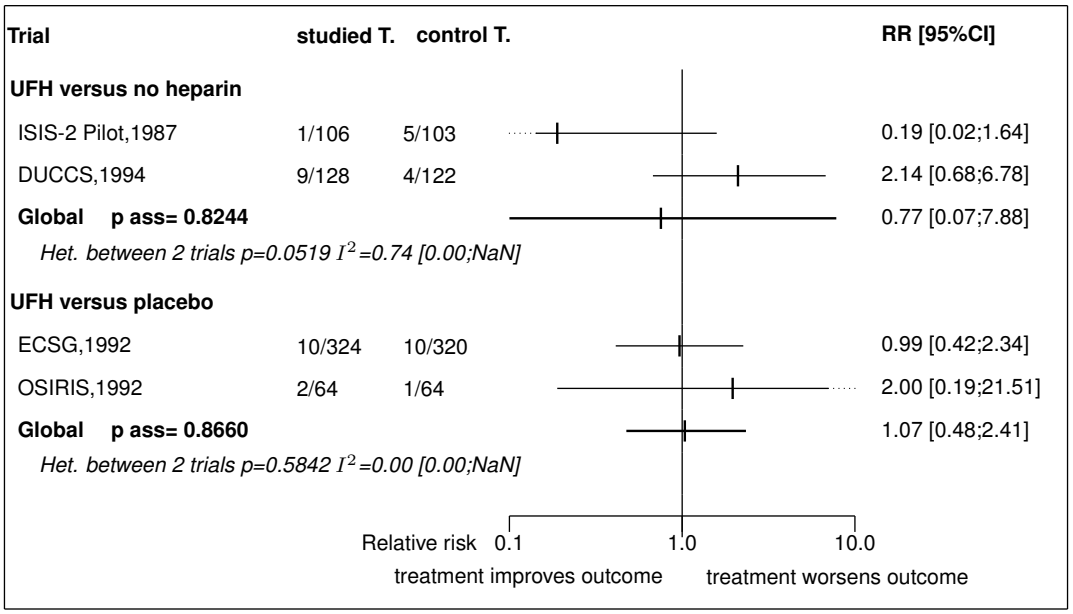
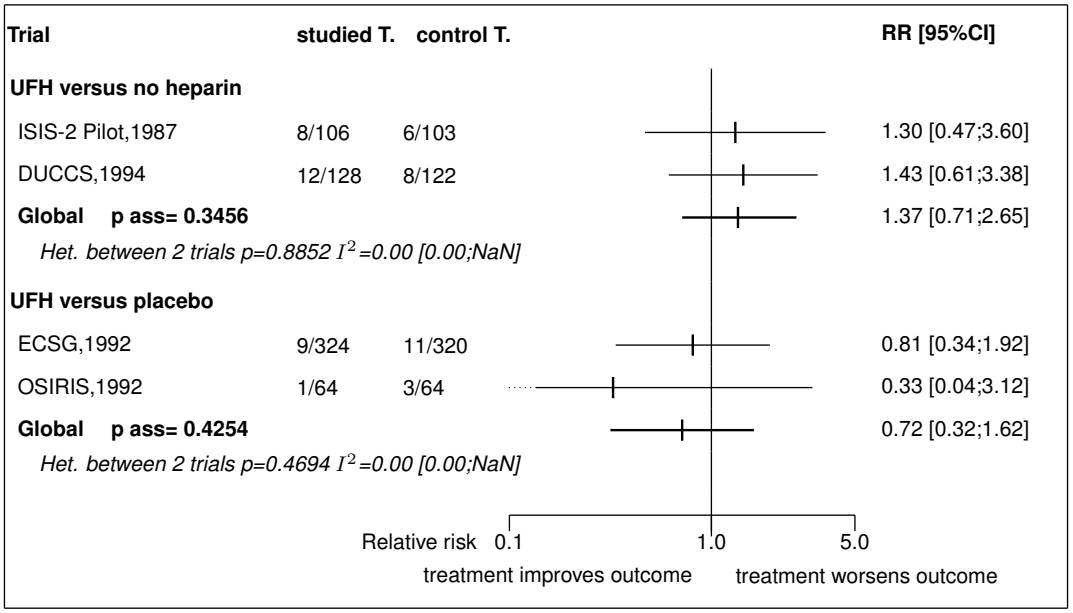


Figure 30.2: *Forest's plot for in-hospital death*



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30.3 Individual trial summaries

Table 30.6: *ISIS-2 Pilot, 1987 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=209 (106 vs. 103) **Follow-up duration:** In-hospital, 1 y (deat **Study design:** Randomized controlled trial Parallel groups Open	Patients with suspected MI <=24 h	**Studied treatment:** UFH nNo bolus, 1000 IU/h for 48 h **Control treatment:** No heparin **Concomittant treat.:**SK 1.5 MU over 1 h	Reinfarction RR=0.19 [0.02;1.64] In-hospital death RR=1.30 [0.47;3.60]

Reference

. Randomized factorial trial of high-dose intravenous streptokinase, of oral aspirin and of intravenous heparin in acute myocardial infarction. ISIS (International Studies of Infarct Survival) pilot study. Eur Heart J 1987;8:634-42 [PMID=2887430]

Table 30.7: *DUCCS, 1994 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=250 (128 vs. 122) **Follow-up duration:** 14 d **Study design:** Randomized controlled trial Parallel groups Open	Patients with acute myocardial infarction four hours after APSAC administration, age <=85 y STEMI <=12 h	**Studied treatment:** UFH no bolus, 15 IU/kg per h for 4 d; target aPTT 5090 s **Control treatment:** No heparin **Concomittant treat.:**APSAC 30 U over 25 min	Reinfarction RR=2.14 [0.68;6.78] In-hospital death RR=1.43 [0.61;3.38]

Reference

O'Connor CM, Meese R, Carney R, Smith J, Conn E, Burks J, Hartman C, Roark S, Shadoff N, Heard M 3rd. A randomized trial of intravenous heparin in conjunction with anistreplase (anisoylated plasminogen streptokinase activator complex) in acute myocardial infarction: the Duke University Clinical Cardiology Study (DUCCS) 1. J Am Coll Cardiol 1994;23:11-8 [PMID=8277068]

Table 30.8: *ECSG, 1992 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=644 (324 vs. 320) **Follow-up duration:** In-hospital **Study design:** Randomized controlled trial Parallel groups Double-blind	Patients treated with alteplase thrombolysis for acute myocardial infarction, Age 2170 y STEMI <=6h	**Studied treatment:** UFH 5000 IU bolus, UFH 1000 IU/h for 48120 h **Control treatment:** Placebo **Concomittant treat.:**tPA 100 mg over 3 h	Reinfarction RR=0.99 [0.42;2.34] In-hospital death RR=0.81 [0.34;1.92]

Reference

de Bono DP, Simoons ML, Tijssen J, Arnold AE, Betriu A, Burgersdijk C, Lpez Bescos L, Mueller E, Pfisterer M, Van de Werf F. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. Br Heart J 1992;67:122-8 [PMID=1540431]

Table 30.9: *OSIRIS, 1992 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=128 (64 vs. 64) **Follow-up duration:** In-hospital **Study design:** Randomized controlled trial Parallel groups Double-blind	STEMI w=6 h	**Studied treatment:** UFH 10 000 IU bolus, 1000 IU/h for 24 h **Control treatment:** Placebo **Concomittant treat.:**SK 1.5 MU over 1 h	Reinfarction RR=2.00 [0.19;21.51] In-hospital death RR=0.33 [0.04;3.12]

Reference

Col J, Decoster O, Hanique G, Delligne B, Boland J, Pirenne B, Cheron. Infusion of heparin conjunct to streptokinase acceleratesreperfusion of acute myocardial infarction: results of a double blindrandomized study (OSIRIS).6891. Circulation. 1992;86(suppl 1):259a

31 Global meta-analysis: all unfractionated heparin

31.1 Global meta-analysis: all unfractionated heparin versus no heparin

Table 31.1: *All unfractionated heparinversus no heparin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
reinfarction	RR=0.77	0.07;7.88	0.8244	0.0519 (0.74)	2	459
in-hospital death	RR=1.37	0.71;2.65	0.3456	0.8852 (0.00)	2	459

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 unfractionated heparin versus placebo

Table 31.2: *All unfractionated heparinversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
reinfarction	RR=1.07	0.48;2.41	0.8660	0.5842 (0.00)	2	772
in-hospital death	RR=0.72	0.32;1.62	0.4254	0.4694 (0.00)	2	772

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 unfractionated heparin

No ongoing trial was identified.

33 Excluded studies for unfractionated heparin

No trial was excluded.

References