Myocardial revascularization for acute coronary syndrome

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 Myocardial revascularization for acute coronary syndrome.

Contents

0.1 Synthesis of the meta-analysis results

In all 27 randomised controlled trials (RCTs) were included. These included 1 studie of **cooling-off strategy** involving 410 patients, 13 studies of **early invasive strategy** involving 14,172 patients, 12 studies of **fibrinolytic** involving 2,758 patients and 1 studie of **surgery** involving 468 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 Cooling-off strategy

Only one trials including 410 patients was found.
Among these comparisons, one trial are about early intervention.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with early intervention for all the endpoints with data in at least one trial are summarized table 1.

Table 1: *Results summary - Early intervention*

Benefit	Harmful	No evidence
	Early intervention versus early strategy	
	↑ deaths or MI RR=1.96* [1.01;3.82] k=1	→ non fatal MI RR=1.72^{NS} [0.87;3.40] k=1 → all cause death RR=5.88^{NS} [0.30;116.74] k=1 → major bleeding RR=1.31^{NS} [0.46;3.70] k=1

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

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

0.1.2 Early invasive strategy

Reports of 13 trials (including 14,172 patients) were identified .
Among these comparisons, one trial are about early invasive management,two about immediate invasive management,7 about routine invasive strategy and 3 about routine invasive strategy - noncomptemporary.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. One ongoing trial was identified.

Early invasive management

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

Table 2: *Results summary - Early invasive management*

Benefit	Harmful	No evidence
Early invasive management versus delayed invasive strategy		
↓ death, MI, stroke, refractory ischemia RR=0.72† [0.58;0.89] k=1		→ in-hospital death RR=0.86^{NS} [0.58;1.28] k=1 → death or stroke or myocardial infarction RR=0.85^{NS} [0.68;1.06] k=1 → repeat intervention RR=1.04^{NS} [0.81;1.33] k=1 → myocardial infarction (fatal and non fatal) RR=0.83^{NS} [0.61;1.13] k=1 → stroke (fatal and non fatal) RR=0.90^{NS} [0.49;1.66] k=1 → all cause death RR=0.81^{NS} [0.60;1.10] k=1 → major bleeding RR=0.89^{NS} [0.60;1.32] k=1

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

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

Immediate invasive management

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

Table 3: *Results summary - Immediate invasive management*

Benefit	Harmful	No evidence
Immediate invasive management versus delayed invasive strategy		
	↑ myocardial infarction (fatal and non fatal) RR=1.66† [1.20;2.30] k=2	→ repeat intervention RR=0.63^{NS} [0.11;3.66] k=1 → all cause death RR=2.53^{NS} [0.50;12.86] k=1 → major bleeding RR=0.55^{NS} [0.26;1.17] k=2

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

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

Routine invasive strategy

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

Table 4: *Results summary - Routine invasive strategy*

Benefit	Harmful	No evidence
Routine invasive strategy versus concervative strategy		

continued...

Benefit	Harmful	No evidence
↓ rehospitalization RR=0.74† [0.62;0.89] H k=6 ↓ long term cardiovascular events RR=0.83† [0.73;0.93] k=3 ↑ no angina (at 6 weeks) RR=1.61¶ [1.52;1.72] k=1 ↓ long term MI RR=0.77¶ [0.67;0.90] k=3 ↓ all cause death RR=0.79* [0.63;0.98] k=7	↑ adverse events RR=2.38¶ [1.42;3.98] k=1	→ in-hospital death RR=1.29^{NS} [0.74;2.27] k=7 → in hospital non fatal MI RR=1.24^{NS} [0.71;2.17] H k=7 → in hospital death or MI RR=1.21^{NS} [0.73;2.00] H k=7 → deaths or MI RR=0.81^{NS} [0.59;1.11] H k=7 → CCS class III-IV angina RR=0.72^{NS} [0.49;1.06] H k=4 → long term cardiovascular death RR=0.84^{NS} [0.69;1.01] k=3 → long term all cause death, MI RR=0.88^{NS} [0.75;1.03] k=3 → myocardial infarction (fatal and non fatal) RR=0.37^{NS} [0.04;3.38] k=1 → long term death RR=1.16^{NS} [0.89;1.52] H k=3 → non fatal MI RR=0.81^{NS} [0.57;1.16] H k=7 → major bleeding RR=2.13^{NS} [0.97;4.70] k=1

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

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

Routine invasive strategy - noncomptemporary

Results obtained with routine invasive strategy - noncomptemporary for all the endpoints with data in at least one trial are summarized table 5.

Table 5: *Results summary - Routine invasive strategy - noncomptemporary*

Benefit	Harmful	No evidence
Routine invasive strategy - noncomptemporary versus concervative strategy		
		→ in-hospital death RR=1.39^{NS} [0.46;4.20] H k=3 → in hospital non fatal MI RR=1.24^{NS} [0.85;1.81] k=3 → in hospital death or MI RR=1.45^{NS} [0.79;2.66] k=3 → deaths or MI RR=1.00^{NS} [0.83;1.19] k=3 → CCS class III-IV angina RR=0.93^{NS} [0.70;1.22] k=3 → rehospitalization RR=0.90^{NS} [0.80;1.01] k=3 → positive 6-wk ETT RR=0.87^{NS} [0.63;1.20] k=1 → no angina (at 6 weeks) RR=1.05^{NS} [0.98;1.12] k=1 → non fatal MI RR=0.87^{NS} [0.70;1.08] k=3 → all cause death RR=1.18^{NS} [0.93;1.51] k=3

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

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

0.1.3 Fibrinolytic

Reports of 12 trials (including 2,758 patients) were identified .
Among these comparisons, one trial are about anistreplase,one about intracoronary urokinase and 10 about t-PA.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Anistreplase

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

Table 6: *Results summary - Anistreplase*

Benefit	Harmful	No evidence
	Anistreplase versus placebo	
	↑ bleeding RR=2.96† [1.34;6.57] k=1	→ in-hospital death RR=2.96^{NS} [0.31;27.88] k=1 → myocardial infarction (fatal and non fatal) RR=1.36^{NS} [0.85;2.18] 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)

Intracoronary urokinase

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

Table 7: *Results summary - Intracoronary urokinase*

Benefit	Harmful	No evidence
	Intracoronary urokinase versus placebo	
		→ myocardial infarction (fatal and non fatal) RR=1.23^{NS} [0.38;3.96] 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)

T-PA

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

Table 8: *Results summary - T-PA*

Benefit	Harmful	No evidence
	T-PA versus placebo	
	↑ bleeding RR=2.60* [1.19;5.71] k=2	→ in-hospital death RR=1.56^{NS} [0.39;6.27] k=5 → myocardial infarction (fatal and non fatal) RR=1.12^{NS} [0.49;2.60] k=5 → all cause death RR=1.00^{NS} [0.07;15.36] 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 Surgery

Only one trials including 468 patients was found.
Among these comparisons, one trial are about surgery.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with surgery for all the endpoints with data in at least one trial are summarized table 9.

Table 9: *Results summary - Surgery*

Benefit	Harmful	No evidence
	Surgery versus medical treatment	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ 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 myocardial revascularization for the treatment of acute coronary syndrome. The following classes of treatment are considered:

1. cooling-off strategy
2. early invasive strategy
3. fibrinolytic
4. surgery

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of myocardial revascularization for the treatment of acute coronary syndrome 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 coronary syndrome.

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

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 Non fatal MI, Deaths or MI, All cause death, Major bleeding, .

1.6 Structure of the report

Each of the eligible studies is summarised in part **??**. A summary of the studies together with an evaluation of their quality is given in part I to **??**, listed by therapeutic class. The therapeutic classes included cooling-off strategy, early invasive strategy, fibrinolytic, surgery,
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

Cooling-off strategy

2 Overview of cooling-off strategy

2.1 Included trials

Only one trial which randomized 410 patients was identified. In all, 1 randomized comparison concerned early intervention.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 21) for early intervention.

This trial included 410 patients and was published in 2003.
This trial was open-label in design.
It was reported in English language.
The table 2.1 (page 18) 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 cooling-off strategy provide the results listed in tables 2.2 to 2.2 (page 19) and in the following graphs.

2.2.1 Early intervention

Early intervention was inferior to **early strategy** in terms of deaths or MI (RR=1.96, 95% CI 1.01 to 3.82, p=0.0472, 1 trial). No significant difference was found on non fatal MI (RR=1.72, 95% CI 0.87 to 3.40, p=0.1208, 1 trial)and all cause death (RR=5.88, 95% CI 0.30 to 116.74, p=0.2450, 1 trial).

Table 2.1: *Main study characteristics - cooling-off strategy*

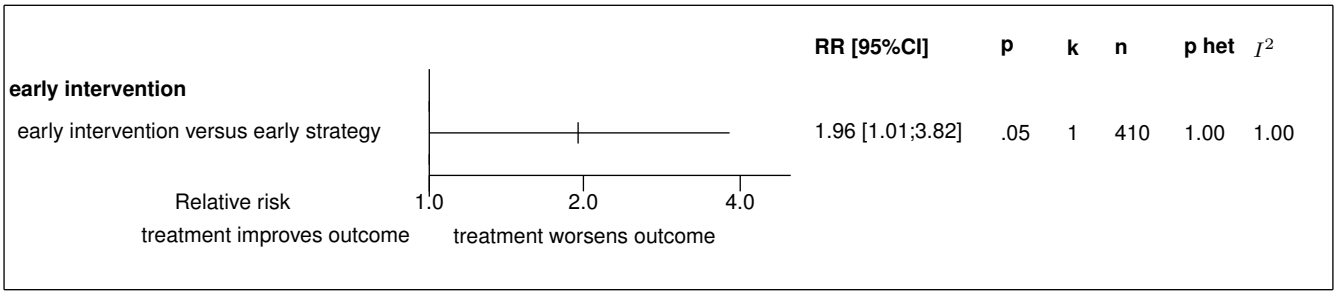
Trial	Patients	Treatments	Trial design and method
Early intervention			
Early intervention versus early strategy			
ISAR-COOL, 2003 [1] n = 207 vs. 203	patients with symptoms of unstable angina plus either ST-segment depression orelevation of cardiac troponin T levels	prolonged (3 to 5 days) antithromboticpretreatment (Cooling-Off strategy)before intervention **versus** early intervention after pretreatment for less than 6 hours	open parallel groups Primary endpoint: death or large MI 2 centres, Germany

Table 2.2: *Summary of all results for early intervention*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
early intervention versus early strategy						
deaths or MI	RR=1.96	1.01;3.82	0.0472	1.0000 (1.00)	1	410
non fatal MI	RR=1.72	0.87;3.40	0.1208	1.0000 (0.00)	1	410
all cause death	RR=5.88	0.30;116.74	0.2450	1.0000 (0.00)	1	410
major bleeding	RR=1.31	0.46;3.70	0.6135	1.0000 (0.00)	1	410

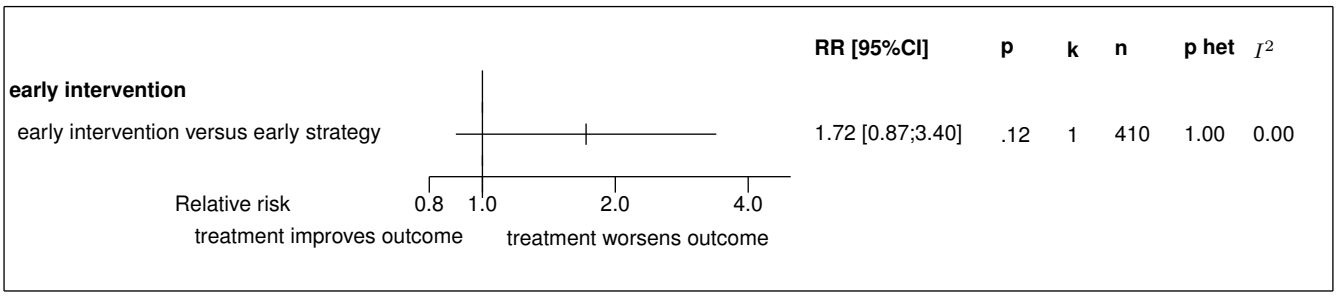
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 2.1: *Forest's plot for deaths or MI*



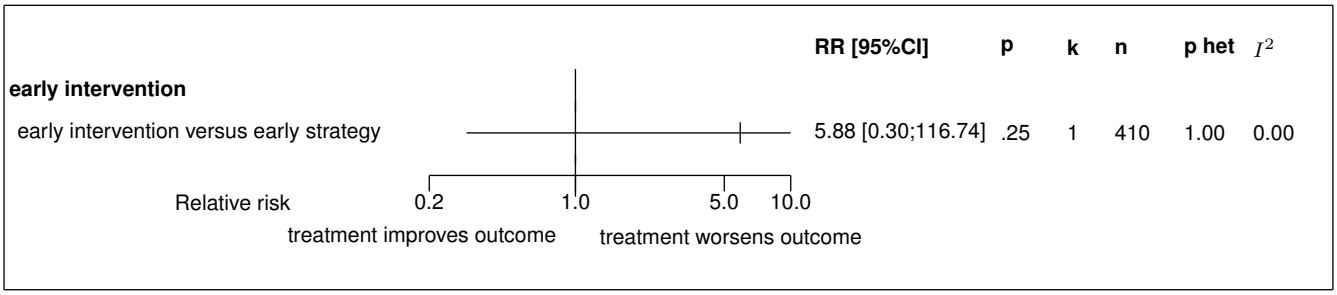
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.2: *Forest's plot for non fatal MI*



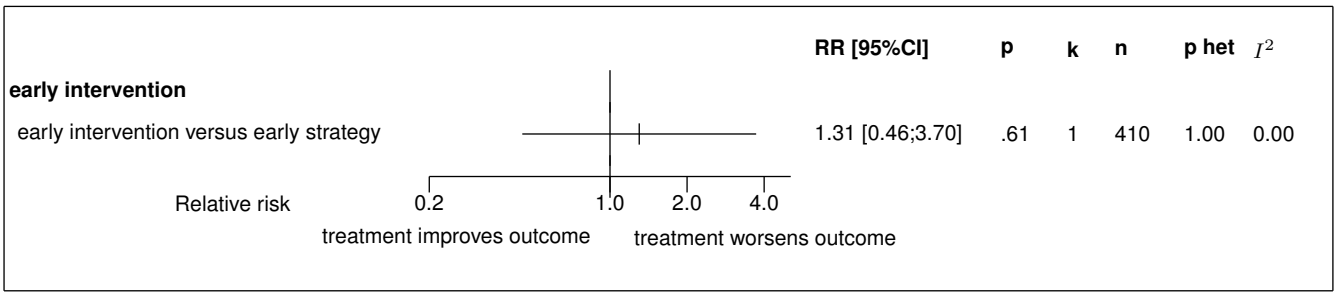
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.3: *Forest's plot for all cause death*



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

Figure 2.4: *Forest's plot for major bleeding*



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

3 Details

3.1 Available trials

Only one trial which randomized 410 patients was identified: it compared early intervention with early strategy.
This trial included 410 patients and was published in 2003.
This trial was open-label in design.
It was reported in English language.
Non fatal MI data was reported in 1 trials; 1 trials reported data on deaths or MI; 1 trials reported data on all cause death; and 1 trials reported data on major bleeding.
Following tables 3.1 (page 21), 3.2 (page 21), 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 early intervention.

Table 3.1: *Treatment description - cooling-off strategy - early intervention*

Trial	Studied treatment	Control treatment
Early intervention versus early strategy		
ISAR-COOL (2003) [1]	Prolonged (3 to 5 days) antithromboticpretreatment (Cooling-Off strategy)before intervention antithrombotic pretreatment for 3to 5 days with intravenous unfractionated heparin (60-U/kgbolus followed by infusion adjusted to maintain partial thromboplastin time of 60 to 85seconds), aspirin (500-mg intravenous bolus followed by 100-mg twice-daily oral dose),oral clopidogrel (600-mg loading dose followed by 75-mg twice-daily dose), and intravenoustirofiban (10-g/kg bolus followed by continuous infusion of 0.10 g/kg per min).D	early intervention after pretreatment for less than 6 hours antithrombotic pretreatment consisted of intravenous unfractionated heparin (60-U/kgbolus followed by infusion adjusted to maintain partial thromboplastin time of 60 to 85seconds), aspirin (500-mg intravenous bolus followed by 100-mg twice-daily oral dose),oral clopidogrel (600-mg loading dose followed by 75-mg twice-daily dose), and intravenoustirofiban (10-g/kg bolus followed by continuous infusion of 0.10 g/kg per min).D
	Concomittant treatment: aspirin (500 mg IV plus 100 mg BID); clopidogrel (600 mg loading dose, 75 mg BID); tirofiban (10 microg/kg plus 0.10 microg/kg/min infusion); unfractionated heparin (UFH) (60 U/kg infusion, target APTT 60-85 seconds)	

Table 3.2: *Descriptions of participants - cooling-off strategy - early intervention*

Trial	Patients
Early intervention versus early strategy	
ISAR-COOL (2003) [1]	Patients with symptoms of unstable angina plus either ST-segment depression orelevation of cardiac troponin T levels
	Inclusion criteria: acute coronary syndrome with either ST depression or a positive troponin T (>=0.03 microg/L) **Exclusion criteria:** ST elevation; CKMB >=18; hemodynamic instability

Table 3.3: *Design and methodological quality of trials - cooling-off strategy - early intervention*

Trial	Design	Duration	Centre	Primary end-point
Early intervention versus early strategy				
ISAR-COOL, 2003 [1] n=410	Parallel groups open	1 mo inclusion period: 20002002	Germany 2 centres	death or large MI

Table 3.4: *Trial characteristics - cooling-off strategy - early intervention*

Trial	Fibrinolysis	non Q wave MI	Time to cardiac catheterization routine invasive group, h	ST-segment depression	T-wave inversion	Thrombolytic therapy
Early intervention versus early strategy						
ISAR-COOL, 2003 [1]						

3.2 Meta-analysis results

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

Early intervention versus early strategy

The single study eligible for this comparison provided data on **deaths or MI**. The analysis detected a statistically significant difference in favor of early strategy in deaths or MI, with a RR of 1.96 (95% CI 1.01 to 3.82, p=0.0472).
The single study eligible for this comparison provided data on **non fatal MI**. No statistically significant difference between the groups was found in non fatal MI, with a RR of 1.72 (95% CI 0.87 to 3.40, p=0.1208).
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 5.88 (95% CI 0.30 to 116.74, p=0.2450).

Table 3.5: *Results details - cooling-off strategy - early intervention*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
early intervention versus early strategy						
deaths or MI	RR=1.96	[1.01;3.82]	0.0472	1.0000 (I^2=1.00)	1	410
non fatal MI	RR=1.72	[0.87;3.40]	0.1208	1.0000 (I^2=0.00)	1	410
all cause death	RR=5.88	[0.30;116.74]	0.2450	1.0000 (I^2=0.00)	1	410
major bleeding	RR=1.31	[0.46;3.70]	0.6135	1.0000 (I^2=0.00)	1	410

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

Figure 3.1: *Forest's plot for deaths or MI*

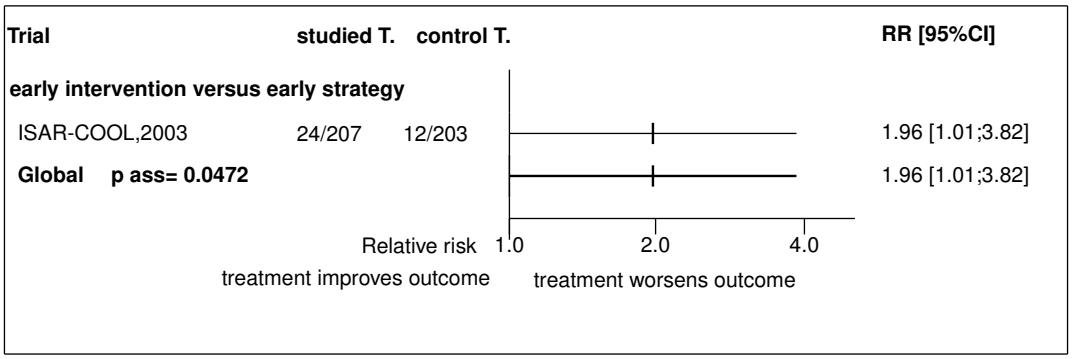


Figure 3.2: *Forest's plot for non fatal MI*

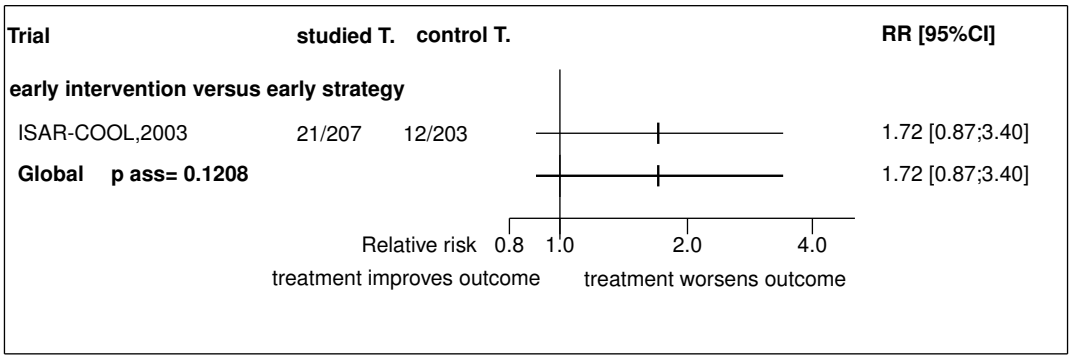


Figure 3.3: *Forest's plot for all cause death*

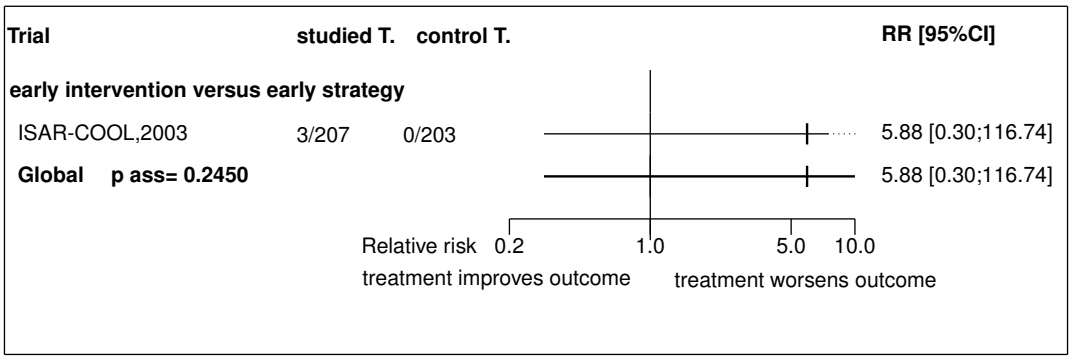
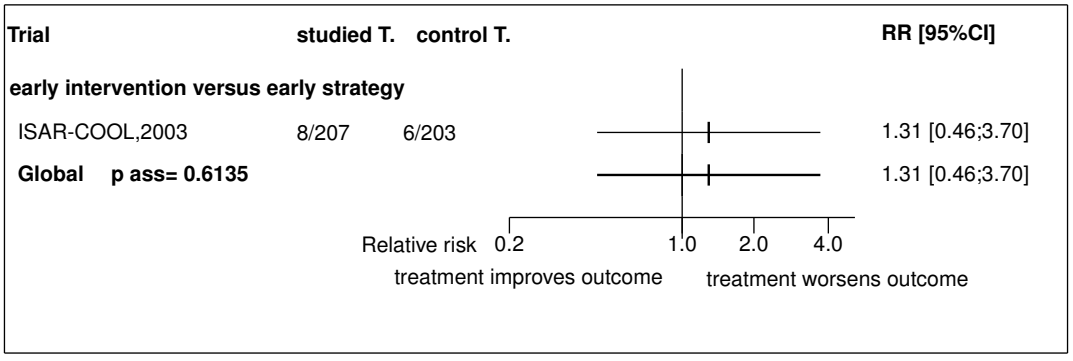


Figure 3.4: *Forest's plot for major bleeding*



References

[1] Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, Schmitt C, Seyfarth M, Dirschinger J, Schömig A. Evaluation of prolonged antithrombotic pretreatment (”cooling-off” strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. JAMA 2003;290:1593-9. [PMID=14506118]

3.3 Individual trial summaries

Table 3.6: *ISAR-COOL, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=410 (207 vs. 203) **Follow-up duration:** 1 mo **Study design:** Randomized controlled trial Parallel groups Open Germany, 2 centres **Inclusion period:** 20002002	Patients with symptoms of unstable angina plus either ST-segment depression orelevation of cardiac troponin T levels **Inclusion criteria:** acute coronary syndrome with either ST depression or a positive troponin T (>=0.03 microg/L) **Exclusion criteria:** ST elevation; CKMB >=18; hemodynamic instability	**Studied treatment:** Prolonged (3 to 5 days) antithromboticpretreatment (Cooling-Off strategy)before intervention antithrombotic pretreatment for 3to 5 days with intravenous unfractionated heparin (60-U/kgbolus followed by infusion adjusted to maintain partial thromboplastin time of 60 to 85seconds), aspirin (500-mg intravenous bolus followed by 100-mg twice-daily oral dose),oral clopidogrel (600-mg loading dose followed by 75-mg twice-daily dose), and intravenoustirofiban (10-g/kg bolus followed by continuous infusion of 0.10 g/kg per min).D **Control treatment:** early intervention after pretreatment for less than 6 hours antithrombotic pretreatment consisted of intravenous unfractionated heparin (60-U/kgbolus followed by infusion adjusted to maintain partial thromboplastin time of 60 to 85seconds), aspirin (500-mg intravenous bolus followed by 100-mg twice-daily oral dose),oral clopidogrel (600-mg loading dose followed by 75-mg twice-daily dose), and intravenoustirofiban (10-g/kg bolus followed by continuous infusion of 0.10 g/kg per min).D **Concomittant treat.:**aspirin (500 mg IV plus 100 mg BID); clopidogrel (600 mg loading dose, 75 mg BID); tirofiban (10 microg/kg plus 0.10 microg/kg/min infusion); unfractionated heparin (UFH) (60 U/kg infusion, target APTT 60-85 seconds)	Deaths or MI RR=1.96 [1.01;3.82] (at 30 days)

continued...

trial details	Patients	Treatments	Outcomes

Reference

Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, Schmitt C, Seyfarth M, Dirschinger J, Schömig A. Evaluation of prolonged antithrombotic pretreatment (”cooling-off” strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. JAMA 2003;290:1593-9 [PMID=14506118]

4 Global meta-analysis: all cooling-off strategy

4.1 Global meta-analysis: all cooling-off strategy versus early strategy

Table 4.1: *All cooling-off strategyversus early strategy*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deaths or MI	RR=1.96	1.01;3.82	0.0472	1.0000 (1.00)	1	410
non fatal MI	RR=1.72	0.87;3.40	0.1208	1.0000 (0.00)	1	410
all cause death	RR=5.88	0.30;116.74	0.2450	1.0000 (0.00)	1	410

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

5 Ongoing studies of cooling-off strategy

No ongoing trial was identified.

6 Excluded studies for cooling-off strategy

No trial was excluded.

References

Part II

Early invasive strategy

7 Overview of early invasive strategy

7.1 Included trials

A total of 13 randomized comparisons which enrolled 14172 patients were identified. In all, 1 randomized comparison concerned early invasive management , two immediate invasive management , 7 routine invasive strategy and 3 routine invasive strategy - noncomptemporary. The detailed descriptions of trials and meta-analysis results is given in section 8 (page 52) for early invasive management, in section 9 (page 62) for immediate invasive management, in section 10 (page 71) for routine invasive strategy and in section 11 (page 97) for routine invasive strategy - noncomptemporary.

The average study size was 1090 patients (range 88 to 3031). The first study was published in 1994, and the last study was published in 2009.
All trials were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 7.1 (page 35) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

7.2 Summary of meta-analysis results

The meta-analysis of the available trials about early invasive strategy provide the results listed in tables 7.2 to 7.5 (page 38) and in the following graphs.

7.2.1 Early invasive management

Early invasive management was superior to **delayed invasive strategy** in terms of death, MI, stroke, refractory ischemia (RR=0.72, 95% CI 0.58 to 0.89, p=0.0026, 1 trial). However, no significant difference was found on in-hospital death (RR=0.86, 95% CI 0.58 to 1.28, p=0.4551, 1 trial), death or stroke or myocardial infarction (RR=0.85, 95% CI 0.68 to 1.06, p=0.1513, 1 trial), repeat intervention (RR=1.04, 95% CI 0.81 to 1.33, p=0.7565, 1 trial), myocardial infarction (fatal and non fatal) (RR=0.83, 95% CI 0.61 to 1.13, p=0.2361, 1 trial), stroke (fatal and non fatal) (RR=0.90, 95% CI 0.49 to 1.66, p=0.7350, 1 trial)and all cause death (RR=0.81, 95% CI 0.60 to 1.10, p=0.1730, 1 trial).

7.2.2 Immediate invasive management

Immediate invasive management was inferior to **delayed invasive strategy** in terms of myocardial infarction (fatal and non fatal) (RR=1.66, 95% CI 1.20 to 2.30, p=0.0024, 2 trials). No significant difference was found on repeat intervention (RR=0.63, 95% CI 0.11 to 3.66, p=0.6068, 1 trial)and all cause death (RR=2.53, 95% CI 0.50 to 12.86, p=0.2636, 1 trial).

7.2.3 Routine invasive strategy

Routine invasive strategy was superior to **concervative strategy** in terms of rehospitalization (RR=0.74, 95% CI 0.62 to 0.89, p=0.0017, 6 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0004)(RR=0.83, 95% CI 0.73 to 0.93, p=0.0024, 3 trials), no angina (at 6 weeks) (RR=1.61, 95% CI 1.52 to 1.72, p=0.0000, 1 trial), long term MI (RR=0.77, 95% CI 0.67

to 0.90, p=0.0000, 3 trials)and all cause death (RR=0.79, 95% CI 0.63 to 0.98, p=0.0326, 7 trials). However, no significant difference was found on in-hospital death (RR=1.29, 95% CI 0.74 to 2.27, p=0.3689, 7 trials), in hospital non fatal MI (RR=1.24, 95% CI 0.71 to 2.17, p=0.4565, 7 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0006)(RR=1.21, 95% CI 0.73 to 2.00, p=0.4512, 7 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0003)(RR=0.81, 95% CI 0.59 to 1.11, p=0.1802, 7 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0001)(RR=0.72, 95% CI 0.49 to 1.06, p=0.0951, 4 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0014)(RR=0.84, 95% CI 0.69 to 1.01, p=0.0701, 3 trials), long term all cause death, MI (RR=0.88, 95% CI 0.75 to 1.03, p=0.1206, 3 trials), myocardial infarction (fatal and non fatal) (RR=0.37, 95% CI 0.04 to 3.38, p=0.3746, 1 trial), long term death (RR=1.16, 95% CI 0.89 to 1.52, p=0.2672, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0320)(RR=0.81, 95% CI 0.57 to 1.16, p=0.2500, 7 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0028)Routine invasive strategy appear to be associated with significantly greater risk of adverse events (RR=2.38, 95% CI 1.42 to 3.98, p=0.0000, 1 trial).

7.2.4 Routine invasive strategy - noncomptemporary

No significant difference was found between **routine invasive strategy - noncomptemporary** and **concervative strategy** in terms of in-hospital death (RR=1.39, 95% CI 0.46 to 4.20, p=0.5628, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0458)(RR=1.24, 95% CI 0.85 to 1.81, p=0.2615, 3 trials), in hospital death or MI (RR=1.45, 95% CI 0.79 to 2.66, p=0.2353, 3 trials), deaths or MI (RR=1.00, 95% CI 0.83 to 1.19, p=0.9713, 3 trials), CCS class III-IV angina (RR=0.93, 95% CI 0.70 to 1.22, p=0.5877, 3 trials), rehospitalization (RR=0.90, 95% CI 0.80 to 1.01, p=0.0748, 3 trials), positive 6-wk ETT (RR=0.87, 95% CI 0.63 to 1.20, p=0.3871, 1 trial), no angina (at 6 weeks) (RR=1.05, 95% CI 0.98 to 1.12, p=0.1699, 1 trial), non fatal MI (RR=0.87, 95% CI 0.70 to 1.08, p=0.2118, 3 trials)and all cause death (RR=1.18, 95% CI 0.93 to 1.51, p=0.1728, 3 trials).

Table 7.1: *Main study characteristics - early invasive strategy*

Trial	Patients	Treatments	Trial design and method
Early invasive management			
Early invasive management versus delayed invasive strategy			
TIMACS, 2009 [1, 2] n = 1593 vs. 1438	patients with unstable angina or non-ST-segment-elevation MI (NSTEMI)	early invasive management: angiography within 24 hours followed by PCI or CABG as appropriate **versus** delayed invasive strategy: angiography after 36 hours followed by PCI or CABG as appropriate	open parallel groups Primary endpoint: death, MI or stroke at 6 months 100 centres, 30 countries
Immediate invasive management			
Immediate invasive management versus delayed invasive strategy			
OPTIMA, 2009 [1] n = 73 vs. 69	patients with non-ST-segment elevationacute coronary syndromes eligible for percutaneous coronary intervention	immediate angioplasty under tripleantiplatelet therapy protection **versus** deferred angioplasty	open parallel groups Primary endpoint: death, MI, unplanned revascularization multicentre, The Netherland, England
ABOARD, 2009 [2] n = 175 vs. 177	patient with non ST-elevation acute coronary syndrome	immediate catheterization and revascularization **versus** catheterization and revascularization on the next working day (between 8 and 60 hours after enrollment)	open parallel groups Primary endpoint: peak troponin-I 13 centres, France
Routine invasive strategy			
Routine invasive strategy versus concervative strategy			

continued...

Trial	Patients	Treatments	Trial design and method
ICTUS, 2007 [1, 2] n = 604 vs. 596	patients with nonST-segment elevation acutec oronary syndrome and elevated cardiac troponin T	early invasive strategy **versus** selective invasive treatment strategy	open parallel groups Primary endpoint: death, MI, rehospitalization 42 centres, Netherlands
FRISC 2, 1999 [3, 4, 5, 6] n = 1222 vs. 1234	patients with nonST-segment elevation acutecoronary syndrome	early invasive treatment strategy: angiography within 7 days aiming for revascularisation **versus** non-invasive treatment strategy: angiography only in patients with refractory or recurrent symptoms despite maximum medical treatment or severe ischemia during exercise test before discharge	open factorial plan Primary endpoint: death or nonfatal myocardial infarction 58 centres, Scandinavia
NQWMI (Eisenberg), 2005 [7] n = 42 vs. 46	patients with nonQ-wave myocardial infarction	invasive (angiography at days 2 to 5) **versus** noninvasive (stress testing at day 2 to 5)	open parallel groups Primary endpoint: maximal endurance 8 centres, Canada
RITA 3, 2002 [8, 9] n = 895 vs. 915	patients with nonST-segment elevation acutecoronary syndrome	routine angiography followed byrevascularisationage/pj **versus** conservative strategy (ischaemia-driven or symptom-driven angiographyS	open parallel groups Primary endpoint: death or non fatal MI 45 centres, UK
TACTICS-TIMI 18, 2001 [10] n = 1114 vs. 1106	patients with nonST-segment elevation acute coronary syndrome	early invasive management strategy **versus** conservative management strategy	open parallel groups 169 centres, 9 countries
TRUCS, 2000 [11] n = 76 vs. 72	patients with nonST-segment elevation acute coronary syndrome in geographically isolated hospitals without cardiac surgicalfacilities	invasive strategy **versus** conservative strategy	parallel groups Greece

continued...

Trial	Patients	Treatments	Trial design and method
VINO, 2002 [12] n = 64 vs. 67	patients with nonST-segment elevation acute coronary syndrome	first day angiography / angioplasty strategy **versus** early conservative therapy	open parallel groups Primary endpoint: death or non-fatal recurrent 10 centres, Czech Republic
Routine invasive strategy - noncomptemporary			
Routine invasive strategy - noncomptemporary versus concervative strategy			
MATE, 1998 [1] n = 111 vs. 90	acute MI ineligible for thrombolytictherapy within 24 h of symptoms	early triage angiography and subsequenttherapies based on the angiogram **versus** conventional medicaltherapy	open parallel groups Primary endpoint: recurrent ischemic events or death 4 centres, US
TIMI 3B (PTCA), 1994 [2] n = 740 vs. 733	patient with unstable angina or non Q wave MI within 24hrs of onset	early invasive strategy: systematic angiography (18-48h after randomisation) and revascularisation (PTCA or CABG) **versus** early elective strategy: angiography and revascularisation only in case of ischemic recurrence (see paper)	open factorial plan USA & Canada
VANQWISH, 1998 [3] n = 462 vs. 458	patients with NonQ-wave myocardial infarction	invasive management **versus** conservative management: medical therapy with subsequent invasive management if indicated by the development of spontaneous or indicible ischemia within 24-72 hours	open parallel groups Primary endpoint: death or nonfatal myocardial infarction 15 centres, US

Table 7.2: *Summary of all results for early invasive management*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
early invasive management versus delayed invasive strategy						
in-hospital death	RR=0.86	0.58;1.28	0.4551	1.0000 (1.00)	1	3031
death or stroke or myocardial infarction	RR=0.85	0.68;1.06	0.1513	1.0000 (0.00)	1	3031
death, MI, stroke, refractory ischemia	RR=0.72	0.58;0.89	0.0026	1.0000 (0.00)	1	3031
repeat intervention	RR=1.04	0.81;1.33	0.7565	1.0000 (0.00)	1	3031
myocardial infarction (fatal and non fatal)	RR=0.83	0.61;1.13	0.2361	1.0000 (0.00)	1	3031
stroke (fatal and non fatal)	RR=0.90	0.49;1.66	0.7350	1.0000 (0.00)	1	3031
all cause death	RR=0.81	0.60;1.10	0.1730	1.0000 (0.00)	1	3031
major bleeding	RR=0.89	0.60;1.32	0.5623	1.0000 (0.00)	1	3031

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 7.3: *Summary of all results for immediate invasive management*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
immediate invasive management versus delayed invasive strategy						
repeat intervention	RR=0.63	0.11;3.66	0.6068	1.0000 (0.00)	1	142
myocardial infarction (fatal and non fatal)	RR=1.66	1.20;2.30	0.0024	0.6077 (0.00)	2	494
all cause death	RR=2.53	0.50;12.86	0.2636	1.0000 (0.00)	1	352
major bleeding	RR=0.55	0.26;1.17	0.1202	0.7889 (0.00)	2	494

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 7.4: *Summary of all results for routine invasive strategy*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
routine invasive strategy versus concervative strategy						
in-hospital death	RR=1.29	0.74;2.27	0.3689	0.2030 (0.29)	7	8054
in hospital non fatal MI	RR=1.24 [1]	0.71;2.17	0.4565	0.0006 (0.75) †	7	8054
in hospital death or MI	RR=1.21 [2]	0.73;2.00	0.4512	0.0003 (0.76) †	7	8054

continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.45 95% CI 1.15;1.82
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.44 95% CI 1.18;1.77

Endpoint	Effect	95% CI	p ass	p het	k	n
deaths or MI	RR=0.81 [3]	0.59;1.11	0.1802	0.0001 (0.80) †	7	8054
CCS class III-IV angina	RR=0.72 [4]	0.49;1.06	0.0951	0.0014 (0.81) †	4	6436
rehospitalization	RR=0.74 [5]	0.62;0.89	0.0017	0.0004 (0.78) †	6	7901
long term cardiovascular death	RR=0.84	0.69;1.01	0.0701	0.3999 (0.00)	3	5467
long term all cause death, MI	RR=0.88	0.75;1.03	0.1206	0.1344 (0.50)	3	5467
long term cardiovascular events	RR=0.83	0.73;0.93	0.0024	0.3913 (0.00)	3	5467
no angina (at 6 weeks)	RR=1.61	1.52;1.72	0.0000	1.0000 (1.00)	1	2457
long term MI	RR=0.77	0.67;0.90	0.0000	0.5919 (0.00)	3	5467
myocardial infarction (fatal and non fatal)	RR=0.37	0.04;3.38	0.3746	1.0000 (1.00)	1	88
long term death	RR=1.16 [6]	0.89;1.52	0.2672	0.0320 (0.71) †	3	5467
non fatal MI	RR=0.81 [7]	0.57;1.16	0.2500	0.0028 (0.70) †	7	8054
all cause death	RR=0.79	0.63;0.98	0.0326	0.3526 (0.10)	7	8053
adverse events	RR=2.38	1.42;3.98	0.0000	1.0000 (0.00)	1	2457
major bleeding	RR=2.13	0.97;4.70	0.0598	1.0000 (0.00)	1	2457

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

Table 7.5: *Summary of all results for routine invasive strategy - noncomptemporary*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
routine invasive strategy - noncomptemporary versus concervative strategy						
in-hospital death	RR=1.39 [8]	0.46;4.20	0.5628	0.0458 (0.68) †	3	2594
in hospital non fatal MI	RR=1.24	0.85;1.81	0.2615	0.6260 (0.00)	3	2594
in hospital death or MI	RR=1.45	0.79;2.66	0.2353	0.0898 (0.59)	3	2594
deaths or MI	RR=1.00	0.83;1.19	0.9713	0.2963 (0.18)	3	2594
CCS class III-IV angina	RR=0.93	0.70;1.22	0.5877	0.2130 (0.35)	3	2594
rehospitalization	RR=0.90	0.80;1.01	0.0748	0.2256 (0.33)	3	2594
positive 6-wk ETT	RR=0.87	0.63;1.20	0.3871	1.0000 (0.00)	1	1473
no angina (at 6 weeks)	RR=1.05	0.98;1.12	0.1699	1.0000 (0.00)	1	1473

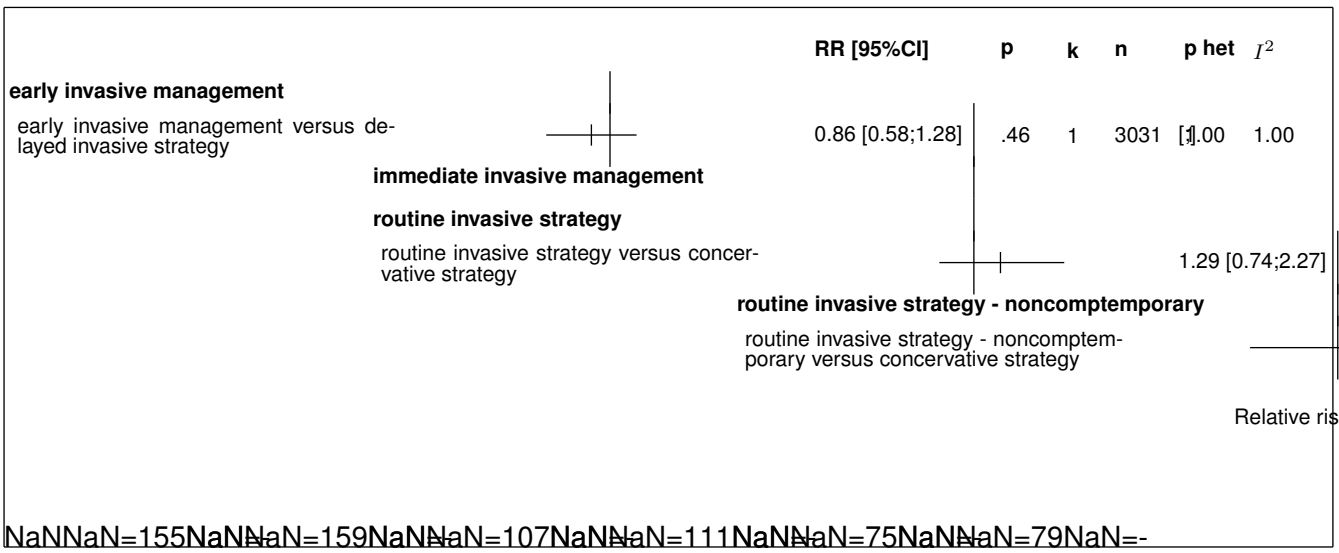
continued...

[3] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.89 95% CI 0.79;1.01
[4] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.76 95% CI 0.67;0.87
[5] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.74 95% CI 0.70;0.79
[6] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.20 95% CI 1.04;1.38
[7] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.86 95% CI 0.74;1.00
[8] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.56 95% CI 0.91;2.68

Endpoint	Effect	95% CI	p ass	p het	k	n
non fatal MI	RR=0.87	0.70;1.08	0.2118	0.7254 (0.00)	3	2594
all cause death	RR=1.18	0.93;1.51	0.1728	0.4188 (0.00)	3	2594

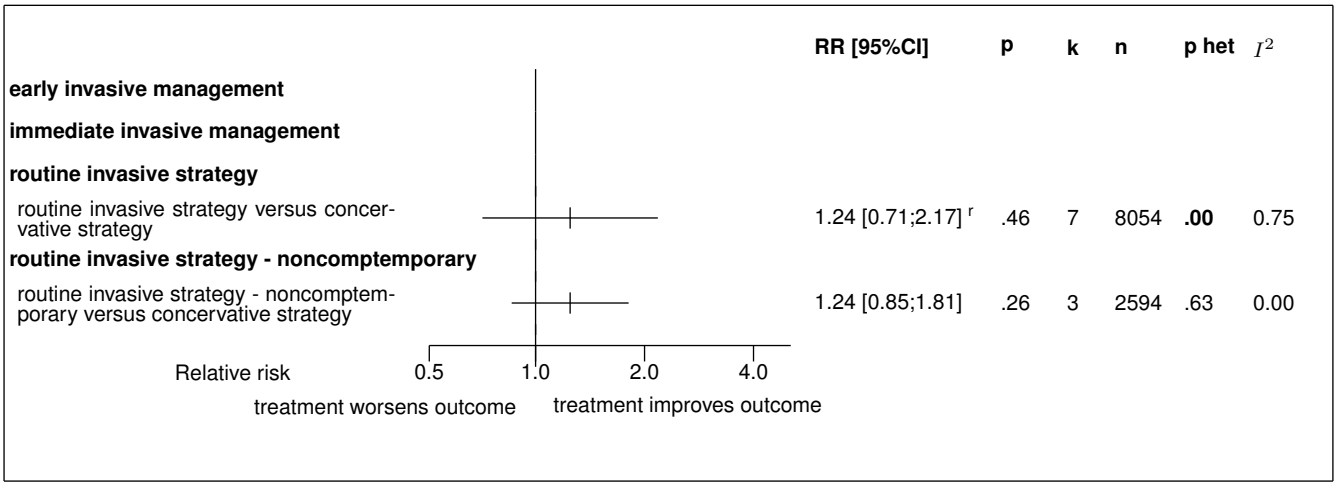
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 7.1: *Forest's plot for in-hospital death*



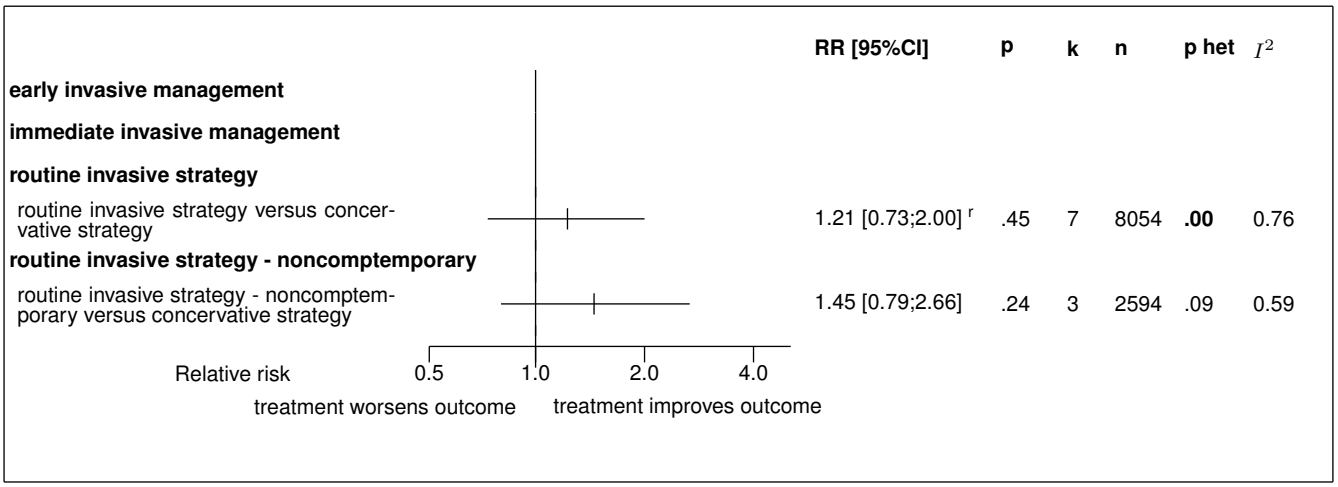
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.2: *Forest's plot for in hospital non fatal MI*



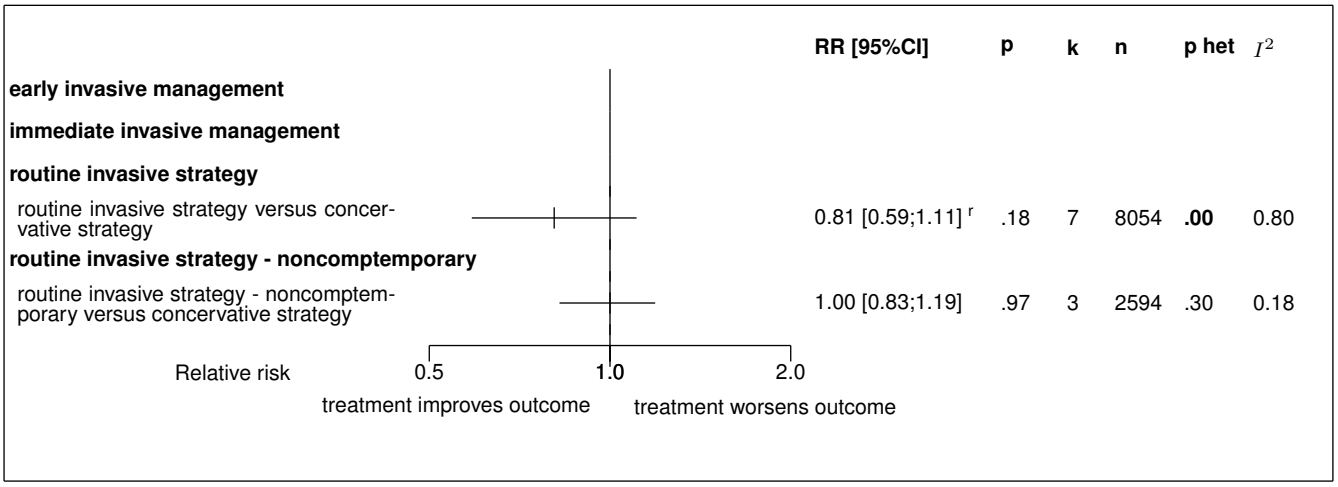
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.3: *Forest's plot for in hospital death or MI*



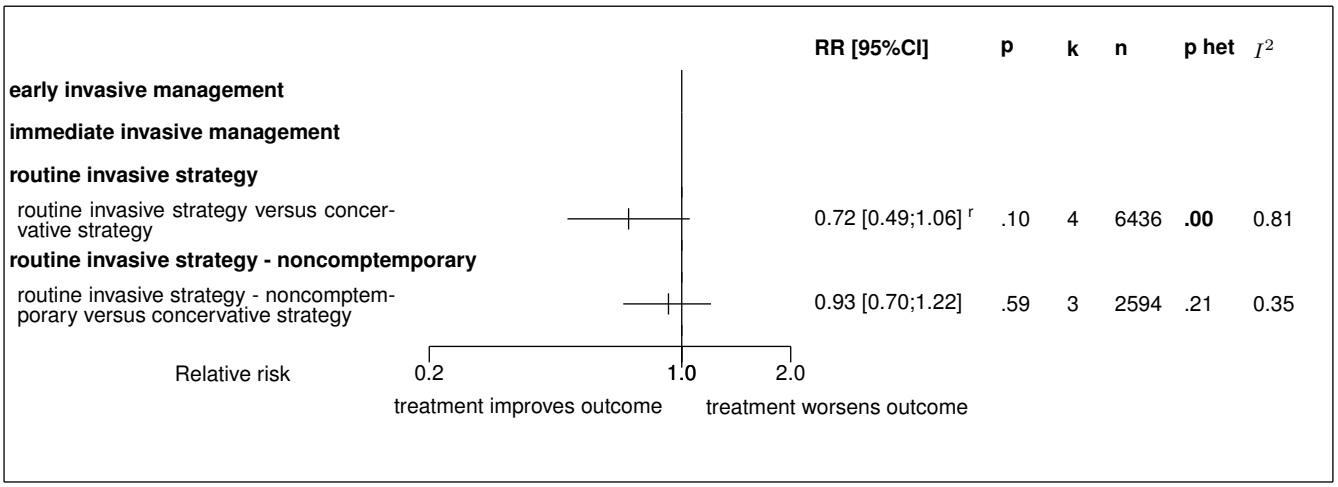
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.4: *Forest's plot for deaths or MI*



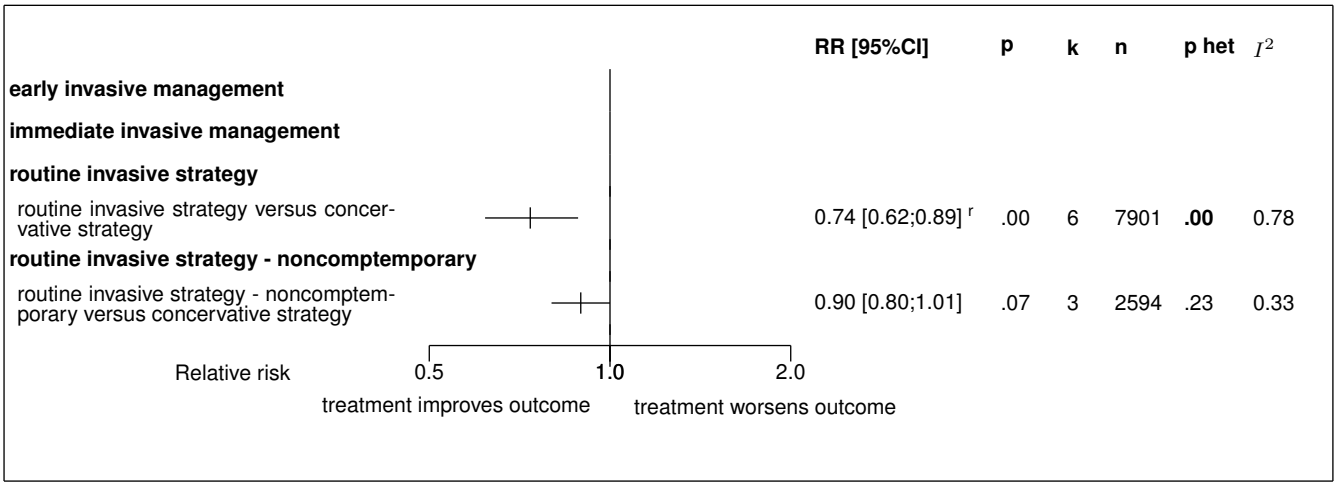
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.5: *Forest's plot for CCS class III-IV angina*



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 7.6: *Forest's plot for rehospitalization*

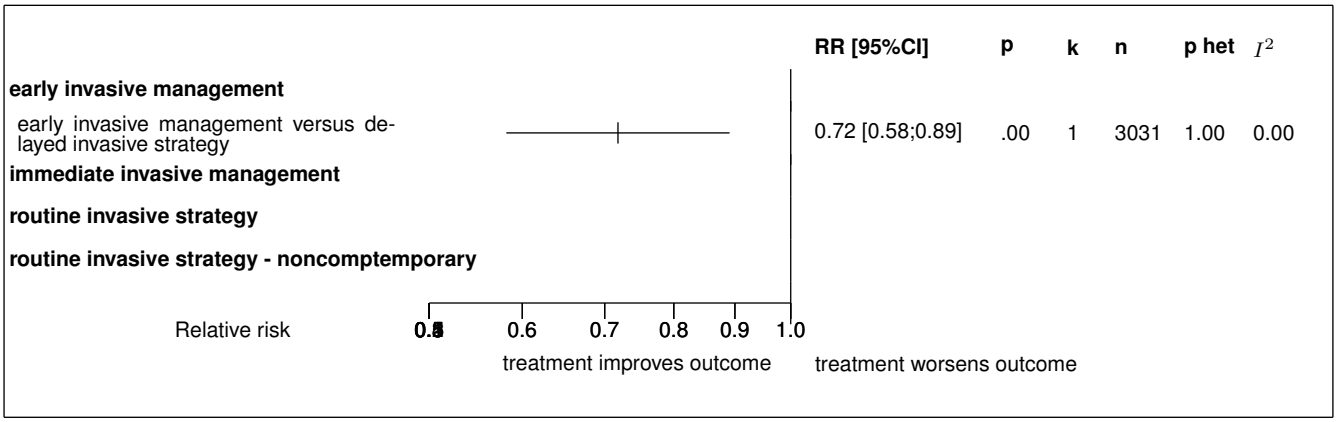


Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.7: *Forest's plot for death or stroke or myocardial infarction*

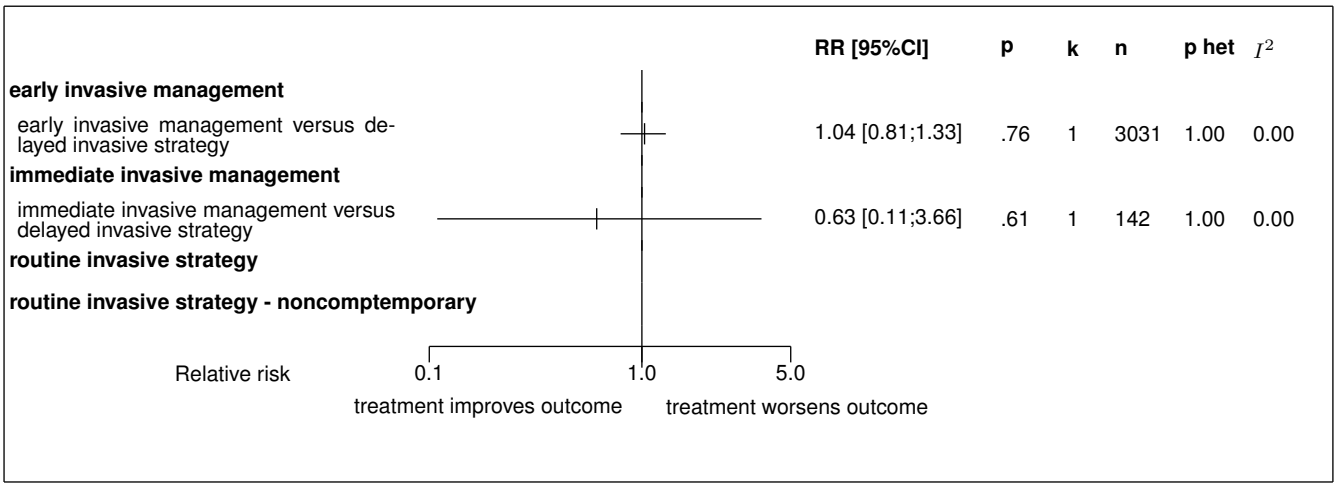
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.8: *Forest's plot for death, MI, stroke, refractory ischemia*



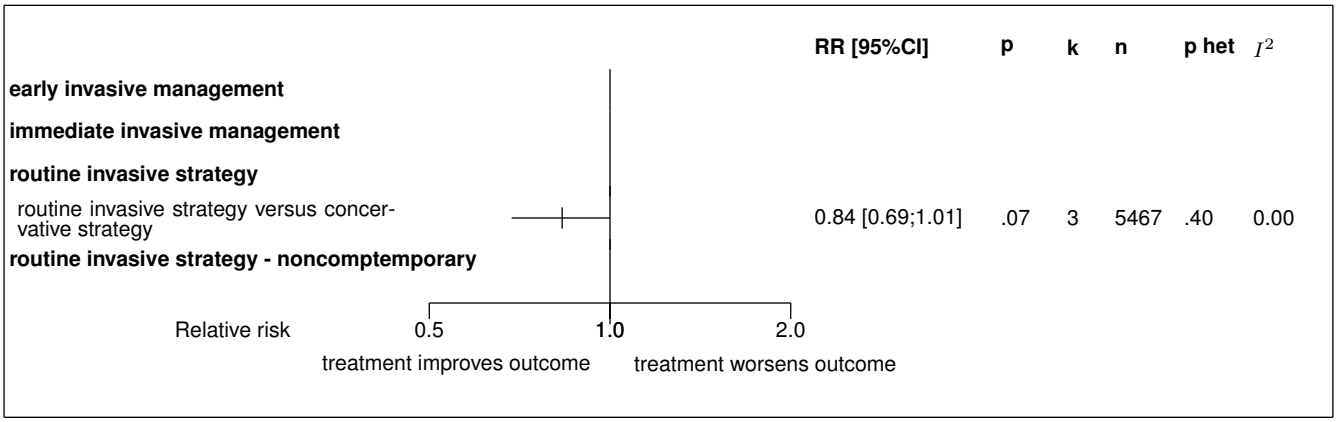
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.9: *Forest's plot for repeat intervention*



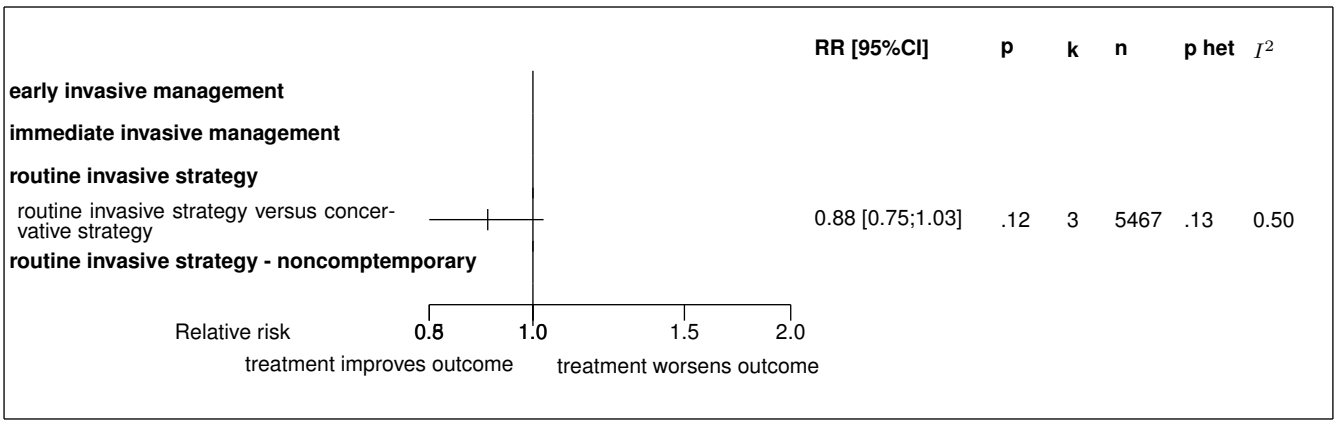
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.10: *Forest's plot for long term cardiovascular death*



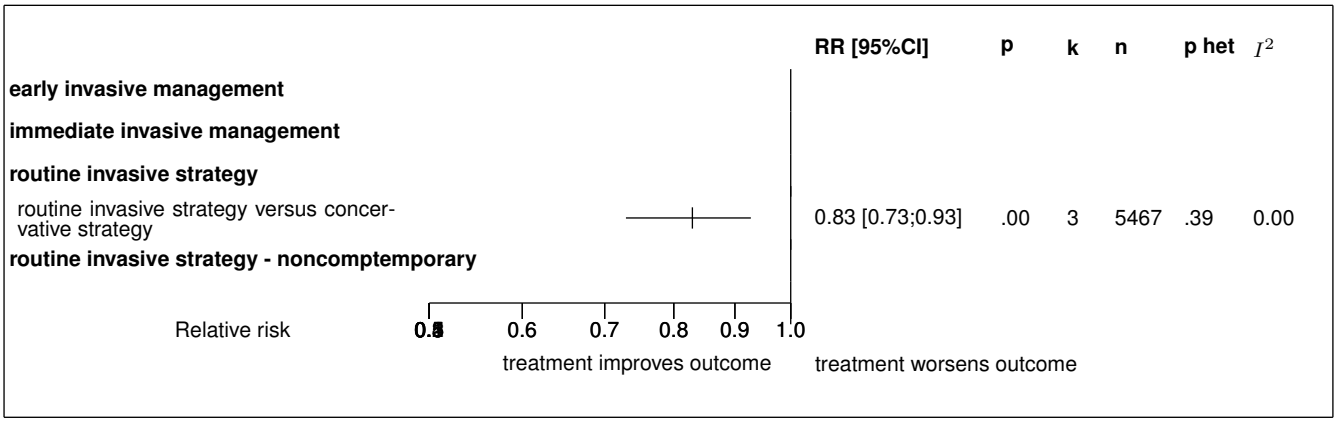
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.11: *Forest's plot for long term all cause death, MI*



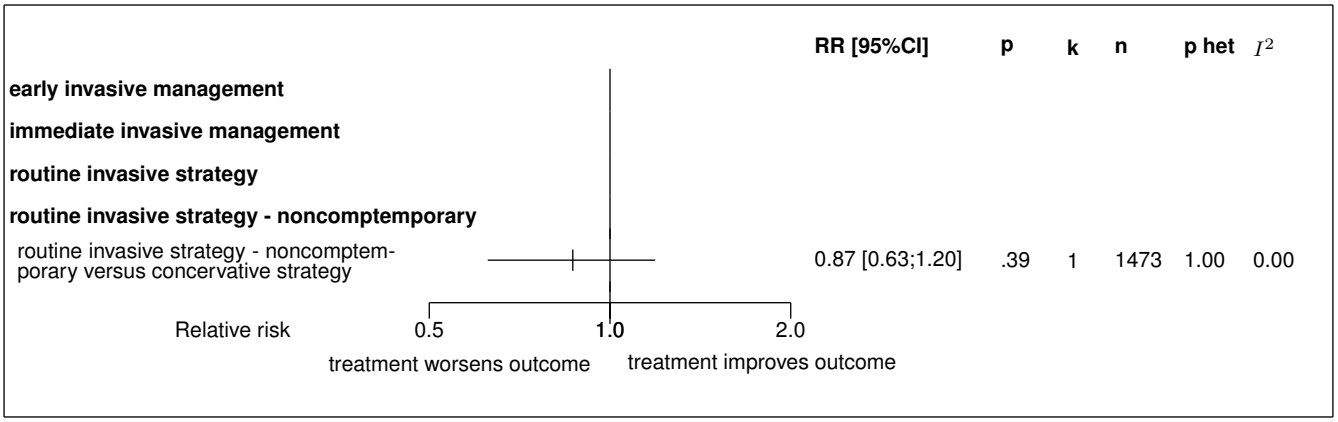
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.12: *Forest's plot for long term cardiovascular events*



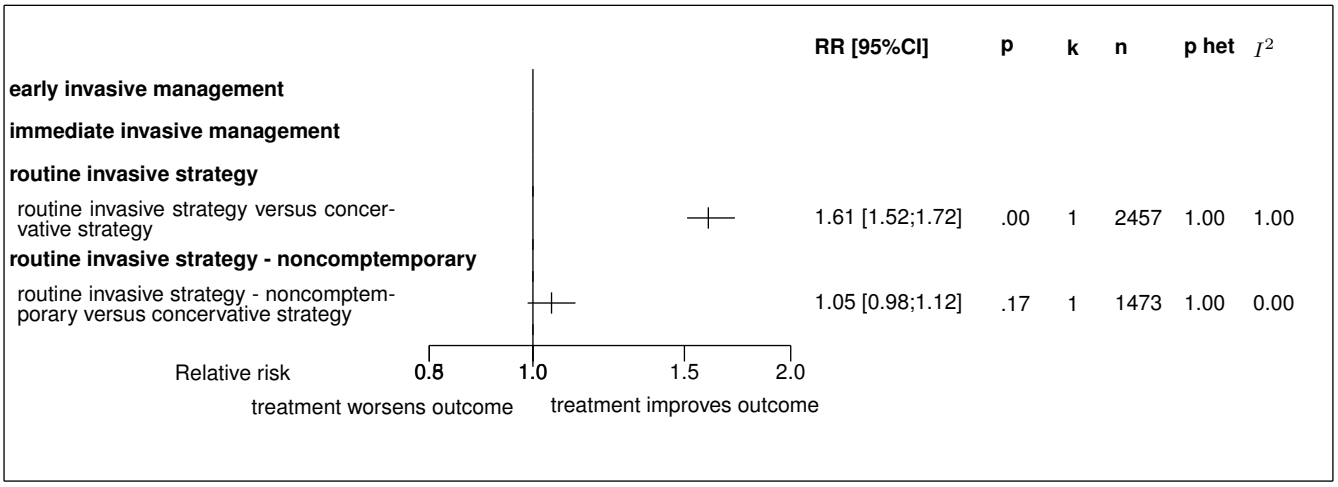
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.13: *Forest's plot for positive 6-wk ETT*



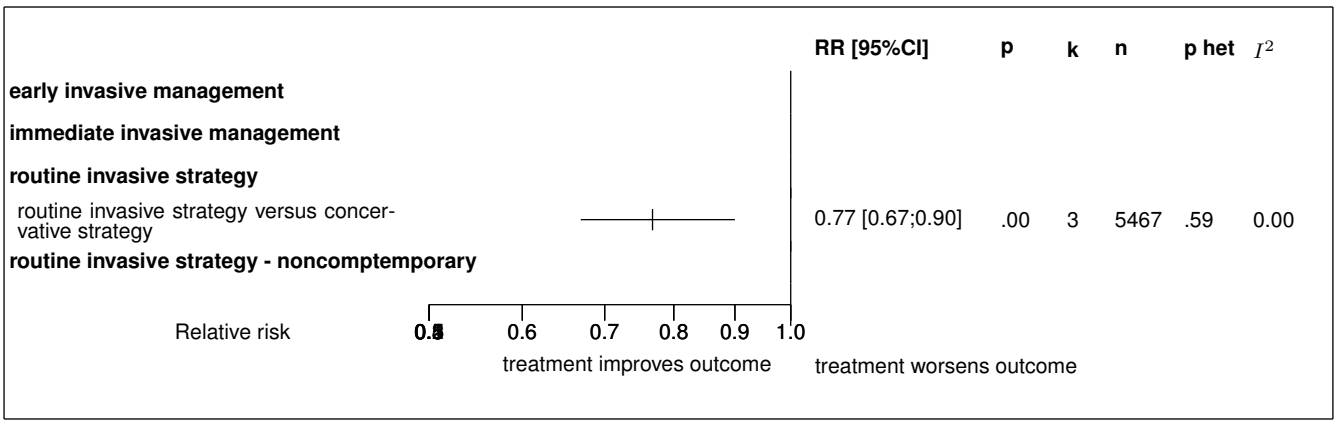
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.14: *Forest's plot for no angina (at 6 weeks)*



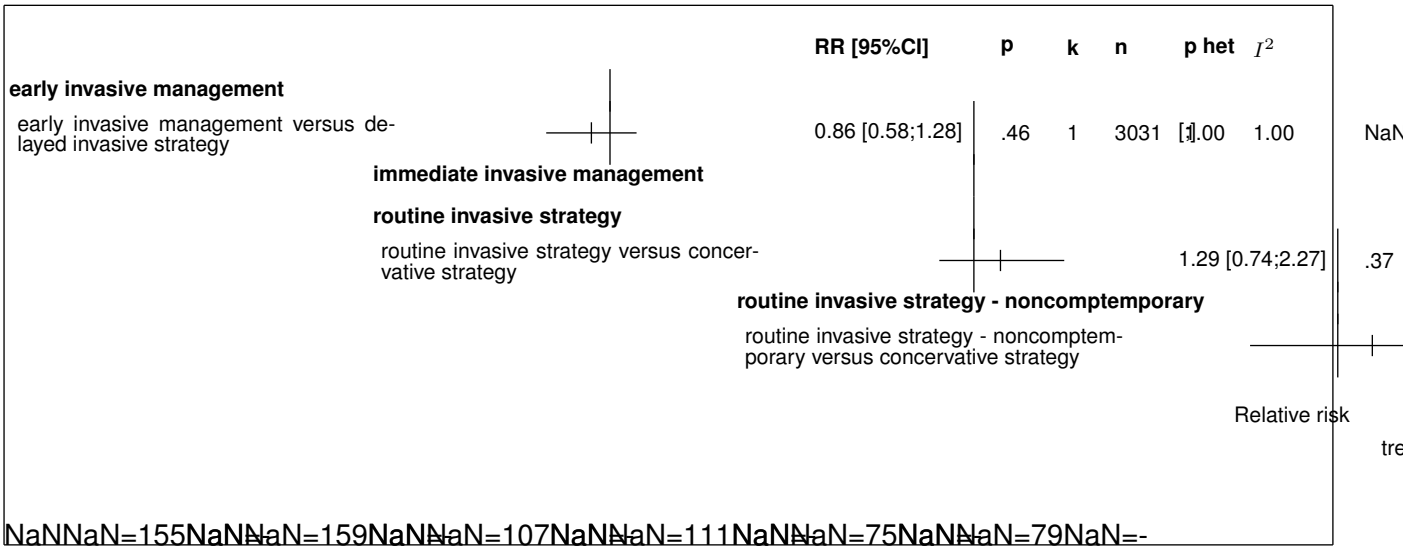
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.15: *Forest's plot for long term MI*



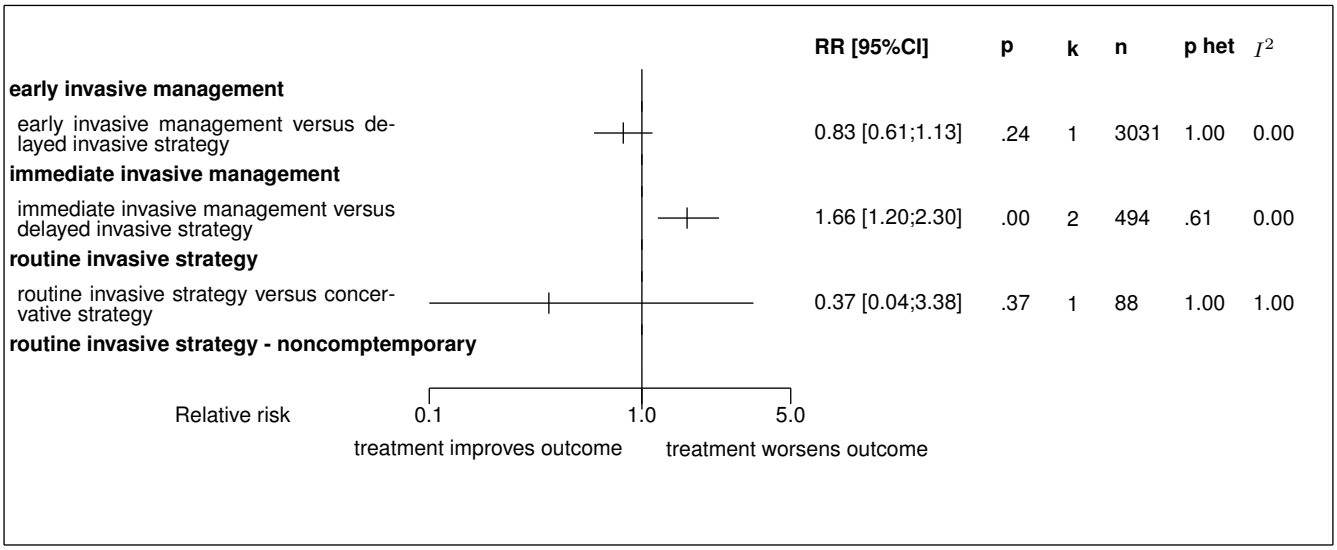
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.16: *Forest's plot for in-hospital death*



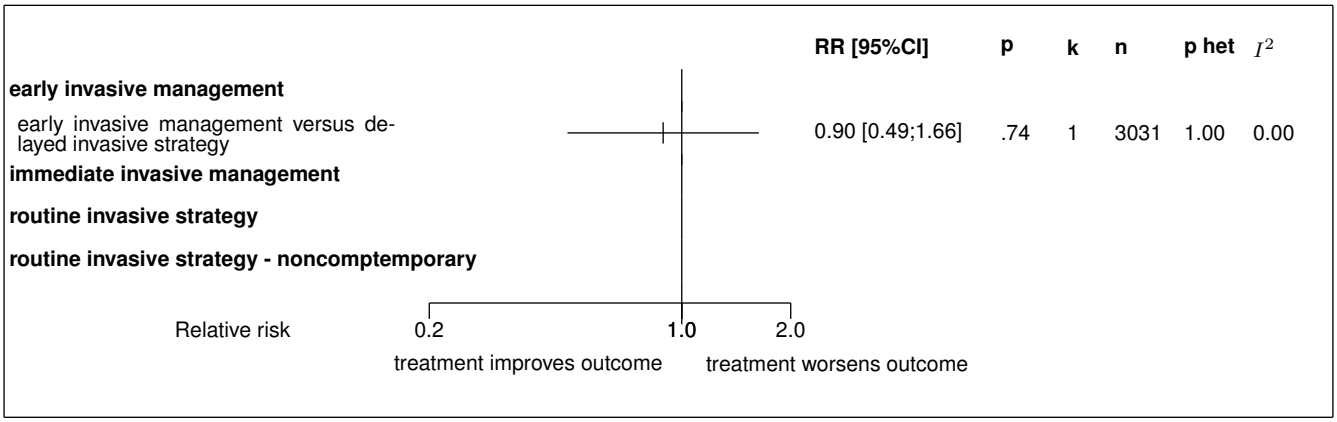
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.17: *Forest's plot for myocardial infarction (fatal and non fatal)*



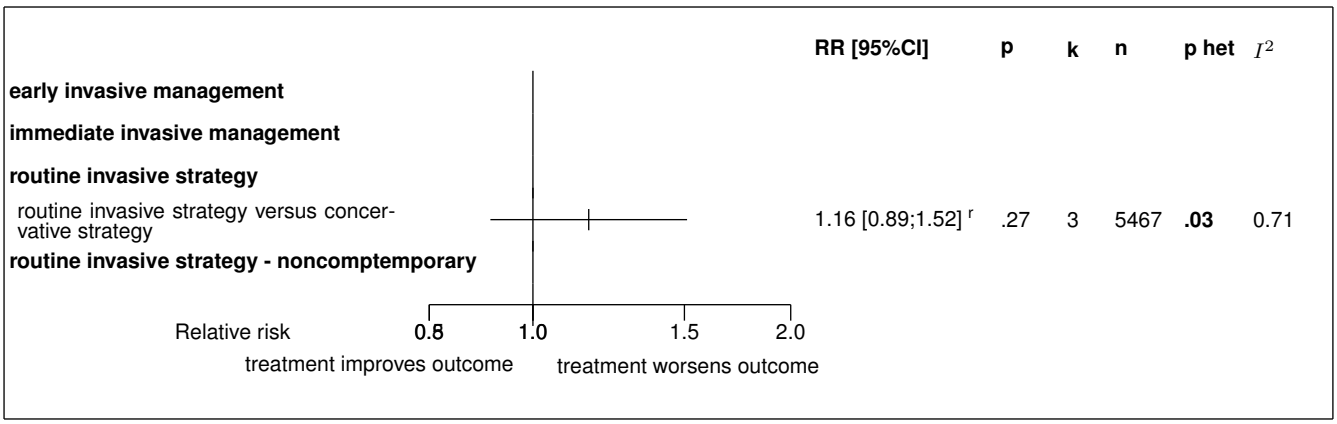
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.18: *Forest's plot for stroke (fatal and non fatal)*



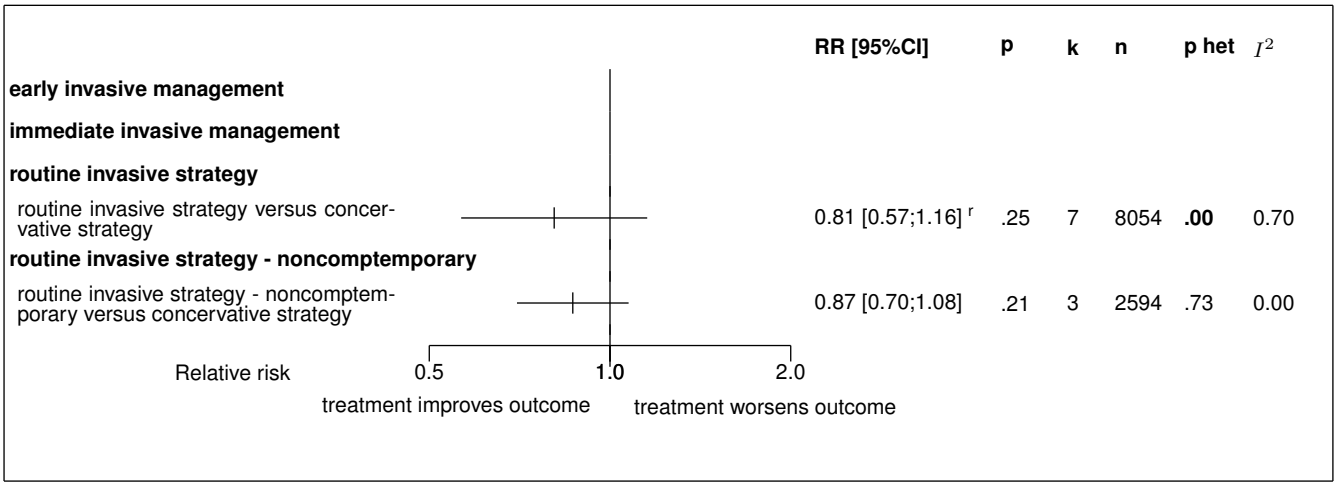
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.19: *Forest's plot for long term death*



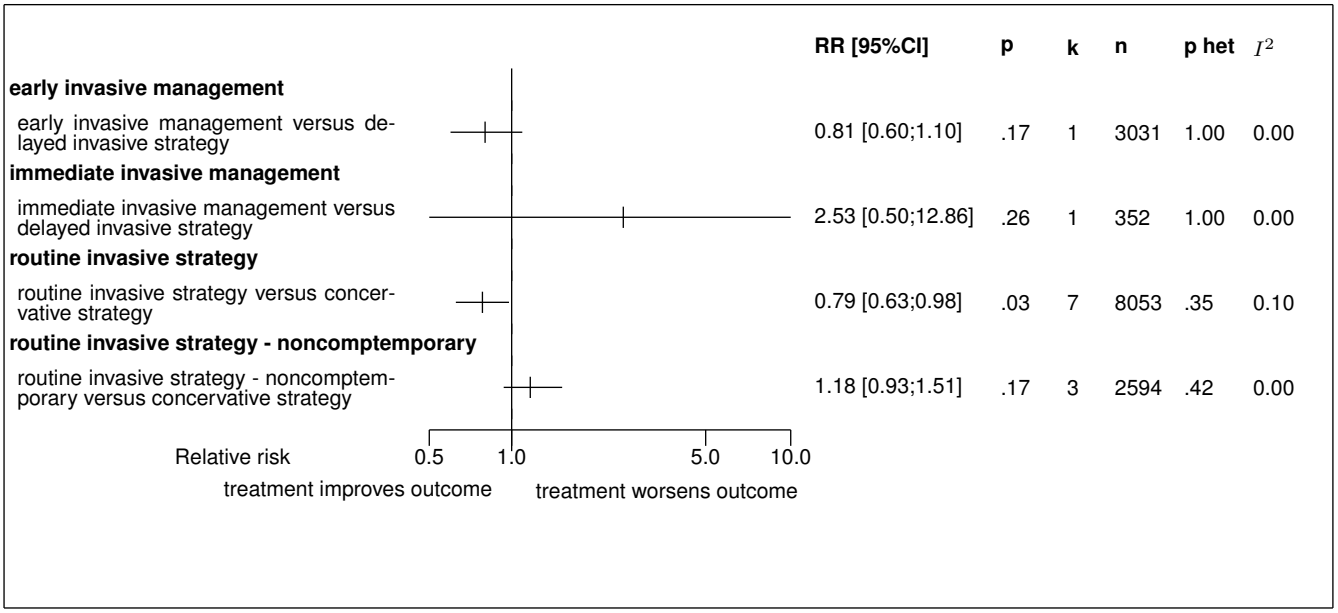
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.20: *Forest's plot for non fatal MI*



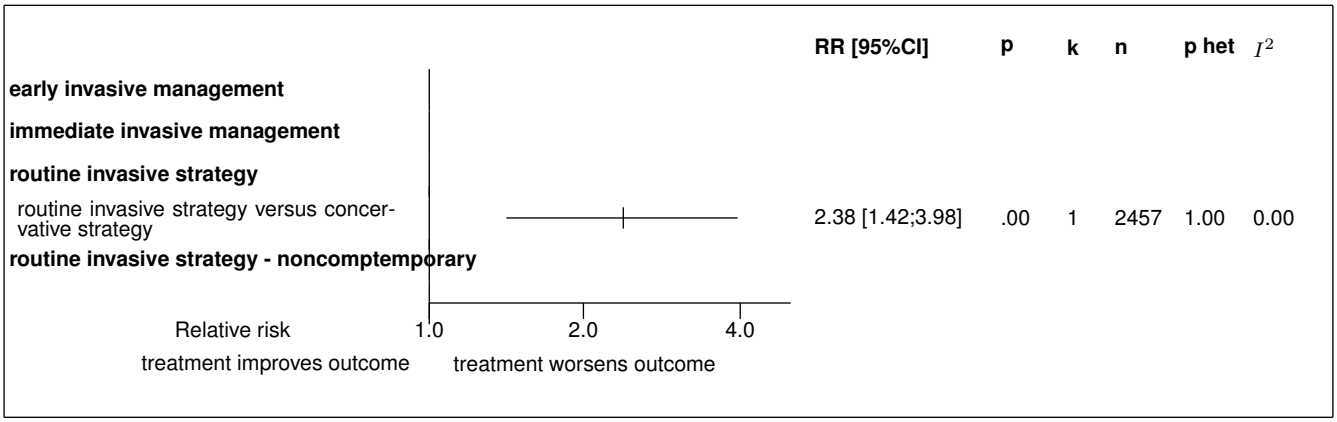
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.21: *Forest's plot for all cause death*



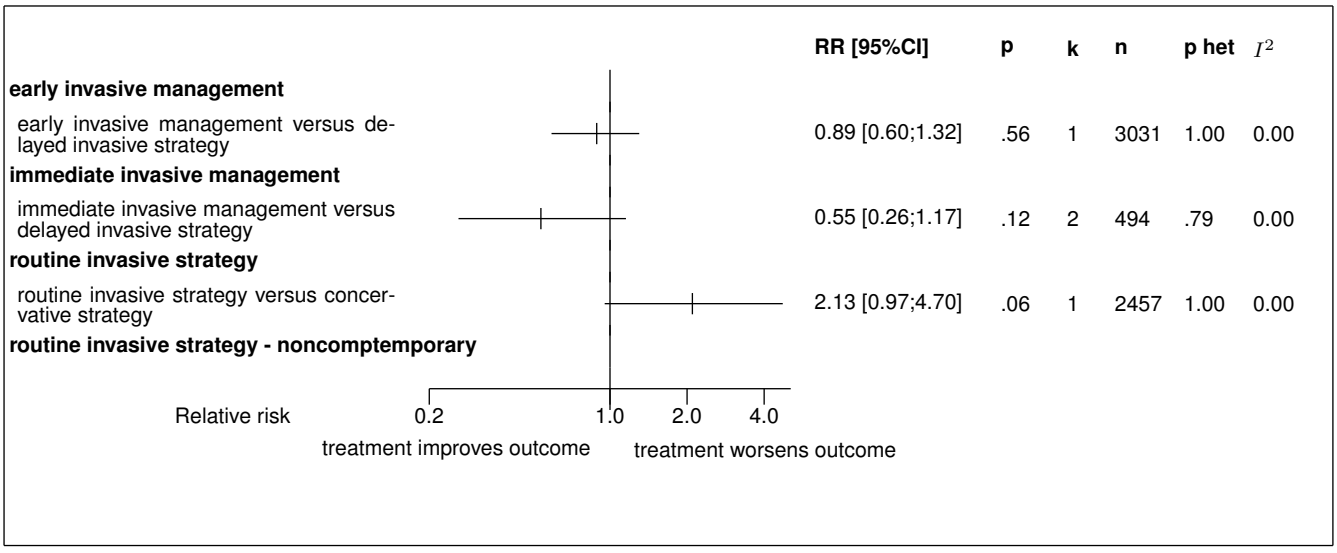
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.22: *Forest's plot for adverse events*



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 7.23: *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

8 Detailed results for early invasive management

8.1 Available trials

Only one trial which randomized 3031 patients was identified: it compared early invasive management with delayed invasive strategy.
This trial included 3031 patients and was published in 2009.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 8.1 (page 52), 8.2 (page 52), 8.4 (page 54), and 8.3 (page 53) summarized the main characteristics of the trial including in this systematic review of randomized trials of early invasive management.

Table 8.1: *Treatment description - early invasive strategy - early invasive management*

Trial	Studied treatment	Control treatment
Early invasive management versus delayed invasive strategy		
TIMACS (2009) [1, 2]	early invasive management: angiography within 24 hours followed by PCI or CABG as appropriate Early Invasive Strategy defined as coronary angiography as soon as possible (and no later than 24 hours) followed by anatomy-driven intervention (PCI or CABG)	delayed invasive strategy: angiography after 36 hours followed by PCI or CABG as appropriate Delayed Invasive Strategy defined as coronary angiography after 36 hours followed by anatomy-driven intervention (PCI or CABG).

Table 8.2: *Descriptions of participants - early invasive strategy - early invasive management*

Trial	Patients	
Early invasive management versus delayed invasive strategy		
TIMACS (2009) [1, 2]	Patients with unstable angina or non-ST-segment-elevation MI (NSTEMI)	
	Inclusion criteria: patients presenting with symptoms/signs compatible with UA/NSTEMI and within 24 hours from symptom onset and at least two of the following 3 criteria: Age >60, Elevated Troponin T or I or CKMB or ischemic ECG changes.	**Exclusion criteria:** age <21 years; life expectancy <6 months; contraindication for low molecular weight heparin; high risk for bleeding; not a suitable candidate for revascularization

Table 8.3: *Design and methodological quality of trials - early invasive strategy - early invasive management*

Trial	Design	Duration	Centre	Primary end-point
Early invasive management versus delayed invasive strategy				
TIMACS, 2009 [1, 2] n=3031	Parallel groups open confirmatory trial at risk of bias	6 months inclusion period: apr 2003 - jun 2008	30 countries 100 centres	death, MI or stroke at 6 months

Table 8.4: *Trial characteristics - early invasive strategy - early invasive management*

Trial	Fibrinolysis	non Q wave MI	Time to cardiac catheterization routine invasive group, h	ST-segment depression	T-wave inversion	Thrombolytic therapy
Early invasive management versus delayed invasive strategy						
TIMACS, 2009 [1, 2]						

8.2 Meta-analysis results

The results are detailed in table 8.5 (page 55). This table is followed by the Forest's plot corresponding to each endpoint.

Early invasive management versus delayed invasive strategy

The single study eligible for this comparison provided data on **in-hospital death**. There was no statistically significant difference in in-hospital death between early invasive management and delayed invasive strategy, with a RR of 0.86 (95%CI 0.58 to 1.28, p=0.4551) in favour of early invasive management. In other words, in-hospital death was slightly lower in the early invasive management group , but this was not statistically significant.
The single study eligible for this comparison provided data on **death or stroke or myocardial infarction**. No statistically significant difference between the groups was found in death or stroke or myocardial infarction, with a RR of 0.85 (95% CI 0.68 to 1.06, p=0.1513).
The single study eligible for this comparison provided data on **death, MI, stroke, refractory ischemia**. The analysis detected a statistically significant difference in favor of early invasive management in death, MI, stroke, refractory ischemia, with a RR of 0.72 (95% CI 0.58 to 0.89, p=0.0026).
The single study eligible for this comparison provided data on **repeat intervention**. No statistically significant difference between the groups was found in repeat intervention, with a RR of 1.04 (95% CI 0.81 to 1.33, p=0.7565).
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 0.83 (95% CI 0.61 to 1.13, p=0.2361).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. No statistically significant difference between the groups was found in stroke (fatal and non fatal), with a RR of 0.90 (95% CI 0.49 to 1.66, p=0.7350).
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 0.81 (95% CI 0.60 to 1.10, p=0.1730).

Table 8.5: *Results details - early invasive strategy - early invasive management*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
early invasive management versus delayed invasive strategy						
in-hospital death	RR=0.86	[0.58;1.28]	0.4551	1.0000 (I^2=1.00)	1	3031
death or stroke or myocardial infarction	RR=0.85	[0.68;1.06]	0.1513	1.0000 (I^2=0.00)	1	3031
death, MI, stroke, refractory ischemia	RR=0.72	[0.58;0.89]	0.0026	1.0000 (I^2=0.00)	1	3031
repeat intervention	RR=1.04	[0.81;1.33]	0.7565	1.0000 (I^2=0.00)	1	3031
myocardial infarction (fatal and non fatal)	RR=0.83	[0.61;1.13]	0.2361	1.0000 (I^2=0.00)	1	3031
stroke (fatal and non fatal)	RR=0.90	[0.49;1.66]	0.7350	1.0000 (I^2=0.00)	1	3031
all cause death	RR=0.81	[0.60;1.10]	0.1730	1.0000 (I^2=0.00)	1	3031

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
major bleeding	RR=0.89	[0.60;1.32]	0.5623	1.0000 (I^2=0.00)	1	3031

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 8.1: *Forest's plot for in-hospital death*

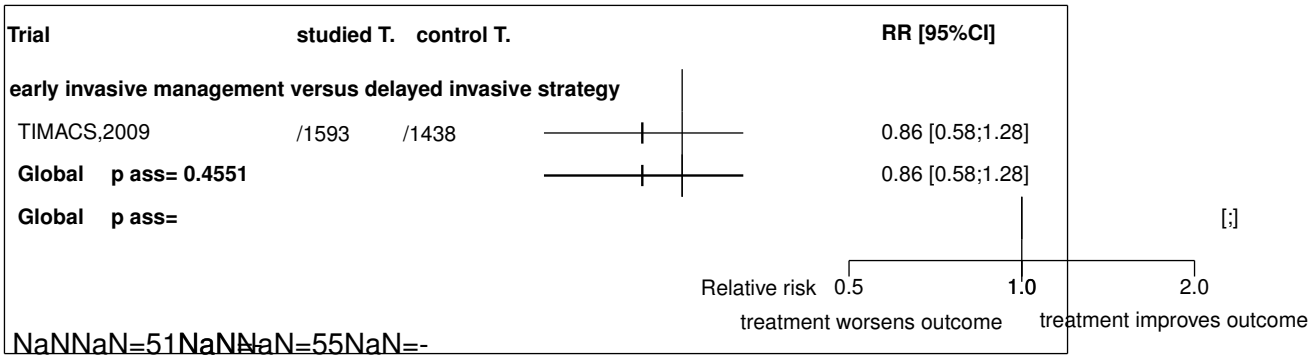


Figure 8.2: *Forest's plot for death or stroke or myocardial infarction*

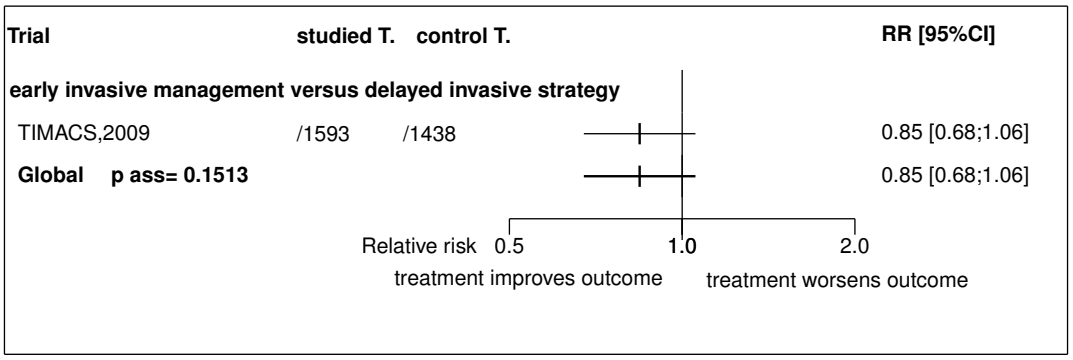


Figure 8.3: *Forest's plot for death, MI, stroke, refractory ischemia*

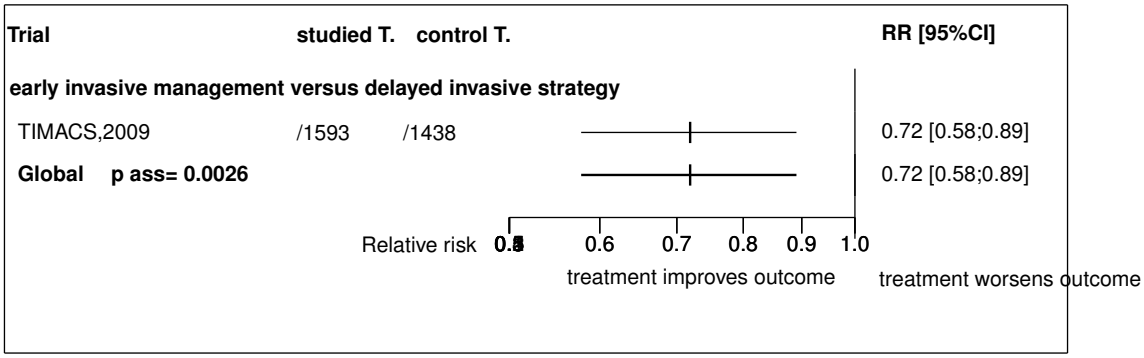


Figure 8.4: *Forest's plot for repeat intervention*

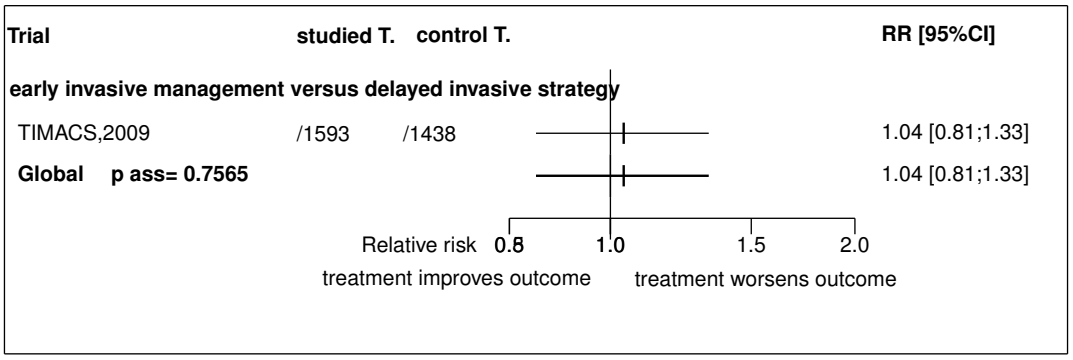


Figure 8.5: *Forest's plot for in-hospital death*

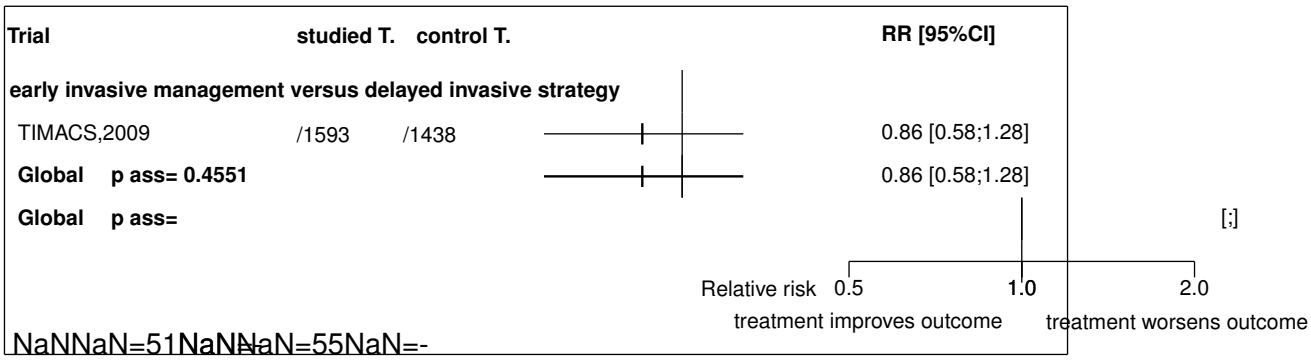


Figure 8.6: *Forest's plot for myocardial infarction (fatal and non fatal)*

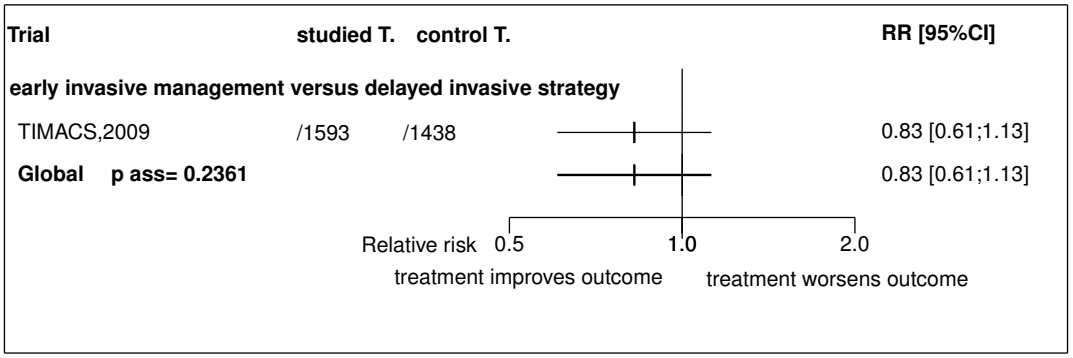


Figure 8.7: *Forest's plot for stroke (fatal and non fatal)*

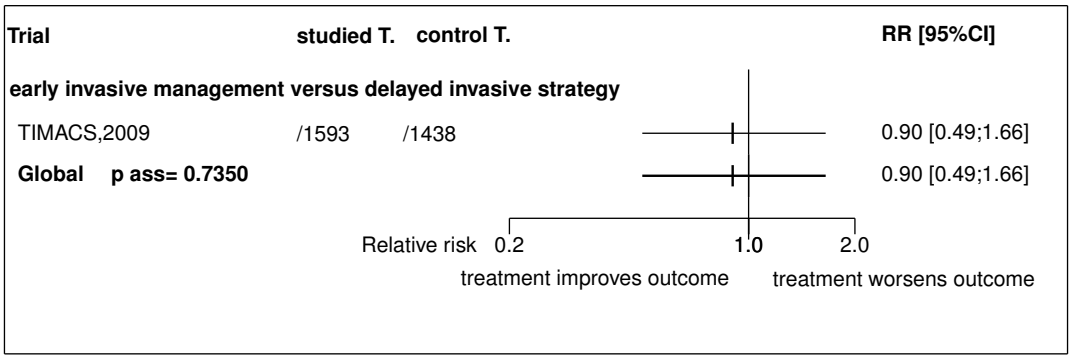


Figure 8.8: *Forest's plot for all cause death*

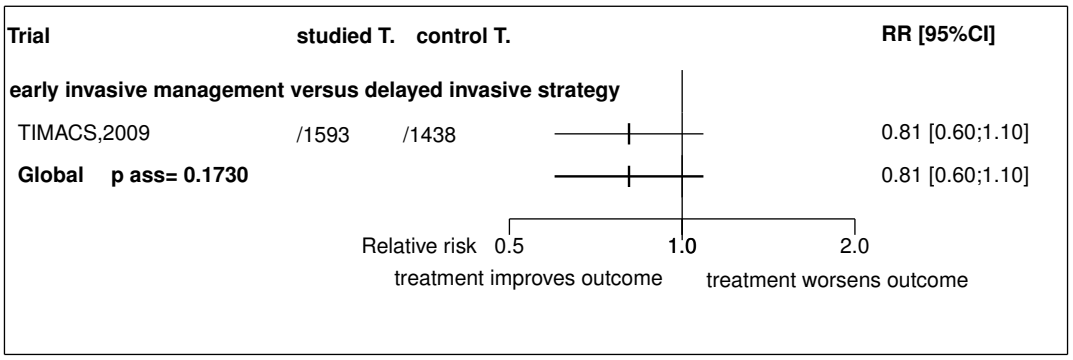
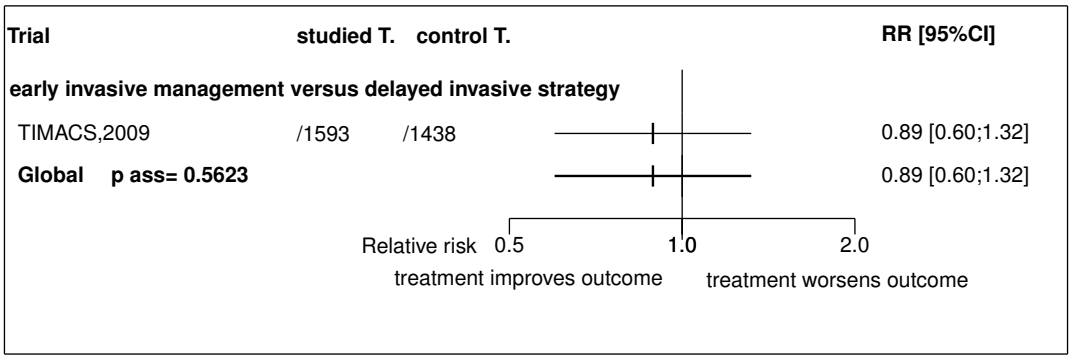


Figure 8.9: *Forest's plot for major bleeding*



References

[1] Mehta SR et al. Randomized comparison of early vs delayed invasive strategies in high risk patients with non-ST-segment elevation acute coronary syndromes: Main results of the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial. American Heart Association 2008 Scientific Sessions; November 10, 2008; New Orleans, LA. Late Breaking Clinical Trials Session 2.

[2] Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009 May 21;360:2165-75. [PMID=19458363]

8.3 Individual trial summaries

Table 8.6: *TIMACS, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3031 (1593 vs. 1438) **Follow-up duration:** 6 months **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias 30 countries, 100 centres **Inclusion period:** apr 2003 - jun 2008	Patients with unstable angina or non-ST-segment-elevation MI (NSTEMI) **Inclusion criteria:** Patients presenting with symptoms/signs compatible with UA/NSTEMI and within 24 hours from symptom onset and at least two of the following 3 criteria: Age >60, Elevated Troponin T or I or CKMB or ischemic ECG changes. **Exclusion criteria:** age <21 years; life expectancy <6 months; contraindication for low molecular weight heparin; high risk for bleeding; not a suitable candidate for revascularization	**Studied treatment:** early invasive management: angiography within 24 hours followed by PCI or CABG as appropriate Early Invasive Strategy defined as coronary angiography as soon as possible (and no later than 24 hours) followed by anatomy-driven intervention (PCI or CABG) **Control treatment:** delayed invasive strategy: angiography after 36 hours followed by PCI or CABG as appropriate Delayed Invasive Strategy defined as coronary angiography after 36 hours followed by anatomy-driven intervention (PCI or CABG).	

References

Mehta SR et al. Randomized comparison of early vs delayed invasive strategies in high risk patients with non-ST-segment elevation acute coronary syndromes: Main results of the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial. American Heart Association 2008 Scientific Sessions; November 10, 2008; New Orleans, LA. Late Breaking Clinical Trials Session 2
Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009 May 21;360:2165-75 [PMID=19458363]

9 Detailed results for immediate invasive management

9.1 Available trials

A total of 2 RCTs which randomized 494 patients were identified: all compared immediate invasive management with delayed invasive strategy.
The average study size was 247 patients (range 142 to 352). The first study was published in 2009, and the last study was published in 2009.
All trials 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 repeat intervention; 1 trials reported data on all cause death; and 2 trials reported data on major bleeding.
Following tables 9.1 (page 62), 9.2 (page 62), 9.4 (page 64), and 9.3 (page 63) summarized the main characteristics of the trials including in this systematic review of randomized trials of immediate invasive management.

Table 9.1: *Treatment description - early invasive strategy - immediate invasive management*

Trial	Studied treatment	Control treatment
Immediate invasive management versus delayed invasive strategy		
OPTIMA (2009) [1]	immediate angioplasty under tripleantiplatelet therapy protection	deferred angioplasty 2448 h afterrandomisation under tripleantiplatelet therapy protection
	Concomittant treatment: procedure with glycoprotein IIb/IIIa blockers and UFH;at admission, bolus of 500 mg aspirin intravenouslyand 300 mg clopidogrel by mouth then followed respectively by 80 and 75 mg orally (aspirin indefinitely and clopidogrel for 12 months); LMWH according cyurrent practice	
ABOARD (2009) [2]	immediate catheterization and revascularization	catheterization and revascularization on the next working day (between 8 and 60 hours after enrollment)

Table 9.2: *Descriptions of participants - early invasive strategy - immediate invasive management*

Trial	Patients
Immediate invasive management versus delayed invasive strategy	

continued...

Trial	Patients	
OPTIMA (2009) [1]	Patients with non-ST-segment elevationacute coronary syndromes eligible for percutaneous coronary intervention	
	Inclusion criteria: age >21 years; typical anginal chest; pain that had lasted for at least 10 min within the past 6 h; no contraindication to PCI; at least one of the following four criteria: >1 mm of ST depression in two contiguous leads, a raised troponin T level (>0.01 ng/l), known coronary artery disease (CAD) or two or more risk factors for CAD	**Exclusion criteria:** chest pain suspected not to be caused by CAD; acute ST elevation myocardial infarction, thrombolytic therapy within 24h; recent PCI (within 14 days); any contraindication for the use of abciximab; angiography did not demonstrate significant coronary stenosis amenable for PCI; coronary artery bypass grafting (CABG) was judged to be the preferred treatment; the culprit lesion was an instent restenosis or a chronic total occlusion
ABOARD (2009) [2]	Patient with non ST-elevation acute coronary syndrome	
	Inclusion criteria: presence of at least 2 ofthe following: symptoms ofmyocardial ischemia; electrocardiographicST-segment abnormalities(depression or transient elevation of at least 0.1 mV) or T-wave inversion in atleast in 2 contiguous leads; anelevated cardiac troponin I value (above the upper limit of normal); TIMI scoreof 3 or greater; indication forcoronary angiography	**Exclusion criteria:** younger than 18years; refractory ischemia, major arrhythmias,or hemodynamic instabilityrequiring immediate catheterization;ongoing treatment with warfarin,fibrinolysis, or glycoprotein IIb/IIIa inhibitor;contraindications to abciximab

Table 9.3: *Design and methodological quality of trials - early invasive strategy - immediate invasive management*

Trial	Design	Duration	Centre	Primary endpoint
Immediate invasive management versus delayed invasive strategy				
OPTIMA, 2009 [1] [(a)] n=142	Parallel groups open confirmatory trial at risk of bias	30 days inclusion period: Mar 2004 - Apr 2007	The Netherland, England multicentre	death, MI, unplanned revascularization
ABOARD, 2009 [2] n=352	Parallel groups open exploratory trial	1 month inclusion period: aug 2006 - sept 2008	France 13 centres	peak troponin-I

a) patients were randomized after initial angiography when suitable coronary anatomy was identified

Table 9.4: *Trial characteristics - early invasive strategy - immediate invasive management*

Trial	Fibrinolysis	non Q wave MI	Time to cardiac catheterization routine invasive group, h	ST-segment depression	T-wave inversion	Thrombolytic therapy
Immediate invasive management versus delayed invasive strategy						
OPTIMA, 2009 [1]						0%
ABOARD, 2009 [2]						

9.2 Meta-analysis results

The results are detailed in table 9.5 (page 65). This table is followed by the Forest's plot corresponding to each endpoint.

Immediate invasive management versus delayed invasive strategy

Only one of the 2 studies eligible for this comparison provided data on **repeat intervention**. No statistically significant difference between the groups was found in repeat intervention, with a RR of 0.63 (95% CI 0.11 to 3.66, p=0.6068).
All the 2 studies had extractable data about the number of participants with **myocardial infarction (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of delayed invasive strategy in myocardial infarction (fatal and non fatal), with a RR of 1.66 (95% CI 1.20 to 2.30, p=0.0024). No heterogeneity was detected (p = 0.6077, I^2 = 0.00%).
Only one of the 2 studies eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 2.53 (95% CI 0.50 to 12.86, p=0.2636).

Table 9.5: *Results details - early invasive strategy - immediate invasive management*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
immediate invasive management versus delayed invasive strategy						
repeat intervention	RR=0.63	[0.11;3.66]	0.6068	1.0000 (I^2=0.00)	1	142
myocardial infarction (fatal and non fatal)	RR=1.66	[1.20;2.30]	0.0024	0.6077 (I^2=0.00)	2	494
all cause death	RR=2.53	[0.50;12.86]	0.2636	1.0000 (I^2=0.00)	1	352
major bleeding	RR=0.55	[0.26;1.17]	0.1202	0.7889 (I^2=0.00)	2	494

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

Figure 9.1: *Forest's plot for repeat intervention*

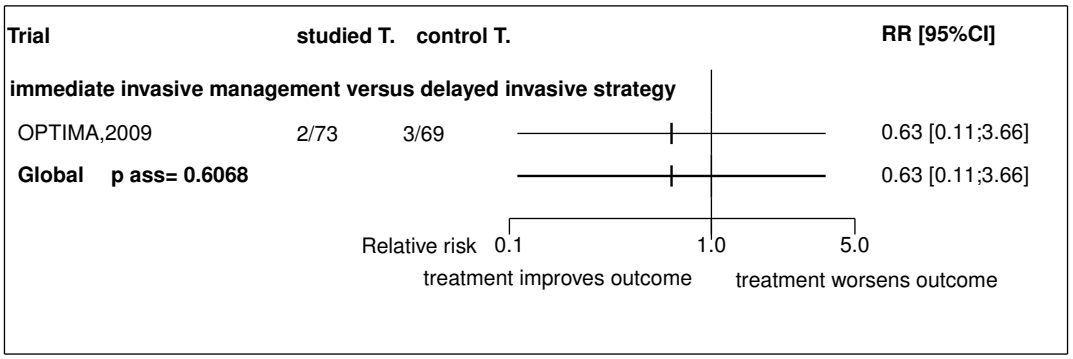


Figure 9.2: *Forest's plot for myocardial infarction (fatal and non fatal)*

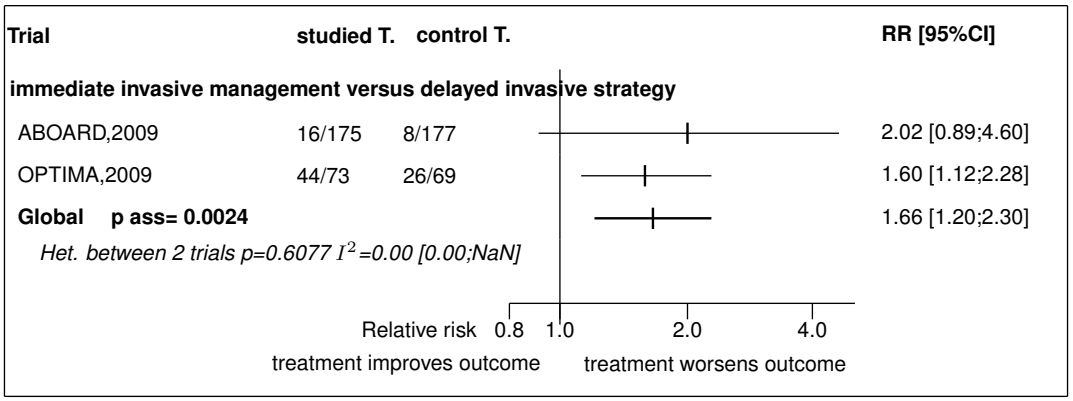


Figure 9.3: *Forest's plot for all cause death*

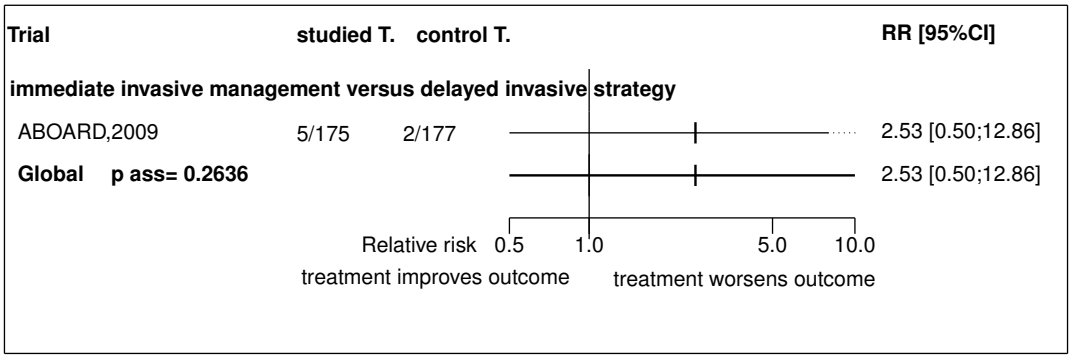
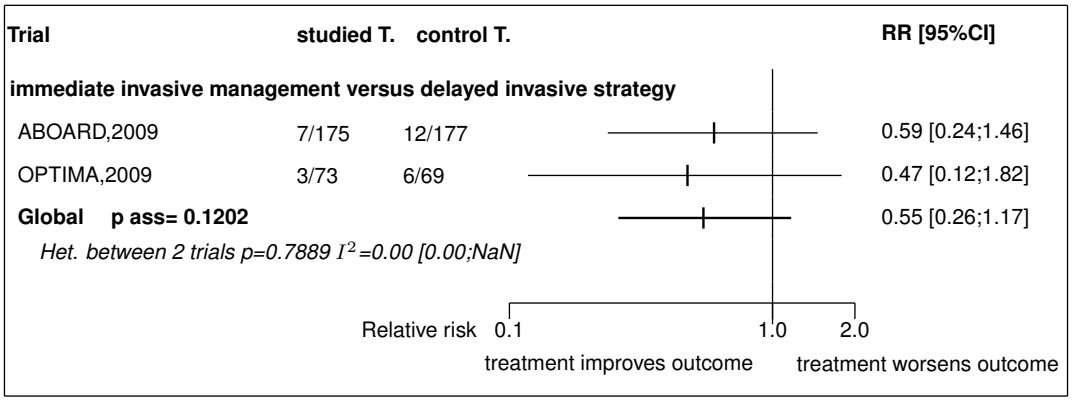


Figure 9.4: *Forest's plot for major bleeding*



References

[1] Riezebos RK, Ronner E, Ter Bals E, Slagboom T, Smits PC, ten Berg JM, Kiemeneij F, Amoroso G, Patterson MS, Suttorp MJ, Tijssen JG, Laarman GJ. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. Heart 2009 May;95:807-12. [PMID=19098058]

[2] Montalescot G, Cayla G, Collet JP, Elhadad S, Beygui F, Le Breton H, Choussat R, Leclercq F, Silvain J, Duclos F, Aout M, Dubois-Rand JL, Barthlmy O, Ducrocq G, Bellemain-Appaix A, Payot L, Steg PG, Henry P, Spaulding C, Vicaut E. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. JAMA 2009 Sep 2;302:947-54. [PMID=19724041]

9.3 Individual trial summaries

Table 9.6: *OPTIMA, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=142 (73 vs. 69) **Follow-up duration:** 30 days **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias The Netherland, England, multicentre **Inclusion period:** Mar 2004 - Apr 2007	Patients with non-ST-segment elevationacute coronary syndromes eligible for percutaneous coronary intervention **Inclusion criteria:** age >21 years; typical anginal chest; pain that had lasted for at least 10 min within the past 6 h; no contraindication to PCI; at least one of the following four criteria: >1 mm of ST depression in two contiguous leads, a raised troponin T level (>0.01 ng/l), known coronary artery disease (CAD) or two or more risk factors for CAD **Exclusion criteria:** chest pain suspected not to be caused by CAD; acute ST elevation myocardial infarction, thrombolytic therapy within 24h; recent PCI (within 14 days); any contraindication for the use of abciximab; angiography did not demonstrate significant coronary stenosis amenable for PCI; coronary artery bypass grafting (CABG) was judged to be the preferred treatment; the culprit lesion was an instent restenosis or a chronic total occlusion	**Studied treatment:** immediate angioplasty under tripleantiplatelet therapy protection **Control treatment:** deferred angioplasty 2448 h afterrandomisation under tripleantiplatelet therapy protection **Concomittant treat.:**procedure with glycoprotein IIb/IIIa blockers and UFH;at admission, bolus of 500 mg aspirin intravenouslyand 300 mg clopidogrel by mouth then followed respectively by 80 and 75 mg orally (aspirin indefinitely and clopidogrel for 12 months); LMWH according cyurrent practice	Repeat intervention RR=0.63 [0.11;3.66] (Unplanned revascularisation at 30 days)

Reference
Riezebos RK, Ronner E, Ter Bals E, Slagboom T, Smits PC, ten Berg JM, Kiemeneij F, Amoroso G, Patterson MS, Suttorp MJ, Tijssen JG, Laarman GJ. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. Heart 2009 May;95:807-12 [PMID=19098058]

Table 9.7: *ABOARD, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=352 (175 vs. 177) **Follow-up duration:** 1 month **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial France, 13 centres **Inclusion period:** aug 2006 - sept 2008	Patient with non ST-elevation acute coronary syndrome **Inclusion criteria:** presence of at least 2 ofthe following: symptoms ofmyocardial ischemia; electrocardiographicST-segment abnormalities(depression or transient elevation of at least 0.1 mV) or T-wave inversion in atleast in 2 contiguous leads; anelevated cardiac troponin I value (above the upper limit of normal); TIMI scoreof 3 or greater; indication forcoronary angiography **Exclusion criteria:** younger than 18years; refractory ischemia, major arrhythmias,or hemodynamic instabilityrequiring immediate catheterization;ongoing treatment with warfarin,fibrinolysis, or glycoprotein IIb/IIIa inhibitor;contraindications to abciximab	**Studied treatment:** immediate catheterization and revascularization **Control treatment:** catheterization and revascularization on the next working day (between 8 and 60 hours after enrollment)	

Reference

Montalescot G, Cayla G, Collet JP, Elhadad S, Beygui F, Le Breton H, Choussat R, Leclercq F, Silvain J, Duclos F, Aout M, Dubois-Rand JL, Barthlmy O, Ducrocq G, Bellemain-Appaix A, Payot L, Steg PG, Henry P, Spaulding C, Vicaut E. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. JAMA 2009 Sep 2;302:947-54 [PMID=19724041]

10 Detailed results for routine invasive strategy

10.1 Available trials

A total of 7 RCTs which randomized 8053 patients were identified: all compared routine invasive strategy with concervative strategy.
The average study size was 1150 patients (range 88 to 2456). The first study was published in 1999, and the last study was published in 2007.
All trials were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Deaths or MI data was reported in 7 trials; 7 trials reported data on all cause death; 7 trials reported data on in-hospital death; 7 trials reported data on non fatal MI; 7 trials reported data on in hospital death or MI; 7 trials reported data on in hospital non fatal MI; 6 trials reported data on rehospitalization; 4 trials reported data on CCS class III-IV angina; 3 trials reported data on long term cardiovascular events; 3 trials reported data on long term cardiovascular death; 3 trials reported data on long term MI; 3 trials reported data on long term all cause death, MI; 3 trials reported data on long term death; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on no angina (at 6 weeks); 1 trials reported data on adverse events; and 1 trials reported data on major bleeding.
Following tables 10.1 (page 71), 10.2 (page 72), 10.4 (page 75), and 10.3 (page 73) summarized the main characteristics of the trials including in this systematic review of randomized trials of routine invasive strategy.

Table 10.1: *Treatment description - early invasive strategy - routine invasive strategy*

Trial	Studied treatment	Control treatment
Routine invasive strategy versus concervative strategy		
ICTUS (2007) [1, 2]	early invasive strategy early invasive strategy including early routine catheterisation and revascularisation where appropriate	selective invasive treatment strategy more selective invasive strategy where catheterisation was done if the patient had refractory angina or recurrent ischaemia
FRISC 2 (1999) [3, 4, 5, 6]	early invasive treatment strategy: angiography within 7 days aiming for revascularisation The direct invasive treatments were coronary angiography within a few days of enrolment, aiming for revascularisation within 7 days of the start of open-label treatment. Revascularisation was recommended in all patients with an obstruction of at least 70% of the diameter of any artery supplying a substantial proportion of the myocardium. Percutaneous coronary intervention was recommended if there were one or two target lesions, and coronary-artery bypass surgery was preferred in patients with three-vessel or left mainartery disease.	non-invasive treatment strategy: angiography only in patients with refractory or recurrent symptoms despite maximum medical treatment or severe ischemia during exercise test before discharge
	Concomittant treatment: 7 days of the dalteparin. Followed by 3 months placebo controlled long-term low-molecular heparin (dalteparin). Aspirin , beta-blockers. Abciximab during PTCA and ticlopidine after stent	

continued...

Trial	Studied treatment	Control treatment
NQWMI (Eisenberg) (2005) [7]	Invasive (angiography at days 2 to 5)	Noninvasive (stress testing at day 2 to 5) angiograpgy recommended if angiography at 2 to 5 days or ST-segment depression of at least 2mm on an ECG recorded during peak exercise or ischemic areas in 2 or more vascular regions by echocardiographyor perfusion imaging
RITA 3 (2002) [8, 9]	routine angiography followed byrevascularisationage/pj coronary arteriography within 72 h with subsequent management guided by the angiographic findings	conservative strategy (ischaemia-driven or symptom-driven angiographyS best medical treatment
TACTICS-TIMI 18 (2001) [10]	early invasive management strategy coronary angiography at 4 to 48 hours	conservative management strategy medical therapy and predischarge exercise testing
TRUCS (2000) [11]	invasive strategy on-site coronary angioplastyor emergency air-ambulance transfer for bypass graftingsurgery	conservative strategy persistent medical treatment
VINO (2002) [12]	first day angiography / angioplasty strategy coronary angiogram followed by: 1) immediate coronary angioplasty of the culprit coronary lesion+stent implantation whenever suitable (single vessel disease or multivessel disease with TIMI 02 flow in the infarct-related artery); 2)carefully timed (34 weeks) coronary bypass surgery in patients with left main coronary artery disease or multivessel disease with TIMI-3 flow in all arteries or 3) urgent (within 1 week) coronary bypass surgery in severe (>70%) left main stenosis or in multivessel disease with recurrent rest chest pain	early conservative therapy medical treatment with coronaryangiography and subsequent revascularization only in the presence of recurrent myocardial ischaemia (rest angina and/or ECG demonstrating 2 mm ST-segment depressions or elevations in at least two leads lasting >5 min or persistent at least 1 mm ST-segment depressions during initial hospitalization) or symptom-limited exercise test positivity (chest pain and ST-segment depressions of at least 2 mm recorded during peak exercise or a redistribution defect in at least one main vascular region on thallium scintigraphy).

Table 10.2: *Descriptions of participants - early invasive strategy - routine invasive strategy*

Trial	Patients
Routine invasive strategy versus concervative strategy	
ICTUS (2007) [1, 2]	Patients with nonST-segment elevation acutec oronary syndrome and elevated cardiac troponin T
FRISC 2 (1999) [3, 4, 5, 6]	Patients with nonST-segment elevation acutecoronary syndrome **Inclusion criteria:** symptoms of ischemia increasing or occurring at rest with the last episode within 48h. Myocardial ischemia verified by ECG or by raised biochemical markers **Exclusion criteria:** raised risk of bleeding, anaemia, thrombolysis in the 24h, angioplasty in the past 6 months, etc.

continued...

Trial	Patients	
NQWMI (Eisenberg) (2005) [7]	Patients with nonQ-wave myocardial infarction	
	Inclusion criteria: chest pain consistent with cardiac ischemia of at least 20min; >=1 mm ST elevation ordepression or T wave inversion in 2 or more contiguous leads and/or creatine kinase (CK) elevation 2 times the upperlimit of normal and/or elevation in CK-MB, troponin T, or troponin I	**Exclusion criteria:**
RITA 3 (2002) [8, 9]	Patients with nonST-segment elevation acutecoronary syndrome	
TACTICS-TIMI 18 (2001) [10]	Patients with nonST-segment elevation acute coronary syndrome	
	Inclusion criteria: older than18 years of age; episode of angina in the preceding24 hours;	**Exclusion criteria:** persistent ST-segment elevation; secondary angina; percutaneous coronary revascularization or coronary bypass surgery within the previous 6 months; a history of gastrointestinal bleeding, platelet disorder, or thrombocytopenia; any history of hemorrhagic cerebrovascular disease or a history of non-hemorrhagic cerebrovascular disease or transient ischemic attack within 1 year; left bundle-branch block or paced rhythm; severe congestive heart failure or cardiogenic shock; clinically important systemic disease; serum creatinine concentration greater than 220 micromol/L; treatment with a glycoprotein IIb/IIIa antagonist within the past 96 hours; or ongoing long-term treatment with ticlopidine, clopidogrel, or warfarin
TRUCS (2000) [11]	Patients with nonST-segment elevation acute coronary syndrome in geographically isolated hospitals without cardiac surgicalfacilities	
VINO (2002) [12]	Patients with nonST-segment elevation acute coronary syndrome	
	Inclusion criteria: rest ischaemic chest pain, lasting more than 20 min, within the last 24 h; ECG evidence of acute myocardial ischaemia without ST-segment elevations (ST-segment depressions minimally 01 mm in at least two contiguous leads and/or negative T waves or documented old LBBB/RBBB; CK-MB higher than 15? upper limit of normal and/or positive troponin I assay	**Exclusion criteria:** unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; Cardiogenic shock; Acute LBBB or RBBB or ST segment elevations <=2 mm in two leads; Q-wave myocardial infarction or intravenous thrombolysis less than 1 month; Coronary angioplasty or bypass surgery less than 6 months; Any concomitant disease which may have possible influence on 1 year prognosis

Table 10.3: *Design and methodological quality of trials - early invasive strategy - routine invasive strategy*

Trial	Design	Duration	Centre	Primary endpoint
Routine invasive strategy versus concervative strategy				
ICTUS, 2007 [1, 2] n=1200	Parallel groups open	12 mo (4y) inclusion period: 20012003	Netherlands 42 centres	death, MI, rehospitalization

continued...

Trial	Design	Duration	Centre	Primary endpoint
FRISC 2, 1999 [3, 4, 5, 6] n=2456	Factorial plan Open	24 mo inclusion period: 19961998	Scandinavia 58 centres	death or nonfatal myocardial infarction
NQWMI (Eisenberg), 2005 [7] n=88	Parallel groups open exploratory trial	12 months inclusion period: oct 1999 - mar 2002	Canada 8 centres	maximal endurance
RITA 3, 2002 [8, 9] n=1810	Parallel groups open	24 mo (60 mo) inclusion period: 19972001	UK 45 centres	death or non fatal MI
TACTICS-TIMI 18, 2001 [10] n=2220	Parallel groups open	6 mo inclusion period: dec 1997 jun 1999	9 countries 169 centres	
TRUCS, 2000 [11] n=148	Parallel groups	12 mo inclusion period: 19971998	Greece	
VINO, 2002 [12] n=131	Parallel groups open	6 mo inclusion period: may 19982000	Czech Republic 10 centres	death or nonfatal recurrent

Table 10.4: *Trial characteristics - early invasive strategy - routine invasive strategy*

Trial	Fibrinolysis	non Q wave MI	Time to cardiac catheterization routine invasive group, h	ST-segment depression	T-wave inversion	Thrombolytic therapy
Routine invasive strategy versus concervative strategy						
ICTUS, 2007 [1, 2]			23 h (median)	46%		
FRISC 2, 1999 [3, 4, 5, 6]	0%	NA	96 h (median)	1114 (46%)	NA	0
NQWMI (Eisenberg), 2005 [7]		100%		NA		
RITA 3, 2002 [8, 9]			48 h (median)	660 (37%)	1298 (72%)	0
TACTICS-TIMI 18, 2001 [10]			22 h (median)	688 (31%)	777 (35%)	0
TRUCS, 2000 [11]				NA		
VINO, 2002 [12]			6.2 h (median)	60 (46%)	NA	0

10.2 Meta-analysis results

The results are detailed in table 10.5 (page 77). This table is followed by the Forest's plot corresponding to each endpoint.

Routine invasive strategy versus concervative strategy

All the 7 studies had extractable data about the number of participants with **in-hospital death**. There was no statistically significant difference in in-hospital death between routine invasive strategy and concervative strategy, with a RR of 1.29 (95%CI 0.74 to 2.27, p=0.3689) in favour of routine invasive strategy. In other words, in-hospital death was slightly lower in the concervative strategy group , but this was not statistically significant. No heterogeneity was detected (p = 0.2030, I^2 = 0.29%).
All the 7 studies had extractable data about the number of participants with **in hospital non fatal MI**. When pooled together, there was no statistically significant difference between the groups in in hospital non fatal MI, with a RR of 1.24 (95% CI 0.71 to 2.17, p=0.4565). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0006, I^2 = 0.75%).
All the 7 studies had extractable data about the number of participants with **in hospital death or MI**. When pooled together, there was no statistically significant difference between the groups in in hospital death or MI, with a RR of 1.21 (95% CI 0.73 to 2.00, p=0.4512). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0003, I^2 = 0.76%).
All the 7 studies had extractable data about the number of participants with **deaths or MI**. When pooled together, there was no statistically significant difference between the groups in deaths or MI, with a RR of 0.81 (95% CI 0.59 to 1.11, p=0.1802). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0001, I^2 = 0.80%).
A total of 4 of the 7 studies eligible for this comparison provided data on **CCS class III-IV angina**. When pooled together, there was no statistically significant difference between the groups in CCS class III-IV angina, with a RR of 0.72 (95% CI 0.49 to 1.06, p=0.0951). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0014, I^2 = 0.81%).
A total of 6 of the 7 studies eligible for this comparison provided data on **rehospitalization**. The analysis detected a statistically significant difference in favor of routine invasive strategy in rehospitalization, with a RR of 0.74 (95% CI 0.62 to 0.89, p=0.0017). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0004, I^2 = 0.78%).
A total of 3 of the 7 studies eligible for this comparison provided data on **long term cardiovascular death**. When pooled together, there was no statistically significant difference between the groups in long term cardiovascular death, with a RR of 0.84 (95% CI 0.69 to 1.01, p=0.0701). No heterogeneity was detected (p = 0.3999, I^2 = 0.00%).
A total of 3 of the 7 studies eligible for this comparison provided data on **long term all cause death, MI**. When pooled together, there was no statistically significant difference between the groups in long term all cause death, MI, with a RR of 0.88 (95% CI 0.75 to 1.03, p=0.1206). No heterogeneity was detected (p = 0.1344, I^2 = 0.50%).
A total of 3 of the 7 studies eligible for this comparison provided data on **long term cardiovascular events**. The analysis detected a statistically significant difference in favor of routine invasive strategy in long term cardiovascular events, with a RR of 0.83 (95% CI 0.73 to 0.93, p=0.0024). No heterogeneity was detected (p = 0.3913, I^2 = 0.00%).
Only one of the 7 studies eligible for this comparison provided data on **no angina (at 6 weeks)**. The analysis detected a statistically significant difference in favor of routine invasive strategy in no angina (at 6 weeks), with a RR of 1.61 (95% CI 1.52 to 1.72, p=0.0000).

A total of 3 of the 7 studies eligible for this comparison provided data on **long term MI**. The analysis detected a statistically significant difference in favor of routine invasive strategy in long term MI, with a RR of 0.77 (95% CI 0.67 to 0.90, p=0.0000). No heterogeneity was detected (p = 0.5919, I^2 = 0.00%).
Only one of the 7 studies eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.37 (95% CI 0.04 to 3.38, p=0.3746).
A total of 3 of the 7 studies eligible for this comparison provided data on **long term death**. When pooled together, there was no statistically significant difference between the groups in long term death, with a RR of 1.16 (95% CI 0.89 to 1.52, p=0.2672). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0320, I^2 = 0.71%).
All the 7 studies had extractable data about the number of participants with **non fatal MI**. When pooled together, there was no statistically significant difference between the groups in non fatal MI, with a RR of 0.81 (95% CI 0.57 to 1.16, p=0.2500). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0028, I^2 = 0.70%).
All the 7 studies had extractable data about the number of participants with **all cause death**. The analysis detected a statistically significant difference in favor of routine invasive strategy in all cause death, with a RR of 0.79 (95% CI 0.63 to 0.98, p=0.0326). No heterogeneity was detected (p = 0.3526, I^2 = 0.10%).

Table 10.5: *Results details - early invasive strategy - routine invasive strategy*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
routine invasive strategy versus concervative strategy						
in-hospital death	RR=1.29	[0.74;2.27]	0.3689	0.2030 (I^2=0.29)	7	8054
in hospital non fatal MI	RR=1.24	[0.71;2.17]	0.4565	0.0006 (I^2=0.75)	7	8054
in hospital death or MI	RR=1.21	[0.73;2.00]	0.4512	0.0003 (I^2=0.76)	7	8054
deaths or MI	RR=0.81	[0.59;1.11]	0.1802	0.0001 (I^2=0.80)	7	8054
CCS class III-IV angina	RR=0.72	[0.49;1.06]	0.0951	0.0014 (I^2=0.81)	4	6436
rehospitalization	RR=0.74	[0.62;0.89]	0.0017	0.0004 (I^2=0.78)	6	7901
long term cardiovascular death	RR=0.84	[0.69;1.01]	0.0701	0.3999 (I^2=0.00)	3	5467
long term all cause death, MI	RR=0.88	[0.75;1.03]	0.1206	0.1344 (I^2=0.50)	3	5467
long term cardiovascular events	RR=0.83	[0.73;0.93]	0.0024	0.3913 (I^2=0.00)	3	5467
no angina (at 6 weeks)	RR=1.61	[1.52;1.72]	0.0000	1.0000 (I^2=1.00)	1	2457
long term MI	RR=0.77	[0.67;0.90]	0.0000	0.5919 (I^2=0.00)	3	5467
myocardial infarction (fatal and non fatal)	RR=0.37	[0.04;3.38]	0.3746	1.0000 (I^2=1.00)	1	88
long term death	RR=1.16	[0.89;1.52]	0.2672	0.0320 (I^2=0.71)	3	5467

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
non fatal MI	RR=0.81	[0.57;1.16]	0.2500	0.0028 (I^2=0.70)	7	8054
all cause death	RR=0.79	[0.63;0.98]	0.0326	0.3526 (I^2=0.10)	7	8053
adverse events	RR=2.38	[1.42;3.98]	0.0000	1.0000 (I^2=0.00)	1	2457
major bleeding	RR=2.13	[0.97;4.70]	0.0598	1.0000 (I^2=0.00)	1	2457

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

Figure 10.1: *Forest's plot for in-hospital death*

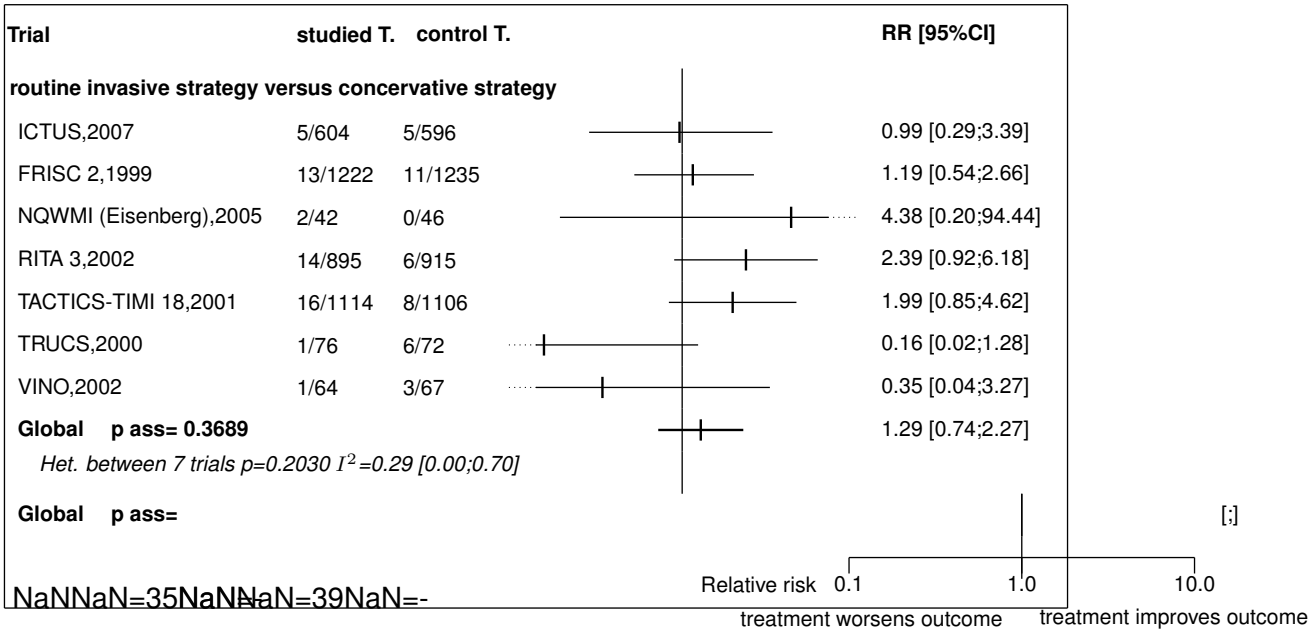


Figure 10.2: *Forest's plot for in hospital non fatal MI*

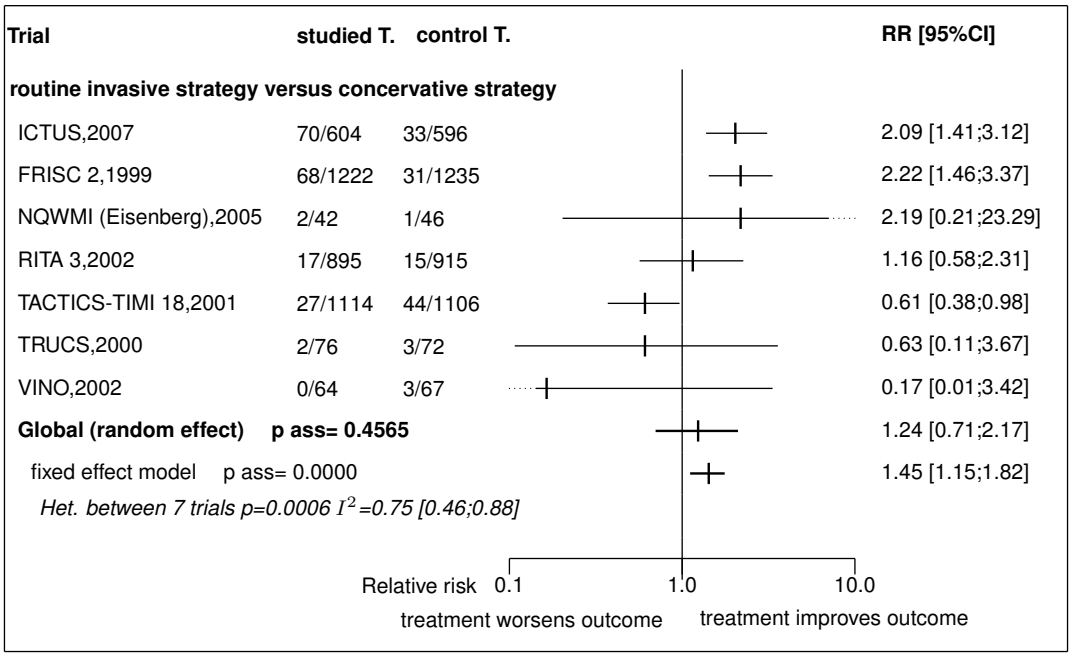


Figure 10.3: *Forest's plot for in hospital death or MI*

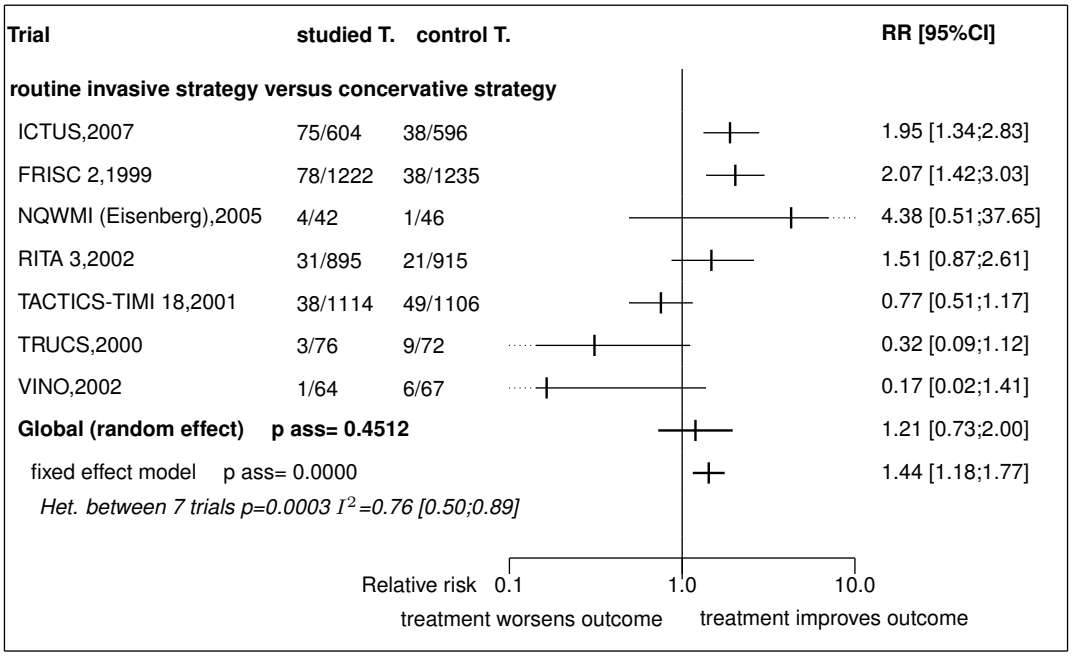


Figure 10.4: *Forest's plot for deaths or MI*

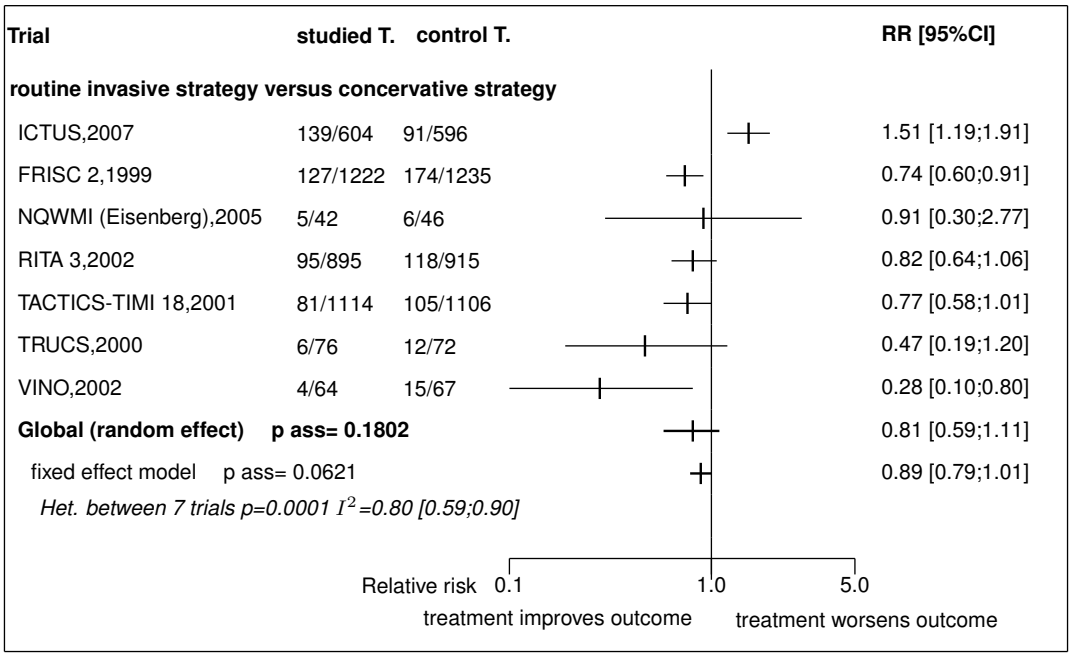


Figure 10.5: *Forest's plot for CCS class III-IV angina*

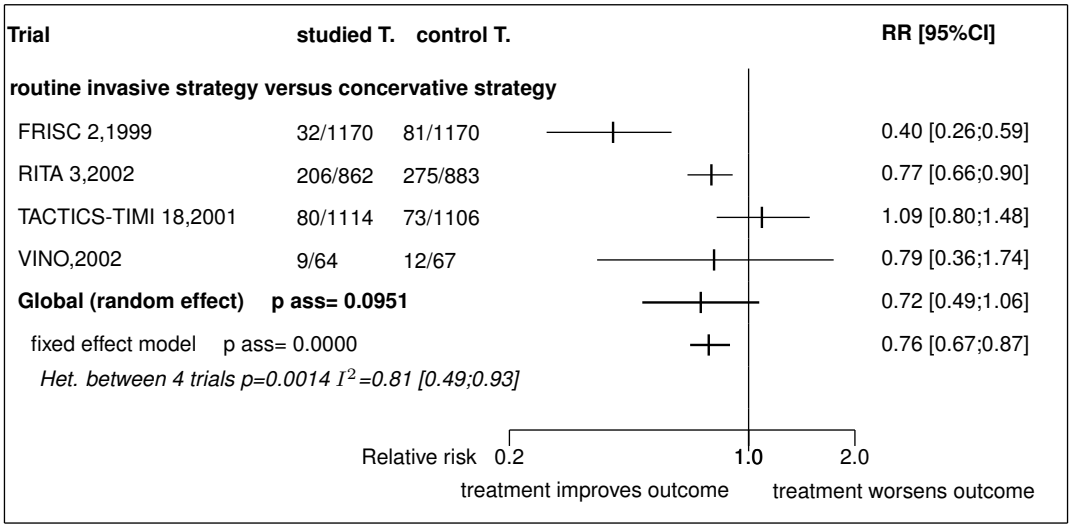


Figure 10.6: *Forest's plot for rehospitalization*

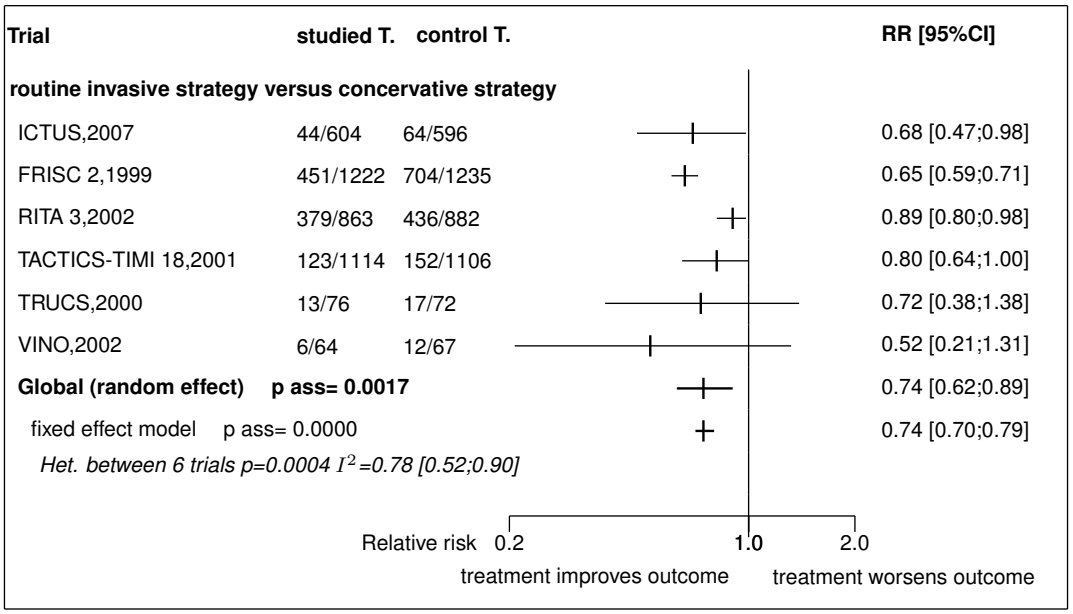


Figure 10.7: *Forest's plot for long term cardiovascular death*

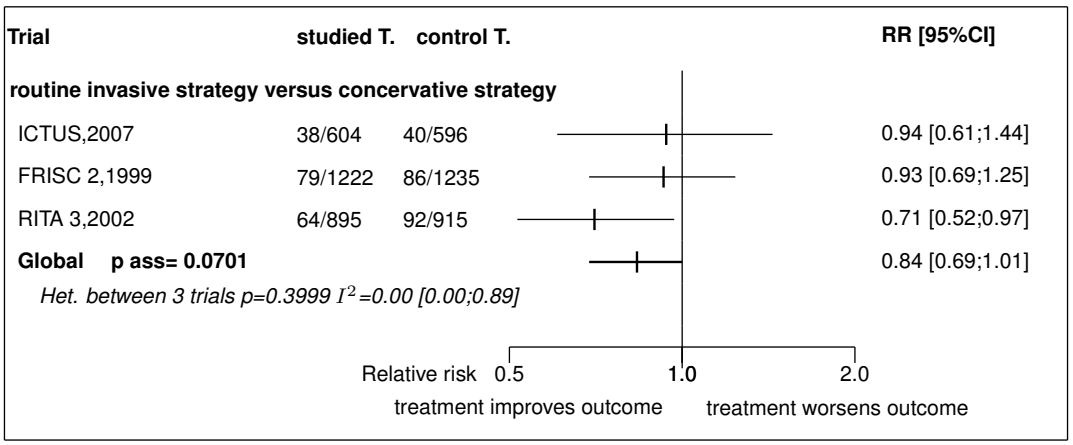


Figure 10.8: *Forest's plot for long term all cause death, MI*

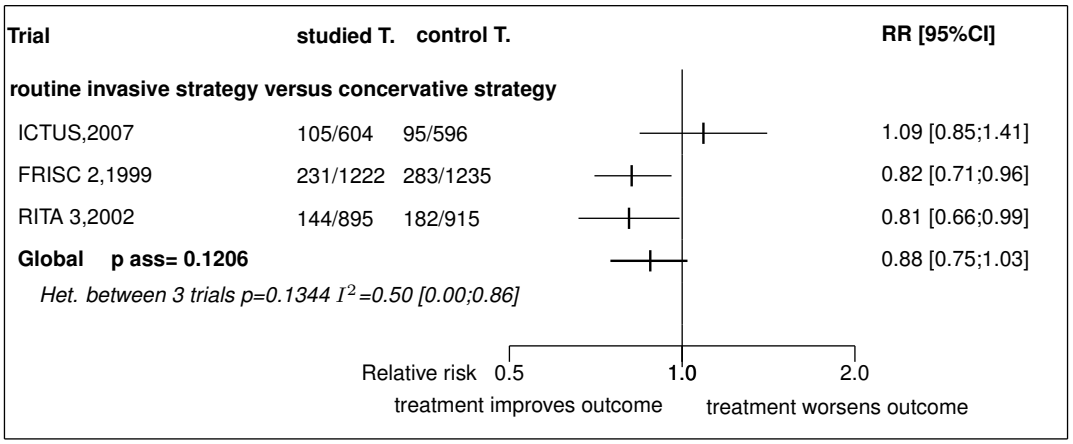


Figure 10.9: *Forest's plot for long term cardiovascular events*

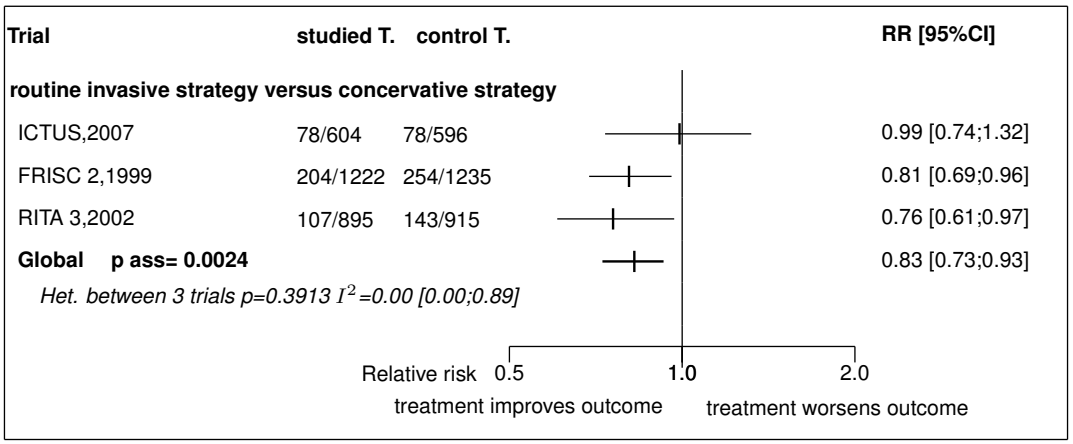


Figure 10.10: *Forest's plot for no angina (at 6 weeks)*

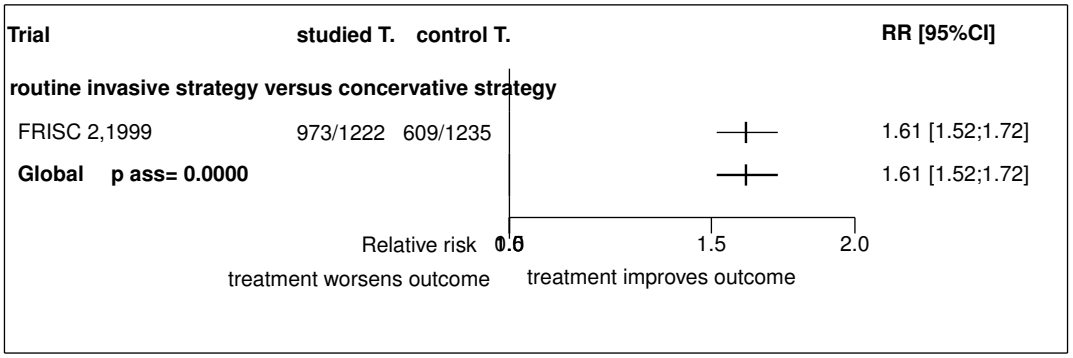


Figure 10.11: *Forest's plot for long term MI*

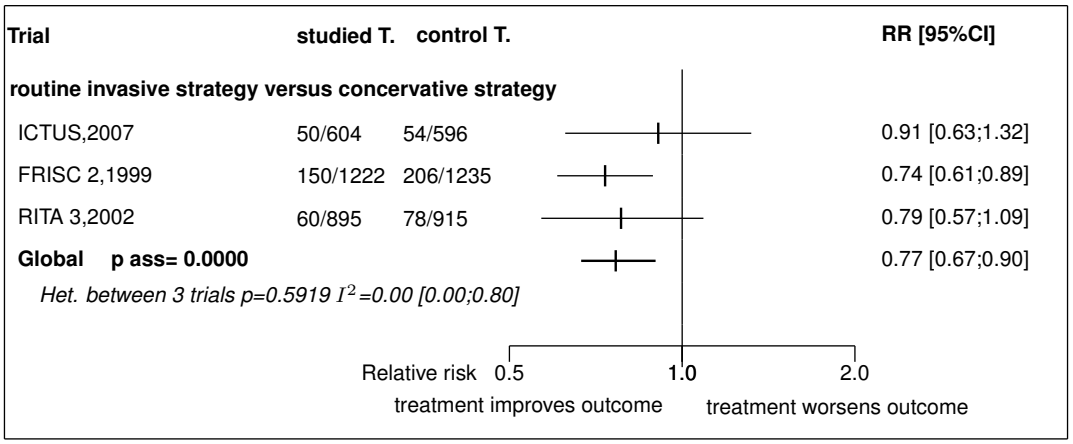


Figure 10.12: *Forest's plot for in-hospital death*

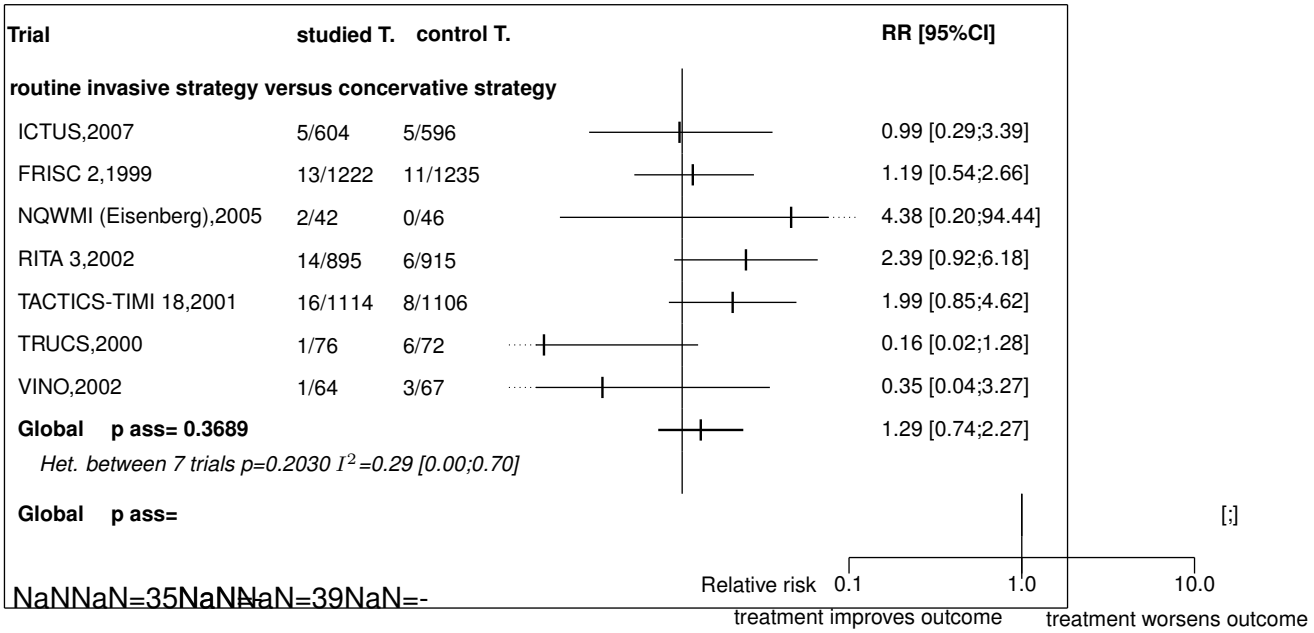


Figure 10.13: *Forest's plot for myocardial infarction (fatal and non fatal)*

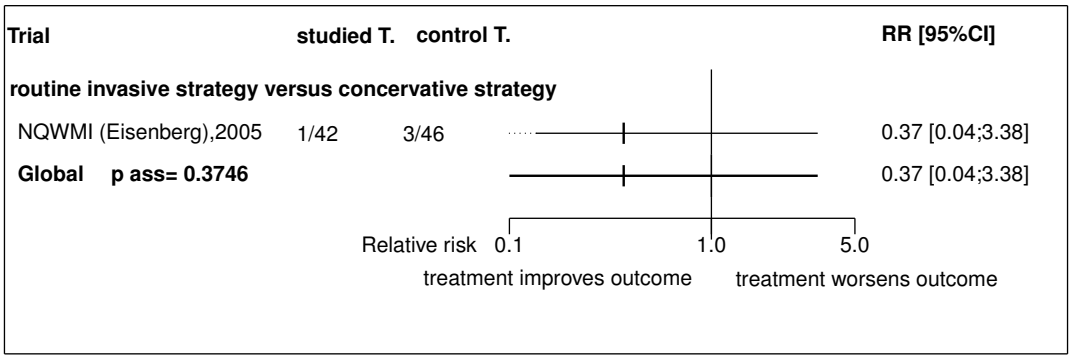


Figure 10.14: *Forest's plot for long term death*

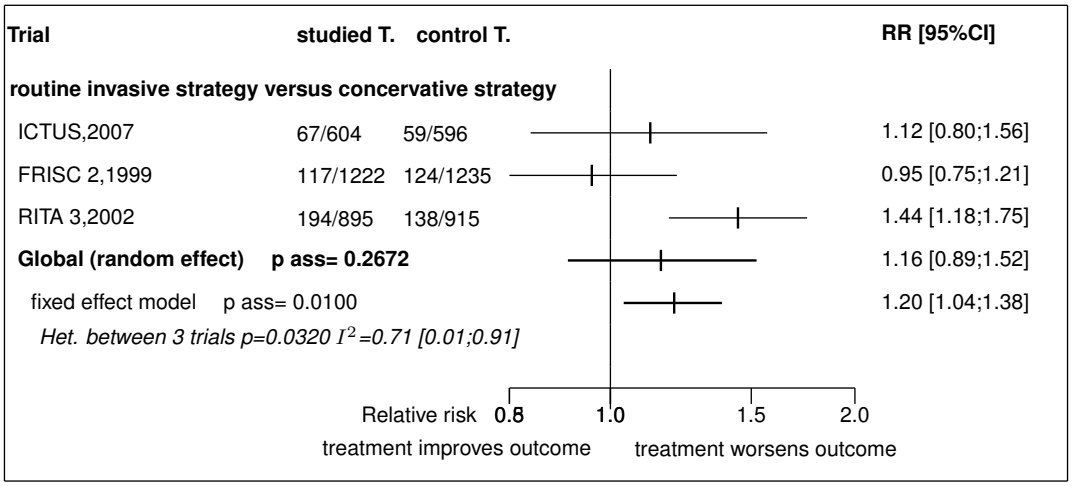


Figure 10.15: *Forest's plot for non fatal MI*

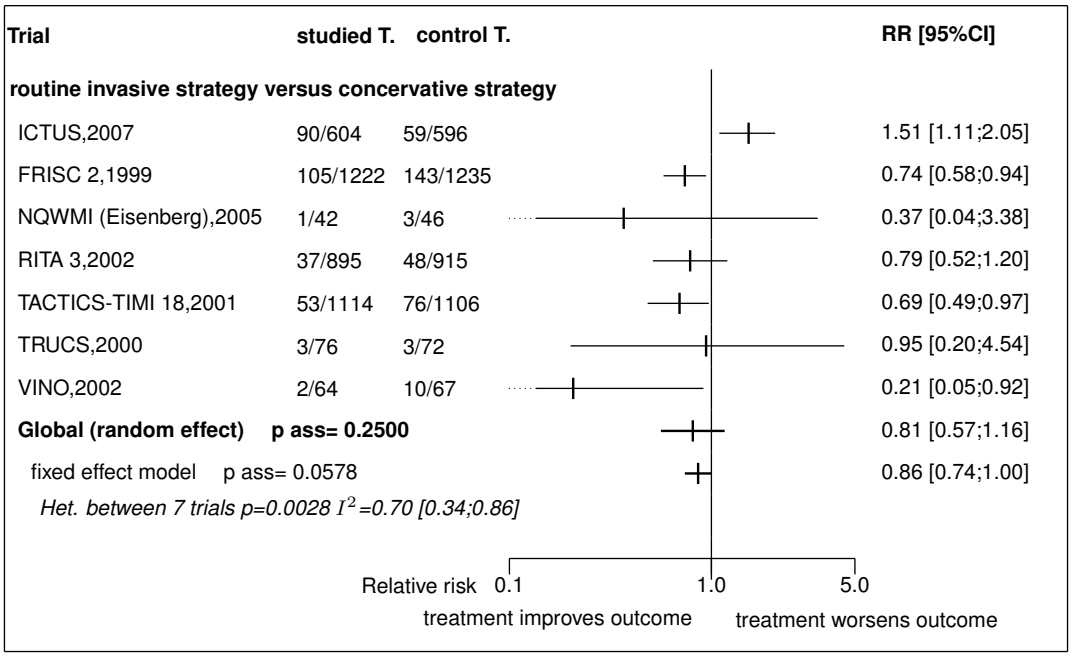


Figure 10.16: *Forest's plot for all cause death*

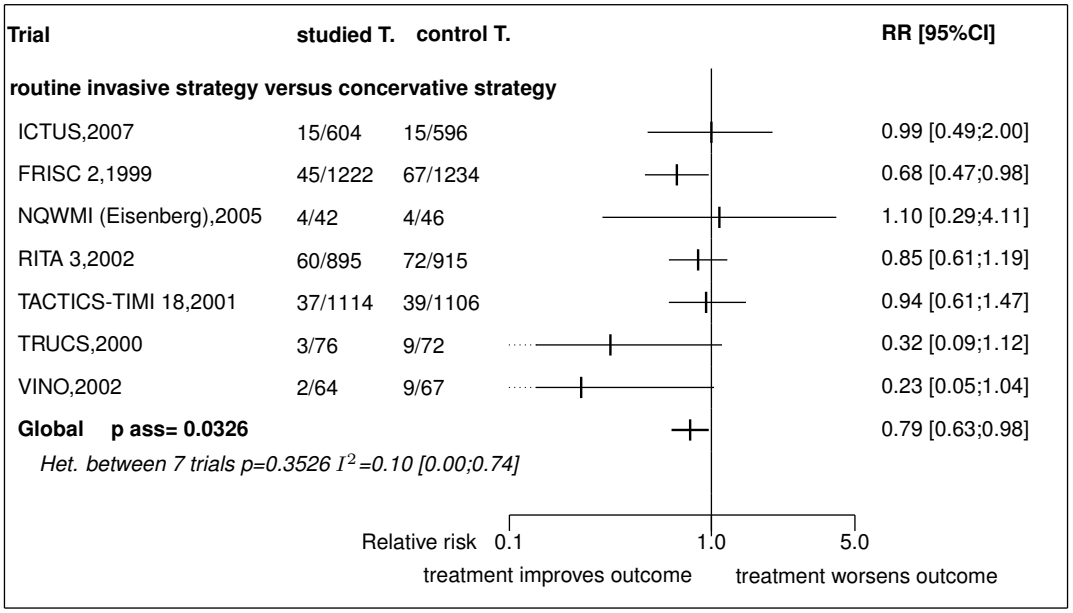


Figure 10.17: *Forest's plot for adverse events*

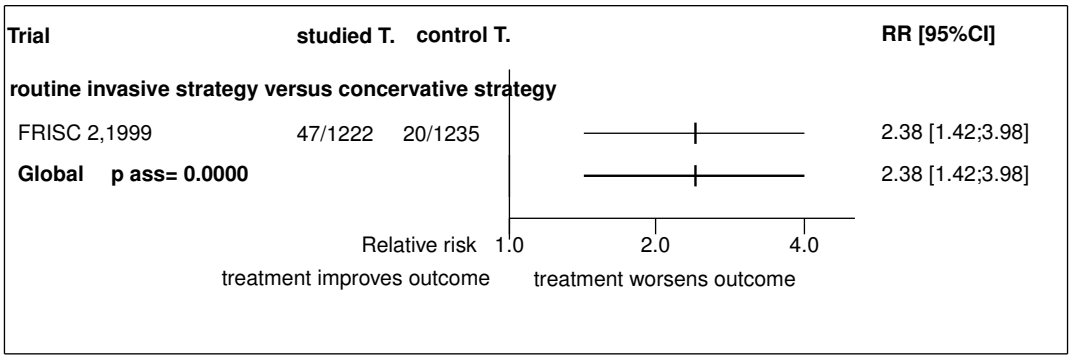
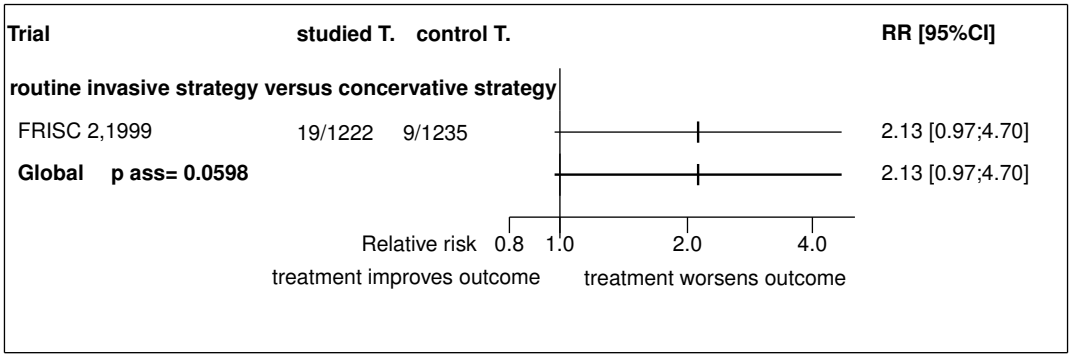


Figure 10.18: *Forest's plot for major bleeding*



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[2] de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, Michels HR, Sanders GT, Tijssen JG, Verheugt FW. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 2005;353:1095-104. [PMID=16162880]

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10.3 Individual trial summaries

Table 10.6: *ICTUS, 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1200 (604 vs. 596) **Follow-up duration:** 12 mo (4y) **Study design:** Randomized controlled trial Parallel groups Open Netherlands, 42 centres **Inclusion period:** 20012003	Patients with nonST-segment elevation acutec oronary syndrome and elevated cardiac troponin T	**Studied treatment:** early invasive strategy early invasive strategy including early routine catheterisation and revascularisation where appropriate **Control treatment:** selective invasive treatment strategy more selective invasive strategy where catheterisation was done if the patient had refractory angina or recurrent ischaemia	In-hospital death RR=0.99 [0.29;3.39] In hospital non fatal MI RR=2.09 [1.41;3.12] In hospital death or MI RR=1.95 [1.34;2.83] Deaths or MI RR=1.51 [1.19;1.91] Rehospitalization RR=0.68 [0.47;0.98] Long term cardiovascular death RR=0.94 [0.61;1.44]

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Hirsch A, Windhausen F, Tijssen JG, Verheugt FW, Cornel JH, de Winter RJ. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. Lancet 2007;369:827-35 [PMID=17350451]
de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, Michels HR, Sanders GT, Tijssen JG, Verheugt FW. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 2005;353:1095-104 [PMID=16162880]

Table 10.7: *FRISC 2, 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2456 (1222 vs. 1234) **Follow-up duration:** 24 mo **Study design:** Randomized controlled trial Factorial plan Open Scandinavia, 58 centres **Inclusion period:** 19961998	Patients with nonST-segment elevation acutecoronary syndrome **Inclusion criteria:** Symptoms of ischemia increasing or occurring at rest with the last episode within 48h. Myocardial ischemia verified by ECG or by raised biochemical markers **Exclusion criteria:** Raised risk of bleeding, anaemia, thrombolysis in the 24h, angioplasty in the past 6 months, etc.	**Studied treatment:** early invasive treatment strategy: angiography within 7 days aiming for revascularisation The direct invasive treatments were coronary angiography within a few days of enrolment, aiming for revascularisation within 7 days of the start of open-label treatment. Revascularisation was recommended in all patients with an obstruction of at least 70% of the diameter of any artery supplying a substantial proportion of the myocardium. Percutaneous coronary intervention was recommended if there were one or two target lesions, and coronary-artery bypass surgery was preferred in patients with t **Control treatment:** non-invasive treatment strategy: angiography only in patients with refractory or recurrent symptoms despite maximum medical treatment or severe ischemia during exercise test before discharge **Concomittant treat.:**7 days of the dalteparin. Followed by 3 months placebo controlled long-term low-molecular heparin (dalteparin). Aspirin , beta-blockers. Abciximab during PTCA and ticlopidine after stent	In-hospital death RR=1.19 [0.54;2.66] In hospital non fatal MI RR=2.22 [1.46;3.37] In hospital death or MI RR=2.07 [1.42;3.03] Deaths or MI RR=0.74 [0.60;0.91] CCS class III-IV angina RR=0.40 [0.26;0.59] Rehospitalization RR=0.65 [0.59;0.71] Long term cardiovascular death RR=0.93 [0.69;1.25]

continued...

trial details	Patients	Treatments	Outcomes

References

. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during In-Stability in Coronary artery disease Investigators. Lancet 1999;354:708-15 [PMID=10475181]
Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet 2006;368:998-1004 [PMID=16980115]
Lagerqvist B, Husted S, Kontny F, Nslund U, Sthle E, Swahn E, Wallentin L. A long-term perspective on the protective effects of an early invasive strategy in unstable coronary artery disease: two-year follow-up of the FRISC-II invasive study. J Am Coll Cardiol 2002;40:1902-14 [PMID=12475448]
Lagerqvist B, Husted S, Kontny F, Sthle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet 2006 Sep 16;368:998-1004 [PMID=16980115]

Table 10.8: *NQWMI (Eisenberg), 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=88 (42 vs. 46) **Follow-up duration:** 12 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Canada, 8 centres **Inclusion period:** oct 1999 - mar 2002	Patients with nonQ-wave myocardial infarction **Inclusion criteria:** chest pain consistent with cardiac ischemia of at least 20min; >=1 mm ST elevation ordepression or T wave inversion in 2 or more contiguous leads and/or creatine kinase (CK) elevation 2 times the upperlimit of normal and/or elevation in CK-MB, troponin T, or troponin I	**Studied treatment:** Invasive (angiography at days 2 to 5) **Control treatment:** Noninvasive (stress testing at day 2 to 5) angiograpgy recommended if angiography at 2 to 5 days or ST-segment depression of at least 2mm on an ECG recorded during peak exercise or ischemic areas in 2 or more vascular regions by echocardiographyor perfusion imaging	In hospital non fatal MI RR=2.19 [0.21;23.29] In hospital death or MI RR=4.38 [0.51;37.65] Deaths or MI RR=0.91 [0.30;2.77]

Reference

Eisenberg MJ, Teng FF, Chaudhry MR, Ortiz J, Sobkowski W, Ebrahim I, Saligrama RS, Serio K, Lader E, Pilote L. Impact of invasive management versus noninvasive management on functional status and quality of life following non-Q-wave myocardial infarction: a randomized clinical trial. Am Heart J 2005;149:813-9 [PMID=15894961]

Table 10.9: *RITA 3, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1810 (895 vs. 915) **Follow-up duration:** 24 mo (60 mo) **Study design:** Randomized controlled trial Parallel groups Open UK, 45 centres **Inclusion period:** 19972001	Patients with nonST-segment elevation acutecoronary syndrome	**Studied treatment:** routine angiography followed byrevascularisationage/pj coronary arteriography within 72 h with subsequent management guided by the angiographic findings **Control treatment:** conservative strategy (ischaemia-driven or symptom-driven angiographyS best medical treatment	In-hospital death RR=2.39 [0.92;6.18] In hospital non fatal MI RR=1.16 [0.58;2.31] In hospital death or MI RR=1.51 [0.87;2.61] Deaths or MI RR=0.82 [0.64;1.06] CCS class III-IV angina RR=0.77 [0.66;0.90] Rehospitalization RR=0.89 [0.80;0.98] Long term cardiovascular death RR=0.71 [0.52;0.97]

References

Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, Wheatley DJ, Pocock SJ. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet 2002 Sep 7;360:743-51 [PMID=12241831]
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Table 10.10: *TACTICS-TIMI 18, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2220 (1114 vs. 1106) **Follow-up duration:** 6 mo **Study design:** Randomized controlled trial Parallel groups Open 9 countries, 169 centres **Inclusion period:** dec 1997 jun 1999	Patients with nonST-segment elevation acute coronary syndrome **Inclusion criteria:** older than18 years of age; episode of angina in the preceding24 hours; **Exclusion criteria:** persistent ST-segment elevation; secondary angina; percutaneous coronary revascularization or coronary bypass surgery within the previous 6 months; a history of gastrointestinal bleeding, platelet disorder, or thrombocytopenia; any history of hemorrhagic cerebrovascular disease or a history of nonhemorrhagic cerebrovascular disease or transient ischemic attack within 1 year; left bundle-branch block or paced rhythm; severe congestive heart failure or cardiogenic shock; clinically important systemic disease; serum creatinine concentration greater than 220 micromol/L; treatment with a glycoprote	**Studied treatment:** early invasive management strategy coronary angiography at 4 to 48 hours **Control treatment:** conservative management strategy medical therapy and predischarge exercise testing	In-hospital death RR=1.99 [0.85;4.62] In hospital non fatal MI RR=0.61 [0.38;0.98] In hospital death or MI RR=0.77 [0.51;1.17] Deaths or MI RR=0.77 [0.58;1.01] CCS class III-IV angina RR=1.09 [0.80;1.48] Rehospitalization RR=0.80 [0.64;1.00]

Reference

Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001 Jun 21;344:1879-87 [PMID=11419424]

Table 10.11: *TRUCS, 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=148 (76 vs. 72) **Follow-up duration:** 12 mo **Study design:** Randomized controlled trial Parallel groups Greece **Inclusion period:** 19971998	Patients with nonST-segment elevation acute coronary syndrome in geographically isolated hospitals without cardiac surgicalfacilities	**Studied treatment:** invasive strategy on-site coronary angioplastyor emergency air-ambulance transfer for bypass graftingsurgery **Control treatment:** conservative strategy persistent medical treatment	In-hospital death RR=0.16 [0.02;1.28] In hospital non fatal MI RR=0.63 [0.11;3.67] In hospital death or MI RR=0.32 [0.09;1.12] Deaths or MI RR=0.47 [0.19;1.20] Rehospitalization RR=0.72 [0.38;1.38]

Reference

Michalis LK, Stroumbis CS, Pappas K, Sourla E, Niokou D, Goudevenos JA, Siogas C, Sideris DA. Treatment of refractory unstable angina in geographically isolated areas without cardiac surgery. Invasive versus conservative strategy (TRUCS study). Eur Heart J 2000;21:1954-9 [PMID=11071801]

Table 10.12: *VINO, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=131 (64 vs. 67) **Follow-up duration:** 6 mo **Study design:** Randomized controlled trial Parallel groups Open Czech Republic, 10 centres **Inclusion period:** may 19982000	Patients with nonST-segment elevation acute coronary syndrome **Inclusion criteria:** Rest ischaemic chest pain, lasting more than 20 min, within the last 24 h; ECG evidence of acute myocardial ischaemia without ST-segment elevations (ST-segment depressions minimally 01 mm in at least two contiguous leads and/or negative T waves or documented old LBBB/RBBB; CK-MB higher than 15? upper limit of normal and/or positive troponin I assay **Exclusion criteria:** Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; Cardiogenic shock; Acute LBBB or RBBB or ST segment elevations <=2 mm in two leads; Q-wave myocardial infarction or intravenous thrombolysis less than 1 month; Coronary angioplasty or bypass surgery less than 6 months; Any concomitant disease which may have possible influence on 1 year prognosis	**Studied treatment:** first day angiography / angioplasty strategy coronary angiogram followed by: 1) immediate coronary angioplasty of the culprit coronary lesion+stent implantation whenever suitable (single vessel disease or multivessel disease with TIMI 02 flow in the infarct-related artery); 2)carefully timed (34 weeks) coronary bypass surgery in patients with left main coronary artery disease or multivessel disease with TIMI-3 flow in all arteries or 3) urgent (within 1 week) coronary bypass surgery in severe (>70%) left main stenosis or in m **Control treatment:** early conservative therapy medical treatment with coronaryangiography and subsequent revascularization only in the presence of recurrent myocardial ischaemia (rest angina and/or ECG demonstrating 2 mm ST-segment depressions or elevations in at least two leads lasting >5 min or persistent at least 1 mm ST-segment depressions during initial hospitalization) or symptom-limited exercise test positivity (chest pain and ST-segment depressions of at least 2 mm recorded during peak exercise or a redistribution defect in at least one main vascular region on thallium scintigraphy).	In-hospital death RR=0.35 [0.04;3.27] In hospital death or MI RR=0.17 [0.02;1.41] Deaths or MI RR=0.28 [0.10;0.80] CCS class III-IV angina RR=0.79 [0.36;1.74] Rehospitalization RR=0.52 [0.21;1.31]

Reference

Spacek R, Widimsky P, Straka Z, Jiresova E, Dvorak J, Polasek R, Karel I, Jirmar R, Lisa L, Budesinsky T, Malek F, Stanka P. Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction: an open multicenter randomized trial. The VINO Study. Eur Heart J 2002 Feb;23:230-8 [PMID=11792138]

11 Detailed results for routine invasive strategy - noncomptemporary

11.1 Available trials

A total of 3 RCTs which randomized 2594 patients were identified: all compared routine invasive strategy - noncomptemporary with concervative strategy.
The average study size was 864 patients (range 201 to 1473). The first study was published in 1994, and the last study was published in 1998.
All trials were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
CCS class III-IV angina data was reported in 3 trials; 3 trials reported data on non fatal MI; 3 trials reported data on in hospital death or MI; 3 trials reported data on in-hospital death; 3 trials reported data on rehospitalization; 3 trials reported data on deaths or MI; 3 trials reported data on all cause death; 3 trials reported data on in hospital non fatal MI; 1 trials reported data on positive 6-wk ETT; and 1 trials reported data on no angina (at 6 weeks).
Following tables 11.1 (page 97), 11.2 (page 98), 11.4 (page 100), and 11.3 (page 99) summarized the main characteristics of the trials including in this systematic review of randomized trials of routine invasive strategy - noncomptemporary.

Table 11.1: *Treatment description - early invasive strategy - routine invasive strategy - noncomptemporary*

Trial	Studied treatment	Control treatment
Routine invasive strategy - noncomptemporary versus concervative strategy		
MATE (1998) [1]	early triage angiography and subsequenttherapies based on the angiogram	conventional medicaltherapy conventional medicaltherapy consisting of aspirin, intravenous heparin, nitroglycerin,beta-blockers, and analgesics.
TIMI 3B (PTCA) (1994) [2]	Early invasive strategy: systematic angiography (18-48h after randomisation) and revascularisation (PTCA or CABG)	Early elective strategy: angiography and revascularisation only in case of ischemic recurrence (see paper)
	Concomittant treatment: thrombolysis with t-PA (factorial plan) see TIMI III B, anti ischemic therapy	

continued...

Trial	Studied treatment	Control treatment
VANQWISH (1998) [3]	invasive management Patients assigned to the early invasive strategy underwent coronary angiography as the initial diagnostic test soon after randomization. Thereafter, the management guidelines of the Thrombolysis in Myocardial Infarction trial (TIMI IIIB) for revascularization were followed. In patients with clinically significant single-vessel coronary artery disease, balloon angioplasty or, rarely, directionalatherectomy was considered, whereas bypass surgery was recommended for patients with multivessel disease. In contrast to the TIMI IIIB guidelines, however, our protocol did not require early myocardial revascularization; investigators at each study site were allowed to decide whether to perform only revascularization of aculprit stenosis, perform complete revascularization, or continue medical therapy.	conservative management: medical therapy with subsequent invasive management if indicated by the development of spontaneous or indicible ischemia within 24-72 hours Patients assigned to the early conservative strategy underwent radionuclide ventriculography to assess left ventricular function as the initial noninvasive test; this was followed before discharge by a symptom-limited treadmill exercise test (according to the standard Bruce protocol) with planar thallium scintigraphy or thallium scintigraphy with single-photon-emission computed tomography. Patients who were unable to exercise to a level of at least 5 metabolic equivalents (MET) received intravenous dipyridamole (0.56 mg per kilogram of body weight) and then underwent perfusion scintigraphy.
	Concomittant treatment: aspirin 325 mg/g, long-acting diltiazem	

Table 11.2: *Descriptions of participants - early invasive strategy - routine invasive strategy - noncomptemporary*

Trial	Patients	
Routine invasive strategy - noncomptemporary versus concervative strategy		
MATE (1998) [1]	Acute MI ineligible for thrombolytictherapy within 24 h of symptoms	
	Inclusion criteria: 18years and older; acute chest pain syndrome consistent with AMI (high-clinical suspicion for AMI with or without immediate enzymaticconfirmation); ineligible forthrombolysis because of a lack of diagnostic ECG changes,symptoms lasting longer than 6 h or because of increasedbleeding or stroke risks	**Exclusion criteria:**
TIMI 3B (PTCA) (1994) [2]	Patient with unstable angina or non Q wave MI within 24hrs of onset	
	Inclusion criteria: unstable angina or non-Q-wave myocardial infarction chest discomfort at rest judged caused by ischemia, lasted >5min <6hrs, within 24h of enrolment, accompanied by ECG evidence of ischemia or documented artery disease	**Exclusion criteria:** recent MI (21d), recent arteriography (30d), PTCA within 6mo, CABG at any time, contraindication to thrombolysis or heparin, severe hypertension, severe illness
VANQWISH (1998) [3]	Patients with NonQ-wave myocardial infarction	
	Inclusion criteria: evolving acute MI, level of CK-MB >x1.5, no new abnormal Q-waves	**Exclusion criteria:** serious coexisting condition, persistent or recurrent ischemia at rest despite intensive medical therapy

Table 11.3: *Design and methodological quality of trials - early invasive strategy - routine invasive strategy - noncomptemporary*

Trial	Design	Duration	Centre	Primary endpoint
Routine invasive strategy - noncomptemporary versus concervative strategy				
MATE, 1998 [1] n=201	Parallel groups open	21 mo	US 4 centres	recurrent ischemic events or death
TIMI 3B (PTCA), 1994 [2] n=1473	Factorial plan Open	12 mo	USA & Canada	
VANQWISH, 1998 [3] n=920	Parallel groups Open	23 mo inclusion period: april 1993 - december 1996	US 15 centres	death or nonfatal myocardial infarction

Table 11.4: *Trial characteristics - early invasive strategy - routine invasive strategy - noncomptemporary*

Trial	Fibrinolysis	non Q wave MI	Time to cardiac catheteriza-tion routine invasive group, h	ST-segment depression	T-wave inversion	Thrombolytic therapy
Routine invasive strategy - noncomptemporary versus concervative strategy						
MATE, 1998 [1]	0%		16 h (median)	47 (23%)	66 (43%)	0%
TIMI 3B (PTCA), 1994 [2]	50%	32%	36 h (median)	486 (33%)	678 (46%)	722 (49%)
VANQWISH, 1998 [3]	12.5%	100%	48 h (median)	356 (41%)	448 (49%)	115 (13%)

11.2 Meta-analysis results

The results are detailed in table 11.5 (page 102). This table is followed by the Forest's plot corresponding to each endpoint.

Routine invasive strategy - noncomptemporary versus concervative strategy

All the 3 studies had extractable data about the number of participants with **in-hospital death**. There was no statistically significant difference in in-hospital death between routine invasive strategy - noncomptemporary and concervative strategy, with a RR of 1.39 (95%CI 0.46 to 4.20, p=0.5628) in favour of routine invasive strategy - noncomptemporary. In other words, in-hospital death was slightly lower in the concervative strategy group , but this was not statistically significant. A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0458, I^2 = 0.68%).
All the 3 studies had extractable data about the number of participants with **in hospital non fatal MI**. When pooled together, there was no statistically significant difference between the groups in in hospital non fatal MI, with a RR of 1.24 (95% CI 0.85 to 1.81, p=0.2615). No heterogeneity was detected (p = 0.6260, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **in hospital death or MI**. When pooled together, there was no statistically significant difference between the groups in in hospital death or MI, with a RR of 1.45 (95% CI 0.79 to 2.66, p=0.2353). No heterogeneity was detected (p = 0.0898, I^2 = 0.59%).
All the 3 studies had extractable data about the number of participants with **deaths or MI**. When pooled together, there was no statistically significant difference between the groups in deaths or MI, with a RR of 1.00 (95% CI 0.83 to 1.19, p=0.9713). No heterogeneity was detected (p = 0.2963, I^2 = 0.18%).
All the 3 studies had extractable data about the number of participants with **CCS class III-IV angina**. When pooled together, there was no statistically significant difference between the groups in CCS class III-IV angina, with a RR of 0.93 (95% CI 0.70 to 1.22, p=0.5877). No heterogeneity was detected (p = 0.2130, I^2 = 0.35%).
All the 3 studies had extractable data about the number of participants with **rehospitalization**. When pooled together, there was no statistically significant difference between the groups in rehospitalization, with a RR of 0.90 (95% CI 0.80 to 1.01, p=0.0748). No heterogeneity was detected (p = 0.2256, I^2 = 0.33%).
Only one of the 3 studies eligible for this comparison provided data on **positive 6-wk ETT**. No statistically significant difference between the groups was found in positive 6-wk ETT, with a RR of 0.87 (95% CI 0.63 to 1.20, p=0.3871).
Only one of the 3 studies eligible for this comparison provided data on **no angina (at 6 weeks)**. No statistically significant difference between the groups was found in no angina (at 6 weeks), with a RR of 1.05 (95% CI 0.98 to 1.12, p=0.1699).
All the 3 studies had extractable data about the number of participants with **non fatal MI**. When pooled together, there was no statistically significant difference between the groups in non fatal MI, with a RR of 0.87 (95% CI 0.70 to 1.08, p=0.2118). No heterogeneity was detected (p = 0.7254, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 1.18 (95% CI 0.93 to 1.51, p=0.1728). No heterogeneity was detected (p = 0.4188, I^2 = 0.00%).

Table 11.5: *Results details - early invasive strategy - routine invasive strategy - noncomptemporary*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
routine invasive strategy - noncomptemporary versus concervative strategy						
in-hospital death	RR=1.39	[0.46;4.20]	0.5628	0.0458 (I^2=0.68)	3	2594
in hospital non fatal MI	RR=1.24	[0.85;1.81]	0.2615	0.6260 (I^2=0.00)	3	2594
in hospital death or MI	RR=1.45	[0.79;2.66]	0.2353	0.0898 (I^2=0.59)	3	2594
deaths or MI	RR=1.00	[0.83;1.19]	0.9713	0.2963 (I^2=0.18)	3	2594
CCS class III-IV angina	RR=0.93	[0.70;1.22]	0.5877	0.2130 (I^2=0.35)	3	2594
rehospitalization	RR=0.90	[0.80;1.01]	0.0748	0.2256 (I^2=0.33)	3	2594
positive 6-wk ETT	RR=0.87	[0.63;1.20]	0.3871	1.0000 (I^2=0.00)	1	1473
no angina (at 6 weeks)	RR=1.05	[0.98;1.12]	0.1699	1.0000 (I^2=0.00)	1	1473
non fatal MI	RR=0.87	[0.70;1.08]	0.2118	0.7254 (I^2=0.00)	3	2594
all cause death	RR=1.18	[0.93;1.51]	0.1728	0.4188 (I^2=0.00)	3	2594

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 in-hospital death*

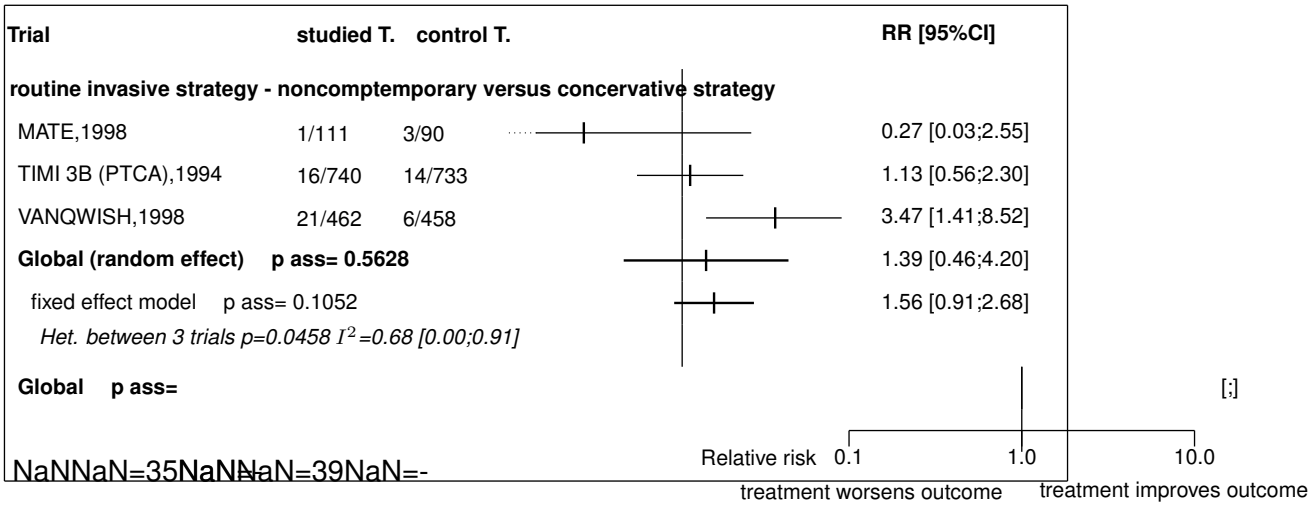


Figure 11.2: *Forest's plot for in hospital non fatal MI*

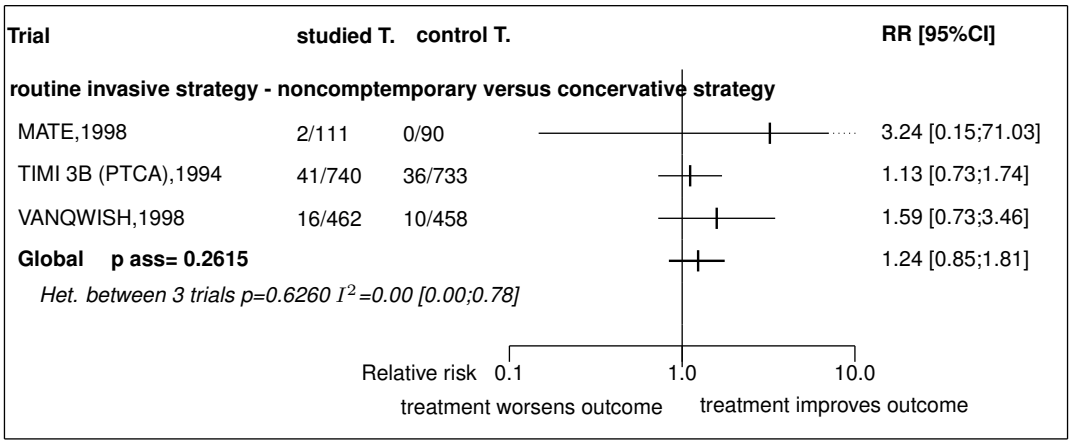


Figure 11.3: *Forest's plot for in hospital death or MI*

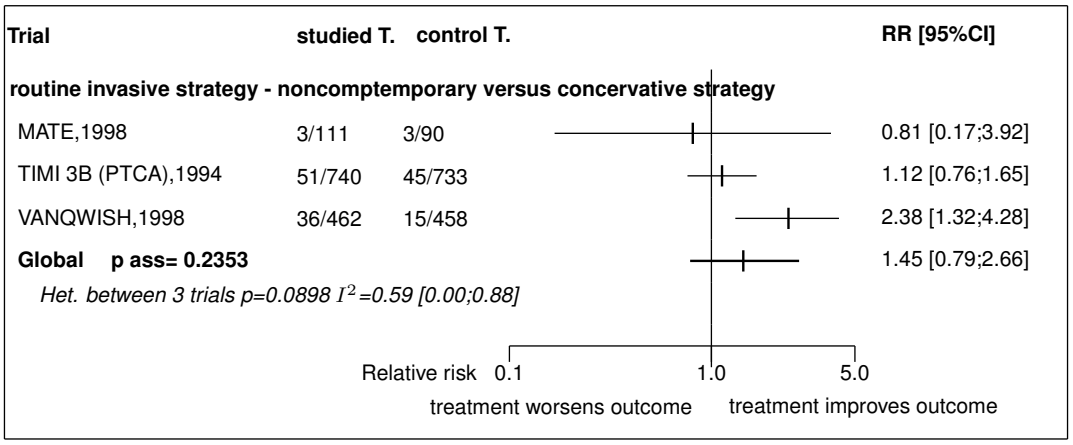


Figure 11.4: *Forest's plot for deaths or MI*

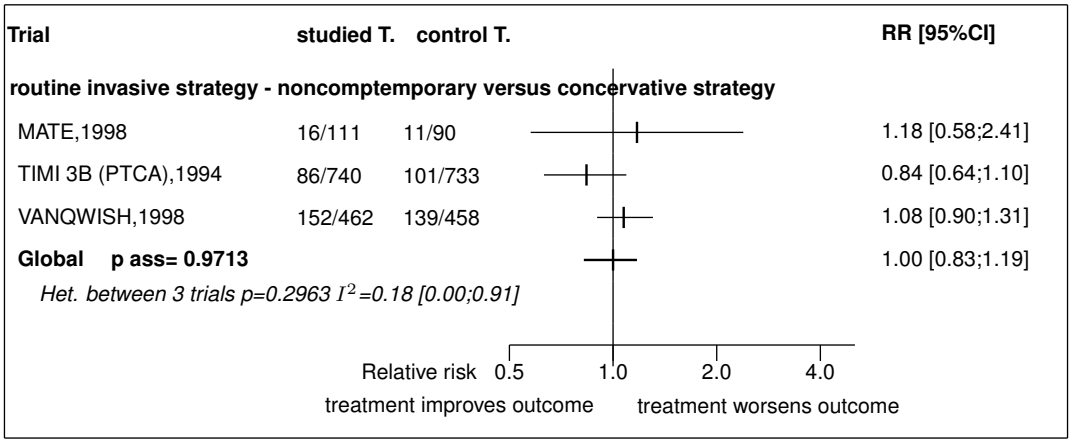


Figure 11.5: *Forest's plot for CCS class III-IV angina*

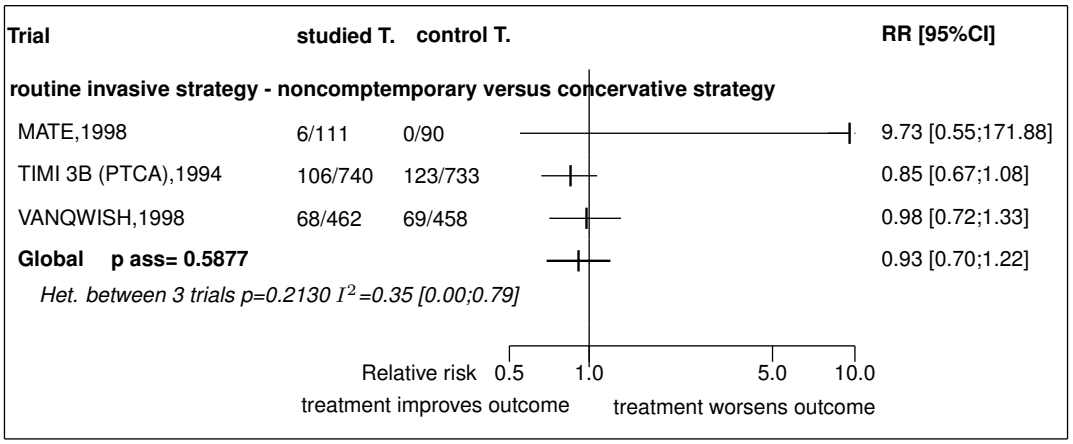


Figure 11.6: *Forest's plot for rehospitalization*

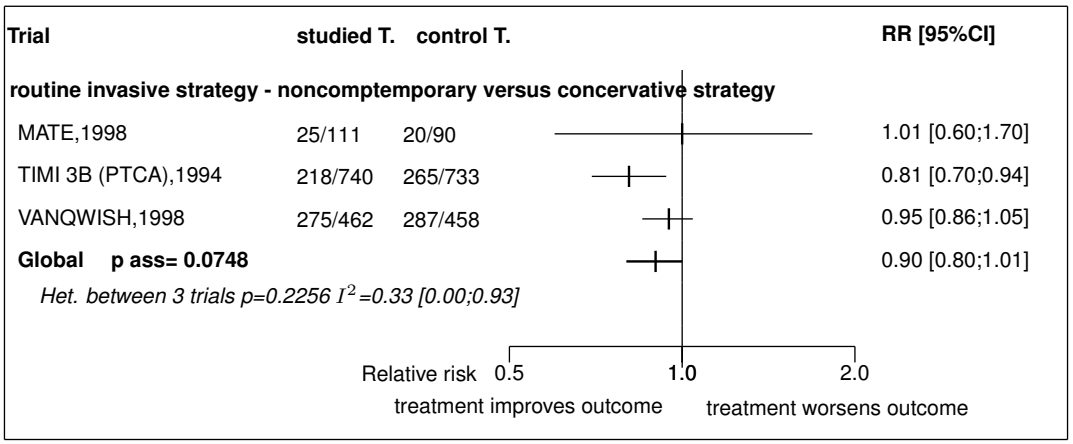


Figure 11.7: *Forest's plot for positive 6-wk ETT*

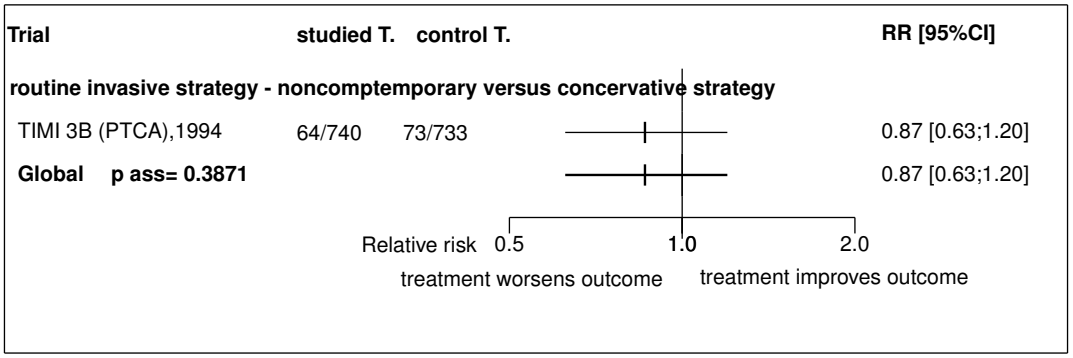


Figure 11.8: *Forest's plot for no angina (at 6 weeks)*

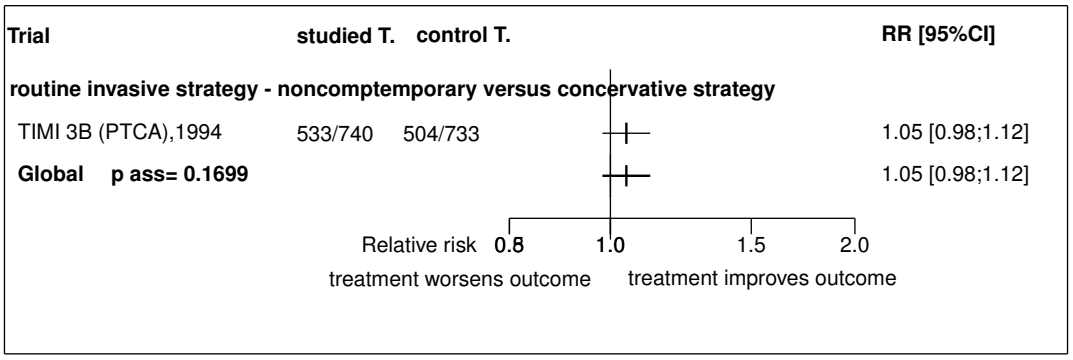


Figure 11.9: *Forest's plot for in-hospital death*

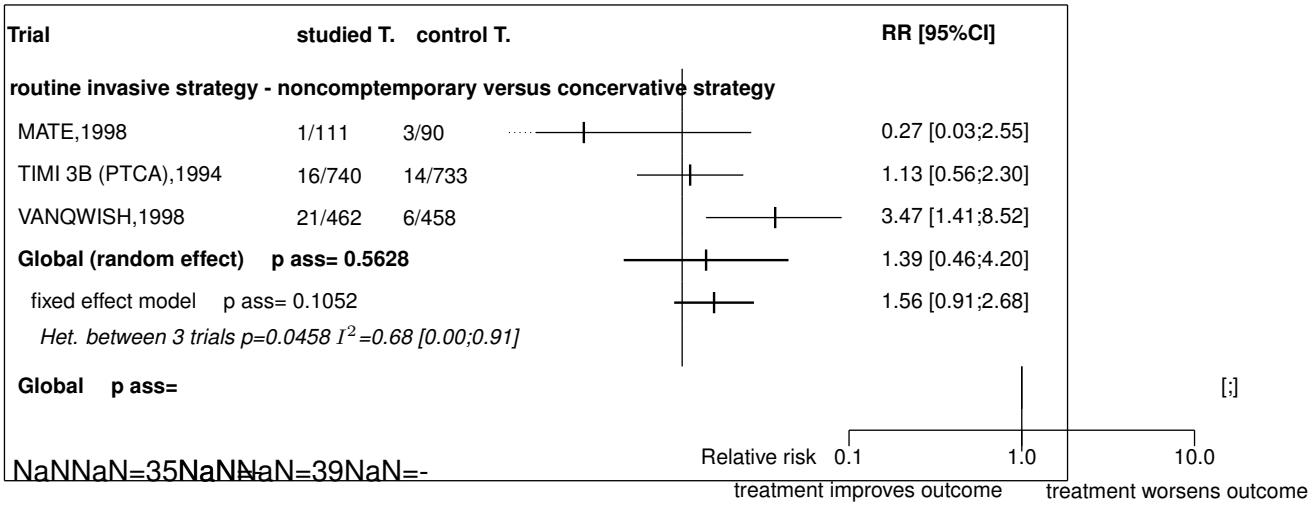


Figure 11.10: *Forest's plot for non fatal MI*

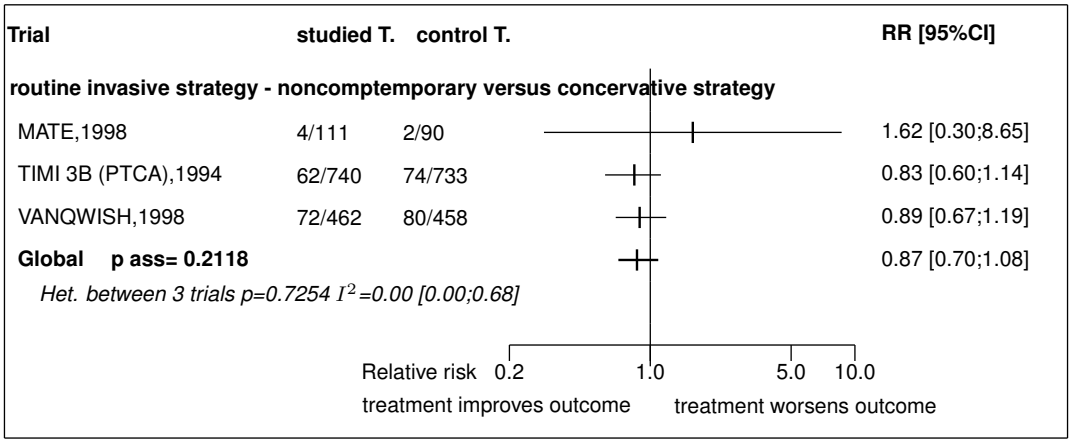
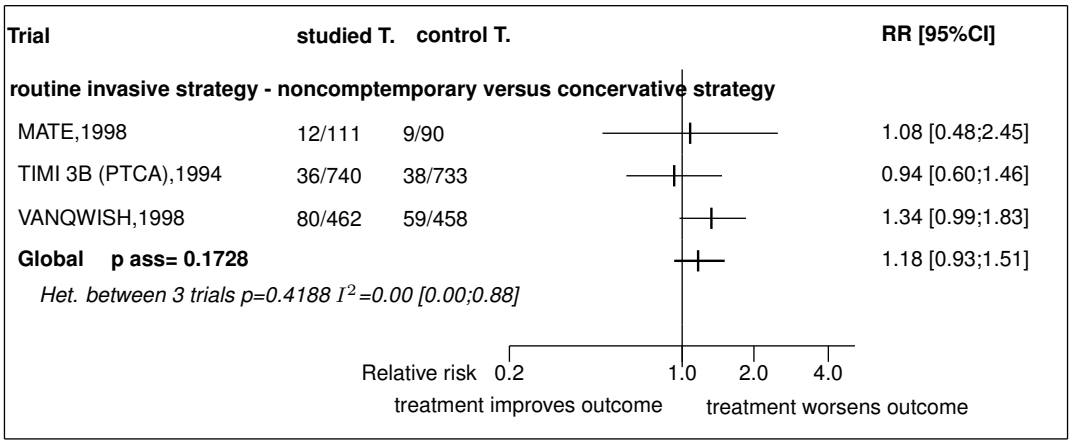


Figure 11.11: *Forest's plot for all cause death*



References

[1] McCullough PA, O'Neill WW, Graham M, Stomel RJ, Rogers F, David S, Farhat A, Kazlauskaite R, Al-Zagoum M, Grines CL. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. J Am Coll Cardiol 1998 Sep;32:596-605. [PMID=9741499]

[2] . Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994;89:1545-56. [PMID=8149520]

[3] Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, Wexler LF, Kleiger RE, Pepine CJ, Ferry DR, Chow BK, Lavori PW. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med 1998;338:1785-92. [PMID=9632444]

11.3 Individual trial summaries

Table 11.6: *MATE, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=201 (111 vs. 90) **Follow-up duration:** 21 mo **Study design:** Randomized controlled trial Parallel groups Open US, 4 centres	Acute MI ineligible for thrombolytictherapy within 24 h of symptoms **Inclusion criteria:** 18years and older; acute chest pain syndrome consistent with AMI (highclinical suspicion for AMI with or without immediate enzymaticconfirmation); ineligible forthrombolysis because of a lack of diagnostic ECG changes,symptoms lasting longer than 6 h or because of increasedbleeding or stroke risks	**Studied treatment:** early triage angiography and subsequenttherapies based on the angiogram **Control treatment:** conventional medicaltherapy conventional medicaltherapy consisting of aspirin, intravenous heparin, nitroglycerin,beta-blockers, and analgesics.	In-hospital death RR=0.27 [0.03;2.55] In hospital death or MI RR=0.81 [0.17;3.92] Deaths or MI RR=1.18 [0.58;2.41] Rehospitalization RR=1.01 [0.60;1.70]

Reference

McCullough PA, O'Neill WW, Graham M, Stomel RJ, Rogers F, David S, Farhat A, Kazlauskaite R, Al-Zagoum M, Grines CL. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. J Am Coll Cardiol 1998 Sep;32:596-605 [PMID=9741499]

Table 11.7: *TIMI 3B (PTCA), 1994 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1473 (740 vs. 733) **Follow-up duration:** 12 mo **Study design:** Randomized controlled trial Factorial plan Open USA & Canada	Patient with unstable angina or non Q wave MI within 24hrs of onset **Inclusion criteria:** unstable angina or non-Q-wave myocardial infarction chest discomfort at rest judged caused by ischemia, lasted >5min <6hrs, within 24h of enrolment, accompanied by ECG evidence of ischemia or documented artery disease **Exclusion criteria:** recent MI (21d), recent arteriography (30d), PTCA within 6mo, CABG at any time, contraindication to thrombolysis or heparin, severe hypertension, severe illness	**Studied treatment:** Early invasive strategy: systematic angiography (18-48h after randomisation) and revascularisation (PTCA or CABG) **Control treatment:** Early elective strategy: angiography and revascularisation only in case of ischemic recurrence (see paper) **Concomittant treat.:**thrombolysis with t-PA (factorial plan) see TIMI III B, anti ischemic therapy	In-hospital death RR=1.13 [0.56;2.30] In hospital non fatal MI RR=1.13 [0.73;1.74] In hospital death or MI RR=1.12 [0.76;1.65] Deaths or MI RR=0.84 [0.64;1.10] CCS class III-IV angina RR=0.85 [0.67;1.08] Rehospitalization RR=0.81 [0.70;0.94]

Reference

. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994;89:1545-56 [PMID=8149520]

Table 11.8: *VANQWISH, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=920 (462 vs. 458) **Follow-up duration:** 23 mo **Study design:** Randomized controlled trial Parallel groups Open US, 15 centres **Inclusion period:** april 1993 - december 1996	Patients with NonQ-wave myocardial infarction **Inclusion criteria:** evolving acute MI, level of CK-MB >x1.5, no new abnormal Q-waves **Exclusion criteria:** serious coexisting condition, persistent or recurrent ischemia at rest despite intensive medical therapy	**Studied treatment:** invasive management Patients assigned to the early invasive strategy underwent coronary angiography as the initial diagnostic test soon after randomization. Thereafter, the management guidelines of the Thrombolysis in Myocardial Infarction trial (TIMI IIIB) for revascularization were followed. In patients with clinically significant single-vessel coronary artery disease, balloon angioplasty or, rarely, directionalatherectomy was considered, whereas bypass surgery was recommended for patients with multivessel diseas **Control treatment:** conservative management: medical therapy with subsequent invasive management if indicated by the development of spontaneous or indicible ischemia within 24-72 hours Patients assigned to the early conservative strategy underwent radionuclide ventriculography to assess left ventricular function as the initial noninvasive test; this was followed before discharge by a symptom-limited treadmill exercise test (according to the standard Bruce protocol) with planar thallium scintigraphy or thallium scintigraphy with single-photon-emission computed tomography. Patients who were unable to exercise to a level of at least 5 metabolic equivalents (MET) received intravenous dipyridamole (0.56 mg per kilogram of body weight) and then underwent perfusion scintigraphy. **Concomittant treat.:**aspirin 325 mg/g, long-acting diltiazem	In-hospital death RR=3.47 [1.41;8.52] In hospital non fatal MI RR=1.59 [0.73;3.46] In hospital death or MI RR=2.38 [1.32;4.28] Deaths or MI RR=1.08 [0.90;1.31] CCS class III-IV angina RR=0.98 [0.72;1.33] Rehospitalization RR=0.95 [0.86;1.05]

continued...

trial details	Patients	Treatments	Outcomes

Reference

Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, Wexler LF, Kleiger RE, Pepine CJ, Ferry DR, Chow BK, Lavori PW. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med 1998;338:1785-92 [PMID=9632444]

12 Global meta-analysis: all early invasive strategy

12.1 Global meta-analysis: all early invasive strategy versus concervative strategy

Table 12.1: *All early invasive strategyversus concervative strategy*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
in-hospital death	RR=1.36	0.84;2.18	0.2102	0.0967 (0.39)	10	10648
in hospital non fatal MI	RR=1.30 [1]	0.88;1.93	0.1905	0.0030 (0.64) †	10	10648
in hospital death or MI	RR=1.31 [2]	0.91;1.88	0.1533	0.0004 (0.70) †	10	10648
deaths or MI	RR=0.88 [3]	0.72;1.09	0.2484	0.0001 (0.73) †	10	10648
CCS class III-IV angina	RR=0.80 [4]	0.63;1.03	0.0785	0.0020 (0.71) †	7	9030
rehospitalization	RR=0.80 [5]	0.70;0.92	0.0017	0.0000 (0.80) †	9	10495
long term cardiovascular death	RR=0.84	0.69;1.01	0.0701	0.3999 (0.00)	3	5467
long term all cause death, MI	RR=0.88	0.75;1.03	0.1206	0.1344 (0.50)	3	5467
long term cardiovascular events	RR=0.83	0.73;0.93	0.0024	0.3913 (0.00)	3	5467
positive 6-wk ETT	RR=0.87	0.63;1.20	0.3871	1.0000 (0.00)	1	1473
no angina (at 6 weeks)	RR=1.30 [6]	0.85;1.99	0.2243	0.0000 (0.99) †	2	3930
long term MI	RR=0.77	0.67;0.90	0.0000	0.5919 (0.00)	3	5467
myocardial infarction (fatal and non fatal)	RR=0.37	0.04;3.38	0.3746	1.0000 (1.00)	1	88
long term death	RR=1.16 [7]	0.89;1.52	0.2672	0.0320 (0.71) †	3	5467
non fatal MI	RR=0.86 [8]	0.68;1.07	0.1682	0.0146 (0.56) †	10	10648
all cause death	RR=0.90	0.72;1.12	0.3365	0.0964 (0.39)	10	10647

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

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.39 95% CI 1.14;1.69
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.42 95% CI 1.20;1.69
[3] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.93 95% CI 0.85;1.03
[4] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.81 95% CI 0.72;0.90
[5] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.80 95% CI 0.76;0.84
[6] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.31 95% CI 1.26;1.38
[7] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.20 95% CI 1.04;1.38
[8] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.87 95% CI 0.77;0.98

12.2 Global meta-analysis: all early invasive strategy versus delayed invasive strategy

Table 12.2: *All early invasive strategyversus delayed invasive strategy*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
in-hospital death	RR=0.86	0.58;1.28	0.4551	1.0000 (1.00)	1	3031
death or stroke or myocardial infarction	RR=0.85	0.68;1.06	0.1513	1.0000 (0.00)	1	3031
death, MI, stroke, refractory ischemia	RR=0.72	0.58;0.89	0.0026	1.0000 (0.00)	1	3031
repeat intervention	RR=1.03	0.81;1.32	0.8141	0.5803 (0.00)	2	3173
myocardial infarction (fatal and non fatal)	RR=1.30 [9]	0.75;2.25	0.3485	0.0091 (0.79) †	3	3525
stroke (fatal and non fatal)	RR=0.90	0.49;1.66	0.7350	1.0000 (0.00)	1	3031
all cause death	RR=1.07	0.41;2.78	0.8917	0.1775 (0.45)	2	3383

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

13 Ongoing studies of early invasive strategy

Only one ongoing study was identified. A brief description of this trial is given table 13.1

Table 13.1: *Ongoing studies for early invasive strategy*

Study	Description
the Italian Elderly ACS study [**?**] NCT00510185	early aggressive approach **vs.** initially conservative approach patients older than 74 years of age with NSTEACS

14 Excluded studies for early invasive strategy

No trial was excluded.

[9] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.15 95% CI 0.92;1.44

References

Part III

Fibrinolytic

15 Overview of fibrinolytic

15.1 Included trials

A total of 12 randomized comparisons which enrolled 2758 patients were identified. In all, 1 randomized comparison concerned anistreplase , one intracoronary urokinase and 10 t-PA.
The detailed descriptions of trials and meta-analysis results is given in section 16 (page 124) for anistreplase, in section 17 (page 131) for intracoronary urokinase and in section 18 (page 136) for t-PA.

The average study size was 229 patients (range 24 to 1473). The first study was published in 1987, and the last study was published in 1995.
A total of 10 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 15.1 (page 118) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

15.2 Summary of meta-analysis results

The meta-analysis of the available trials about fibrinolytic provide the results listed in tables 15.2 to 15.4 (page 120) and in the following graphs.

15.2.1 Anistreplase

No significant difference was found between **anistreplase** and **placebo** in terms of in-hospital death (RR=2.96, 95% CI 0.31 to 27.88, p=0.3423, 1 trial)and myocardial infarction (fatal and non fatal) (RR=1.36, 95% CI 0.85 to 2.18, p=0.1936, 1 trial). Anistreplase appear to be associated with significantly greater risk of bleeding (RR=2.96, 95% CI 1.34 to 6.57, p=0.0076, 1 trial).

15.2.2 Intracoronary urokinase

No significant difference was found between **intracoronary urokinase** and **placebo** in terms of myocardial infarction (fatal and non fatal) (RR=1.23, 95% CI 0.38 to 3.96, p=0.7336, 1 trial).

15.2.3 T-PA

No significant difference was found between **t-PA** and **placebo** in terms of in-hospital death (RR=1.56, 95% CI 0.39 to 6.27, p=0.5321, 5 trials), myocardial infarction (fatal and non fatal) (RR=1.12, 95% CI 0.49 to 2.60, p=0.7852, 5 trials)and all cause death (RR=1.00, 95% CI 0.07 to 15.36, p=1.0000, 1 trial). T-PA appear to be associated with significantly greater risk of bleeding (RR=2.60, 95% CI 1.19 to 5.71, p=0.0171, 2 trials).

Table 15.1: *Main study characteristics - fibrinolytic*

Trial	Patients	Treatments	Trial design and method
Anistreplase			
Anistreplase versus placebo			
UNASEM, 1992 [1] n = 80 vs. 79	patients without a previous myocardial infarction, with a typical history of unstable angina and ECG abnormalities indicative of ischemia	anistreplase IV 30 UI over 5 minutes **versus** placebo	double blind parallel groups Primary endpoint: CA 9 centres, Europe
Intracoronary urokinase			
Intracoronary urokinase versus placebo			
TAUSA, 1994 [1] n = 232 vs. 237	ischemic rest pain with or without a recent (<1 month) infarction	intracoronary urokinase 250000 UI or 500000 UI **versus** placebo	double blind parallel groups Primary endpoint: none defined USA
T-PA			
T-PA versus placebo			
Topol, 1988 [1] n = 20 vs. 20	patients with angina at rest and provocable ischemia (pacing induced)	intravenous tissue plasminogen activator (t-PA) **versus** placebo	open parallel groups USA
TIMI 3A, 1993 [2] n = 150 vs. 156	patients with unstable angina or non-Q wave myocardial infarction	90-minute front-loaded infusion of t-PA (0.8 mg/kg i.v.; maximum, 80 mg) **versus** placebo	double blind parallel groups Primary endpoint: culprit lesion caliber 17 centres, USA, canada
Nicklas, 1989 [3] n = 20 vs. 20	patients with rest angina, angiographically documented coronary artery disease and pacing-induced ischemia	rt-PA, 150 mg/8 h **versus** placebo	double blind parallel groups Primary endpoint: ischemic pacing threshold USA

continued...

Trial	Patients	Treatments	Trial design and method
Gold, 1987 [4] n = 12 vs. 12	chest pain at rest with transient ST segment deviation of at least 1 mm	intravenous recombinant human tissue-type plasminogen activator (rt-PA). **versus** placebo	parallel groups
Williams, 1990 [5] n = 45 vs. 22	rest angina and angiographic evidence of coronary stenosis	tissue-type plasminogen activator (rt-PA) (0.75 mg/kg over 1 hour or (0.75 mg/kg over 1 hour; total dose, 100 mg over 6 hours) **versus** placebo	double blind parallel groups Primary endpoint: change in luminal diameter 4 centres, USA
Freeman, 1992 [6] n = 35 vs. 35	patients with unstable angina	tissue-type plasminogen activator (t-PA) (0.49 MU/kg for 1 hour followed by 0.07 MU/kg per hour for 9 hours) **versus** placebo	double blind parallel groups Primary endpoint: in-hospital death, myocardial infarction, and urgent revascularization 2 centres, USA
van der Brand, 1991 [7] n = 19 vs. 17	patients with angina at rest, despite bedrest and medical treatment	alteplase 100 mg in 3 h **versus** placebo	double blind parallel groups The Netherlands
charbonnier, 1992 [8] n = 25 vs. 25	unstable angina pectoris	rt-PA 100 mg/90 minutes (10 mg bolus + 90 mg/90 minutes **versus** placebo	double blind parallel groups
Ardissino, 1990 [9] n = 12 vs. 12	unstable angina refractory to conventional medical treatment	recombinant tissue-type plasminogen activator (rt-PA) followed by heparin **versus** heparin alone	double blind parallel groups Italy
TIMI 3B, 1995 [10] n = 729 vs. 744	patients with unstable angina and non-Q wave myocardial infarction	tissue-type plasminogen activator (t-PA) **versus** placebo	double blind factorial plan Primary endpoint: death or MI

Table 15.2: *Summary of all results for anistreplase*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
anistreplase versus placebo						
in-hospital death	RR=2.96	0.31;27.88	0.3423	1.0000 (1.00)	1	159
myocardial infarction (fatal and non fatal)	RR=1.36	0.85;2.18	0.1936	1.0000 (0.00)	1	159
bleeding	RR=2.96	1.34;6.57	0.0076	1.0000 (0.00)	1	159

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

Table 15.3: *Summary of all results for intracoronary urokinase*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
intracoronary urokinase versus placebo						
myocardial infarction (fatal and non fatal)	RR=1.23	0.38;3.96	0.7336	1.0000 (0.00)	1	469

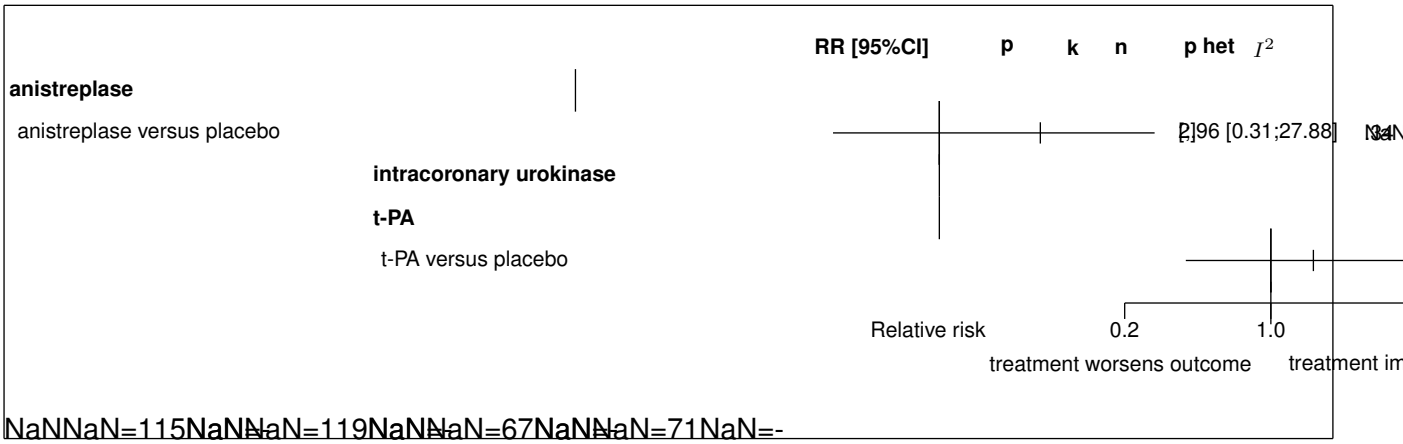
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 15.4: *Summary of all results for t-PA*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
t-PA versus placebo						
in-hospital death	RR=1.56	0.39;6.27	0.5321	0.7534 (0.00)	5	217
myocardial infarction (fatal and non fatal)	RR=1.12	0.49;2.60	0.7852	0.9383 (0.00)	5	237
all cause death	RR=1.00	0.07;15.36	1.0000	1.0000 (0.00)	1	70
bleeding	RR=2.60	1.19;5.71	0.0171	0.3736 (0.00)	2	103

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

Figure 15.1: *Forest's plot for in-hospital death*



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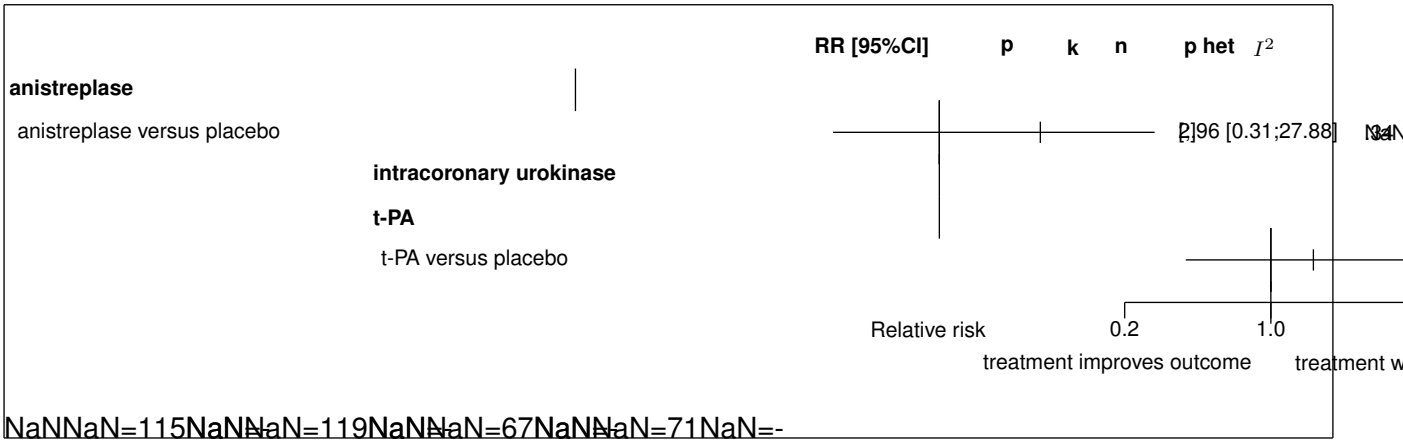
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

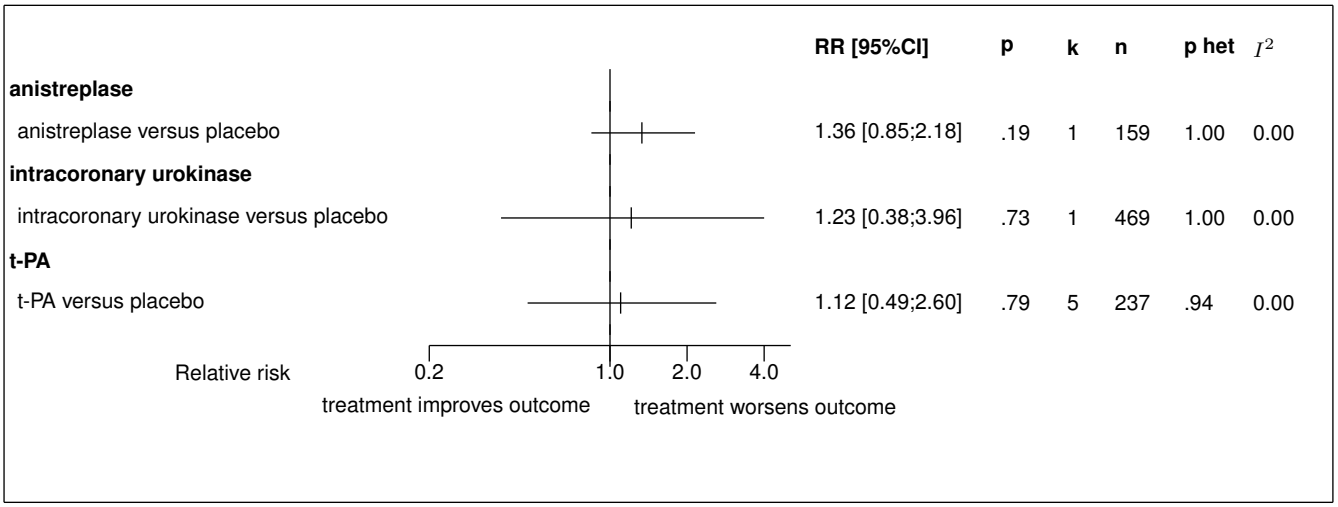
Figure 15.2: *Forest's plot for in-hospital death*



NaNNaN=115NaNNaN=119NaNNaN=67NaNNaN=71NaN=-

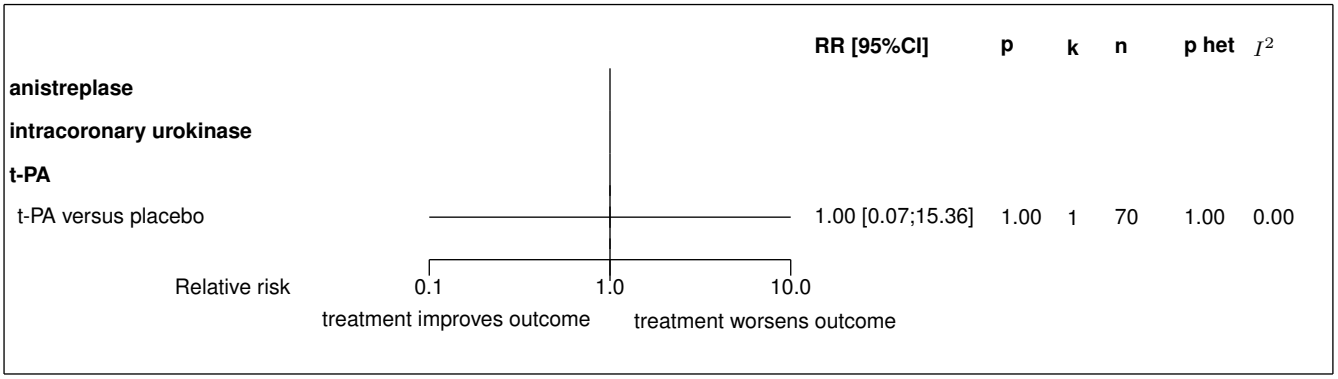
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 15.3: *Forest's plot for myocardial infarction (fatal and non fatal)*



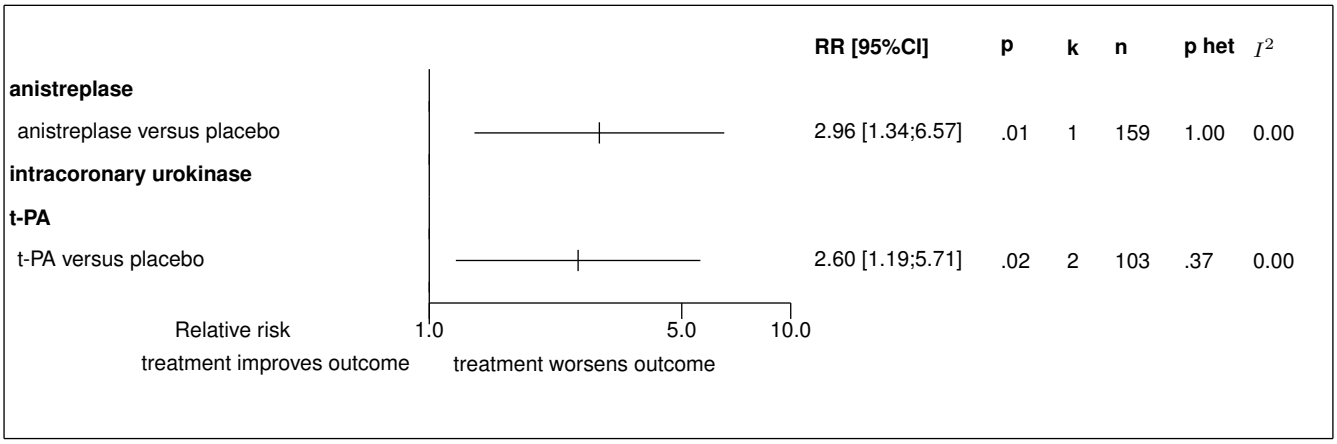
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 15.4: *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 15.5: *Forest's plot for bleeding*



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

16 Detailed results for anistreplase

16.1 Available trials

Only one trial which randomized 159 patients was identified: it compared anistreplase with placebo.
This trial included 159 patients and was published in 1992.
This trial was double blind in design.
It was reported in English language.
Myocardial infarction (fatal and non fatal) data was reported in 1 trials; 1 trials reported data on in-hospital death; and 1 trials reported data on bleeding.
Following tables 16.1 (page 124), 16.2 (page 124), 16.4 (page 125), and 16.3 (page 124) summarized the main characteristics of the trial including in this systematic review of randomized trials of anistreplase.

Table 16.1: *Treatment description - fibrinolytic - anistreplase*

Trial	Studied treatment	Control treatment
Anistreplase versus placebo		
UNASEM (1992) [1]	anistreplase IV 30 UI over 5 minutes	placebo

Table 16.2: *Descriptions of participants - fibrinolytic - anistreplase*

Trial	Patients
Anistreplase versus placebo	
UNASEM (1992) [1]	Patients without a previous myocardial infarction, with a typical history of unstable angina and ECG abnormalities indicative of ischemia

Table 16.3: *Design and methodological quality of trials - fibrinolytic - anistreplase*

Trial	Design	Duration	Centre	Primary end-point
Anistreplase versus placebo				
UNASEM, 1992 [1] n=159	Parallel groups double blind exploratory trial	hospital stay, 1y	Europe 9 centres	CA

Table 16.4: *Trial characteristics - fibrinolytic - anistreplase*

Trial
Anistreplase versus placebo
UNASEM, 1992 [1]

16.2 Meta-analysis results

The results are detailed in table 16.5 (page 126). This table is followed by the Forest's plot corresponding to each endpoint.

Anistreplase versus placebo

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 2.96 (95% CI 0.31 to 27.88, p=0.3423).
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 1.36 (95% CI 0.85 to 2.18, p=0.1936).

Table 16.5: *Results details - fibrinolytic - anistreplase*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
anistreplase versus placebo						
in-hospital death	RR=2.96	[0.31;27.88]	0.3423	1.0000 (I^2=1.00)	1	159
myocardial infarction (fatal and non fatal)	RR=1.36	[0.85;2.18]	0.1936	1.0000 (I^2=0.00)	1	159
bleeding	RR=2.96	[1.34;6.57]	0.0076	1.0000 (I^2=0.00)	1	159

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

Figure 16.1: *Forest's plot for in-hospital death*

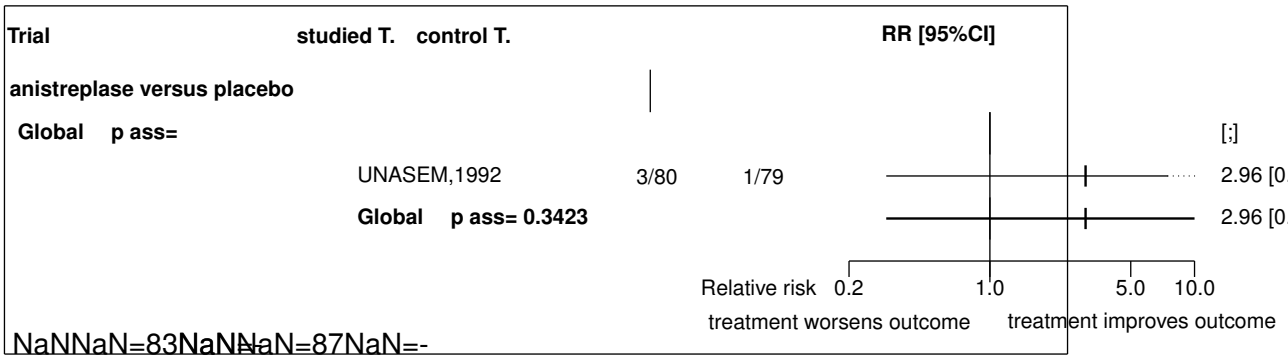


Figure 16.2: *Forest's plot for in-hospital death*

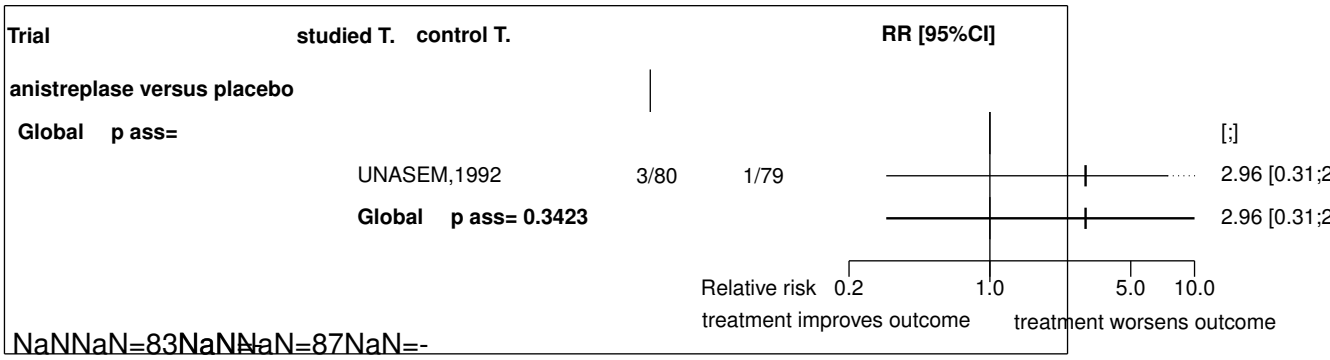


Figure 16.3: *Forest's plot for myocardial infarction (fatal and non fatal)*

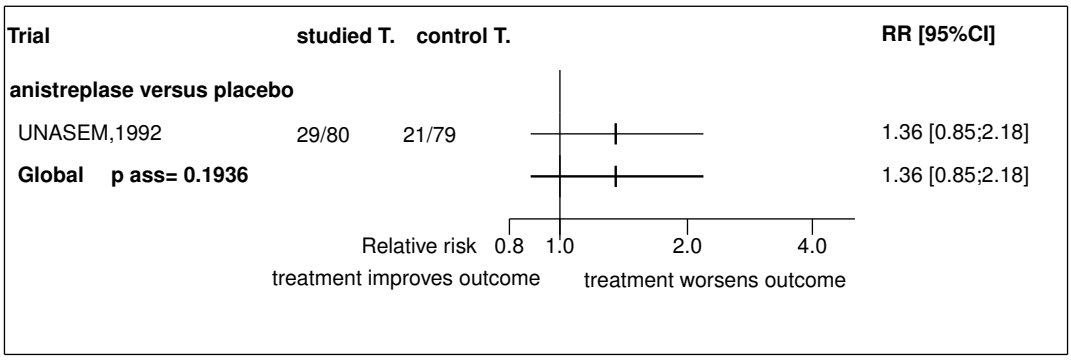
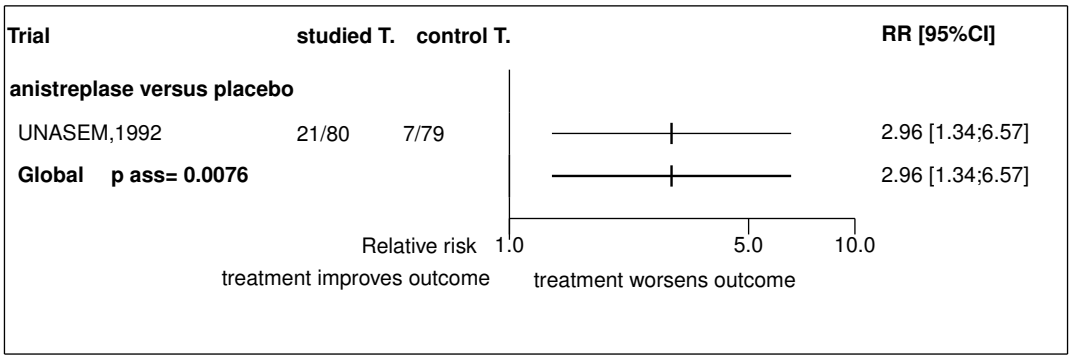


Figure 16.4: *Forest's plot for bleeding*



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[1] Br FW, Verheugt FW, Col J, Materne P, Monassier JP, Geslin PG, Metzger J, Raynaud P, Foucault J, de Zwaan C. Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome. Results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase. Circulation 1992;86:131-7. [PMID=1617766]

16.3 Individual trial summaries

Table 16.6: *UNASEM, 1992 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=159 (80 vs. 79) **Follow-up duration:** hospital stay, 1y **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Europe, 9 centres	Patients without a previous myocardial infarction, with a typical history of unstable angina and ECG abnormalities indicative of ischemia	**Studied treatment:** anistreplase IV 30 UI over 5 minutes **Control treatment:** placebo	

Reference

Br FW, Verheugt FW, Col J, Materne P, Monassier JP, Geslin PG, Metzger J, Raynaud P, Foucault J, de Zwaan C. Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome. Results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase. Circulation 1992;86:131-7 [PMID=1617766]

17 Detailed results for intracoronary urokinase

17.1 Available trials

Only one trial which randomized 469 patients was identified: it compared intracoronary urokinase with placebo.
This trial included 469 patients and was published in 1994.
This trial was double blind in design.
It was reported in English language.
Myocardial infarction (fatal and non fatal) data was reported in 1 trials;
Following tables 17.1 (page 131), 17.2 (page 131), 17.4 (page 132), and 17.3 (page 131) summarized the main characteristics of the trial including in this systematic review of randomized trials of intracoronary urokinase.

Table 17.1: *Treatment description - fibrinolytic - intracoronary urokinase*

Trial	Studied treatment	Control treatment
Intracoronary urokinase versus placebo		
TAUSA (1994) [1]	intracoronary urokinase 250000 UI or 500000 UI	placebo

Table 17.2: *Descriptions of participants - fibrinolytic - intracoronary urokinase*

Trial	Patients
Intracoronary urokinase versus placebo	
TAUSA (1994) [1]	Ischemic rest pain with or without a recent ($<$1 month) infarction

Table 17.3: *Design and methodological quality of trials - fibrinolytic - intracoronary urokinase*

Trial	Design	Duration	Centre	Primary endpoint
Intracoronary urokinase versus placebo				
TAUSA, 1994 [1] n=469	Parallel groups double blind exploratory trial	hospital stay inclusion period: Jul 1990 - Sept 1992	USA	none defined

Table 17.4: *Trial characteristics - fibrinolytic - intracoronary urokinase*

Trial
Intracoronary urokinase versus placebo
TAUSA, 1994 [1]

17.2 Meta-analysis results

The results are detailed in table 17.5 (page 133). This table is followed by the Forest's plot corresponding to each endpoint.

Intracoronary urokinase versus placebo

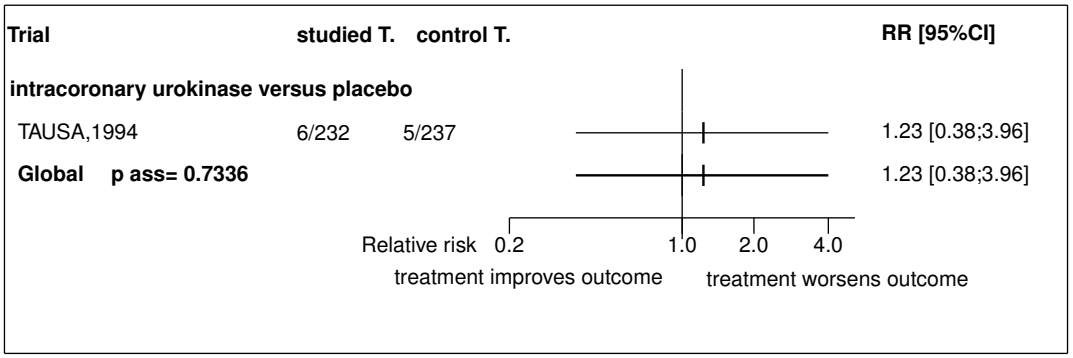
The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 1.23 (95% CI 0.38 to 3.96, p=0.7336).

Table 17.5: *Results details - fibrinolytic - intracoronary urokinase*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
intracoronary urokinase versus placebo						
myocardial infarction (fatal and non fatal)	RR=1.23	[0.38;3.96]	0.7336	1.0000 (I^2=0.00)	1	469

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)*



References

[1] Ambrose JA, Almeida OD, Sharma SK, Torre SR, Marmur JD, Israel DH, Ratner DE, Weiss MB, Hjemdahl-Monsen CE, Myler RK. Adjunctive thrombolytic therapy during angioplasty for ischemic rest angina. Results of the TAUSA Trial. TAUSA Investigators. Thrombolysis and Angioplasty in Unstable Angina trial. Circulation 1994;90:69-77. [PMID=8026054]

17.3 Individual trial summaries

Table 17.6: *TAUSA, 1994 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=469 (232 vs. 237) **Follow-up duration:** hospital stay **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial USA **Inclusion period:** Jul 1990 - Sept 1992	Ischemic rest pain with or without a recent (<1 month) infarction	**Studied treatment:** intracoronary urokinase 250000 UI or 500000 UI **Control treatment:** placebo	

Reference

Ambrose JA, Almeida OD, Sharma SK, Torre SR, Marmur JD, Israel DH, Ratner DE, Weiss MB, Hjemdahl-Monsen CE, Myler RK. Adjunctive thrombolytic therapy during angioplasty for ischemic rest angina. Results of the TAUSA Trial. TAUSA Investigators. Thrombolysis and Angioplasty in Unstable Angina trial. Circulation 1994;90:69-77 [PMID=8026054]

18 Detailed results for t-PA

18.1 Available trials

A total of 10 RCTs which randomized 2130 patients were identified: all compared t-PA with placebo.
The average study size was 213 patients (range 24 to 1473). The first study was published in 1987, and the last study was published in 1995.
A total of 8 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 5 trials; 5 trials reported data on in-hospital death; 1 trials reported data on all cause death; and 2 trials reported data on bleeding.
Following tables 18.1 (page 136), 18.2 (page 137), 18.4 (page 139), and 18.3 (page 138) summarized the main characteristics of the trials including in this systematic review of randomized trials of t-PA.

Table 18.1: *Treatment description - fibrinolytic - t-PA*

Trial	Studied treatment	Control treatment
T-PA versus placebo		
Topol (1988) [1]	intravenous tissue plasminogen activator (t-PA) **Concomittant treatment:** diltiazem, nitrates, beta blockers, aspirin and intravenous heparin.	placebo
TIMI 3A (1993) [2]	90-minute front-loaded infusion of t-PA (0.8 mg/kg i.v.; maximum, 80 mg)	placebo
Nicklas (1989) [3]	rt-PA, 150 mg/8 h intravenous recombinant tissue-type plasminogen activator (rt-PA, 150 mg/8 h) **Concomittant treatment:** nitrates, a beta-adrenergic blocking agent, a calcium channel blocker, aspirin and heparin	placebo placebo
Gold (1987) [4]	intravenous recombinant human tissue-type plasminogen activator (rt-PA).	placebo
Williams (1990) [5] [e]	tissue-type plasminogen activator (rt-PA) (0.75 mg/kg over 1 hour or (0.75 mg/kg over 1 hour; total dose, 100 mg over 6 hours)	placebo
Freeman (1992) [6]	tissue-type plasminogen activator (t-PA) (0.49 MU/kg for 1 hour followed by 0.07 MU/kg per hour for 9 hours)	placebo
van der Brand (1991) [7]	alteplase 100 mg in 3 h	placebo
charbonnier (1992) [8]	rt-PA 100 mg/90 minutes (10 mg bolus + 90 mg/90 minutes	placebo

continued...

Trial	Studied treatment	Control treatment
Ardissino (1990) [9]	recombinant tissue-type plasminogen activator (rt-PA) followed by heparin	heparin alone
TIMI 3B (1995) [10] [j]	tissue-type plasminogen activator (t-PA)	placebo

e) 3 arms study comparing low-dose and high dose of rt-PA to placebo j) factorial design: early invasive management strategy with coronary arteriography at 18 to 48 h, followed by revascularization as soon as possible if appropriate, compared to an early conservative strategy with arteriography and revascularization reserved for failure of initial therapy to prevent recurrent ischemia

Table 18.2: *Descriptions of participants - fibrinolytic - t-PA*

Trial	Patients
T-PA versus placebo	
Topol (1988) [1]	Patients with angina at rest and provocable ischemia (pacing induced)
TIMI 3A (1993) [2]	Patients with unstable angina or non-Q wave myocardial infarction
Nicklas (1989) [3]	Patients with rest angina, angiographically documented coronary artery disease and pacing-induced ischemia
Gold (1987) [4]	Chest pain at rest with transient ST segment deviation of at least 1 mm
Williams (1990) [5]	Rest angina and angiographic evidence of coronary stenosis
Freeman (1992) [6]	Patients with unstable angina
van der Brand (1991) [7]	Patients with angina at rest, despite bedrest and medical treatment
charbonnier (1992) [8]	Unstable angina pectoris
Ardissino (1990) [9]	Unstable angina refractory to conventional medical treatment
TIMI 3B (1995) [10]	Patients with unstable angina and non-Q wave myocardial infarction **Inclusion criteria:** men and women; 21 to 79 years; chest discomfort at rest suggestive of myocardial ischemia, lasting >=5 min but <=6 h, that occurred within 24 h of the time of enrollment; either transient ST segment elevation or transient or persistent ST segment depression or T wave inversion on the qualifying electrocardiograms. No ECG changes were required if a patient had a documented history of coronary artery disease. **Exclusion criteria:**

Table 18.3: *Design and methodological quality of trials - fibrinolytic - t-PA*

Trial	Design	Duration	Centre	Primary endpoint
T-PA versus placebo				
Topol, 1988 [1] n=40	Parallel groups open exploratory trial	hospital stay inclusion period: mar 1986 - apr 1987	USA	
TIMI 3A, 1993 [2] n=306	Parallel groups double blind exploratory trial	hospital stay	USA, canada 17 centres	culprit lesion caliber
Nicklas, 1989 [3] n=40	Parallel groups Double blind exploratory trial	inclusion period: mar 1986 - apr 1987	USA	ischemic pacing threshold
Gold, 1987 [4] n=24	Parallel groups exploratory trial			
Williams, 1990 [5] n=67	Parallel groups double blind exploratory trial		USA 4 centres	change in luminal diameter
Freeman, 1992 [6] n=70	Parallel groups double blind confirmatory trial at low risk of bias	in hospital inclusion period: Jun 1988 - Mar 1990	USA 2 centres	in-hospital death, myocardial infarction, and urgent revascularization
van der Brand, 1991 [7] n=36	Parallel groups double blind exploratory trial	hospital stay inclusion period: nov 1987 - apr 1989	The Netherlands	
charbonnier, 1992 [8] n=50	Parallel groups double blind exploratory trial			
Ardissino, 1990 [9] n=24	Parallel groups double blind exploratory trial	in hospital	Italy	
TIMI 3B, 1995 [10] n=1473	Factorial plan Double blind confirmatory trial at low risk of bias	1 year		death or MI

Table 18.4: *Trial characteristics - fibrinolytic - t-PA*

Trial
T-PA versus placebo
Topol, 1988 [1]
TIMI 3A, 1993 [2]
Nicklas, 1989 [3]
Gold, 1987 [4]
Williams, 1990 [5]
Freeman, 1992 [6]
van der Brand, 1991 [7]
charbonnier, 1992 [8]
Ardissino, 1990 [9]
TIMI 3B, 1995 [10]

18.2 Meta-analysis results

The results are detailed in table 18.5 (page 140). This table is followed by the Forest's plot corresponding to each endpoint.

T-PA versus placebo

A total of 5 of the 10 studies eligible for this comparison provided data on **in-hospital death**. When pooled together, there was no statistically significant difference between the groups in in-hospital death, with a RR of 1.56 (95% CI 0.39 to 6.27, p=0.5321). No heterogeneity was detected (p = 0.7534, I^2 = 0.00%).
A total of 5 of the 10 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 1.12 (95% CI 0.49 to 2.60, p=0.7852). No heterogeneity was detected (p = 0.9383, I^2 = 0.00%).
Only one of the 10 studies eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.00 (95% CI 0.07 to 15.36, p=1.0000).

Table 18.5: *Results details - fibrinolytic - t-PA*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
t-PA versus placebo						
in-hospital death	RR=1.56	[0.39;6.27]	0.5321	0.7534 (I^2=0.00)	5	217
myocardial infarction (fatal and non fatal)	RR=1.12	[0.49;2.60]	0.7852	0.9383 (I^2=0.00)	5	237
all cause death	RR=1.00	[0.07;15.36]	1.0000	1.0000 (I^2=0.00)	1	70
bleeding	RR=2.60	[1.19;5.71]	0.0171	0.3736 (I^2=0.00)	2	103

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 in-hospital death*

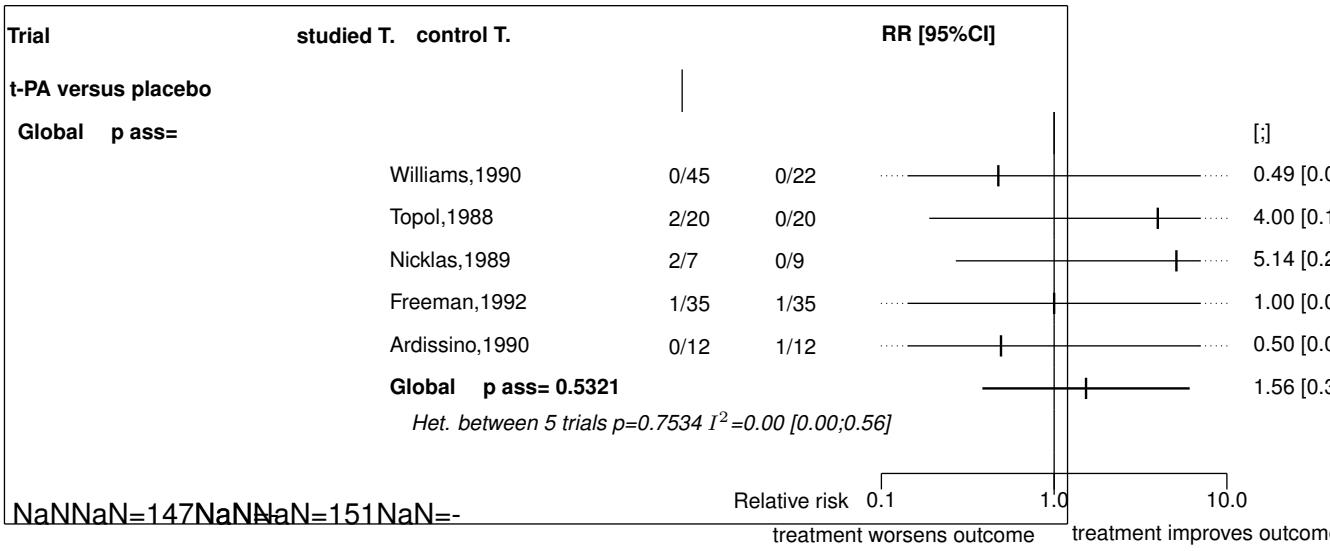


Figure 18.2: *Forest's plot for in-hospital death*

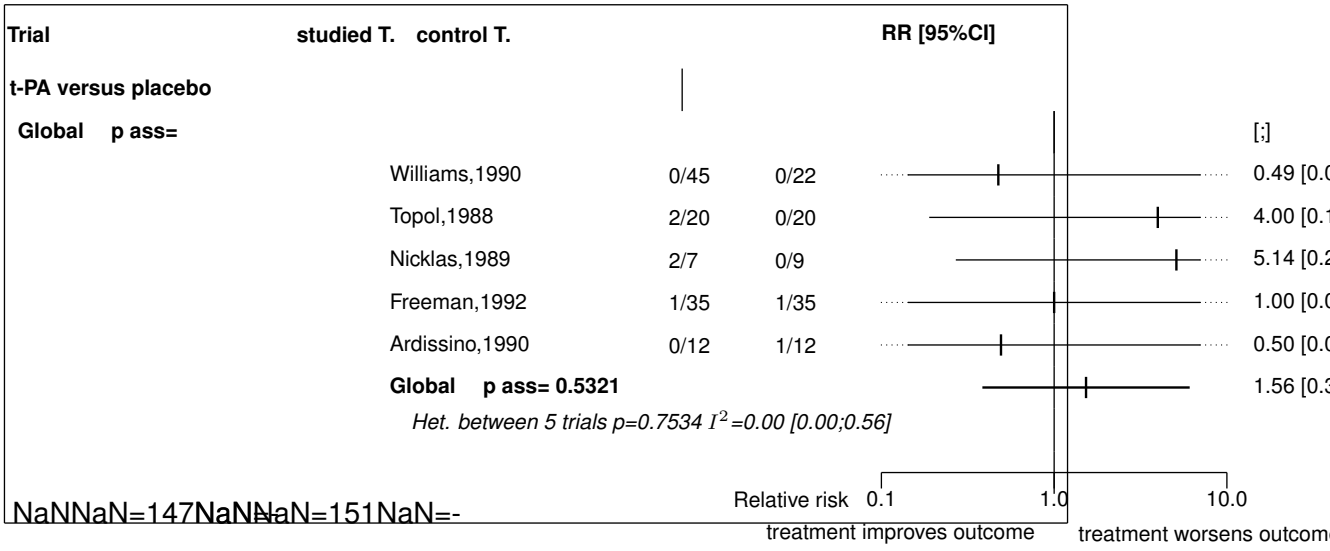


Figure 18.3: *Forest's plot for myocardial infarction (fatal and non fatal)*

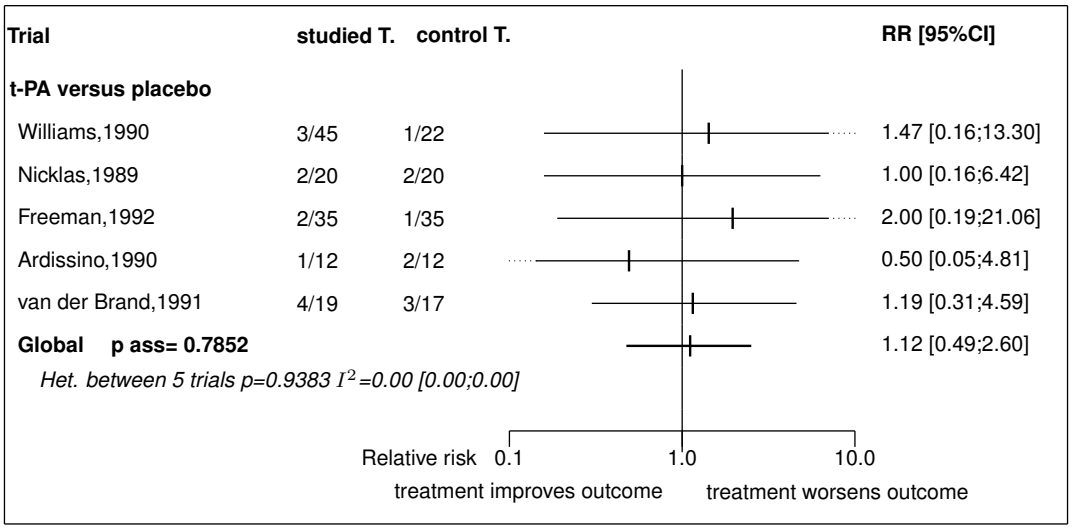


Figure 18.4: *Forest's plot for all cause death*

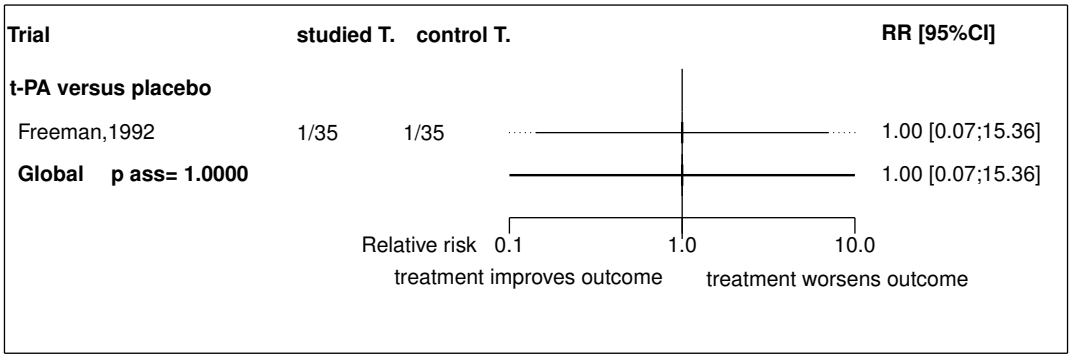
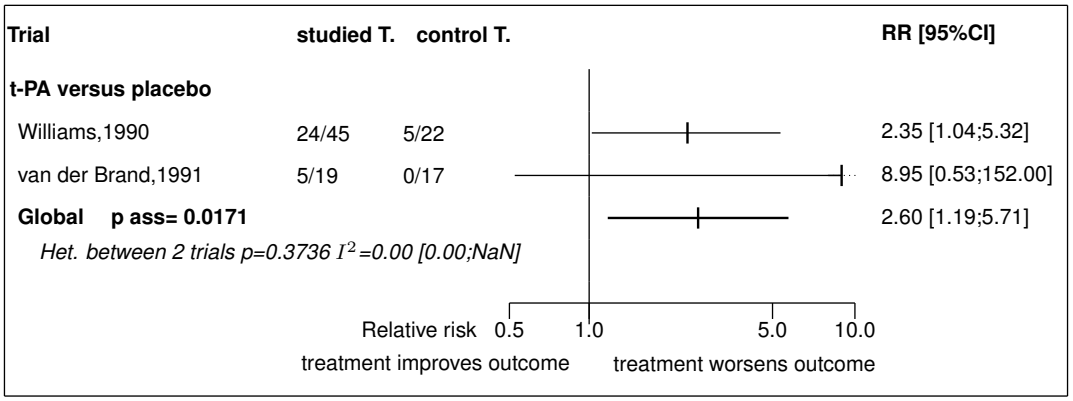


Figure 18.5: *Forest's plot for bleeding*



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[9] Ardissino D, Barberis P, De Servi S, Mussini A, Rolla A, Visani L, Specchia G. Recombinant tissue-type plasminogen activator followed by heparin compared with heparin alone for refractory unstable angina pectoris. Am J Cardiol 1990;66:910-4. [PMID=2121016]

[10] Anderson HV, Cannon CP, Stone PH, Williams DO, McCabe CH, Knatterud GL, Thompson B, Willerson JT, Braunwald E. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. J Am Coll Cardiol 1995;26:1643-50. [PMID=7594098]

18.3 Individual trial summaries

Table 18.6: *Topol, 1988 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=40 (20 vs. 20) **Follow-up duration:** hospital stay **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial USA **Inclusion period:** mar 1986 - apr 1987	Patients with angina at rest and provocable ischemia (pacing induced)	**Studied treatment:** intravenous tissue plasminogen activator (t-PA) **Control treatment:** placebo **Concomittant treat.:**diltiazem, nitrates, beta blockers, aspirin and intravenous heparin.	

Reference

Topol EJ, Nicklas JM, Kander NH, Walton JA, Ellis SG, Gorman L, Pitt B. Coronary revascularization after intravenous tissue plasminogen activator for unstable angina pectoris: results of a randomized, double-blind, placebo-controlled trial. Am J Cardiol 1988;62:368-71 [PMID=2970776]

Table 18.7: *TIMI 3A, 1993 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=306 (150 vs. 156) **Follow-up duration:** hospital stay **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial USA, canada, 17 centres	Patients with unstable angina or non-Q wave myocardial infarction	**Studied treatment:** 90-minute front-loaded infusion of t-PA (0.8 mg/kg i.v.; maximum, 80 mg) **Control treatment:** placebo	

Reference

. Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest. Results of the Thrombolysis in Myocardial Ischemia (TIMI IIIA) Trial. Circulation 1993 Jan;87:38-52 [PMID=8419023]

Table 18.8: *Nicklas, 1989 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=40 (20 vs. 20) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial USA **Inclusion period:** mar 1986 - apr 1987	Patients with rest angina, angiographically documented coronary artery disease and pacing-induced ischemia	**Studied treatment:** rt-PA, 150 mg/8 h intravenous recombinant tissue-type plasminogen activator (rt-PA, 150 mg/8 h) **Control treatment:** placebo placebo **Concomittant treat.:**nitrates, a beta-adrenergic blocking agent, a calcium channel blocker, aspirin and heparin	

Reference

Nicklas JM, Topol EJ, Kander N, O'Neill WW, Walton JA, Ellis SG, Gorman L, Pitt B. Randomized, double-blind, placebo-controlled trial of tissue plasminogen activator in unstable angina. J Am Coll Cardiol 1989;13:434-41 [PMID=2492325]

Table 18.9: *Gold, 1987 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=24 (12 vs. 12) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Exploratory trial	Chest pain at rest with transient ST segment deviation of at least 1 mm	**Studied treatment:** intravenous recombinant human tissue-type plasminogen activator (rt-PA). **Control treatment:** placebo	

Reference

Gold HK, Johns JA, Leinbach RC, Yasuda T, Grossbard E, Zusman R, Collen D. A randomized, blinded, placebo-controlled trial of recombinant human tissue-type plasminogen activator in patients with unstable angina pectoris. Circulation 1987 Jun;75:1192-9 [PMID=3105913]

Table 18.10: *Williams, 1990 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=67 (45 vs. 22) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial USA, 4 centres	Rest angina and angiographic evidence of coronary stenosis	**Studied treatment:** tissue-type plasminogen activator (rt-PA) (0.75 mg/kg over 1 hour or (0.75 mg/kg over 1 hour; total dose, 100 mg over 6 hours) **Control treatment:** placebo **note:** 3 arms study comparing low-dose and high dose of rt-PA to placebo	

Reference

Williams DO, Topol EJ, Califf RM, Roberts R, Mancini GB, Joelson JM, Ellis SG, Kleiman NS. Intravenous recombinant tissue-type plasminogen activator in patients with unstable angina pectoris. Results of a placebo-controlled, randomized trial. Circulation 1990 Aug;82:376-83 [PMID=2115407]

Table 18.11: *Freeman, 1992 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=70 (35 vs. 35) **Follow-up duration:** in hospital **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias USA, 2 centres **Inclusion period:** Jun 1988 - Mar 1990	Patients with unstable angina	**Studied treatment:** tissue-type plasminogen activator (t-PA) (0.49 MU/kg for 1 hour followed by 0.07 MU/kg per hour for 9 hours) **Control treatment:** placebo	

Reference

Freeman MR, Langer A, Wilson RF, Morgan CD, Armstrong PW. Thrombolysis in unstable angina. Randomized double-blind trial of t-PA and placebo. Circulation 1992;85:150-7 [PMID=1728444]

Table 18.12: *van der Brand, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=36 (19 vs. 17) **Follow-up duration:** hospital stay **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial The Netherlands **Inclusion period:** nov 1987 - apr 1989	Patients with angina at rest, despite bedrest and medical treatment	**Studied treatment:** alteplase 100 mg in 3 h **Control treatment:** placebo	

Reference

van den Brand M, van Zijl A, Geuskens R, de Feyter PJ, Serruys PW, Simoons ML. Tissue plasminogen activator in refractory unstable angina. A randomized double-blind placebo-controlled trial in patients with refractory unstable angina and subsequent angioplasty. Eur Heart J 1991;12:1208-14 [PMID=1782951]

Table 18.13: *charbonnier, 1992 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=50 (25 vs. 25) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Unstable angina pectoris	**Studied treatment:** rt-PA 100 mg/90 minutes (10 mg bolus + 90 mg/90 minutes **Control treatment:** placebo	

Reference

Charbonnier B, Bernadet P, Schiele F, Thery C, Baudouy M, Bauters C. [Intravenous thrombolysis by recombinant plasminogen activator (rt-PA) in unstable angina. A randomized multicenter study versus placebo]. Arch Mal Coeur Vaiss 1992;85:1471-7 [PMID=1297297]

Table 18.14: *Ardissino, 1990 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=24 (12 vs. 12) **Follow-up duration:** in hospital **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Italy	Unstable angina refractory to conventional medical treatment	**Studied treatment:** recombinant tissue-type plasminogen activator (rt-PA) followed by heparin **Control treatment:** heparin alone	

Reference

Ardissino D, Barberis P, De Servi S, Mussini A, Rolla A, Visani L, Specchia G. Recombinant tissue-type plasminogen activator followed by heparin compared with heparin alone for refractory unstable angina pectoris. Am J Cardiol 1990;66:910-4 [PMID=2121016]

Table 18.15: *TIMI 3B, 1995 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1473 (729 vs. 744) **Follow-up duration:** 1 year **Study design:** Randomized controlled trial Factorial plan Double blind Confirmatory trial at low risk of bias	Patients with unstable angina and non-Q wave myocardial infarction **Inclusion criteria:** men and women; 21 to 79 years; chest discomfort at rest suggestive of myocardial ischemia, lasting >=5 min but <=6 h, that occurred within 24 h of the time of enrollment; either transient ST segment elevation or transient or persistent ST segment depression or T wave inversion on the qualifying electrocardiograms. No ECG changes were required if a patient had a documented history of coronary artery disease.	**Studied treatment:** tissue-type plasminogen activator (t-PA) **Control treatment:** placebo **note:** factorial design: early invasive management strategy with coronary arteriography at 18 to 48 h, followed by revascularization as soon as possible if appropriate, compared to an early conservative strategy with arteriography and revascularization reserved for failure of initial therapy to prevent recurrent ischemia	

Reference

Anderson HV, Cannon CP, Stone PH, Williams DO, McCabe CH, Knatterud GL, Thompson B, Willerson JT, Braunwald E. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. J Am Coll Cardiol 1995;26:1643-50 [PMID=7594098]

19 Global meta-analysis: all fibrinolytic

19.1 Global meta-analysis: all fibrinolytic versus placebo

Table 19.1: *All fibrinolyticversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
in-hospital death	RR=1.86	0.57;6.08	0.3022	0.8306 (0.00)	6	376
myocardial infarction (fatal and non fatal)	RR=1.29	0.88;1.90	0.1904	0.9869 (0.00)	7	865
all cause death	RR=1.00	0.07;15.36	1.0000	1.0000 (0.00)	1	70

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

20 Ongoing studies of fibrinolytic

No ongoing trial was identified.

21 Excluded studies for fibrinolytic

No trial was excluded.

References

Part IV

Surgery

22 Overview of surgery

22.1 Included trials

Only one trial which randomized 468 patients was identified. In all, 1 randomized comparison concerned surgery.
The detailed descriptions of trials and meta-analysis results is given in section 23 (page 162) for surgery.

This trial included 468 patients and was published in 1987.
This trial was open-label in design.
It was reported in English language.
The table 22.1 (page 160) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

22.2 Summary of meta-analysis results

The meta-analysis of the available trials about surgery provide the results listed in tables 22.2 to 22.2 (page 161) and in the following graphs.

22.2.1 Surgery

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

Table 22.1: *Main study characteristics - surgery*

Trial	Patients	Treatments	Trial design and method
Surgery			
Surgery versus medical treatment			
VA cooperative, 1987 [1, 2, 3, 4] n = 231 vs. 237	men with unstable angina pectoris	coronary-artery bypass surgery plus medical therapy **versus** medical therapy alone	open parallel groups US

Table 22.2: *Summary of all results for surgery*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
surgery versus medical treatment						
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

23 Details

23.1 Available trials

Only one trial which randomized 468 patients was identified: it compared surgery with medical treatment.
This trial included 468 patients and was published in 1987.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 23.1 (page 162), 23.2 (page 162), 23.4 (page 164), and 23.3 (page 162) summarized the main characteristics of the trial including in this systematic review of randomized trials of surgery.

Table 23.1: *Treatment description - surgery - surgery*

Trial	Studied treatment	Control treatment
Surgery versus medical treatment		
VA cooperative (1987) [1, 2, 3, 4]	coronary-artery bypass surgery plus medical therapy	medical therapy alone

Table 23.2: *Descriptions of participants - surgery - surgery*

Trial	Patients
Surgery versus medical treatment	
VA cooperative (1987) [1, 2, 3, 4]	Men with unstable angina pectoris

Table 23.3: *Design and methodological quality of trials - surgery - surgery*

Trial	Design	Duration	Centre	Primary endpoint
Surgery versus medical treatment				

continued...

Trial	Design	Duration	Centre	Primary end-point
VA cooperative, 1987 [1, 2, 3, 4] n=468	Parallel groups open confirmatory trial at risk of bias	2 years (5,10 years) inclusion period: Jun 1976 - Jun 1982	US	

Table 23.4: *Trial characteristics - surgery - surgery*

Trial	Fibrinolysis	non Q wave MI	Time to cardiac catheterization routine invasive group, h	ST-segment depression	T-wave inversion	Thrombolytic therapy
Surgery versus medical treatment						
VA cooperative, 1987 [1, 2, 3, 4]						

23.2 Meta-analysis results

The results are detailed in table 23.5 (page 165). This table is followed by the Forest's plot corresponding to each endpoint.

Surgery versus medical treatment

No data were presented in the 1 trial identified

Table 23.5: *Results details - surgery - surgery*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
surgery versus medical treatment						
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] Luchi RJ, Scott SM, Deupree RH. Comparison of medical and surgical treatment for unstable angina pectoris. Results of a Veterans Administration Cooperative Study. N Engl J Med 1987 Apr 16;316:977-84. [PMID=2882420]

[2] Parisi AF, Khuri S, Deupree RH, Sharma GV, Scott SM, Luchi RJ. Medical compared with surgical management of unstable angina. 5-year mortality and morbidity in the Veterans Administration Study. Circulation 1989 Nov;80:1176-89. [PMID=2680157]

[3] Scott SM, Deupree RH, Sharma GV, Luchi RJ. VA Study of Unstable Angina. 10-year results show duration of surgical advantage for patients with impaired ejection fraction. Circulation 1994 Nov;90:II120-3. [PMID=7955237]

[4] Sharma GV, Deupree RH, Khuri SF, Parisi AF, Luchi RJ, Scott SM. Coronary bypass surgery improves survival in high-risk unstable angina. Results of a Veterans Administration Cooperative study with an 8-year follow-up. Veterans Administration Unstable Angina Cooperative Study Group. Circulation 1991 Nov;84:III260-7. [PMID=1934418]

23.3 Individual trial summaries

Table 23.6: *VA cooperative, 1987 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=468 (231 vs. 237) **Follow-up duration:** 2 years (5,10 years) **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias US **Inclusion period:** Jun 1976 - Jun 1982	Men with unstable angina pectoris	**Studied treatment:** coronary-artery bypass surgery plus medical therapy **Control treatment:** medical therapy alone	

References

Luchi RJ, Scott SM, Deupree RH. Comparison of medical and surgical treatment for unstable angina pectoris. Results of a Veterans Administration Cooperative Study. N Engl J Med 1987 Apr 16;316:977-84 [PMID=2882420]
Parisi AF, Khuri S, Deupree RH, Sharma GV, Scott SM, Luchi RJ. Medical compared with surgical management of unstable angina. 5-year mortality and morbidity in the Veterans Administration Study. Circulation 1989 Nov;80:1176-89 [PMID=2680157]
Scott SM, Deupree RH, Sharma GV, Luchi RJ. VA Study of Unstable Angina. 10-year results show duration of surgical advantage for patients with impaired ejection fraction. Circulation 1994 Nov;90:II120-3 [PMID=7955237]
Sharma GV, Deupree RH, Khuri SF, Parisi AF, Luchi RJ, Scott SM. Coronary bypass surgery improves survival in high-risk unstable angina. Results of a Veterans Administration Cooperative study with an 8-year follow-up. Veterans Administration Unstable Angina Cooperative Study Group. Circulation 1991 Nov;84:III260-7 [PMID=1934418]

24 Global meta-analysis: all surgery

24.1 Global meta-analysis: all surgery versus medical treatment

Table 24.1: *All surgeryversus medical treatment*

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

25 Ongoing studies of surgery

No ongoing trial was identified.

26 Excluded studies for surgery

No trial was excluded.

References