Cholesterol lowering intervention for acute coronary syndrome in early initiation

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 Cholesterol lowering intervention for acute coronary syndrome in early initiation.

Contents

0.1 Synthesis of the meta-analysis results

In all 15 randomised controlled trials (RCTs) were included. These included 1 studie of **ezetimibe** involving 18,144 patients and 14 studies of **statins** involving 17,484 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 Ezetimibe

Only one trials including 18144 patients was found.
Among these comparisons, one trial are about ezetimibe.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with ezetimibe for all the endpoints with data in at least one trial are summarized table 1.

Table 1: *Results summary - Ezetimibe*

Benefit	Harmful	No evidence
	Ezetimibe versus control	
	↑ cardiovascular events RR=1.07† [1.02;1.12] k=1	→ cardiovascular death RR=1.00^{NS} [0.89;1.13] k=1
	↑ stroke (fatal and non fatal) RR=1.17* [1.00;1.36] k=1	→ coronary death RR=1.05^{NS} [0.92;1.19] k=1
	↑ coronary event RR=1.15¶ [1.06;1.24] k=1	→ all cause death RR=1.01^{NS} [0.94;1.09] k=1

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

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

0.1.2 Statins

Reports of 14 trials (including 17,186 patients) were identified .
Among these comparisons, 4 trials are about atorvastatin,two about fluvastatin,one about pitavastatin,6 about pravastatin and one about simvastatin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. One ongoing trial was identified.

Atorvastatin

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

Table 2: *Results summary - Atorvastatin*

Benefit	Harmful	No evidence
	Atorvastatin versus placebo	

continued...

Benefit	Harmful	No evidence
↓ recurrent angina RR=0.74* [0.57;0.95] k=1 ↓ non fatal stroke RR=0.41* [0.19;0.89] k=1		→ deaths or MI RR=0.92^{NS} [0.75;1.13] k=1 → cardiovascular events at 1 month RR=1.06^{NS} [0.81;1.39] k=1 → cardiovascular events at 4 months RR=0.89^{NS} [0.73;1.09] k=1 → PTCA RR=1.06^{NS} [0.85;1.31] k=1 → cardiovascular events RR=0.92^{NS} [0.75;1.13] k=1 → stroke (fatal and non fatal) RR=0.50^{NS} [0.25;1.00] k=1 → cardiac death RR=0.86^{NS} [0.59;1.23] k=1 → CABG RR=0.97^{NS} [0.75;1.25] k=1 → fatal MI RR=0.95^{NS} [0.49;1.84] k=1 → non fatal MI RR=0.90^{NS} [0.69;1.17] k=1 → revascularization RR=1.02^{NS} [0.87;1.20] k=1 → all cause death RR=0.95^{NS} [0.68;1.32] k=1
Atorvastatin versus usual care		
		→ cardiovascular events at 1 month RR=0.17^{NS} [0.01;3.30] k=1 → cardiovascular events at 4 months RR=0.56^{NS} [0.22;1.47] k=2 → cardiovascular events RR=0.56^{NS} [0.22;1.47] k=2 → stroke (fatal and non fatal) RR=0.61^{NS} [0.08;4.62] k=2 → cardiac death RR=0.73^{NS} [0.15;3.55] k=2 → fatal MI RR=0.73^{NS} [0.15;3.55] k=2 → non fatal MI RR=0.48^{NS} [0.14;1.61] k=2 → revascularization RR=1.00^{NS} [0.43;2.32] k=2 → all cause death RR=0.72^{NS} [0.19;2.69] k=2
Atorvastatin versus pravastatin		
↓ cardiovascular events RR=0.76¶ [0.66;0.88] k=1		→ all cause death RR=0.72^{NS} [0.50;1.03] k=1

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

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

Fluvastatin

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

Table 3: *Results summary - Fluvastatin*

Benefit	Harmful	No evidence
	Fluvastatin versus placebo	
		→ cardiovascular events at 1 month RR=1.31^{NS} [0.45;3.87] k=2 → cardiovascular events at 4 months RR=1.43^{NS} [0.61;3.36] k=2 → recurrent angina RR=1.04^{NS} [0.57;1.88] k=1 → cardiovascular events RR=1.27^{NS} [0.52;3.12] k=2 → stroke (fatal and non fatal) RR=0.68^{NS} [0.05;8.83] k=2 → cardiac death RR=0.56^{NS} [0.19;1.68] k=2 → CABG RR=0.66^{NS} [0.32;1.32] k=1 → fatal MI RR=0.33^{NS} [0.03;3.52] k=2 → non fatal MI RR=1.48^{NS} [0.74;2.96] k=2 → revascularization RR=0.89^{NS} [0.71;1.11] k=2 → all cause death RR=0.68^{NS} [0.31;1.50] k=2

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

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

Pitavastatin

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

Table 4: *Results summary - Pitavastatin*

Benefit	Harmful	No evidence
	Pitavastatin versus atorvastatin	

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

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

Pravastatin

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

Table 5: *Results summary - Pravastatin*

Benefit	Harmful	No evidence
	Pravastatin versus placebo	

continued...

Benefit	Harmful	No evidence
		→ cardiovascular events at 1 month RR=0.88^{NS} [0.67;1.16] k=3 → cardiovascular events at 4 months RR=0.95^{NS} [0.35;2.60] k=2 → cardiovascular events RR=0.95^{NS} [0.35;2.60] k=2 → stroke (fatal and non fatal) RR=0.74^{NS} [0.32;1.72] k=4 → cardiac death RR=0.79^{NS} [0.49;1.28] k=4 → fatal MI RR=0.90^{NS} [0.46;1.76] k=4 → non fatal MI RR=0.38^{NS} [0.08;1.79] H k=4 → revascularization RR=1.17^{NS} [0.55;2.45] k=3 → all cause death RR=0.72^{NS} [0.45;1.14] k=4
Pravastatin versus usual care		
↓ cardiovascular events at 1 month RR=0.36* [0.13;0.99] k=2		→ cardiovascular events at 4 months RR=0.39^{NS} [0.10;1.48] k=2 → cardiovascular events RR=0.39^{NS} [0.10;1.48] k=2 → stroke (fatal and non fatal) RR=0.64^{NS} [0.05;8.21] k=2 → cardiac death RR=0.31^{NS} [0.03;3.32] k=2 → fatal MI RR=0.31^{NS} [0.03;3.32] k=2 → non fatal MI RR=0.44^{NS} [0.06;3.06] k=2 → revascularization RR=0.58^{NS} [0.33;1.05] k=2 → all cause death RR=0.45^{NS} [0.08;2.52] k=2

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

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

Simvastatin

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

Table 6: *Results summary - Simvastatin*

Benefit	Harmful	No evidence
Simvastatin versus placebo		

continued...

Benefit	Harmful	No evidence
		→ cardiovascular events at 1 month RR=0.93^{NS} [0.71;1.22] k=1 → cardiovascular events at 4 months RR=0.99^{NS} [0.80;1.22] k=1 → cardiovascular events RR=0.89^{NS} [0.77;1.02] k=1 → stroke (fatal and non fatal) RR=0.79^{NS} [0.48;1.29] k=1 → cardiac death RR=0.86^{NS} [0.57;1.30] k=1 → fatal MI RR=0.62^{NS} [0.35;1.11] k=1 → non fatal MI RR=0.99^{NS} [0.77;1.29] k=1 → revascularization RR=0.95^{NS} [0.74;1.21] k=1 → all cause death RR=0.90^{NS} [0.60;1.35] k=1

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

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

1 Introduction

1.1 Aim of the report

This report review all the randomized clinical trials of cholesterol lowering intervention for the treatment of acute coronary syndrome in early initiation. The following classes of treatment are considered:

1. ezetimibe
2. statins

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of cholesterol lowering intervention for the treatment of acute coronary syndrome in early initiation.

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

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 Coronary death, All cause death, cardiovascular events, stroke (fatal and non fatal), Cardiovascular death, Coronary event, .

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 ezetimibe, statins,
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

Ezetimibe

2 Overview of ezetimibe

2.1 Included trials

Only one trial which randomized 18144 patients was identified. In all, 1 randomized comparison concerned ezetimibe.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 22) for ezetimibe.

This trial included 18144 patients and was published in 2014.
This trial was double blind 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 ezetimibe provide the results listed in tables 2.2 to 2.2 (page 19) and in the following graphs.

2.2.1 Ezetimibe

Ezetimibe was inferior to **control** in terms of cardiovascular events (RR=1.07, 95% CI 1.02 to 1.12, p=0.0048, 1 trial), stroke (fatal and non fatal) (RR=1.17, 95% CI 1.00 to 1.36, p=0.0474, 1 trial)and coronary event (RR=1.15, 95% CI 1.06 to 1.24, p=0.0000, 1 trial). No significant difference was found on cardiovascular death (RR=1.00, 95% CI 0.89 to 1.13, p=0.9601, 1 trial), coronary death (RR=1.05, 95% CI 0.92 to 1.19, p=0.4626, 1 trial)and all cause death (RR=1.01, 95% CI 0.94 to 1.09, p=0.7061, 1 trial).

Table 2.1: *Main study characteristics - ezetimibe*

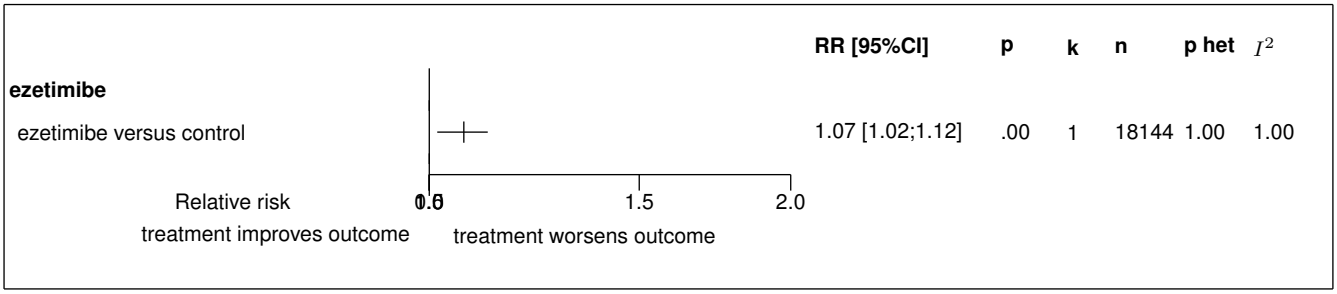
Trial	Patients	Treatments	Trial design and method
Ezetimibe			
Ezetimibe versus control			
IMPROVE-IT, 2014 [1] n = 9067 vs. 9077	subjects with stabilized high-risk acute coronary syndrome	10 mg/day of ezetimibe and 40 mg/day of simvastatin **versus** simvastatin 40 mg/day LDL change, at end of study (%): -24% LDL change, end of study (mmol/L): -0.43	double blind parallel groups Primary endpoint: CV death, MI, hospitalization for unstable angina, stroke and coronary revascularization 1158 centres, 39 countries

Table 2.2: *Summary of all results for ezetimibe*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
ezetimibe versus control						
cardiovascular events	RR=1.07	1.02;1.12	0.0048	1.0000 (1.00)	1	18144
cardiovascular death	RR=1.00	0.89;1.13	0.9601	1.0000 (0.00)	1	18144
stroke (fatal and non fatal)	RR=1.17	1.00;1.36	0.0474	1.0000 (0.00)	1	18144
coronary event	RR=1.15	1.06;1.24	0.0000	1.0000 (0.00)	1	18144
coronary death	RR=1.05	0.92;1.19	0.4626	1.0000 (0.00)	1	18144
all cause death	RR=1.01	0.94;1.09	0.7061	1.0000 (0.00)	1	18144

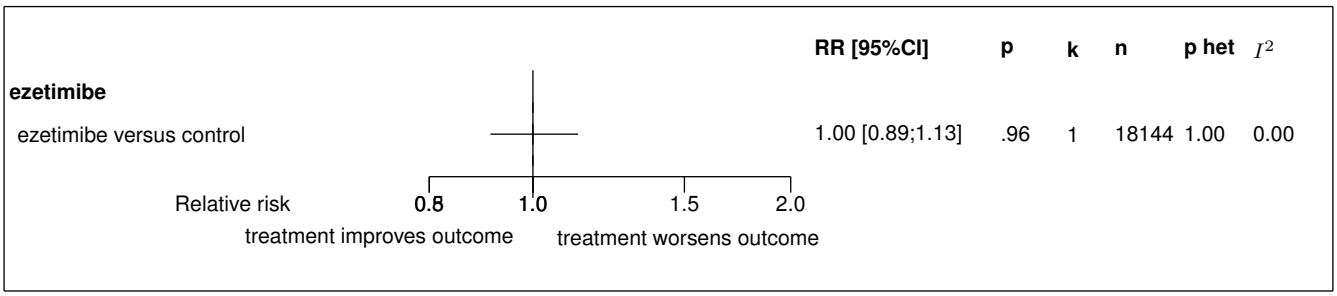
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 2.1: *Forest's plot for cardiovascular events*



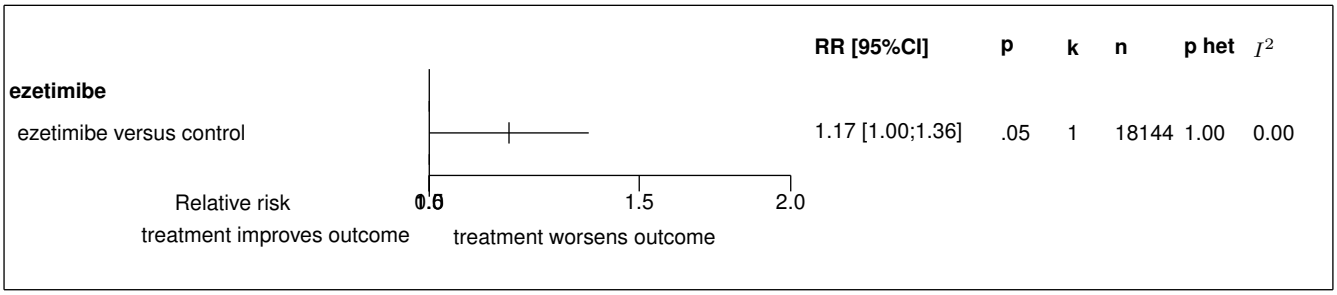
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.2: *Forest's plot for cardiovascular death*



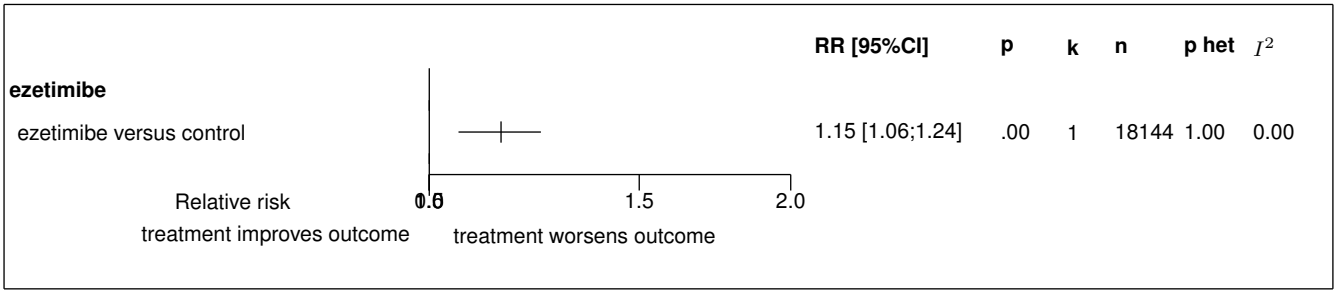
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.3: *Forest's plot for stroke (fatal and non fatal)*



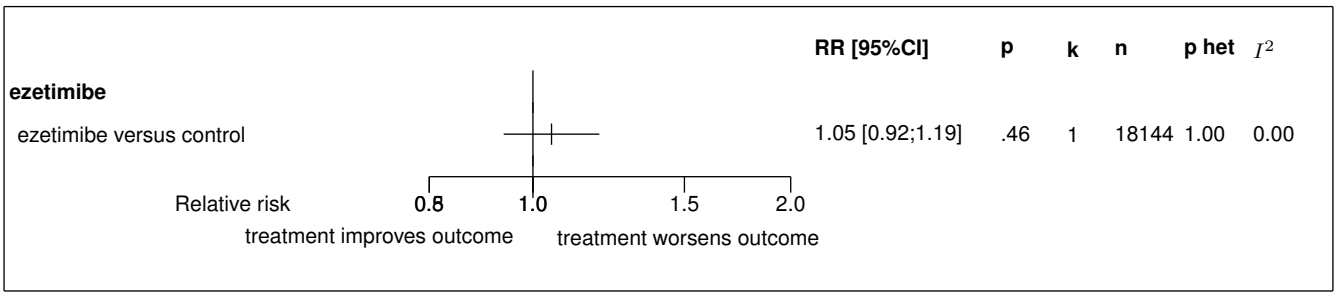
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.4: *Forest's plot for coronary event*



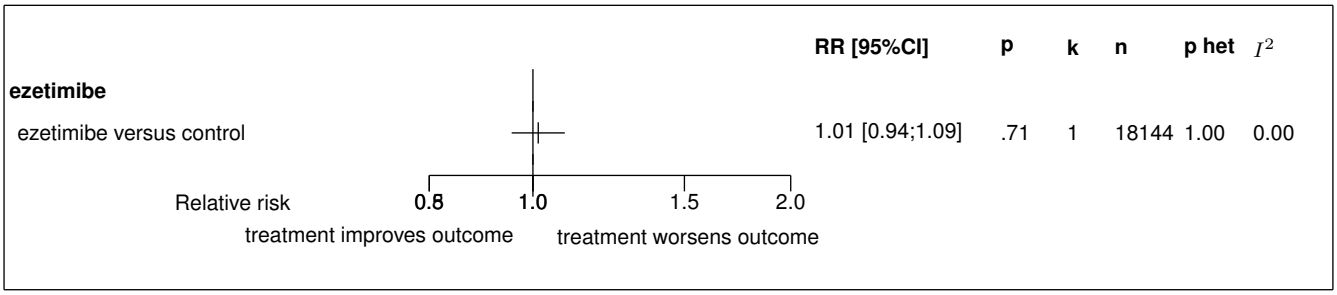
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.5: *Forest's plot for coronary death*



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

Figure 2.6: *Forest's plot for all cause death*



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

3 Details

3.1 Available trials

Only one trial which randomized 18144 patients was identified: it compared ezetimibe with control.
This trial included 18144 patients and was published in 2014.
This trial was double blind in design.
It was reported in English language.
Coronary death data was reported in 1 trials; 1 trials reported data on all cause death; 1 trials reported data on cardiovascular events; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on cardiovascular death; and 1 trials reported data on coronary event.
Following tables 3.1 (page 22), 3.2 (page 22), 3.4 (page 24), and 3.3 (page 23) summarized the main characteristics of the trial including in this systematic review of randomized trials of ezetimibe.

Table 3.1: *Treatment description - ezetimibe - ezetimibe*

Trial	Studied treatment	Control treatment
Ezetimibe versus control		
IMPROVE-IT (2014) [1] [a]	10 mg/day of ezetimibe and 40 mg/day of simvastatin	simvastatin 40 mg/day

a) If LDL-C response is inadequate, the dose of simvastatin may be increased to 80 mg

Table 3.2: *Descriptions of participants - ezetimibe - ezetimibe*

Trial	Patients	
Ezetimibe versus control		
IMPROVE-IT (2014) [1]	Subjects with stabilized high-risk acute coronary syndrome	
	Inclusion criteria: clinically stable subjects may be eligible to enroll within 10 days following hospital admission with high-risk acute coronary syndrome (either STEMI or Non-STEMI or unstable angina);subjects not taking a statin must have an LDL-C of 125 mg/dl or less. Subjects taking a statin must have an LDL-C of 100 mg/dl or less.	**Exclusion criteria:** pregnant or lactating woman, or intending to become pregnant; active liver disease or persistent unexplained serum transaminase elevation; history of alcohol or drug abuse; history of sensitivity to statin or ezetimibe; discontinuation of existing lipid lowering regimen poses an unacceptable risk

Table 3.3: *Design and methodological quality of trials - ezetimibe - ezetimibe*

Trial	Design	Duration	Centre	Primary endpoint
Ezetimibe versus control				
IMPROVE-IT, 2014 [1] n=18144	Parallel groups double blind	5.68 years	39 countries 1158 centres	CV death, MI, hospitalization for unstable angina, stroke and coronary revascularization

Table 3.4: *Trial characteristics - ezetimibe - ezetimibe*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Ezetimibe versus control		
IMPROVE-IT, 2014 [1]	-24%	-0.43

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 25). This table is followed by the Forest's plot corresponding to each endpoint.

Ezetimibe versus control

The single study eligible for this comparison provided data on **cardiovascular events**. The analysis detected a statistically significant difference in favor of control in cardiovascular events, with a RR of 1.07 (95% CI 1.02 to 1.12, p=0.0048).
The single study eligible for this comparison provided data on **cardiovascular death**. No statistically significant difference between the groups was found in cardiovascular death, with a RR of 1.00 (95% CI 0.89 to 1.13, p=0.9601).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of control in stroke (fatal and non fatal), with a RR of 1.17 (95% CI 1.00 to 1.36, p=0.0474).
The single study eligible for this comparison provided data on **coronary event**. The analysis detected a statistically significant difference in favor of control in coronary event, with a RR of 1.15 (95% CI 1.06 to 1.24, p=0.0000).
The single study eligible for this comparison provided data on **coronary death**. No statistically significant difference between the groups was found in coronary death, with a RR of 1.05 (95% CI 0.92 to 1.19, p=0.4626).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.01 (95% CI 0.94 to 1.09, p=0.7061).

Table 3.5: *Results details - ezetimibe - ezetimibe*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ezetimibe versus control						
cardiovascular events	RR=1.07	[1.02;1.12]	0.0048	1.0000 (I^2=1.00)	1	18144
cardiovascular death	RR=1.00	[0.89;1.13]	0.9601	1.0000 (I^2=0.00)	1	18144
stroke (fatal and non fatal)	RR=1.17	[1.00;1.36]	0.0474	1.0000 (I^2=0.00)	1	18144
coronary event	RR=1.15	[1.06;1.24]	0.0000	1.0000 (I^2=0.00)	1	18144
coronary death	RR=1.05	[0.92;1.19]	0.4626	1.0000 (I^2=0.00)	1	18144
all cause death	RR=1.01	[0.94;1.09]	0.7061	1.0000 (I^2=0.00)	1	18144

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 cardiovascular events*

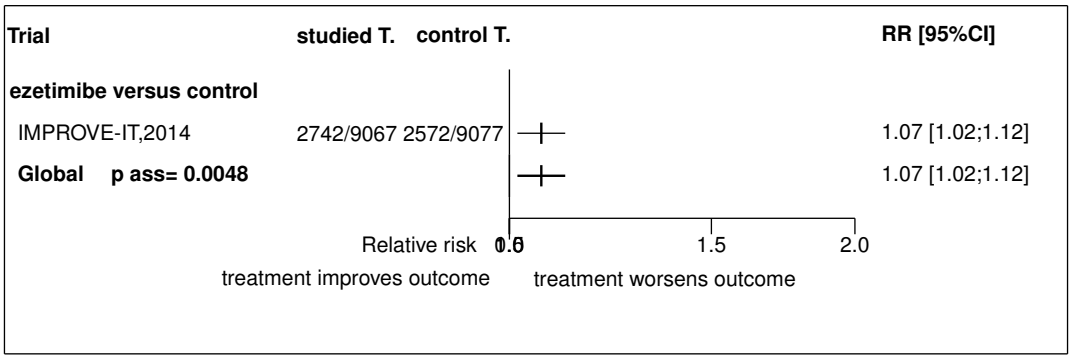


Figure 3.2: *Forest's plot for cardiovascular death*

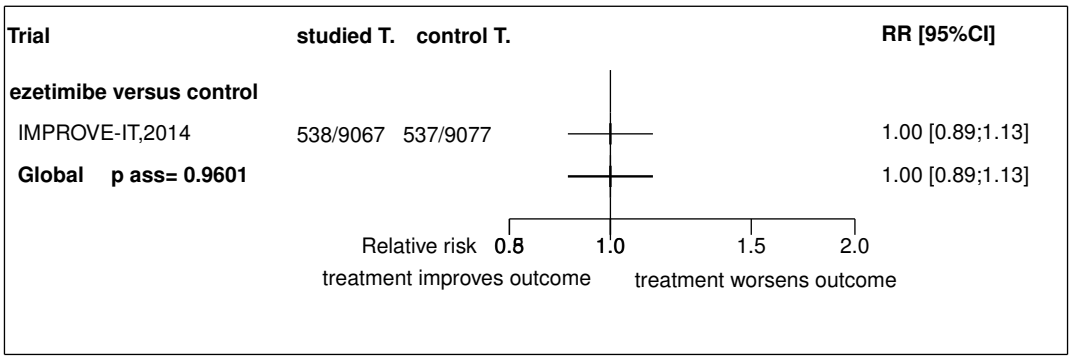


Figure 3.3: *Forest's plot for stroke (fatal and non fatal)*

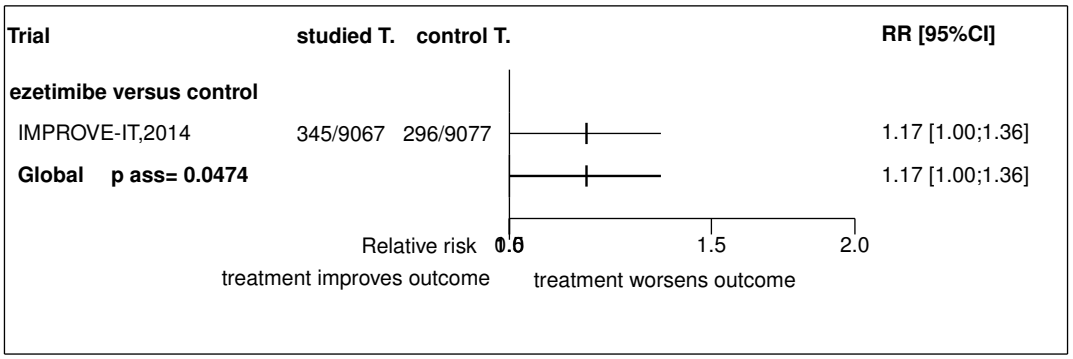


Figure 3.4: *Forest's plot for coronary event*

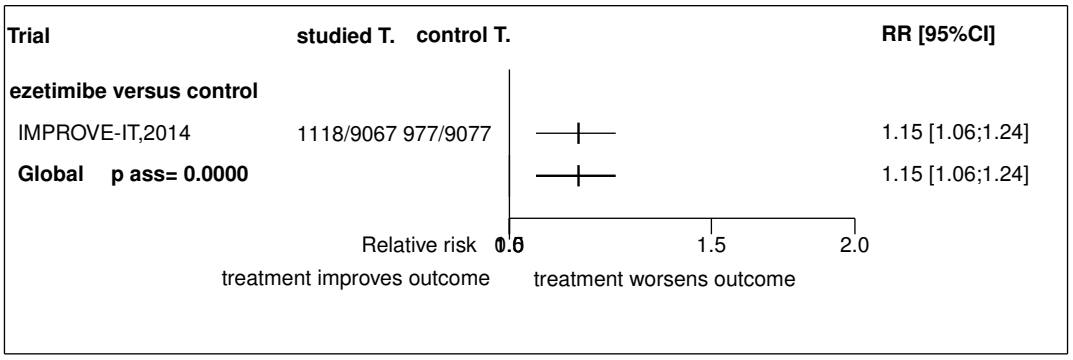


Figure 3.5: *Forest's plot for coronary death*

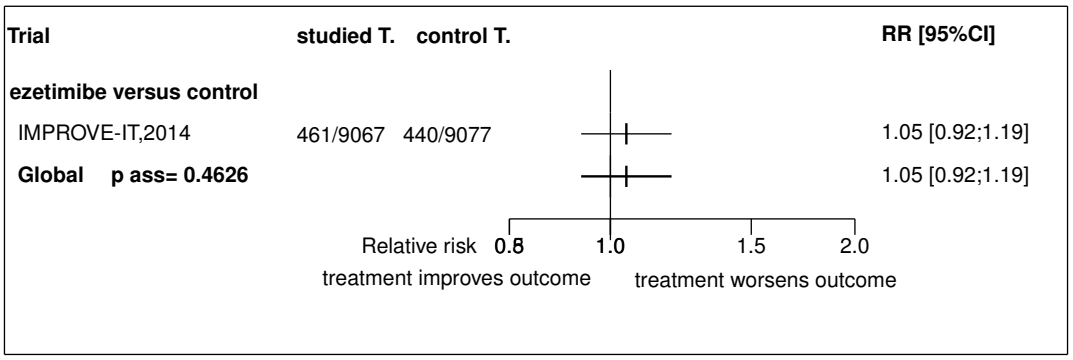
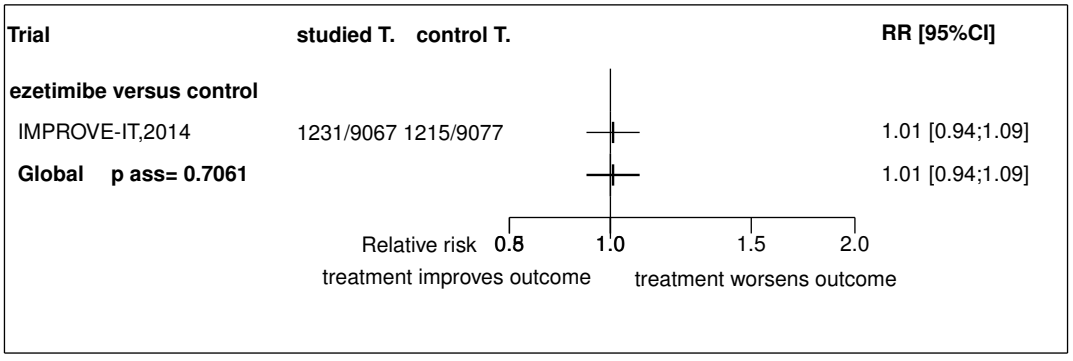


Figure 3.6: *Forest's plot for all cause death*



References

[1] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;372:2387-97. [PMID=26039521]

3.3 Individual trial summaries

Table 3.6: *IMPROVE-IT, 2014 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=18144 (9067 vs. 9077) **Follow-up duration:** 5.68 years **Study design:** Randomized controlled trial Parallel groups Double blind 39 countries, 1158 centres	Subjects with stabilized high-risk acute coronary syndrome **Inclusion criteria:** clinically stable subjects may be eligible to enroll within 10 days following hospital admission with high-risk acute coronary syndrome (either STEMI or Non-STEMI or unstable angina);subjects not taking a statin must have an LDL-C of 125 mg/dl or less. Subjects taking a statin must have an LDL-C of 100 mg/dl or less. **Exclusion criteria:** pregnant or lactating woman, or intending to become pregnant; active liver disease or persistent unexplained serum transaminase elevation; history of alcohol or drug abuse; history of sensitivity to statin or ezetimibe; discontinuation of existing lipid lowering regimen poses an unacceptable risk	**Studied treatment:** 10 mg/day of ezetimibe and 40 mg/day of simvastatin **Control treatment:** simvastatin 40 mg/day **note:** If LDL-C response is inadequate, the dose of simvastatin may be increased to 80 mg	Cardiovascular events RR=1.07 [1.02;1.12] (Primary end point: death from cardiovascular causes, major coronary event, or non-fatal strok) Cardiovascular death RR=1.00 [0.89;1.13] (Death from cardiovascular causes) Stroke (fatal and non fatal) RR=1.17 [1.00;1.36] (Any stroke) Coronary event RR=1.15 [1.06;1.24] (Any MI)

Reference
Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;372:2387-97 [PMID=26039521]

4 Global meta-analysis: all ezetimibe

4.1 Global meta-analysis: all ezetimibe versus control

Table 4.1: *All ezetimibeversus control*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=1.07	1.02;1.12	0.0048	1.0000 (1.00)	1	18144
cardiovascular death	RR=1.00	0.89;1.13	0.9601	1.0000 (0.00)	1	18144
stroke (fatal and non fatal)	RR=1.17	1.00;1.36	0.0474	1.0000 (0.00)	1	18144
coronary event	RR=1.15	1.06;1.24	0.0000	1.0000 (0.00)	1	18144
coronary death	RR=1.05	0.92;1.19	0.4626	1.0000 (0.00)	1	18144
all cause death	RR=1.01	0.94;1.09	0.7061	1.0000 (0.00)	1	18144

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 ezetimibe

No ongoing trial was identified.

6 Excluded studies for ezetimibe

No trial was excluded.

References

Part II

Statins

7 Overview of statins

7.1 Included trials

A total of 14 randomized comparisons which enrolled 17186 patients were identified. In all, 4 randomized comparisons concerned atorvastatin , two fluvastatin , one pitavastatin , 6 pravastatin and one simvastatin.
The detailed descriptions of trials and meta-analysis results is given in section 8 (page 56) for atorvastatin, in section 9 (page 76) for fluvastatin, in section 10 (page 88) for pitavastatin, in section 11 (page 93) for pravastatin and in section 12 (page 112) for simvastatin.

The average study size was 1322 patients (range 60 to 4497). The first study was published in 1997, and the last study was published in 2009.
A total of 9 trials were double blind and 5 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 7.1 (page 37) 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 statins provide the results listed in tables 7.2 to 7.6 (page 40) and in the following graphs.

7.2.1 Atorvastatin

Atorvastatin was superior to **placebo** in terms of recurrent angina (RR=0.74, 95% CI 0.57 to 0.95, p=0.0182, 1 trial)and non fatal stroke (RR=0.41, 95% CI 0.19 to 0.89, p=0.0243, 1 trial). However, no significant difference was found on deaths or MI (RR=0.92, 95% CI 0.75 to 1.13, p=0.4471, 1 trial), cardiovascular events at 1 month (RR=1.06, 95% CI 0.81 to 1.39, p=0.6781, 1 trial), cardiovascular events at 4 months (RR=0.89, 95% CI 0.73 to 1.09, p=0.2564, 1 trial), PTCA (RR=1.06, 95% CI 0.85 to 1.31, p=0.6255, 1 trial), cardiovascular events (RR=0.92, 95% CI 0.75 to 1.13, p=0.4471, 1 trial), stroke (fatal and non fatal) (RR=0.50, 95% CI 0.25 to 1.00, p=0.0509, 1 trial), cardiac death (RR=0.86, 95% CI 0.59 to 1.23, p=0.4041, 1 trial), CABG (RR=0.97, 95% CI 0.75 to 1.25, p=0.8159, 1 trial), fatal MI (RR=0.95, 95% CI 0.49 to 1.84, p=0.8802, 1 trial), non fatal MI (RR=0.90, 95% CI 0.69 to 1.17, p=0.4233, 1 trial), revascularization (RR=1.02, 95% CI 0.87 to 1.20, p=0.7838, 1 trial)and all cause death (RR=0.95, 95% CI 0.68 to 1.32, p=0.7507, 1 trial).

No significant difference was found between **atorvastatin** and **usual care** in terms of cardiovascular events at 1 month (RR=0.17, 95% CI 0.01 to 3.30, p=0.2423, 1 trial), cardiovascular events at 4 months (RR=0.56, 95% CI 0.22 to 1.47, p=0.2419, 2 trials), cardiovascular events (RR=0.56, 95% CI 0.22 to 1.47, p=0.2419, 2 trials), stroke (fatal and non fatal) (RR=0.61, 95% CI 0.08 to 4.62, p=0.6351, 2 trials), cardiac death (RR=0.73, 95% CI 0.15 to 3.55, p=0.6945, 2 trials), fatal MI (RR=0.73, 95% CI 0.15 to 3.55, p=0.6945, 2 trials), non fatal MI (RR=0.48, 95% CI 0.14 to 1.61, p=0.2317, 2 trials), revascularization (RR=1.00, 95% CI 0.43 to 2.32, p=0.9979, 2 trials)and all cause death (RR=0.72, 95% CI 0.19 to 2.69, p=0.6245, 2 trials).

Atorvastatin was superior to **pravastatin** in terms of cardiovascular events (RR=0.76, 95% CI 0.66 to 0.88, p=0.0000, 1 trial). However, no significant difference was found on all cause death (RR=0.72, 95% CI 0.50 to 1.03, p=0.0748, 1 trial).

7.2.2 Fluvastatin

No significant difference was found between **fluvastatin** and **placebo** in terms of cardiovascular events at 1 month (RR=1.31, 95% CI 0.45 to 3.87, p=0.6191, 2 trials), cardiovascular events at 4 months (RR=1.43, 95% CI 0.61 to 3.36, p=0.4170, 2 trials), recurrent angina (RR=1.04, 95% CI 0.57 to 1.88, p=0.9031, 1 trial), cardiovascular events (RR=1.27, 95% CI 0.52 to 3.12, p=0.6040, 2 trials), stroke (fatal and non fatal) (RR=0.68, 95% CI 0.05 to 8.83, p=0.7682, 2 trials), cardiac death (RR=0.56, 95% CI 0.19 to 1.68, p=0.3037, 2 trials), CABG (RR=0.66, 95% CI 0.32 to 1.32, p=0.2387, 1 trial), fatal MI (RR=0.33, 95% CI 0.03 to 3.52, p=0.3565, 2 trials), non fatal MI (RR=1.48, 95% CI 0.74 to 2.96, p=0.2735, 2 trials), revascularization (RR=0.89, 95% CI 0.71 to 1.11, p=0.2986, 2 trials)and all cause death (RR=0.68, 95% CI 0.31 to 1.50, p=0.3386, 2 trials).

7.2.3 Pitavastatin

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

7.2.4 Pravastatin

No significant difference was found between **pravastatin** and **placebo** in terms of cardiovascular events at 1 month (RR=0.88, 95% CI 0.67 to 1.16, p=0.3645, 3 trials), cardiovascular events at 4 months (RR=0.95, 95% CI 0.35 to 2.60, p=0.9238, 2 trials), cardiovascular events (RR=0.95, 95% CI 0.35 to 2.60, p=0.9238, 2 trials), stroke (fatal and non fatal) (RR=0.74, 95% CI 0.32 to 1.72, p=0.4844, 4 trials), cardiac death (RR=0.79, 95% CI 0.49 to 1.28, p=0.3336, 4 trials), fatal MI (RR=0.90, 95% CI 0.46 to 1.76, p=0.7614, 4 trials), non fatal MI (RR=0.38, 95% CI 0.08 to 1.79, p=0.2199, 4 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0414)(RR=1.17, 95% CI 0.55 to 2.45, p=0.6845, 3 trials)and all cause death (RR=0.72, 95% CI 0.45 to 1.14, p=0.1625, 4 trials).

Pravastatin was superior to **usual care** in terms of cardiovascular events at 1 month (RR=0.36, 95% CI 0.13 to 0.99, p=0.0476, 2 trials). However, no significant difference was found on cardiovascular events at 4 months (RR=0.39, 95% CI 0.10 to 1.48, p=0.1657, 2 trials), cardiovascular events (RR=0.39, 95% CI 0.10 to 1.48, p=0.1657, 2 trials), stroke (fatal and non fatal) (RR=0.64, 95% CI 0.05 to 8.21, p=0.7301, 2 trials), cardiac death (RR=0.31, 95% CI 0.03 to 3.32, p=0.3335, 2 trials), fatal MI (RR=0.31, 95% CI 0.03 to 3.32, p=0.3335, 2 trials), non fatal MI (RR=0.44, 95% CI 0.06 to 3.06, p=0.4048, 2 trials), revascularization (RR=0.58, 95% CI 0.33 to 1.05, p=0.0725, 2 trials)and all cause death (RR=0.45, 95% CI 0.08 to 2.52, p=0.3635, 2 trials).

7.2.5 Simvastatin

No significant difference was found between **simvastatin** and **placebo** in terms of cardiovascular events at 1 month (RR=0.93, 95% CI 0.71 to 1.22, p=0.5912, 1 trial), cardiovascular events at 4 months (RR=0.99, 95% CI 0.80 to 1.22, p=0.9374, 1 trial), cardiovascular events (RR=0.89, 95% CI 0.77 to 1.02, p=0.0994, 1 trial), stroke (fatal and non fatal) (RR=0.79, 95% CI 0.48 to 1.29, p=0.3440, 1 trial), cardiac death (RR=0.86, 95% CI 0.57 to 1.30, p=0.4773, 1 trial), fatal MI (RR=0.62, 95% CI 0.35 to 1.11, p=0.1060, 1 trial), non fatal MI (RR=0.99, 95% CI 0.77 to 1.29, p=0.9631, 1 trial), revascularization (RR=0.95, 95% CI 0.74 to 1.21, p=0.6520, 1 trial)and all cause death (RR=0.90, 95% CI 0.60 to 1.35, p=0.6210, 1 trial).

Table 7.1: *Main study characteristics - statins*

Trial	Patients	Treatments	Trial design and method
Atorvastatin			
Atorvastatin versus placebo			
MIRACL, 2001 [1] n = 1538 vs. 1548	unstable angina or nonQ-wave acute MI	atorvastatin, 80 mg (early initiation) **versus** placebo	double blind parallel groups Primary endpoint: death, MI, recurrent ischemia requiring hospitalization 122 centres, Europe, North America, South Africa, and Australasia
Atorvastatin versus usual care			
Colivicchi, 2002 [2] n = 40 vs. 41	unstable angina pectoris or non-Q-wave myocardial infarction	atorvastatin, 80 mg daily early initiation **versus** usual care	open parallel groups Primary endpoint: cardiac death, MI, objective recurrent ischemia 1 centres, Italy
ESTABLISH, 2004 [3] n = 35 vs. 35	patients with ACS undergoing emergency coronary angiography and percutaneous coronary intervention	atorvastatin, 20 mg early initiation **versus** usual care	open parallel groups Primary endpoint: none defined single center, Japan
Atorvastatin versus pravastatin			
PROVE IT - TIMI 22, 2004 [4, 5, 6, 7, 8] n = 2099 vs. 2063	patients who had been hospitalized for an acute coronary syndromewithin the preceding 10 days	80 mg of atorvastatin daily (intensive therapy). **versus** 40 mg of pravastatin daily (standard therapy)	double blind parallel groups Primary endpoint: death, MI, unstable angina, revascularization, stroke 349 centres, UK, US, AUstralia, Italy, France, Germany, Spain, Canada
Fluvastatin			
Fluvastatin versus placebo			

continued...

Trial	Patients	Treatments	Trial design and method
LIPS (sub groups), 2002 [1] n = 417 vs. 407	patients with unstable angina and successful first percutaneous coronary intervention	fluvastatin, 80 mg **versus** placebo	double blind parallel groups Primary endpoint: MACE 57 centres, Europe, Canada, and Brazil
FLORIDA, 2002 [2] n = 265 vs. 275	patients with an AMI and total cholesterol of <6.5 mmol.l	fluvastatin, 80 mg (early initiation) **versus** placebo	double blind parallel groups multicentre, The Netherlands
Pitavastatin			
Pitavastatin versus atorvastatin			
JAPAN ACS, 2009 [1] n = 307 vs. NA	patients with acute coronary syndrome undergoing IVUS-guided percutaneous coronary intervention	pitavastatin 4 mg daily **versus** atorvastatin 20mg daily	open parallel groups Primary endpoint: change in nonculprit coronary plaque volume 33 centres, Japan
Pravastatin			
Pravastatin versus placebo			
LAMIL, 1997 [1] n = 36 vs. 33	patients suffering an acute myocardial infarction	pravastatin, 10-20 mg (starting at D3) **versus** placebo	double blind parallel groups Belgium
RECIFE, 1999 [2] n = 30 vs. 30	patients with acute myocardial infarction or unstable angina and total cholesterol levels at admission >=5.2 mmol/L or LDL >=3.4 mmol/L	pravastatin, 40 mg **versus** placebo	double blind parallel groups Primary endpoint: none defined 1 centres, Canada
PAIS, 2001 [3] n = 50 vs. 49	patients with acute coronary syndromes	pravastatin, 40 mg (initiated within 48 hours of hospital admission) **versus** placebo	double blind parallel groups The Netherlands

continued...

Trial	Patients	Treatments	Trial design and method
PACT, 2004 [4, 5] n = 1710 vs. 1698	patients with unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction within 24 hours of the onset of symptoms	pravastatin, 20-40 mg within 24 hours of the onset of symptoms in **versus** placebo	double blind parallel groups Primary endpoint: death, recurrence of MI, or rehospital for unstable angina multicentre, Australia
Pravastatin versus usual care			
L-CAD, 2000 [6] n = 70 vs. 56	patients with acute coronary syndrome	pravastatin, 20-40 mg (strating on average at D6) **versus** usual care	open parallel groups Primary endpoint: death, MI, stroke, coronary intervention, PVD Germany
PTT, 2002 [7] n = 79 vs. 85	patients who underwent coronary balloon angioplasty of the infarct-related artery during the first month of acute myocardial infarction	pravastatin, 40 mg **versus** usual care	open parallel groups Turkey
Simvastatin			
Simvastatin versus placebo			
A to Z, 2004 [1] n = 2265 vs. 2232	patient with an acute coronary syndrome (ACS)	simvastatin, 40-80 mg early initiation **versus** placebo	double aveugle parallel groups Primary endpoint: cardiovascular death, MI, rehospitalization for ACS or stroke 322 centres, 41 countries

Table 7.2: *Summary of all results for atorvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
atorvastatin versus placebo						
deaths or MI	RR=0.92	0.75;1.13	0.4471	1.0000 (0.00)	1	3086
cardiovascular events at 1 month	RR=1.06	0.81;1.39	0.6781	1.0000 (0.00)	1	3086
cardiovascular events at 4 months	RR=0.89	0.73;1.09	0.2564	1.0000 (0.00)	1	3086
PTCA	RR=1.06	0.85;1.31	0.6255	1.0000 (0.00)	1	3086
recurrent angina	RR=0.74	0.57;0.95	0.0182	1.0000 (0.00)	1	3086
cardiovascular events	RR=0.92	0.75;1.13	0.4471	1.0000 (0.00)	1	3086
stroke (fatal and non fatal)	RR=0.50	0.25;1.00	0.0509	1.0000 (0.00)	1	3086
cardiac death	RR=0.86	0.59;1.23	0.4041	1.0000 (0.00)	1	3086
CABG	RR=0.97	0.75;1.25	0.8159	1.0000 (0.00)	1	3086
fatal MI	RR=0.95	0.49;1.84	0.8802	1.0000 (0.00)	1	3086
non fatal MI	RR=0.90	0.69;1.17	0.4233	1.0000 (0.00)	1	3086
revascularization	RR=1.02	0.87;1.20	0.7838	1.0000 (0.00)	1	3086
all cause death	RR=0.95	0.68;1.32	0.7507	1.0000 (0.00)	1	3086
non fatal stroke	RR=0.41	0.19;0.89	0.0243	1.0000 (0.00)	1	3086
atorvastatin versus usual care						
cardiovascular events at 1 month	RR=0.17	0.01;3.30	0.2423	1.0000 (0.00)	1	81
cardiovascular events at 4 months	RR=0.56	0.22;1.47	0.2419	0.9421 (0.00)	2	151
cardiovascular events	RR=0.56	0.22;1.47	0.2419	0.9421 (0.00)	2	151
stroke (fatal and non fatal)	RR=0.61	0.08;4.62	0.6351	0.7735 (0.00)	2	151
cardiac death	RR=0.73	0.15;3.55	0.6945	0.8610 (0.00)	2	151
fatal MI	RR=0.73	0.15;3.55	0.6945	0.8610 (0.00)	2	151
non fatal MI	RR=0.48	0.14;1.61	0.2317	0.6939 (0.00)	2	151
revascularization	RR=1.00	0.43;2.32	0.9979	0.9903 (0.00)	2	151
all cause death	RR=0.72	0.19;2.69	0.6245	0.8176 (0.00)	2	151
atorvastatin versus pravastatin						
cardiovascular events	RR=0.76	0.66;0.88	0.0000	1.0000 (0.00)	1	4152
all cause death	RR=0.72	0.50;1.03	0.0748	1.0000 (0.00)	1	4152

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n

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

Table 7.3: *Summary of all results for fluvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
fluvastatin versus placebo						
cardiovascular events at 1 month	RR=1.31	0.45;3.87	0.6191	0.4291 (0.00)	2	1364
cardiovascular events at 4 months	RR=1.43	0.61;3.36	0.4170	0.2526 (0.24)	2	1364
recurrent angina	RR=1.04	0.57;1.88	0.9031	1.0000 (0.00)	1	540
cardiovascular events	RR=1.27	0.52;3.12	0.6040	0.1429 (0.53)	2	1364
stroke (fatal and non fatal)	RR=0.68	0.05;8.83	0.7682	0.8111 (0.00)	2	1364
cardiac death	RR=0.56	0.19;1.68	0.3037	0.8439 (0.00)	2	1364
CABG	RR=0.66	0.32;1.32	0.2387	1.0000 (0.00)	1	540
fatal MI	RR=0.33	0.03;3.52	0.3565	0.4913 (0.00)	2	1364
non fatal MI	RR=1.48	0.74;2.96	0.2735	0.7528 (0.00)	2	1364
revascularization	RR=0.89	0.71;1.11	0.2986	0.8769 (0.00)	2	1364
all cause death	RR=0.68	0.31;1.50	0.3386	0.9086 (0.00)	2	1364

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 pitavastatin*

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

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

Table 7.5: *Summary of all results for pravastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
pravastatin versus placebo						
cardiovascular events at 1 month	RR=0.88	0.67;1.16	0.3645	0.8930 (0.00)	3	3567

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
cardiovascular events at 4 months	RR=0.95	0.35;2.60	0.9238	0.9485 (0.00)	2	168
cardiovascular events	RR=0.95	0.35;2.60	0.9238	0.9485 (0.00)	2	168
stroke (fatal and non fatal)	RR=0.74	0.32;1.72	0.4844	0.9069 (0.00)	4	3636
cardiac death	RR=0.79	0.49;1.28	0.3336	0.9549 (0.00)	4	3636
fatal MI	RR=0.90	0.46;1.76	0.7614	0.8788 (0.00)	4	3636
non fatal MI	RR=0.38 [1]	0.08;1.79	0.2199	0.0414 (0.64) †	4	3636
revascularization	RR=1.17	0.55;2.45	0.6845	0.9801 (0.00)	3	228
all cause death	RR=0.72	0.45;1.14	0.1625	0.9280 (0.00)	4	3636
pravastatin versus usual care						
cardiovascular events at 1 month	RR=0.36	0.13;0.99	0.0476	0.3613 (0.00)	2	290
cardiovascular events at 4 months	RR=0.39	0.10;1.48	0.1657	0.5520 (0.00)	2	290
cardiovascular events	RR=0.39	0.10;1.48	0.1657	0.5520 (0.00)	2	290
stroke (fatal and non fatal)	RR=0.64	0.05;8.21	0.7301	0.8803 (0.00)	2	290
cardiac death	RR=0.31	0.03;3.32	0.3335	0.5506 (0.00)	2	290
fatal MI	RR=0.31	0.03;3.32	0.3335	0.5506 (0.00)	2	290
non fatal MI	RR=0.44	0.06;3.06	0.4048	0.7269 (0.00)	2	290
revascularization	RR=0.58	0.33;1.05	0.0725	0.2965 (0.08)	2	290
all cause death	RR=0.45	0.08;2.52	0.3635	0.5969 (0.00)	2	203

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 7.6: *Summary of all results for simvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
simvastatin versus placebo						
cardiovascular events at 1 month	RR=0.93	0.71;1.22	0.5912	1.0000 (0.00)	1	4497
cardiovascular events at 4 months	RR=0.99	0.80;1.22	0.9374	1.0000 (0.00)	1	4497
cardiovascular events	RR=0.89	0.77;1.02	0.0994	1.0000 (0.00)	1	4496
stroke (fatal and non fatal)	RR=0.79	0.48;1.29	0.3440	1.0000 (0.00)	1	4496
cardiac death	RR=0.86	0.57;1.30	0.4773	1.0000 (0.00)	1	4496

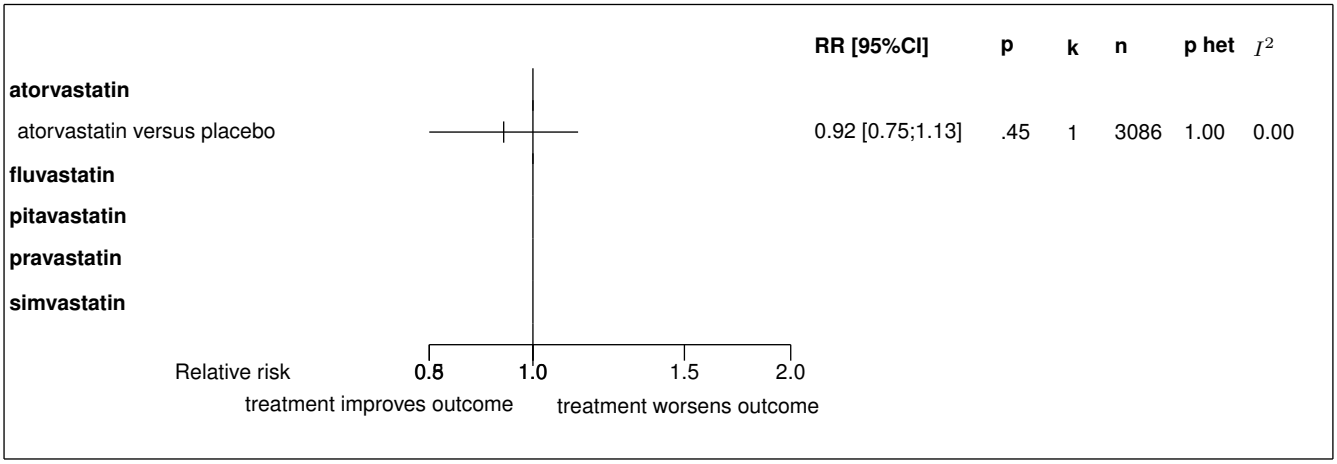
continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.19 95% CI 0.09;0.41

Endpoint	Effect	95% CI	p ass	p het	k	n
fatal MI	RR=0.62	0.35;1.11	0.1060	1.0000 (0.00)	1	4497
non fatal MI	RR=0.99	0.77;1.29	0.9631	1.0000 (0.00)	1	4496
revascularization	RR=0.95	0.74;1.21	0.6520	1.0000 (0.00)	1	4496
all cause death	RR=0.90	0.60;1.35	0.6210	1.0000 (0.00)	1	4496

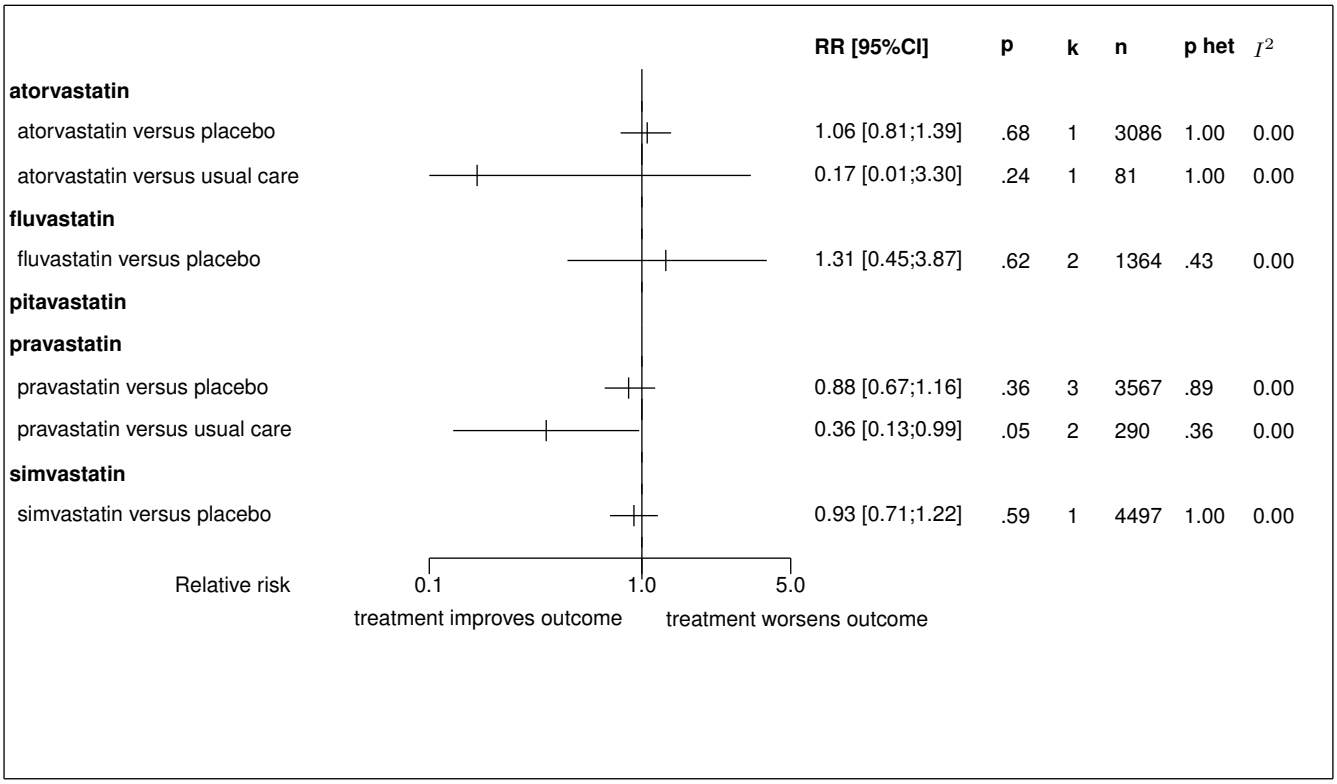
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 7.1: *Forest's plot for deaths or MI*



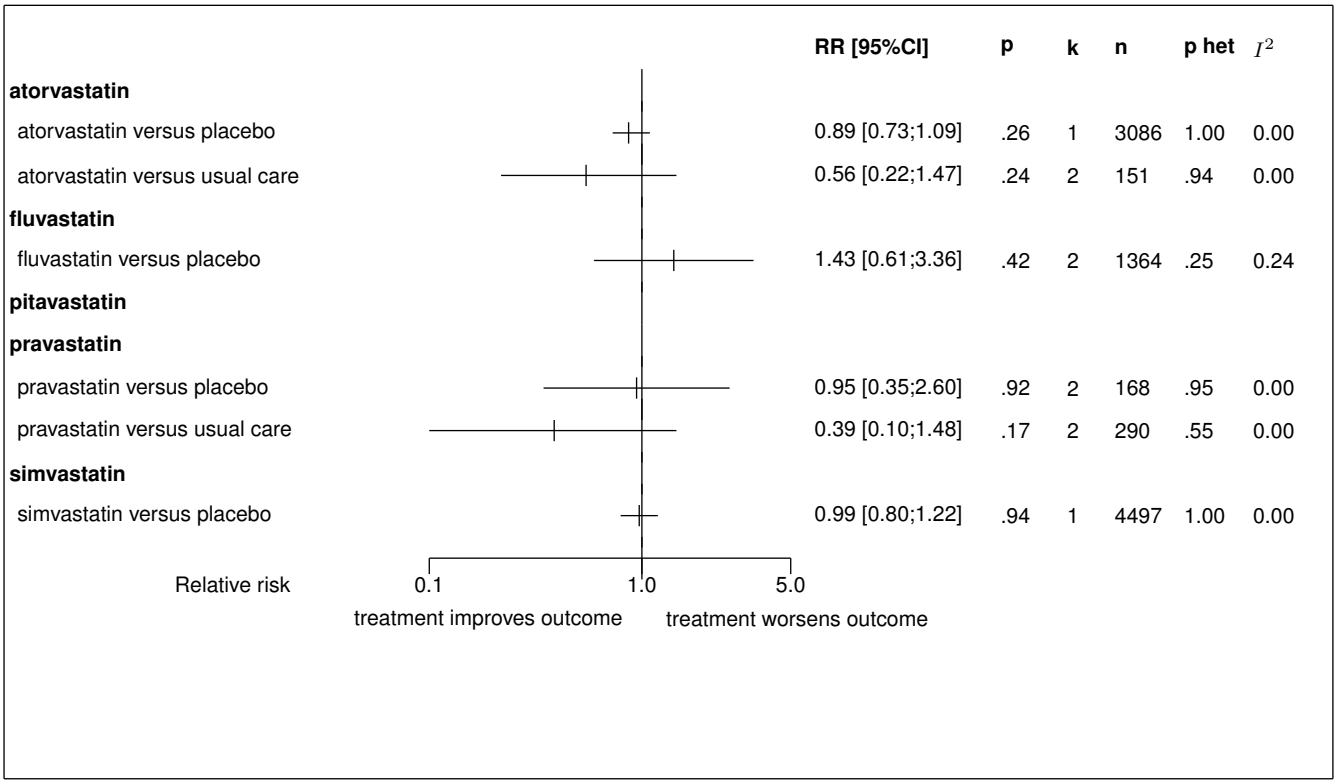
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.2: *Forest's plot for cardiovascular events at 1 month*



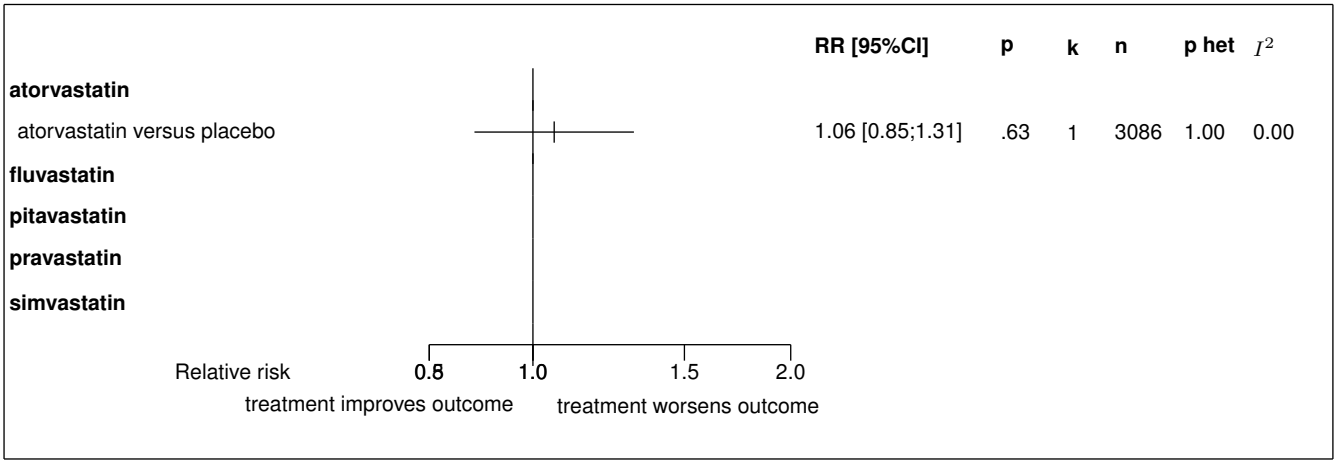
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.3: *Forest's plot for cardiovascular events at 4 months*



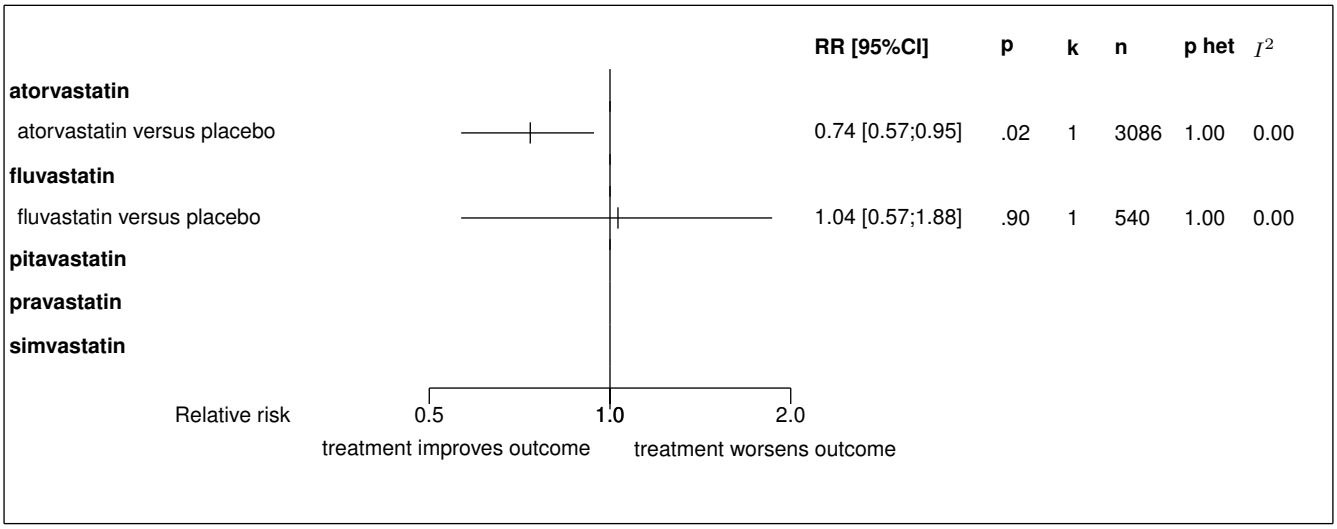
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.4: *Forest's plot for PTCA*



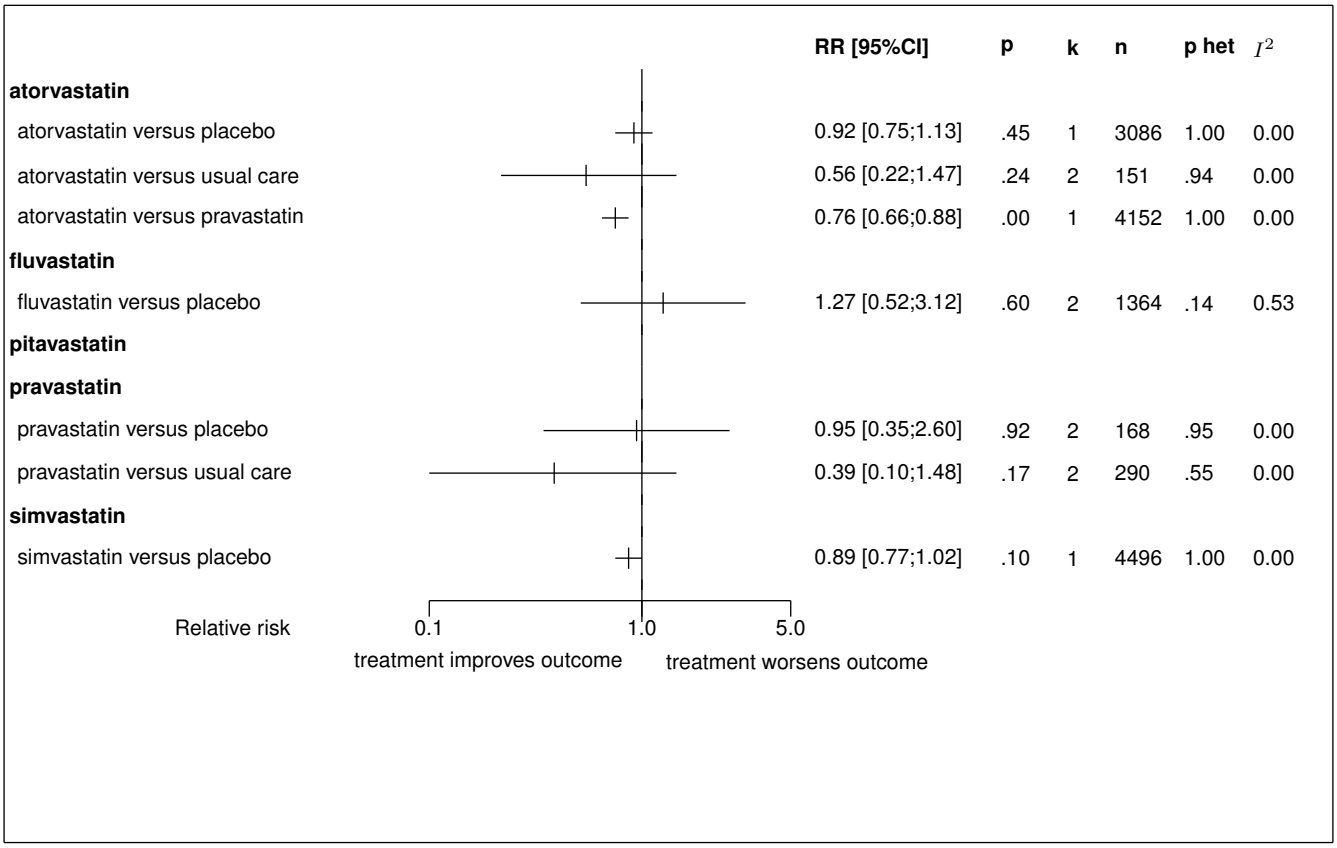
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.5: *Forest's plot for recurrent angina*



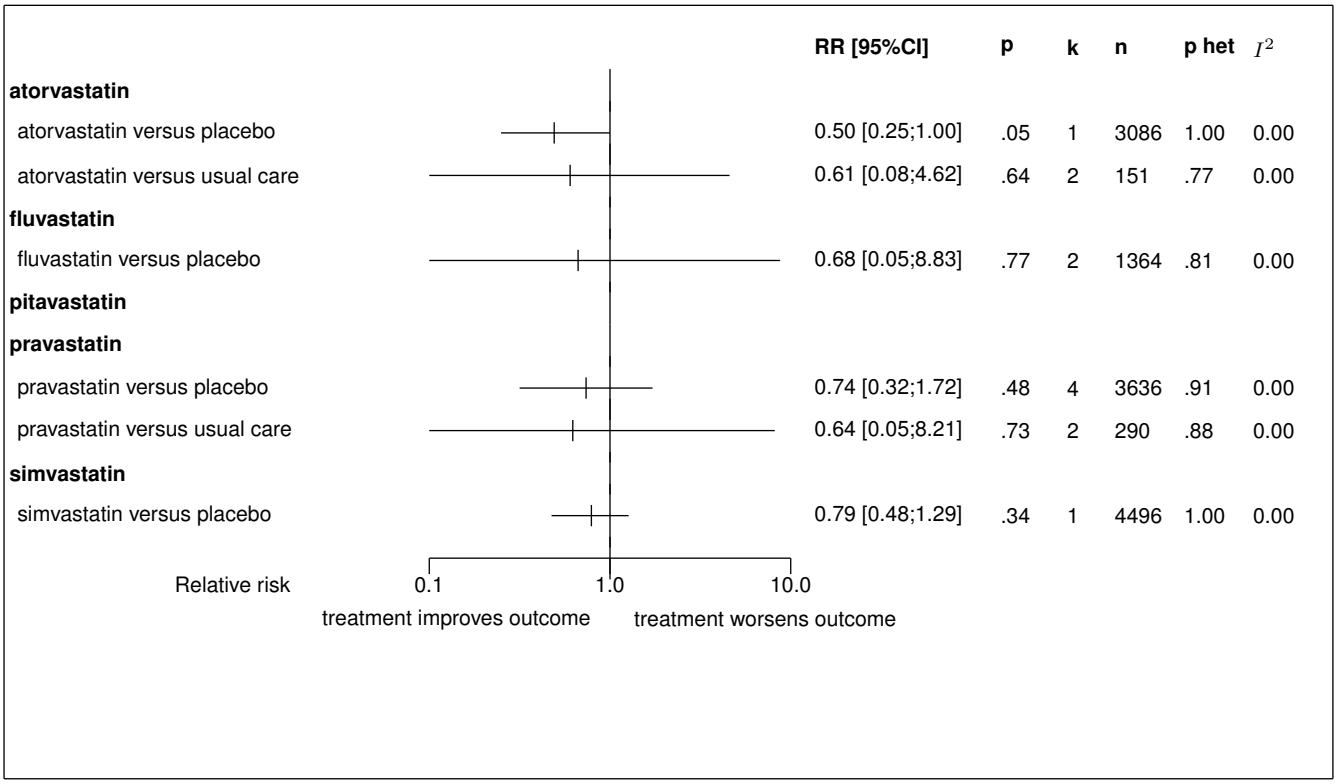
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.6: *Forest's plot for cardiovascular events*



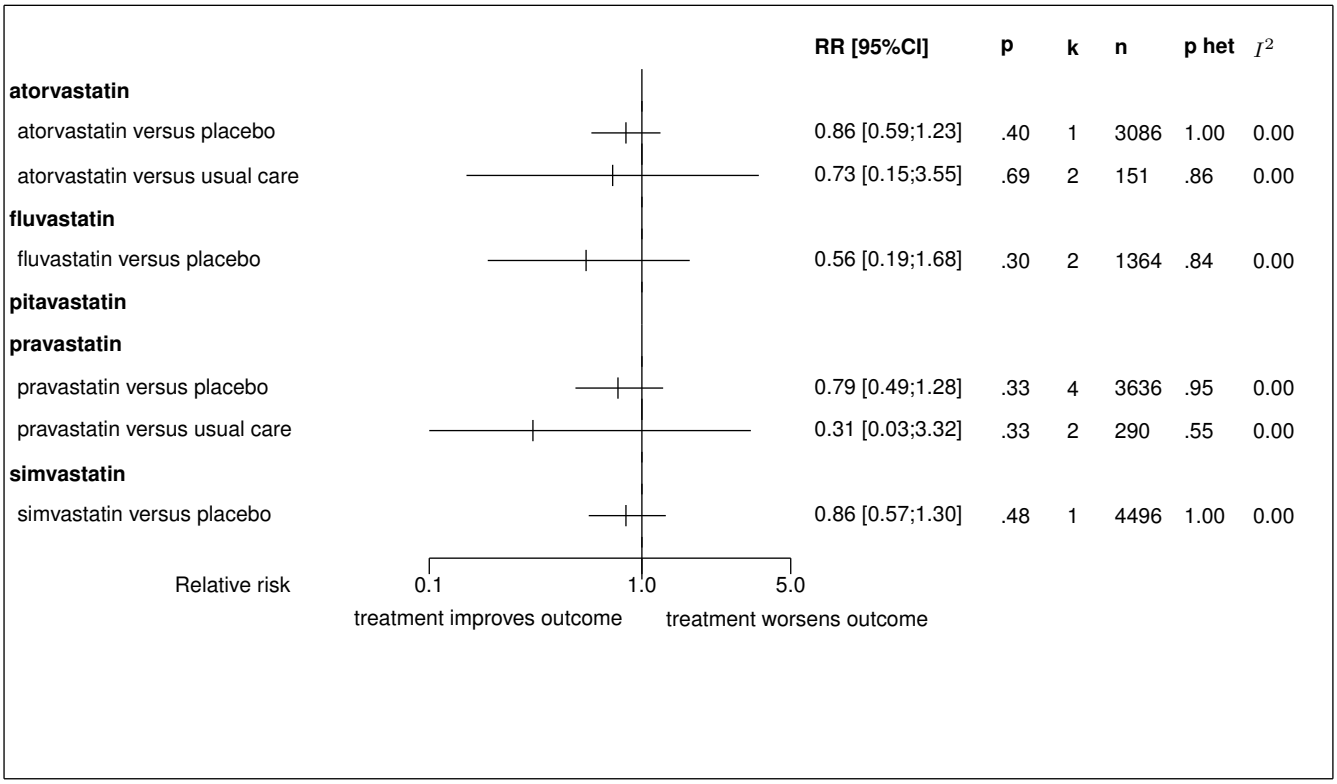
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.7: *Forest's plot for stroke (fatal and non fatal)*



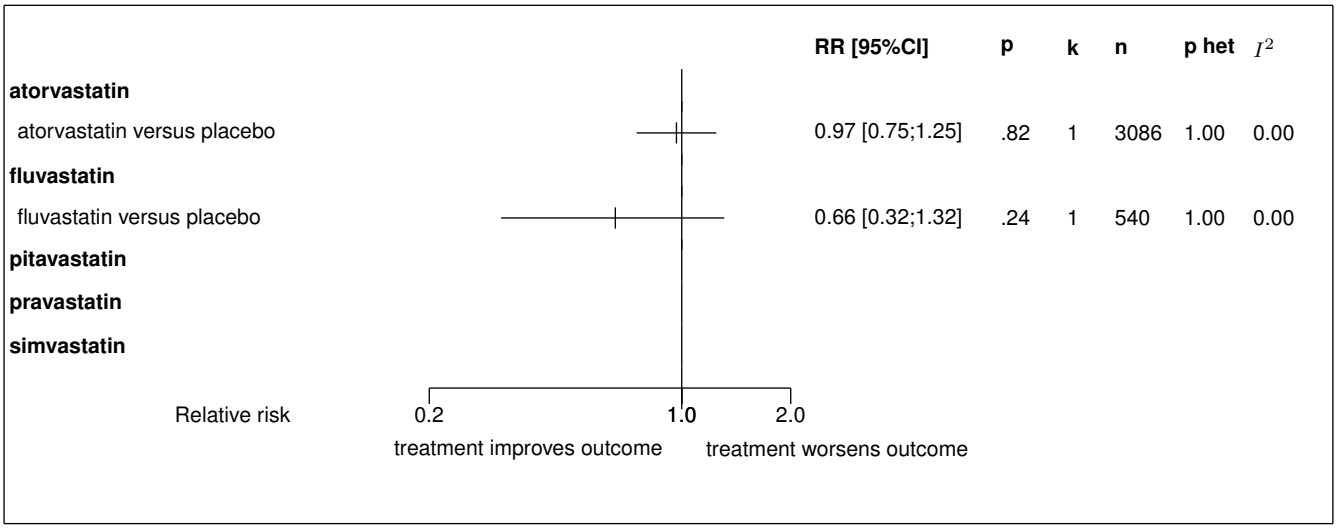
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.8: *Forest's plot for cardiac death*



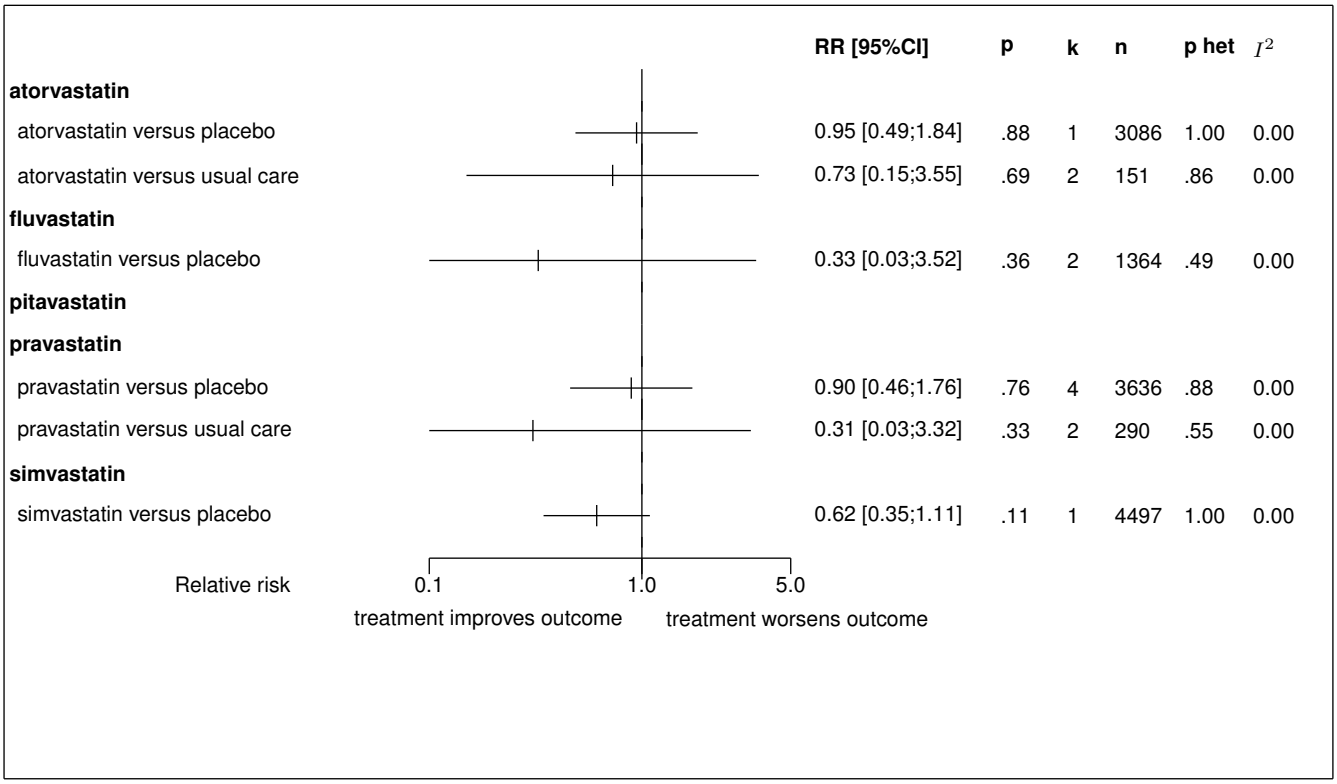
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.9: *Forest's plot for CABG*



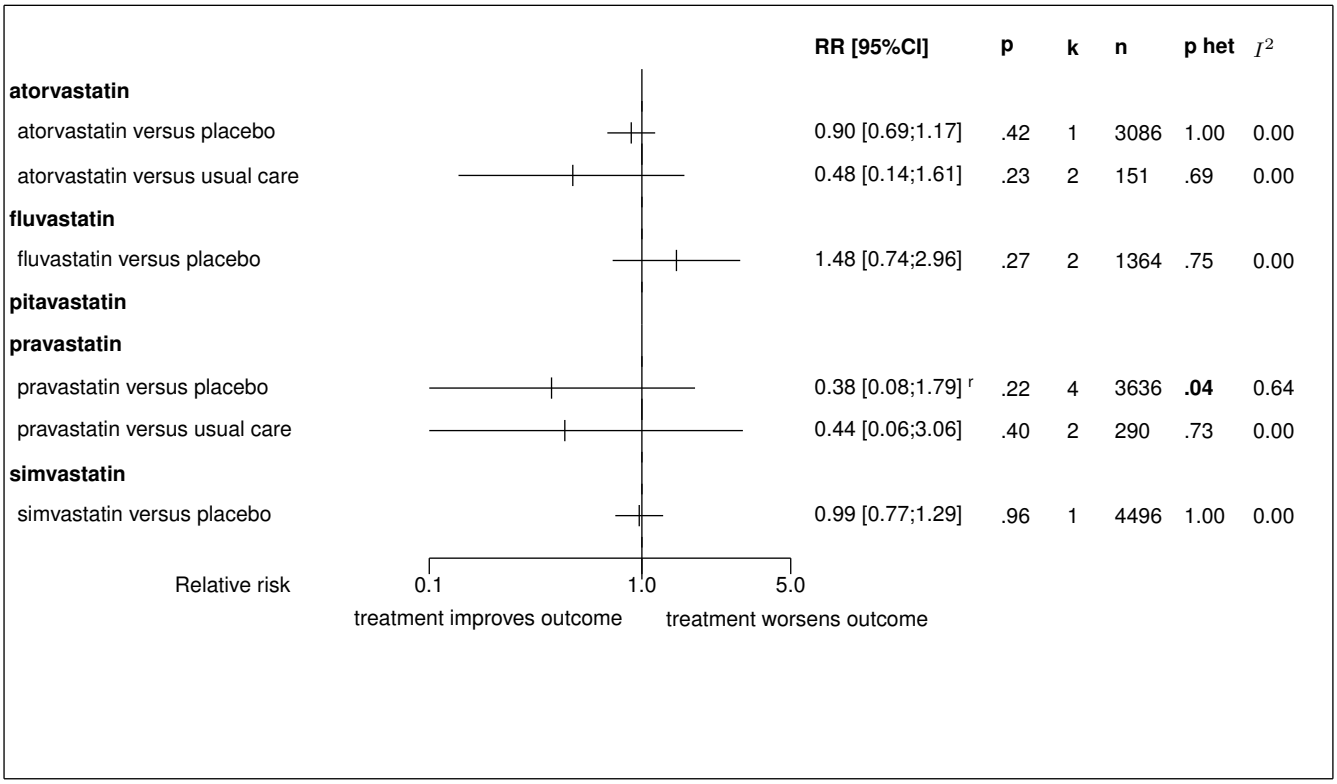
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.10: *Forest's plot for fatal MI*



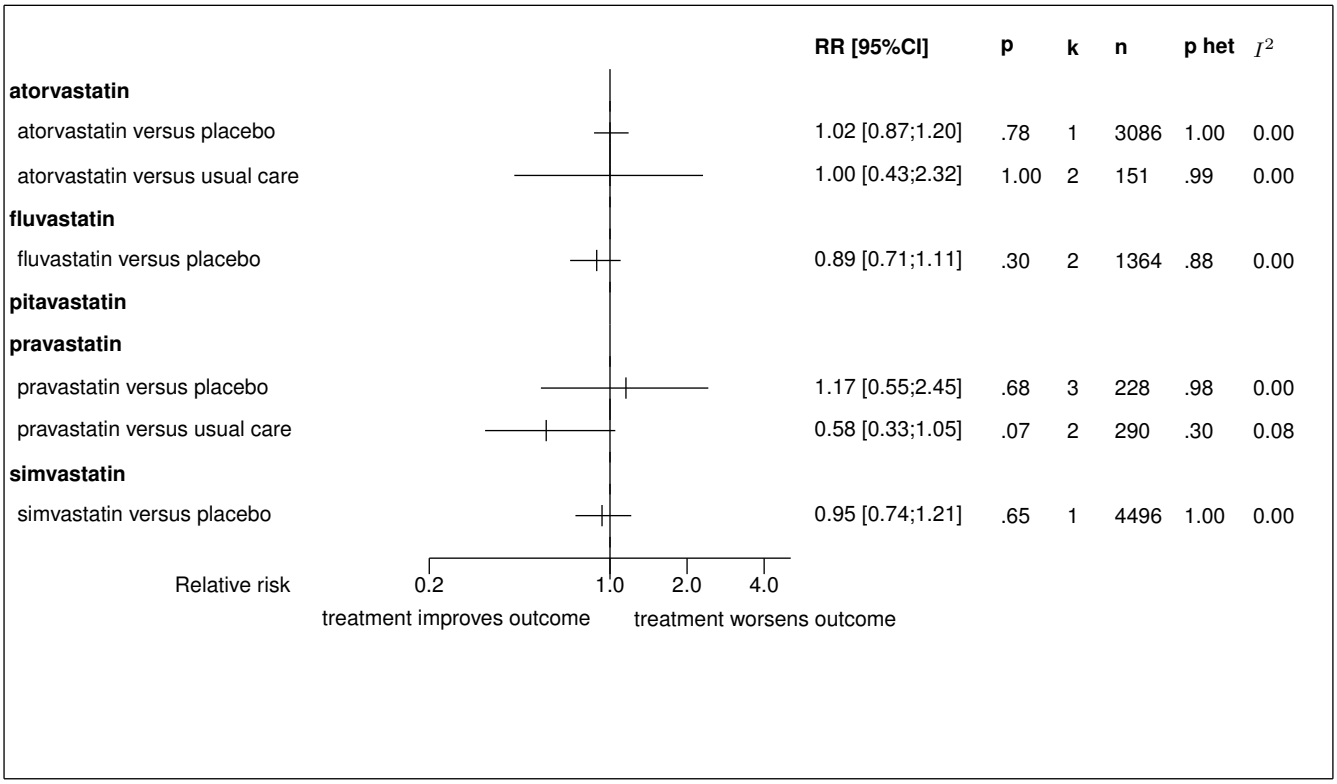
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.11: *Forest's plot for non fatal MI*



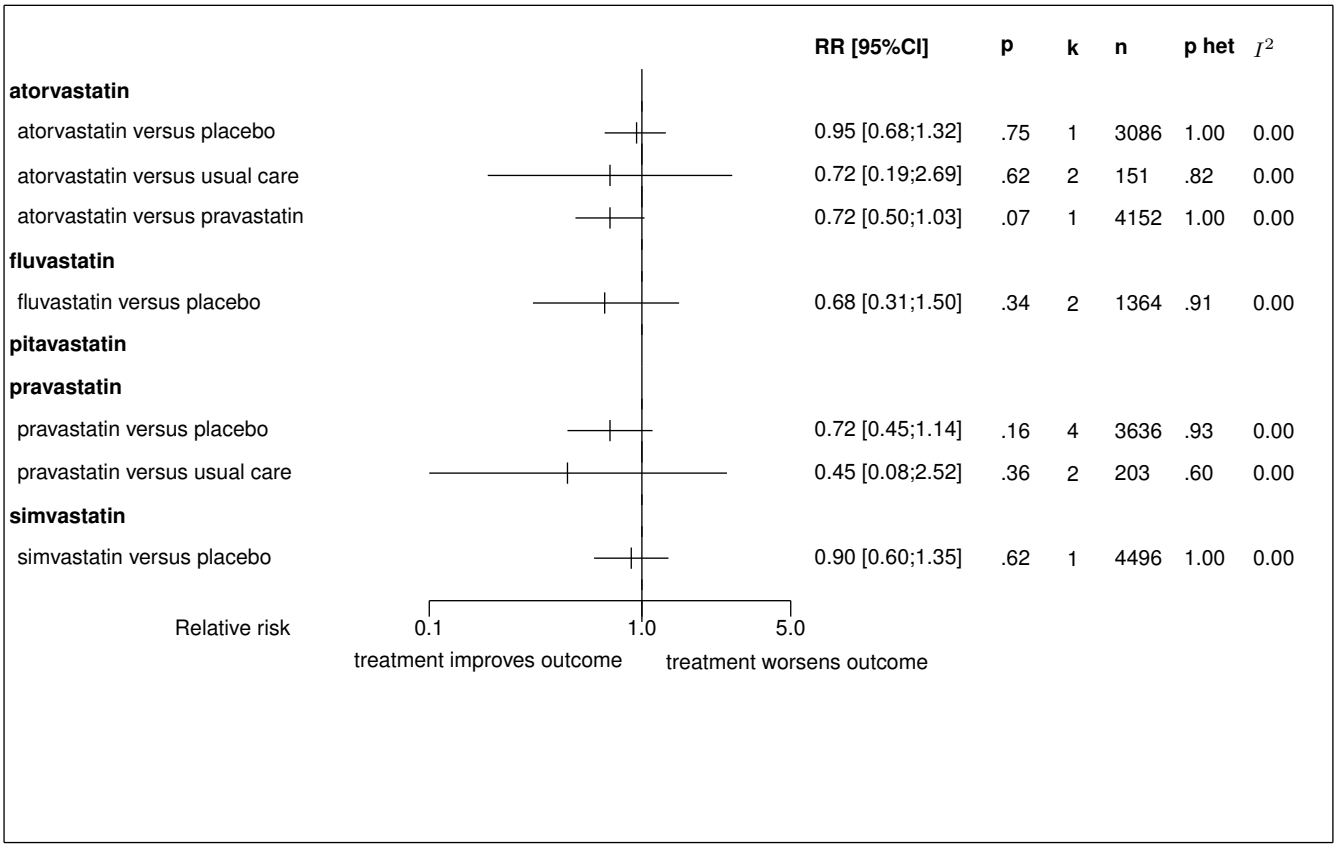
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.12: *Forest's plot for revascularization*



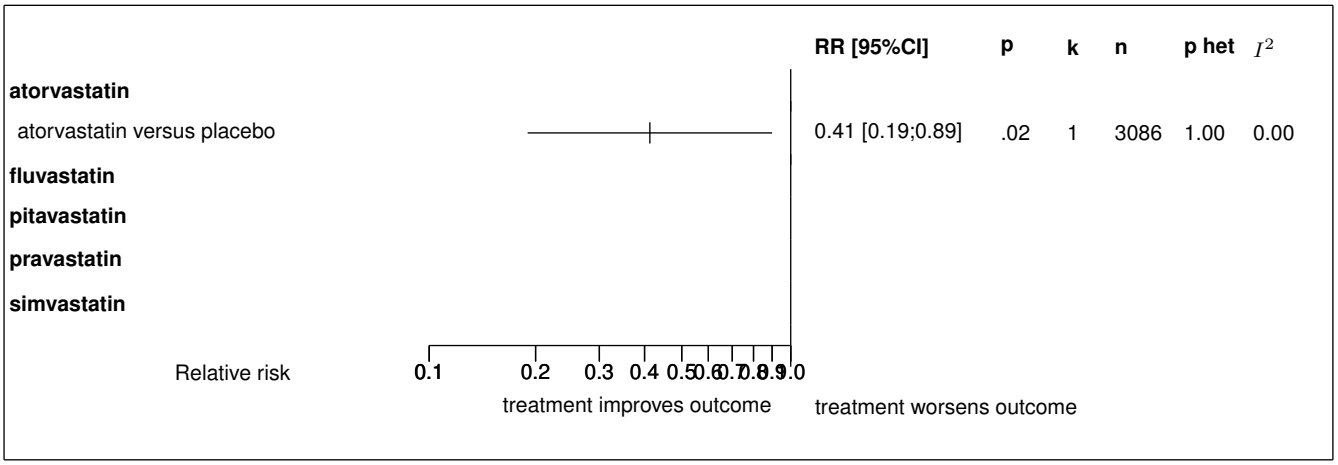
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.13: *Forest's plot for all cause death*



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

Figure 7.14: *Forest's plot for non fatal stroke*



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

8 Detailed results for atorvastatin

8.1 Available trials

A total of 4 RCTs which randomized 7399 patients were identified: it compared atorvastatin with placebo , 2 trials compared atorvastatin with usual care and it compared atorvastatin with pravastatin.
The average study size was 1849 patients (range 70 to 4162). The first study was published in 2001, and the last study was published in 2004.
A total of 2 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 4 trials; 3 trials reported data on cardiovascular events at 4 months; 3 trials reported data on cardiovascular events; 3 trials reported data on non fatal MI; 3 trials reported data on fatal MI; 3 trials reported data on cardiac death; 3 trials reported data on revascularization; 3 trials reported data on stroke (fatal and non fatal); 2 trials reported data on cardiovascular events at 1 month; 1 trials reported data on recurrent angina; 1 trials reported data on PTCA; 1 trials reported data on non fatal stroke; 1 trials reported data on CABG; and 1 trials reported data on deaths or MI.
Following tables 8.1 (page 56), 8.2 (page 57), 8.4 (page 59), and 8.3 (page 57) summarized the main characteristics of the trials including in this systematic review of randomized trials of atorvastatin.

Table 8.1: *Treatment description - statins - atorvastatin*

Trial	Studied treatment	Control treatment
Atorvastatin versus placebo		
MIRACL (2001) [1]	Atorvastatin, 80 mg (early initiation)	Placebo
	Concomittant treatment: instruction and counseling to promote compliance with a National CholesterolEducation Program Step I diet	
Atorvastatin versus usual care		
Colivicchi (2002) [2]	Atorvastatin, 80 mg daily early initiation	Usual care
ESTABLISH (2004) [3]	Atorvastatin, 20 mg early initiation	Usual care
Atorvastatin versus pravastatin		
PROVE IT - TIMI 22 (2004) [4, 5, 6, 7, 8]	80 mg of atorvastatin daily (intensive therapy).	40 mg of pravastatin daily (standard therapy)

Table 8.2: *Descriptions of participants - statins - atorvastatin*

Trial	Patients	
Atorvastatin versus placebo		
MIRACL (2001) [1]	Unstable angina or nonQ-wave acute MI	
	Inclusion criteria: aged 18 years or older with chest pain or discomfort of at least 15minutes' duration that occurred at rest or with minimal exertion within the 24-hour periodpreceding hospitalization and represented a change from their usual anginal pattern. Inaddition, diagnosis of unstable angina required evidence of myocardial ischemia by at least 1of the following 13: new or dynamic ST-wave or T-wave changes in at least 2 contiguousstandard electrocardiographic leads, a new wall motion abnormality by echocardiography, anew and reversible myocardial perfusion defect by radionuclide scintigraphy, or elevation ofcardiac troponin to a level not exceeding 2 times the upper limit of normal (ULN). Diagnosis ofnonQ-wave acute MI required elevation of serum creatine kinase or its MB fraction, ortroponin to a level exceeding 2 times the ULN.	**Exclusion criteria:** patients were excluded if the serum total cholesterol level at screening exceeded 270mg/dL (7 mmol/L) (sites in Poland and South Africa used levels of 310 mg/dL [8 mmol/L]).There was no lower limit on cholesterol level at entry. Patients were excluded if coronaryrevascularization was planned or anticipated at the time of screening. Other exclusion criteriawere: evidence of Q-wave acute MI within the preceding 4 weeks; coronary artery bypasssurgery within the preceding 3 months; percutaneous coronary intervention within thepreceding 6 months; left bundle-branch block or paced ventricular rhythm; severe congestiveheart failure (New York Heart Association class IIIb or IV); concurrent treatment with otherlipid-regulating agents (except niacin at doses of 500 mg/d), vitamin E (except at doses <=400 IU/d), or drugs associated with rhabdomyolysis in combination with statins; severeanemia; renal failure requiring dialysis; hepatic dysfunction (alanine aminotransferase greaterthan 2 times ULN); insulin-dependent diabetes; pregnancy or lactation
Atorvastatin versus usual care		
Colivicchi (2002) [2]	Unstable angina pectoris or non-Q-wave myocardial infarction	
ESTABLISH (2004) [3]	Patients with ACS undergoing emergency coronary angiography and percutaneous coronary intervention	
Atorvastatin versus pravastatin		
PROVE IT - TIMI 22 (2004) [4, 5, 6, 7, 8]	Patients who had been hospitalized for an acute coronary syndromewithin the preceding 10 days	

Table 8.3: *Design and methodological quality of trials - statins - atorvastatin*

Trial	Design	Duration	Centre	Primary endpoint
Atorvastatin versus placebo				
MIRACL, 2001 [1] n=3086	Parallel groups Double blind confirmatory trial at low risk of bias	1 and 4 months	Europe, North America, South Africa, and Australasia 122 centres	death, MI, recurrent ischemia requiring hospitalization

continued...

Trial	Design	Duration	Centre	Primary endpoint
Atorvastatin versus usual care				
Colivicchi, 2002 [2] n=81	Parallel groups open exploratory trial	1, 3, and 6 months inclusion period: jan 1999 - jul 2001	Italy 1 centres	cardiac death, MI, objective recurrent ischemia
ESTABLISH, 2004 [3] n=70	Parallel groups open exploratory trial	1, 4, and 6 months inclusion period: Nov 2001 - aug 2003	Japan single center	none defined
Atorvastatin versus pravastatin				
PROVE IT - TIMI 22, 2004 [4, 5, 6, 7, 8] n=4162	Parallel groups double blind	24 mo (18-36 mo) inclusion period: nov 2000 - dec 2001	UK, US, AUstralia, Italy, France, Germany, Spain, Canada 349 centres	death, MI, unstable angina, revascularization, stroke

Table 8.4: *Trial characteristics - statins - atorvastatin*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Atorvastatin versus placebo		
MIRACL, 2001 [1]	-52	
Atorvastatin versus usual care		
Colivicchi, 2002 [2]		
ESTABLISH, 2004 [3]		
Atorvastatin versus pravastatin		
PROVE IT - TIMI 22, 2004 [4, 5, 6, 7, 8]	-33	-0.86

8.2 Meta-analysis results

The results are detailed in table 8.5 (page 62). This table is followed by the Forest's plot corresponding to each endpoint.

Atorvastatin versus placebo

The single study eligible for this comparison provided data on **deaths or MI**. There was no statistically significant difference in deaths or MI between atorvastatin and placebo, with a RR of 0.92 (95%CI 0.75 to 1.13, p=0.4471) in favour of atorvastatin. In other words, deaths or MI was slightly lower in the atorvastatin group , but this was not statistically significant.
The single study eligible for this comparison provided data on **cardiovascular events at 1 month**. No statistically significant difference between the groups was found in cardiovascular events at 1 month, with a RR of 1.06 (95% CI 0.81 to 1.39, p=0.6781).
The single study eligible for this comparison provided data on **cardiovascular events at 4 months**. No statistically significant difference between the groups was found in cardiovascular events at 4 months, with a RR of 0.89 (95% CI 0.73 to 1.09, p=0.2564).
The single study eligible for this comparison provided data on **PTCA**. No statistically significant difference between the groups was found in PTCA, with a RR of 1.06 (95% CI 0.85 to 1.31, p=0.6255).
The single study eligible for this comparison provided data on **recurrent angina**. The analysis detected a statistically significant difference in favor of atorvastatin in recurrent angina, with a RR of 0.74 (95% CI 0.57 to 0.95, p=0.0182).
The single study eligible for this comparison provided data on **cardiovascular events**. No statistically significant difference between the groups was found in cardiovascular events, with a RR of 0.92 (95% CI 0.75 to 1.13, p=0.4471).
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 0.50 (95% CI 0.25 to 1.00, p=0.0509).
The single study eligible for this comparison provided data on **cardiac death**. No statistically significant difference between the groups was found in cardiac death, with a RR of 0.86 (95% CI 0.59 to 1.23, p=0.4041).
The single study eligible for this comparison provided data on **CABG**. No statistically significant difference between the groups was found in CABG, with a RR of 0.97 (95% CI 0.75 to 1.25, p=0.8159).
The single study eligible for this comparison provided data on **fatal MI**. No statistically significant difference between the groups was found in fatal MI, with a RR of 0.95 (95% CI 0.49 to 1.84, p=0.8802).
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 0.90 (95% CI 0.69 to 1.17, p=0.4233).
The single study eligible for this comparison provided data on **revascularization**. No statistically significant difference between the groups was found in revascularization, with a RR of 1.02 (95% CI 0.87 to 1.20, p=0.7838).
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 0.95 (95% CI 0.68 to 1.32, p=0.7507).
The single study eligible for this comparison provided data on **non fatal stroke**. The analysis detected a statistically significant difference in favor of atorvastatin in non fatal stroke, with a RR of 0.41 (95% CI 0.19 to 0.89, p=0.0243).

Atorvastatin versus usual care

Only one of the 2 studies eligible for this comparison provided data on **cardiovascular events at 1 month**. No statistically significant difference between the groups was found in cardiovascular events at 1 month, with a RR of 0.17 (95% CI 0.01 to 3.30, p=0.2423).
All the 2 studies had extractable data about the number of participants with **cardiovascular events at 4 months**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events at 4 months, with a RR of 0.56 (95% CI 0.22 to 1.47, p=0.2419). No heterogeneity was detected (p = 0.9421, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 0.56 (95% CI 0.22 to 1.47, p=0.2419). No heterogeneity was detected (p = 0.9421, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.61 (95% CI 0.08 to 4.62, p=0.6351). No heterogeneity was detected (p = 0.7735, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiac death**. When pooled together, there was no statistically significant difference between the groups in cardiac death, with a RR of 0.73 (95% CI 0.15 to 3.55, p=0.6945). No heterogeneity was detected (p = 0.8610, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **fatal MI**. When pooled together, there was no statistically significant difference between the groups in fatal MI, with a RR of 0.73 (95% CI 0.15 to 3.55, p=0.6945). No heterogeneity was detected (p = 0.8610, I^2 = 0.00%).
All the 2 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 0.48 (95% CI 0.14 to 1.61, p=0.2317). No heterogeneity was detected (p = 0.6939, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **revascularization**. When pooled together, there was no statistically significant difference between the groups in revascularization, with a RR of 1.00 (95% CI 0.43 to 2.32, p=0.9979). No heterogeneity was detected (p = 0.9903, I^2 = 0.00%).
All the 2 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 0.72 (95% CI 0.19 to 2.69, p=0.6245). No heterogeneity was detected (p = 0.8176, I^2 = 0.00%).

Atorvastatin versus pravastatin

The single study eligible for this comparison provided data on **cardiovascular events**. The analysis detected a statistically significant difference in favor of atorvastatin in cardiovascular events, with a RR of 0.76 (95% CI 0.66 to 0.88, p=0.0000).
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 0.72 (95% CI 0.50 to 1.03, p=0.0748).

Table 8.5: *Results details - statins - atorvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
atorvastatin versus placebo						
deaths or MI	RR=0.92	[0.75;1.13]	0.4471	1.0000 (I^2=0.00)	1	3086
cardiovascular events at 1 month	RR=1.06	[0.81;1.39]	0.6781	1.0000 (I^2=0.00)	1	3086
cardiovascular events at 4 months	RR=0.89	[0.73;1.09]	0.2564	1.0000 (I^2=0.00)	1	3086
PTCA	RR=1.06	[0.85;1.31]	0.6255	1.0000 (I^2=0.00)	1	3086
recurrent angina	RR=0.74	[0.57;0.95]	0.0182	1.0000 (I^2=0.00)	1	3086
cardiovascular events	RR=0.92	[0.75;1.13]	0.4471	1.0000 (I^2=0.00)	1	3086
stroke (fatal and non fatal)	RR=0.50	[0.25;1.00]	0.0509	1.0000 (I^2=0.00)	1	3086
cardiac death	RR=0.86	[0.59;1.23]	0.4041	1.0000 (I^2=0.00)	1	3086
CABG	RR=0.97	[0.75;1.25]	0.8159	1.0000 (I^2=0.00)	1	3086
fatal MI	RR=0.95	[0.49;1.84]	0.8802	1.0000 (I^2=0.00)	1	3086
non fatal MI	RR=0.90	[0.69;1.17]	0.4233	1.0000 (I^2=0.00)	1	3086
revascularization	RR=1.02	[0.87;1.20]	0.7838	1.0000 (I^2=0.00)	1	3086
all cause death	RR=0.95	[0.68;1.32]	0.7507	1.0000 (I^2=0.00)	1	3086
non fatal stroke	RR=0.41	[0.19;0.89]	0.0243	1.0000 (I^2=0.00)	1	3086
atorvastatin versus usual care						
cardiovascular events at 1 month	RR=0.17	[0.01;3.30]	0.2423	1.0000 (I^2=0.00)	1	81
cardiovascular events at 4 months	RR=0.56	[0.22;1.47]	0.2419	0.9421 (I^2=0.00)	2	151
cardiovascular events	RR=0.56	[0.22;1.47]	0.2419	0.9421 (I^2=0.00)	2	151
stroke (fatal and non fatal)	RR=0.61	[0.08;4.62]	0.6351	0.7735 (I^2=0.00)	2	151
cardiac death	RR=0.73	[0.15;3.55]	0.6945	0.8610 (I^2=0.00)	2	151
fatal MI	RR=0.73	[0.15;3.55]	0.6945	0.8610 (I^2=0.00)	2	151
non fatal MI	RR=0.48	[0.14;1.61]	0.2317	0.6939 (I^2=0.00)	2	151
revascularization	RR=1.00	[0.43;2.32]	0.9979	0.9903 (I^2=0.00)	2	151
all cause death	RR=0.72	[0.19;2.69]	0.6245	0.8176 (I^2=0.00)	2	151
atorvastatin versus pravastatin						
cardiovascular events	RR=0.76	[0.66;0.88]	0.0000	1.0000 (I^2=0.00)	1	4152
all cause death	RR=0.72	[0.50;1.03]	0.0748	1.0000 (I^2=0.00)	1	4152

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 deaths or MI*

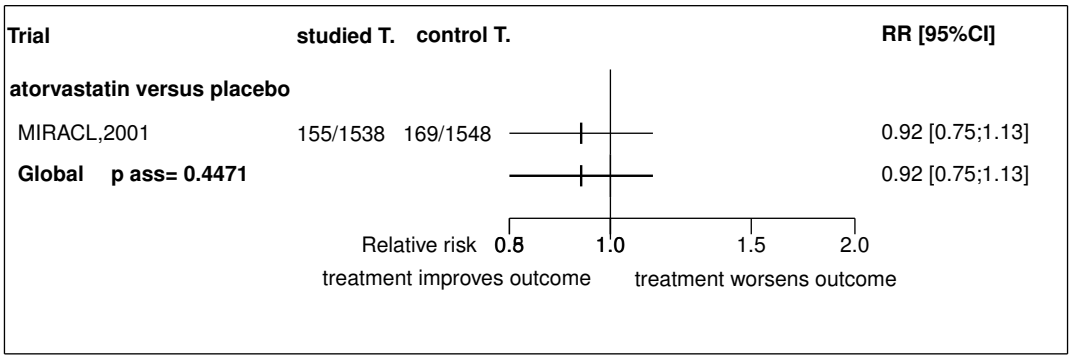


Figure 8.2: *Forest's plot for cardiovascular events at 1 month*

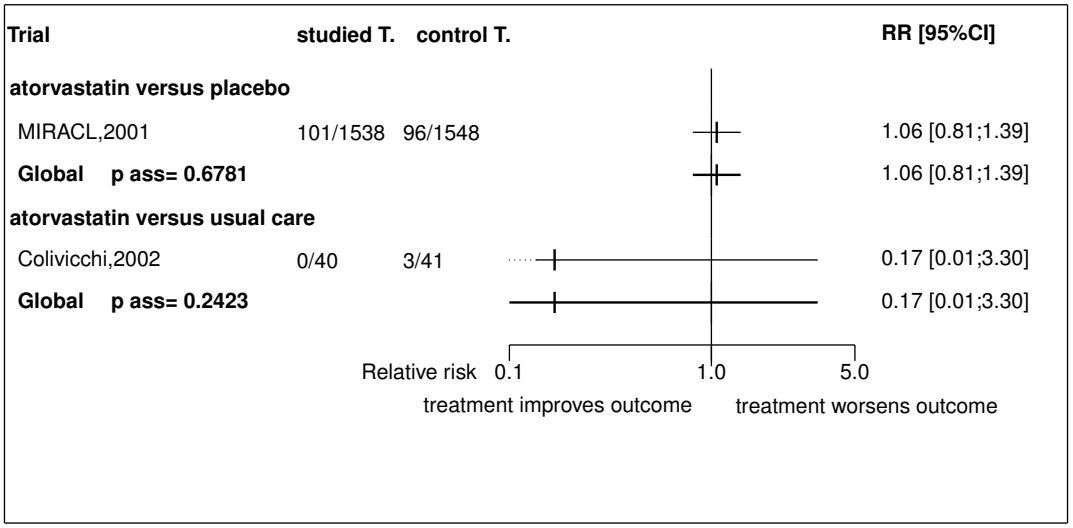


Figure 8.3: *Forest's plot for cardiovascular events at 4 months*

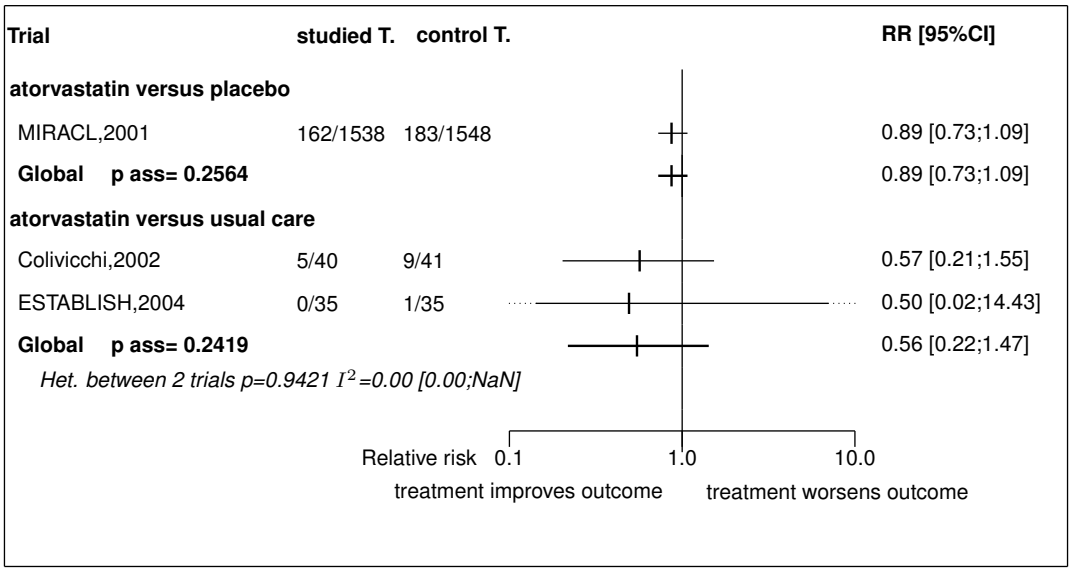


Figure 8.4: *Forest's plot for PTCA*

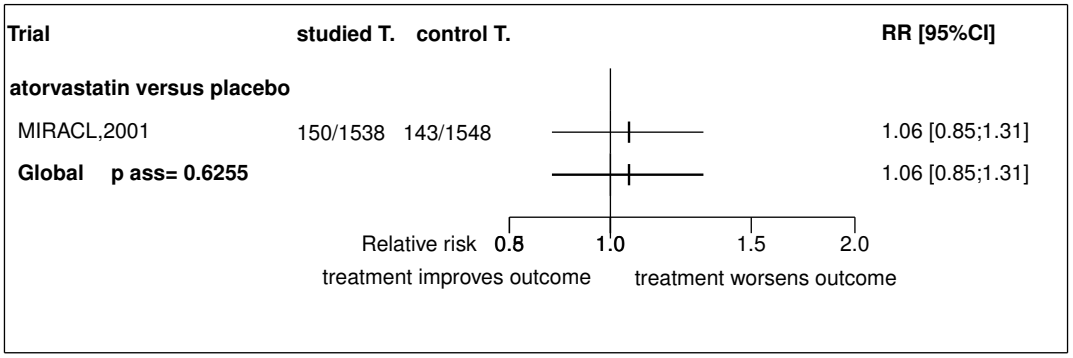


Figure 8.5: *Forest's plot for recurrent angina*

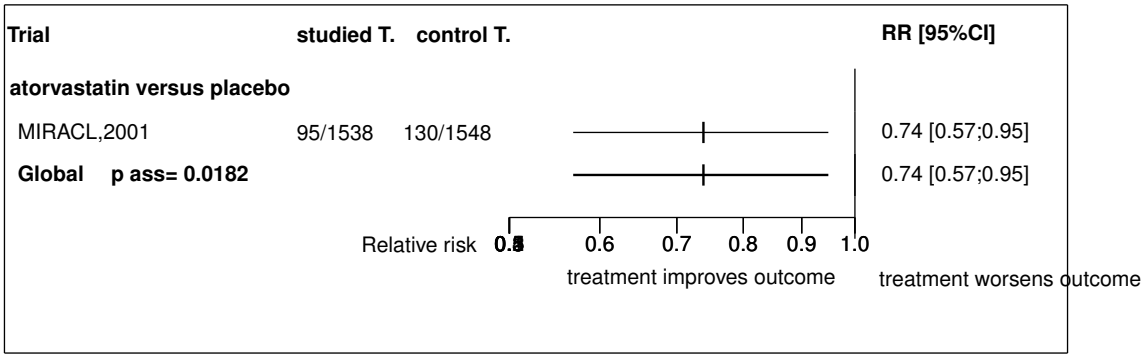


Figure 8.6: *Forest's plot for cardiovascular events*

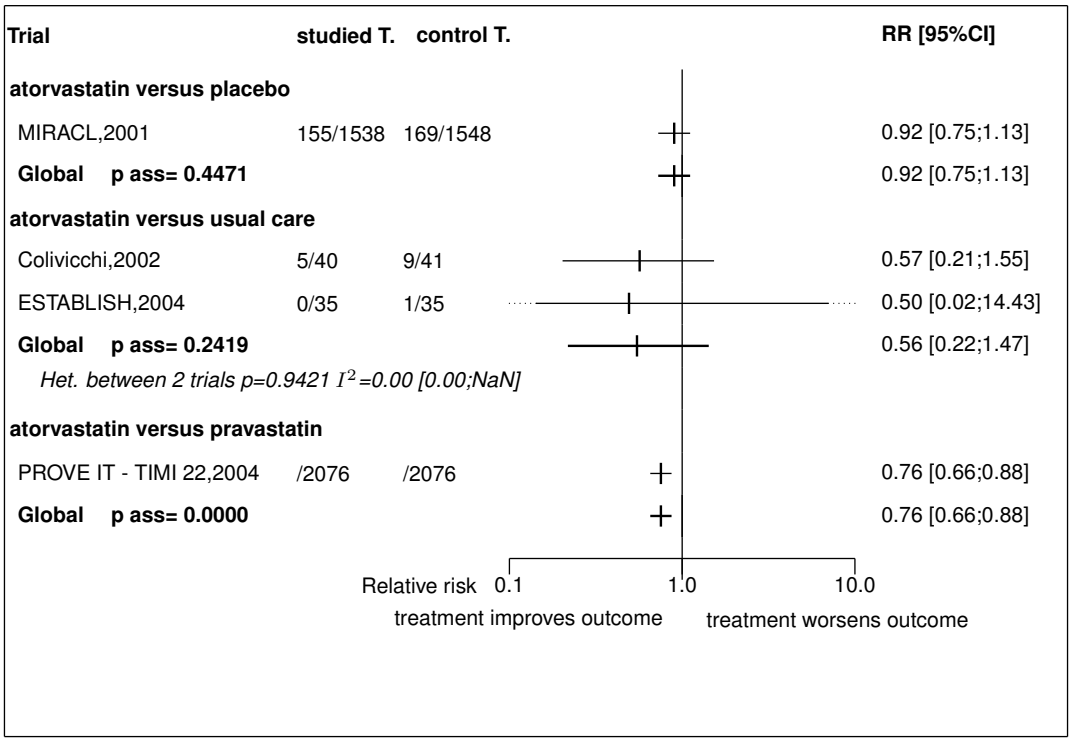


Figure 8.7: *Forest's plot for stroke (fatal and non fatal)*

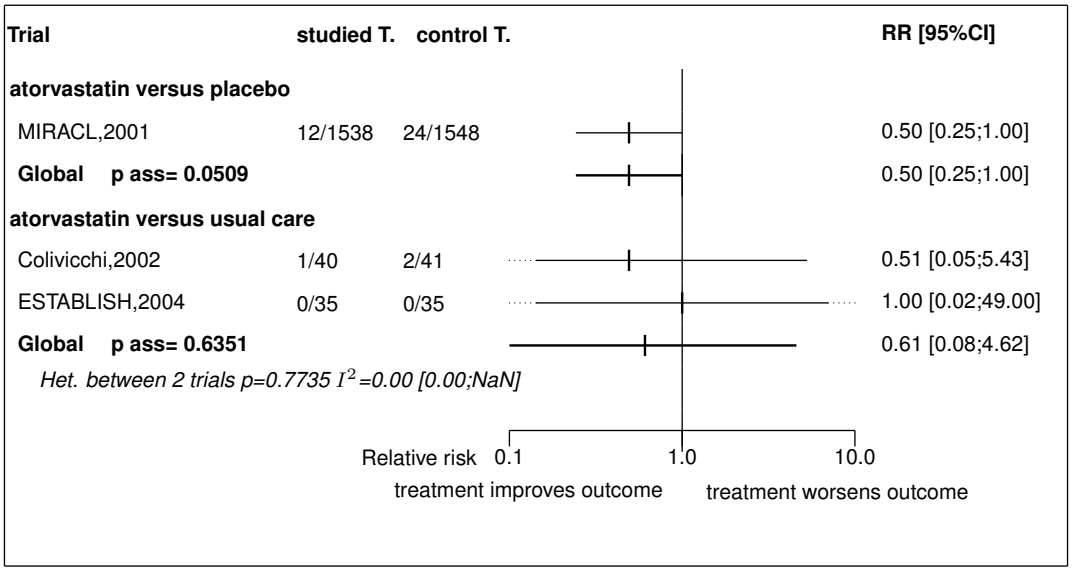


Figure 8.8: *Forest's plot for cardiac death*

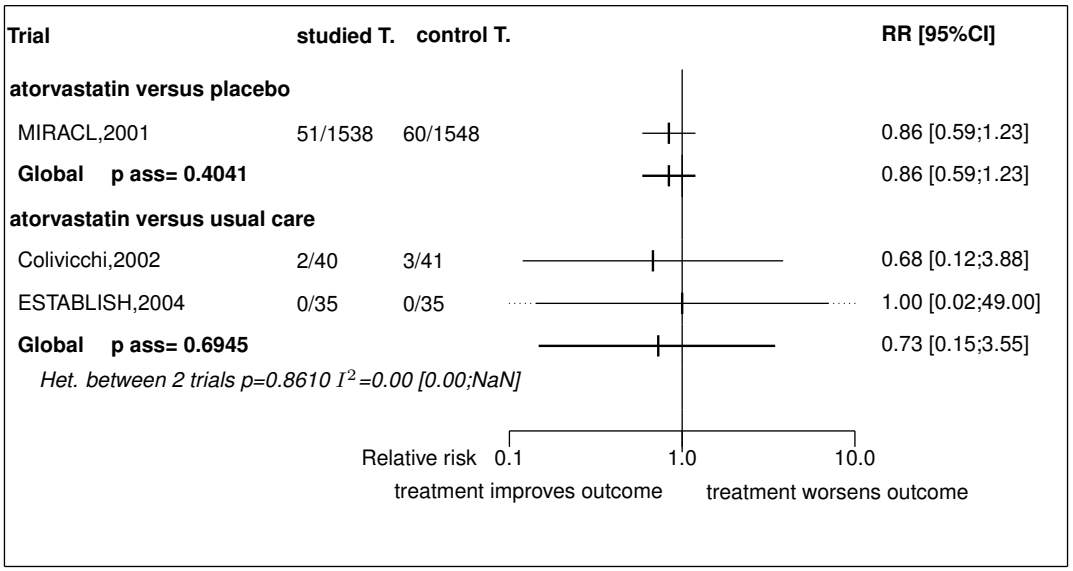


Figure 8.9: *Forest's plot for CABG*

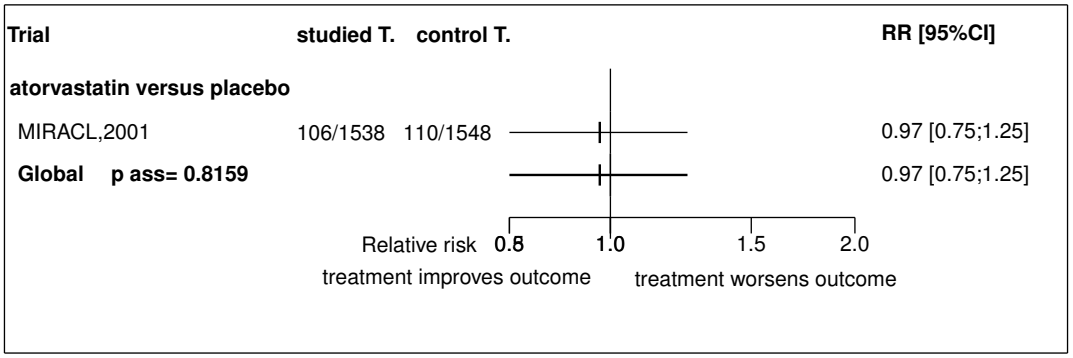


Figure 8.10: *Forest's plot for fatal MI*

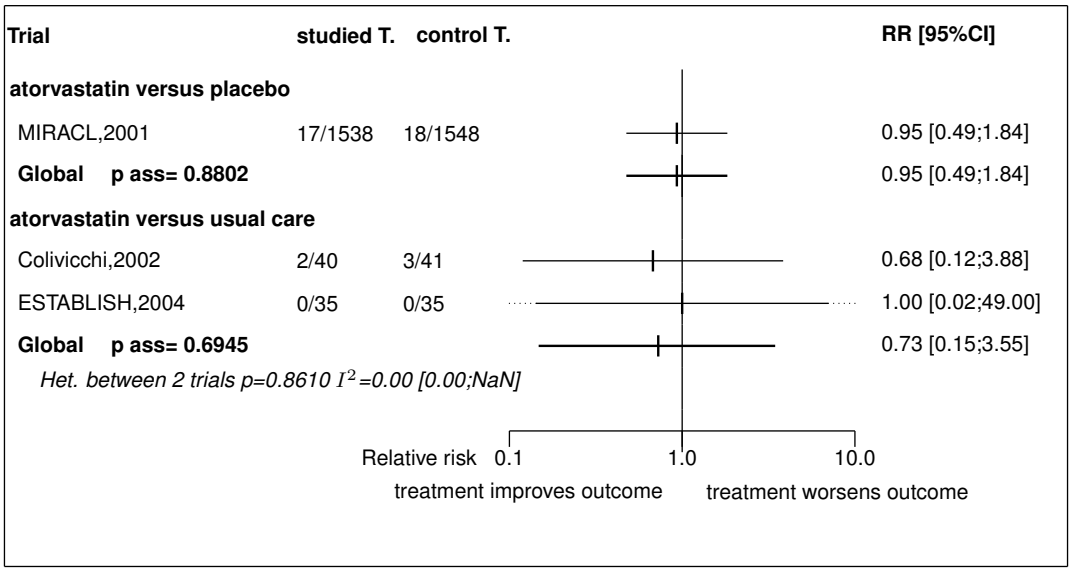


Figure 8.11: *Forest's plot for non fatal MI*

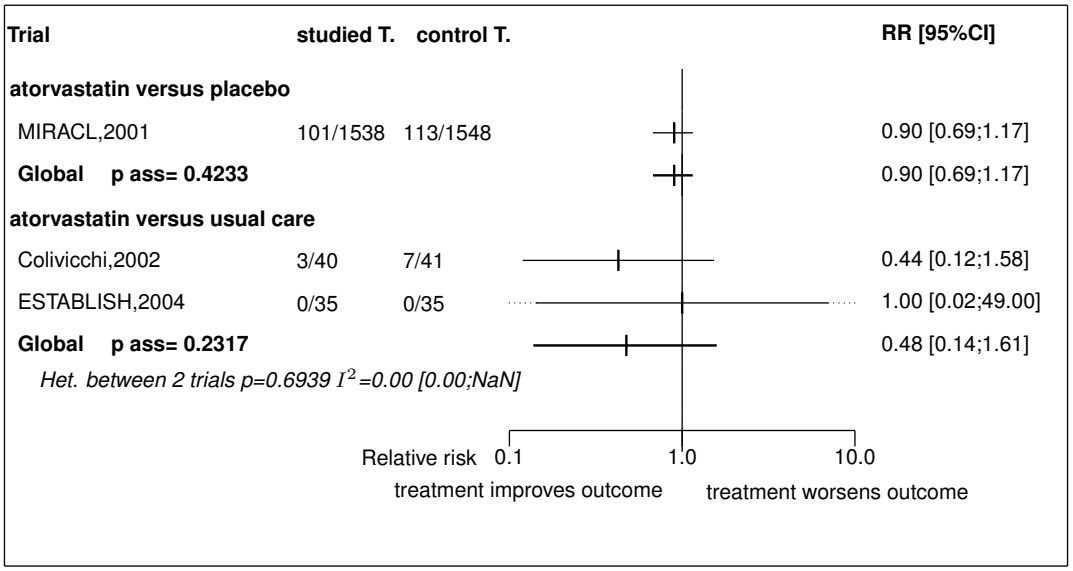


Figure 8.12: *Forest's plot for revascularization*

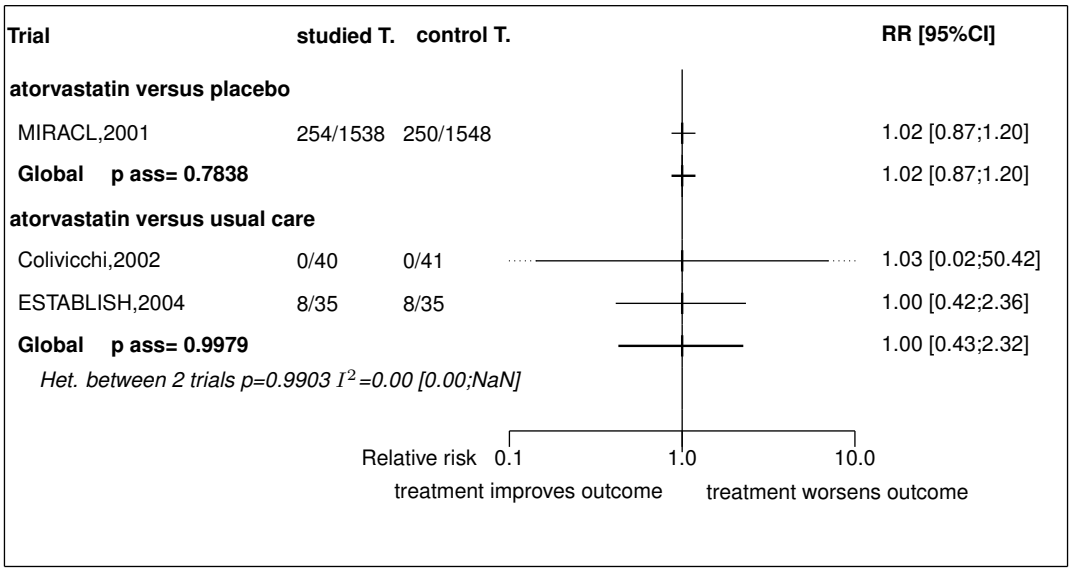


Figure 8.13: *Forest's plot for all cause death*

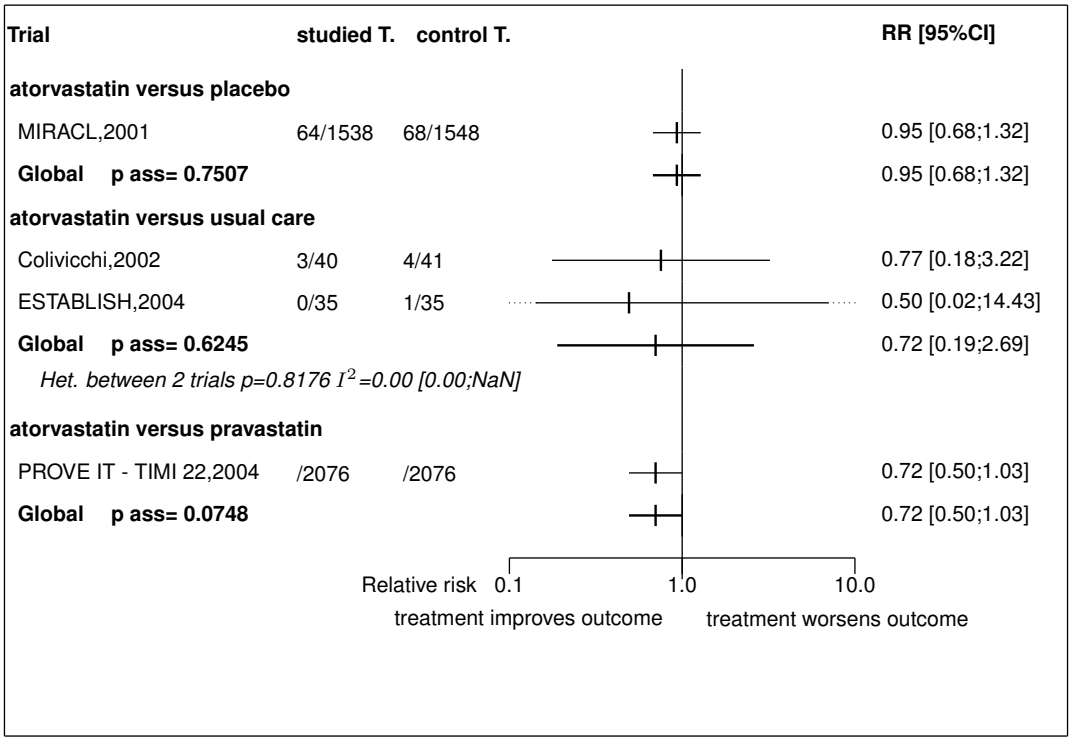
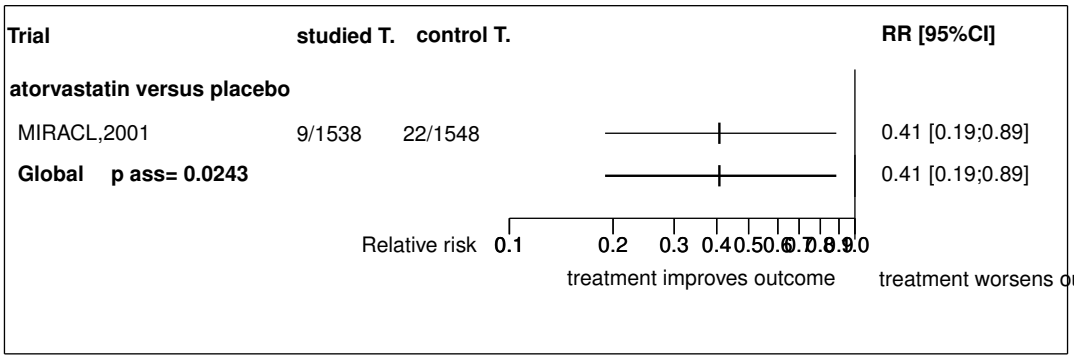


Figure 8.14: *Forest's plot for non fatal stroke*



References

[1] Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001 Apr 4;285:1711-8. [PMID=11277825]

[2] Colivicchi F, Guido V, Tubaro M, Ammirati F, Montefoschi N, Varveri A, Santini M. Effects of atorvastatin 80 mg daily early after onset of unstable angina pectoris or non-Q-wave myocardial infarction. Am J Cardiol 2002;90:872-4. [PMID=12372577]

[3] Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, Daida H. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004;110:1061-8. [PMID=15326073]

[4] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004 Apr 8;350:1495-504. [PMID=15007110]

[5] Rouleau J. Improved outcome after acute coronary syndromes with an intensive versus standard lipid-lowering regimen: results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. Am J Med 2005 Dec;118 Suppl 12A:28-35. [PMID=16356805]

[6] Murphy SA, Cannon CP, Wiviott SD, de Lemos JA, Blazing MA, McCabe CH, Califf RM, Braunwald E. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). Am J Cardiol 2007 Oct 1;100:1047-51. [PMID=17884359]

[7] Ray KK, Cannon CP, McCabe CH, Cairns R, Tonkin AM, Sacks FM, Jackson G, Braunwald E. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2005 Oct 18;46:1405-10. [PMID=16226162]

[8] Giraldez RR, Giugliano RP, Mohanavelu S, Murphy SA, McCabe CH, Cannon CP, Braunwald E. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a

PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis. J Am Coll Cardiol 2008 Sep 9;52:914-20. [PMID=18772061]

8.3 Individual trial summaries

Table 8.6: *MIRACL, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3086 (1538 vs. 1548) **Follow-up duration:** 1 and 4 months **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Europe, North America, South Africa, and Australasia, 122 centres	Unstable angina or nonQ-wave acute MI **Inclusion criteria:** aged 18 years or older with chest pain or discomfort of at least 15minutes' duration that occurred at rest or with minimal exertion within the 24-hour periodpreceding hospitalization and represented a change from their usual anginal pattern. Inaddition, diagnosis of unstable angina required evidence of myocardial ischemia by at least 1of the following 13: new or dynamic ST-wave or T-wave changes in at least 2 contiguousstandard electrocardiographic leads, a new wall motion abnormality by echocardiography, anew and reversible myocardial perfusion defect by radionuclide scintigraphy, or elevatio **Exclusion criteria:** Patients were excluded if the serum total cholesterol level at screening exceeded 270mg/dL (7 mmol/L) (sites in Poland and South Africa used levels of 310 mg/dL [8 mmol/L]).There was no lower limit on cholesterol level at entry. Patients were excluded if coronaryrevascularization was planned or anticipated at the time of screening. Other exclusion criteriawere: evidence of Q-wave acute MI within the preceding 4 weeks; coronary artery bypasssurgery within the preceding 3 months; percutaneous coronary intervention within thepreceding 6 months; left bundle-branch block or paced ventricular rhythm	**Studied treatment:** Atorvastatin, 80 mg (early initiation) **Control treatment:** Placebo **Concomittant treat.:**instruction and counseling to promote compliance with a National CholesterolEducation Program Step I diet	Deaths or MI RR=0.92 [0.75;1.13] Cardiovascular events at 1 month RR=1.06 [0.81;1.39] Cardiovascular events at 4 months RR=0.89 [0.73;1.09] PTCA RR=1.06 [0.85;1.31] Recurrent angina RR=0.74 [0.57;0.95] Cardiovascular events RR=0.92 [0.75;1.13] (death and non fatal MI) Stroke (fatal and non fatal) RR=0.50 [0.25;1.00]

Reference

Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001 Apr 4;285:1711-8 [PMID=11277825]

Table 8.7: *Colivicchi, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=81 (40 vs. 41) **Follow-up duration:** 1, 3, and 6 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Italy, 1 centres **Inclusion period:** jan 1999 - jul 2001	Unstable angina pectoris or non-Q-wave myocardial infarction	**Studied treatment:** Atorvastatin, 80 mg daily early initiation **Control treatment:** Usual care	Cardiovascular events at 4 months RR=0.57 [0.21;1.55] Cardiovascular events RR=0.57 [0.21;1.55] (at 4 months) Stroke (fatal and non fatal) RR=0.51 [0.05;5.43]

Reference

Colivicchi F, Guido V, Tubaro M, Ammirati F, Montefoschi N, Varveri A, Santini M. Effects of atorvastatin 80 mg daily early after onset of unstable angina pectoris or non-Q-wave myocardial infarction. Am J Cardiol 2002;90:872-4 [PMID=12372577]

Table 8.8: *ESTABLISH, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=70 (35 vs. 35) **Follow-up duration:** 1, 4, and 6 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Japan, single center **Inclusion period:** Nov 2001 - aug 2003	Patients with ACS undergoing emergency coronary angiography and percutaneous coronary intervention	**Studied treatment:** Atorvastatin, 20 mg early initiation **Control treatment:** Usual care	

Reference

Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, Daida H. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004;110:1061-8 [PMID=15326073]

Table 8.9: *PROVE IT - TIMI 22, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4162 (2099 vs. 2063) **Follow-up duration:** 24 mo (18-36 mo) **Study design:** Randomized controlled trial Parallel groups Double blind UK, US, AUstralia, Italy, France, Germany, Spain, Canada, 349 centres **Inclusion period:** nov 2000 - dec 2001	Patients who had been hospitalized for an acute coronary syndromewithin the preceding 10 days	**Studied treatment:** 80 mg of atorvastatin daily (intensive therapy). **Control treatment:** 40 mg of pravastatin daily (standard therapy)	

References

Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004 Apr 8;350:1495-504 [PMID=15007110]
Rouleau J. Improved outcome after acute coronary syndromes with an intensive versus standard lipid-lowering regimen: results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. Am J Med 2005 Dec;118 Suppl 12A:28-35 [PMID=16356805]
Murphy SA, Cannon CP, Wiviott SD, de Lemos JA, Blazing MA, McCabe CH, Califf RM, Braunwald E. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). Am J Cardiol 2007 Oct 1;100:1047-51 [PMID=17884359]
Ray KK, Cannon CP, McCabe CH, Cairns R, Tonkin AM, Sacks FM, Jackson G, Braunwald E. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2005 Oct 18;46:1405-10 [PMID=16226162]
Giraldez RR, Giugliano RP, Mohanavelu S, Murphy SA, McCabe CH, Cannon CP, Braunwald E. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis. J Am Coll Cardiol 2008 Sep 9;52:914-20 [PMID=18772061]

9 Detailed results for fluvastatin

9.1 Available trials

A total of 2 RCTs which randomized 1364 patients were identified: all compared fluvastatin with placebo.
The average study size was 682 patients (range 540 to 824). The first study was published in 2002, and the last study was published in 2002.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Fatal MI data was reported in 2 trials; 2 trials reported data on cardiovascular events at 1 month; 2 trials reported data on cardiac death; 2 trials reported data on stroke (fatal and non fatal); 2 trials reported data on all cause death; 2 trials reported data on cardiovascular events at 4 months; 2 trials reported data on cardiovascular events; 2 trials reported data on revascularization; 2 trials reported data on non fatal MI; 1 trials reported data on recurrent angina; and 1 trials reported data on CABG.
Following tables 9.1 (page 76), 9.2 (page 76), 9.4 (page 78), and 9.3 (page 77) summarized the main characteristics of the trials including in this systematic review of randomized trials of fluvastatin.

Table 9.1: *Treatment description - statins - fluvastatin*

Trial	Studied treatment	Control treatment
Fluvastatin versus placebo		
LIPS (sub groups) (2002) [1]	Fluvastatin, 80 mg	Placebo
FLORIDA (2002) [2]	Fluvastatin, 80 mg (early initiation)	Placebo

Table 9.2: *Descriptions of participants - statins - fluvastatin*

Trial	Patients
Fluvastatin versus placebo	
LIPS (sub groups) (2002) [1] [a]	Patients with unstable angina and successful first percutaneous coronary intervention
FLORIDA (2002) [2]	Patients with an AMI and total cholesterol of $<$6.5 mmol.l

a) initially this study included patients with unstable or stable coronary heart disease (844 vs 833)

Table 9.3: *Design and methodological quality of trials - statins - fluvastatin*

Trial	Design	Duration	Centre	Primary end-point
Fluvastatin versus placebo				
LIPS (sub groups), 2002 [1] [(a)] n=824	Parallel groups double blind exploratory trial	1, 4, and 6 months inclusion period: Apr 1996 - oct 1998	Europe, Canada, and Brazil 57 centres	MACE
FLORIDA, 2002 [2] n=540	Parallel groups double blind confirmatory trial at low risk of bias	1, 4, and 6 months inclusion period: Jul 1997 - May 1999	The Netherlands multicentre	

a) sub group of patients with unstable angina

Table 9.4: *Trial characteristics - statins - fluvastatin*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Fluvastatin versus placebo		
LIPS (sub groups), 2002 [1]		
FLORIDA, 2002 [2]		

9.2 Meta-analysis results

The results are detailed in table 9.5 (page 80). This table is followed by the Forest's plot corresponding to each endpoint.

Fluvastatin versus placebo

All the 2 studies had extractable data about the number of participants with **cardiovascular events at 1 month**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events at 1 month, with a RR of 1.31 (95% CI 0.45 to 3.87, p=0.6191). No heterogeneity was detected (p = 0.4291, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiovascular events at 4 months**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events at 4 months, with a RR of 1.43 (95% CI 0.61 to 3.36, p=0.4170). No heterogeneity was detected (p = 0.2526, I^2 = 0.24%).
Only one of the 2 studies eligible for this comparison provided data on **recurrent angina**. No statistically significant difference between the groups was found in recurrent angina, with a RR of 1.04 (95% CI 0.57 to 1.88, p=0.9031).
All the 2 studies had extractable data about the number of participants with **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 1.27 (95% CI 0.52 to 3.12, p=0.6040). No heterogeneity was detected (p = 0.1429, I^2 = 0.53%).
All the 2 studies had extractable data about the number of participants with **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.68 (95% CI 0.05 to 8.83, p=0.7682). No heterogeneity was detected (p = 0.8111, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiac death**. When pooled together, there was no statistically significant difference between the groups in cardiac death, with a RR of 0.56 (95% CI 0.19 to 1.68, p=0.3037). No heterogeneity was detected (p = 0.8439, I^2 = 0.00%).
Only one of the 2 studies eligible for this comparison provided data on **CABG**. No statistically significant difference between the groups was found in CABG, with a RR of 0.66 (95% CI 0.32 to 1.32, p=0.2387).
All the 2 studies had extractable data about the number of participants with **fatal MI**. When pooled together, there was no statistically significant difference between the groups in fatal MI, with a RR of 0.33 (95% CI 0.03 to 3.52, p=0.3565). No heterogeneity was detected (p = 0.4913, I^2 = 0.00%).
All the 2 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 1.48 (95% CI 0.74 to 2.96, p=0.2735). No heterogeneity was detected (p = 0.7528, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **revascularization**. When pooled together, there was no statistically significant difference between the groups in revascularization, with a RR of 0.89 (95% CI 0.71 to 1.11, p=0.2986). No heterogeneity was detected (p = 0.8769, I^2 = 0.00%).
All the 2 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 0.68 (95% CI 0.31 to 1.50, p=0.3386). No heterogeneity was detected (p = 0.9086, I^2 = 0.00%).

Table 9.5: *Results details - statins - fluvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fluvastatin versus placebo						
cardiovascular events at 1 month	RR=1.31	[0.45;3.87]	0.6191	0.4291 (I^2=0.00)	2	1364
cardiovascular events at 4 months	RR=1.43	[0.61;3.36]	0.4170	0.2526 (I^2=0.24)	2	1364
recurrent angina	RR=1.04	[0.57;1.88]	0.9031	1.0000 (I^2=0.00)	1	540
cardiovascular events	RR=1.27	[0.52;3.12]	0.6040	0.1429 (I^2=0.53)	2	1364
stroke (fatal and non fatal)	RR=0.68	[0.05;8.83]	0.7682	0.8111 (I^2=0.00)	2	1364
cardiac death	RR=0.56	[0.19;1.68]	0.3037	0.8439 (I^2=0.00)	2	1364
CABG	RR=0.66	[0.32;1.32]	0.2387	1.0000 (I^2=0.00)	1	540
fatal MI	RR=0.33	[0.03;3.52]	0.3565	0.4913 (I^2=0.00)	2	1364
non fatal MI	RR=1.48	[0.74;2.96]	0.2735	0.7528 (I^2=0.00)	2	1364
revascularization	RR=0.89	[0.71;1.11]	0.2986	0.8769 (I^2=0.00)	2	1364
all cause death	RR=0.68	[0.31;1.50]	0.3386	0.9086 (I^2=0.00)	2	1364

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 cardiovascular events at 1 month*

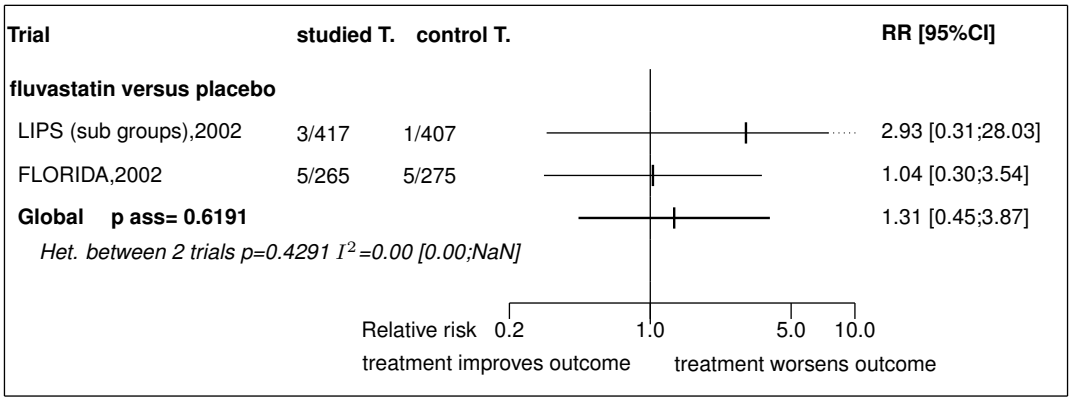


Figure 9.2: *Forest's plot for cardiovascular events at 4 months*

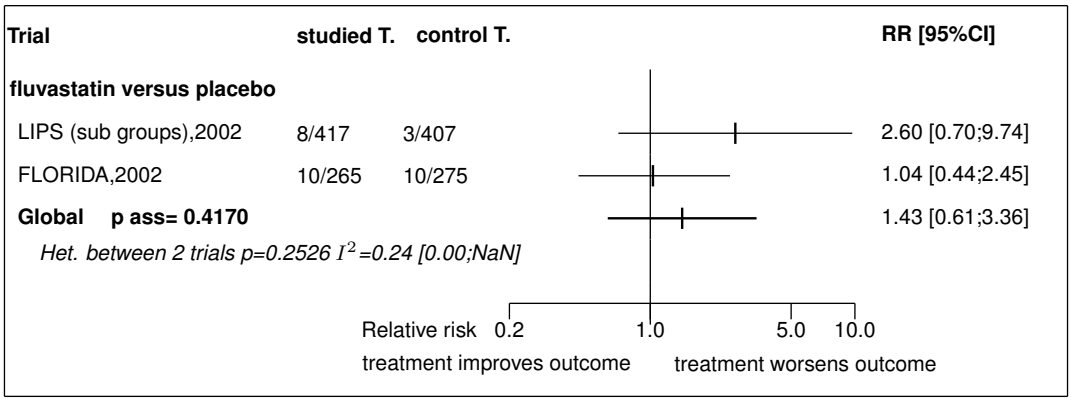


Figure 9.3: *Forest's plot for recurrent angina*

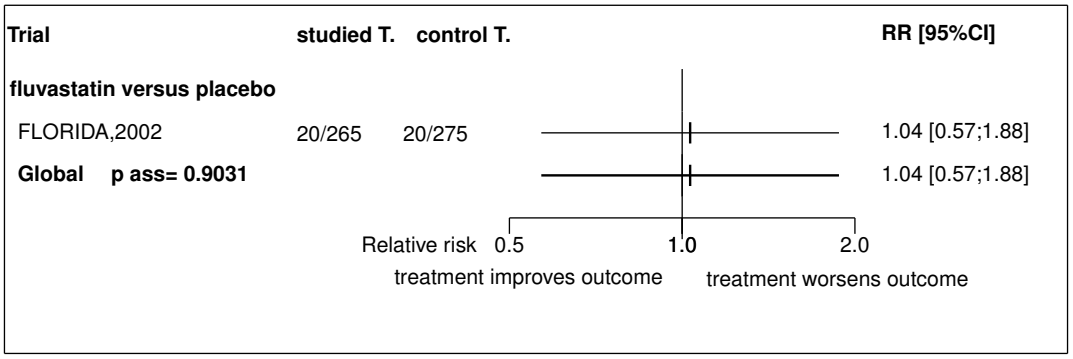


Figure 9.4: *Forest's plot for cardiovascular events*

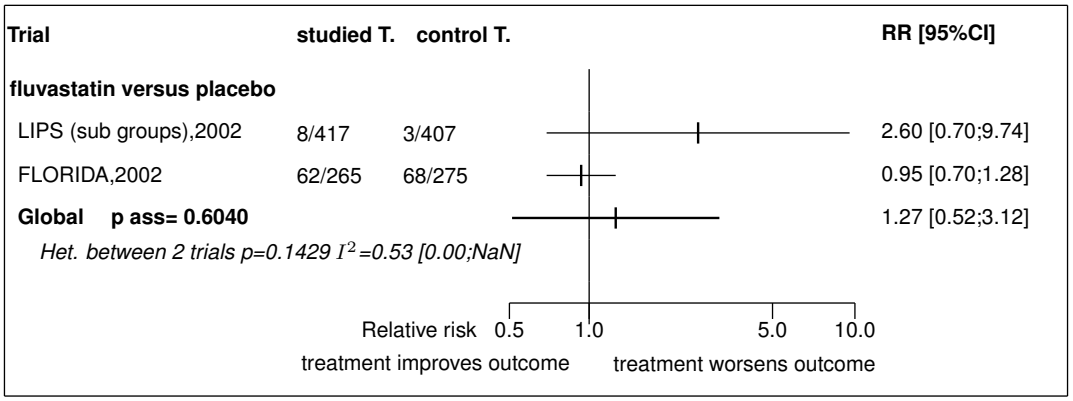


Figure 9.5: *Forest's plot for stroke (fatal and non fatal)*

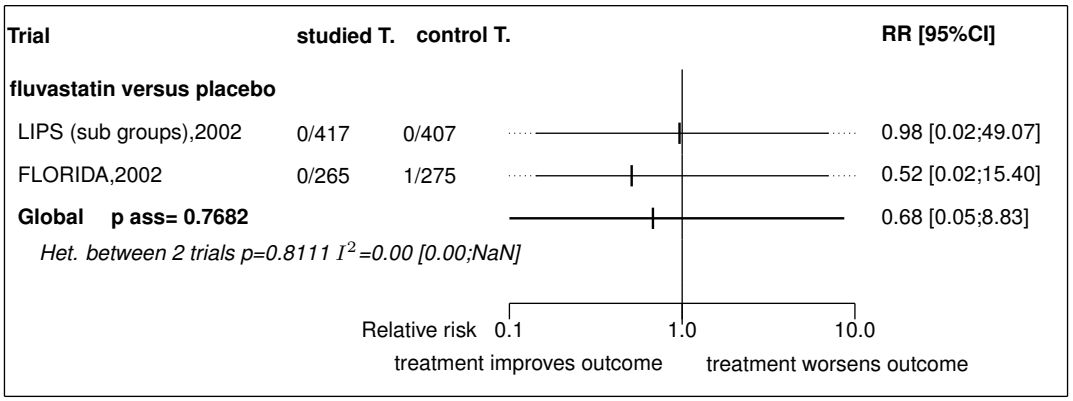


Figure 9.6: *Forest's plot for cardiac death*

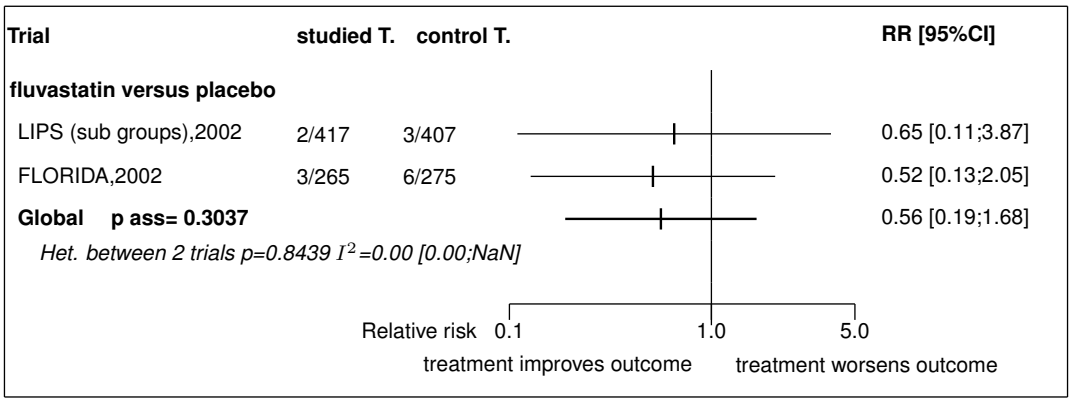


Figure 9.7: *Forest's plot for CABG*

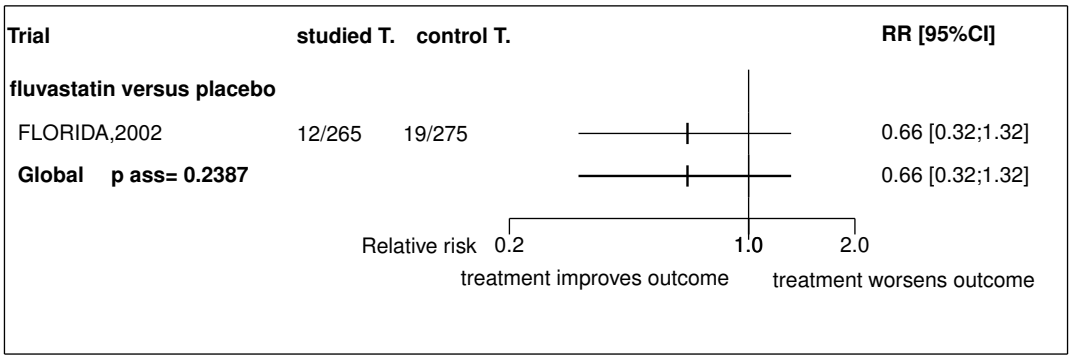


Figure 9.8: *Forest's plot for fatal MI*

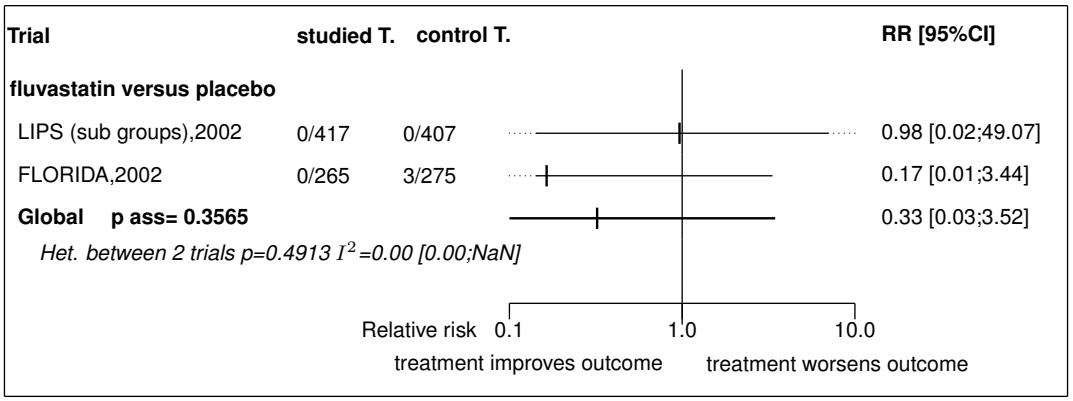


Figure 9.9: *Forest's plot for non fatal MI*

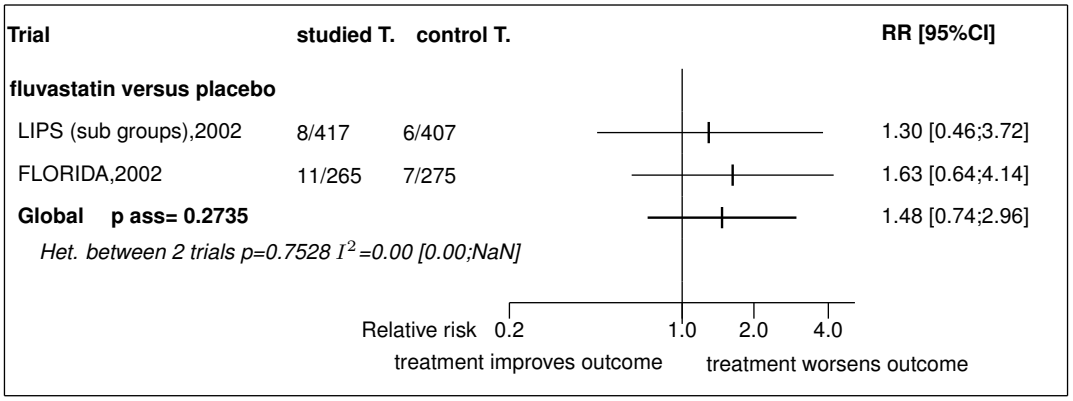


Figure 9.10: *Forest's plot for revascularization*

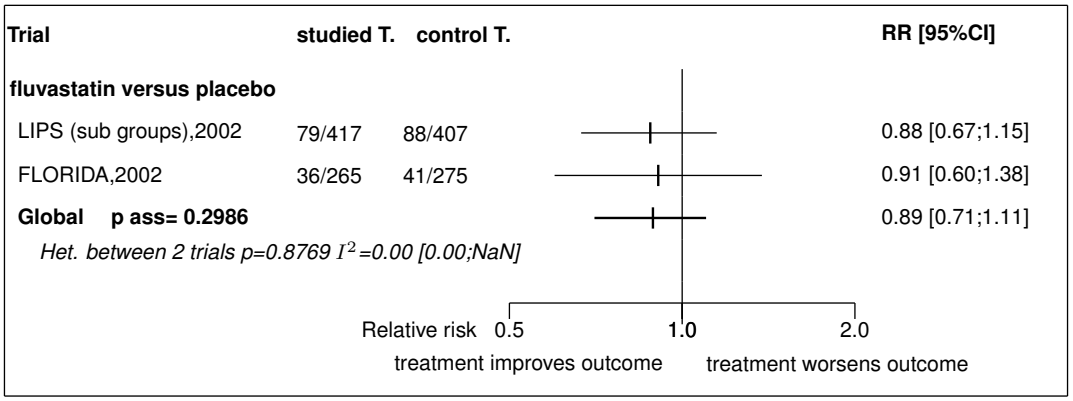
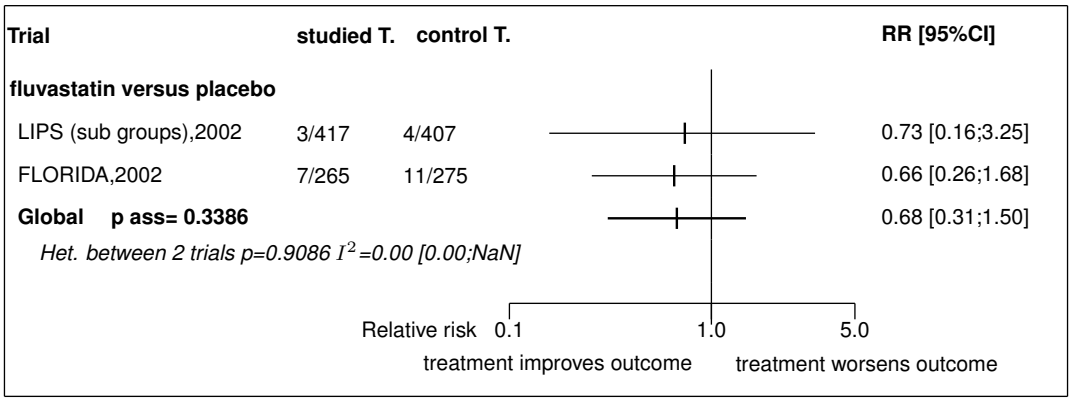


Figure 9.11: *Forest's plot for all cause death*



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[1] Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA 2002 Jun 26;287:3215-22. [PMID=12076217]

[2] Liem AH, van Boven AJ, Veeger NJ, Withagen AJ, Robles de Medina RM, Tijssen JG, van Veldhuisen DJ. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. Eur Heart J 2002;23:1931-7. [PMID=12473255]

9.3 Individual trial summaries

Table 9.6: *LIPS (sub groups), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=824 (417 vs. 407) **Follow-up duration:** 1, 4, and 6 months **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Europe, Canada, and Brazil, 57 centres **Inclusion period:** Apr 1996 - oct 1998	Patients with unstable angina and successful first percutaneous coronary intervention **note:** initially this study included patients with unstable or stable coronary heart disease (844 vs 833)	**Studied treatment:** Fluvastatin, 80 mg **Control treatment:** Placebo	Cardiovascular events at 1 month RR=2.93 [0.31;28.03] Cardiovascular events at 4 months RR=2.60 [0.70;9.74] Cardiovascular events RR=2.60 [0.70;9.74] (at 4 months)

Reference

Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA 2002 Jun 26;287:3215-22 [PMID=12076217]

Table 9.7: *FLORIDA, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=540 (265 vs. 275) **Follow-up duration:** 1, 4, and 6 months **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias The Netherlands, multicentre **Inclusion period:** Jul 1997 - May 1999	Patients with an AMI and total cholesterol of <6.5 mmol.l	**Studied treatment:** Fluvastatin, 80 mg (early initiation) **Control treatment:** Placebo	Cardiovascular events at 1 month RR=1.04 [0.30;3.54] Cardiovascular events at 4 months RR=1.04 [0.44;2.45] Recurrent angina RR=1.04 [0.57;1.88] Cardiovascular events RR=0.95 [0.70;1.28]

Reference

Liem AH, van Boven AJ, Veeger NJ, Withagen AJ, Robles de Medina RM, Tijssen JG, van Veldhuisen DJ. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. Eur Heart J 2002;23:1931-7 [PMID=12473255]

10 Detailed results for pitavastatin

10.1 Available trials

Only one trial which randomized 0 patients was identified: it compared pitavastatin with atorvastatin.
This trial included NaN 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 10.1 (page 88), 10.2 (page 88), 10.4 (page 89), and 10.3 (page 88) summarized the main characteristics of the trial including in this systematic review of randomized trials of pitavastatin.

Table 10.1: *Treatment description - statins - pitavastatin*

Trial	Studied treatment	Control treatment
Pitavastatin versus atorvastatin		
JAPAN ACS (2009) [1]	pitavastatin 4 mg daily	atorvastatin 20mg daily

Table 10.2: *Descriptions of participants - statins - pitavastatin*

Trial	Patients
Pitavastatin versus atorvastatin	
JAPAN ACS (2009) [1]	Patients with acute coronary syndrome undergoing IVUS-guided percutaneous coronary intervention

Table 10.3: *Design and methodological quality of trials - statins - pitavastatin*

Trial	Design	Duration	Centre	Primary endpoint
Pitavastatin versus atorvastatin				
JAPAN ACS, 2009 [1] n=NaN	Parallel groups open exploratory trial	8-12 months	Japan 33 centres	change in non-culprit coronary plaque volume

Table 10.4: *Trial characteristics - statins - pitavastatin*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Pitavastatin versus atorvastatin		
JAPAN ACS, 2009 [1]		

10.2 Meta-analysis results

The results are detailed in table 10.5 (page 90). This table is followed by the Forest's plot corresponding to each endpoint.

Pitavastatin versus atorvastatin

No data were presented in the 1 trial identified

Table 10.5: *Results details - statins - pitavastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pitavastatin versus atorvastatin						
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] Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009 Jul 21;54:293-302. [PMID=19608026]

10.3 Individual trial summaries

Table 10.6: *JAPAN ACS, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (307 vs. NA) **Follow-up duration:** 8-12 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Japan, 33 centres	Patients with acute coronary syndrome undergoing IVUS-guided percutaneous coronary intervention	**Studied treatment:** pitavastatin 4 mg daily **Control treatment:** atorvastatin 20mg daily	

Reference

Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009 Jul 21;54:293-302 [PMID=19608026]

11 Detailed results for pravastatin

11.1 Available trials

A total of 6 RCTs which randomized 3926 patients were identified: 4 trials compared pravastatin with placebo and 2 trials compared pravastatin with usual care.
The average study size was 654 patients (range 60 to 3408). The first study was published in 1997, and the last study was published in 2004.
A total of 4 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Stroke (fatal and non fatal) data was reported in 7 trials; 7 trials reported data on all cause death; 7 trials reported data on non fatal MI; 6 trials reported data on cardiac death; 6 trials reported data on fatal MI; 5 trials reported data on cardiovascular events at 1 month; 5 trials reported data on revascularization; 4 trials reported data on cardiovascular events at 4 months; and 4 trials reported data on cardiovascular events.
Following tables 11.1 (page 93), 11.2 (page 94), 11.4 (page 96), and 11.3 (page 94) summarized the main characteristics of the trials including in this systematic review of randomized trials of pravastatin.

Table 11.1: *Treatment description - statins - pravastatin*

Trial	Studied treatment	Control treatment
Pravastatin versus placebo		
LAMIL (1997) [1]	Pravastatin, 10-20 mg (starting at D3)	Placebo
RECIFE (1999) [2]	Pravastatin, 40 mg	Placebo
PAIS (2001) [3]	Pravastatin, 40 mg (initiated within 48 hours of hospital admission)	Placebo
PACT (2004) [4, 5]	Pravastatin, 20-40 mg within 24 hours of the onset of symptoms in	Placebo
Pravastatin versus usual care		
L-CAD (2000) [6]	Pravastatin, 20-40 mg (strating on average at D6)	Usual care
PTT (2002) [7]	Pravastatin, 40 mg	Usual care

Table 11.2: *Descriptions of participants - statins - pravastatin*

Trial	Patients
Pravastatin versus placebo	
LAMIL (1997) [1]	Patients suffering an acute myocardial infarction
RECIFE (1999) [2]	Patients with acute myocardial infarction or unstable angina and total cholesterol levels at admission >=5.2 mmol/L or LDL >=3.4 mmol/L
PAIS (2001) [3]	Patients with acute coronary syndromes
PACT (2004) [4, 5]	Patients with unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction within 24 hours of the onset of symptoms
Pravastatin versus usual care	
L-CAD (2000) [6]	Patients with acute coronary syndrome
PTT (2002) [7]	Patients who underwent coronary balloon angioplasty of the infarct-related artery during the first month of acute myocardial infarction

Table 11.3: *Design and methodological quality of trials - statins - pravastatin*

Trial	Design	Duration	Centre	Primary endpoint
Pravastatin versus placebo				
LAMIL, 1997 [1] n=69	Parallel groups double blind exploratory trial	1 and 3 months	Belgium	
RECIFE, 1999 [2] n=60	Parallel groups double blind exploratory trial	1.5 months	Canada 1 centres	none defined
PAIS, 2001 [3] n=99	Parallel groups double blind exploratory trial	1 and 3 months	The Netherlands	
PACT, 2004 [4, 5] n=3408	Parallel groups double blind confirmatory trial at low risk of bias	1 months	Australia multicentre	death, recurrence of MI, or rehospital for unstable angina
Pravastatin versus usual care				
L-CAD, 2000 [6] n=126	Parallel groups open exploratory trial	1, 4, and 6 months	Germany	death, MI, stroke, coronary intervention, PVD

continued...

Trial	Design	Duration	Centre	Primary end-point
PTT, 2002 [7] n=164	Parallel groups open exploratory trial	1 and 6 months	Turkey	

Table 11.4: *Trial characteristics - statins - pravastatin*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Pravastatin versus placebo		
LAMIL, 1997 [1]		
RECIFE, 1999 [2]		
PAIS, 2001 [3]		
PACT, 2004 [4, 5]		
Pravastatin versus usual care		
L-CAD, 2000 [6]		
PTT, 2002 [7]		

11.2 Meta-analysis results

The results are detailed in table 11.5 (page 98). This table is followed by the Forest's plot corresponding to each endpoint.

Pravastatin versus placebo

A total of 3 of the 4 studies eligible for this comparison provided data on **cardiovascular events at 1 month**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events at 1 month, with a RR of 0.88 (95% CI 0.67 to 1.16, p=0.3645). No heterogeneity was detected (p = 0.8930, I^2 = 0.00%).
A total of 2 of the 4 studies eligible for this comparison provided data on **cardiovascular events at 4 months**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events at 4 months, with a RR of 0.95 (95% CI 0.35 to 2.60, p=0.9238). No heterogeneity was detected (p = 0.9485, I^2 = 0.00%).
A total of 2 of the 4 studies eligible for this comparison provided data on **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 0.95 (95% CI 0.35 to 2.60, p=0.9238). No heterogeneity was detected (p = 0.9485, I^2 = 0.00%).
All the 4 studies had extractable data about the number of participants with **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.74 (95% CI 0.32 to 1.72, p=0.4844). No heterogeneity was detected (p = 0.9069, I^2 = 0.00%).
All the 4 studies had extractable data about the number of participants with **cardiac death**. When pooled together, there was no statistically significant difference between the groups in cardiac death, with a RR of 0.79 (95% CI 0.49 to 1.28, p=0.3336). No heterogeneity was detected (p = 0.9549, I^2 = 0.00%).
All the 4 studies had extractable data about the number of participants with **fatal MI**. When pooled together, there was no statistically significant difference between the groups in fatal MI, with a RR of 0.90 (95% CI 0.46 to 1.76, p=0.7614). No heterogeneity was detected (p = 0.8788, I^2 = 0.00%).
All the 4 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 0.38 (95% CI 0.08 to 1.79, p=0.2199). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0414, I^2 = 0.64%).
A total of 3 of the 4 studies eligible for this comparison provided data on **revascularization**. When pooled together, there was no statistically significant difference between the groups in revascularization, with a RR of 1.17 (95% CI 0.55 to 2.45, p=0.6845). No heterogeneity was detected (p = 0.9801, I^2 = 0.00%).
All the 4 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 0.72 (95% CI 0.45 to 1.14, p=0.1625). No heterogeneity was detected (p = 0.9280, I^2 = 0.00%).

Pravastatin versus usual care

All the 2 studies had extractable data about the number of participants with **cardiovascular events at 1 month**. The analysis detected a statistically significant difference in favor of pravastatin in cardiovascular events at 1 month, with a RR of 0.36 (95% CI 0.13 to 0.99, p=0.0476). No heterogeneity was detected (p = 0.3613, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiovascular events at 4 months**. When pooled together, there was no statistically significant difference

between the groups in cardiovascular events at 4 months, with a RR of 0.39 (95% CI 0.10 to 1.48, p=0.1657). No heterogeneity was detected (p = 0.5520, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiovascular events**. When pooled together, there was no statistically significant difference between the groups in cardiovascular events, with a RR of 0.39 (95% CI 0.10 to 1.48, p=0.1657). No heterogeneity was detected (p = 0.5520, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.64 (95% CI 0.05 to 8.21, p=0.7301). No heterogeneity was detected (p = 0.8803, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiac death**. When pooled together, there was no statistically significant difference between the groups in cardiac death, with a RR of 0.31 (95% CI 0.03 to 3.32, p=0.3335). No heterogeneity was detected (p = 0.5506, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **fatal MI**. When pooled together, there was no statistically significant difference between the groups in fatal MI, with a RR of 0.31 (95% CI 0.03 to 3.32, p=0.3335). No heterogeneity was detected (p = 0.5506, I^2 = 0.00%).
All the 2 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 0.44 (95% CI 0.06 to 3.06, p=0.4048). No heterogeneity was detected (p = 0.7269, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **revascularization**. When pooled together, there was no statistically significant difference between the groups in revascularization, with a RR of 0.58 (95% CI 0.33 to 1.05, p=0.0725). No heterogeneity was detected (p = 0.2965, I^2 = 0.08%).
All the 2 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 0.45 (95% CI 0.08 to 2.52, p=0.3635). No heterogeneity was detected (p = 0.5969, I^2 = 0.00%).

Table 11.5: *Results details - statins - pravastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pravastatin versus placebo						
cardiovascular events at 1 month	RR=0.88	[0.67;1.16]	0.3645	0.8930 (I^2=0.00)	3	3567
cardiovascular events at 4 months	RR=0.95	[0.35;2.60]	0.9238	0.9485 (I^2=0.00)	2	168
cardiovascular events	RR=0.95	[0.35;2.60]	0.9238	0.9485 (I^2=0.00)	2	168
stroke (fatal and non fatal)	RR=0.74	[0.32;1.72]	0.4844	0.9069 (I^2=0.00)	4	3636
cardiac death	RR=0.79	[0.49;1.28]	0.3336	0.9549 (I^2=0.00)	4	3636
fatal MI	RR=0.90	[0.46;1.76]	0.7614	0.8788 (I^2=0.00)	4	3636
non fatal MI	RR=0.38	[0.08;1.79]	0.2199	0.0414 (I^2=0.64)	4	3636
revascularization	RR=1.17	[0.55;2.45]	0.6845	0.9801 (I^2=0.00)	3	228

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
all cause death	RR=0.72	[0.45;1.14]	0.1625	0.9280 (I^2=0.00)	4	3636
pravastatin versus usual care						
cardiovascular events at 1 month	RR=0.36	[0.13;0.99]	0.0476	0.3613 (I^2=0.00)	2	290
cardiovascular events at 4 months	RR=0.39	[0.10;1.48]	0.1657	0.5520 (I^2=0.00)	2	290
cardiovascular events	RR=0.39	[0.10;1.48]	0.1657	0.5520 (I^2=0.00)	2	290
stroke (fatal and non fatal)	RR=0.64	[0.05;8.21]	0.7301	0.8803 (I^2=0.00)	2	290
cardiac death	RR=0.31	[0.03;3.32]	0.3335	0.5506 (I^2=0.00)	2	290
fatal MI	RR=0.31	[0.03;3.32]	0.3335	0.5506 (I^2=0.00)	2	290
non fatal MI	RR=0.44	[0.06;3.06]	0.4048	0.7269 (I^2=0.00)	2	290
revascularization	RR=0.58	[0.33;1.05]	0.0725	0.2965 (I^2=0.08)	2	290
all cause death	RR=0.45	[0.08;2.52]	0.3635	0.5969 (I^2=0.00)	2	203

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 cardiovascular events at 1 month*

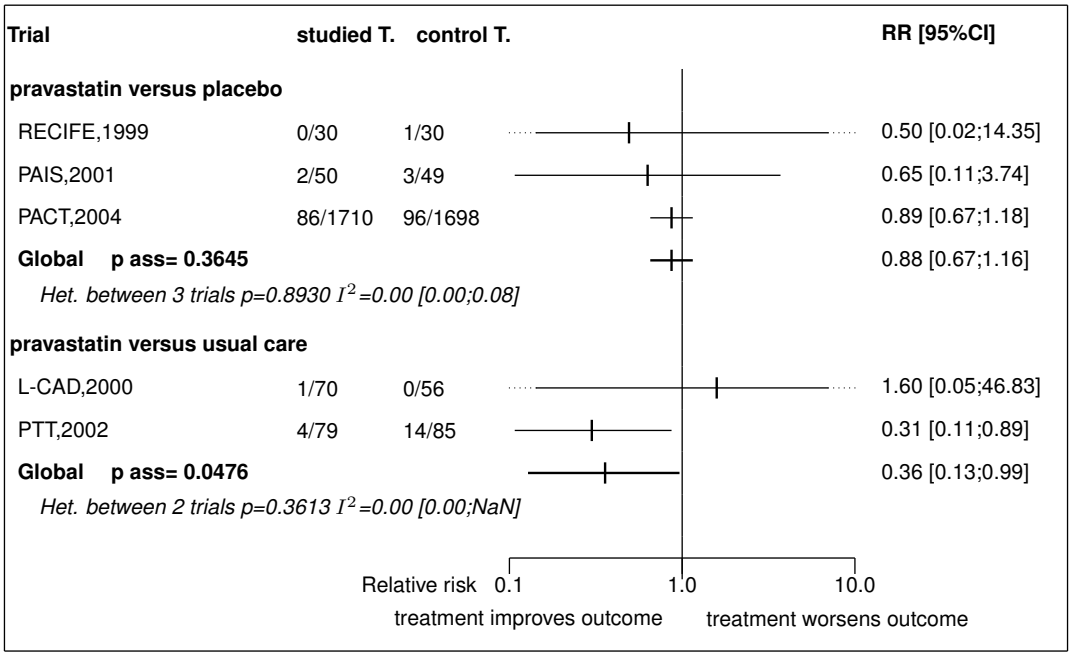


Figure 11.2: *Forest's plot for cardiovascular events at 4 months*

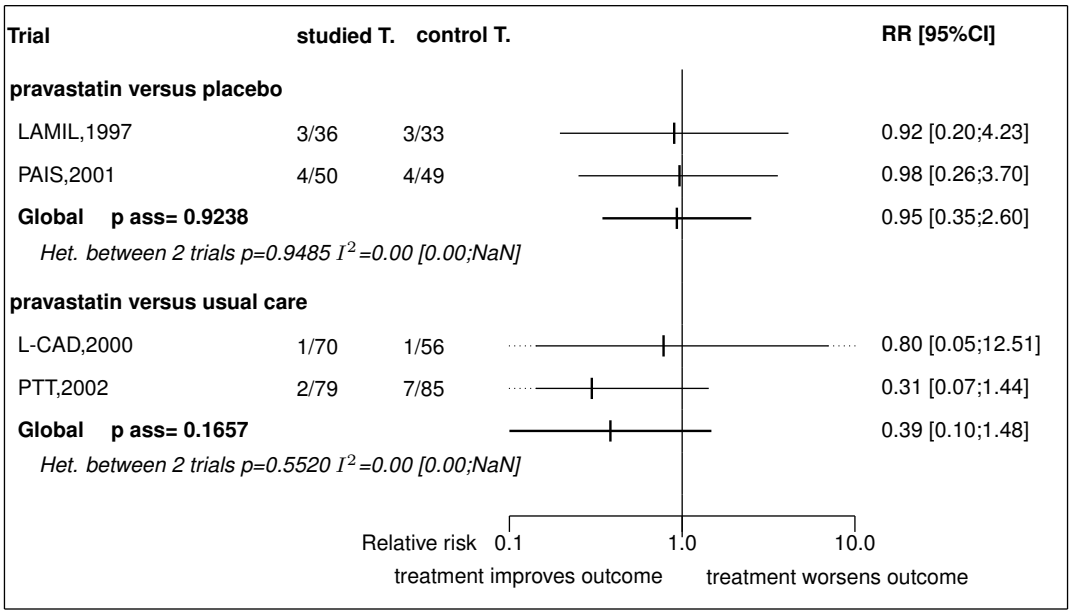


Figure 11.3: *Forest's plot for cardiovascular events*

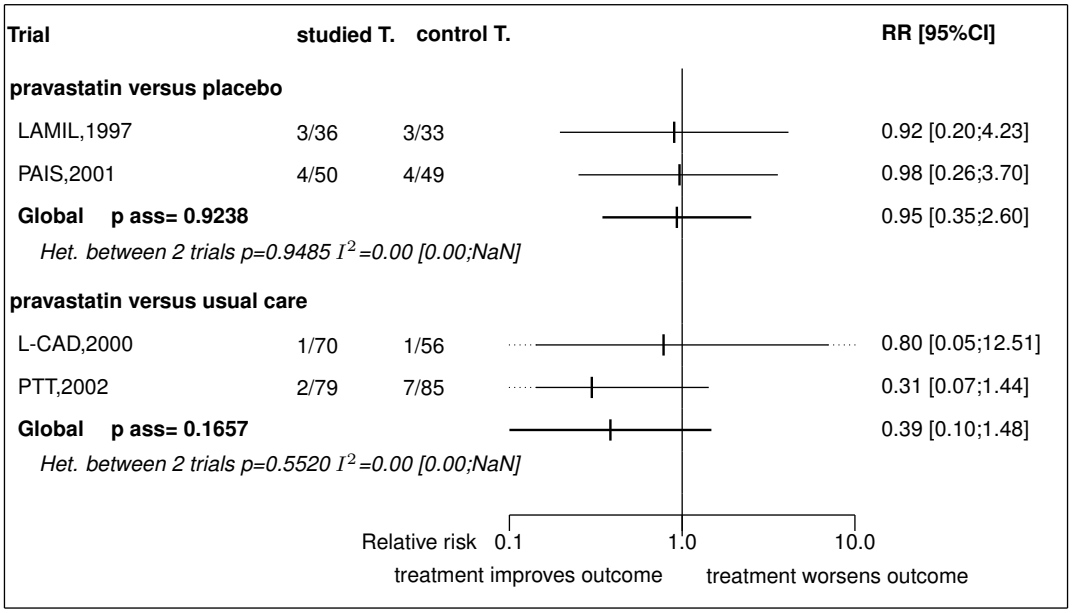


Figure 11.4: *Forest's plot for stroke (fatal and non fatal)*

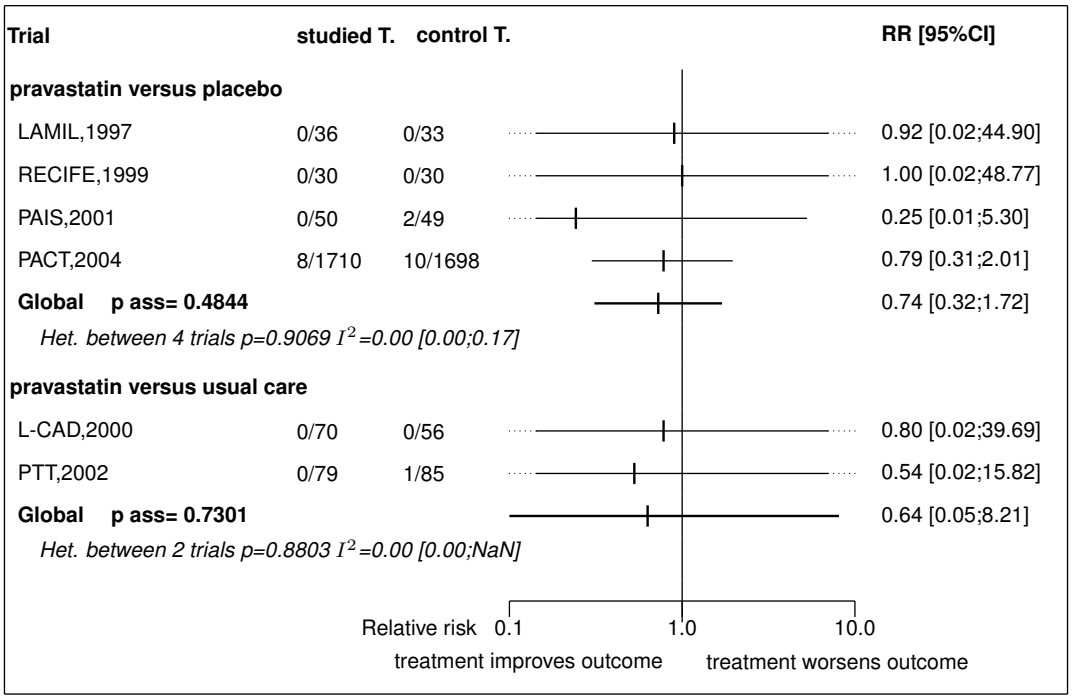


Figure 11.5: *Forest's plot for cardiac death*

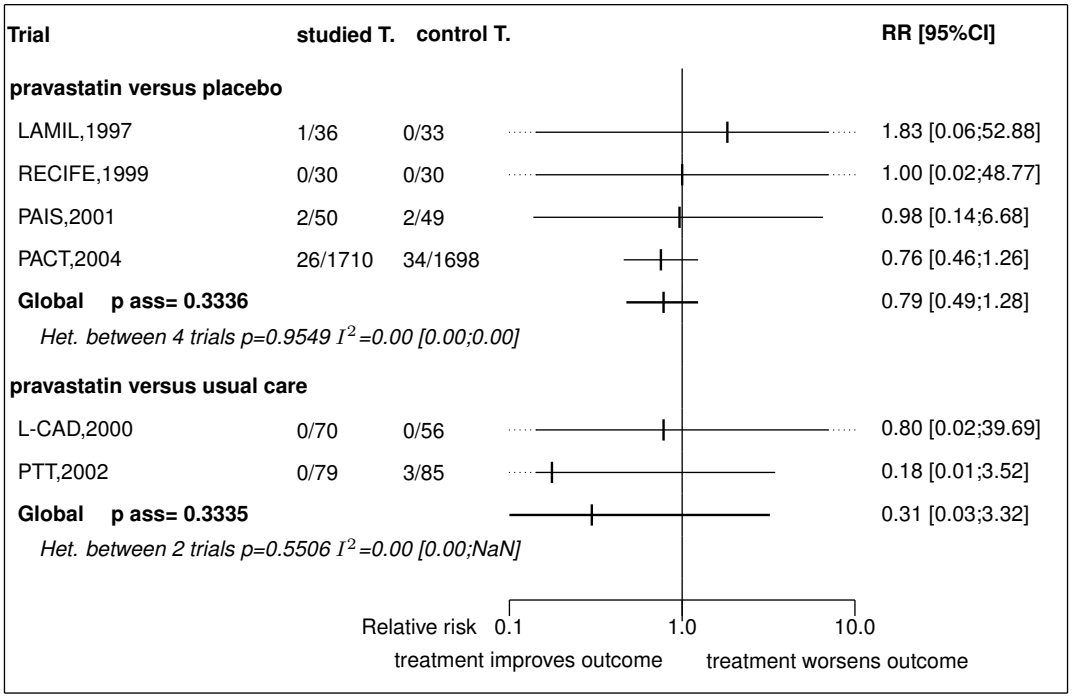


Figure 11.6: *Forest's plot for fatal MI*

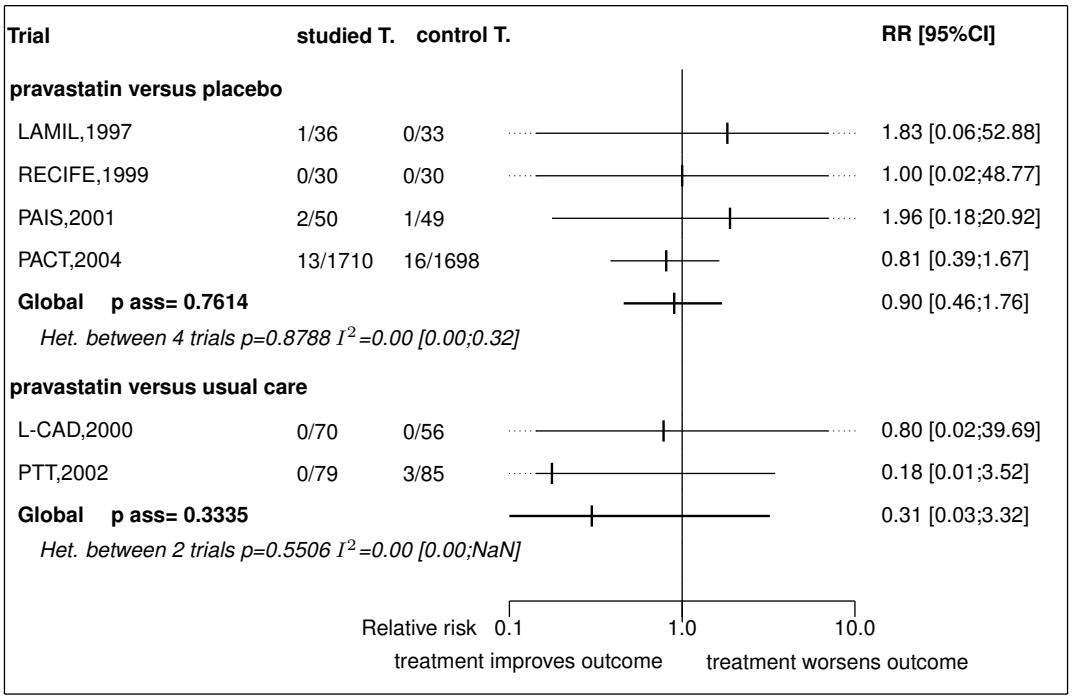


Figure 11.7: *Forest's plot for non fatal MI*

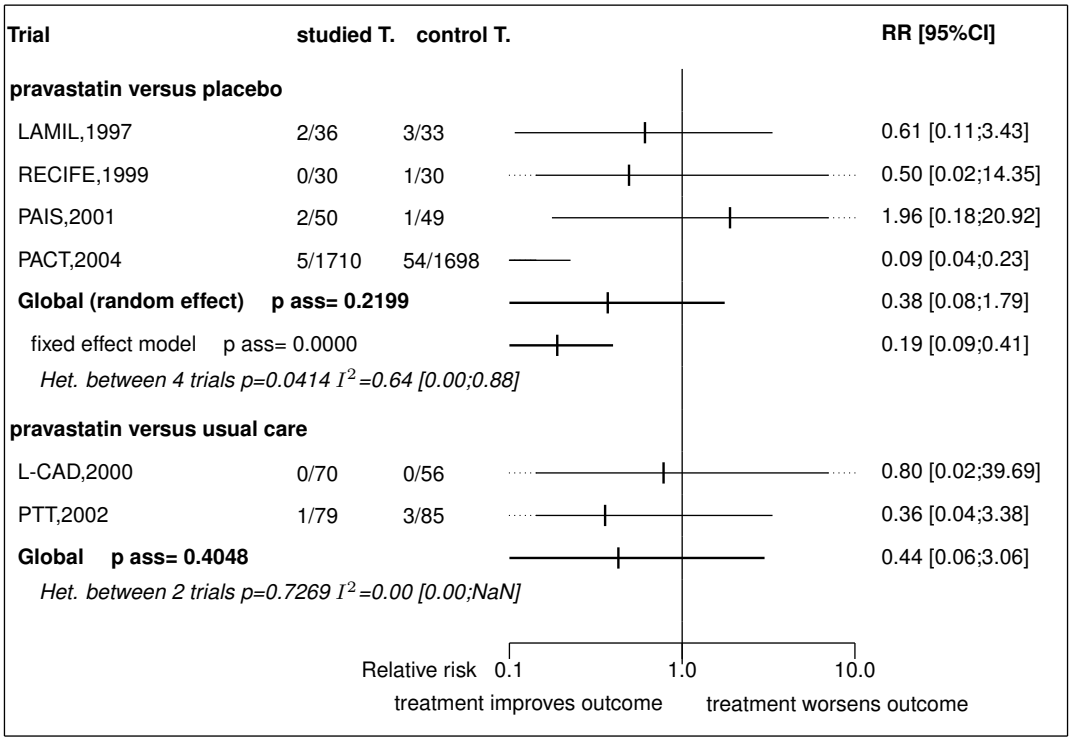


Figure 11.8: *Forest's plot for revascularization*

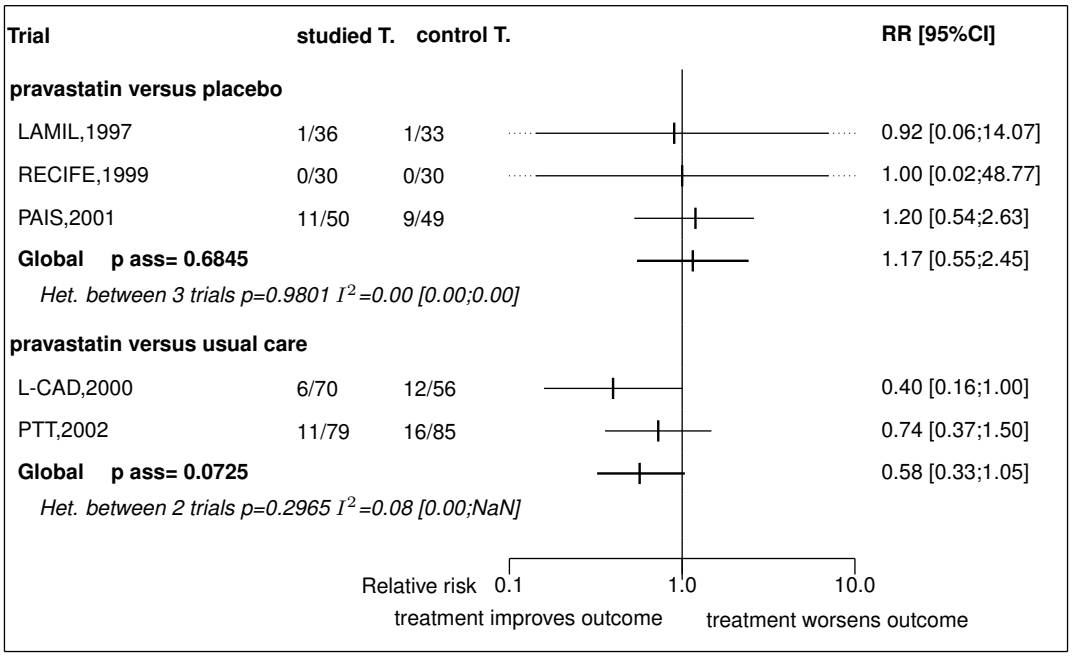
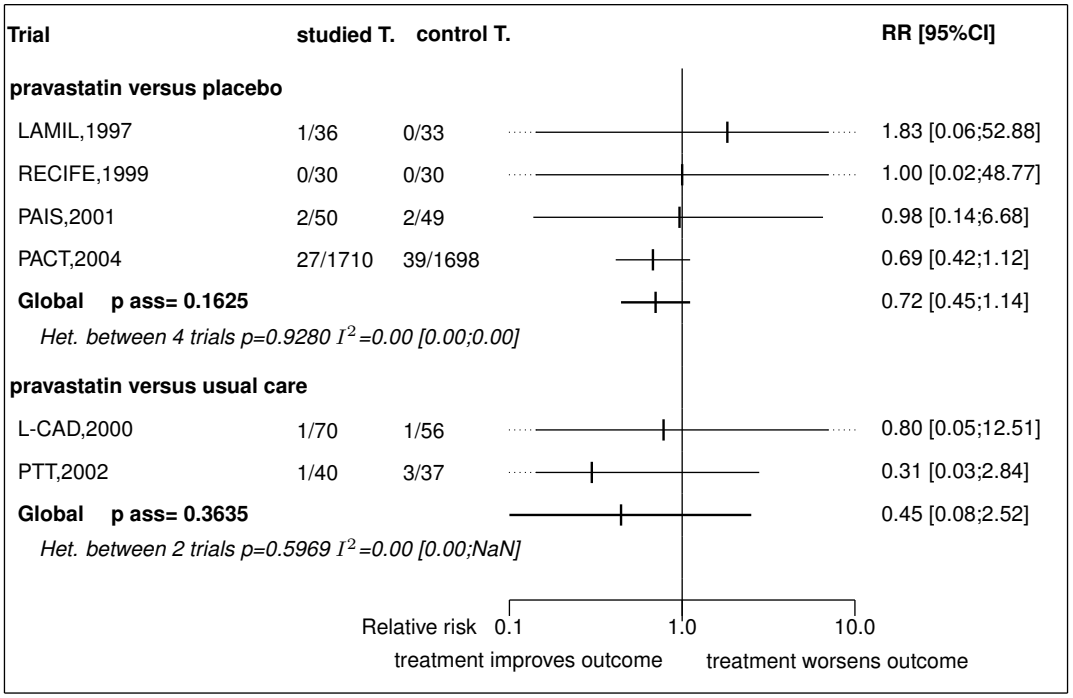


Figure 11.9: *Forest's plot for all cause death*



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11.3 Individual trial summaries

Table 11.6: *LAMIL, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=69 (36 vs. 33) **Follow-up duration:** 1 and 3 months **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Belgium	Patients suffering an acute myocardial infarction	**Studied treatment:** Pravastatin, 10-20 mg (starting at D3) **Control treatment:** Placebo	Cardiovascular events at 4 months RR=0.92 [0.20;4.23] Cardiovascular events RR=0.92 [0.20;4.23] (at 4 months)

Reference

Kesteloot H, Claeys G, Blanckaert N, Lesaffre E. Time course of serum lipids and apolipoproteins after acute myocardial infarction: modification by pravastatin. Acta Cardiol 1997;52:107-16 [PMID=9187418]

Table 11.7: *RECIFE, 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=60 (30 vs. 30) **Follow-up duration:** 1.5 months **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Canada, 1 centres	Patients with acute myocardial infarction or unstable angina and total cholesterol levels at admission >=5.2 mmol/L or LDL >=3.4 mmol/L	**Studied treatment:** Pravastatin, 40 mg **Control treatment:** Placebo	

Reference

Dupuis J, Tardif JC, Cernacek P, Throux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (reduction of cholesterol in ischemia and function of the endothelium) trial. Circulation 1999;99:3227-33 [PMID=10385495]

Table 11.8: *PAIS, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=99 (50 vs. 49) **Follow-up duration:** 1 and 3 months **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial The Netherlands	Patients with acute coronary syndromes	**Studied treatment:** Pravastatin, 40 mg (initiated within 48 hours of hospital admission) **Control treatment:** Placebo	Cardiovascular events at 1 month RR=0.65 [0.11;3.74] Cardiovascular events at 4 months RR=0.98 [0.26;3.70] Cardiovascular events RR=0.98 [0.26;3.70] (at 4 months)

Reference

Den Hartog FR, Van Kalmthout PM, Van Loenhout TT, Schaafsma HJ, Rila H, Verheugt FW. Pravastatin in acute ischaemic syndromes: results of a randomised placebo-controlled trial. Int J Clin Pract 2001;55:300-4 [PMID=11452676]

Table 11.9: *PACT, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3408 (1710 vs. 1698) **Follow-up duration:** 1 months **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Australia, multicentre	Patients with unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction within 24 hours of the onset of symptoms	**Studied treatment:** Pravastatin, 20-40 mg within 24 hours of the onset of symptoms in **Control treatment:** Placebo	Cardiovascular events at 1 month RR=0.89 [0.67;1.18] Stroke (fatal and non fatal) RR=0.79 [0.31;2.01]

References

Thompson PL, Meredith I, Amerena J, et al. Effectof pravastatin compared with placebo initiated within24 hours of onset of acute myocardial infarction orunstable angina: the Pravastatin in Acute CoronaryTreatment (PACT) trial. Am Heart J. 2004;148:e2
Thompson PL, Meredith I, Amerena J, Campbell TJ, Sloman JG, Harris PJ. Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial. Am Heart J 2004;148:e2 [PMID=15215811]

Table 11.10: *L-CAD, 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=126 (70 vs. 56) **Follow-up duration:** 1, 4, and 6 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Germany	Patients with acute coronary syndrome	**Studied treatment:** Pravastatin, 20-40 mg (strating on average at D6) **Control treatment:** Usual care	Cardiovascular events at 4 months RR=0.80 [0.05;12.51] Cardiovascular events RR=0.80 [0.05;12.51] (at 4 months)

Reference

Arntz HR, Agrawal R, Wunderlich W, Schnitzer L, Stern R, Fischer F, Schultheiss HP. Beneficial effects of pravastatin (+/-colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). Am J Cardiol 2000;86:1293-8 [PMID=11113401]

Table 11.11: *PTT, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=164 (79 vs. 85) **Follow-up duration:** 1 and 6 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Turkey	Patients who underwent coronary balloon angioplasty of the infarct-related artery during the first month of acute myocardial infarction	**Studied treatment:** Pravastatin, 40 mg **Control treatment:** Usual care	Cardiovascular events at 1 month RR=0.31 [0.11;0.89] Cardiovascular events at 4 months RR=0.31 [0.07;1.44] Cardiovascular events RR=0.31 [0.07;1.44] (at 4 months)

Reference

Kayikioglu M, Can L, Kltrsay H, Payzin S, Turkoglu C. Early use of pravastatin in patients with acute myocardial infarction undergoing coronary angioplasty. Acta Cardiol 2002;57:295-302 [PMID=12222700]

12 Detailed results for simvastatin

12.1 Available trials

Only one trial which randomized 4497 patients was identified: it compared simvastatin with placebo.
This trial included 4497 patients and was published in 2004.
This trial was double blind in design.
It was reported in English language.
Fatal MI data was reported in 1 trials; 1 trials reported data on cardiovascular events at 1 month; 1 trials reported data on cardiac death; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on cardiovascular events at 4 months; 1 trials reported data on cardiovascular events; 1 trials reported data on revascularization; and 1 trials reported data on non fatal MI.
Following tables 12.1 (page 112), 12.2 (page 112), 12.4 (page 114), and 12.3 (page 113) summarized the main characteristics of the trial including in this systematic review of randomized trials of simvastatin.

Table 12.1: *Treatment description - statins - simvastatin*

Trial	Studied treatment	Control treatment
Simvastatin versus placebo		
A to Z (2004) [1]	Simvastatin, 40-80 mg early initiation receiving 40 mg/d of simvastatin for 1 month followed by 80mg/d thereafter4	Placebo placebo for 4 monthsfollowed by 20 mg/d of simvastatinateur=na

Table 12.2: *Descriptions of participants - statins - simvastatin*

Trial	Patients
Simvastatin versus placebo	

continued...

Trial	Patients		
A to Z (2004) [1]	Patient with an acute coronary syndrome (ACS)		
	Inclusion criteria: patients between the ages of 21 and80 years with either nonST-elevationACS or ST-elevation MI were eligible forenrollment if they had a total cholesterollevel of 250 mg/dL (6.48 mmol/L)or lower. Initially, patients were enteredinto phase Z only if they presentedwith nonST-elevation ACS, werestabilized during phase A of the trial forat least 12 consecutive hours within 5days after symptom onset, and met atleast 1 of the following high-risk characteristics:age older than 70 years; diabetesmellitus; prior history of coronaryartery disease, peripheral arterialdisease, or stroke; elevation of serum creatinekinaseMB or troponin levels; recurrentangina with ST-segmentchanges; electrocardiographic evidenceof ischemia on a predischargestress test; or multivessel coronary arterydisease determined by coronary angiography.The protocol was amended to allowpatients with nonST-elevationACSwhowere not enrolled in phase A and patientswith ST-elevation MI to enter directlyinto phase Z. Patients in the lattercategory were required to receive fibrinolytictherapy or primary percutaneouscoronary intervention (PCI) if theypresented within 12 hours of symptomonset and no reperfusion therapy ifsymptom onset was longer than 12 hoursprior to presentation. Patients were alsorequired to meet criteria for stability andhave at least 1 high-risk feature in additionto cardiac biomarker elevation	**Exclusion criteria:** statin therapy at the time of randomization; coronary artery bypass graft surgery planned; PCI was planned withinthe first 2 weeks after enrollment; ALT >20% above the ULN; increased risk for myopathy due to renal impairment or concomitanttherapy with agents known to enhancemyopathy risk, such as fibrates, cyclosporine, macrolide antibiotics, azole antifungals, amiodarone, or verapamil; prior history of nonexerciserelatedelevations in creatine kinase levelor nontraumatic rhabdomyolysis

Table 12.3: *Design and methodological quality of trials - statins - simvastatin*

Trial	Design	Duration	Centre	Primary endpoint
Simvastatin versus placebo				
A to Z, 2004 [1] n=4497	Parallel groups Double aveugle	1 and 4 months inclusion period: Dec 1999 - Jan 2003	41 countries 322 centres	cardiovascular death, MI, rehospitalization for ACS or stroke

Table 12.4: *Trial characteristics - statins - simvastatin*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Simvastatin versus placebo		
A to Z, 2004 [1]	-18	-.39

12.2 Meta-analysis results

The results are detailed in table 12.5 (page 115). This table is followed by the Forest's plot corresponding to each endpoint.

Simvastatin versus placebo

The single study eligible for this comparison provided data on **cardiovascular events at 1 month**. No statistically significant difference between the groups was found in cardiovascular events at 1 month, with a RR of 0.93 (95% CI 0.71 to 1.22, p=0.5912).
The single study eligible for this comparison provided data on **cardiovascular events at 4 months**. No statistically significant difference between the groups was found in cardiovascular events at 4 months, with a RR of 0.99 (95% CI 0.80 to 1.22, p=0.9374).
The single study eligible for this comparison provided data on **cardiovascular events**. No statistically significant difference between the groups was found in cardiovascular events, with a RR of 0.89 (95% CI 0.77 to 1.02, p=0.0994).
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 0.79 (95% CI 0.48 to 1.29, p=0.3440).
The single study eligible for this comparison provided data on **cardiac death**. No statistically significant difference between the groups was found in cardiac death, with a RR of 0.86 (95% CI 0.57 to 1.30, p=0.4773).
The single study eligible for this comparison provided data on **fatal MI**. No statistically significant difference between the groups was found in fatal MI, with a RR of 0.62 (95% CI 0.35 to 1.11, p=0.1060).
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 0.99 (95% CI 0.77 to 1.29, p=0.9631).
The single study eligible for this comparison provided data on **revascularization**. No statistically significant difference between the groups was found in revascularization, with a RR of 0.95 (95% CI 0.74 to 1.21, p=0.6520).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.90 (95% CI 0.60 to 1.35, p=0.6210).

Table 12.5: *Results details - statins - simvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
simvastatin versus placebo						
cardiovascular events at 1 month	RR=0.93	[0.71;1.22]	0.5912	1.0000 (I^2=0.00)	1	4497
cardiovascular events at 4 months	RR=0.99	[0.80;1.22]	0.9374	1.0000 (I^2=0.00)	1	4497
cardiovascular events	RR=0.89	[0.77;1.02]	0.0994	1.0000 (I^2=0.00)	1	4496
stroke (fatal and non fatal)	RR=0.79	[0.48;1.29]	0.3440	1.0000 (I^2=0.00)	1	4496
cardiac death	RR=0.86	[0.57;1.30]	0.4773	1.0000 (I^2=0.00)	1	4496
fatal MI	RR=0.62	[0.35;1.11]	0.1060	1.0000 (I^2=0.00)	1	4497

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
non fatal MI	RR=0.99	[0.77;1.29]	0.9631	1.0000 (I^2=0.00)	1	4496
revascularization	RR=0.95	[0.74;1.21]	0.6520	1.0000 (I^2=0.00)	1	4496
all cause death	RR=0.90	[0.60;1.35]	0.6210	1.0000 (I^2=0.00)	1	4496

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

Figure 12.1: *Forest's plot for cardiovascular events at 1 month*

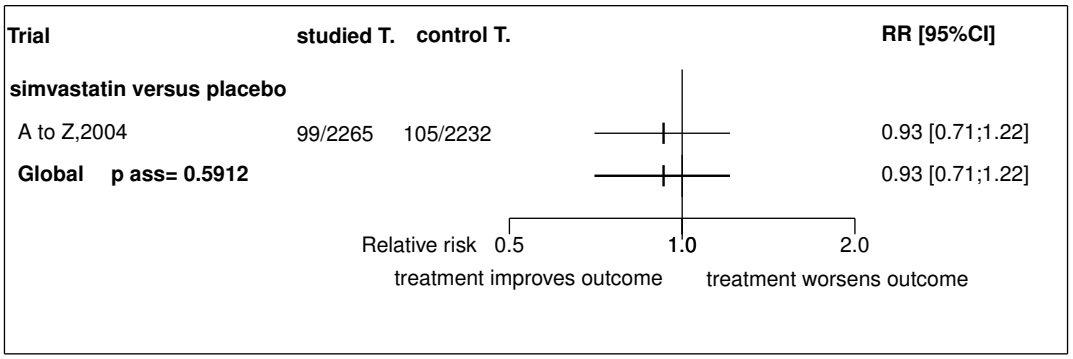


Figure 12.2: *Forest's plot for cardiovascular events at 4 months*

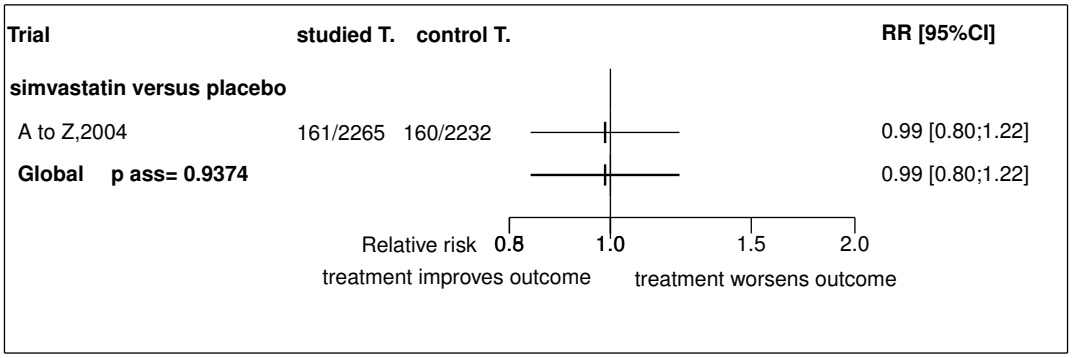


Figure 12.3: *Forest's plot for cardiovascular events*

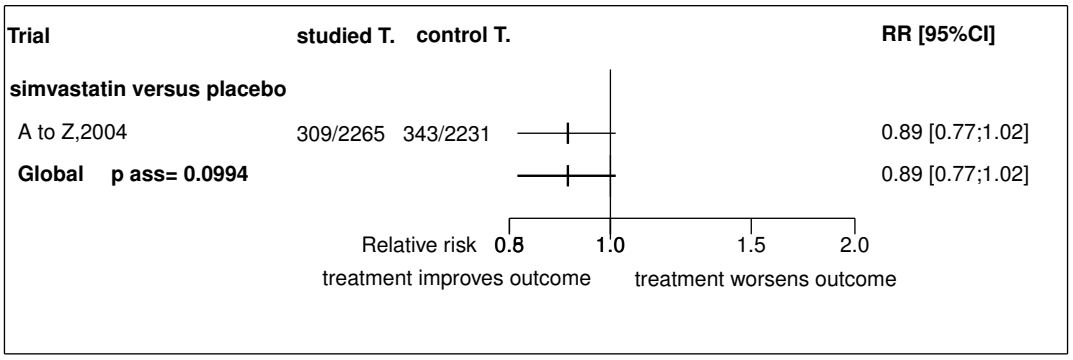


Figure 12.4: *Forest's plot for stroke (fatal and non fatal)*

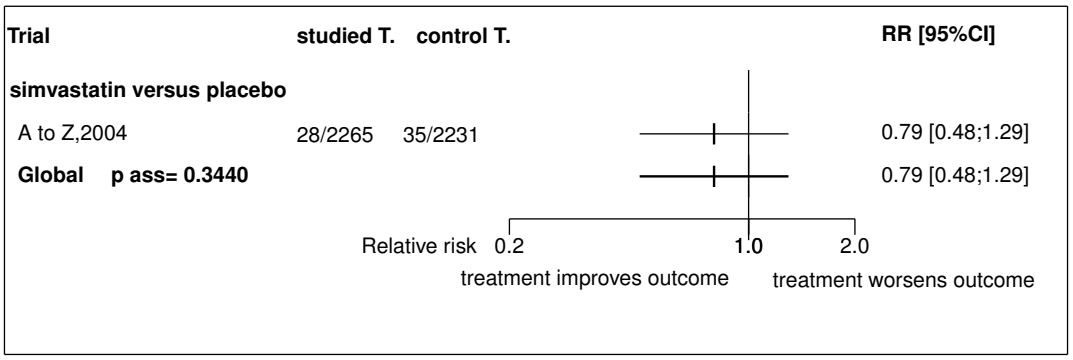


Figure 12.5: *Forest's plot for cardiac death*

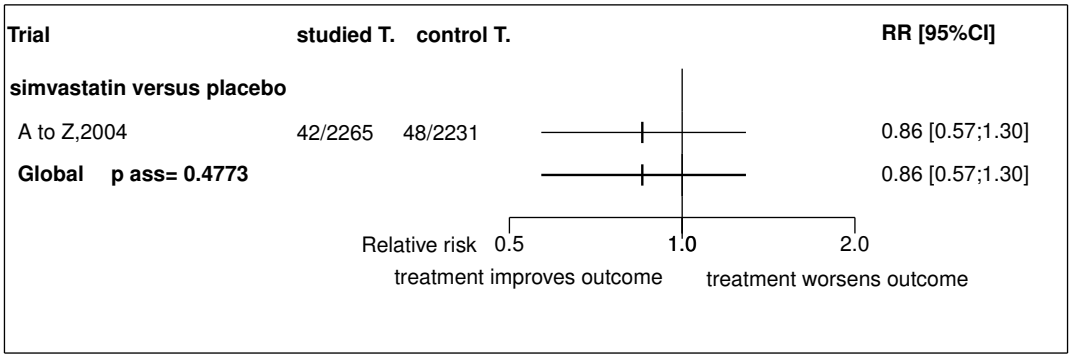


Figure 12.6: *Forest's plot for fatal MI*

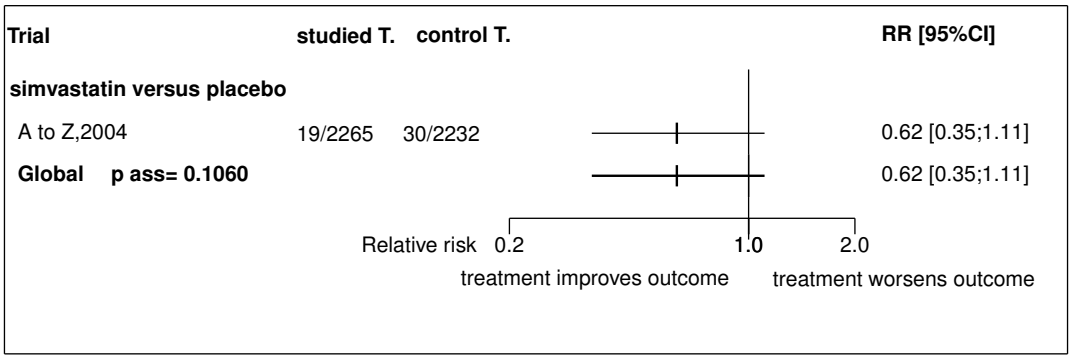


Figure 12.7: *Forest's plot for non fatal MI*

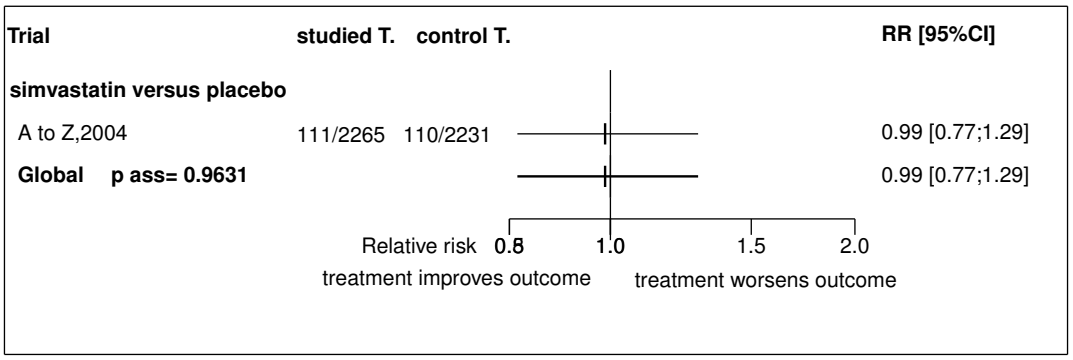


Figure 12.8: *Forest's plot for revascularization*

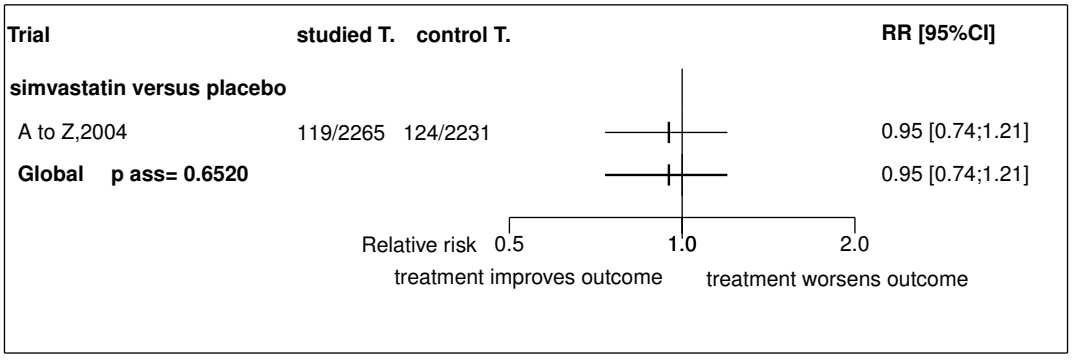
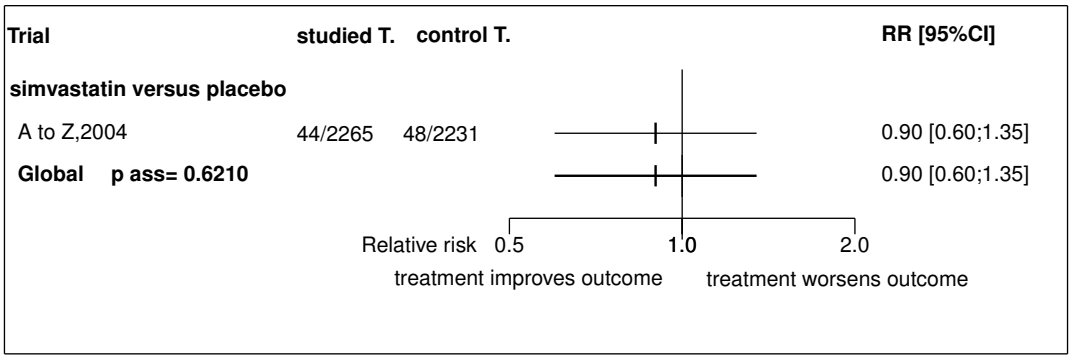


Figure 12.9: *Forest's plot for all cause death*



References

[1] de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004 Sep 15;292:1307-16. [PMID=15337732]

12.3 Individual trial summaries

Table 12.6: *A to Z, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4497 (2265 vs. 2232) **Follow-up duration:** 1 and 4 months **Study design:** Randomized controlled trial Parallel groups Double aveugle 41 countries, 322 centres **Inclusion period:** Dec 1999 - Jan 2003	Patient with an acute coronary syndrome (ACS) **Inclusion criteria:** Patients between the ages of 21 and80 years with either nonST-elevationACS or ST-elevation MI were eligible forenrollment if they had a total cholesterollevel of 250 mg/dL (6.48 mmol/L)or lower. Initially, patients were enteredinto phase Z only if they presentedwith nonST-elevation ACS, werestabilized during phase A of the trial forat least 12 consecutive hours within 5days after symptom onset, and met atleast 1 of the following high-risk characteristics:age older than 70 years; diabetesmellitus; prior history of coronaryartery disease, peripheral arterialdisease, or stroke; elevation of serum **Exclusion criteria:** statin therapy at the time of randomization; coronary artery bypass graft surgery planned; PCI was planned withinthe first 2 weeks after enrollment; ALT >20% above the ULN; increased risk for myopathy due to renal impairment or concomitanttherapy with agents known to enhancemyopathy risk, such as fibrates, cyclosporine, macrolide antibiotics, azole antifungals, amiodarone, or verapamil; prior history of nonexerciserelatedelevations in creatine kinase levelor nontraumatic rhabdomyolysis	**Studied treatment:** Simvastatin, 40-80 mg early initiation receiving 40 mg/d of simvastatin for 1 month followed by 80mg/d thereafter4 **Control treatment:** Placebo placebo for 4 monthsfollowed by 20 mg/d of simvastatinateur=na	Cardiovascular events at 1 month RR=0.93 [0.71;1.22] Cardiovascular events at 4 months RR=0.99 [0.80;1.22] Cardiovascular events RR=0.89 [0.77;1.02] (CV death, rehospilazition for ACS, MI, stroke) Stroke (fatal and non fatal) RR=0.79 [0.48;1.29]

Reference

de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004 Sep 15;292:1307-16 [PMID=15337732]

13 Global meta-analysis: all statins

13.1 Global meta-analysis: all statins versus atorvastatin

Table 13.1: *All statinsversus atorvastatin*

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

13.2 Global meta-analysis: all statins versus placebo

Table 13.2: *All statinsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deaths or MI	RR=0.92	0.75;1.13	0.4471	1.0000 (0.00)	1	3086
cardiovascular events at 1 month	RR=0.96	0.82;1.12	0.6119	0.9079 (0.00)	7	12514
cardiovascular events at 4 months	RR=0.95	0.83;1.09	0.4832	0.7245 (0.00)	6	9115
PTCA	RR=1.06	0.85;1.31	0.6255	1.0000 (0.00)	1	3086
recurrent angina	RR=0.78	0.60;1.01	0.0644	0.2983 (0.08)	2	3626
cardiovascular events	RR=0.91	0.82;1.02	0.0940	0.7538 (0.00)	6	9114
stroke (fatal and non fatal)	RR=0.69	0.48;0.98	0.0411	0.9737 (0.00)	8	12582
cardiac death	RR=0.83	0.65;1.04	0.1060	0.9957 (0.00)	8	12582
CABG	RR=0.92	0.71;1.20	0.5314	0.3047 (0.05)	2	3626
fatal MI	RR=0.77	0.54;1.11	0.1618	0.9054 (0.00)	8	12583
non fatal MI	RR=0.76 [1]	0.46;1.25	0.2761	0.0003 (0.74) †	8	12582
revascularization	RR=0.97	0.87;1.09	0.6359	0.9680 (0.00)	7	9174
all cause death	RR=0.86	0.69;1.07	0.1659	0.9718 (0.00)	8	12582
non fatal stroke	RR=0.41	0.19;0.89	0.0243	1.0000 (0.00)	1	3086

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=0.89 95% CI 0.75;1.06

13.3 Global meta-analysis: all statins versus pravastatin

Table 13.3: *All statinsversus pravastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.76	0.66;0.88	0.0000	1.0000 (0.00)	1	4152
all cause death	RR=0.72	0.50;1.03	0.0748	1.0000 (0.00)	1	4152

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

13.4 Global meta-analysis: all statins versus usual care

Table 13.4: *All statinsversus usual care*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events at 1 month	RR=0.33	0.13;0.87	0.0242	0.5926 (0.00)	3	371
cardiovascular events at 4 months	RR=0.50	0.23;1.08	0.0787	0.9057 (0.00)	4	441
cardiovascular events	RR=0.50	0.23;1.08	0.0787	0.9057 (0.00)	4	441
stroke (fatal and non fatal)	RR=0.62	0.13;3.04	0.5577	0.9911 (0.00)	4	441
cardiac death	RR=0.56	0.15;2.09	0.3874	0.8663 (0.00)	4	441
fatal MI	RR=0.56	0.15;2.09	0.3874	0.8663 (0.00)	4	441
non fatal MI	RR=0.46	0.17;1.30	0.1455	0.9634 (0.00)	4	441
revascularization	RR=0.69	0.43;1.10	0.1211	0.5408 (0.00)	4	441
all cause death	RR=0.60	0.21;1.72	0.3470	0.9158 (0.00)	4	354

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

14 Ongoing studies of statins

Only one ongoing study was identified. A brief description of this trial is given table 14.1

Table 14.1: *Ongoing studies for statins*

Study	Description
Czech trial NCT00171275	fluvastatin **vs.** placebo

15 Excluded studies for statins

No trial was excluded.

References