Cholesterol lowering intervention for cardiovascular prevention in patients with LDL elevation and without CHD

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 cardiovascular prevention in patients with LDL elevation and without CHD.

Contents

0.1 Synthesis of the meta-analysis results

In all 36 randomised controlled trials (RCTs) were included. These included 6 studies of **diet** involving 103,658 patients, 3 studies of **fibrates** involving 14,748 patients, 1 studie of **inhibitor of lipoprotein-associated phospholipase** involving -18 patients, 1 studie of **probucol** involving 163 patients, 5 studies of **resins** involving 6,282 patients and 20 studies of **statins** involving 31,487 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 Diet

Reports of 6 trials (including 103,658 patients) were identified .
Among these comparisons, 6 trials are about diet.
During the selection 1 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with diet for all the endpoints with data in at least one trial are summarized table 1.

Table 1: *Results summary - Diet*

Benefit	Harmful	No evidence
	Diet versus usual diet	
↓ non fatal MI RR=0.41* [0.20;0.86] k=1	↑ death from cancer RR=1.81* [1.02;3.23] k=1	→ stroke (fatal and non fatal) RR=0.59^{NS} [0.30;1.15] k=1 → coronary event RR=0.80^{NS} [0.57;1.12] k=1 → coronary death RR=0.82^{NS} [0.55;1.21] k=1 → all cause death RR=0.98^{NS} [0.83;1.15] 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 Fibrates

Reports of 3 trials (including 14,748 patients) were identified .
Among these comparisons, two trials are about clofibrate and one about gemfibrozil.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Clofibrate

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

Table 2: *Results summary - Clofibrate*

Benefit	Harmful	No evidence
	Clofibrate versus placebo	
↓ non fatal MI RR=0.75* [0.60;0.94] k=1	↑ all cause death RR=1.27* [1.01;1.59] k=1	→ coronary event RR=0.83^{NS} [0.68;1.00] k=1 → coronary death RR=1.12^{NS} [0.76;1.65] k=1 → death from cancer RR=1.35^{NS} [0.96;1.91] k=1

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

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

Gemfibrozil

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

Table 3: *Results summary - Gemfibrozil*

Benefit	Harmful	No evidence
	Gemfibrozil versus placebo	
↓ coronary event RR=0.66* [0.48;0.92] k=1 ↓ non fatal MI RR=0.63* [0.44;0.91] k=1		→ coronary death RR=0.73^{NS} [0.37;1.46] k=1 → death from cancer RR=0.99^{NS} [0.43;2.29] k=1 → all cause death RR=1.02^{NS} [0.67;1.54] k=1

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

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

0.1.3 Inhibitor of lipoprotein-associated phospholipase

Only one trials including 0 patients was found.
Among these comparisons, one trial are about darapladib.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with darapladib for all the endpoints with data in at least one trial are summarized table 4.

Table 4: *Results summary - Darapladib*

Benefit	Harmful	No evidence
	Darapladib versus placebo	

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

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

0.1.4 Probucol

Only one trials including 163 patients was found.
Among these comparisons, one trial are about probucol.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with probucol for all the endpoints with data in at least one trial are summarized table 5.

Table 5: *Results summary - Probucol*

Benefit	Harmful	No evidence
	Probucol versus control	

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

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

0.1.5 Resins

Reports of 5 trials (including 6,282 patients) were identified .
Among these comparisons, one trial are about cholestyramine and 4 about colestipol.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Cholestyramine

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

Table 6: *Results summary - Cholestyramine*

Benefit	Harmful	No evidence
	Cholestyramine versus placebo	
		→ coronary event RR=0.83^{NS} [0.67;1.01] k=1 → coronary death RR=0.79^{NS} [0.49;1.26] k=1 → death from cancer RR=1.06^{NS} [0.53;2.14] k=1 → non fatal MI RR=0.82^{NS} [0.66;1.03] k=1 → all cause death RR=0.95^{NS} [0.69;1.32] k=1

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

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

Colestipol

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

Table 7: *Results summary - Colestipol*

Benefit	Harmful	No evidence
	Colestipol versus placebo	
		→ coronary death RR=0.60^{NS} [0.34;1.06] k=1 → death from cancer RR=0.98^{NS} [0.14;6.96] k=1 → all cause death RR=0.76^{NS} [0.50;1.15] k=1

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

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

0.1.6 Statins

Reports of 20 trials (including 31,225 patients) were identified .
Among these comparisons, one trial are about any statin,5 about atorvastatin,two about fluvastatin,one about lovastatin,one about pitavastatin,8 about pravastatin and two about simvastatin. No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. One ongoing trial was identified.

Any statin

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

Table 8: *Results summary - Any statin*

Benefit	Harmful	No evidence
	Any statin versus no statin	

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

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

Atorvastatin

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

Table 9: *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 → 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 → 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 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 → 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 10.

Table 10: *Results summary - Fluvastatin*

Benefit	Harmful	No evidence
Fluvastatin versus placebo		

continued...

Benefit	Harmful	No evidence
		→ 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 → 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 $p < 0.05$)

Lovastatin

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

Table 11: *Results summary - Lovastatin*

Benefit	Harmful	No evidence
	Lovastatin versus placebo	
↓ coronary event RR=0.76† [0.62;0.92] k=1 ↓ coronary death and non fatal MI RR=0.76† [0.62;0.92] k=1		→ cardiovascular death RR=0.68^{NS} [0.37;1.26] k=1 → stroke (fatal and non fatal) RR=0.82^{NS} [0.41;1.67] k=1 → coronary death RR=0.73^{NS} [0.34;1.59] k=1 → rhabdomyolysis RR=0.50^{NS} [0.05;5.51] k=1 → all cause death RR=1.04^{NS} [0.76;1.41] k=1

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

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

Pitavastatin

Results obtained with pitavastatin for all the endpoints with data in at least one trial are summarized table 12.

Table 12: *Results summary - Pitavastatin*

Benefit	Harmful	No evidence
	Pitavastatin versus atorvastatin	

continued...

Benefit	Harmful	No evidence

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

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

Pravastatin

Results obtained with pravastatin for all the endpoints with data in at least one trial are summarized table 13.

Table 13: *Results summary - Pravastatin*

Benefit	Harmful	No evidence
Pravastatin versus placebo		
↓ cardiovascular events RR=0.59¶ [0.49;0.72] k=3 ↓ cardiovascular death RR=0.68* [0.48;0.98] k=1 ↓ coronary event RR=0.70¶ [0.58;0.84] k=1 ↓ coronary death and non fatal MI RR=0.70¶ [0.58;0.84] k=1 ↓ all cause death RR=0.76* [0.61;0.95] k=5		→ stroke (fatal and non fatal) RR=0.87^{NS} [0.61;1.24] k=5 → coronary death RR=0.73^{NS} [0.48;1.10] k=1 → cardiac death RR=0.79^{NS} [0.49;1.28] k=4 → death from cancer RR=0.90^{NS} [0.60;1.34] k=1 → rhabdomyolysis RR=1.00^{NS} [0.02;50.25] k=1 → non fatal MI RR=0.44^{NS} [0.14;1.44] H k=5 → revascularization RR=1.17^{NS} [0.55;2.45] k=3
Pravastatin versus usual care		
		→ 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 → 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 14.

Table 14: *Results summary - Simvastatin*

Benefit	Harmful	No evidence
Simvastatin versus placebo		

continued...

Benefit	Harmful	No evidence
		→ 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 → 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 cardiovascular prevention in patients with LDL elevation and without CHD. The following classes of treatment are considered:

1. diet
2. fibrates
3. inhibitor of lipoprotein-associated phospholipase
4. Probucol
5. resins
6. 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 cardiovascular prevention in patients with LDL elevation and without CHD.

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 cardiovascular prevention.

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 event, Non fatal MI, Coronary death, stroke (fatal and non fatal), Death from cancer, All cause death, .

1.6 Structure of the report

Each of the eligible studies is summarised in part **??**. A summary of the studies together with an evaluation of their quality is given in part I to **??**, listed by therapeutic class. The therapeutic classes included diet, fibrates, inhibitor of lipoprotein-associated phospholipase, Probucol, resins, 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

Diet

2 Overview of diet

2.1 Included trials

A total of 6 randomized comparisons which enrolled 103658 patients were identified. In all, 6 randomized comparisons concerned diet.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 24) for diet.

The average study size was 17276 patients (range 846 to 57460). The first study was published in 1969, and the last study was published in 1986.
A total of 1 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 2.1 (page 20) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

2.2 Summary of meta-analysis results

The meta-analysis of the available trials about diet provide the results listed in tables 2.2 to 2.2 (page 21) and in the following graphs.

2.2.1 Diet

Diet was superior to **usual diet** in terms of non fatal MI (RR=0.41, 95% CI 0.20 to 0.86, p=0.0174, 1 trial). However, no significant difference was found on stroke (fatal and non fatal) (RR=0.59, 95% CI 0.30 to 1.15, p=0.1217, 1 trial), coronary event (RR=0.80, 95% CI 0.57 to 1.12, p=0.1875, 1 trial)and coronary death (RR=0.82, 95% CI 0.55 to 1.21, p=0.3076, 1 trial). Diet appear to be associated with significantly greater risk of death from cancer (RR=1.81, 95% CI 1.02 to 3.23, p=0.0425, 1 trial).

Table 2.1: *Main study characteristics - diet*

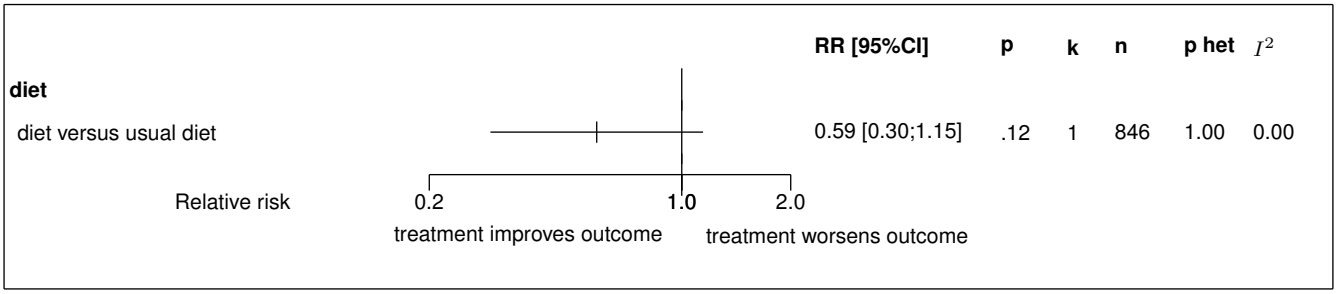
Trial	Patients	Treatments	Trial design and method
Diet			
Diet versus usual diet			
Finnish Mental Hospital (Miettinen), 1985 [1, 2, 3] n = 612 vs. 610	middle-aged institionalized women without CHD	cholesterol-lowering diet (low in saturated fats and cholesterol and relatively high in polyunsaturated fats) **versus** usual diet	open, blind assessment cluster-randomized cross-ove Finland
Goteborg, 1986 [4] n = 10004 vs. 20028	men, 47-55 years old at entry	multifactorial intervention programme **versus** no intervention	open parallel groups Primary endpoint: not defined Sweden
Hjermann, 1981 [5] n = 604 vs. 628	healthy, normotensive men at high risk of coronary heart disease	diet **versus** usual diet	open parallel groups Primary endpoint: not defined Sweden
MRFIT, 1982 [6] n = 6428 vs. 6438	high-risk men aged 35 to 57 years	multifactor intervention program **versus** usual diet	open parallel groups Primary endpoint: CHD death
Veterans Ad. (Dayton), 1969 [7] n = 424 vs. 422	men in domicilary care, age >55, with or without CHD	cholesterol lowering diet **versus** usual diet	double blind parallel groups Primary endpoint: MI, sudden death multicentre, USA
WHO Collaborative, 1986 [8] n = 30489 vs. 26971	middle-aged men	multifactorial prevention **versus** usual diet	open parallel groups 80 centres, Belgium, Italy, Poland, UK

Table 2.2: *Summary of all results for diet*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
diet versus usual diet						
stroke (fatal and non fatal)	RR=0.59	0.30;1.15	0.1217	1.0000 (0.00)	1	846
coronary event	RR=0.80	0.57;1.12	0.1875	1.0000 (0.00)	1	846
coronary death	RR=0.82	0.55;1.21	0.3076	1.0000 (0.00)	1	846
death from cancer	RR=1.81	1.02;3.23	0.0425	1.0000 (0.00)	1	846
non fatal MI	RR=0.41	0.20;0.86	0.0174	1.0000 (0.00)	1	846
all cause death	RR=0.98	0.83;1.15	0.7893	1.0000 (0.00)	1	846

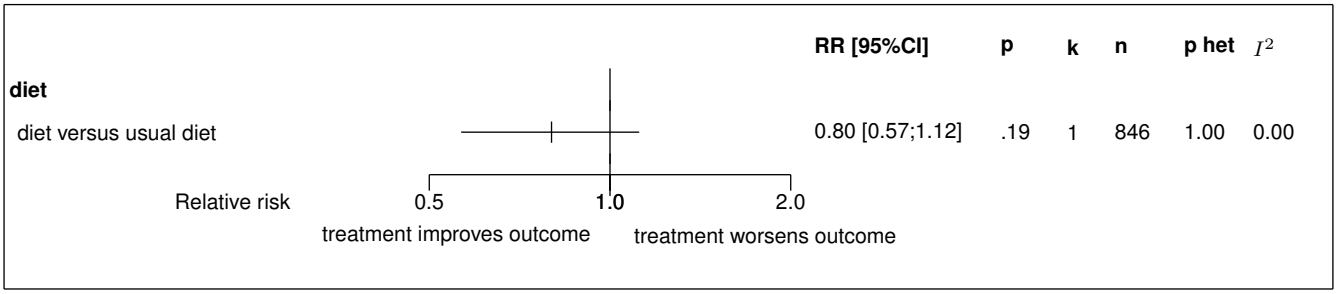
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 2.1: *Forest's plot for stroke (fatal and non fatal)*



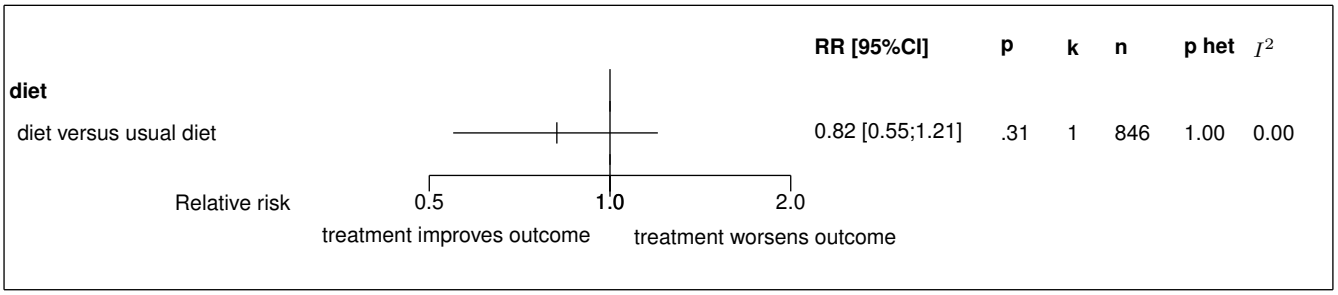
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.2: *Forest's plot for coronary event*



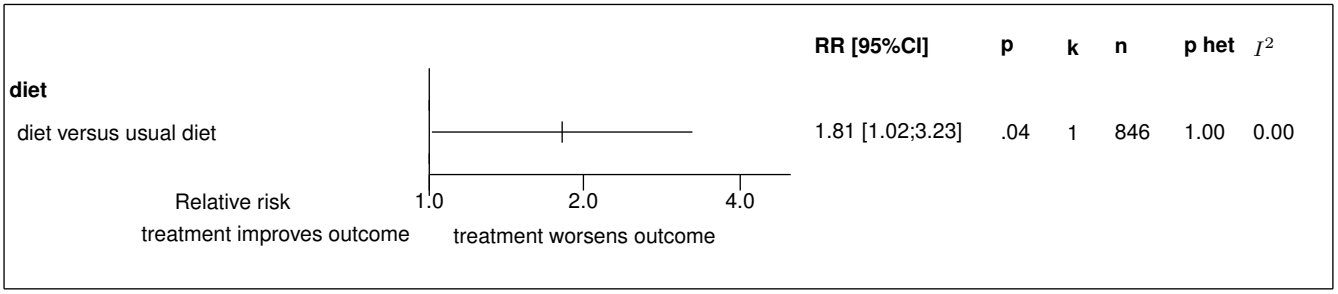
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.3: *Forest's plot for coronary death*



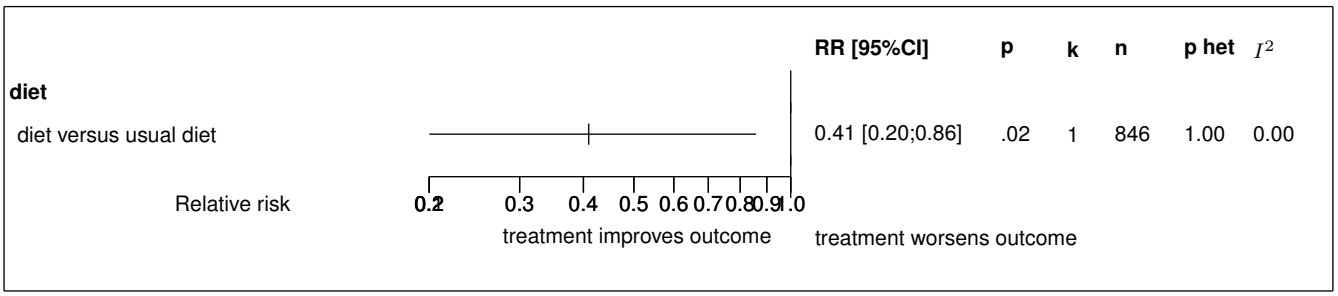
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.4: *Forest's plot for death from cancer*



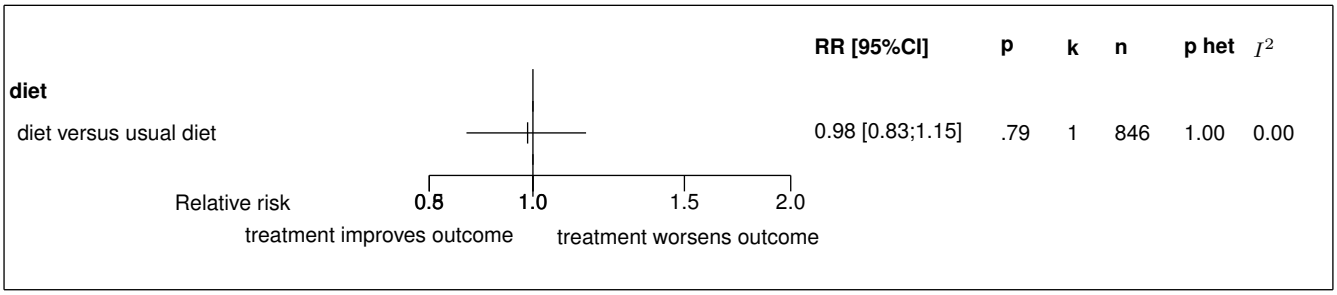
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.5: *Forest's plot for non fatal MI*



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

Figure 2.6: *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

A total of 6 RCTs which randomized 103658 patients were identified: all compared diet with usual diet.
The average study size was 17276 patients (range 846 to 57460). The first study was published in 1969, and the last study was published in 1986.
A total of 1 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.
Coronary event data was reported in 1 trials; 1 trials reported data on non fatal MI; 1 trials reported data on coronary death; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on death from cancer; and 1 trials reported data on all cause death.
Following tables 3.1 (page 24), 3.2 (page 24), 3.4 (page 27), and 3.3 (page 25) summarized the main characteristics of the trials including in this systematic review of randomized trials of diet.

Table 3.1: *Treatment description - diet - diet*

Trial	Studied treatment	Control treatment
Diet versus usual diet		
Finnish Mental Hospital (Miettinen) (1985) [1, 2, 3]	cholesterol-lowering diet (low in saturated fats and cholesterol and relatively high in polyunsaturated fats)	usual diet
Goteborg (1986) [4]	multifactorial intervention programme	no intervention
Hjermann (1981) [5]	diet	usual diet
MRFIT (1982) [6]	multifactor intervention program	usual diet
Veterans Ad. (Dayton) (1969) [7]	cholesterol lowering diet	usual diet
WHO Collaborative (1986) [8]	multifactorial prevention	usual diet

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

Trial	Patients
Diet versus usual diet	
Finnish Mental Hospital (Miettinen) (1985) [1, 2, 3]	Middle-aged institionalized women without CHD
Goteborg (1986) [4]	Men, 47-55 years old at entry
Hjermann (1981) [5]	Healthy, normotensive men at high risk of coronary heart disease
MRFIT (1982) [6]	High-risk men aged 35 to 57 years
Veterans Ad. (Dayton) (1969) [7]	Men in domicilary care, age >55, with or without CHD **Inclusion criteria:** **Exclusion criteria:** diabetes; alcohol abuse; serious illness
WHO Collaborative (1986) [8]	Middle-aged men

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

Trial	Design	Duration	Centre	Primary end-point
Diet versus usual diet				
Finnish Mental Hospital (Miettinen), 1985 [1, 2, 3] n=1222	Cluster-randomized cross-ove open, blind assessment exploratory trial	6.0 years	Finland	
Goteborg, 1986 [4] n=30032	Parallel groups open confirmatory trial at risk of bias	10 years	Sweden	not defined
Hjermann, 1981 [5] n=1232	Parallel groups open confirmatory trial at risk of bias	6.5 years	Sweden	not defined
MRFIT, 1982 [6] n=12866	Parallel groups open confirmatory trial at risk of bias	6.5 y		CHD death

continued...

Trial	Design	Duration	Centre	Primary endpoint
Veterans Ad. (Dayton), 1969 [7] n=846	Parallel groups double blind confirmatory trial at low risk of bias	3.6 and 8 y	USA multicentre	MI, sudden death
WHO Collaborative, 1986 [8] n=57460	Parallel groups open confirmatory trial at low risk of bias	5.5 years	Belgium, Italy, Poland, UK 80 centres	

Table 3.4: *Trial characteristics - diet - diet*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Diet versus usual diet				
Finnish Mental Hospital (Miettinen), 1985 [1, 2, 3]				
Goteborg, 1986 [4]				
Hjermann, 1981 [5]				
MRFIT, 1982 [6]				
Veterans Ad. (Dayton), 1969 [7]				
WHO Collaborative, 1986 [8]				

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 28). This table is followed by the Forest's plot corresponding to each endpoint.

Diet versus usual diet

Only one of the 6 studies 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 0.59 (95% CI 0.30 to 1.15, p=0.1217).
Only one of the 6 studies eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 0.80 (95% CI 0.57 to 1.12, p=0.1875).
Only one of the 6 studies 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 0.82 (95% CI 0.55 to 1.21, p=0.3076).
Only one of the 6 studies eligible for this comparison provided data on **non fatal MI**. The analysis detected a statistically significant difference in favor of diet in non fatal MI, with a RR of 0.41 (95% CI 0.20 to 0.86, p=0.0174).

Table 3.5: *Results details - diet - diet*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
diet versus usual diet						
stroke (fatal and non fatal)	RR=0.59	[0.30;1.15]	0.1217	1.0000 (I^2=0.00)	1	846
coronary event	RR=0.80	[0.57;1.12]	0.1875	1.0000 (I^2=0.00)	1	846
coronary death	RR=0.82	[0.55;1.21]	0.3076	1.0000 (I^2=0.00)	1	846
death from cancer	RR=1.81	[1.02;3.23]	0.0425	1.0000 (I^2=0.00)	1	846
non fatal MI	RR=0.41	[0.20;0.86]	0.0174	1.0000 (I^2=0.00)	1	846
all cause death	RR=0.98	[0.83;1.15]	0.7893	1.0000 (I^2=0.00)	1	846

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 stroke (fatal and non fatal)*

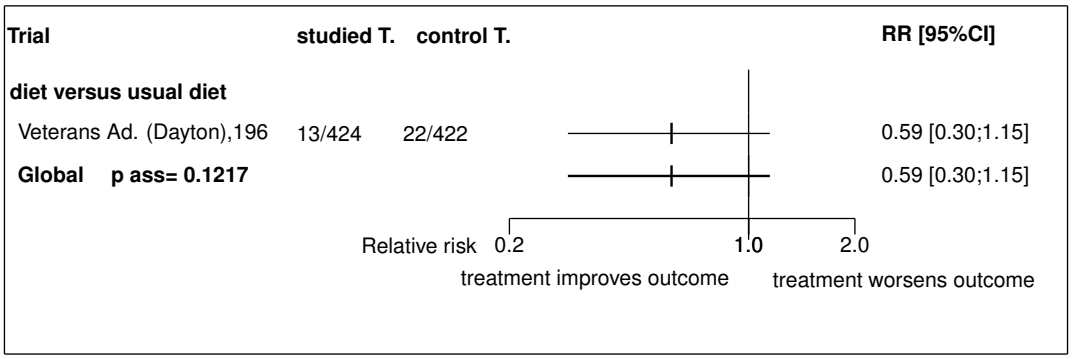


Figure 3.2: *Forest's plot for coronary event*

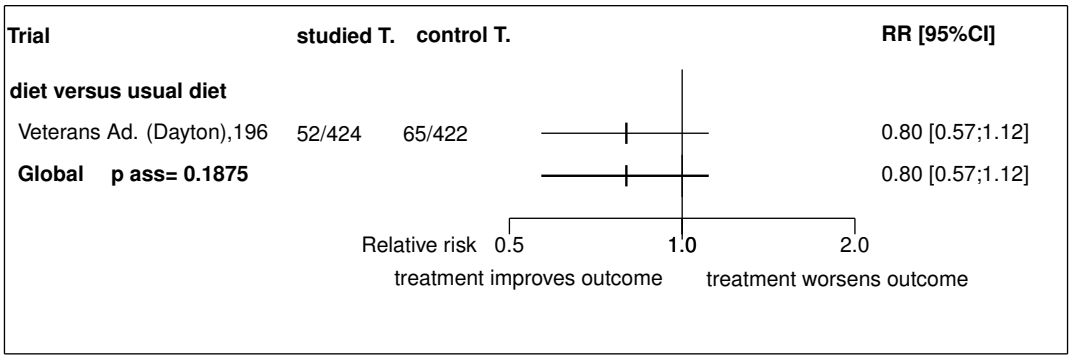


Figure 3.3: *Forest's plot for coronary death*

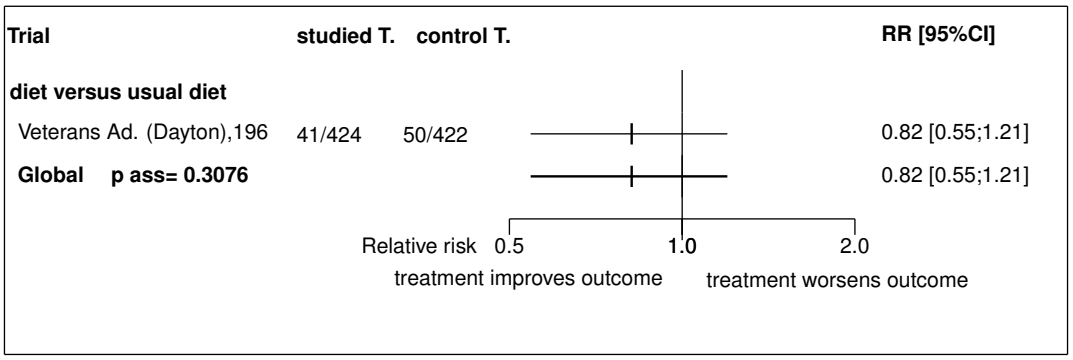


Figure 3.4: *Forest's plot for death from cancer*

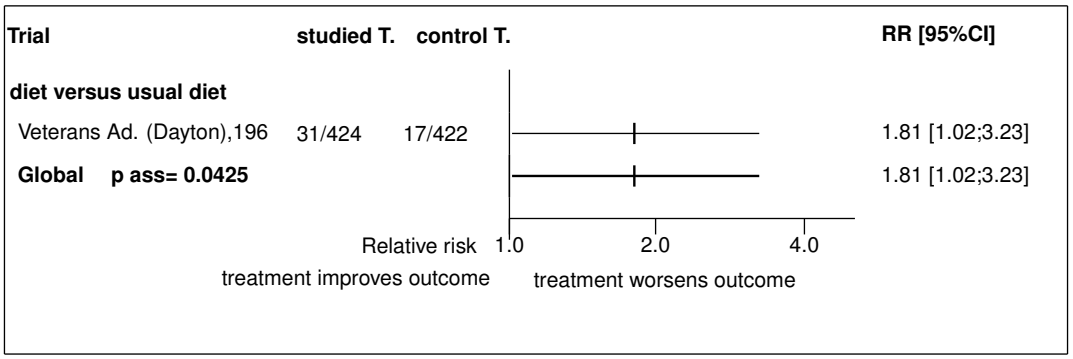


Figure 3.5: *Forest's plot for non fatal MI*

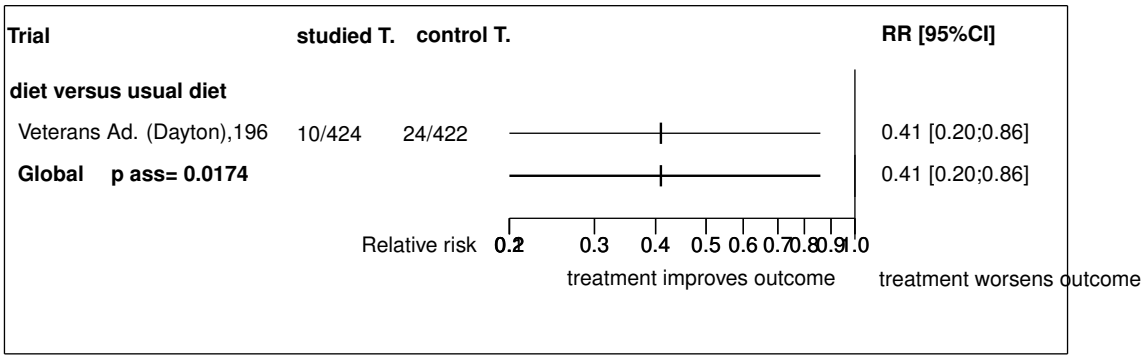
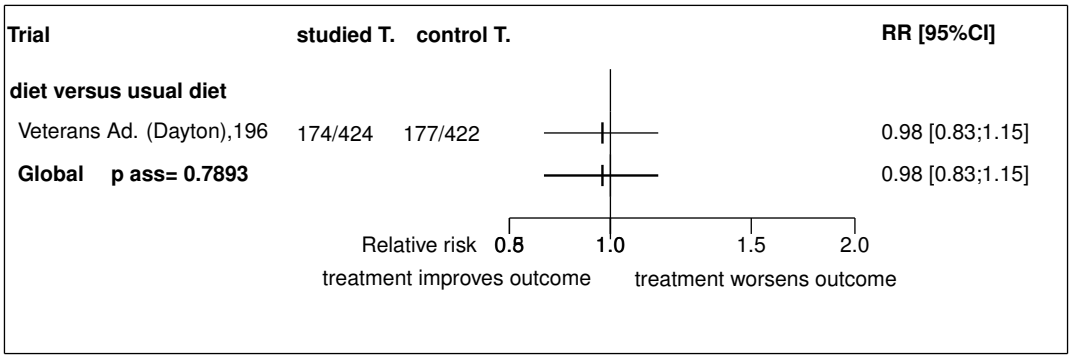


Figure 3.6: *Forest's plot for all cause death*



References

[1] . European collaborative trial of multifactorial prevention of coronary heart disease: final report on the 6-year results. World Health Organisation European Collaborative Group. Lancet 1986;1:869-72. [PMID=2870351]

[2] Miettinen TA, Huttunen JK, Naukkarinen V, Strandberg T, Mattila S, Kumlin T, Sarna S. Multifactorial primary prevention of cardiovascular diseases in middle-aged men. Risk factor changes, incidence, and mortality. JAMA 1985;254:2097-102. [PMID=4046137]

[3] Miettinen M, Turpeinen O, Karvonen MJ, Pekkarinen M, Paavilainen E, Elosuo R. Dietary prevention of coronary heart disease in women: the Finnish mental hospital study. Int J Epidemiol 1983;12:17-25. [PMID=6840954]

[4] Wilhelmsen L, Berglund G, Elmfeldt D, Tibblin G, Wedel H, Pennert K, Vedin A, Wilhelmsson C, Werkö L. The multifactor primary prevention trial in Göteborg, Sweden. Eur Heart J 1986;7:279-88. [PMID=3720755]

[5] Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. Lancet 1981;2:1303-10. [PMID=6118715]

[6] . Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. JAMA 1982;248:1465-77. [PMID=7050440]

[7] Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation 1969; 40(supp 2):1-55. [PMID=0]

[8] . European collaborative trial of multifactorial prevention of coronary heart disease: final report on the 6-year results. World Health Organisation European Collaborative Group. Lancet 1986;1:869-72. [PMID=2870351]

3.3 Individual trial summaries

Table 3.6: *Finnish Mental Hospital (Miettinen), 1985 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1222 (612 vs. 610) **Follow-up duration:** 6.0 years **Study design:** Randomized controlled trial Cluster-randomized cross-ove Open, blind assessment Exploratory trial Finland	Middle-aged institionalized women without CHD	**Studied treatment:** cholesterol-lowering diet (low in saturated fats and cholesterol and relatively high in polyunsaturated fats) **Control treatment:** usual diet	

References

. European collaborative trial of multifactorial prevention of coronary heart disease: final report on the 6-year results. World Health Organisation European Collaborative Group. Lancet 1986;1:869-72 [PMID=2870351]
Miettinen TA, Huttunen JK, Naukkarinen V, Strandberg T, Mattila S, Kumlin T, Sarna S. Multifactorial primary prevention of cardiovascular diseases in middle-aged men. Risk factor changes, incidence, and mortality. JAMA 1985;254:2097-102 [PMID=4046137]
Miettinen M, Turpeinen O, Karvonen MJ, Pekkarinen M, Paavilainen E, Elosuo R. Dietary prevention of coronary heart disease in women: the Finnish mental hospital study. Int J Epidemiol 1983;12:17-25 [PMID=6840954]

Table 3.7: *Goteborg, 1986 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=30032 (10004 vs. 20028) **Follow-up duration:** 10 years **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Sweden	Men, 47-55 years old at entry	**Studied treatment:** multifactorial intervention programme **Control treatment:** no intervention	

Reference

Wilhelmsen L, Berglund G, Elmfeldt D, Tibblin G, Wedel H, Pennert K, Vedin A, Wilhelmsson C, Werkö L. The multifactor primary prevention trial in Göteborg, Sweden. Eur Heart J 1986;7:279-88 [PMID=3720755]

Table 3.8: *Hjermann, 1981 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1232 (604 vs. 628) **Follow-up duration:** 6.5 years **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Sweden	Healthy, normotensive men at high risk of coronary heart disease	**Studied treatment:** diet **Control treatment:** usual diet	

Reference

Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. Lancet 1981;2:1303-10 [PMID=6118715]

Table 3.9: *MRFIT, 1982 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=12866 (6428 vs. 6438) **Follow-up duration:** 6.5 y **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias	High-risk men aged 35 to 57 years	**Studied treatment:** multifactor intervention program **Control treatment:** usual diet	

Reference

. Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. JAMA 1982;248:1465-77 [PMID=7050440]

Table 3.10: *Veterans Ad. (Dayton), 1969 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=846 (424 vs. 422) **Follow-up duration:** 3.6 and 8 y **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias USA, multicentre	Men in domicilary care, age >55, with or without CHD **Exclusion criteria:** diabetes; alcohol abuse; serious illness	**Studied treatment:** cholesterol lowering diet **Control treatment:** usual diet	Stroke (fatal and non fatal) RR=0.59 [0.30;1.15] Coronary event RR=0.80 [0.57;1.12]

Reference

Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation 1969; 40(supp 2):1-55 [PMID=0]

Table 3.11: *WHO Collaborative, 1986 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=57460 (30489 vs. 26971) **Follow-up duration:** 5.5 years **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at low risk of bias Belgium, Italy, Poland, UK, 80 centres	Middle-aged men	**Studied treatment:** multifactorial prevention **Control treatment:** usual diet	

Reference

. European collaborative trial of multifactorial prevention of coronary heart disease: final report on the 6-year results. World Health Organisation European Collaborative Group. Lancet 1986;1:869-72 [PMID=2870351]

4 Global meta-analysis: all diet

4.1 Global meta-analysis: all diet versus usual diet

Table 4.1: *All dietversus usual diet*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
stroke (fatal and non fatal)	RR=0.59	0.30;1.15	0.1217	1.0000 (0.00)	1	846
coronary event	RR=0.80	0.57;1.12	0.1875	1.0000 (0.00)	1	846
coronary death	RR=0.82	0.55;1.21	0.3076	1.0000 (0.00)	1	846
non fatal MI	RR=0.41	0.20;0.86	0.0174	1.0000 (0.00)	1	846

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 diet

No ongoing trial was identified.

6 Excluded studies for diet

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table 6.1.

Table 6.1: *Excluded studies of diet*

Study	Exclusion reason
Minnesota (1989) [1, 2]	

References

[1] Frantz ID Jr, Dawson EA, Ashman PL, Gatewood LC, Bartsch GE, Kuba K, Brewer ER. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. Arteriosclerosis 1989;9:129-35. [PMID=2643423]

[2] Frantz ID Jr, Dawson EA, Ashman PL, Gatewood LC, Bartsch GE, Kuba K, Brewer ER. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. Arteriosclerosis 1989 Jan-Feb;9:129-35. [PMID=2643423]

Part II

Fibrates

7 Overview of fibrates

7.1 Included trials

A total of 3 randomized comparisons which enrolled 14748 patients were identified. In all, 2 randomized comparisons concerned clofibrate and one gemfibrozil.
The detailed descriptions of trials and meta-analysis results is given in section 8 (page 50) for clofibrate and in section 9 (page 59) for gemfibrozil.

The average study size was 4916 patients (range 40 to 10627). The first study was published in 1974, and the last study was published in 1987.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 7.1 (page 44) 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 fibrates provide the results listed in tables 7.2 to 7.3 (page 45) and in the following graphs.

7.2.1 Clofibrate

Clofibrate was superior to **placebo** in terms of non fatal MI (RR=0.75, 95% CI 0.60 to 0.94, p=0.0109, 1 trial). However, no significant difference was found on coronary event (RR=0.83, 95% CI 0.68 to 1.00, p=0.0530, 1 trial)and coronary death (RR=1.12, 95% CI 0.76 to 1.65, p=0.5733, 1 trial).

7.2.2 Gemfibrozil

Gemfibrozil was superior to **placebo** in terms of total cholesterol (at 1 y) (WMD=-0.66, 95% CI -0.71 to -0.61, p=0.0000, 1 trial)and LDL (WMD=-0.47, 95% CI -0.52 to -0.42, p=0.0000, 1 trial).
But gemfibrozil worsened HDL (at 1 y) (WMD=0.06, 95% CI 0.04 to 0.08, p=0.0000, 1 trial).

Table 7.1: *Main study characteristics - fibrates*

Trial	Patients	Treatments	Trial design and method
Clofibrate			
Clofibrate versus placebo			
Cullen, 1974 n = 20 vs. 20		clofibrate **versus** placebo	parallel groups
WHO clofibrate, 1978 [1, 2] n = 5331 vs. 5296	primary prevention, Hommes, de 30 59 ans	clofibrate 1.6 g daily **versus** olive oil	double blind parallel groups Primary endpoint: IDM et/ou mort subite et/ou ischmie Scotland, Hungary, Czech Republic
Gemfibrozil			
Gemfibrozil versus placebo			
Helsinki (HHS), 1987 [1, 2] n = 2046 vs. 2035	asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non-HDL cholesterol greater than or equal to 200 mg per deciliter [5.2 mmol per liter]	gemfibrozil 1,2 g/d **versus** placebo	double blind parallel groups Primary endpoint: CHD events 37 centres, Finland

Table 7.2: *Summary of all results for clofibrate*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
clofibrate versus placebo						
coronary event	RR=0.83	0.68;1.00	0.0530	1.0000 (0.00)	1	10627
coronary death	RR=1.12	0.76;1.65	0.5733	1.0000 (0.00)	1	10627
death from cancer	RR=1.35	0.96;1.91	0.0854	1.0000 (0.00)	1	10627
non fatal MI	RR=0.75	0.60;0.94	0.0109	1.0000 (0.00)	1	10627
all cause death	RR=1.27	1.01;1.59	0.0428	1.0000 (1.00)	1	10627

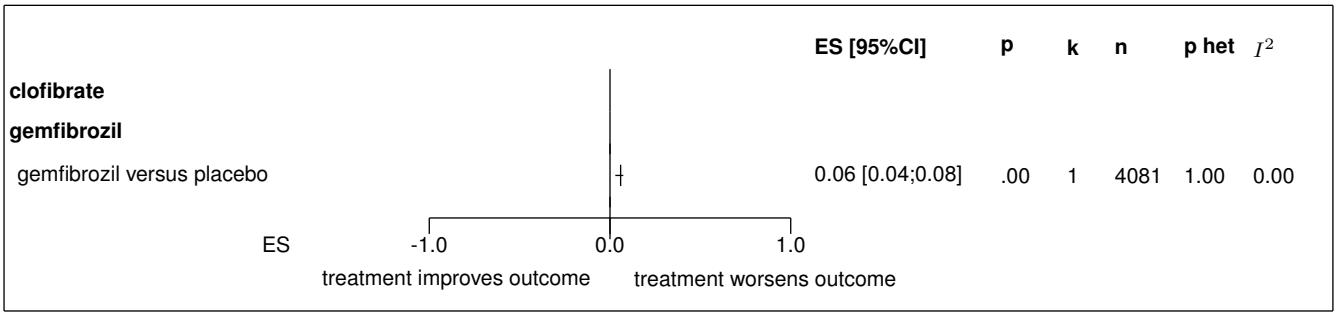
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 7.3: *Summary of all results for gemfibrozil*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
gemfibrozil versus placebo						
HDL (at 1 y)	ES=0.06	0.04;0.08	0.0000	1.0000 (0.00)	1	4081
total cholesterol (at 1 y)	ES=-0.66	-0.71;-0.61	0.0000	1.0000 (0.00)	1	4081
coronary event	RR=0.66	0.48;0.92	0.0154	1.0000 (0.00)	1	4081
coronary death	RR=0.73	0.37;1.46	0.3757	1.0000 (0.00)	1	4081
death from cancer	RR=0.99	0.43;2.29	0.9899	1.0000 (0.00)	1	4081
LDL	ES=-0.47	-0.52;-0.42	0.0000	1.0000 (1.00)	1	4081
non fatal MI	RR=0.63	0.44;0.91	0.0141	1.0000 (0.00)	1	4081
all cause death	RR=1.02	0.67;1.54	0.9339	1.0000 (0.00)	1	4081

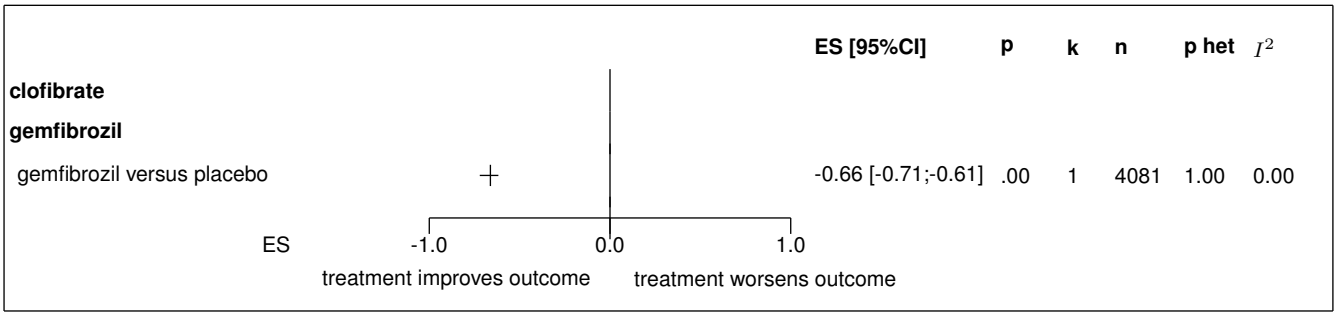
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 7.1: *Forest's plot for HDL (at 1 y)*



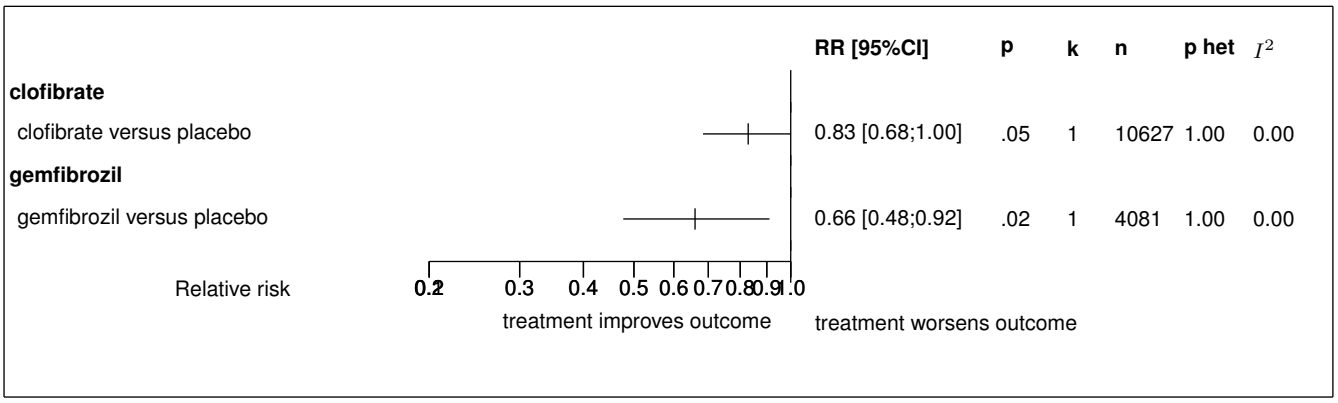
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 7.2: *Forest's plot for total cholesterol (at 1 y)*



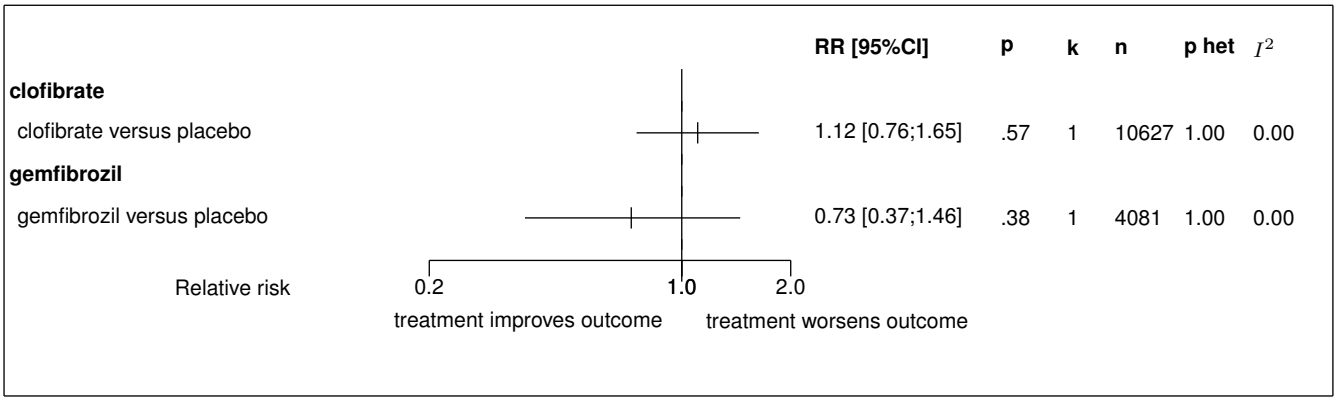
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 7.3: *Forest's plot for coronary event*



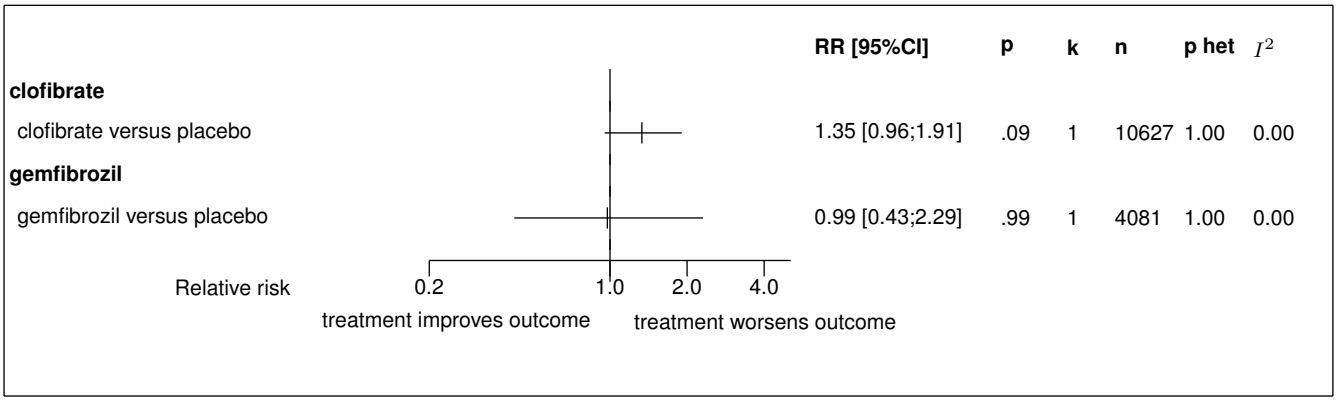
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.4: *Forest's plot for coronary death*



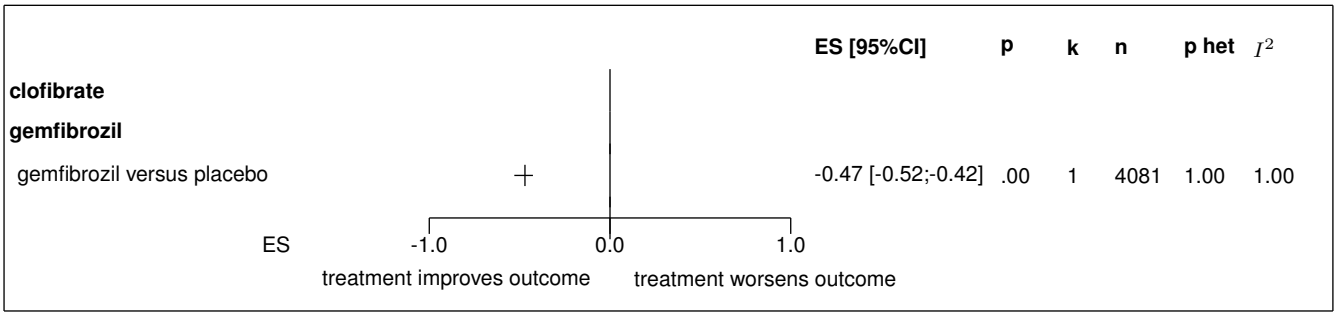
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.5: *Forest's plot for death from cancer*



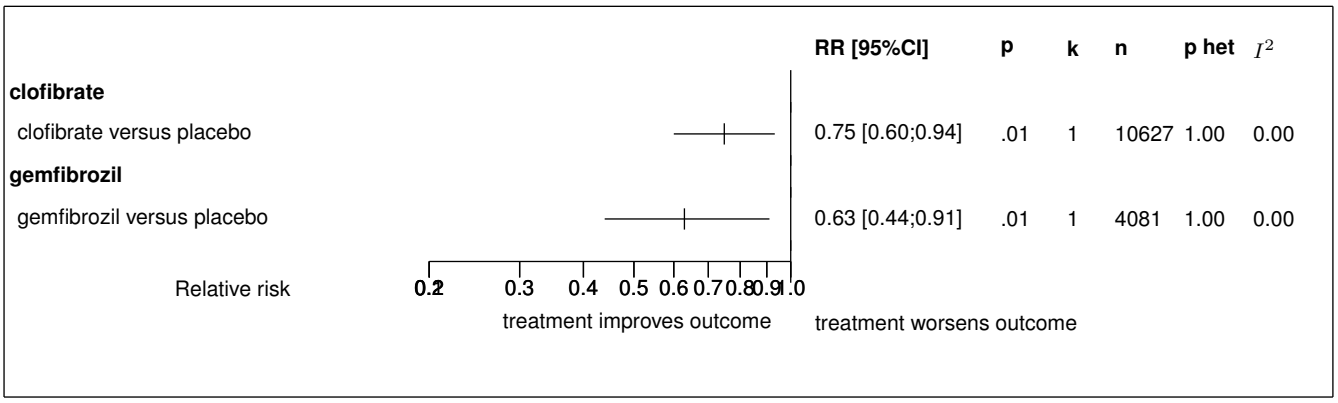
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.6: *Forest's plot for LDL*



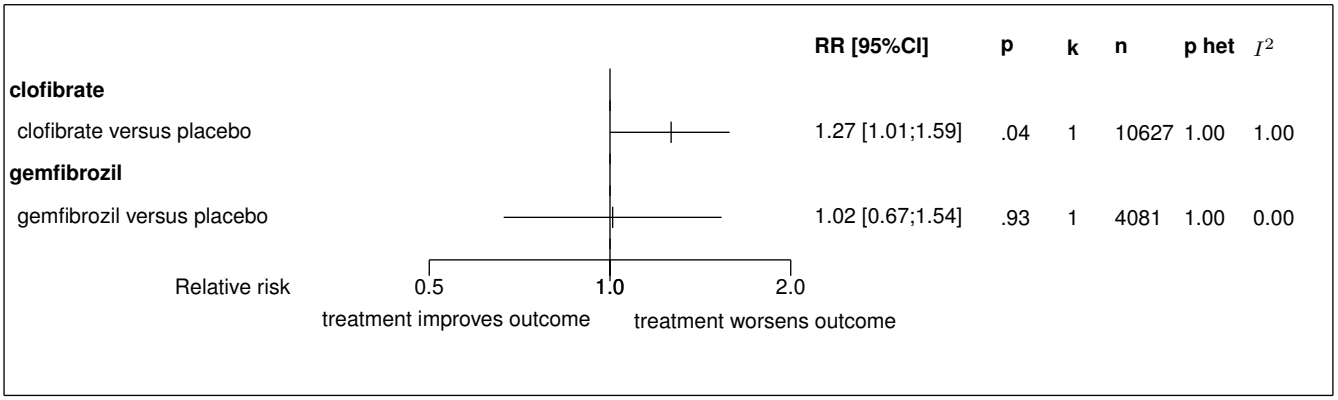
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ʳ: random effect model used

Figure 7.7: *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; ᶠ: random effect model used

Figure 7.8: *Forest's plot for all cause death*



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

8 Detailed results for clofibrate

8.1 Available trials

A total of 2 RCTs which randomized 10667 patients were identified: all compared clofibrate with placebo.
The average study size was 5333 patients (range 40 to 10627). The first study was published in 1974, and the last study was published in 1978.
This trial was double blind in design.
All included studies were reported in English language. We did not found any unpublished trial.
Coronary death data was reported in 1 trials; 1 trials reported data on coronary event; 1 trials reported data on non fatal MI; 1 trials reported data on death from cancer; and 1 trials reported data on all cause death.
Following tables 8.1 (page 50), 8.2 (page 50), 8.4 (page 52), and 8.3 (page 51) summarized the main characteristics of the trials including in this systematic review of randomized trials of clofibrate.

Table 8.1: *Treatment description - fibrates - clofibrate*

Trial	Studied treatment	Control treatment
Clofibrate versus placebo		
Cullen (1974)	clofibrate	placebo
WHO clofibrate (1978) [1, 2]	clofibrate 1.6 g daily	olive oil

Table 8.2: *Descriptions of participants - fibrates - clofibrate*

Trial	Patients	
Clofibrate versus placebo		
Cullen (1974)		
WHO clofibrate (1978) [1, 2]	Primary prevention, Hommes, de 30 59 ans	
	Inclusion criteria: CT dans le tiers suprieur de la distribution de la population considre	**Exclusion criteria:** antcdents ou manifestatons actuelles de maladies cardiaques; hypertension systmique; maladies pulmonairees; diabte ncessitant traitement; cancer; paralysie due a un dommage crbral; maladie renale chronique avance avec manifestations systmiques; cirrhose du foie avec manifestations systmiques

Table 8.3: *Design and methodological quality of trials - fibrates - clofibrate*

Trial	Design	Duration	Centre	Primary end-point
Clofibrate versus placebo				
Cullen, 1974 n=40	Parallel groups confirmatory trial at low risk of bias	2 years		
WHO clofibrate, 1978 [1, 2] n=10627	Parallel groups double blind confirmatory trial at low risk of bias	5.3 years	Scotland, Hungary, Czech Republic	IDM et/ou mort subite et/ou ischmie

Table 8.4: *Trial characteristics - fibrates - clofibrate*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Clofibrate versus placebo				
Cullen, 1974				
WHO clofibrate, 1978 [1, 2]		-0.6 mmol/L		

8.2 Meta-analysis results

The results are detailed in table 8.5 (page 53). This table is followed by the Forest's plot corresponding to each endpoint.

Clofibrate versus placebo

Only one of the 2 studies eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 0.83 (95% CI 0.68 to 1.00, p=0.0530).
Only one of the 2 studies 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 1.12 (95% CI 0.76 to 1.65, p=0.5733).
Only one of the 2 studies eligible for this comparison provided data on **non fatal MI**. The analysis detected a statistically significant difference in favor of clofibrate in non fatal MI, with a RR of 0.75 (95% CI 0.60 to 0.94, p=0.0109).

Table 8.5: *Results details - fibrates - clofibrate*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
clofibrate versus placebo						
coronary event	RR=0.83	[0.68;1.00]	0.0530	1.0000 (I^2=0.00)	1	10627
coronary death	RR=1.12	[0.76;1.65]	0.5733	1.0000 (I^2=0.00)	1	10627
death from cancer	RR=1.35	[0.96;1.91]	0.0854	1.0000 (I^2=0.00)	1	10627
non fatal MI	RR=0.75	[0.60;0.94]	0.0109	1.0000 (I^2=0.00)	1	10627
all cause death	RR=1.27	[1.01;1.59]	0.0428	1.0000 (I^2=1.00)	1	10627

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 coronary event*

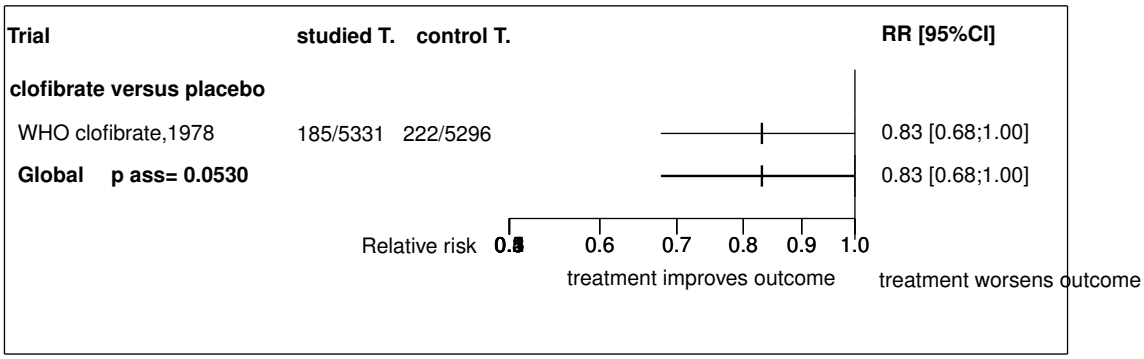


Figure 8.2: *Forest's plot for coronary death*

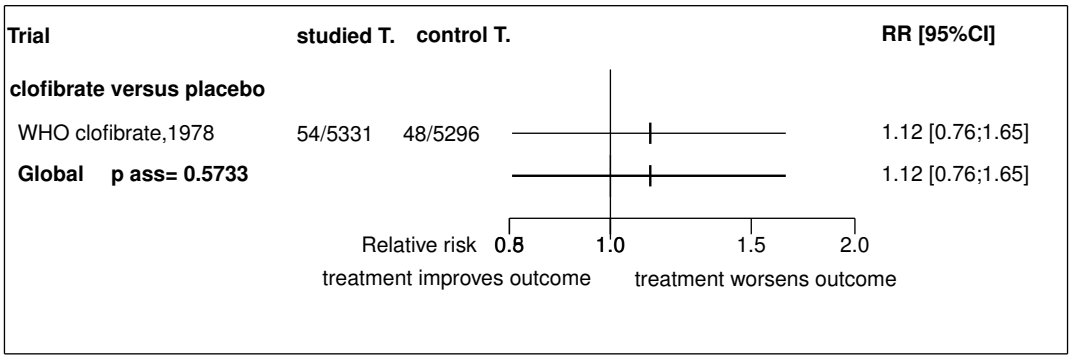


Figure 8.3: *Forest's plot for death from cancer*

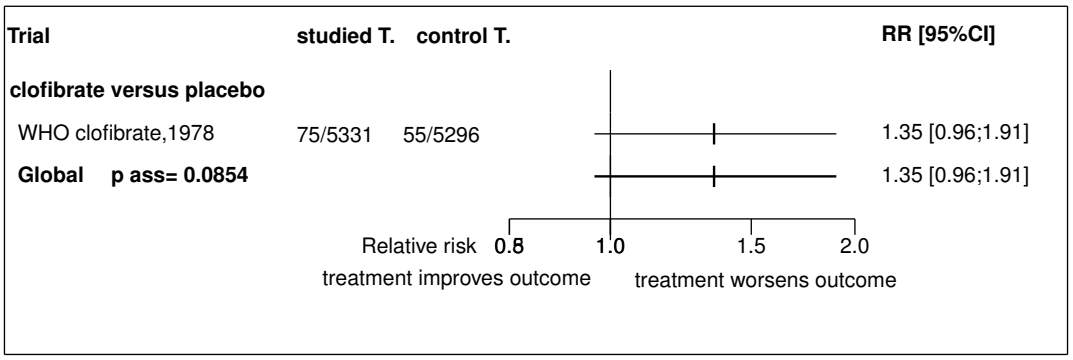


Figure 8.4: *Forest's plot for non fatal MI*

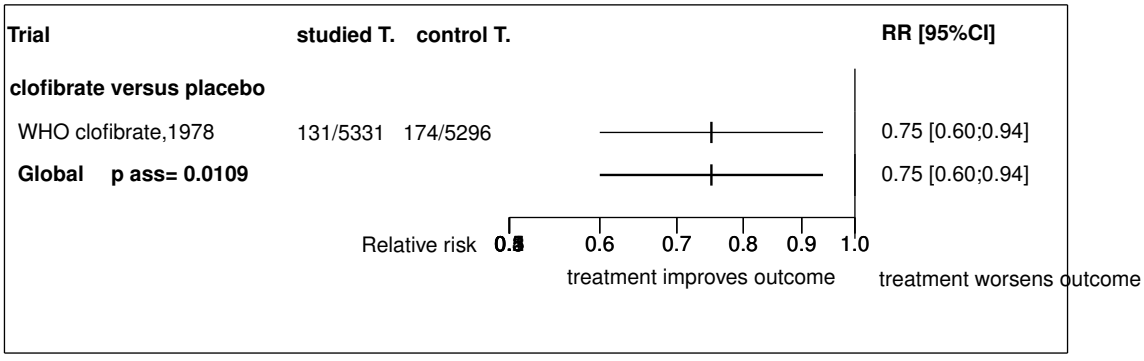
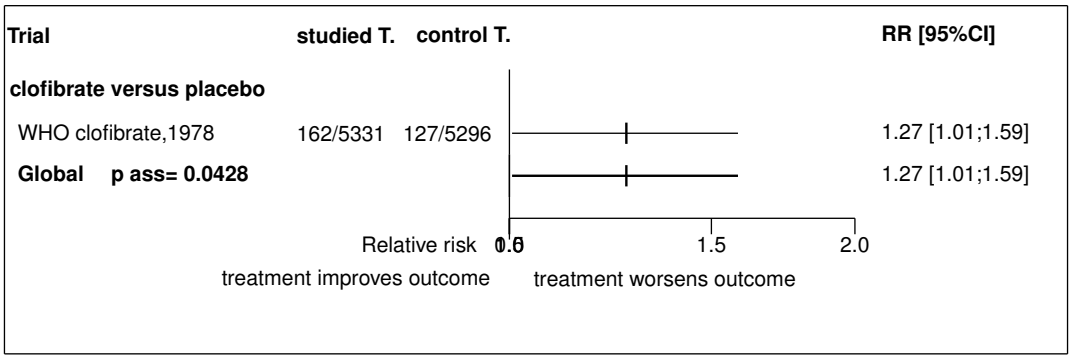


Figure 8.5: *Forest's plot for all cause death*



References

[1] ,. WHO cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. Report of the Committee of Principal Investigators. Lancet 1984; 2:600-4. [PMID=6147641]

[2] Heady JA, Morris JN, Oliver MF,. WHO clofibrate/cholesterol trial: clarifications. Lancet 1992; 340:1405-6. [PMID=1360101]

8.3 Individual trial summaries

Table 8.6: *Cullen, 1974 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=40 (20 vs. 20) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Confirmatory trial at low risk of bias		**Studied treatment:** clofibrate **Control treatment:** placebo	
Reference			

Table 8.7: *WHO clofibrate, 1978 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=10627 (5331 vs. 5296) **Follow-up duration:** 5.3 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Scotland, Hungary, Czech Republic	Primary prevention, Hommes, de 30 59 ans **Inclusion criteria:** CT dans le tiers suprieur de la distribution de la population considre **Exclusion criteria:** Antcdents ou manifestatons actuelles de maladies cardiaques; hypertension systmique; maladies pulmonairees; diabte ncessitant traitement; cancer; paralysie due a un dommage crbral; maladie renale chronique avance avec manifestations systmiques; cirrhose du foie avec manifestations systmiques	**Studied treatment:** clofibrate 1.6 g daily **Control treatment:** olive oil	Coronary event RR=0.83 [0.68;1.00]

References

,. WHO cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. Report of the Committee of Principal Investigators. Lancet 1984; 2:600-4 [PMID=6147641]
Heady JA, Morris JN, Oliver MF,. WHO clofibrate/cholesterol trial: clarifications. Lancet 1992; 340:1405-6 [PMID=1360101]

9 Detailed results for gemfibrozil

9.1 Available trials

Only one trial which randomized 4081 patients was identified: it compared gemfibrozil with placebo.
This trial included 4081 patients and was published in 1987.
This trial was double blind in design.
It was reported in English language.
Total cholesterol (at 1 y) data was reported in 1 trials; 1 trials reported data on LDL; 1 trials reported data on coronary death; 1 trials reported data on HDL (at 1 y); 1 trials reported data on coronary event; 1 trials reported data on non fatal MI; 1 trials reported data on death from cancer; and 1 trials reported data on all cause death.
Following tables 9.1 (page 59), 9.2 (page 59), 9.4 (page 61), and 9.3 (page 60) summarized the main characteristics of the trial including in this systematic review of randomized trials of gemfibrozil.

Table 9.1: *Treatment description - fibrates - gemfibrozil*

Trial	Studied treatment	Control treatment
Gemfibrozil versus placebo		
Helsinki (HHS) (1987) [1, 2]	gemfibrozil 1,2 g/d	placebo
	Concomittant treatment: Rgimes	

Table 9.2: *Descriptions of participants - fibrates - gemfibrozil*

Trial	Patients	
Gemfibrozil versus placebo		
Helsinki (HHS) (1987) [1, 2]	Asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non-HDL cholesterol greater than or equal to 200 mg per deciliter [5.2 mmol per liter]	
	Inclusion criteria: CT - HDL >ou = 5.2 mmol/l lors de 2 mesures conscutives	**Exclusion criteria:** manifestations cliniques de maladies cardiaques coronariennes; anomalies ECG; insuffisance cardiaque congestive

Table 9.3: *Design and methodological quality of trials - fibrates - gemfibrozil*

Trial	Design	Duration	Centre	Primary end-point
Gemfibrozil versus placebo				
Helsinki (HHS), 1987 [1, 2] n=4081	Parallel groups double blind confirmatory trial at low risk of bias	5 years inclusion period: ND	Finland 37 centres	CHD events

Table 9.4: *Trial characteristics - fibrates - gemfibrozil*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Gemfibrozil versus placebo				
Helsinki (HHS), 1987 [1, 2]		-0.5 mmol/L		

9.2 Meta-analysis results

The results are detailed in table 9.5 (page 62). This table is followed by the Forest's plot corresponding to each endpoint.

Gemfibrozil versus placebo

The single study eligible for this comparison provided data on **HDL (at 1 y)**. The analysis detected a statistically significant difference in favor of placebo in HDL (at 1 y), with a WMD of 0.06 (95% CI 0.04 to 0.08, p=0.0000).
The single study eligible for this comparison provided data on **total cholesterol (at 1 y)**. The analysis detected a statistically significant difference in favor of gemfibrozil in total cholesterol (at 1 y), with a WMD of -0.66 (95% CI -0.71 to -0.61, p=0.0000).
The single study eligible for this comparison provided data on **coronary event**. The analysis detected a statistically significant difference in favor of gemfibrozil in coronary event, with a RR of 0.66 (95% CI 0.48 to 0.92, p=0.0154).
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 0.73 (95% CI 0.37 to 1.46, p=0.3757).
The single study eligible for this comparison provided data on **LDL**. The analysis detected a statistically significant difference in favor of gemfibrozil in LDL, with a WMD of -0.47 (95% CI -0.52 to -0.42, p=0.0000).
The single study eligible for this comparison provided data on **non fatal MI**. The analysis detected a statistically significant difference in favor of gemfibrozil in non fatal MI, with a RR of 0.63 (95% CI 0.44 to 0.91, p=0.0141).

Table 9.5: *Results details - fibrates - gemfibrozil*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
gemfibrozil versus placebo						
HDL (at 1 y)	ES=0.06	[0.04;0.08]	0.0000	1.0000 (I^2=0.00)	1	4081
total cholesterol (at 1 y)	ES=-0.66	[-0.71;-0.61]	0.0000	1.0000 (I^2=0.00)	1	4081
coronary event	RR=0.66	[0.48;0.92]	0.0154	1.0000 (I^2=0.00)	1	4081
coronary death	RR=0.73	[0.37;1.46]	0.3757	1.0000 (I^2=0.00)	1	4081
death from cancer	RR=0.99	[0.43;2.29]	0.9899	1.0000 (I^2=0.00)	1	4081
LDL	ES=-0.47	[-0.52;-0.42]	0.0000	1.0000 (I^2=1.00)	1	4081
non fatal MI	RR=0.63	[0.44;0.91]	0.0141	1.0000 (I^2=0.00)	1	4081
all cause death	RR=1.02	[0.67;1.54]	0.9339	1.0000 (I^2=0.00)	1	4081

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 HDL (at 1 y)*

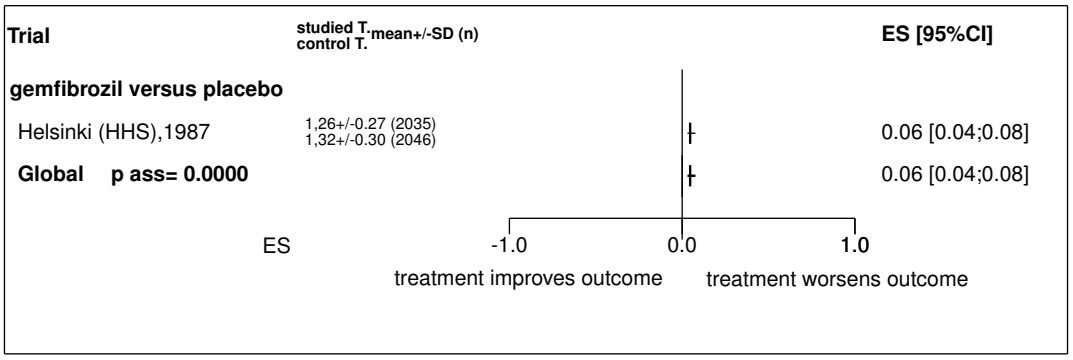


Figure 9.2: *Forest's plot for total cholesterol (at 1 y)*

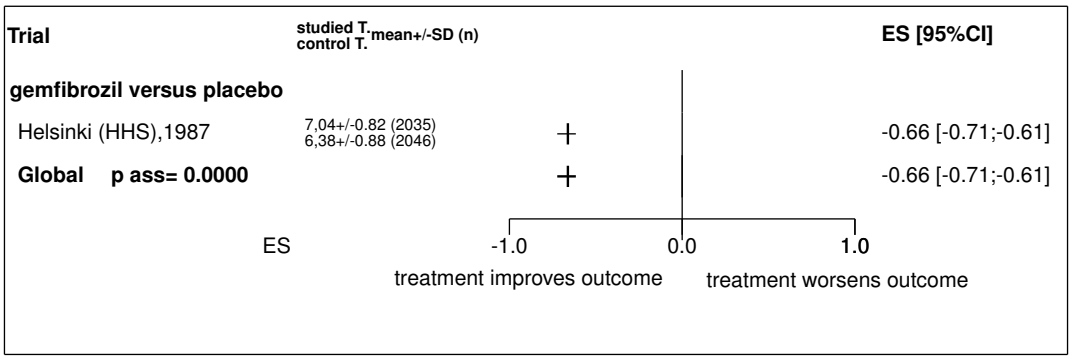


Figure 9.3: *Forest's plot for coronary event*

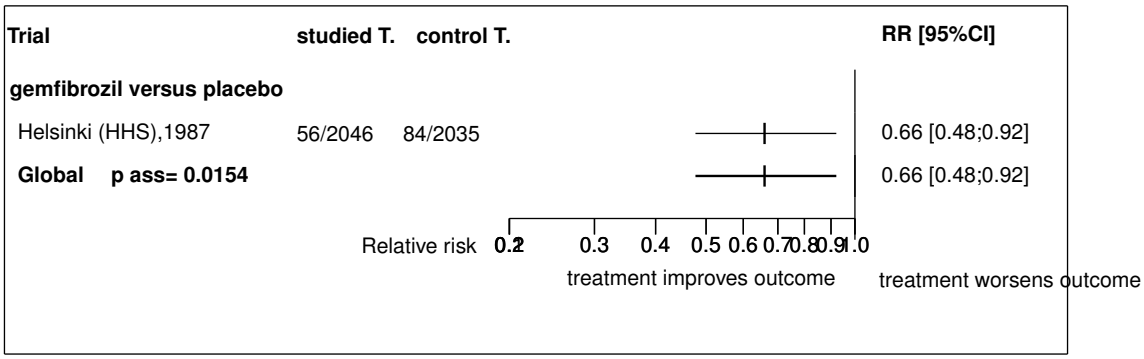


Figure 9.4: *Forest's plot for coronary death*

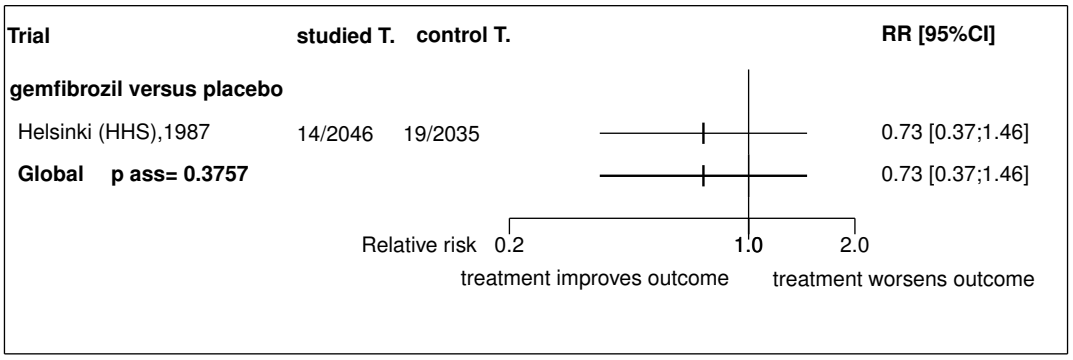


Figure 9.5: *Forest's plot for death from cancer*

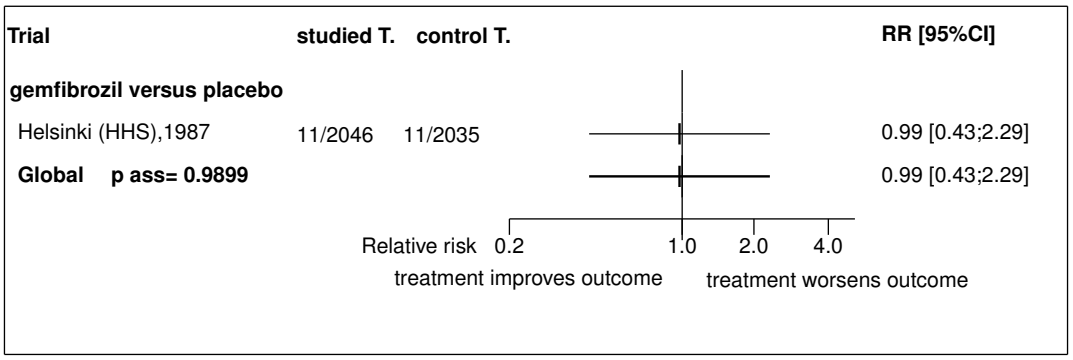


Figure 9.6: *Forest's plot for LDL*

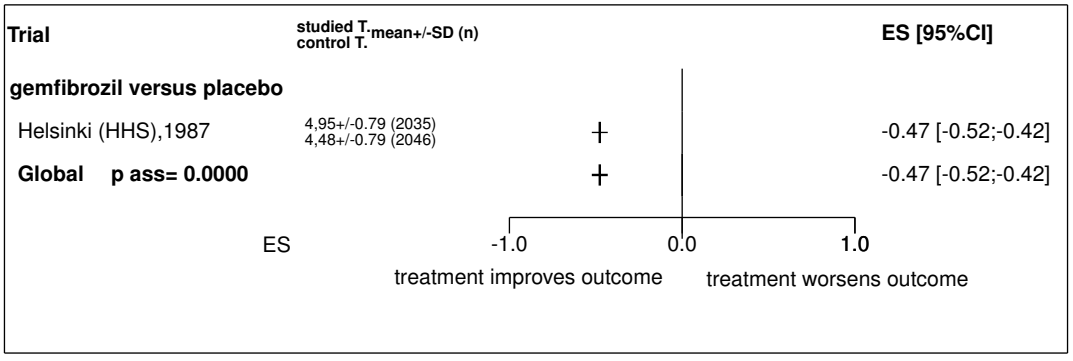


Figure 9.7: *Forest's plot for non fatal MI*

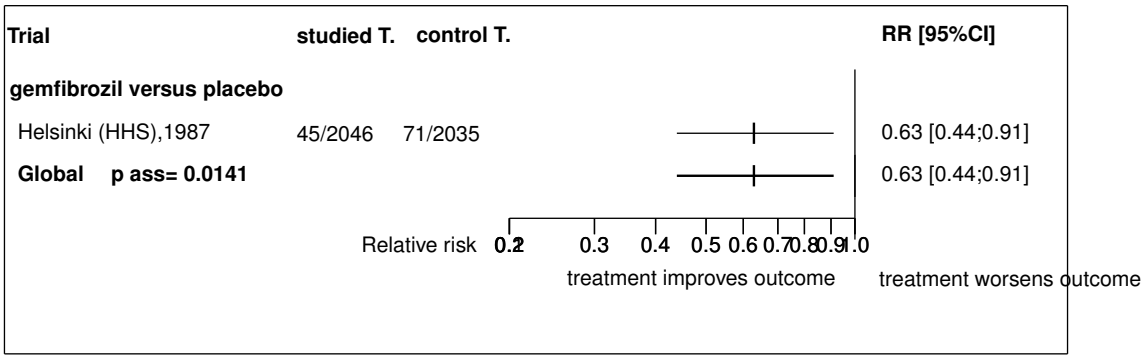
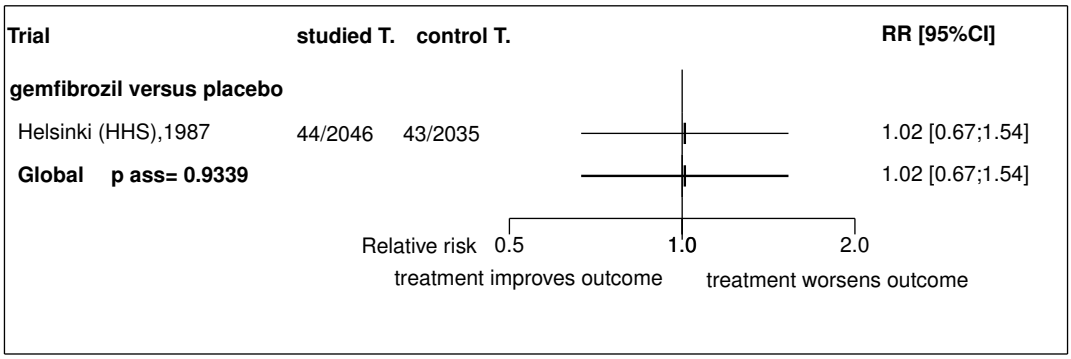


Figure 9.8: *Forest's plot for all cause death*



References

[1] Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, et al,. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 1988; 260:641-51. [PMID=3164788]

[2] Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45. [PMID=3313041]

9.3 Individual trial summaries

Table 9.6: *Helsinki (HHS), 1987 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4081 (2046 vs. 2035) **Follow-up duration:** 5 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Finland, 37 centres **Inclusion period:** ND	Asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non-HDL cholesterol greater than or equal to 200 mg per deciliter [5.2 mmol per liter] **Inclusion criteria:** CT - HDL >ou = 5.2 mmol/l lors de 2 mesures conscutives **Exclusion criteria:** Manifestations cliniques de maladies cardiaques coronariennes; anomalies ECG; insuffisance cardiaque congestive	**Studied treatment:** gemfibrozil 1,2 g/d **Control treatment:** placebo **Concomittant treat.:**Rgimes	Coronary event RR=0.66 [0.48;0.92] HDL (at 1 y) WMD=0.06 [0.04;0.08] Total cholesterol (at 1 y) WMD=-0.66 [-0.71;-0.61]

References

Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, et al,. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 1988; 260:641-51 [PMID=3164788]
Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45 [PMID=3313041]

10 Global meta-analysis: all fibrates

10.1 Global meta-analysis: all fibrates versus placebo

Table 10.1: *All fibratesversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
HDL (at 1 y)	ES=0.06	0.04;0.08	0.0000	1.0000 (0.00)	1	4081
total cholesterol (at 1 y)	ES=-0.66	-0.71;-0.61	0.0000	1.0000 (0.00)	1	4081
coronary event	RR=0.77	0.63;0.95	0.0120	0.2569 (0.22)	2	14708
coronary death	RR=1.00	0.69;1.44	0.9994	0.2945 (0.09)	2	14708
LDL	ES=-0.47	-0.52;-0.42	0.0000	1.0000 (1.00)	1	4081
non fatal MI	RR=0.71	0.59;0.86	0.0000	0.4368 (0.00)	2	14708

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

11 Ongoing studies of fibrates

No ongoing trial was identified.

12 Excluded studies for fibrates

No trial was excluded.

References

Part III

Inhibitor of lipoprotein-associated phospholipase

13 Overview of inhibitor of lipoprotein-associated phospholipase

13.1 Included trials

Only one trial which randomized 0 patients was identified. In all, 1 randomized comparison concerned darapladib.
The detailed descriptions of trials and meta-analysis results is given in section 14 (page 74) for darapladib.

This trial included NaN patients and was published in .
Erreur ??? 0 et 0.
It was reported in English language.
The table 13.1 (page 72) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

13.2 Summary of meta-analysis results

The meta-analysis of the available trials about inhibitor of lipoprotein-associated phospholipase provide the results listed in tables 13.2 to 13.2 (page 73) and in the following graphs.

13.2.1 Darapladib

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

Table 13.1: *Main study characteristics - inhibitor of lipoprotein-associated phospholipase*

Trial	Patients	Treatments	Trial design and method
Darapladib			
Darapladib versus placebo			
SOLID-TIMI 52, [1] n = NA vs. NA		**versus**	

Table 13.2: *Summary of all results for darapladib*

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

14 Details

14.1 Available trials

Only one trial which randomized 0 patients was identified: it compared darapladib with placebo. This trial included NaN patients and was published in .
Erreur ??? 0 et 0.
It was reported in English language.
data was reported in trials;
Following tables 14.1 (page 74), 14.2 (page 74), 14.4 (page 76), and 14.3 (page 74) summarized the main characteristics of the trial including in this systematic review of randomized trials of darapladib.

Table 14.1: *Treatment description - inhibitor of lipoprotein-associated phospholipase - darapladib*

Trial	Studied treatment	Control treatment
Darapladib versus placebo		
SOLID-TIMI 52 () [1]		

Table 14.2: *Descriptions of participants - inhibitor of lipoprotein-associated phospholipase - darapladib*

Trial	Patients
Darapladib versus placebo	
SOLID-TIMI 52 () [1]	

Table 14.3: *Design and methodological quality of trials - inhibitor of lipoprotein-associated phospholipase - darapladib*

Trial	Design	Duration	Centre	Primary endpoint
Darapladib versus placebo				
SOLID-TIMI 52, [1] n=NaN				

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 14.4: *Trial characteristics - inhibitor of lipoprotein-associated phospholipase - darapladib*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Darapladib versus placebo		
SOLID-TIMI 52, [1]		

14.2 Meta-analysis results

The results are detailed in table 14.5 (page 77). This table is followed by the Forest's plot corresponding to each endpoint.

Darapladib versus placebo

No data were presented in the 1 trial identified

Table 14.5: *Results details - inhibitor of lipoprotein-associated phospholipase - darapladib*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
darapladib versus placebo						
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] O'Donoghue ML, Braunwald E, White HD, Steen DP, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP. Effect of Darapladib on Major Coronary Events After an Acute Coronary Syndrome: The SOLID-TIMI 52 Randomized Clinical Trial. JAMA 2014 Aug 31;:. [PMID=25173516]

14.3 Individual trial summaries

Table 14.6: *SOLID-TIMI 52, - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** **Study design:** Randomized controlled trial		**Studied treatment:** **Control treatment:**	

Reference

O'Donoghue ML, Braunwald E, White HD, Steen DP, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP. Effect of Darapladib on Major Coronary Events After an Acute Coronary Syndrome: The SOLID-TIMI 52 Randomized Clinical Trial. JAMA 2014 Aug 31;: [PMID=25173516]

15 Global meta-analysis: all inhibitor of lipoprotein-associated phospholipase

15.1 Global meta-analysis: all inhibitor of lipoprotein-associated phospholipase versus placebo

Table 15.1: *All inhibitor of lipoprotein-associated phospholipaseversus placebo*

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

16 Ongoing studies of inhibitor of lipoprotein-associated phospholipase

No ongoing trial was identified.

17 Excluded studies for inhibitor of lipoprotein-associated phospholipase

No trial was excluded.

References

Part IV

Probucol

18 Overview of probucol

18.1 Included trials

Only one trial which randomized 163 patients was identified. In all, 1 randomized comparison concerned probucol.
The detailed descriptions of trials and meta-analysis results is given in section 19 (page 86) for probucol.

This trial included 163 patients and was published in 2002.
This trial was open-label in design.
It was reported in English language.
The table 18.1 (page 84) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

18.2 Summary of meta-analysis results

The meta-analysis of the available trials about probucol provide the results listed in tables 18.2 to 18.2 (page 85) and in the following graphs.

18.2.1 Probucol

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

Table 18.1: *Main study characteristics - Probucol*

Trial	Patients	Treatments	Trial design and method
Probucol			
Probucol versus control			
FATS Fukosawa (probucol), 2002 [1] n = 82 vs. 81	asymptomatic patients with hypercholesterolemia	probucol 500 mg/day **versus** diet alone	open parallel groups Primary endpoint: change in IMT in the common carotid artery Japan

Table 18.2: *Summary of all results for probucol*

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

19 Details

19.1 Available trials

Only one trial which randomized 163 patients was identified: it compared probucol with control.
This trial included 163 patients and was published in 2002.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 19.1 (page 86), 19.2 (page 86), 19.4 (page 87), and 19.3 (page 86) summarized the main characteristics of the trial including in this systematic review of randomized trials of probucol.

Table 19.1: *Treatment description - Probucol - probucol*

Trial	Studied treatment	Control treatment
Probucol versus control		
FATS Fukosawa (probucol) (2002) [1]	probucol 500 mg/day	diet alone

Table 19.2: *Descriptions of participants - Probucol - probucol*

Trial	Patients
Probucol versus control	
FATS Fukosawa (probucol) (2002) [1]	Asymptomatic patients with hypercholesterolemia

Table 19.3: *Design and methodological quality of trials - Probucol - probucol*

Trial	Design	Duration	Centre	Primary endpoint
Probucol versus control				
FATS Fukosawa (probucol), 2002 [1] n=163	Parallel groups open exploratory trial	2 years	Japan	change in IMT in the common carotid artery

Table 19.4: *Trial characteristics - Probucol - probucol*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Probucol versus control				
FATS Fukosawa (probucol), 2002 [1]	-0.8			

19.2 Meta-analysis results

The results are detailed in table 19.5 (page 88). This table is followed by the Forest's plot corresponding to each endpoint.

Probucol versus control

No data were presented in the 1 trial identified

Table 19.5: *Results details - Probucol - probucol*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
probucol versus control						
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] Sawayama Y, Shimizu C, Maeda N, Tatsukawa M, Kinukawa N, Koyanagi S, Kashiwagi S, Hayashi J. Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST). J Am Coll Cardiol 2002 Feb 20;39:610-6. [PMID=11849859]

19.3 Individual trial summaries

Table 19.6: *FATS Fukosawa (probucol), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=163 (82 vs. 81) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Japan	Asymptomatic patients with hypercholesterolemia	**Studied treatment:** probucol 500 mg/day **Control treatment:** diet alone	

Reference

Sawayama Y, Shimizu C, Maeda N, Tatsukawa M, Kinukawa N, Koyanagi S, Kashiwagi S, Hayashi J. Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST). J Am Coll Cardiol 2002 Feb 20;39:610-6 [PMID=11849859]

20 Global meta-analysis: all Probucol

20.1 Global meta-analysis: all Probucol versus control

Table 20.1: *All Probucolversus control*

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

21 Ongoing studies of Probucol

No ongoing trial was identified.

22 Excluded studies for Probucol

No trial was excluded.

References

Part V

Resins

23 Overview of resins

23.1 Included trials

A total of 5 randomized comparisons which enrolled 6282 patients were identified. In all, 1 randomized comparison concerned cholestyramine and 4 colestipol.
The detailed descriptions of trials and meta-analysis results is given in section 24 (page 100) for cholestyramine and in section 25 (page 108) for colestipol.

The average study size was 1256 patients (range 40 to 3806). The first study was published in 1974, and the last study was published in 1984.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 23.1 (page 96) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

23.2 Summary of meta-analysis results

The meta-analysis of the available trials about resins provide the results listed in tables 23.2 to 23.3 (page 97) and in the following graphs.

23.2.1 Cholestyramine

No significant difference was found between **cholestyramine** and **placebo** in terms of coronary event (RR=0.83, 95% CI 0.67 to 1.01, p=0.0657, 1 trial), coronary death (RR=0.79, 95% CI 0.49 to 1.26, p=0.3224, 1 trial)and non fatal MI (RR=0.82, 95% CI 0.66 to 1.03, p=0.0818, 1 trial).

23.2.2 Colestipol

No significant difference was found between **colestipol** and **placebo** in terms of coronary death (RR=0.60, 95% CI 0.34 to 1.06, p=0.0786, 1 trial).

Table 23.1: *Main study characteristics - resins*

Trial	Patients	Treatments	Trial design and method
Cholestyramine			
Cholestyramine versus placebo			
LRC, 1984 [1] n = 1906 vs. 1900	asymptomatic middle-aged men with primary hypercholesterolemia (type II hyperlipoproteinemia)	cholestyramine 24 g daily **versus** placebo	double blind parallel groups Primary endpoint: definite CHD death, MI multicentre, USA
Colestipol			
Colestipol versus placebo			
Gundersen, 1976 [1] n = 36 vs. 30	hypercholesterolemic patients	colestipol 10g twice daily **versus** placebo	double-blind parallel groups
Ruoff, 1978 [2] n = 21 vs. 19	hypercholesterolemic patients	colestipol **versus** placebo	parallel groups
Ryan, 1974 [3] n = 44 vs. 48	patients with hypercholesterolemia	colestipol15 g/day **versus** placebo	parallel groups
UCS (Dorr), 1978 [4] n = 1149 vs. 1129	hommes et femmes, >18 ans	colestipol hydrochloride 32 mg/dl **versus** placebo	double blind parallel groups Primary endpoint: death

Table 23.2: *Summary of all results for cholestyramine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cholestyramine versus placebo						
coronary event	RR=0.83	0.67;1.01	0.0657	1.0000 (0.00)	1	3806
coronary death	RR=0.79	0.49;1.26	0.3224	1.0000 (0.00)	1	3806
death from cancer	RR=1.06	0.53;2.14	0.8638	1.0000 (0.00)	1	3806
non fatal MI	RR=0.82	0.66;1.03	0.0818	1.0000 (0.00)	1	3806
all cause death	RR=0.95	0.69;1.32	0.7809	1.0000 (0.00)	1	3806

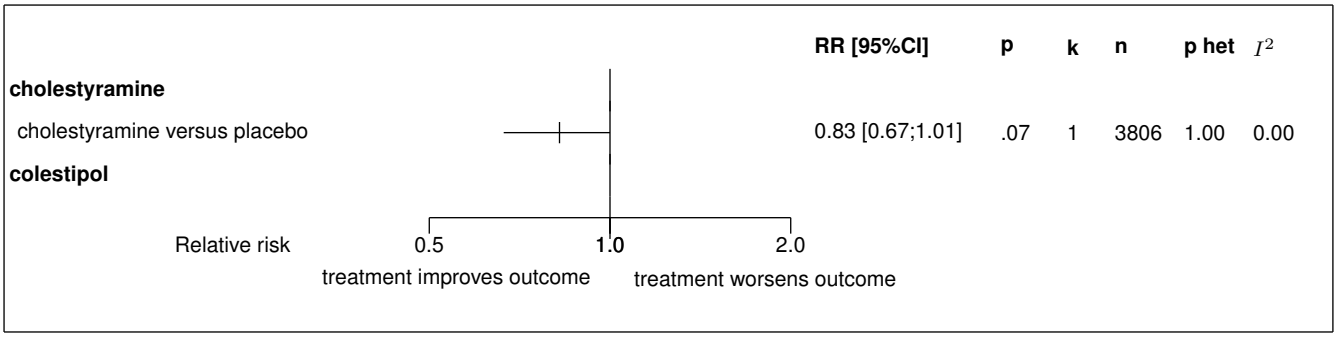
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 23.3: *Summary of all results for colestipol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
colestipol versus placebo						
coronary death	RR=0.60	0.34;1.06	0.0786	1.0000 (0.00)	1	2278
death from cancer	RR=0.98	0.14;6.96	0.9860	1.0000 (0.00)	1	2278
all cause death	RR=0.76	0.50;1.15	0.1957	1.0000 (0.00)	1	2278

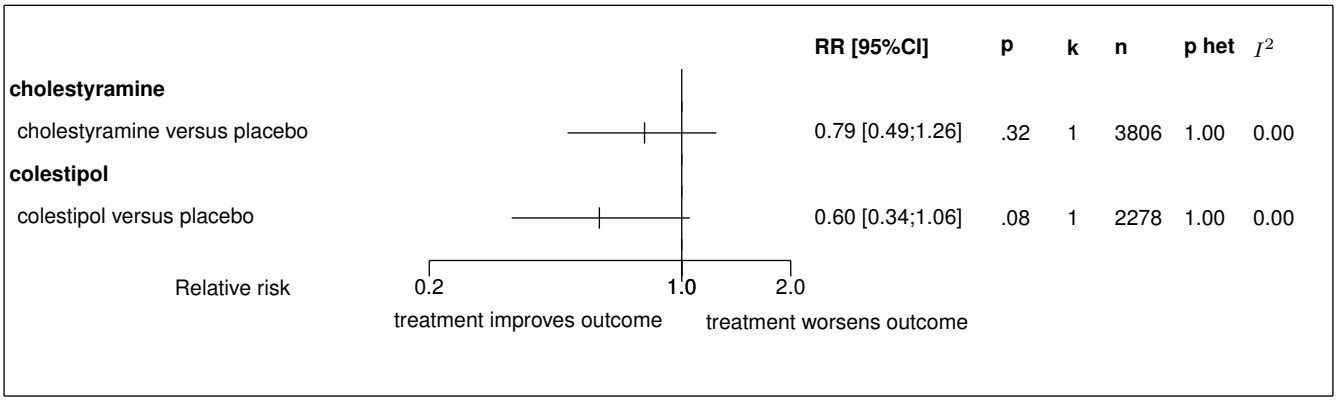
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 23.1: *Forest's plot for coronary event*



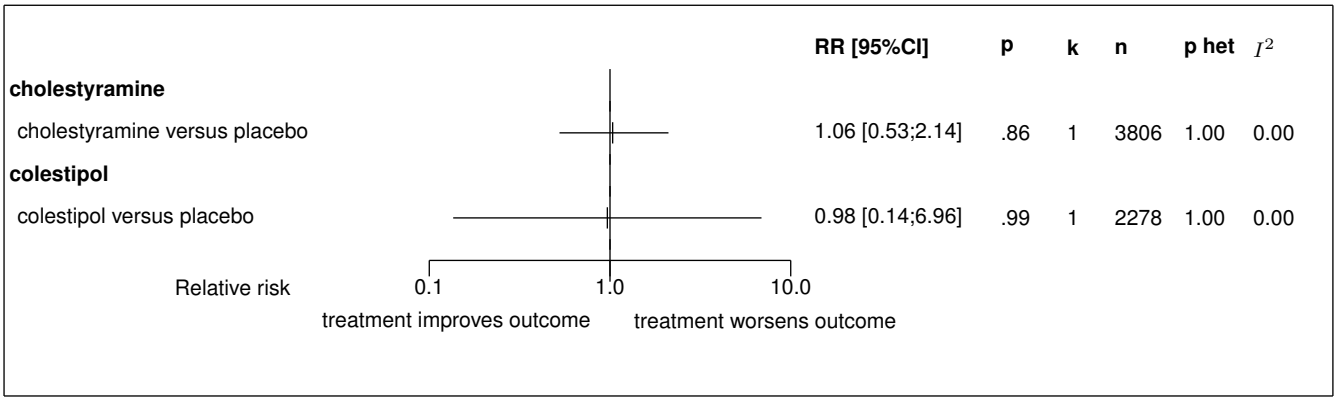
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 23.2: *Forest's plot for coronary death*



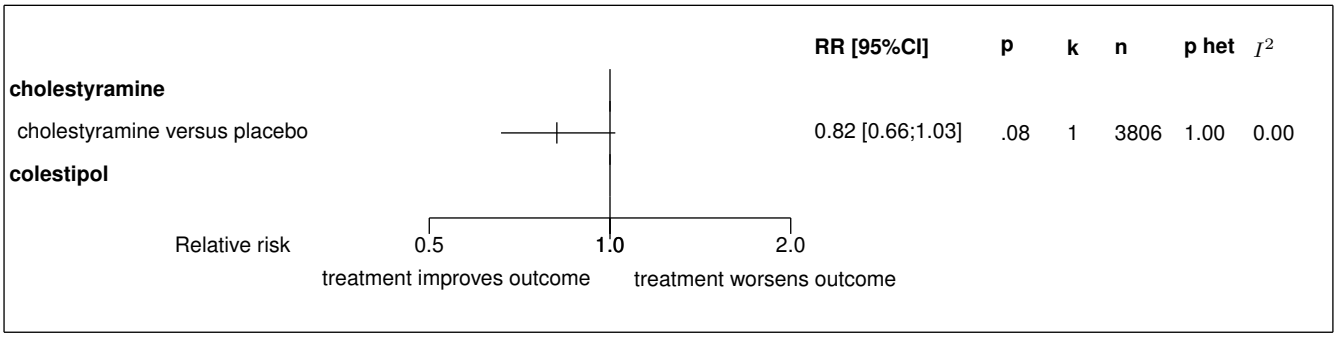
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 23.3: *Forest's plot for death from cancer*



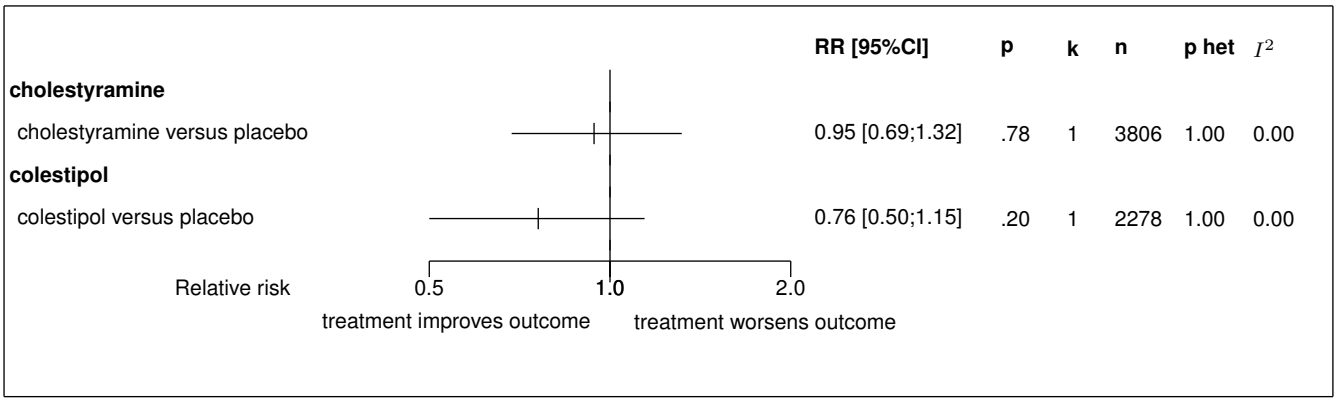
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 23.4: *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 23.5: *Forest's plot for all cause death*



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

24 Detailed results for cholestyramine

24.1 Available trials

Only one trial which randomized 3806 patients was identified: it compared cholestyramine with placebo.
This trial included 3806 patients and was published in 1984.
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 coronary event; 1 trials reported data on non fatal MI; 1 trials reported data on death from cancer; and 1 trials reported data on all cause death.
Following tables 24.1 (page 100), 24.2 (page 100), 24.4 (page 102), and 24.3 (page 101) summarized the main characteristics of the trial including in this systematic review of randomized trials of cholestyramine.

Table 24.1: *Treatment description - resins - cholestyramine*

Trial	Studied treatment	Control treatment
Cholestyramine versus placebo		
LRC (1984) [1]	cholestyramine 24 g daily	placebo
	Concomittant treatment: Rgime	

Table 24.2: *Descriptions of participants - resins - cholestyramine*

Trial	Patients	
Cholestyramine versus placebo		
LRC (1984) [1]	Asymptomatic middle-aged men with primary hypercholesterolemia (type II hyperlipoproteinemia)	
	Inclusion criteria: CT >ou = 6.85 mmol/l; LDL >ou = 4.91 mmol/l	**Exclusion criteria:** TG >300 mg/dl; hyperlipoproteinemia; antcdents IDM; angor; anomalies ECG; ; insuffisance cardiaque congestive; hypertension; cancer; maladie cardiovasculaire non-athrosclrotique

Table 24.3: *Design and methodological quality of trials - resins - cholestyramine*

Trial	Design	Duration	Centre	Primary end-point
Cholestyramine versus placebo				
LRC, 1984 [1] n=3806	Parallel groups double blind confirmatory trial at low risk of bias	7.4 years	USA multicentre	definite CHD death, MI

Table 24.4: *Trial characteristics - resins - cholestyramine*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Cholestyramine versus placebo				
LRC, 1984 [1]		-0.9 mmol/L		

24.2 Meta-analysis results

The results are detailed in table 24.5 (page 103). This table is followed by the Forest's plot corresponding to each endpoint.

Cholestyramine versus placebo

The single study eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 0.83 (95% CI 0.67 to 1.01, p=0.0657).
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 0.79 (95% CI 0.49 to 1.26, p=0.3224).
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 0.82 (95% CI 0.66 to 1.03, p=0.0818).

Table 24.5: *Results details - resins - cholestyramine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
cholestyramine versus placebo						
coronary event	RR=0.83	[0.67;1.01]	0.0657	1.0000 (I^2=0.00)	1	3806
coronary death	RR=0.79	[0.49;1.26]	0.3224	1.0000 (I^2=0.00)	1	3806
death from cancer	RR=1.06	[0.53;2.14]	0.8638	1.0000 (I^2=0.00)	1	3806
non fatal MI	RR=0.82	[0.66;1.03]	0.0818	1.0000 (I^2=0.00)	1	3806
all cause death	RR=0.95	[0.69;1.32]	0.7809	1.0000 (I^2=0.00)	1	3806

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

Figure 24.1: *Forest's plot for coronary event*

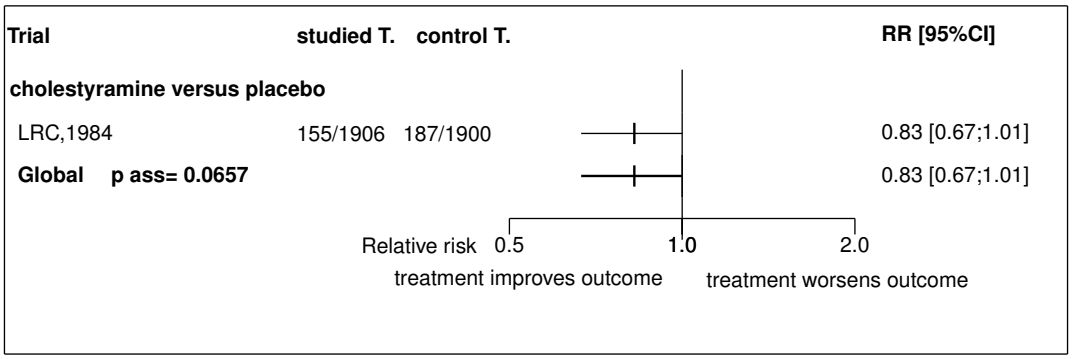


Figure 24.2: *Forest's plot for coronary death*

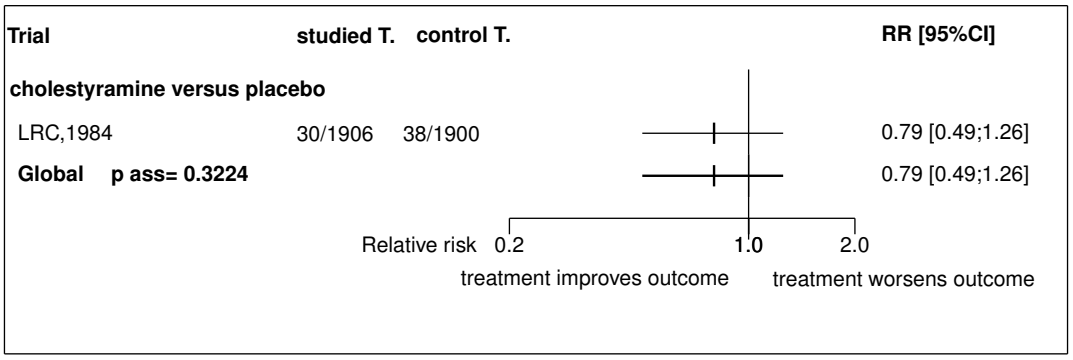


Figure 24.3: *Forest's plot for death from cancer*

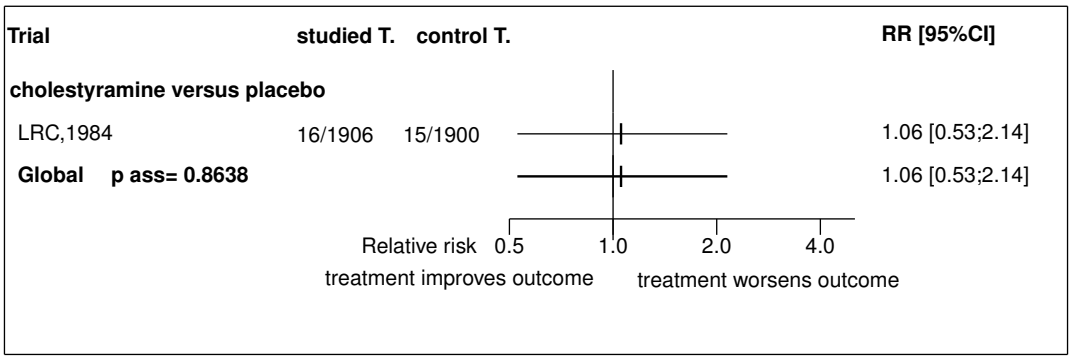


Figure 24.4: *Forest's plot for non fatal MI*

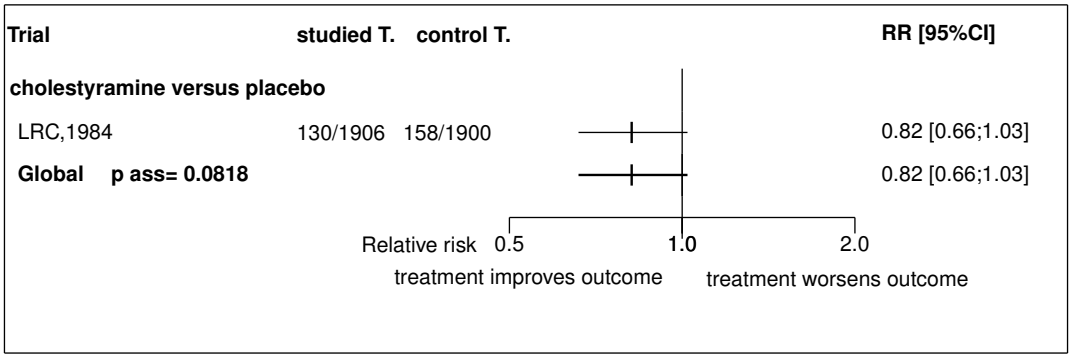
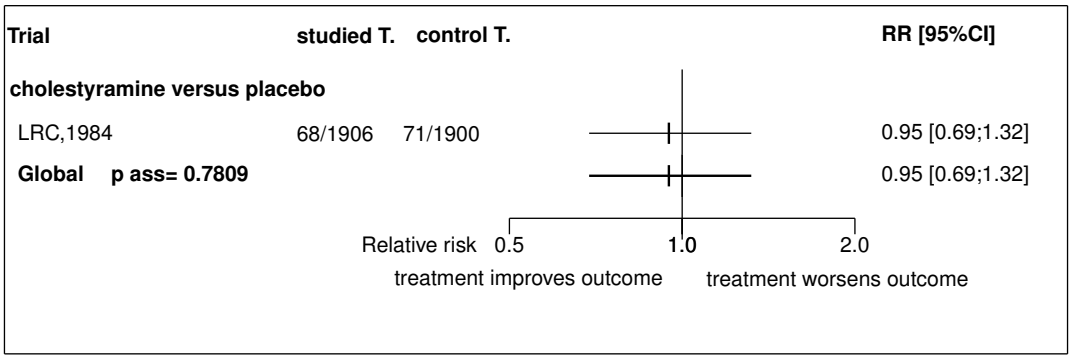


Figure 24.5: *Forest's plot for all cause death*



References

[1] ,. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984; 251:351-64. [PMID=6361299]

24.3 Individual trial summaries

Table 24.6: *LRC, 1984 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3806 (1906 vs. 1900) **Follow-up duration:** 7.4 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias USA, multicentre	Asymptomatic middle-aged men with primary hypercholesterolemia (type II hyperlipoproteinemia) **Inclusion criteria:** CT >ou = 6.85 mmol/l; LDL >ou = 4.91 mmol/l **Exclusion criteria:** TG >300 mg/dl; hyperlipoproteinemia; antcdents IDM; angor; anomalies ECG; ; insuffisance cardiaque congestive; hypertension; cancer; maladie cardiovasculaire non-athrosclrotique	**Studied treatment:** cholestyramine 24 g daily **Control treatment:** placebo **Concomittant treat.:**Rgime	Coronary event RR=0.83 [0.67;1.01]

Reference

,. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984; 251:351-64 [PMID=6361299]

25 Detailed results for colestipol

25.1 Available trials

A total of 4 RCTs which randomized 2476 patients were identified: all compared colestipol with placebo.
The average study size was 619 patients (range 40 to 2278). The first study was published in 1974, and the last study was published in 1978.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Coronary death data was reported in 1 trials; 1 trials reported data on death from cancer; and 1 trials reported data on all cause death.
Following tables 25.1 (page 108), 25.2 (page 108), 25.4 (page 110), and 25.3 (page 109) summarized the main characteristics of the trials including in this systematic review of randomized trials of colestipol.

Table 25.1: *Treatment description - resins - colestipol*

Trial	Studied treatment	Control treatment
Colestipol versus placebo		
Gundersen (1976) [1]	colestipol 10g twice daily	placebo
Ruoff (1978) [2]	colestipol	placebo
Ryan (1974) [3]	colestipol15 g/day	placebo
UCS (Dorr) (1978) [4]	colestipol hydrochloride 32 mg/dl	placebo

Table 25.2: *Descriptions of participants - resins - colestipol*

Trial	Patients
Colestipol versus placebo	
Gundersen (1976) [1]	Hypercholesterolemic patients
Ruoff (1978) [2]	Hypercholesterolemic patients
Ryan (1974) [3]	Patients with hypercholesterolemia

continued...

Trial	Patients	
UCS (Dorr) (1978) [4]	Hommes et femmes, >18 ans **Inclusion criteria:** CT >6.5 mol/l	**Exclusion criteria:** femmes en ge de procrer; traitement par stroides, autres hormones (sauf insuline), anticoagulants, mdicaments diminuant les lipides <3 mois; hypothyroidie; maladie hpatique, rnale ou hematologique

Table 25.3: *Design and methodological quality of trials - resins - colestipol*

Trial	Design	Duration	Centre	Primary endpoint
Colestipol versus placebo				
Gundersen, 1976 [1] n=66	Parallel groups double-blind exploratory trial	0.8 years		
Ruoff, 1978 [2] n=40	Parallel groups confirmatory trial at low risk of bias	3.2 years		
Ryan, 1974 [3] n=92	Parallel groups confirmatory trial at low risk of bias	3.0 years		
UCS (Dorr), 1978 [4] n=2278	Parallel groups double blind confirmatory trial at low risk of bias	1.9 years		death

Table 25.4: *Trial characteristics - resins - colestipol*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Colestipol versus placebo				
Gundersen, 1976 [1]				
Ruoff, 1978 [2]				
Ryan, 1974 [3]				
UCS (Dorr), 1978 [4]				

25.2 Meta-analysis results

The results are detailed in table 25.5 (page 111). This table is followed by the Forest's plot corresponding to each endpoint.

Colestipol versus placebo

Only one of the 4 studies 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 0.60 (95% CI 0.34 to 1.06, p=0.0786).

Table 25.5: *Results details - resins - colestipol*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
colestipol versus placebo						
coronary death	RR=0.60	[0.34;1.06]	0.0786	1.0000 (I^2=0.00)	1	2278
death from cancer	RR=0.98	[0.14;6.96]	0.9860	1.0000 (I^2=0.00)	1	2278
all cause death	RR=0.76	[0.50;1.15]	0.1957	1.0000 (I^2=0.00)	1	2278

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

Figure 25.1: *Forest's plot for coronary death*

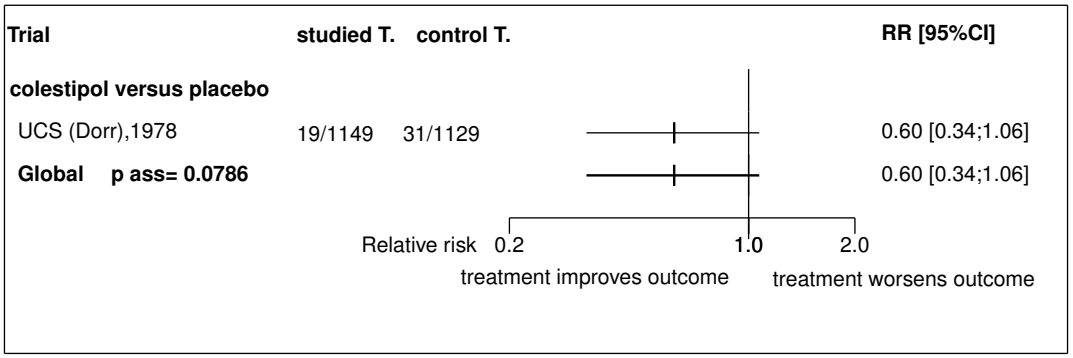


Figure 25.2: *Forest's plot for death from cancer*

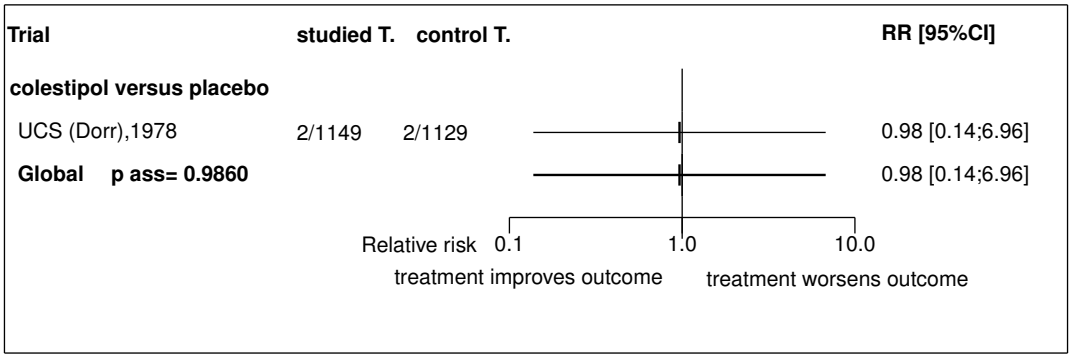
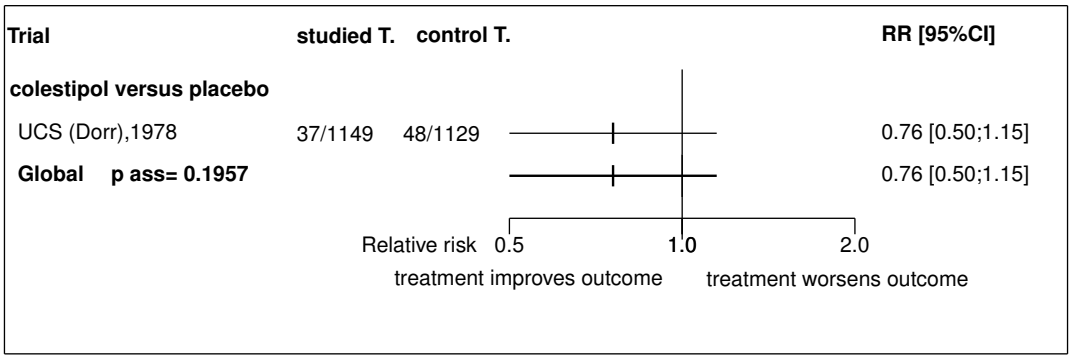


Figure 25.3: *Forest's plot for all cause death*



References

[1] Gundersen K, Cooper EE, Ruoff G, Nikolai T, Assenzo JR. Cholesterol-lowering effect of colestipol hydrochloride given twice daily in hypercholesterolemic patients. Atherosclerosis 1976;25:303-10. [PMID=795441]

[2] Ruoff G. Colestipol hydrochloride for treatment of hypercholesterolemia in a family practice: five-year study. J Am Geriatr Soc 1978;26:121-6. [PMID=624819]

[3] Ryan JR, Jain AK, McMahon FG. Long-term treatment of hypercholesterolemia with colestipol hydrochloride. Clin Pharmacol Ther 1975;17:83-7. [PMID=1091391]

[4] Dorr AE, Gundersen K, Schneider JC Jr, Spencer TW, Martin WB,. Colestipol hydrochloride in hypercholesterolemic patients–effect on serum cholesterol and mortality. J Chronic Dis 1978; 31:5-14. [PMID=346598]

25.3 Individual trial summaries

Table 25.6: *Gundersen, 1976 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=66 (36 vs. 30) **Follow-up duration:** 0.8 years **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Hypercholesterolemic patients	**Studied treatment:** colestipol 10g twice daily **Control treatment:** placebo	

Reference

Gundersen K, Cooper EE, Ruoff G, Nikolai T, Assenzo JR. Cholesterol-lowering effect of colestipol hydrochloride given twice daily in hypercholesterolemic patients. Atherosclerosis 1976;25:303-10 [PMID=795441]

Table 25.7: *Ruoff, 1978 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=40 (21 vs. 19) **Follow-up duration:** 3.2 years **Study design:** Randomized controlled trial Parallel groups Confirmatory trial at low risk of bias	Hypercholesterolemic patients	**Studied treatment:** colestipol **Control treatment:** placebo	

Reference

Ruoff G. Colestipol hydrochloride for treatment of hypercholesterolemia in a family practice: five-year study. J Am Geriatr Soc 1978;26:121-6 [PMID=624819]

Table 25.8: *Ryan, 1974 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=92 (44 vs. 48) **Follow-up duration:** 3.0 years **Study design:** Randomized controlled trial Parallel groups Confirmatory trial at low risk of bias	Patients with hypercholesterolemia	**Studied treatment:** colestipol15 g/day **Control treatment:** placebo	

Reference

Ryan JR, Jain AK, McMahon FG. Long-term treatment of hypercholesterolemia with colestipol hydrochloride. Clin Pharmacol Ther 1975;17:83-7 [PMID=1091391]

Table 25.9: *UCS (Dorr), 1978 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2278 (1149 vs. 1129) **Follow-up duration:** 1.9 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias	Hommes et femmes, >18 ans **Inclusion criteria:** CT >6.5 mol/l **Exclusion criteria:** Femmes en ge de procrer; traitement par stroides, autres hormones (sauf insuline), anticoagulants, mdicaments diminuant les lipides <3 mois; hypothyroidie; maladie hpatique, rnale ou hematologique	**Studied treatment:** colestipol hydrochloride 32 mg/dl **Control treatment:** placebo	

Reference

Dorr AE, Gundersen K, Schneider JC Jr, Spencer TW, Martin WB,. Colestipol hydrochloride in hypercholesterolemic patients–effect on serum cholesterol and mortality. J Chronic Dis 1978; 31:5-14 [PMID=346598]

26 Global meta-analysis: all resins

26.1 Global meta-analysis: all resins versus placebo

Table 26.1: *All resinsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
coronary event	RR=0.83	0.67;1.01	0.0657	1.0000 (0.00)	1	3806
coronary death	RR=0.70	0.49;1.01	0.0589	0.4773 (0.00)	2	6084
non fatal MI	RR=0.82	0.66;1.03	0.0818	1.0000 (0.00)	1	3806

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

27 Ongoing studies of resins

No ongoing trial was identified.

28 Excluded studies for resins

No trial was excluded.

References

Part VI

Statins

29 Overview of statins

29.1 Included trials

A total of 20 randomized comparisons which enrolled 31225 patients were identified. In all, 1 randomized comparison concerned any statin , 5 atorvastatin , two fluvastatin , one lovastatin , one pitavastatin , 8 pravastatin and two simvastatin.
The detailed descriptions of trials and meta-analysis results is given in section 30 (page 144) for any statin, in section 31 (page 150) for atorvastatin, in section 32 (page 168) for fluvastatin, in section 33 (page 178) for lovastatin, in section 34 (page 187) for pitavastatin, in section 35 (page 192) for pravastatin and in section 36 (page 214) for simvastatin.

The average study size was 1836 patients (range 60 to 6605). The first study was published in 1995, and the last study was published in 2009.
A total of 13 trials were double blind and 7 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 29.1 (page 123) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

29.2 Summary of meta-analysis results

The meta-analysis of the available trials about statins provide the results listed in tables 29.2 to 29.8 (page 127) and in the following graphs.

29.2.1 Any statin

Data were insufficient to compare **any statin** to **no statin**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

29.2.2 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), 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), non fatal MI (RR=0.90, 95% CI 0.69 to 1.17, p=0.4233, 1 trial)and revascularization (RR=1.02, 95% CI 0.87 to 1.20, p=0.7838, 1 trial).

No significant difference was found between **atorvastatin** and **usual care** in terms of 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), non fatal MI (RR=0.48, 95% CI 0.14 to 1.61, p=0.2317, 2 trials)and revascularization (RR=1.00, 95% CI 0.43 to 2.32, p=0.9979, 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).

29.2.3 Fluvastatin

No significant difference was found between **fluvastatin** and **placebo** in terms of 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), non fatal MI (RR=1.48, 95% CI 0.74 to 2.96, p=0.2735, 2 trials)and revascularization (RR=0.89, 95% CI 0.71 to 1.11, p=0.2986, 2 trials).

29.2.4 Lovastatin

Lovastatin was superior to **placebo** in terms of coronary event (RR=0.76, 95% CI 0.62 to 0.92, p=0.0059, 1 trial)and coronary death and non fatal MI (RR=0.76, 95% CI 0.62 to 0.92, p=0.0059, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.68, 95% CI 0.37 to 1.26, p=0.2174, 1 trial), stroke (fatal and non fatal) (RR=0.82, 95% CI 0.41 to 1.67, p=0.5880, 1 trial)and coronary death (RR=0.73, 95% CI 0.34 to 1.59, p=0.4324, 1 trial).

29.2.5 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.

29.2.6 Pravastatin

Pravastatin was superior to **placebo** in terms of cardiovascular events (RR=0.59, 95% CI 0.49 to 0.72, p=0.0000, 3 trials), cardiovascular death (RR=0.68, 95% CI 0.48 to 0.98, p=0.0361, 1 trial), coronary event (RR=0.70, 95% CI 0.58 to 0.84, p=0.0000, 1 trial)and coronary death and non fatal MI (RR=0.70, 95% CI 0.58 to 0.84, p=0.0000, 1 trial). However, no significant difference was found on stroke (fatal and non fatal) (RR=0.87, 95% CI 0.61 to 1.24, p=0.4403, 5 trials), coronary death (RR=0.73, 95% CI 0.48 to 1.10, p=0.1356, 1 trial), cardiac death (RR=0.79, 95% CI 0.49 to 1.28, p=0.3336, 4 trials), non fatal MI (RR=0.44, 95% CI 0.14 to 1.44, p=0.1774, 5 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0008)(RR=1.17, 95% CI 0.55 to 2.45, p=0.6845, 3 trials).

No significant difference was found between **pravastatin** and **usual care** in terms of 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), non fatal MI (RR=0.44, 95% CI 0.06 to 3.06, p=0.4048, 2 trials)and revascularization (RR=0.58, 95% CI 0.33 to 1.05, p=0.0725, 2 trials).

29.2.7 Simvastatin

No significant difference was found between **simvastatin** and **placebo** in terms of 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), non fatal MI (RR=0.99, 95% CI 0.77 to 1.29, p=0.9631, 1 trial)and revascularization (RR=0.95, 95% CI 0.74 to 1.21, p=0.6520, 1 trial).

Table 29.1: *Main study characteristics - statins*

Trial	Patients	Treatments	Trial design and method
Any statin			
Any statin versus no statin			
Sakamoto, 2006 [1] n = 241 vs. 245	japanese patients with AMI within 96 hours of AMI onset	any available statin **versus** no statin	open parallel groups Primary endpoint: cardiovascular death, nonfatal AMI, recurrent symptomatic myocardial ischemia, HF, and stroke Japan
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
macin, 2005 [2] n = NA vs. NA	patients admitted within 48 hours of onset of ACS with CRP levels >or =1.4 mg/dL	atorvastatin 40 mg daily for 30 days **versus** placebo	double-blind parallel groups
Atorvastatin versus usual care			
Colivicchi, 2002 [3] 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

continued...

Trial	Patients	Treatments	Trial design and method
ESTABLISH, 2004 [4] 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 [5, 6, 7, 8, 9] 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			
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
Lovastatin			
Lovastatin versus placebo			
AFCAPS/TexCAPS, 1998 [1, 2] n = 3304 vs. 3301	men and women without clinically evident atherosclerotic cardiovascular disease with average total cholesterol (TC) and LDL-C levels and below-average high-density lipoprotein cholesterol (HDL-C) levels	lovastatin 20-40 mg/d **versus** placebo	double blind parallel groups Primary endpoint: major coronary event 2 centres, USA
Pitavastatin			
Pitavastatin versus atorvastatin			

continued...

Trial	Patients	Treatments	Trial design and method
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
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
WOSCOPS, 1995 [6, 7] n = 3302 vs. 3293	men aged 45-64 yr with no history of myocardial infarction and with raised plasma cholesterol levels (LDL cholesterol of at least 155 mg/dL, total cholesterolof at least 252 mg/dL)	pravastatine 40 mg daily **versus** placebo	double blind parallel groups Primary endpoint: coronary events (CHD death, MI) multicenter, Scotland
Pravastatin versus usual care			

continued...

Trial	Patients	Treatments	Trial design and method
L-CAD, 2000 [8] 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 [9] 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
OACIS-LIPID, 2008 [10] n = 176 vs. 177	patients with AMI who had plasma total cholesterol levels of 200-250 mg/dl and triglyceride levels $<$300 mg/dl	pravastatin 10 mg/daily **versus** no pravastatin	open parallel groups Primary endpoint: death, nonfatal MI, unstable angina, stroke, revascularization, and rehospitalization
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
Ren, 2009 [2] n = NA vs. NA	patients with unstable angina pectoris	simvastatin (40 mg/d for 4 weeks) **versus** placebo	double-blind parallel groups Primary endpoint: plasma interleukin-6 (IL-6)

Table 29.2: *Summary of all results for any statin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
any statin versus no statin						
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 29.3: *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
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
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	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
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

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 29.4: *Summary of all results for fluvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
fluvastatin versus placebo						
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
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 29.5: *Summary of all results for lovastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
lovastatin versus placebo						
cardiovascular death	RR=0.68	0.37;1.26	0.2174	1.0000 (0.00)	1	6605
stroke (fatal and non fatal)	RR=0.82	0.41;1.67	0.5880	1.0000 (0.00)	1	6605
coronary event	RR=0.76	0.62;0.92	0.0059	1.0000 (0.00)	1	6605
coronary death and non fatal MI	RR=0.76	0.62;0.92	0.0059	1.0000 (0.00)	1	6605
coronary death	RR=0.73	0.34;1.59	0.4324	1.0000 (0.00)	1	6605
rhabdomyolysis	RR=0.50	0.05;5.51	0.5708	1.0000 (0.00)	1	6605
all cause death	RR=1.04	0.76;1.41	0.8130	1.0000 (0.00)	1	6605

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 29.6: *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 29.7: *Summary of all results for pravastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
pravastatin versus placebo						
cardiovascular events	RR=0.59	0.49;0.72	0.0000	0.6415 (0.00)	3	6763
cardiovascular death	RR=0.68	0.48;0.98	0.0361	1.0000 (0.00)	1	6595
stroke (fatal and non fatal)	RR=0.87	0.61;1.24	0.4403	0.9485 (0.00)	5	10231
coronary event	RR=0.70	0.58;0.84	0.0000	1.0000 (0.00)	1	6595
coronary death and non fatal MI	RR=0.70	0.58;0.84	0.0000	1.0000 (0.00)	1	6595
coronary death	RR=0.73	0.48;1.10	0.1356	1.0000 (0.00)	1	6595
cardiac death	RR=0.79	0.49;1.28	0.3336	0.9549 (0.00)	4	3636
death from cancer	RR=0.90	0.60;1.34	0.5926	1.0000 (0.00)	1	6595
rhabdomyolysis	RR=1.00	0.02;50.25	0.9989	1.0000 (0.00)	1	6595
non fatal MI	RR=0.44 [1]	0.14;1.44	0.1774	0.0008 (0.79) †	5	10231
revascularization	RR=1.17	0.55;2.45	0.6845	0.9801 (0.00)	3	228
all cause death	RR=0.76	0.61;0.95	0.0161	0.9692 (0.00)	5	10231
pravastatin versus usual care						
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
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 29.8: *Summary of all results for simvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
simvastatin versus placebo						
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
non fatal MI	RR=0.99	0.77;1.29	0.9631	1.0000 (0.00)	1	4496

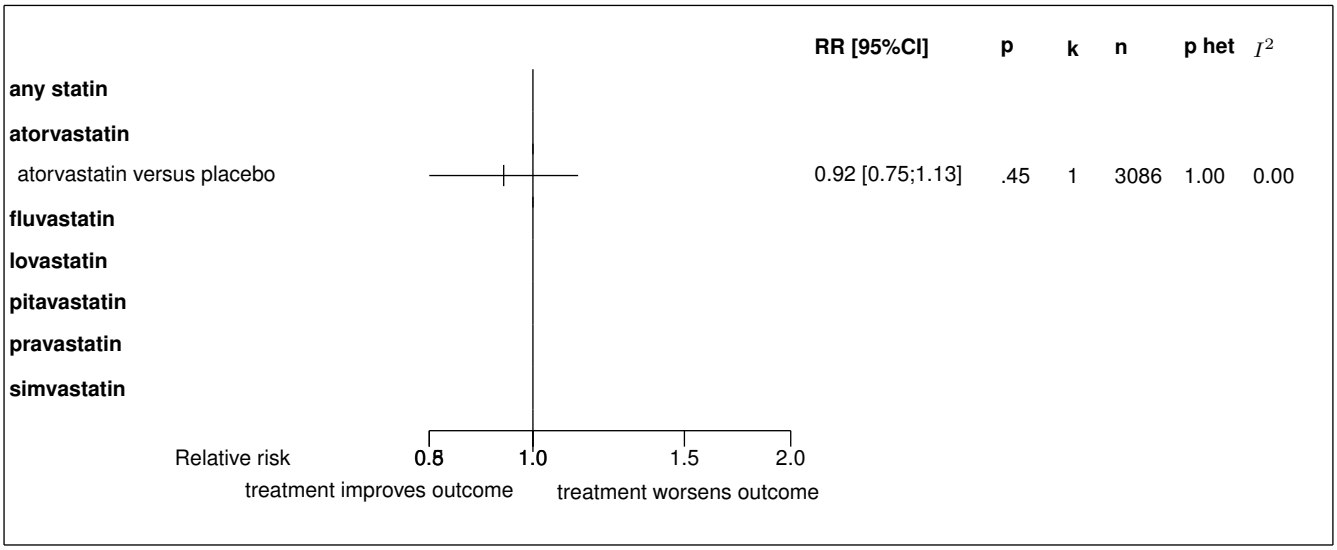
continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.64 95% CI 0.52;0.78

Endpoint	Effect	95% CI	p ass	p het	k	n
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

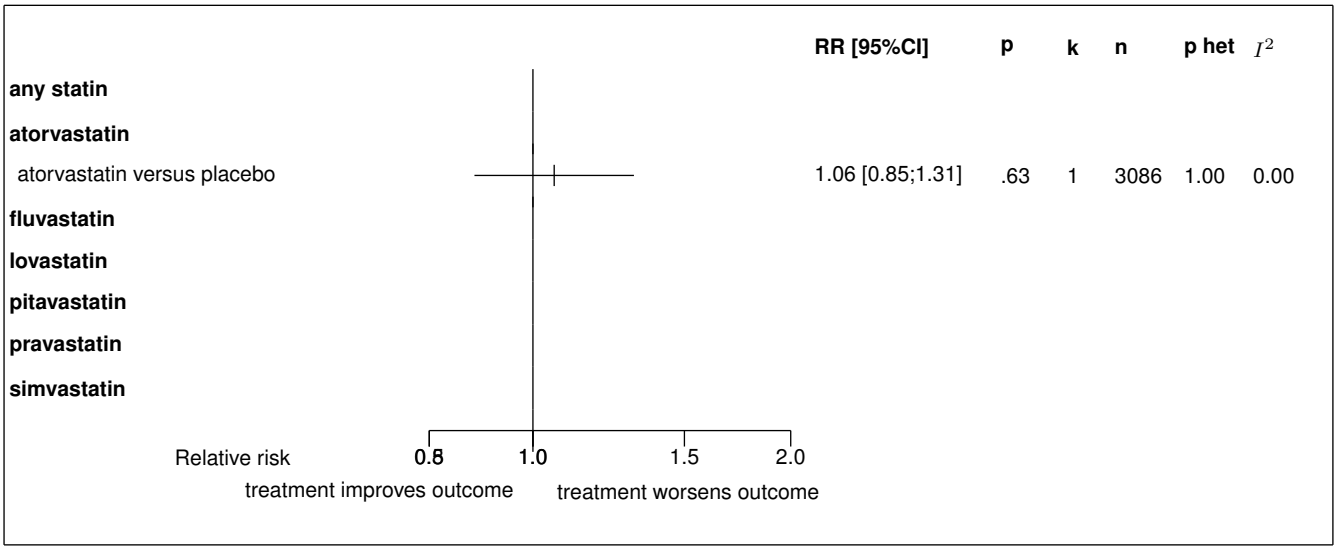
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 29.1: *Forest's plot for deaths or MI*



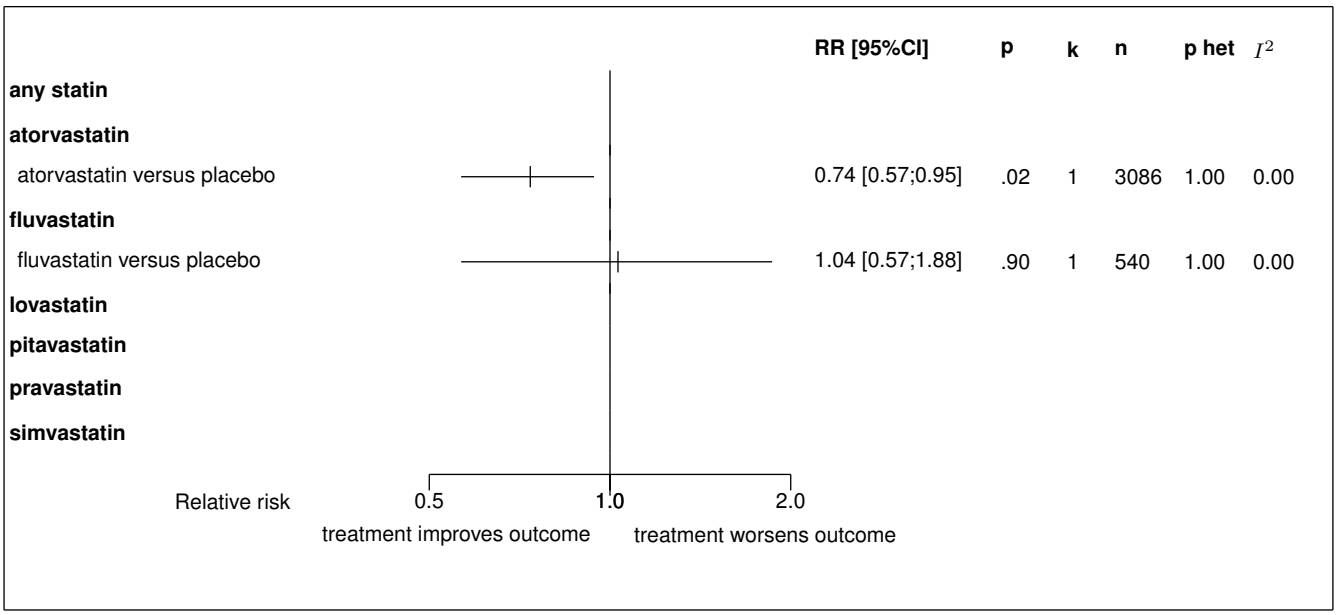
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.2: *Forest's plot for PTCA*



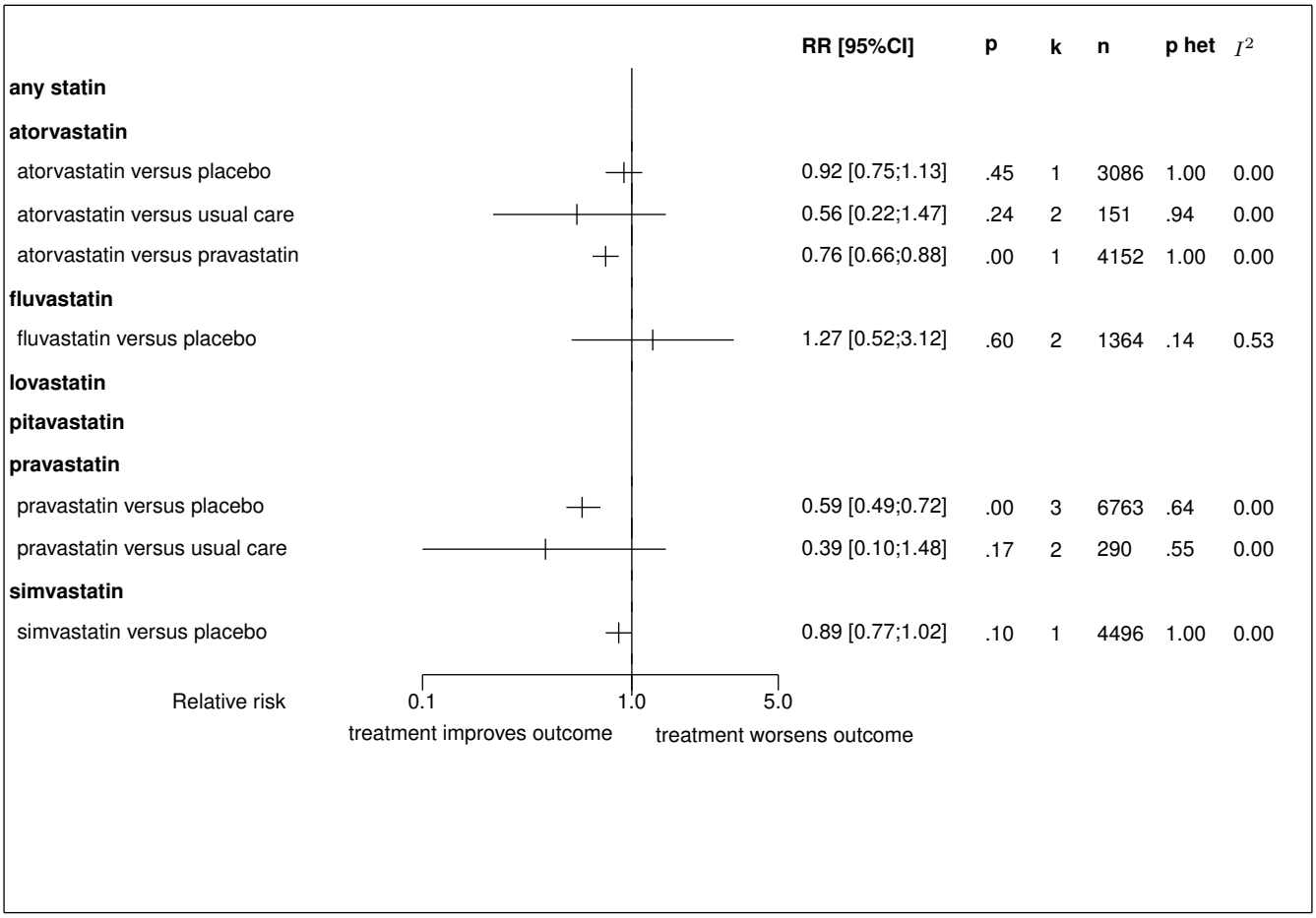
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.3: *Forest's plot for recurrent angina*



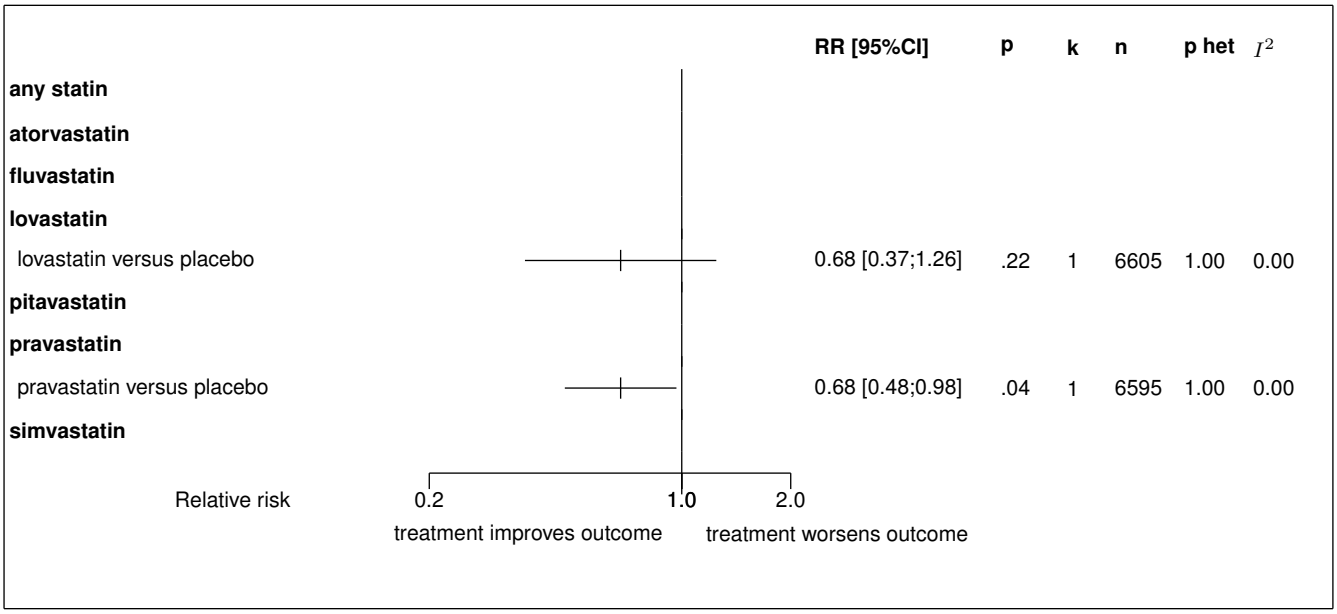
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.4: *Forest's plot for cardiovascular events*



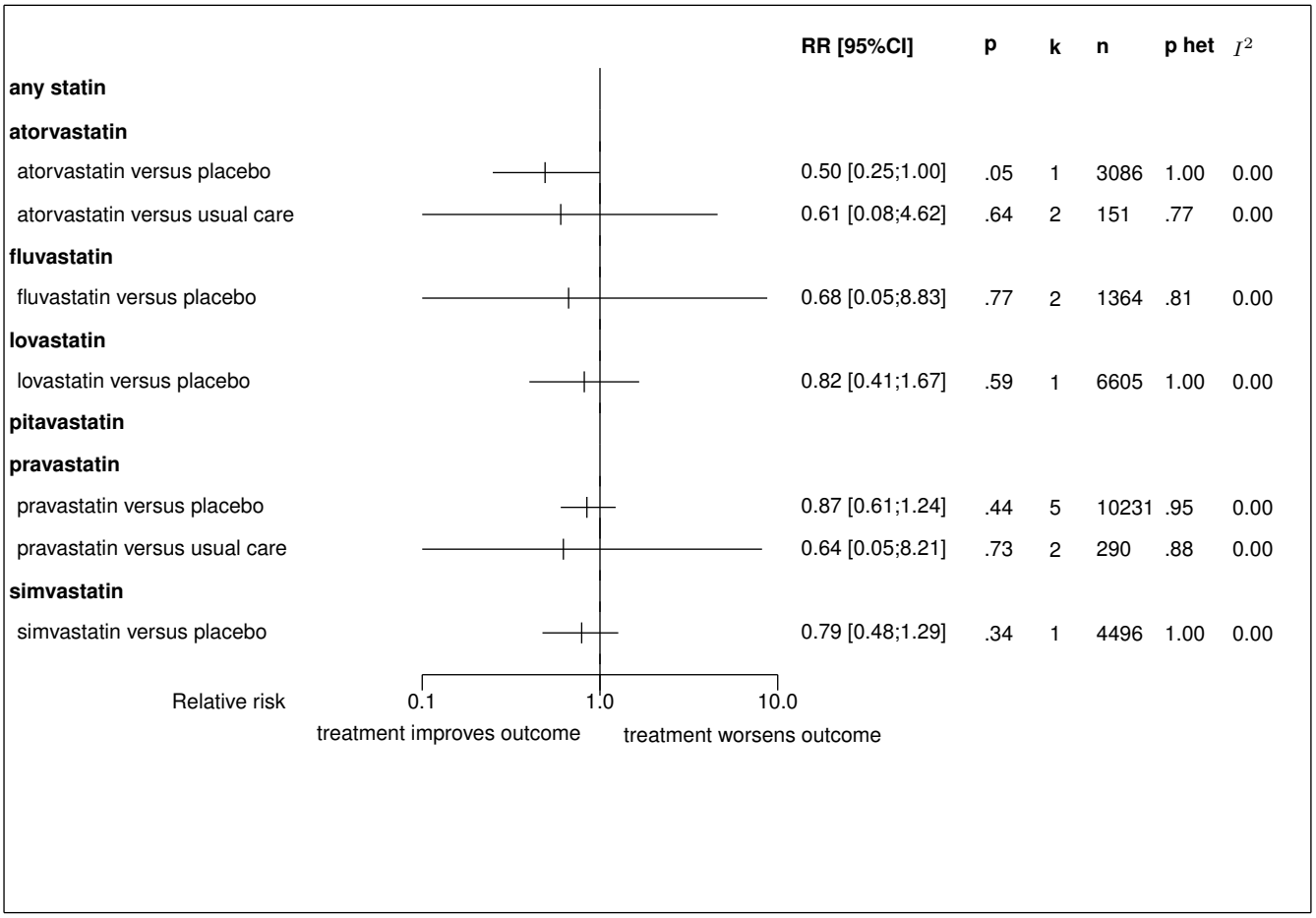
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.5: *Forest's plot for cardiovascular death*



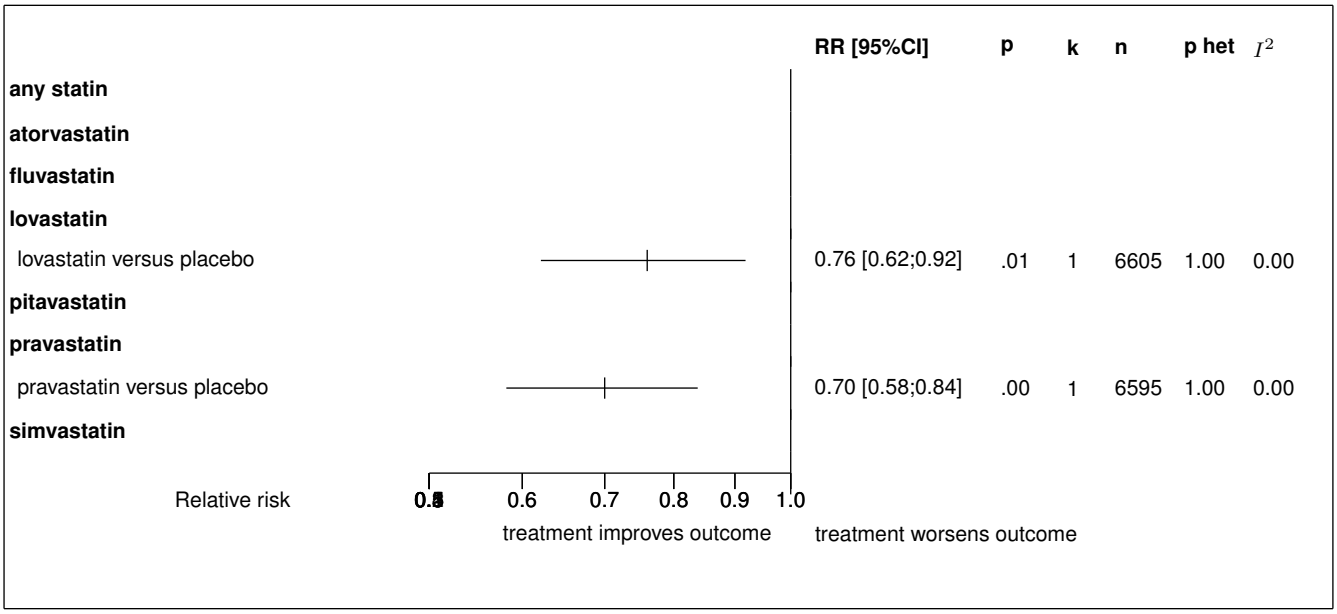
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.6: *Forest's plot for stroke (fatal and non fatal)*



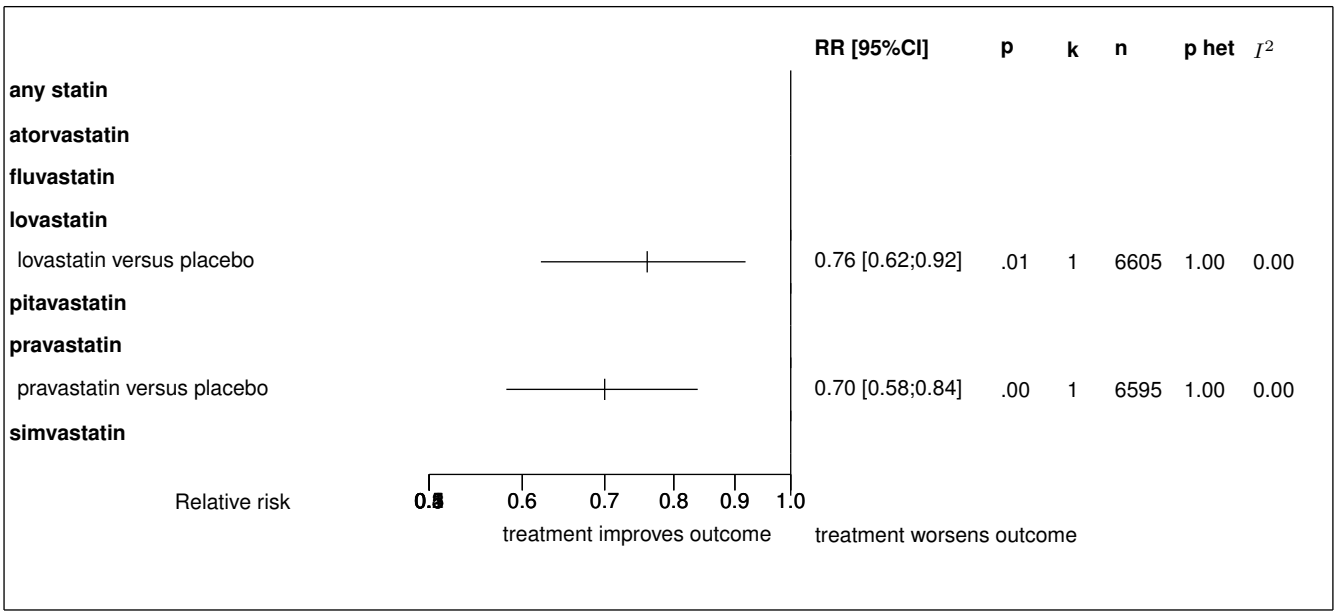
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.7: *Forest's plot for coronary event*



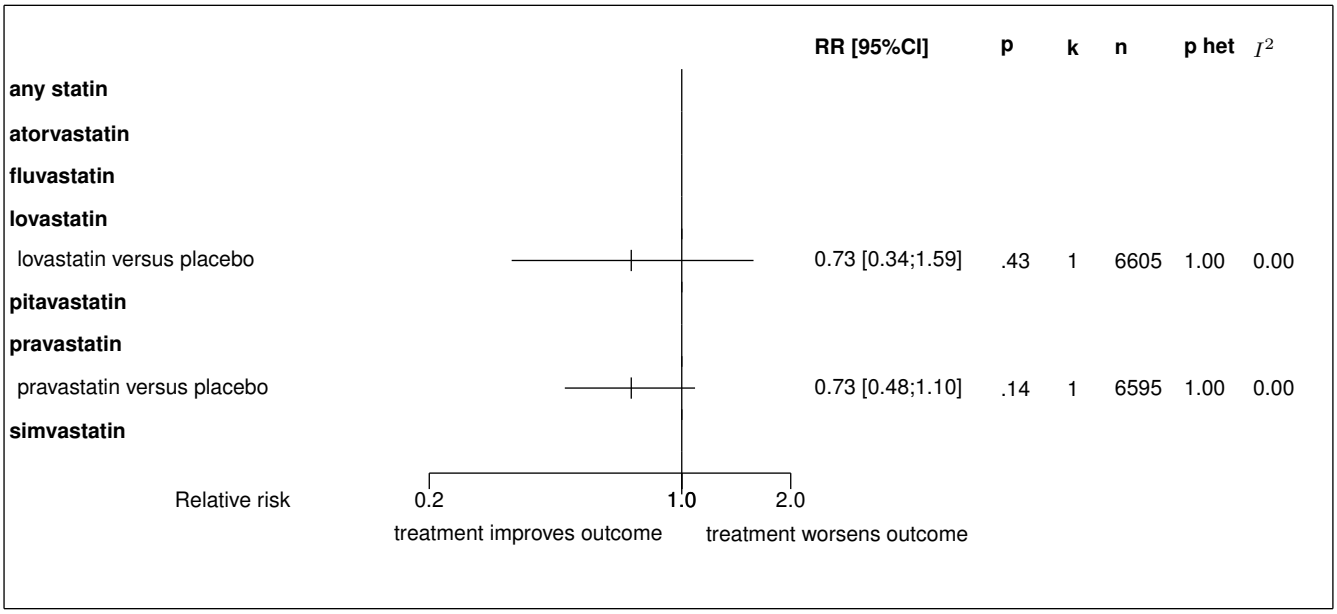
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.8: *Forest's plot for coronary death and non fatal MI*



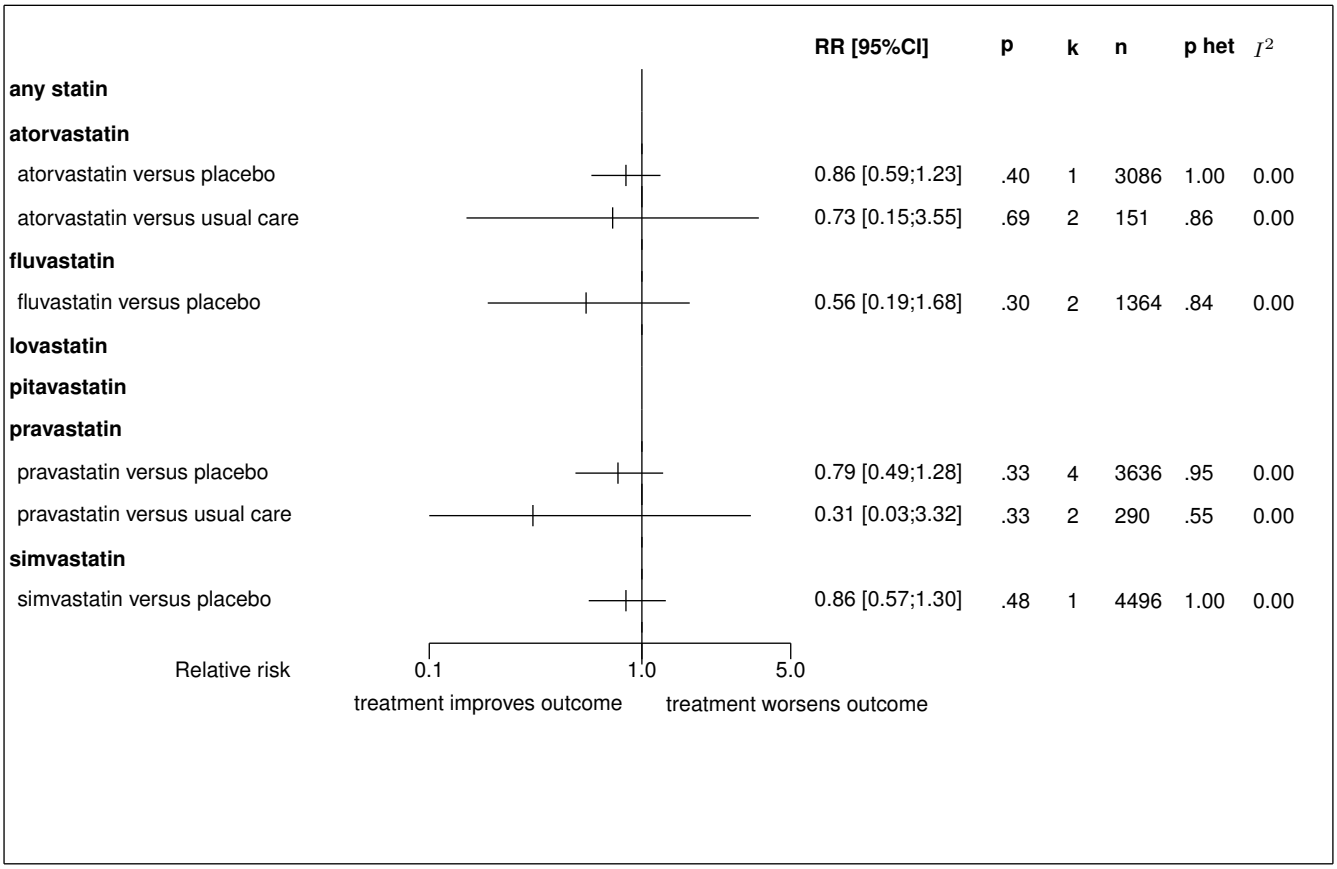
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.9: *Forest's plot for coronary death*



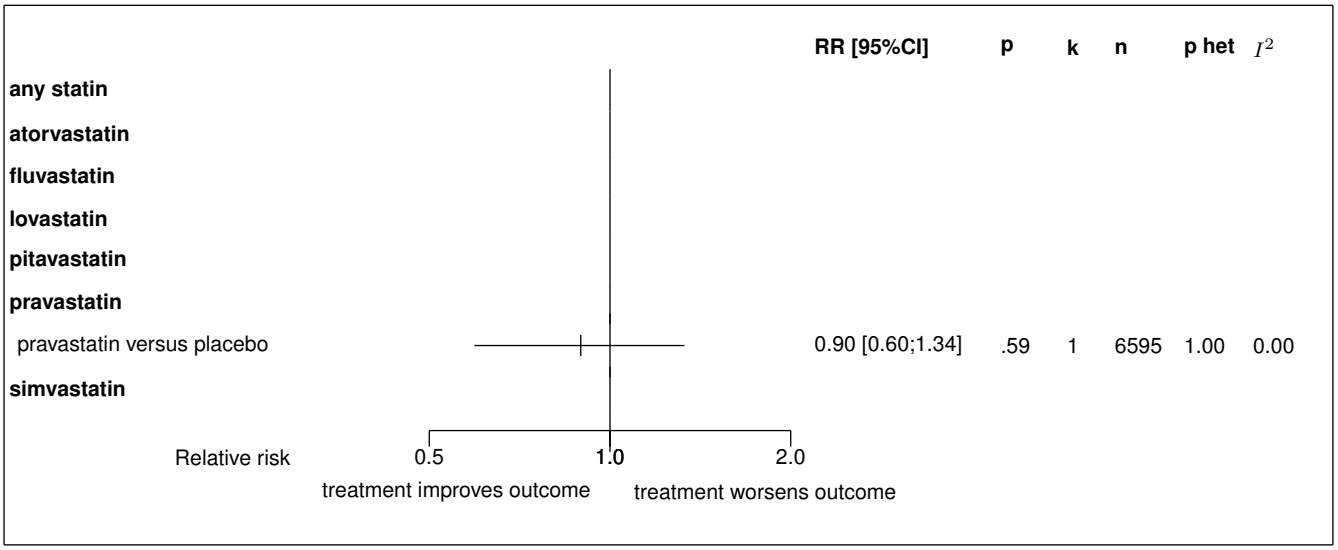
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.10: *Forest's plot for cardiac death*



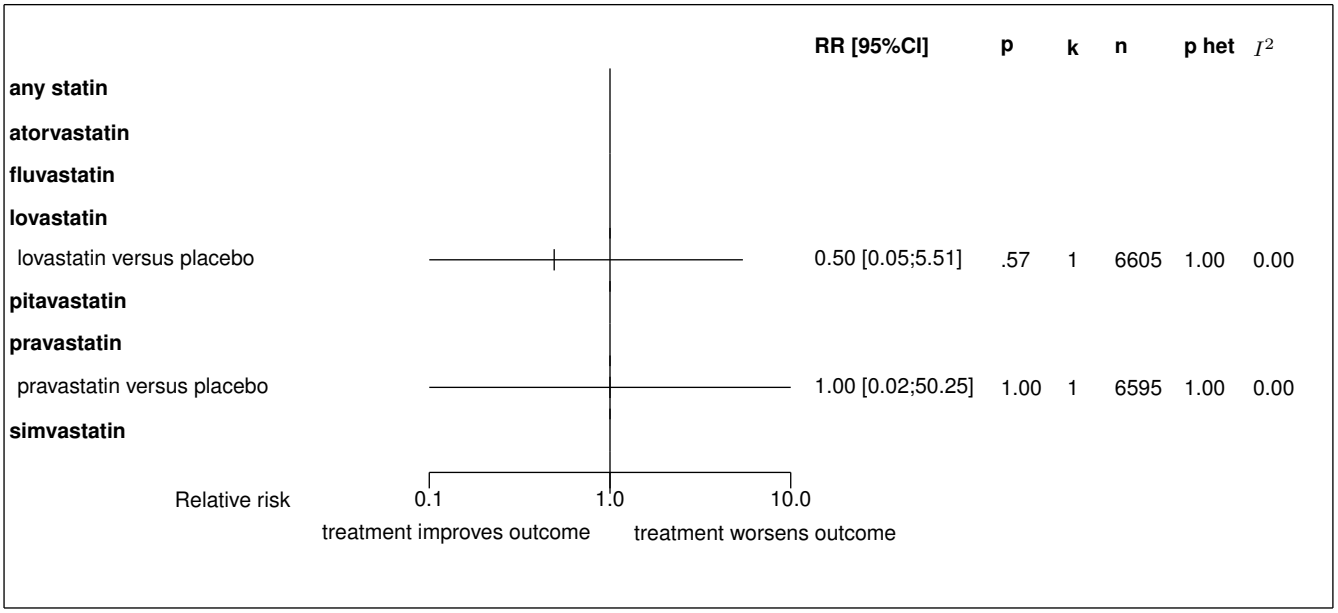
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.11: *Forest's plot for death from cancer*



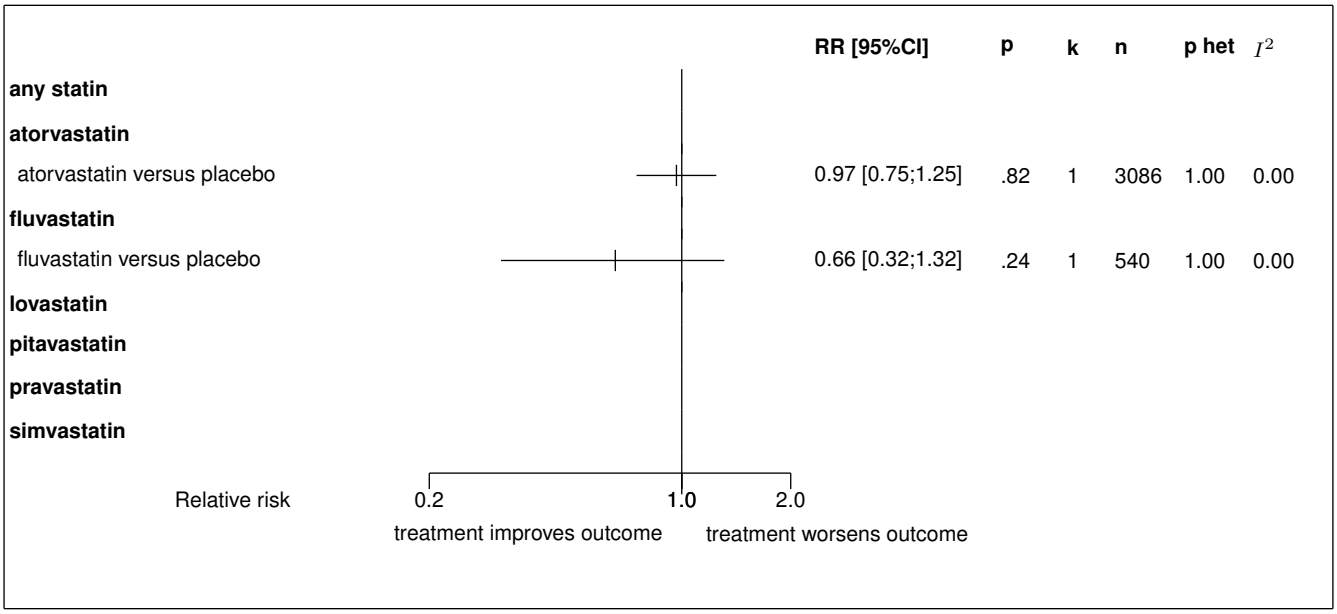
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.12: *Forest's plot for rhabdomyolysis*



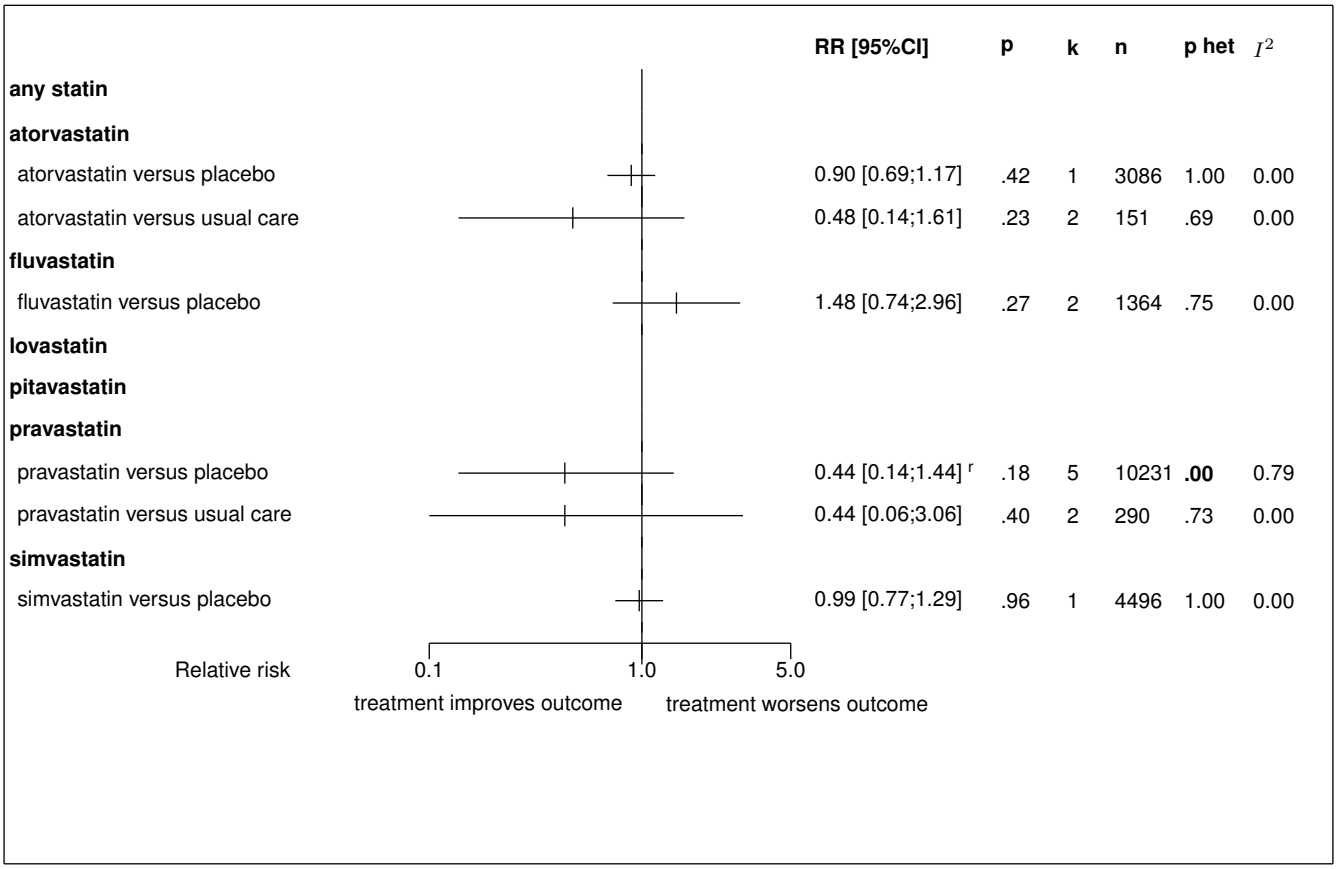
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.13: *Forest's plot for CABG*



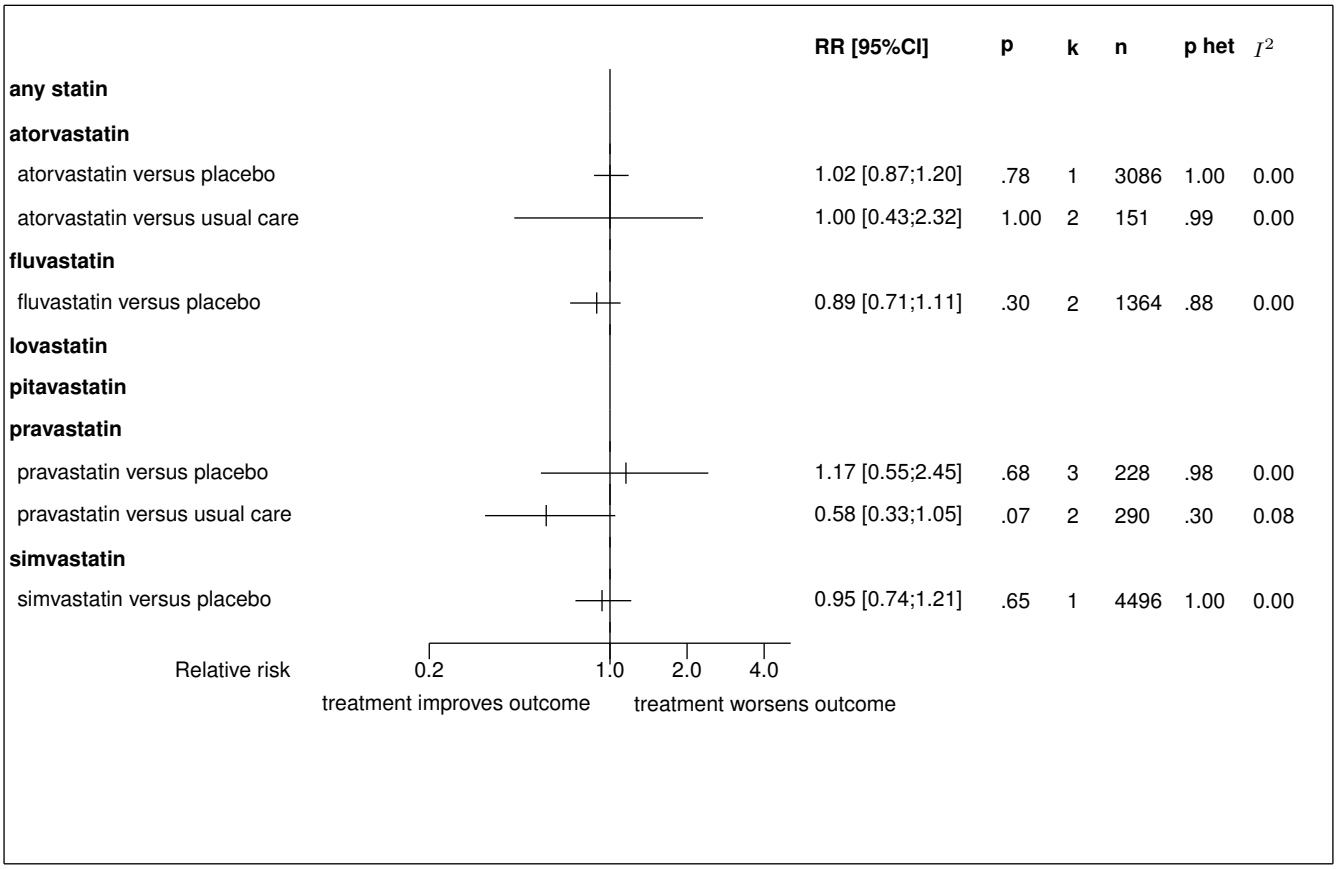
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.14: *Forest's plot for non fatal MI*



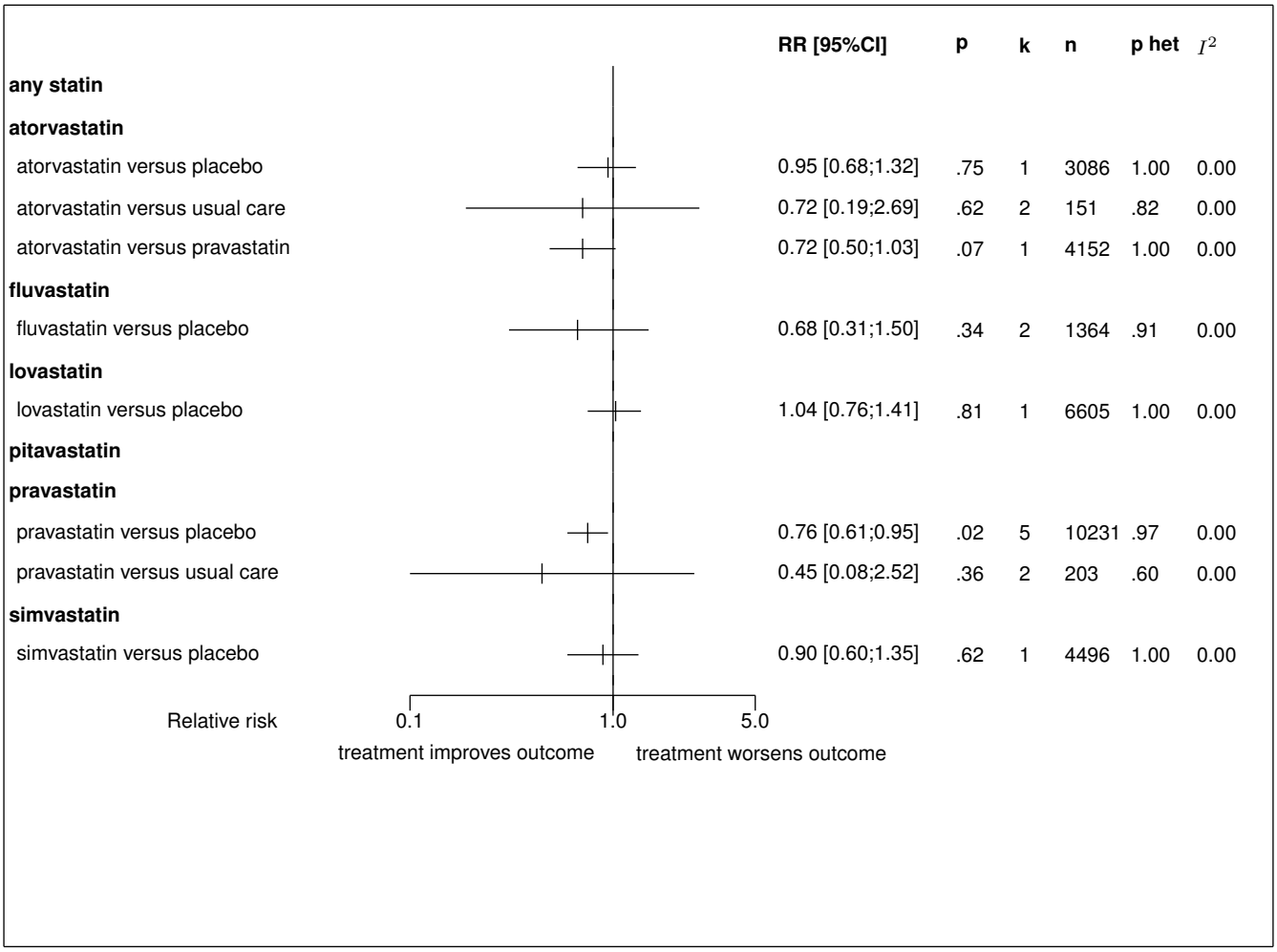
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.15: *Forest's plot for revascularization*



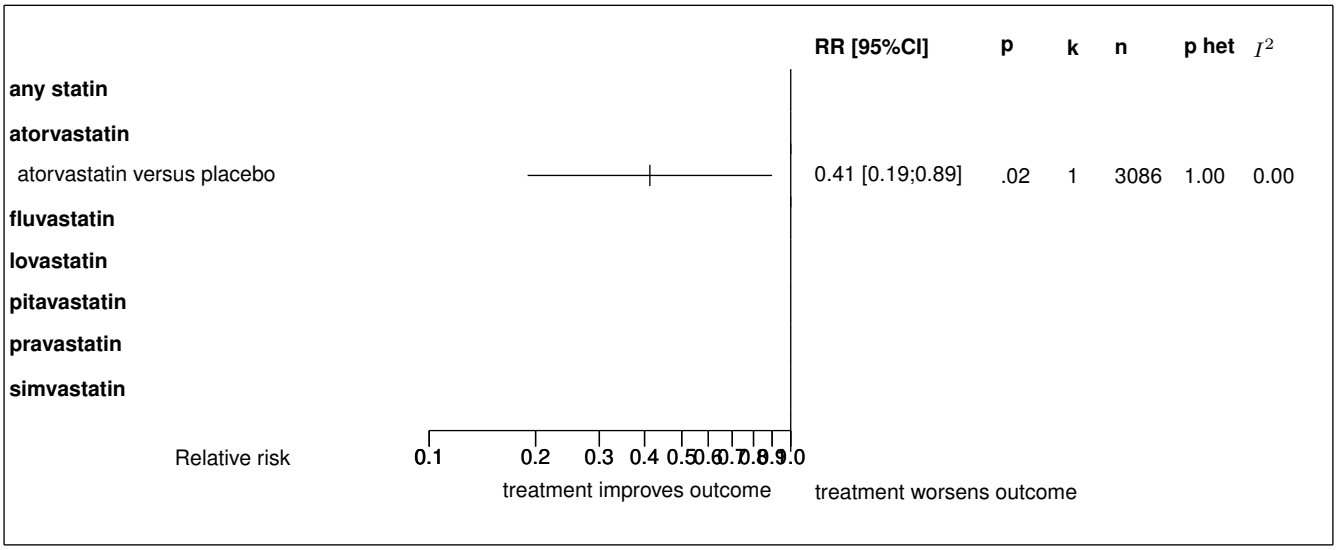
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 29.16: *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 29.17: *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; ˡ: random effect model used

30 Detailed results for any statin

30.1 Available trials

Only one trial which randomized 486 patients was identified: it compared any statin with no statin.
This trial included 486 patients and was published in 2006.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 30.1 (page 144), 30.2 (page 144), 30.4 (page 146), and 30.3 (page 144) summarized the main characteristics of the trial including in this systematic review of randomized trials of any statin.

Table 30.1: *Treatment description - statins - any statin*

Trial	Studied treatment	Control treatment
Any statin versus no statin		
Sakamoto (2006) [1]	any available statin	no statin

Table 30.2: *Descriptions of participants - statins - any statin*

Trial	Patients
Any statin versus no statin	
Sakamoto (2006) [1]	Japanese patients with AMI within 96 hours of AMI onset

Table 30.3: *Design and methodological quality of trials - statins - any statin*

Trial	Design	Duration	Centre	Primary endpoint
Any statin versus no statin				
Sakamoto, 2006 [1] n=486	Parallel groups open confirmatory trial at risk of bias	up to 24 months	Japan	cardiovascular death, nonfatal AMI, recurrent symptomatic myocardial ischemia, HF, and stroke

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 30.4: *Trial characteristics - statins - any statin*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Any statin versus no statin		
Sakamoto, 2006 [1]		

30.2 Meta-analysis results

The results are detailed in table 30.5 (page 147). This table is followed by the Forest's plot corresponding to each endpoint.

Any statin versus no statin

No data were presented in the 1 trial identified

Table 30.5: *Results details - statins - any statin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
any statin versus no statin						
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] Sakamoto T, Kojima S, Ogawa H, Shimomura H, Kimura K, Ogata Y, Sakaino N, Kitagawa A. Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. Am J Cardiol 2006;97:1165-71. [PMID=16616020]

30.3 Individual trial summaries

Table 30.6: *Sakamoto, 2006 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=486 (241 vs. 245) **Follow-up duration:** up to 24 months **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Japan	Japanese patients with AMI within 96 hours of AMI onset	**Studied treatment:** any available statin **Control treatment:** no statin	

Reference

Sakamoto T, Kojima S, Ogawa H, Shimomura H, Kimura K, Ogata Y, Sakaino N, Kitagawa A. Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. Am J Cardiol 2006;97:1165-71 [PMID=16616020]

31 Detailed results for atorvastatin

31.1 Available trials

A total of 5 RCTs which randomized 7399 patients were identified: 2 trials 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 2005.
A total of 3 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 cardiac death; 3 trials reported data on revascularization; 3 trials reported data on stroke (fatal and non fatal); 3 trials reported data on cardiovascular events; 3 trials reported data on non fatal MI; 1 trials reported data on CABG; 1 trials reported data on deaths or MI; 1 trials reported data on recurrent angina; 1 trials reported data on PTCA; and 1 trials reported data on non fatal stroke.
Following tables 31.1 (page 150), 31.2 (page 151), 31.4 (page 153), and 31.3 (page 151) summarized the main characteristics of the trials including in this systematic review of randomized trials of atorvastatin.

Table 31.1: *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	
macin (2005) [2]	atorvastatin 40 mg daily for 30 days	placebo
Atorvastatin versus usual care		
Colivicchi (2002) [3]	Atorvastatin, 80 mg daily early initiation	Usual care
ESTABLISH (2004) [4]	Atorvastatin, 20 mg early initiation	Usual care
Atorvastatin versus pravastatin		
PROVE IT - TIMI 22 (2004) [5, 6, 7, 8, 9]	80 mg of atorvastatin daily (intensive therapy).	40 mg of pravastatin daily (standard therapy)

Table 31.2: *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
macin (2005) [2]	Patients admitted within 48 hours of onset of ACS with CRP levels >or =1.4 mg/dL	
Atorvastatin versus usual care		
Colivicchi (2002) [3]	Unstable angina pectoris or non-Q-wave myocardial infarction	
ESTABLISH (2004) [4]	Patients with ACS undergoing emergency coronary angiography and percutaneous coronary intervention	
Atorvastatin versus pravastatin		
PROVE IT - TIMI 22 (2004) [5, 6, 7, 8, 9]	Patients who had been hospitalized for an acute coronary syndromewithin the preceding 10 days	

Table 31.3: *Design and methodological quality of trials - statins - atorvastatin*

Trial	Design	Duration	Centre	Primary endpoint
Atorvastatin versus placebo				

continued...

Trial	Design	Duration	Centre	Primary endpoint
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
macin, 2005 [2] n=NaN	Parallel groups double-blind exploratory trial	30 days		
Atorvastatin versus usual care				
Colivicchi, 2002 [3] 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 [4] 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 [5, 6, 7, 8, 9] 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 31.4: *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	
macin, 2005 [2]		
Atorvastatin versus usual care		
Colivicchi, 2002 [3]		
ESTABLISH, 2004 [4]		
Atorvastatin versus pravastatin		
PROVE IT - TIMI 22, 2004 [5, 6, 7, 8, 9]	-33	-0.86

31.2 Meta-analysis results

The results are detailed in table 31.5 (page 155). This table is followed by the Forest's plot corresponding to each endpoint.

Atorvastatin versus placebo

Only one of the 2 studies eligible for this comparison provided data on **deaths or MI**. No statistically significant difference between the groups was found in deaths or MI, with a RR of 0.92 (95% CI 0.75 to 1.13, p=0.4471).
Only one of the 2 studies 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).
Only one of the 2 studies 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).
Only one of the 2 studies 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).
Only one of the 2 studies 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).
Only one of the 2 studies 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).
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 0.97 (95% CI 0.75 to 1.25, p=0.8159).
Only one of the 2 studies 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).
Only one of the 2 studies 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).
Only one of the 2 studies 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

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 **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%).

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).

Table 31.5: *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
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
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	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
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

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
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 31.1: *Forest's plot for deaths or MI*

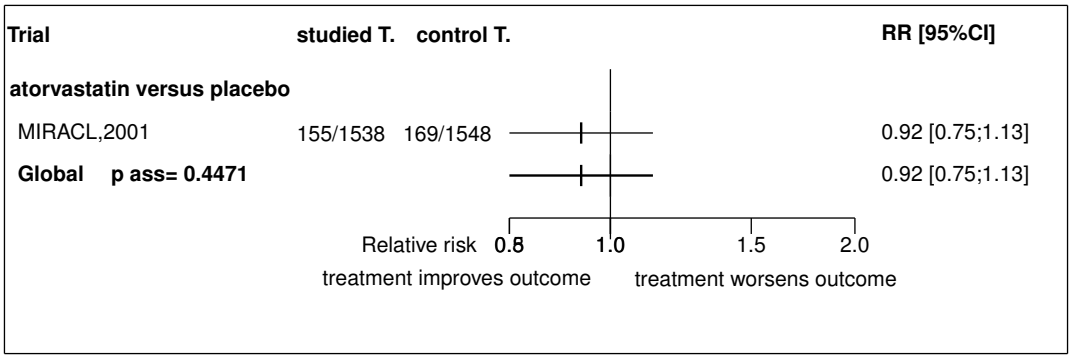


Figure 31.2: *Forest's plot for PTCA*

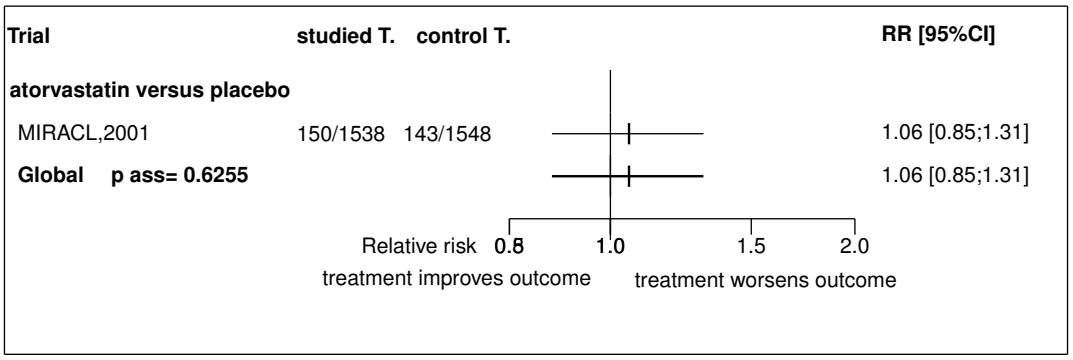


Figure 31.3: *Forest's plot for recurrent angina*

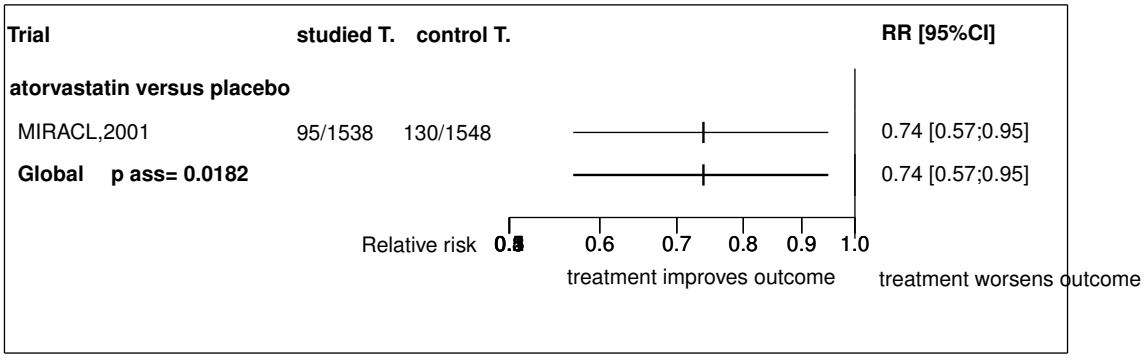


Figure 31.4: *Forest's plot for cardiovascular events*

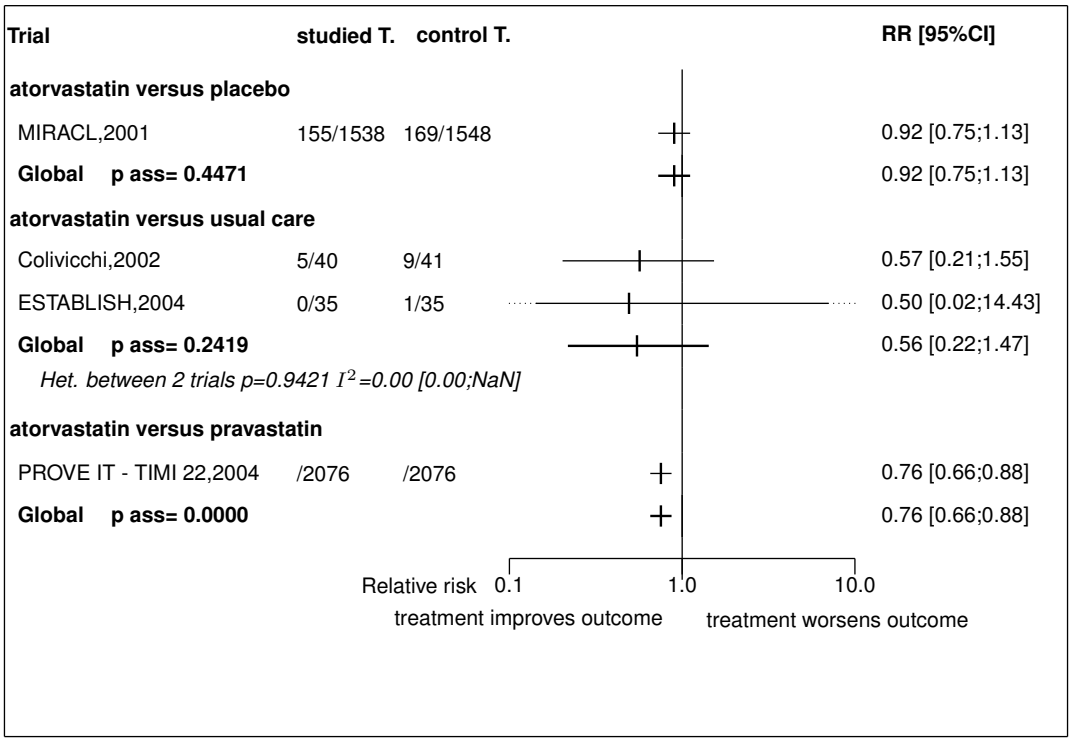


Figure 31.5: *Forest's plot for stroke (fatal and non fatal)*

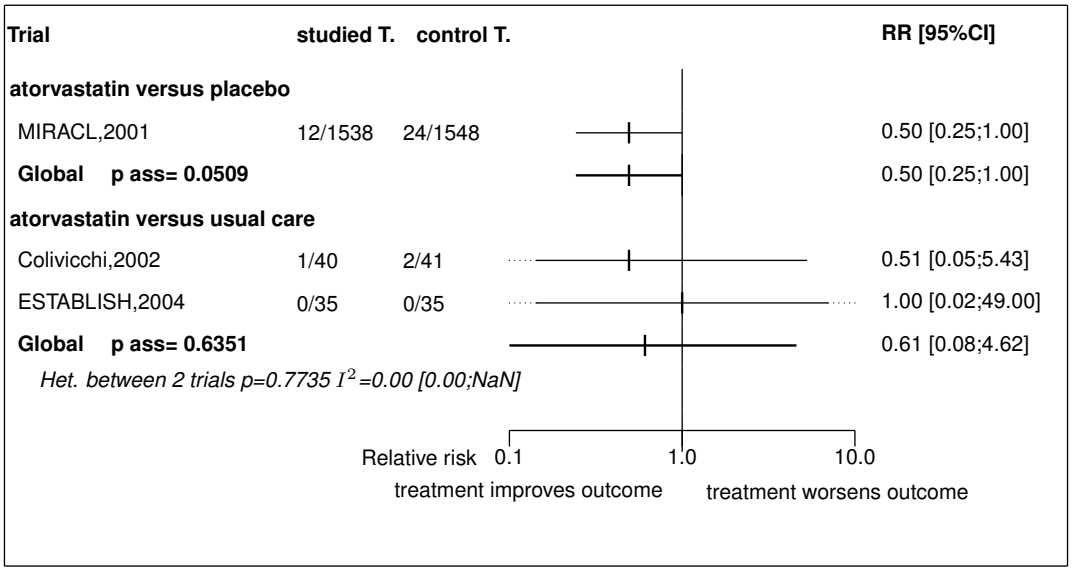


Figure 31.6: *Forest's plot for cardiac death*

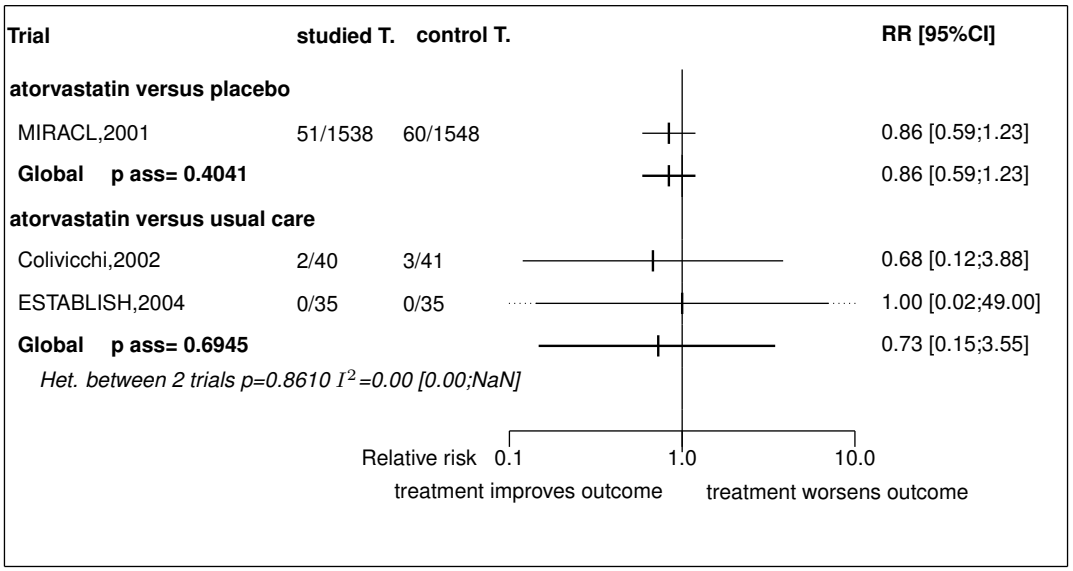


Figure 31.7: *Forest's plot for CABG*

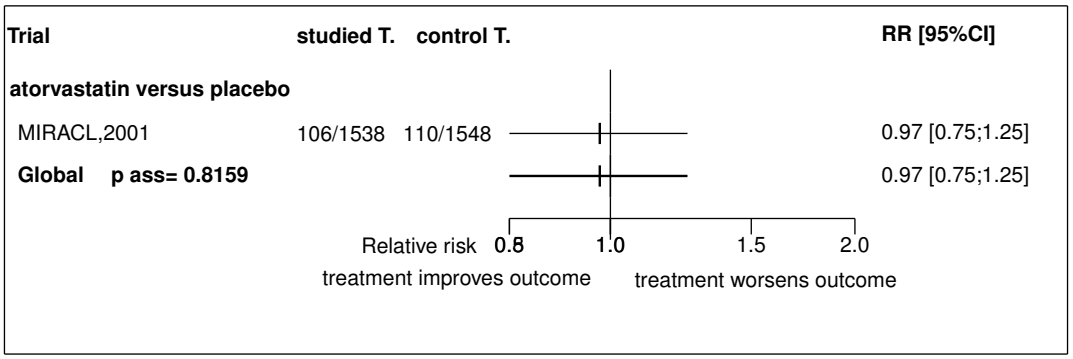


Figure 31.8: *Forest's plot for non fatal MI*

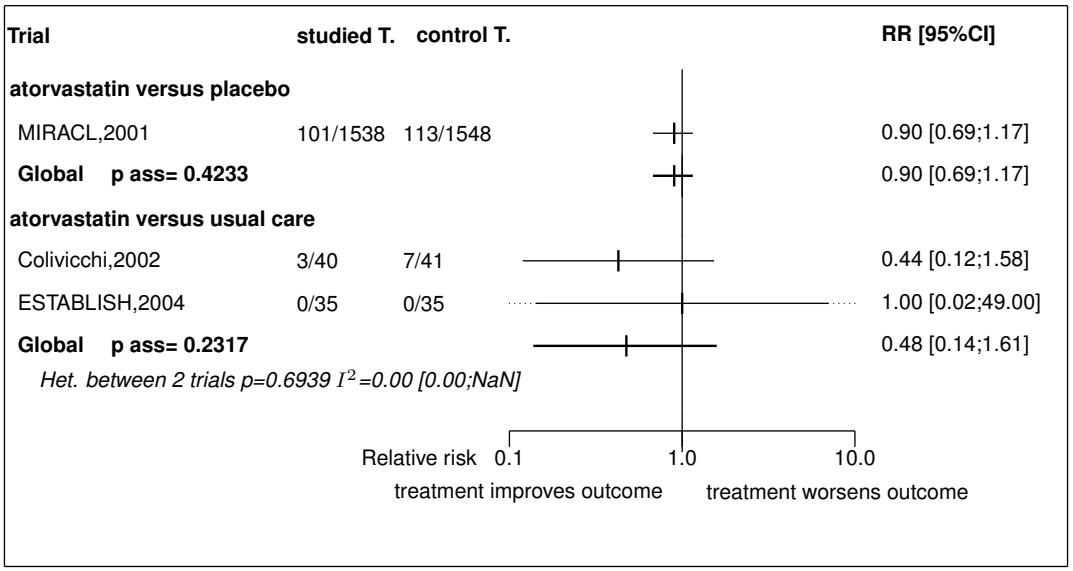


Figure 31.9: *Forest's plot for revascularization*

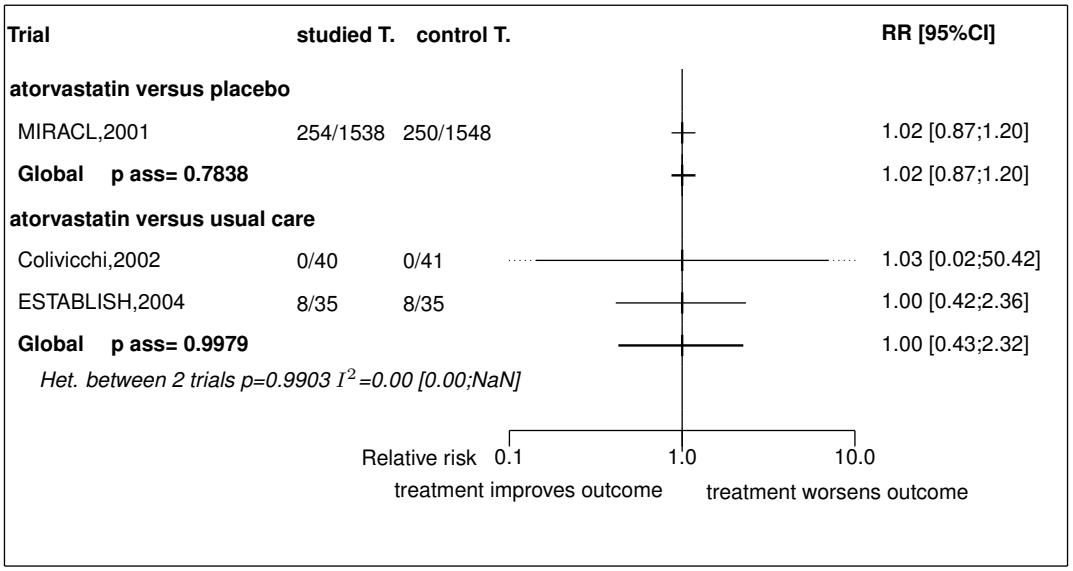


Figure 31.10: *Forest's plot for all cause death*

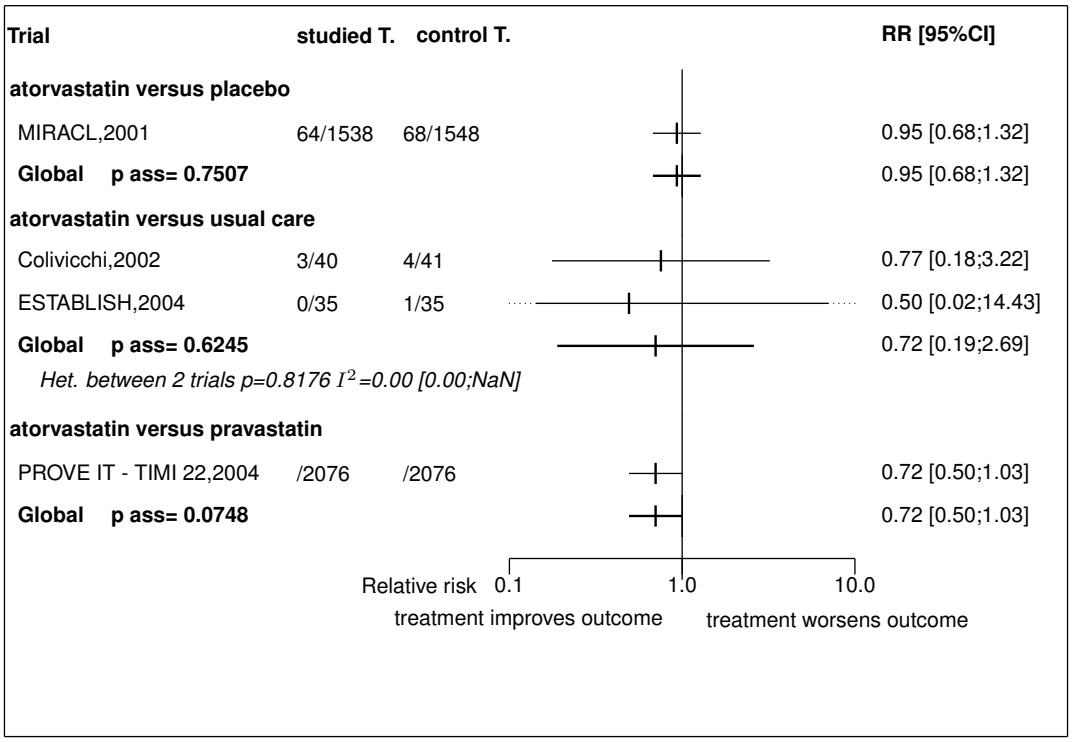
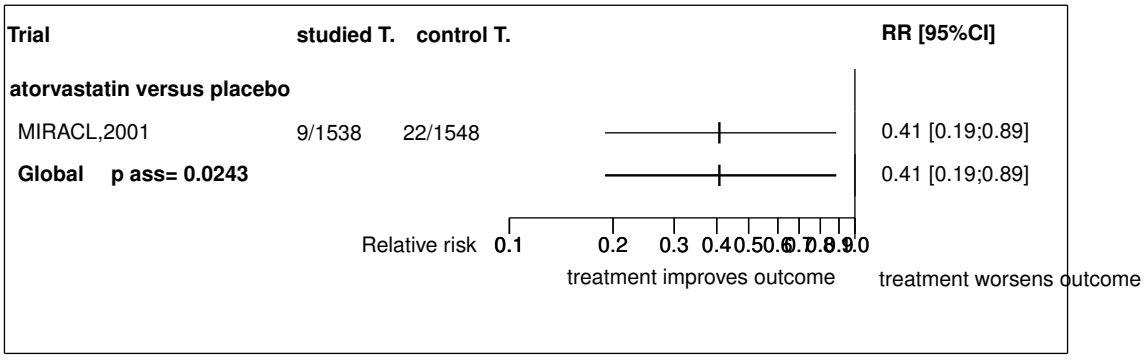


Figure 31.11: *Forest's plot for non fatal stroke*



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[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] Macin SM, Perna ER, Faras EF, Franciosi V, Cialzeta JR, Brizuela M, Medina F, Tajer C, Doval H, Badaracco R.

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[3] 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]

[4] 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]

[5] 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]

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[8] 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]

[9] 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]

31.3 Individual trial summaries

Table 31.6: *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] 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 31.7: *macin, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** 30 days **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Patients admitted within 48 hours of onset of ACS with CRP levels >or =1.4 mg/dL	**Studied treatment:** atorvastatin 40 mg daily for 30 days **Control treatment:** placebo	

Reference

Macin SM, Perna ER, Faras EF, Franciosi V, Cialzeta JR, Brizuela M, Medina F, Tajer C, Doval H, Badaracco R. Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome: results of a randomized, double-blind, placebo-controlled study. Am Heart J 2005;149:451-7 [PMID=15864233]

Table 31.8: *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 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 31.9: *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 31.10: *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]
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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]

32 Detailed results for fluvastatin

32.1 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.
Cardiovascular events data was reported in 2 trials; 2 trials reported data on revascularization; 2 trials reported data on non fatal MI; 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; 1 trials reported data on recurrent angina; and 1 trials reported data on CABG.
Following tables 32.1 (page 168), 32.2 (page 168), 32.4 (page 170), and 32.3 (page 169) summarized the main characteristics of the trials including in this systematic review of randomized trials of fluvastatin.

Table 32.1: *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 32.2: *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 32.3: *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 32.4: *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]		

32.2 Meta-analysis results

The results are detailed in table 32.5 (page 171). This table is followed by the Forest's plot corresponding to each endpoint.

Fluvastatin versus placebo

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 **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%).

Table 32.5: *Results details - statins - fluvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fluvastatin versus placebo						
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
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 32.1: *Forest's plot for recurrent angina*

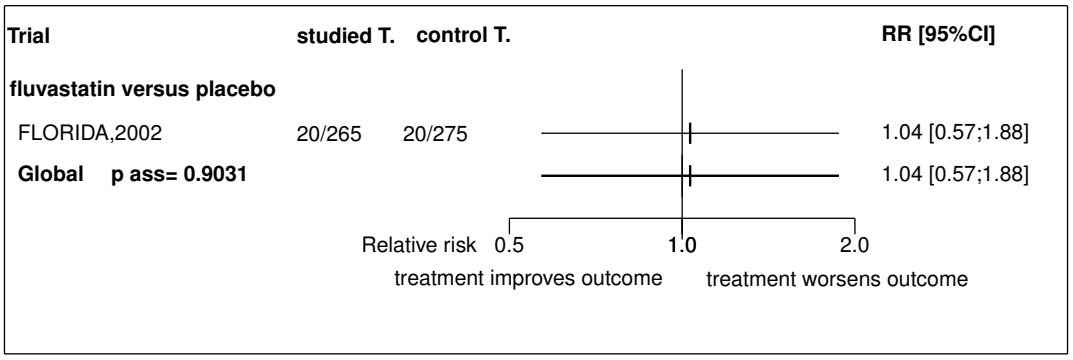


Figure 32.2: *Forest's plot for cardiovascular events*

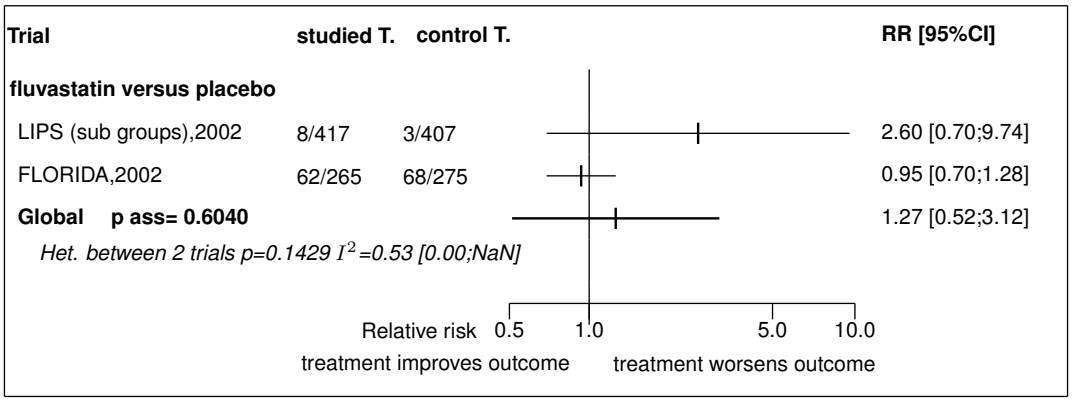


Figure 32.3: *Forest's plot for stroke (fatal and non fatal)*

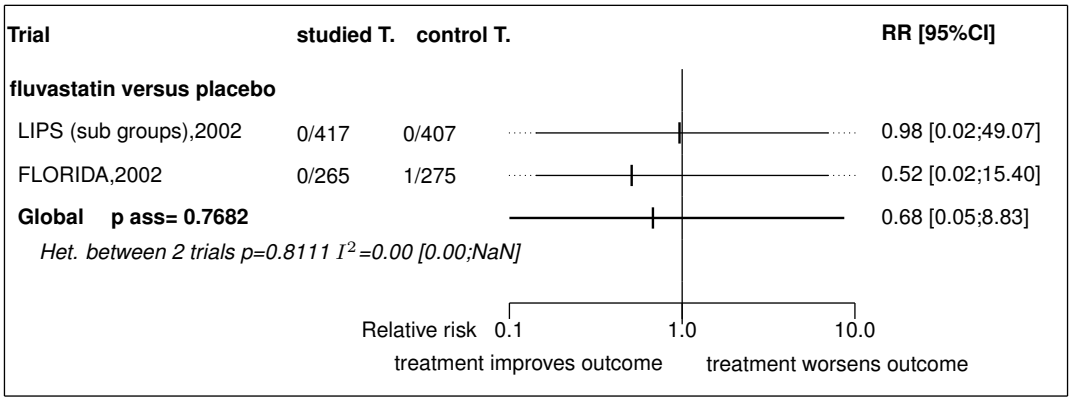


Figure 32.4: *Forest's plot for cardiac death*

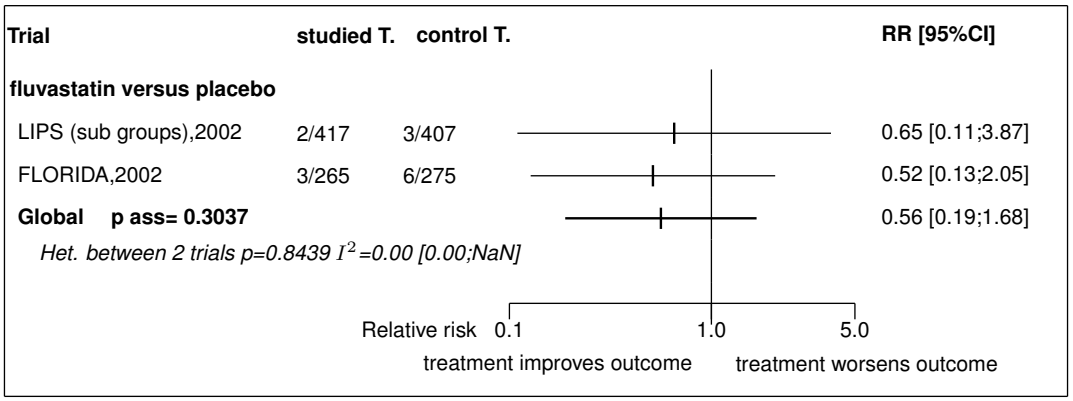


Figure 32.5: *Forest's plot for CABG*

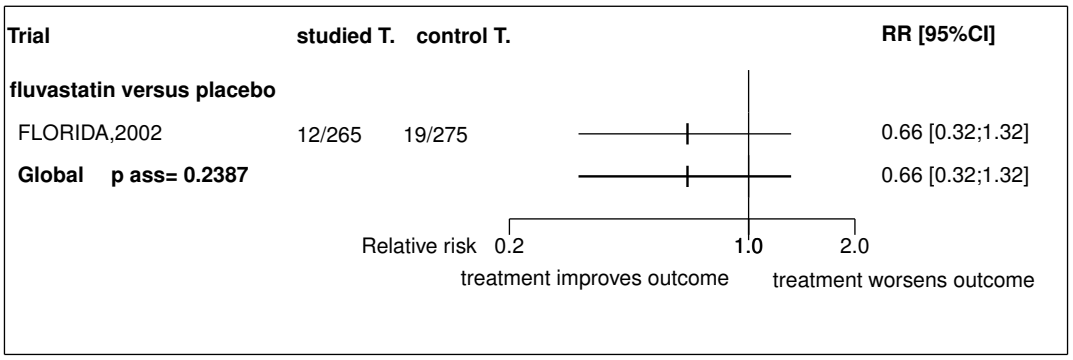


Figure 32.6: *Forest's plot for non fatal MI*

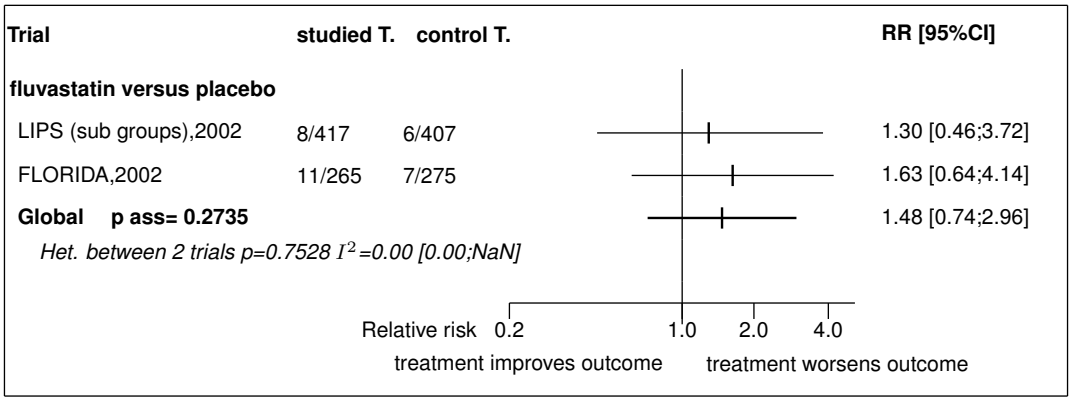


Figure 32.7: *Forest's plot for revascularization*

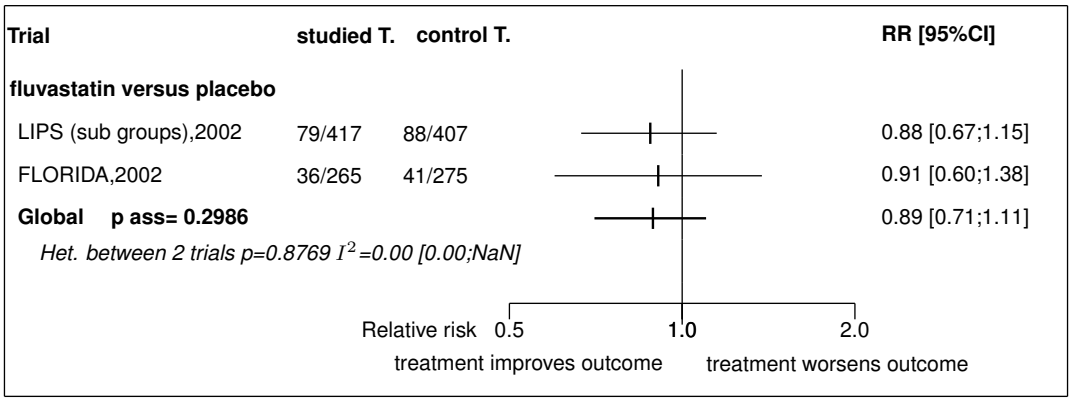
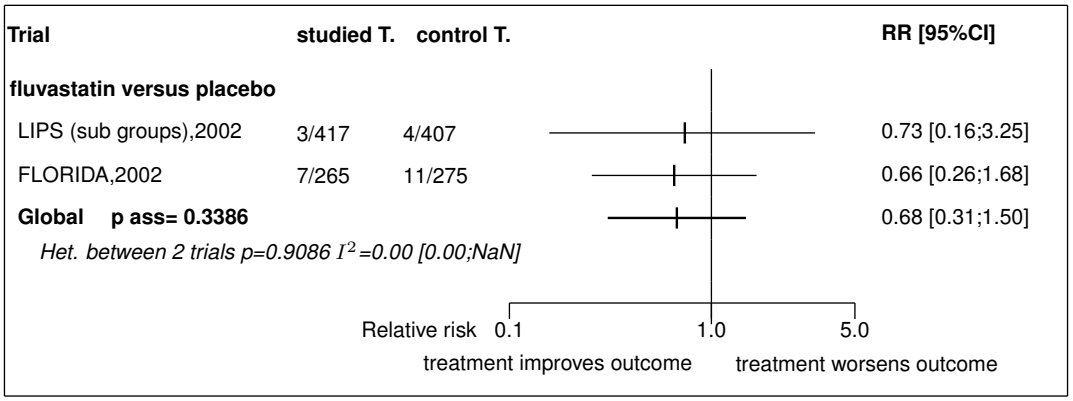


Figure 32.8: *Forest's plot for all cause death*



References

[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]

32.3 Individual trial summaries

Table 32.6: *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 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 32.7: *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	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]

33 Detailed results for lovastatin

33.1 Available trials

Only one trial which randomized 6605 patients was identified: it compared lovastatin with placebo.
This trial included 6605 patients and was published in 1998.
This trial was double blind in design.
It was reported in English language.
Coronary event data was reported in 1 trials; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on coronary death and non fatal MI; 1 trials reported data on coronary death; 1 trials reported data on cardiovascular death; 1 trials reported data on rhabdomyolysis; and 1 trials reported data on all cause death.
Following tables 33.1 (page 178), 33.2 (page 178), 33.4 (page 180), and 33.3 (page 179) summarized the main characteristics of the trial including in this systematic review of randomized trials of lovastatin.

Table 33.1: *Treatment description - statins - lovastatin*

Trial	Studied treatment	Control treatment
Lovastatin versus placebo		
AFCAPS/TexCAPS (1998) [1, 2]	lovastatin 20-40 mg/d	placebo
	Concomittant treatment: diet	

Table 33.2: *Descriptions of participants - statins - lovastatin*

Trial	Patients	
Lovastatin versus placebo		
AFCAPS/TexCAPS (1998) [1, 2]	Men and women without clinically evident atherosclerotic cardiovascular disease with average total cholesterol (TC) and LDL-C levels and below-average high-density lipoprotein cholesterol (HDL-C) levels	
	Inclusion criteria: men aged 45 to 73 years and postmenopausai women aged 55 to 73 years; no prior history, signs, or symptoms of definite myocardial infarction,angina,claudication, cerebrovascular accident, or transient ischemic attack; TC between 180-264 mg/dL, LDL between 130-190 mg/dL, HDL <=45 mg/dL for mena and <=47 mg/dL for women and TG <=400 mg/dL or LDL between 125-129 mg/dl and ratio of TG/HDL >6	**Exclusion criteria:** uncontrolled hypertension, secondary hyperlipidemia, or type 1 or type 2 diabetes mellitus that was either managed with insulin or associated with a glycohemoglobin level of at least 10%

continued...

Trial	Patients

Table 33.3: *Design and methodological quality of trials - statins - lovastatin*

Trial	Design	Duration	Centre	Primary endpoint
Lovastatin versus placebo				
AFCAPS/TexCAPS, 1998 [1, 2] n=6605	Parallel groups double blind confirmatory trial at low risk of bias	5.2 years inclusion period: may 1990, Fev 1993	USA 2 centres	major coronary event

Table 33.4: *Trial characteristics - statins - lovastatin*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Lovastatin versus placebo				
AFCAPS/TexCAPS, 1998 [1, 2]	-1			

33.2 Meta-analysis results

The results are detailed in table 33.5 (page 181). This table is followed by the Forest's plot corresponding to each endpoint.

Lovastatin versus placebo

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 0.68 (95% CI 0.37 to 1.26, p=0.2174).
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 0.82 (95% CI 0.41 to 1.67, p=0.5880).
The single study eligible for this comparison provided data on **coronary event**. The analysis detected a statistically significant difference in favor of lovastatin in coronary event, with a RR of 0.76 (95% CI 0.62 to 0.92, p=0.0059).
The single study eligible for this comparison provided data on **coronary death and non fatal MI**. The analysis detected a statistically significant difference in favor of lovastatin in coronary death and non fatal MI, with a RR of 0.76 (95% CI 0.62 to 0.92, p=0.0059).
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 0.73 (95% CI 0.34 to 1.59, p=0.4324).

Table 33.5: *Results details - statins - lovastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
lovastatin versus placebo						
cardiovascular death	RR=0.68	[0.37;1.26]	0.2174	1.0000 (I^2=0.00)	1	6605
stroke (fatal and non fatal)	RR=0.82	[0.41;1.67]	0.5880	1.0000 (I^2=0.00)	1	6605
coronary event	RR=0.76	[0.62;0.92]	0.0059	1.0000 (I^2=0.00)	1	6605
coronary death and non fatal MI	RR=0.76	[0.62;0.92]	0.0059	1.0000 (I^2=0.00)	1	6605
coronary death	RR=0.73	[0.34;1.59]	0.4324	1.0000 (I^2=0.00)	1	6605
rhabdomyolysis	RR=0.50	[0.05;5.51]	0.5708	1.0000 (I^2=0.00)	1	6605
all cause death	RR=1.04	[0.76;1.41]	0.8130	1.0000 (I^2=0.00)	1	6605

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 33.1: *Forest's plot for cardiovascular death*

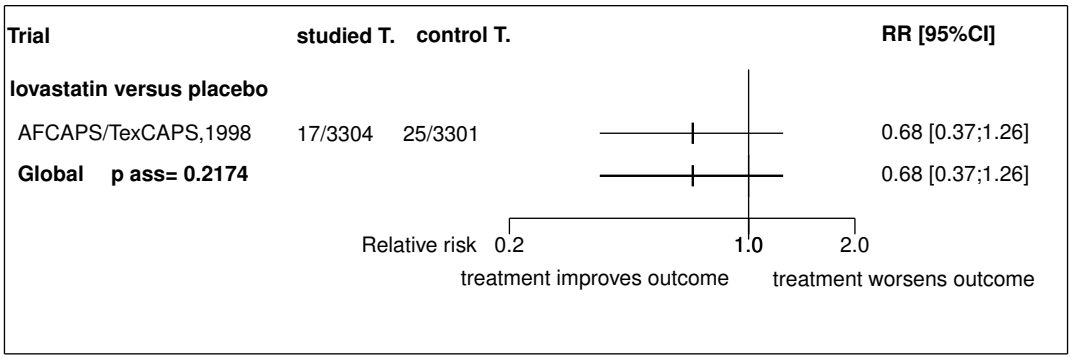


Figure 33.2: *Forest's plot for stroke (fatal and non fatal)*

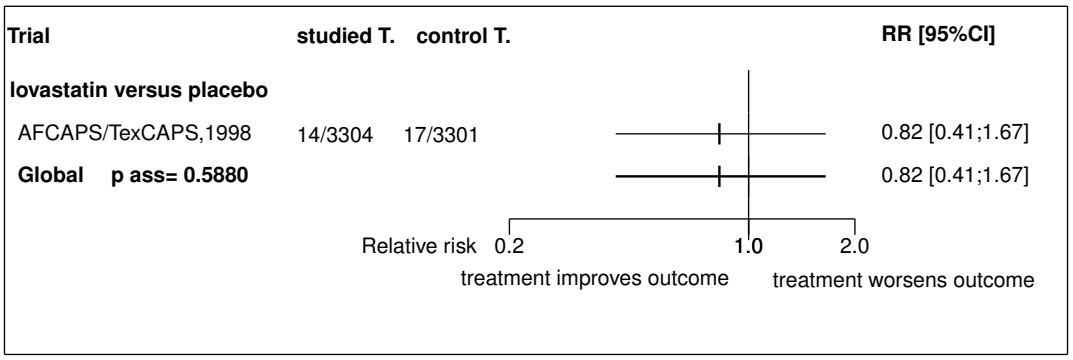


Figure 33.3: *Forest's plot for coronary event*

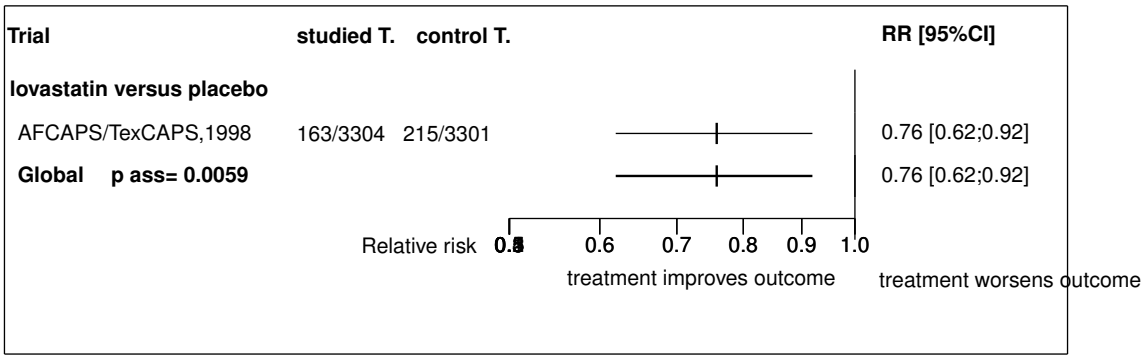


Figure 33.4: *Forest's plot for coronary death and non fatal MI*

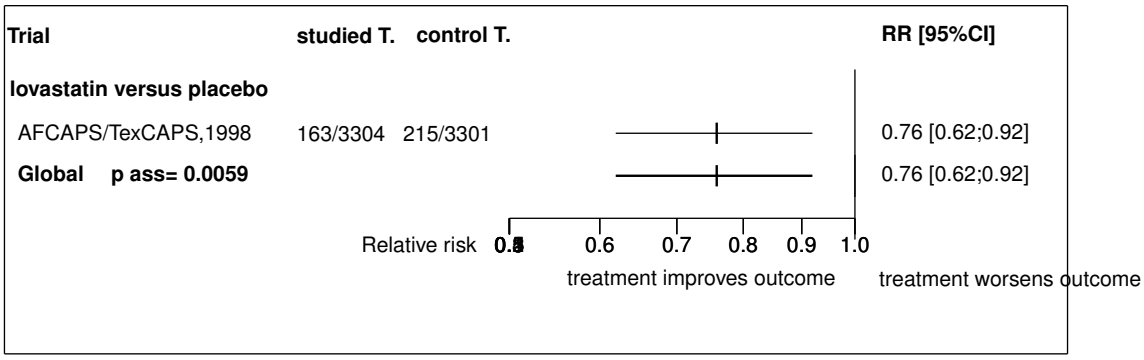


Figure 33.5: *Forest's plot for coronary death*

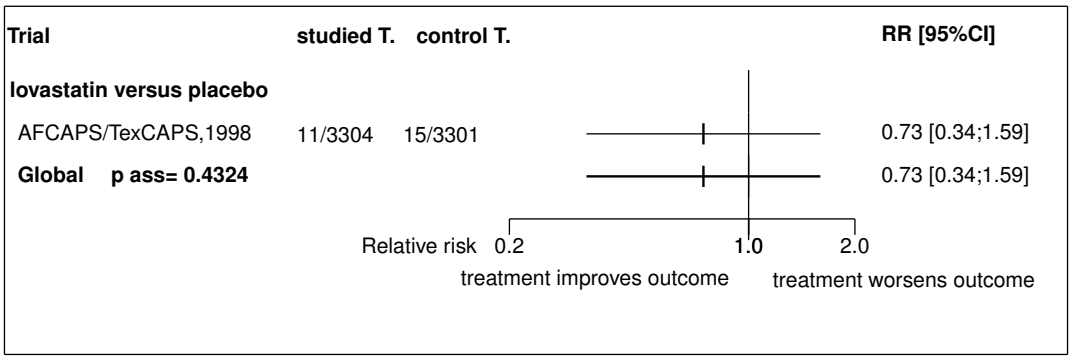


Figure 33.6: *Forest's plot for rhabdomyolysis*

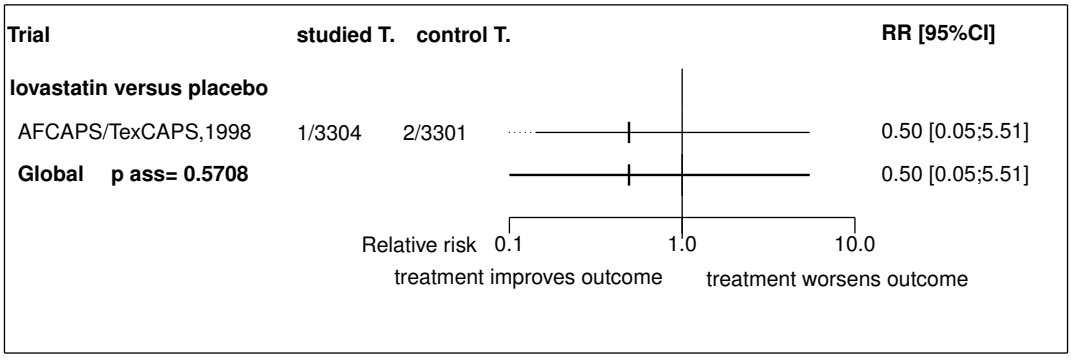
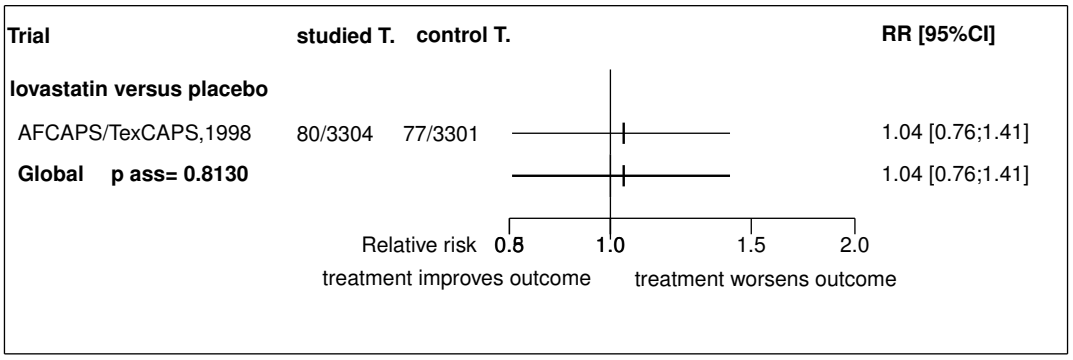


Figure 33.7: *Forest's plot for all cause death*



References

[1] Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr,. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279:1615-22. [PMID=9613910]

[2] Cui Y, Watson DJ, Girman CJ, Shapiro DR, Gotto AM, Hiserote P, Clearfield MB. Effects of increasing high-density lipoprotein cholesterol and decreasing low-density lipoprotein cholesterol on the incidence of first acute coronary events (from the Air Force/Texas Coronary Atherosclerosis Prevention Study). Am J Cardiol 2009;104:829-34. [PMID=19733719]

33.3 Individual trial summaries

Table 33.6: *AFCAPS/TexCAPS, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=6605 (3304 vs. 3301) **Follow-up duration:** 5.2 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias USA, 2 centres **Inclusion period:** may 1990, Fev 1993	Men and women without clinically evident atherosclerotic cardiovascular disease with average total cholesterol (TC) and LDL-C levels and below-average high-density lipoprotein cholesterol (HDL-C) levels **Inclusion criteria:** Men aged 45 to 73 years and postmenopausai women aged 55 to 73 years; no prior history, signs, or symptoms of definite myocardial infarction,angina,claudication, cerebrovascular accident, or transient ischemic attack; TC between 180-264 mg/dL, LDL between 130-190 mg/dL, HDL <=45 mg/dL for mena and <=47 mg/dL for women and TG <=400 mg/dL or LDL between 125-129 mg/dl and ratio of TG/HDL >6 **Exclusion criteria:** uncontrolled hypertension, secondary hyperlipidemia, or type 1 or type 2 diabetes mellitus that was either managed with insulin or associated with a glycohemoglobin level of at least 10%	**Studied treatment:** lovastatin 20-40 mg/d **Control treatment:** placebo **Concomitant treat.:**diet	Cardiovascular death RR=0.68 [0.37;1.26] Stroke (fatal and non fatal) RR=0.82 [0.41;1.67] Coronary event RR=0.76 [0.62;0.92] Coronary death and non fatal MI RR=0.76 [0.62;0.92]

References

Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr,. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279:1615-22 [PMID=9613910]
Cui Y, Watson DJ, Girman CJ, Shapiro DR, Gotto AM, Hiserote P, Clearfield MB. Effects of increasing high-density lipoprotein cholesterol and decreasing low-density lipoprotein cholesterol on the incidence of first acute coronary events (from the Air Force/Texas Coronary Atherosclerosis Prevention Study). Am J Cardiol 2009;104:829-34 [PMID=19733719]

34 Detailed results for pitavastatin

34.1 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 34.1 (page 187), 34.2 (page 187), 34.4 (page 188), and 34.3 (page 187) summarized the main characteristics of the trial including in this systematic review of randomized trials of pitavastatin.

Table 34.1: *Treatment description - statins - pitavastatin*

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

Table 34.2: *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 34.3: *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 34.4: *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]		

34.2 Meta-analysis results

The results are detailed in table 34.5 (page 189). 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 34.5: *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]

34.3 Individual trial summaries

Table 34.6: *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]

35 Detailed results for pravastatin

35.1 Available trials

A total of 8 RCTs which randomized 10874 patients were identified: 5 trials compared pravastatin with placebo and 3 trials compared pravastatin with usual care.
The average study size was 1359 patients (range 60 to 6595). The first study was published in 1995, and the last study was published in 2008.
A total of 5 trials were double blind and 3 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Non fatal MI data was reported in 8 trials; 8 trials reported data on stroke (fatal and non fatal); 7 trials reported data on all cause death; 6 trials reported data on cardiac death; 5 trials reported data on cardiovascular events; 5 trials reported data on revascularization; 1 trials reported data on cardiovascular death; 1 trials reported data on coronary event; 1 trials reported data on coronary death and non fatal MI; 1 trials reported data on coronary death; 1 trials reported data on rhabdomyolysis; 1 trials reported data on death from cancer; and 1 trials reported data on all cause death.
Following tables 35.1 (page 192), 35.2 (page 193), 35.4 (page 195), and 35.3 (page 194) summarized the main characteristics of the trials including in this systematic review of randomized trials of pravastatin.

Table 35.1: *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
WOSCOPS (1995) [6, 7]	pravastatine 40 mg daily **Concomittant treatment:** diet	placebo
Pravastatin versus usual care		
L-CAD (2000) [8]	Pravastatin, 20-40 mg (strating on average at D6)	Usual care
PTT (2002) [9]	Pravastatin, 40 mg	Usual care
OACIS-LIPID (2008) [10]	pravastatin 10 mg/daily	no pravastatin

continued...

Trial	Studied treatment	Control treatment

Table 35.2: *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
WOSCOPS (1995) [6, 7]	Men aged 45-64 yr with no history of myocardial infarction and with raised plasma cholesterol levels (LDL cholesterol of at least 155 mg/dL, total cholesterolof at least 252 mg/dL) **Inclusion criteria:** fasting LDL cholesterol level of at least 155 mg per deciliter during the second and third visits, with at least one value of 174 mg per deciliter or above (4.5 mmol per liter) and one value of 232 mg per deciliter or below (6.0 mmol per liter); no serious ECG abnormalities according to Minnesota code 1 (pathologic Q waves), 4-1, 5-1, or 7-1-1 or arrhythmia such as atrial fibrillation; and no history of myocardial infarction or other serious illness, although men with stable angina who had not been hospitalized within the previous 12 months were eligible **Exclusion criteria:**
Pravastatin versus usual care	
L-CAD (2000) [8]	Patients with acute coronary syndrome
PTT (2002) [9]	Patients who underwent coronary balloon angioplasty of the infarct-related artery during the first month of acute myocardial infarction
OACIS-LIPID (2008) [10]	Patients with AMI who had plasma total cholesterol levels of 200-250 mg/dl and triglyceride levels <300 mg/dl

Table 35.3: *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
WOSCOPS, 1995 [6, 7] n=6595	Parallel groups double blind confirmatory trial at low risk of bias	4.9 years inclusion period: Fev 1989 - Sep 1991	Scotland multicenter	coronary events (CHD death, MI)
Pravastatin versus usual care				
L-CAD, 2000 [8] n=126	Parallel groups open exploratory trial	1, 4, and 6 months	Germany	death, MI, stroke, coronary intervention, PVD
PTT, 2002 [9] n=164	Parallel groups open exploratory trial	1 and 6 months	Turkey	
OACIS-LIPID, 2008 [10] n=353	Parallel groups open confirmatory trial at low risk of bias	9 months		death, nonfatal MI, unstable angina, stroke, revascularization, and rehospitalization

Table 35.4: *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]		
WOSCOPS, 1995 [6, 7]	-1	
Pravastatin versus usual care		
L-CAD, 2000 [8]		
PTT, 2002 [9]		
OACIS-LIPID, 2008 [10]		

35.2 Meta-analysis results

The results are detailed in table 35.5 (page 197). This table is followed by the Forest's plot corresponding to each endpoint.

Pravastatin versus placebo

A total of 3 of the 5 studies eligible for this comparison provided data on **cardiovascular events**. The analysis detected a statistically significant difference in favor of pravastatin in cardiovascular events, with a RR of 0.59 (95% CI 0.49 to 0.72, p=0.0000). No heterogeneity was detected (p = 0.6415, I^2 = 0.00%).
Only one of the 5 studies eligible for this comparison provided data on **cardiovascular death**. The analysis detected a statistically significant difference in favor of pravastatin in cardiovascular death, with a RR of 0.68 (95% CI 0.48 to 0.98, p=0.0361).
All the 5 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 0.87 (95% CI 0.61 to 1.24, p=0.4403). No heterogeneity was detected (p = 0.9485, I^2 = 0.00%).
Only one of the 5 studies eligible for this comparison provided data on **coronary event**. The analysis detected a statistically significant difference in favor of pravastatin in coronary event, with a RR of 0.70 (95% CI 0.58 to 0.84, p=0.0000).
Only one of the 5 studies eligible for this comparison provided data on **coronary death and non fatal MI**. The analysis detected a statistically significant difference in favor of pravastatin in coronary death and non fatal MI, with a RR of 0.70 (95% CI 0.58 to 0.84, p=0.0000).
Only one of the 5 studies 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 0.73 (95% CI 0.48 to 1.10, p=0.1356).
A total of 4 of the 5 studies eligible for this comparison provided data on **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 5 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 0.14 to 1.44, p=0.1774). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0008, I^2 = 0.79%).
A total of 3 of the 5 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%).

Pravastatin versus usual care

A total of 2 of the 3 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 0.39 (95% CI 0.10 to 1.48, p=0.1657). No heterogeneity was detected (p = 0.5520, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **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%).
A total of 2 of the 3 studies eligible for this comparison provided data on **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%).
A total of 2 of the 3 studies eligible for this comparison provided data on **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%).
A total of 2 of the 3 studies eligible for this comparison provided data on **revascularization**. When pooled together, there was no statistically significant difference between the groups in revascularization, with a RR of 0.58 (95% CI 0.33 to 1.05, p=0.0725). No heterogeneity was detected (p = 0.2965, I^2 = 0.08%).

Table 35.5: *Results details - statins - pravastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pravastatin versus placebo						
cardiovascular events	RR=0.59	[0.49;0.72]	0.0000	0.6415 (I^2=0.00)	3	6763
cardiovascular death	RR=0.68	[0.48;0.98]	0.0361	1.0000 (I^2=0.00)	1	6595
stroke (fatal and non fatal)	RR=0.87	[0.61;1.24]	0.4403	0.9485 (I^2=0.00)	5	10231
coronary event	RR=0.70	[0.58;0.84]	0.0000	1.0000 (I^2=0.00)	1	6595
coronary death and non fatal MI	RR=0.70	[0.58;0.84]	0.0000	1.0000 (I^2=0.00)	1	6595
coronary death	RR=0.73	[0.48;1.10]	0.1356	1.0000 (I^2=0.00)	1	6595
cardiac death	RR=0.79	[0.49;1.28]	0.3336	0.9549 (I^2=0.00)	4	3636
death from cancer	RR=0.90	[0.60;1.34]	0.5926	1.0000 (I^2=0.00)	1	6595
rhabdomyolysis	RR=1.00	[0.02;50.25]	0.9989	1.0000 (I^2=0.00)	1	6595
non fatal MI	RR=0.44	[0.14;1.44]	0.1774	0.0008 (I^2=0.79)	5	10231
revascularization	RR=1.17	[0.55;2.45]	0.6845	0.9801 (I^2=0.00)	3	228
all cause death	RR=0.76	[0.61;0.95]	0.0161	0.9692 (I^2=0.00)	5	10231
pravastatin versus usual care						
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
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 35.1: *Forest's plot for cardiovascular events*

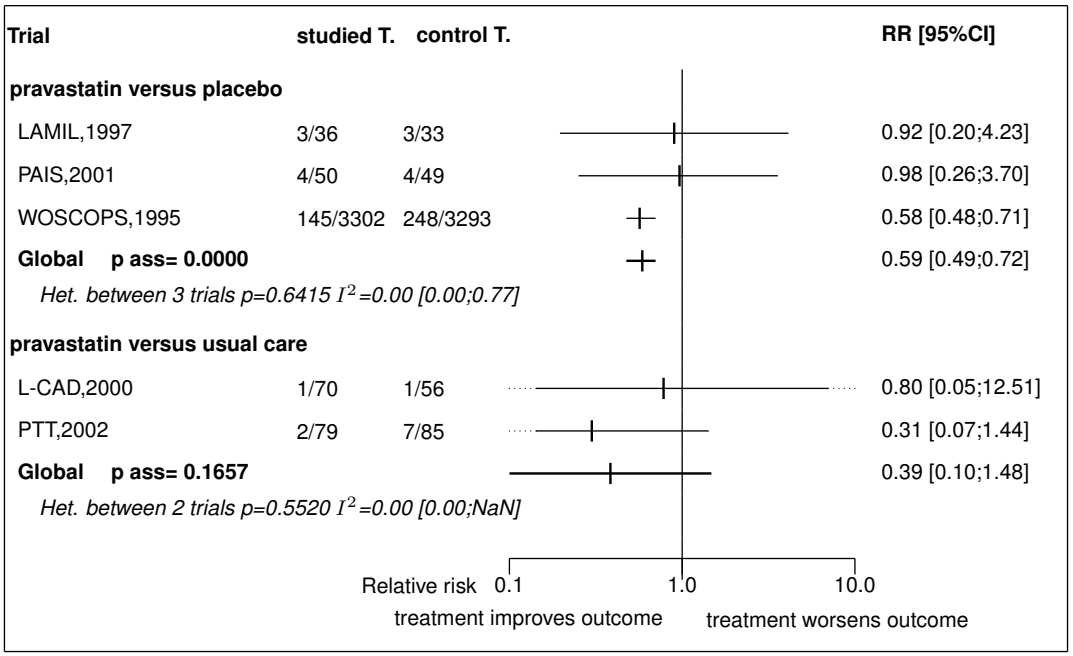


Figure 35.2: *Forest's plot for cardiovascular death*

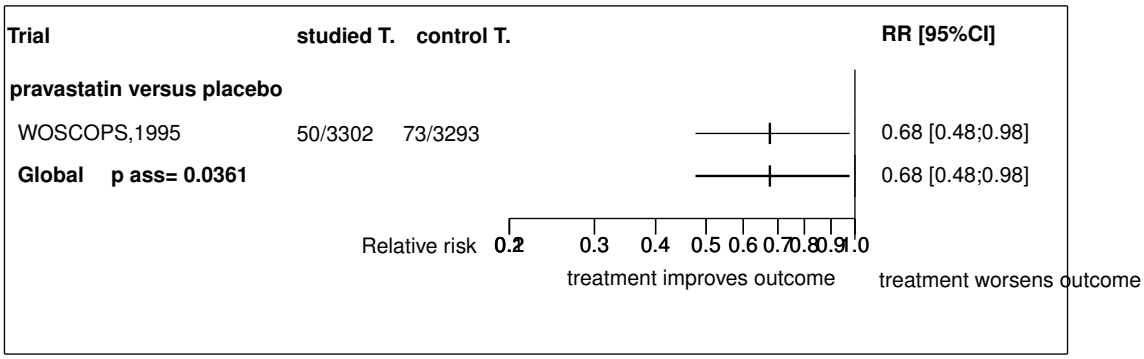


Figure 35.3: *Forest's plot for stroke (fatal and non fatal)*

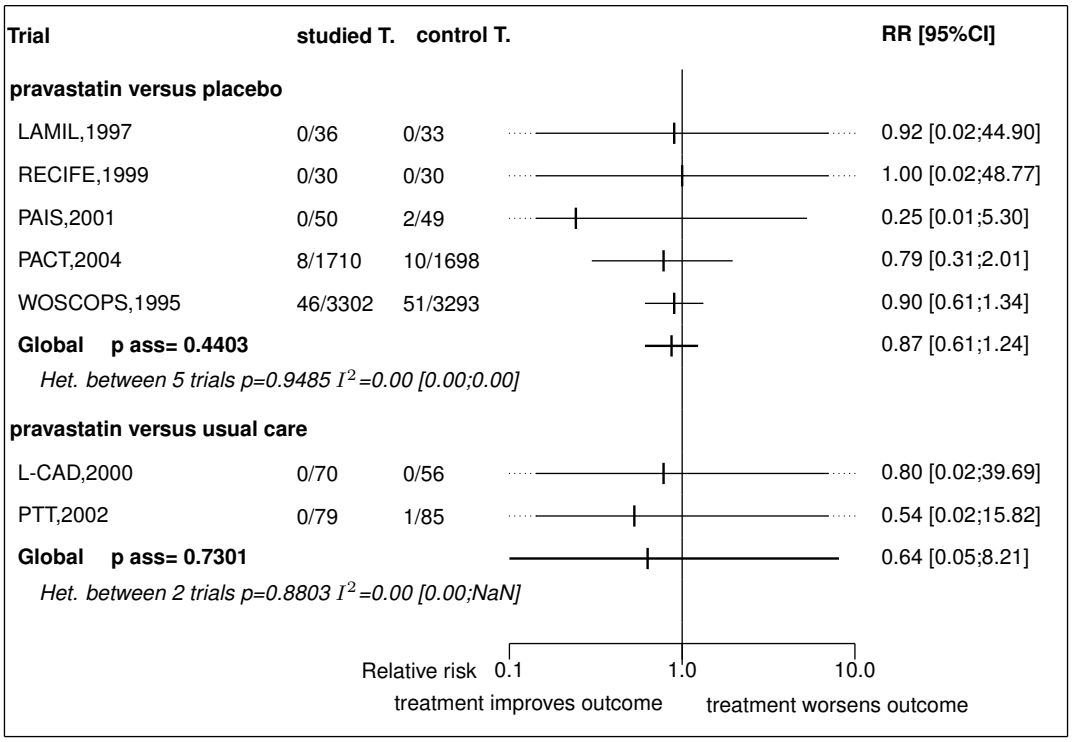


Figure 35.4: *Forest's plot for coronary event*

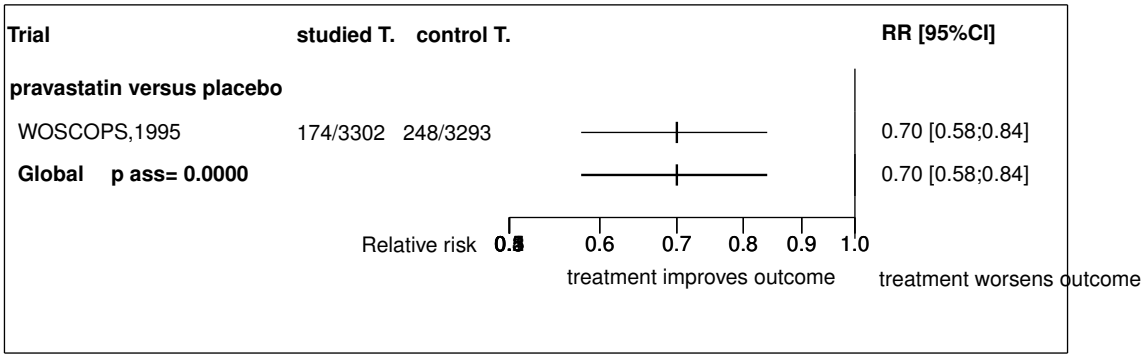


Figure 35.5: *Forest's plot for coronary death and non fatal MI*

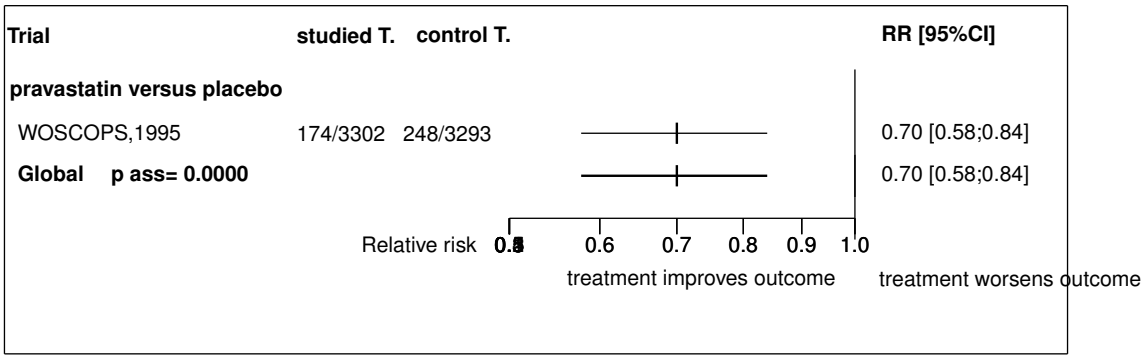


Figure 35.6: *Forest's plot for coronary death*

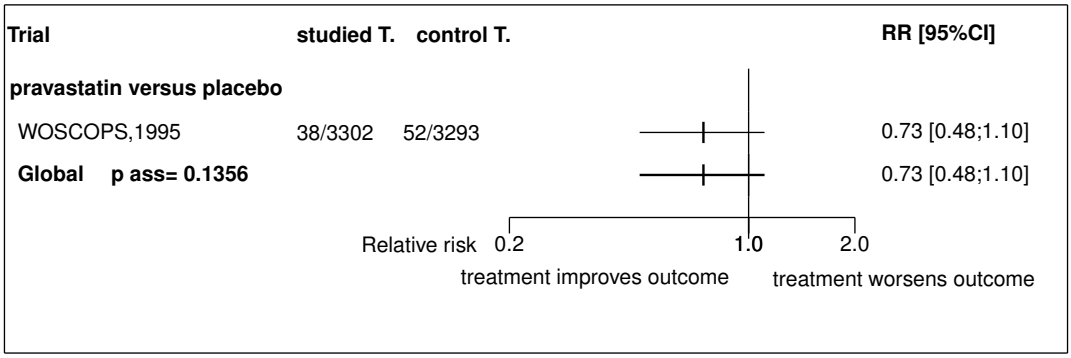


Figure 35.7: *Forest's plot for cardiac death*

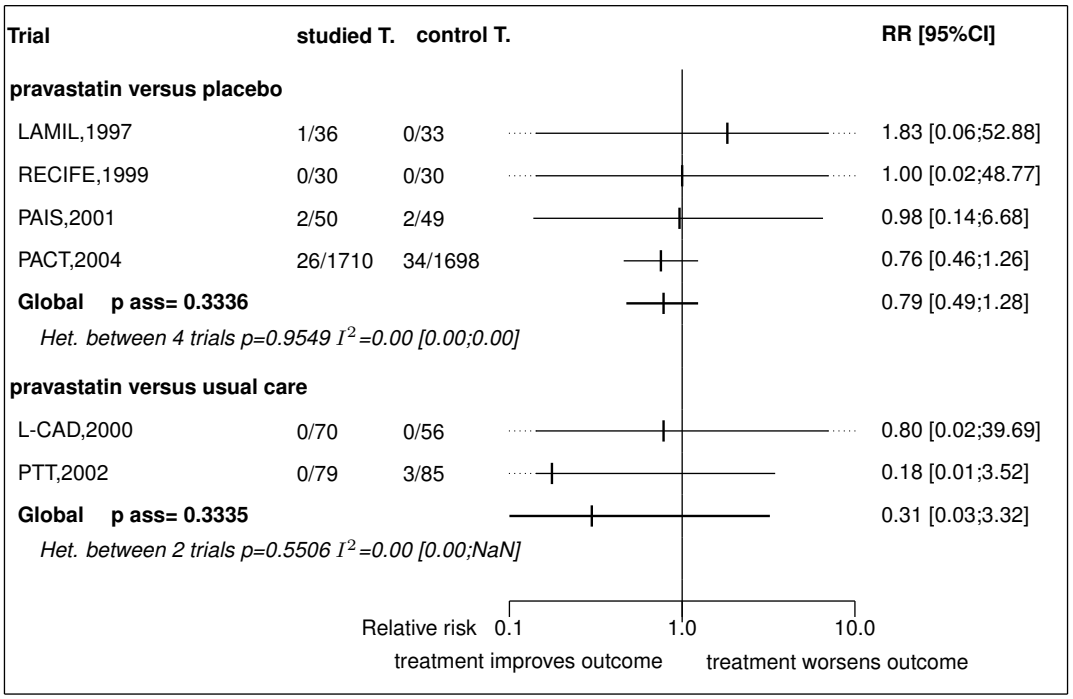


Figure 35.8: *Forest's plot for death from cancer*

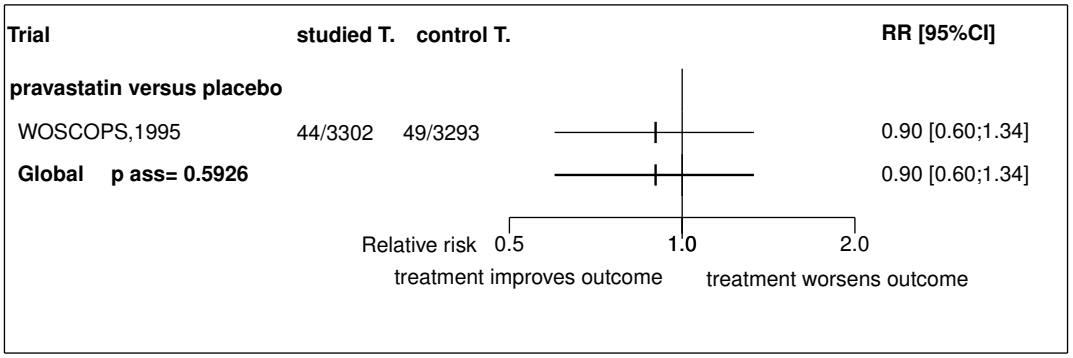


Figure 35.9: *Forest's plot for rhabdomyolysis*

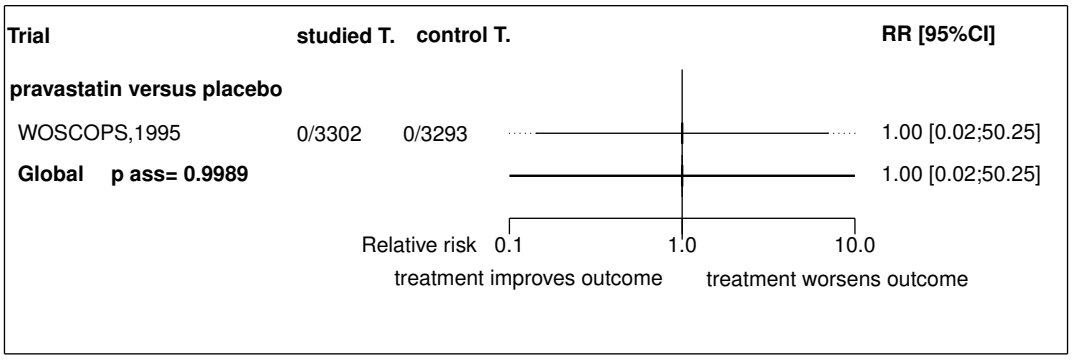


Figure 35.10: *Forest's plot for non fatal MI*

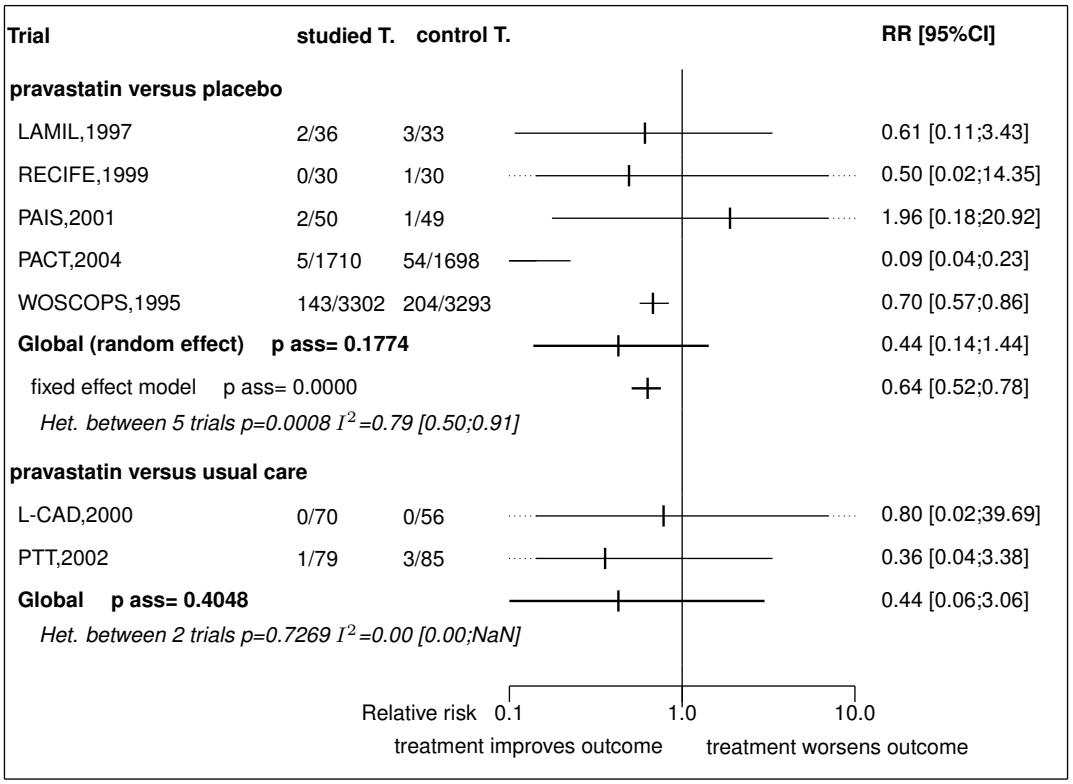


Figure 35.11: *Forest's plot for revascularization*

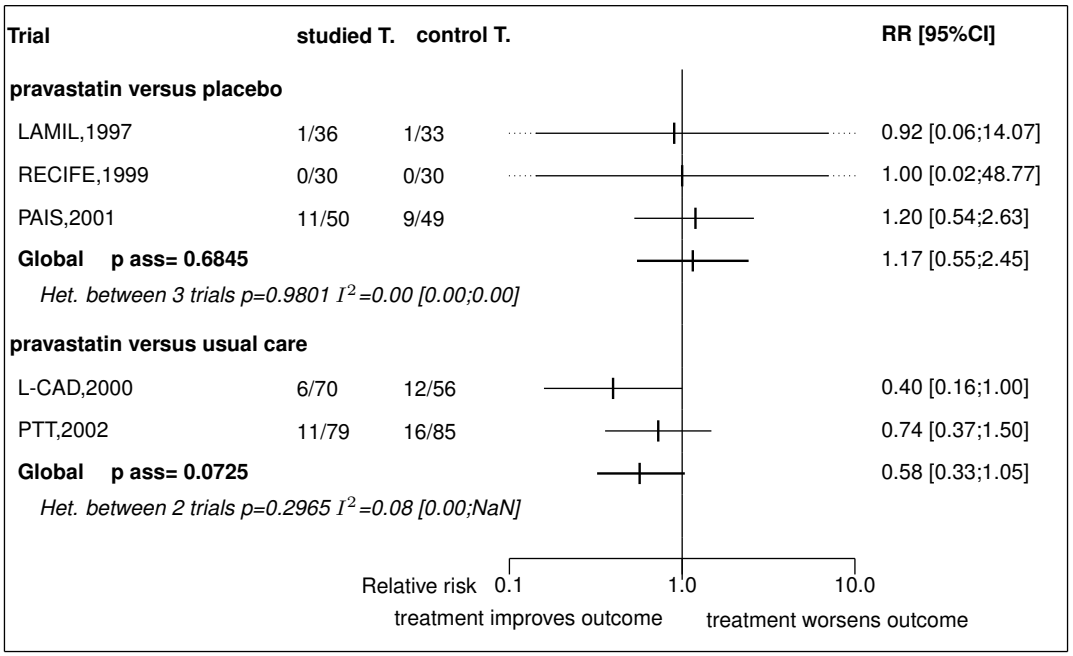
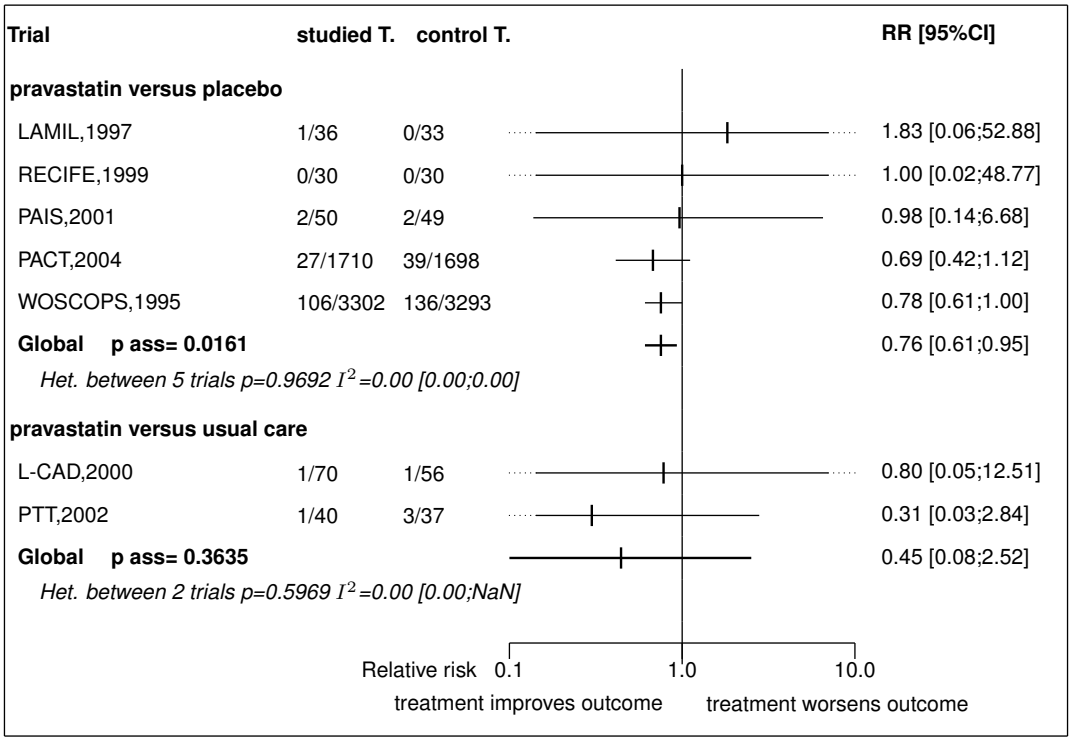


Figure 35.12: *Forest's plot for all cause death*



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[4] 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.

[5] 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]

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[9] 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]

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35.3 Individual trial summaries

Table 35.6: *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 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 35.7: *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 35.8: *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 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 35.9: *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	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 35.10: *WOSCOPS, 1995 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=6595 (3302 vs. 3293) **Follow-up duration:** 4.9 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Scotland, multicenter **Inclusion period:** Fev 1989 - Sep 1991	Men aged 45-64 yr with no history of myocardial infarction and with raised plasma cholesterol levels (LDL cholesterol of at least 155 mg/dL, total cholesterolof at least 252 mg/dL) **Inclusion criteria:** fasting LDL cholesterol level of at least 155 mg per deciliter during the second and third visits, with at least one value of 174 mg per deciliter or above (4.5 mmol per liter) and one value of 232 mg per deciliter or below (6.0 mmol per liter); no serious ECG abnormalities according to Minnesota code 1 (pathologic Q waves), 4-1, 5-1, or 7-1-1 or arrhythmia such as atrial fibrillation; and no history of myocardial infarction or other serious illness, although men with stable angina who had not been hospitalized within the previous 12 months were eligible	**Studied treatment:** pravastatine 40 mg daily **Control treatment:** placebo **Concomittant treat.:**diet	Cardiovascular events RR=0.58 [0.48;0.71] Cardiovascular death RR=0.68 [0.48;0.98] Stroke (fatal and non fatal) RR=0.90 [0.61;1.34] Coronary event RR=0.70 [0.58;0.84] Coronary death and non fatal MI RR=0.70 [0.58;0.84]

References

Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ,. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333:1301-7 [PMID=7566020] . A coronary primary prevention study of Scottish men aged 45-64 years: trial design. The West of Scotland Coronary Prevention Study Group. J Clin Epidemiol 1992;45:849-60 [PMID=1624967]

Table 35.11: *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 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 35.12: *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 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]

Table 35.13: *OACIS-LIPID, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=353 (176 vs. 177) **Follow-up duration:** 9 months **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at low risk of bias	Patients with AMI who had plasma total cholesterol levels of 200-250 mg/dl and triglyceride levels <300 mg/dl	**Studied treatment:** pravastatin 10 mg/daily **Control treatment:** no pravastatin	

Reference

Sato H, Kinjo K, Ito H, Hirayama A, Nanto S, Fukunami M, Nishino M, Lim YJ, Kijima Y, Koretsune Y, Nakatani D, Mizuno H, Shimizu M, Hori M. Effect of early use of low-dose pravastatin on major adverse cardiac events in patients with acute myocardial infarction: the OACIS-LIPID Study. Circ J 2008;72:17-22 [PMID=18159093]

36 Detailed results for simvastatin

36.1 Available trials

A total of 2 RCTs which randomized 4497 patients were identified: all compared simvastatin with placebo.
The average study size was 4497 patients (range 4497 to 4497). The first study was published in 2004, and the last study was published in 2009.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Cardiovascular events data was reported in 1 trials; 1 trials reported data on revascularization; 1 trials reported data on non fatal MI; 1 trials reported data on cardiac death; 1 trials reported data on stroke (fatal and non fatal); and 1 trials reported data on all cause death.
Following tables 36.1 (page 214), 36.2 (page 214), 36.4 (page 216), and 36.3 (page 215) summarized the main characteristics of the trials including in this systematic review of randomized trials of simvastatin.

Table 36.1: *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
Ren (2009) [2]	simvastatin (40 mg/d for 4 weeks)	placebo

Table 36.2: *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
Ren (2009) [2]	Patients with unstable angina pectoris		

Table 36.3: *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
Ren, 2009 [2] n=NaN	Parallel groups double-blind exploratory trial			plasma interleukin-6 (IL-6)

Table 36.4: *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
Ren, 2009 [2]		

36.2 Meta-analysis results

The results are detailed in table 36.5 (page 217). This table is followed by the Forest's plot corresponding to each endpoint.

Simvastatin versus placebo

Only one of the 2 studies 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).
Only one of the 2 studies 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).
Only one of the 2 studies 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).
Only one of the 2 studies 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).
Only one of the 2 studies 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).

Table 36.5: *Results details - statins - simvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
simvastatin versus placebo						
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
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 36.1: *Forest's plot for cardiovascular events*

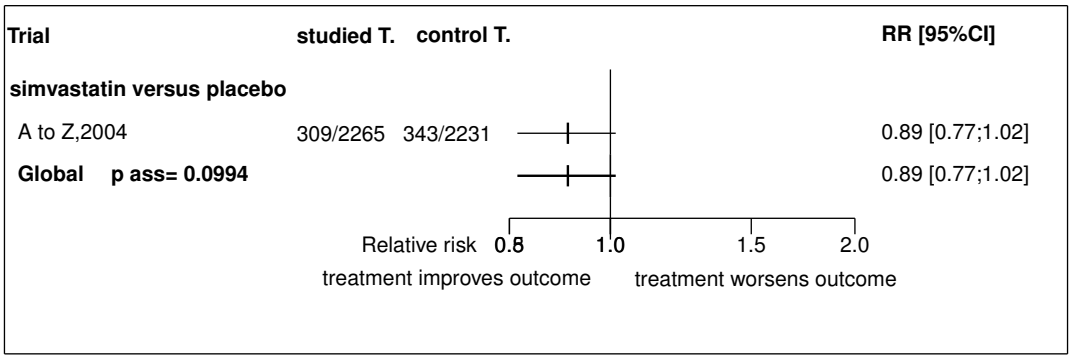


Figure 36.2: *Forest's plot for stroke (fatal and non fatal)*

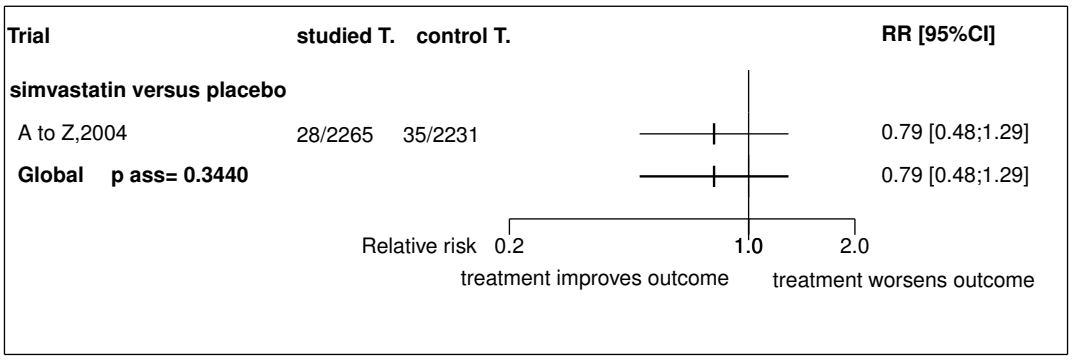


Figure 36.3: *Forest's plot for cardiac death*

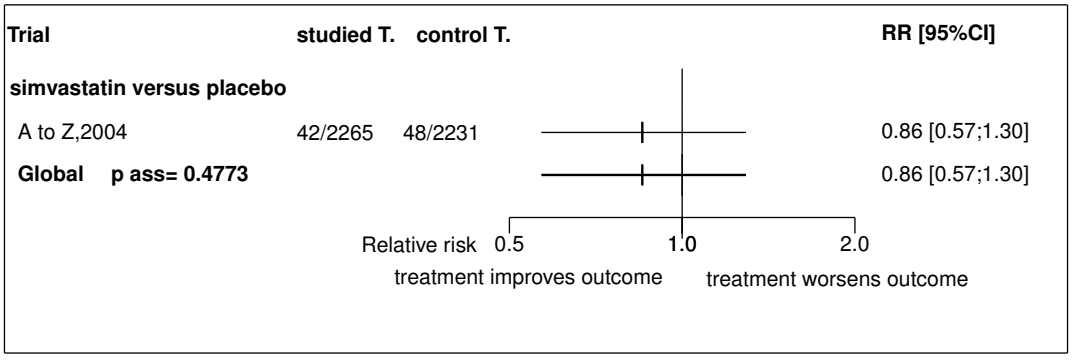


Figure 36.4: *Forest's plot for non fatal MI*

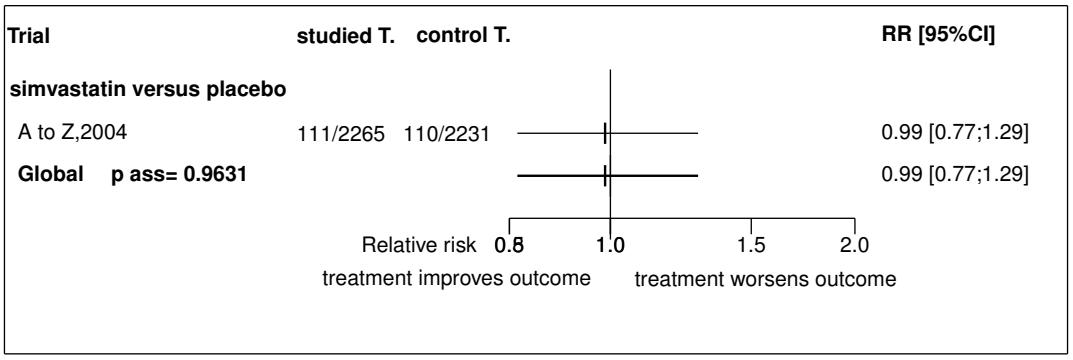


Figure 36.5: *Forest's plot for revascularization*

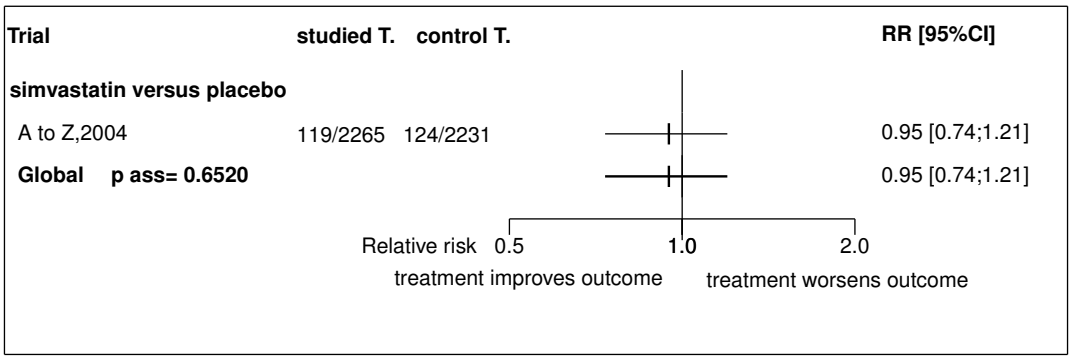
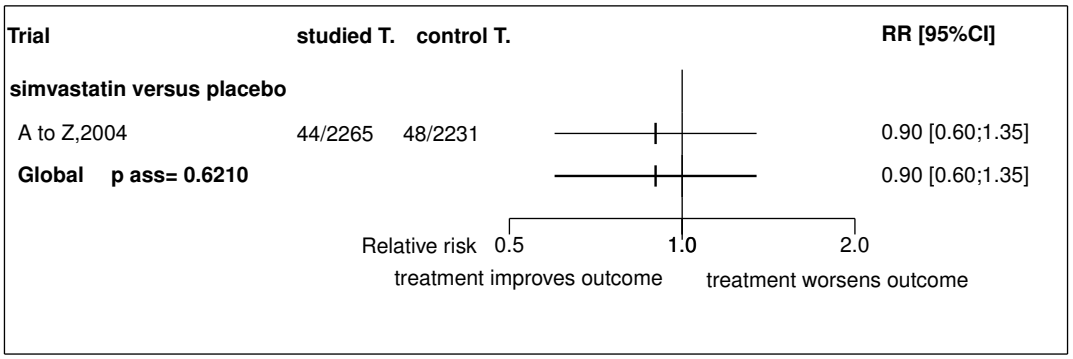


Figure 36.6: *Forest's plot for all cause death*



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]

[2] Ren HZ, Ma LL, Wang LX. Effect of simvastatin on plasma interleukin-6 in patients with unstable angina. Clin Invest Med 2009;32:E280-4. [PMID=19640331]

36.3 Individual trial summaries

Table 36.6: *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 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]

Table 36.7: *Ren, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Patients with unstable angina pectoris	**Studied treatment:** simvastatin (40 mg/d for 4 weeks) **Control treatment:** placebo	

Reference

Ren HZ, Ma LL, Wang LX. Effect of simvastatin on plasma interleukin-6 in patients with unstable angina. Clin Invest Med 2009;32:E280-4 [PMID=19640331]

37 Global meta-analysis: all statins

37.1 Global meta-analysis: all statins versus atorvastatin

Table 37.1: *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

37.2 Global meta-analysis: all statins versus no statin

Table 37.2: *All statinsversus no statin*

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

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

37.3 Global meta-analysis: all statins versus placebo

Table 37.3: *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
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=0.84 [1]	0.68;1.05	0.1196	0.0073 (0.66) †	7	15709
cardiovascular death	RR=0.68	0.50;0.93	0.0150	0.9881 (0.00)	2	13200
stroke (fatal and non fatal)	RR=0.78	0.61;1.00	0.0528	0.9747 (0.00)	10	25782
coronary event	RR=0.73	0.63;0.83	0.0000	0.5686 (0.00)	2	13200
coronary death and non fatal MI	RR=0.73	0.63;0.83	0.0000	0.5686 (0.00)	2	13200
coronary death	RR=0.73	0.51;1.05	0.0917	0.9906 (0.00)	2	13200
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

continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.82 95% CI 0.75;0.91

Endpoint	Effect	95% CI	p ass	p het	k	n
non fatal MI	RR=0.76 [2]	0.52;1.09	0.1366	0.0002 (0.74) †	9	19177
revascularization	RR=0.97	0.87;1.09	0.6359	0.9680 (0.00)	7	9174
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

37.4 Global meta-analysis: all statins versus pravastatin

Table 37.4: *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

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

37.5 Global meta-analysis: all statins versus usual care

Table 37.5: *All statinsversus usual care*

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

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

38 Ongoing studies of statins

Only one ongoing study was identified. A brief description of this trial is given table 38.1

[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.81 95% CI 0.71;0.92

Table 38.1: *Ongoing studies for statins*

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

39 Excluded studies for statins

No trial was excluded.

References