Cholesterol lowering intervention for cardiovascular prevention in high risk patients with or without LDL cholesterol elevation

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 high risk patients with or without LDL cholesterol elevation.

Contents

0.1 Synthesis of the meta-analysis results

In all 8 randomised controlled trials (RCTs) were included. These included 1 studie of **ezetimibe** involving -18 patients and 7 studies of **statins** involving 66,749 patients. Results obtained by the meta-analysis are reported in the following tables, with the endpoints categorized according their results. Three classes are considered: endpoints for wich a benefit effect was detected, endpoints revealing a harmful effect and the other for wich no statistically significant difference was obtained (no evidence).

0.1.1 Ezetimibe

Only one trials including 0 patients was found.
Among these comparisons, one trial are about ezetimibe.
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 ezetimibe for all the endpoints with data in at least one trial are summarized table 1.

Table 1: *Results summary - Ezetimibe*

Benefit	Harmful	No evidence
	Ezetimibe versus niacin	

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

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

0.1.2 Statins

Reports of 7 trials (including 66,749 patients) were identified .
Among these comparisons, one trial are about atorvastatin,4 about pravastatin,one about rosuvastatin and one about simvastatin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Atorvastatin

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

Table 2: *Results summary - Atorvastatin*

Benefit	Harmful	No evidence
	Atorvastatin versus placebo	

continued...

Benefit	Harmful	No evidence
↓ stroke (fatal and non fatal) RR=0.73* [0.56;0.96] k=1 ↓ coronary death and non fatal MI RR=0.65¶ [0.50;0.83] k=1 ↓ coronary event RR=0.72¶ [0.59;0.87] k=1 ↓ MACE RR=0.80¶ [0.70;0.90] k=1		→ cardiovascular death RR=0.90^{NS} [0.66;1.23] k=1 → rhabdomyolysis RR=1.99^{NS} [0.07;59.25] k=1 → all cause death RR=0.87^{NS} [0.71;1.05] k=1

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

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

Pravastatin

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

Table 3: *Results summary - Pravastatin*

Benefit	Harmful	No evidence
Pravastatin versus placebo		
↓ coronary death and non fatal MI RR=0.82† [0.71;0.95] k=2 ↓ coronary event RR=0.82† [0.71;0.95] k=2		→ cardiovascular events RR=0.74^{NS} [0.51;1.08] H k=2 → cardiovascular death RR=0.87^{NS} [0.69;1.08] k=1 → stroke (fatal and non fatal) RR=1.04^{NS} [0.82;1.31] k=1 → coronary death RR=0.78^{NS} [0.60;1.01] k=2 → MACE RR=0.74^{NS} [0.50;1.09] H k=2 → death from cancer RR=1.27^{NS} [0.97;1.67] k=1 → rhabdomyolysis RR=0.99^{NS} [0.06;15.76] k=2 → myopathy RR=1.13^{NS} [0.71;1.82] k=1 → non fatal MI RR=0.88^{NS} [0.74;1.05] k=1 → all cause death RR=0.97^{NS} [0.84;1.13] k=2 → non cardiovascular death RR=0.96^{NS} [0.14;6.82] k=1
Pravastatin versus usual care		

continued...

Benefit	Harmful	No evidence
		→ cardiovascular events RR=0.91[NS] [0.79;1.03] k=1 → cardiovascular death RR=0.99[NS] [0.84;1.15] k=1 → stroke (fatal and non fatal) RR=0.91[NS] [0.76;1.09] k=1 → coronary death and non fatal MI RR=0.91[NS] [0.79;1.03] k=1 → coronary event RR=0.91[NS] [0.79;1.03] k=1 → coronary death RR=0.99[NS] [0.80;1.23] k=1 → death from cancer RR=1.10[NS] [0.89;1.38] k=1 → cancer RR=1.03[NS] [0.89;1.18] k=1 → all cause death RR=0.99[NS] [0.89;1.09] k=1

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

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

Rosuvastatin

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

Table 4: *Results summary - Rosuvastatin*

Benefit	Harmful	No evidence
	Rosuvastatin versus placebo	

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

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

Simvastatin

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

Table 5: *Results summary - Simvastatin*

Benefit	Harmful	No evidence
	Simvastatin versus placebo	

continued...

Benefit	Harmful	No evidence
↓ cardiovascular death RR=0.83[¶] [0.76;0.91] k=1		→ death from cancer RR=1.04[NS] [0.90;1.20] k=1
↓ stroke (fatal and non fatal) RR=0.76[¶] [0.67;0.86] k=1		→ rhabdomyolysis RR=1.67[NS] [0.40;6.97] k=1
↓ coronary death and non fatal MI RR=0.74[¶] [0.68;0.80] k=1		→ myopathy RR=2.50[NS] [0.78;7.97] k=1
↓ coronary event RR=0.74[¶] [0.68;0.80] k=1		
↓ coronary death RR=0.83[¶] [0.75;0.92] k=1		
↓ non fatal MI RR=0.62[¶] [0.55;0.71] k=1		
↓ all cause death RR=0.88[¶] [0.82;0.94] 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 high risk patients with or without LDL cholesterol elevation. The following classes of treatment are considered:

1. ezetimibe
2. statins

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of cholesterol lowering intervention for the treatment of cardiovascular prevention in high risk patients with or without LDL cholesterol elevation.

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 .

1.6 Structure of the report

Each of the eligible studies is summarised in part **??**. A summary of the studies together with an evaluation of their quality is given in part I to **??**, listed by therapeutic class. The therapeutic classes included ezetimibe, statins,
In these sections, studies in which an active intervention was compared with placebo or no treatment are discussed first, by intervention, followed by a discussion of those studies in which two or more active interventions were compared.

Part I

Ezetimibe

2 Overview of ezetimibe

2.1 Included trials

Only one trial which randomized 0 patients was identified. In all, 1 randomized comparison concerned ezetimibe.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 18) for ezetimibe.

This trial included NaN patients and was published in 2010.
This trial was open-label in design.
It was reported in English language.
The table 2.1 (page 16) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

2.2 Summary of meta-analysis results

The meta-analysis of the available trials about ezetimibe provide the results listed in tables 2.2 to 2.2 (page 17) and in the following graphs.

2.2.1 Ezetimibe

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

Table 2.1: *Main study characteristics - ezetimibe*

Trial	Patients	Treatments	Trial design and method
Ezetimibe			
Ezetimibe versus niacin			
ARBITER-HALTS 6, 2010 [1] n = NA vs. NA	patients at high risk for vascular disease but with LDL-cholesterol levels <100 mg/dL and moderately low HDL-cholesterol levels (<50 mg/dL)	addition of ezetimibe (10 mg/daily) to statin therapy **versus** extended-release niacin 2000 mg/daily LDL change, at end of study (%): NA LDL change, end of study (mmol/L): -0.26	open parallel groups Primary endpoint: carotid IMT

Table 2.2: *Summary of all results for ezetimibe*

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

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

3 Details

3.1 Available trials

Only one trial which randomized 0 patients was identified: it compared ezetimibe with niacin.
This trial included NaN patients and was published in 2010.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 3.1 (page 18), 3.2 (page 18), 3.4 (page 20), and 3.3 (page 18) summarized the main characteristics of the trial including in this systematic review of randomized trials of ezetimibe.

Table 3.1: *Treatment description - ezetimibe - ezetimibe*

Trial	Studied treatment	Control treatment
Ezetimibe versus niacin		
ARBITER-HALTS 6 (2010) [1]	addition of ezetimibe (10 mg/daily) to statin therapy	extended-release niacin 2000 mg/daily

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

Trial	Patients
Ezetimibe versus niacin	
ARBITER-HALTS 6 (2010) [1]	Patients at high risk for vascular disease but with LDL-cholesterol levels $<$100 mg/dL and moderately low HDL-cholesterol levels ($<$50 mg/dL)

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

Trial	Design	Duration	Centre	Primary end-point
Ezetimibe versus niacin				
ARBITER-HALTS 6, 2010 [1] [(a)] n=NaN	Parallel groups open exploratory trial	14 months		carotid IMT

continued...

Trial	Design	Duration	Centre	Primary end-point

a) stopped early on the basis of a prespecified interim analysis showing that niacin was superior to ezetimibe on the end point of change in the carotid IMT

Table 3.4: *Trial characteristics - ezetimibe - ezetimibe*

Trial	LDL change, at end of study (%)	LDL change, end of study (mmol/L)
Ezetimibe versus niacin		
ARBITER-HALTS 6, 2010 [1]	NA	-0.26

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 21). This table is followed by the Forest's plot corresponding to each endpoint.

Ezetimibe versus niacin

No data were presented in the 1 trial identified

Table 3.5: *Results details - ezetimibe - ezetimibe*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ezetimibe versus niacin						
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] . . .

3.3 Individual trial summaries

Table 3.6: *ARBITER-HALTS 6, 2010 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** 14 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial	Patients at high risk for vascular disease but with LDL-cholesterol levels <100 mg/dL and moderately low HDL-cholesterol levels (<50 mg/dL)	**Studied treatment:** addition of ezetimibe (10 mg/daily) to statin therapy **Control treatment:** extended-release niacin 2000 mg/daily	
Reference . .			

4 Global meta-analysis: all ezetimibe

4.1 Global meta-analysis: all ezetimibe versus niacin

Table 4.1: *All ezetimibeversus niacin*

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

5 Ongoing studies of ezetimibe

No ongoing trial was identified.

6 Excluded studies for ezetimibe

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 ezetimibe*

Study	Exclusion reason
ZETELD (2010) [1]	exploratory trial on biological parameters. No focused on the clinical events

References

[1] Zieve F, Wenger NK, Ben-Yehuda O, Constance C, Bird S, Lee R, Hanson ME, Jones-Burton C, Tershakovec AM. Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients >or = 65 years of age (from the ZETia in the ELDerly [ZETELD] study). Am J Cardiol 2010;105:656-63. [PMID=20185012]

Part II

Statins

7 Overview of statins

7.1 Included trials

A total of 7 randomized comparisons which enrolled 66749 patients were identified. In all, 1 randomized comparison concerned atorvastatin , 4 pravastatin , one rosuvastatin and one simvastatin.
The detailed descriptions of trials and meta-analysis results is given in section 8 (page 40) for atorvastatin, in section 9 (page 49) for pravastatin, in section 10 (page 67) for rosuvastatin and in section 11 (page 73) for simvastatin.

The average study size was 9535 patients (range 885 to 20536). The first study was published in 1993, and the last study was published in 2008.
A total of 6 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 7.1 (page 29) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

7.2 Summary of meta-analysis results

The meta-analysis of the available trials about statins provide the results listed in tables 7.2 to 7.5 (page 31) and in the following graphs.

7.2.1 Atorvastatin

Atorvastatin was superior to **placebo** in terms of stroke (fatal and non fatal) (RR=0.73, 95% CI 0.56 to 0.96, p=0.0235, 1 trial), coronary death and non fatal MI (RR=0.65, 95% CI 0.50 to 0.83, p=0.0000, 1 trial), coronary event (RR=0.72, 95% CI 0.59 to 0.87, p=0.0000, 1 trial)and MACE (RR=0.80, 95% CI 0.70 to 0.90, p=0.0000, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.90, 95% CI 0.66 to 1.23, p=0.4947, 1 trial).

7.2.2 Pravastatin

Pravastatin was superior to **placebo** in terms of coronary death and non fatal MI (RR=0.82, 95% CI 0.71 to 0.95, p=0.0066, 2 trials)and coronary event (RR=0.82, 95% CI 0.71 to 0.95, p=0.0081, 2 trials). However, no significant difference was found on cardiovascular events (RR=0.74, 95% CI 0.51 to 1.08, p=0.1156, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0306)(RR=0.87, 95% CI 0.69 to 1.08, p=0.2101, 1 trial), stroke (fatal and non fatal) (RR=1.04, 95% CI 0.82 to 1.31, p=0.7533, 1 trial), coronary death (RR=0.78, 95% CI 0.60 to 1.01, p=0.0610, 2 trials), MACE (RR=0.74, 95% CI 0.50 to 1.09, p=0.1257, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0269)(RR=0.88, 95% CI 0.74 to 1.05, p=0.1489, 1 trial)and non cardiovascular death (RR=0.96, 95% CI 0.14 to 6.82, p=0.9711, 1 trial).

No significant difference was found between **pravastatin** and **usual care** in terms of cardiovascular events (RR=0.91, 95% CI 0.79 to 1.03, p=0.1430, 1 trial), cardiovascular death (RR=0.99, 95% CI 0.84 to 1.15, p=0.8613, 1 trial), stroke (fatal and non fatal) (RR=0.91, 95% CI 0.76 to 1.09, p=0.2982, 1 trial), coronary death and non fatal MI (RR=0.91, 95% CI 0.79 to 1.03, p=0.1430, 1 trial), coronary event (RR=0.91, 95% CI 0.79 to 1.03, p=0.1430, 1 trial)and coronary death (RR=0.99, 95% CI 0.80 to 1.23, p=0.9308, 1 trial).

7.2.3 Rosuvastatin

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

7.2.4 Simvastatin

Simvastatin was superior to **placebo** in terms of cardiovascular death (RR=0.83, 95% CI 0.76 to 0.91, p=0.0000, 1 trial), stroke (fatal and non fatal) (RR=0.76, 95% CI 0.67 to 0.86, p=0.0000, 1 trial), coronary death and non fatal MI (RR=0.74, 95% CI 0.68 to 0.80, p=0.0000, 1 trial), coronary event (RR=0.74, 95% CI 0.68 to 0.80, p=0.0000, 1 trial), coronary death (RR=0.83, 95% CI 0.75 to 0.92, p=0.0000, 1 trial)and non fatal MI (RR=0.62, 95% CI 0.55 to 0.71, p=0.0000, 1 trial).

Table 7.1: *Main study characteristics - statins*

Trial	Patients	Treatments	Trial design and method
Atorvastatin			
Atorvastatin versus placebo			
ASCOT, 2003 [1] n = 5168 vs. 5137	hypertensive patients aged 40-79 years with at least three other cardiovascular risk factors	atorvastatin 10mg/d **versus** placebo	double blind parallel groups Primary endpoint: infractus non mortel et dcs coronariens multicentre, UK et Scandinavie
Pravastatin			
Pravastatin versus placebo			
PMSG, 1993 [1] n = 530 vs. 532	patients with hypercholesterolemia(serum total cholesterol concentrations of 5.2 to 7.8 mmol/liter) and >or = 2 additional risk factors for atherosclerotic coronary artery disease	pravastatin 20 mg once daily **versus** placebo	double blind parallel groups Primary endpoint: not defined
PROSPER, 2002 [2] n = 2891 vs. 2913	men and women aged 70-82 years with a history of, or risk factors for, vascular disease	pravastatin 40mg daily **versus** placebo	double blind parallel groups Primary endpoint: death, MI , stroke multicenter, Ecosse, Irelande, Pays bas
REGRESS, 1995 [3, 4] n = 450 vs. 435	symptomatic men with normal to moderately elevated serum cholesterol levels	pravastatin 40 mg daily **versus** placebo	double blind parallel groups Primary endpoint: change in average mean segment diameter Netherlands
Pravastatin versus usual care			
ALLHAT, 2002 [5] n = 5170 vs. 5185	older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor	pravastatin 40mg/d **versus** usual care	open factorial plan Primary endpoint: all cause death 513 centres, USA, Puerto Rico, Canada

continued...

Trial	Patients	Treatments	Trial design and method
Rosuvastatin			
Rosuvastatin versus placebo			
JUPITER, 2008 [1] n = 8901 vs. 8901	apparently healthy individuals with low LDL-cholesterol levels of less than 130 mg per deciliter but elevated C-reactive-protein (high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher)	rosuvastatin 20 mg daily **versus** placebo	double blind parallel groups Primary endpoint: MI, stroke, arterial revascularization, hospitalization for unstable angina, cardiovascular death 1200 centres, 26 countries
Simvastatin			
Simvastatin versus placebo			
HPS, 2002 [1, 2, 3] n = 10269 vs. 10267	adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabete	simvastatin 40 mg/d **versus** placebo	double blind factorial plan Primary endpoint: all cause death multicentrique, UK

Table 7.2: *Summary of all results for atorvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
atorvastatin versus placebo						
cardiovascular death	RR=0.90	0.66;1.23	0.4947	1.0000 (0.00)	1	10305
stroke (fatal and non fatal)	RR=0.73	0.56;0.96	0.0235	1.0000 (0.00)	1	10305
coronary death and non fatal MI	RR=0.65	0.50;0.83	0.0000	1.0000 (0.00)	1	10305
coronary event	RR=0.72	0.59;0.87	0.0000	1.0000 (0.00)	1	10305
MACE	RR=0.80	0.70;0.90	0.0000	1.0000 (0.00)	1	10305
rhabdomyolysis	RR=1.99	0.07;59.25	0.6916	1.0000 (0.00)	1	10305
all cause death	RR=0.87	0.71;1.05	0.1494	1.0000 (0.00)	1	10305

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 pravastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
pravastatin versus placebo						
cardiovascular events	RR=0.74 [1]	0.51;1.08	0.1156	0.0306 (0.79) †	2	6689
cardiovascular death	RR=0.87	0.69;1.08	0.2101	1.0000 (0.00)	1	5804
stroke (fatal and non fatal)	RR=1.04	0.82;1.31	0.7533	1.0000 (0.00)	1	5804
coronary death and non fatal MI	RR=0.82	0.71;0.95	0.0066	0.5435 (0.00)	2	6689
coronary event	RR=0.82	0.71;0.95	0.0081	0.7284 (0.00)	2	6689
coronary death	RR=0.78	0.60;1.01	0.0610	0.8785 (0.00)	2	6688
MACE	RR=0.74 [2]	0.50;1.09	0.1257	0.0269 (0.80) †	2	6689
death from cancer	RR=1.27	0.97;1.67	0.0795	1.0000 (0.00)	1	5804
rhabdomyolysis	RR=0.99	0.06;15.76	0.9926	0.9883 (0.00)	2	6689
myopathy	RR=1.13	0.71;1.82	0.6037	1.0000 (0.00)	1	5804
non fatal MI	RR=0.88	0.74;1.05	0.1489	1.0000 (0.00)	1	5804
all cause death	RR=0.97	0.84;1.13	0.7160	0.3937 (0.00)	2	6688
non cardiovascular death	RR=0.96	0.14;6.82	0.9711	1.0000 (0.00)	1	884
pravastatin versus usual care						
cardiovascular events	RR=0.91	0.79;1.03	0.1430	1.0000 (0.00)	1	10355

continued...

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.83 95% CI 0.74;0.93
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.84 95% CI 0.75;0.93

Endpoint	Effect	95% CI	p ass	p het	k	n
cardiovascular death	RR=0.99	0.84;1.15	0.8613	1.0000 (0.00)	1	10355
stroke (fatal and non fatal)	RR=0.91	0.76;1.09	0.2982	1.0000 (0.00)	1	10355
coronary death and non fatal MI	RR=0.91	0.79;1.03	0.1430	1.0000 (0.00)	1	10355
coronary event	RR=0.91	0.79;1.03	0.1430	1.0000 (0.00)	1	10355
coronary death	RR=0.99	0.80;1.23	0.9308	1.0000 (0.00)	1	10355
death from cancer	RR=1.10	0.89;1.38	0.3739	1.0000 (0.00)	1	10355
cancer	RR=1.03	0.89;1.18	0.7018	1.0000 (0.00)	1	10355
all cause death	RR=0.99	0.89;1.09	0.8071	1.0000 (0.00)	1	10355

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

Table 7.4: *Summary of all results for rosuvastatin*

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

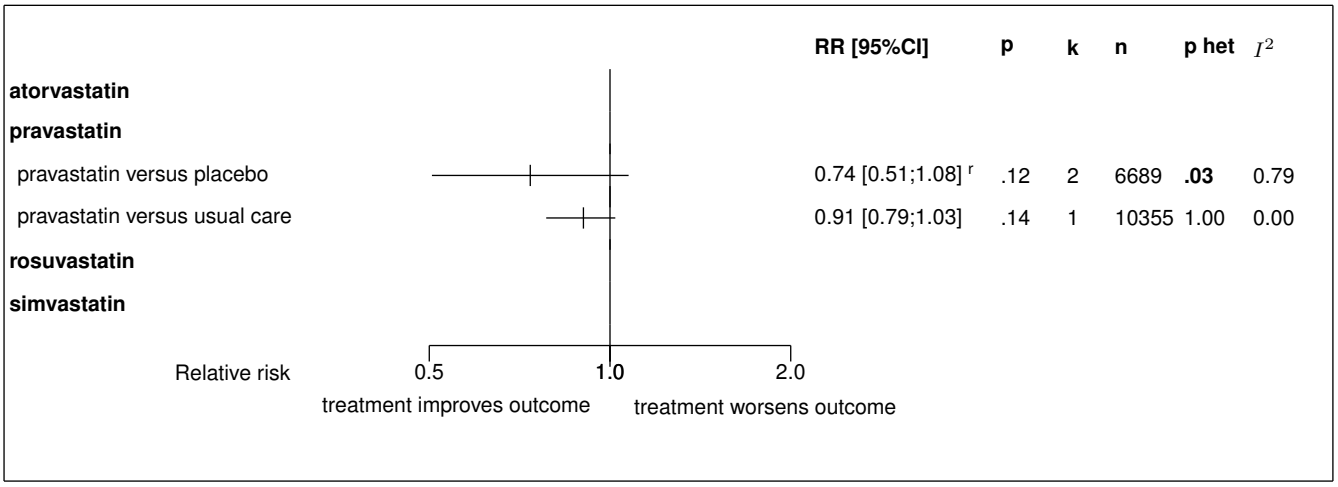
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 7.5: *Summary of all results for simvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
simvastatin versus placebo						
cardiovascular death	RR=0.83	0.76;0.91	0.0000	1.0000 (0.00)	1	20536
stroke (fatal and non fatal)	RR=0.76	0.67;0.86	0.0000	1.0000 (0.00)	1	20536
coronary death and non fatal MI	RR=0.74	0.68;0.80	0.0000	1.0000 (0.00)	1	20536
coronary event	RR=0.74	0.68;0.80	0.0000	1.0000 (0.00)	1	20536
coronary death	RR=0.83	0.75;0.92	0.0000	1.0000 (0.00)	1	20536
death from cancer	RR=1.04	0.90;1.20	0.5932	1.0000 (0.00)	1	20536
rhabdomyolysis	RR=1.67	0.40;6.97	0.4843	1.0000 (0.00)	1	20536
myopathy	RR=2.50	0.78;7.97	0.1214	1.0000 (0.00)	1	20536
non fatal MI	RR=0.62	0.55;0.71	0.0000	1.0000 (0.00)	1	20536
all cause death	RR=0.88	0.82;0.94	0.0000	1.0000 (0.00)	1	20536

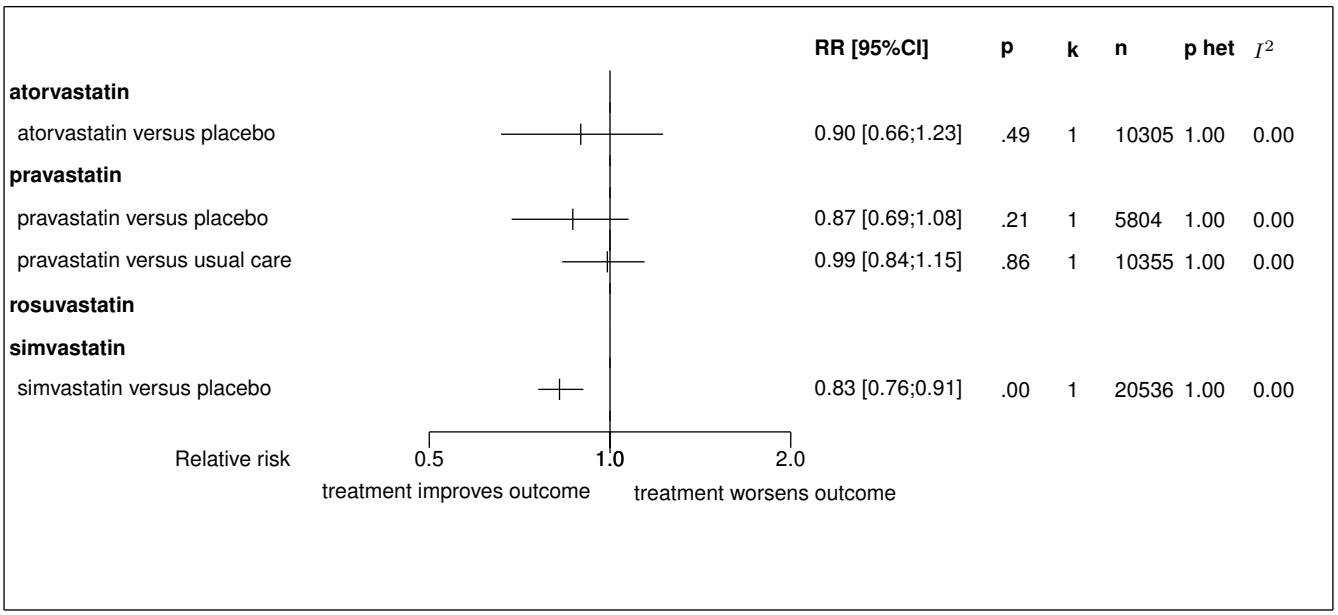
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 7.1: *Forest's plot for cardiovascular events*



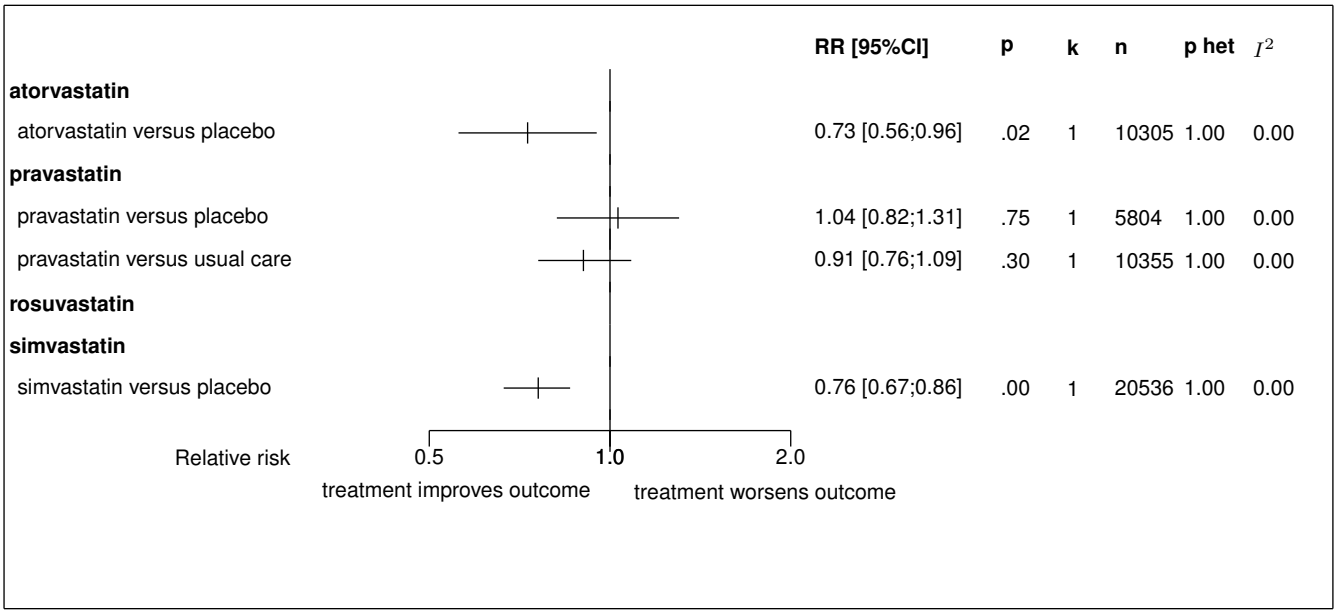
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.2: *Forest's plot for cardiovascular death*



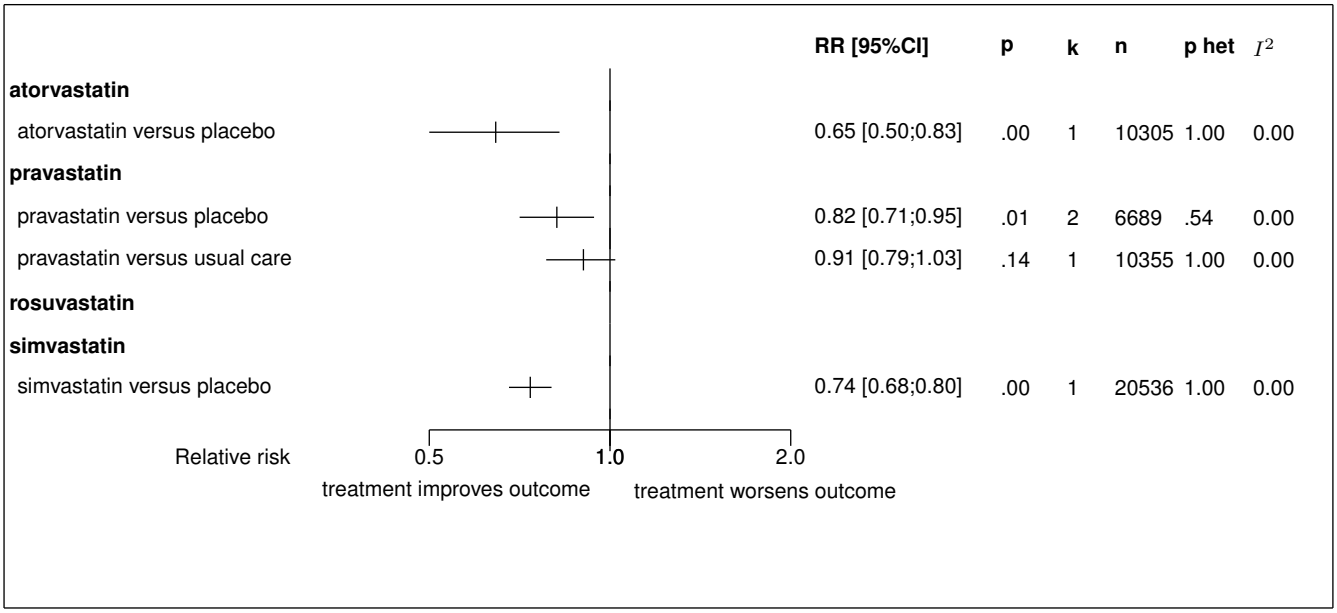
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.3: *Forest's plot for stroke (fatal and non fatal)*



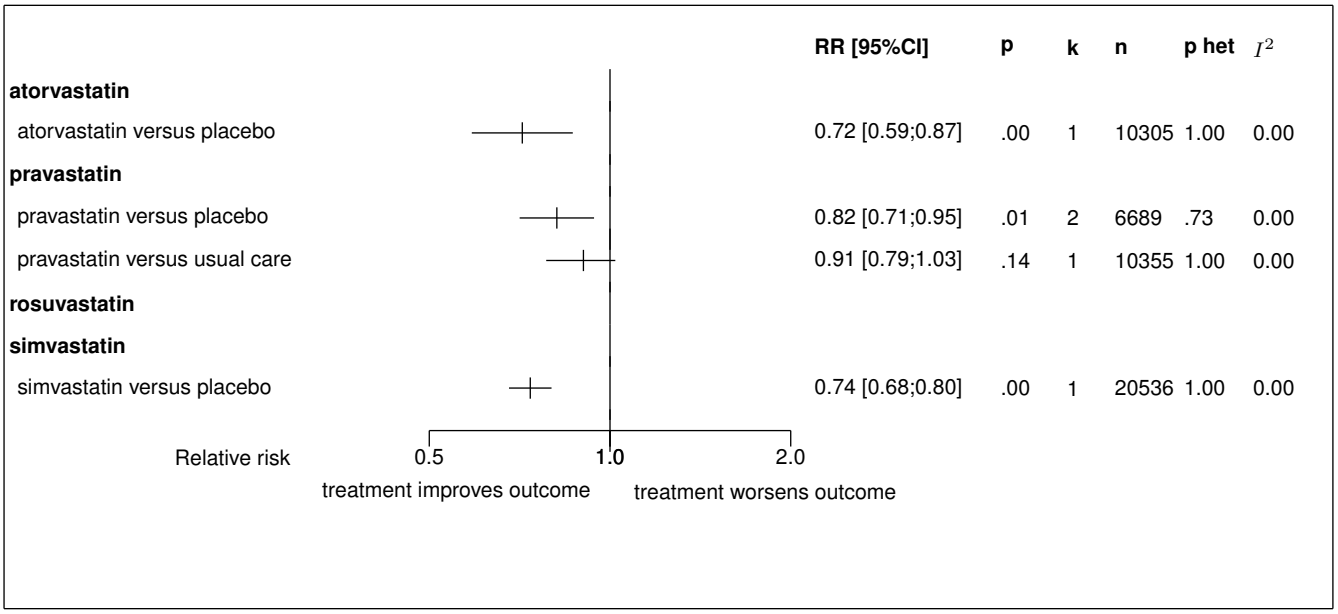
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.4: *Forest's plot for coronary death and non fatal MI*



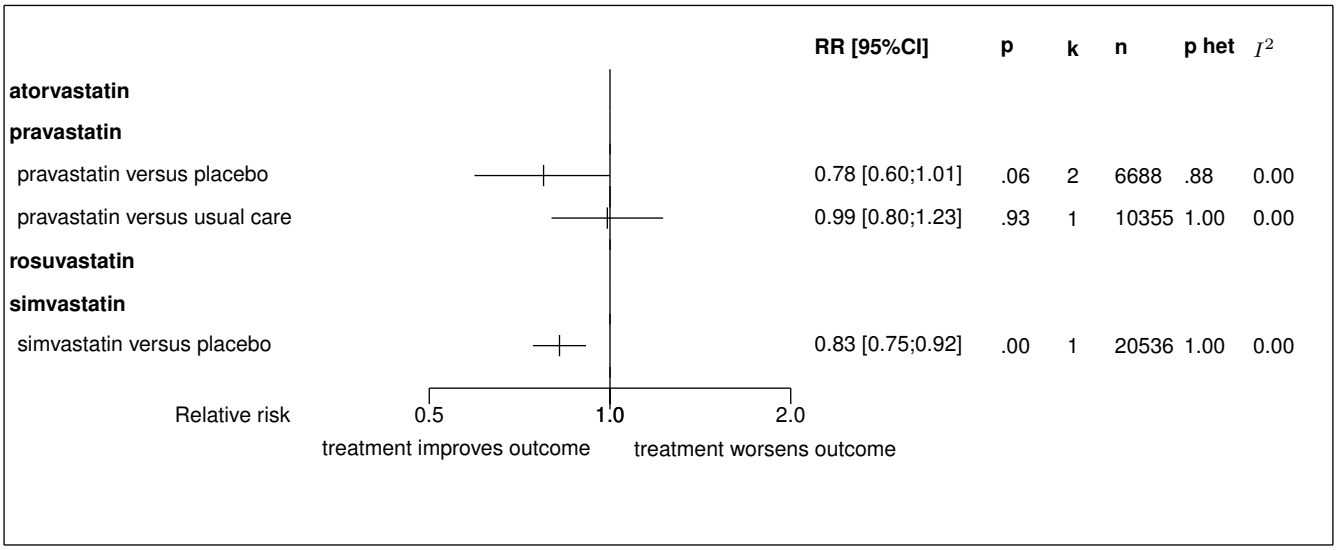
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.5: *Forest's plot for coronary event*



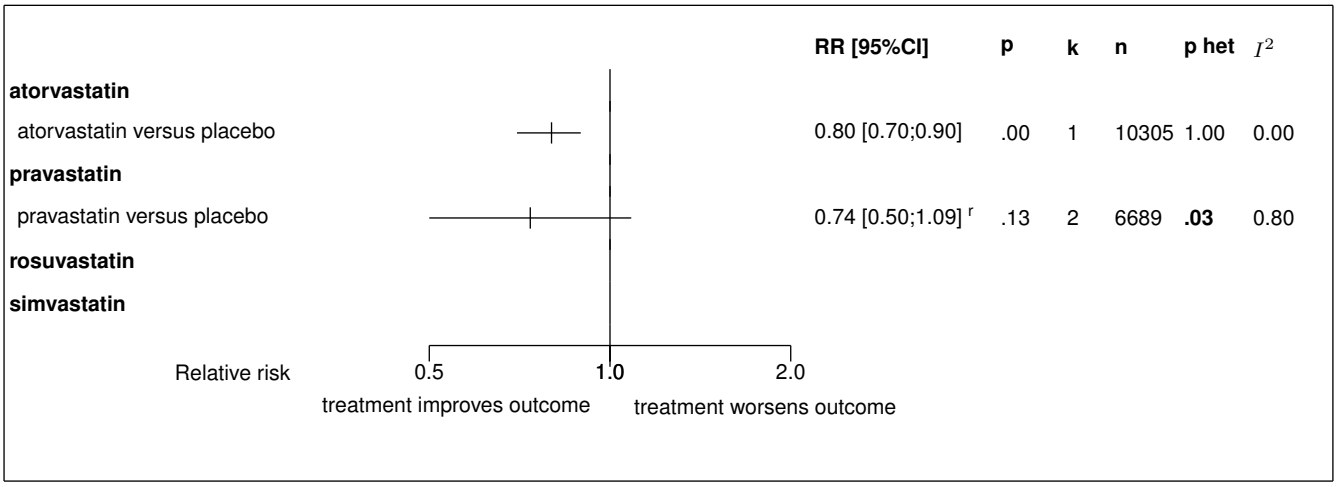
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.6: *Forest's plot for coronary death*



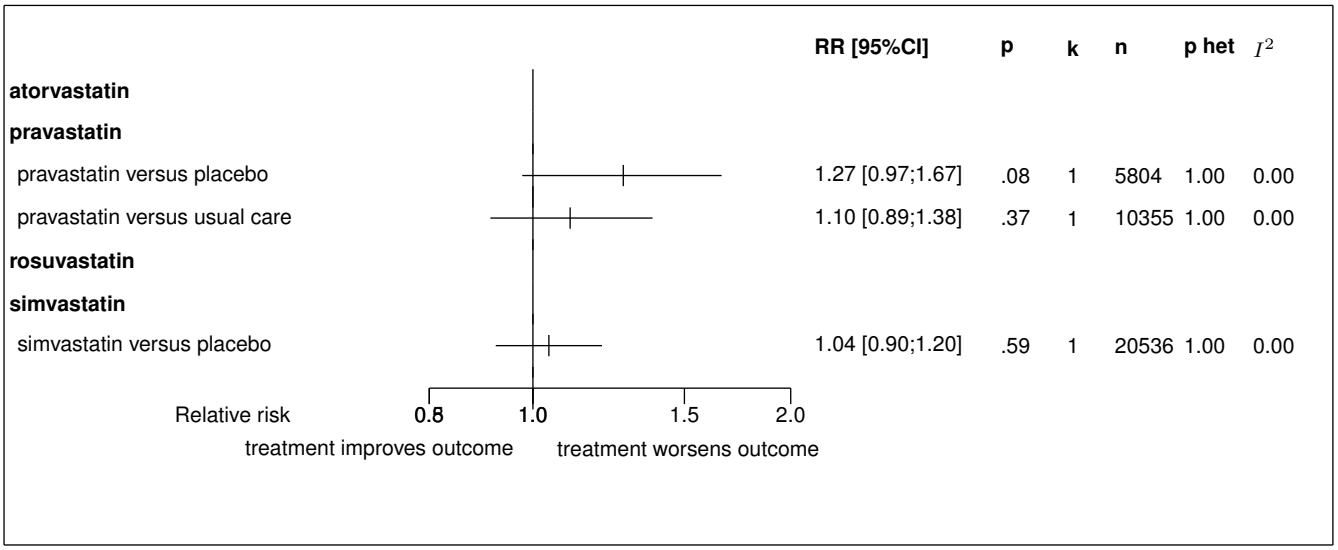
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.7: *Forest's plot for MACE*



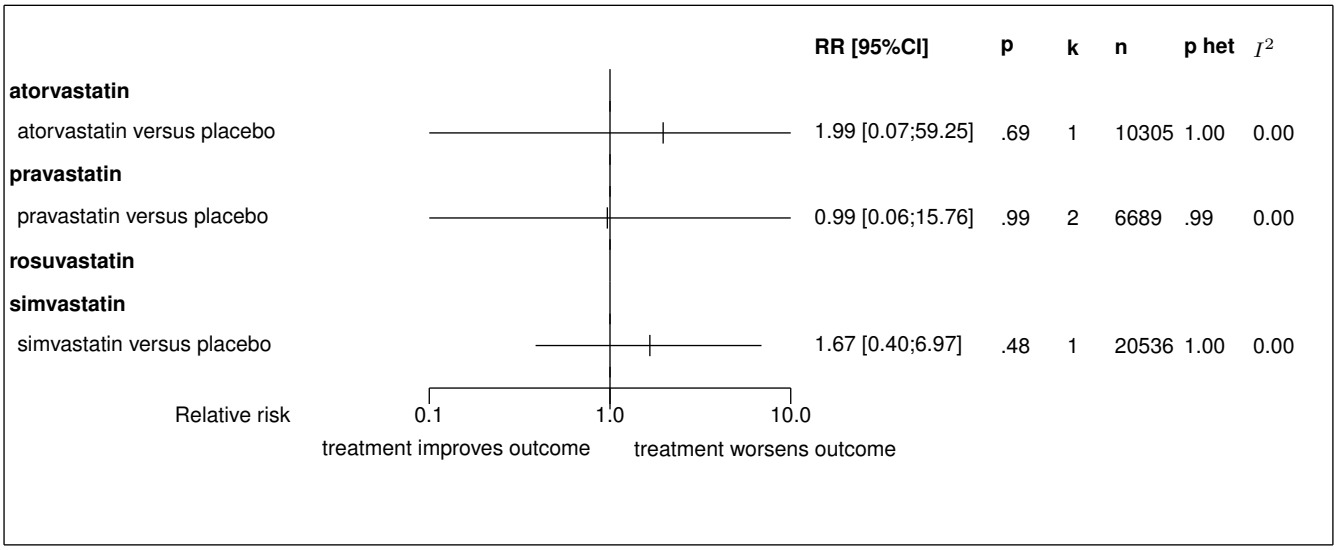
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.8: *Forest's plot for death from cancer*



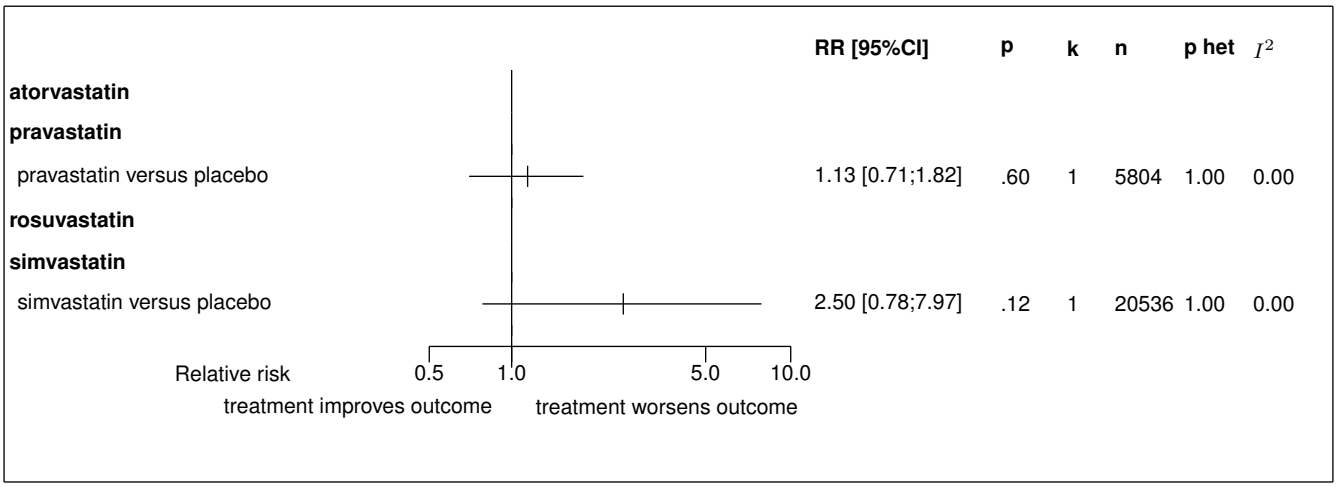
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.9: *Forest's plot for rhabdomyolysis*



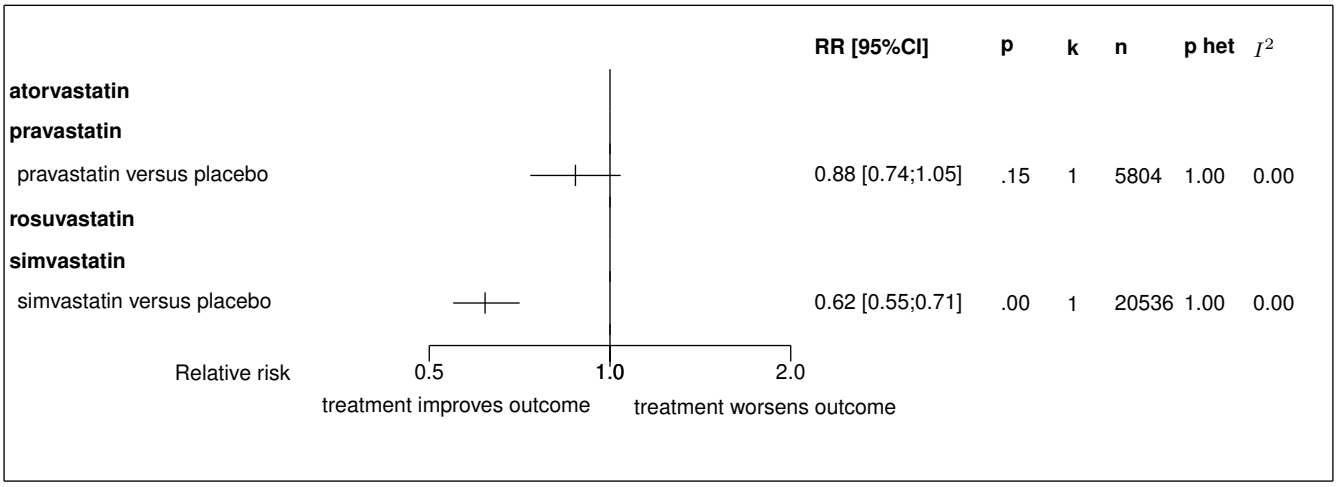
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.10: *Forest's plot for myopathy*



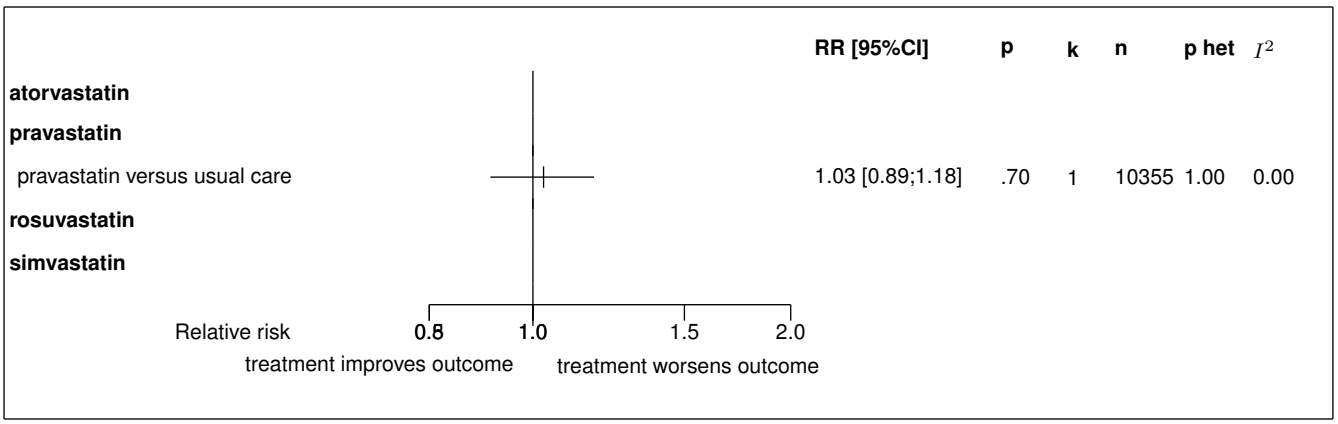
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



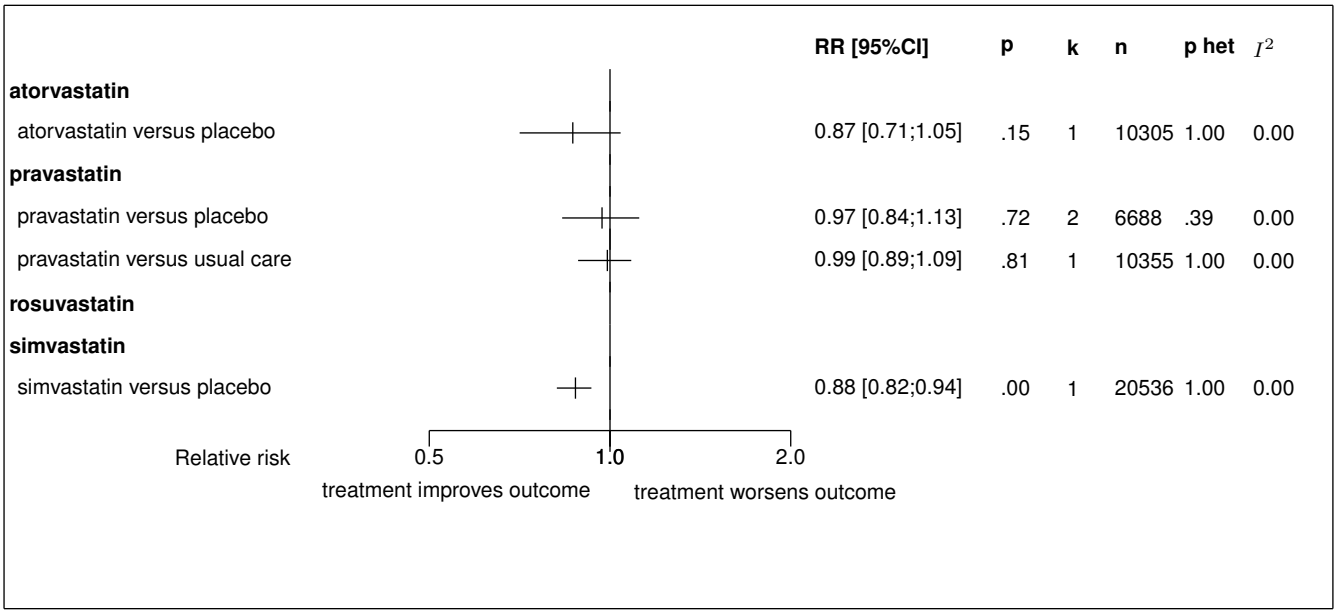
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.12: *Forest's plot for 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 7.13: *Forest's plot for all cause death*



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

Figure 7.14: *Forest's plot for non 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

8 Detailed results for atorvastatin

8.1 Available trials

Only one trial which randomized 10305 patients was identified: it compared atorvastatin with placebo.
This trial included 10305 patients and was published in 2003.
This trial was double blind in design.
It was reported in English language.
MACE data was reported in 1 trials; 1 trials reported data on stroke (fatal and non fatal); 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 rhabdomyolysis; and 1 trials reported data on all cause death.
Following tables 8.1 (page 40), 8.2 (page 40), 8.4 (page 42), and 8.3 (page 41) summarized the main characteristics of the trial including in this systematic review of randomized trials of atorvastatin.

Table 8.1: *Treatment description - statins - atorvastatin*

Trial	Studied treatment	Control treatment
Atorvastatin versus placebo		
ASCOT (2003) [1]	atorvastatin 10mg/d	placebo

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

Trial	Patients
Atorvastatin versus placebo	

continued...

Trial	Patients	
ASCOT (2003) [1]	Hypertensive patients aged 40-79 years with at least three other cardiovascular risk factors	
	Inclusion criteria: men and women aged between 40 and 79 years; either untreated hypertension, defined as systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, or both, or treated hypertension with systolic blood pressure of 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or both; total cholesterol concentrations of 65 mmol/L or lower; not currently be taking a statin or a fibrate; at least three of the following risk factors for cardiovascular disease: left-ventricular hypertrophy, other specified abnormalities on electrocardiogram, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack, male sex, age 55 years or older, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL-cholesterol of 6 or higher, or premature family history of CHD	**Exclusion criteria:** previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglycerides higher than 45 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important haematological or biochemical abnormality

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

Trial	Design	Duration	Centre	Primary endpoint
Atorvastatin versus placebo				
ASCOT, 2003 [1] n=10305	Parallel groups double blind confirmatory trial at low risk of bias	3.3 years inclusion period: feb 1998, May 2000	UK et Scandinavie multicentre	Infractus non mortel et dcs coronariens

Table 8.4: *Trial characteristics - statins - atorvastatin*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Atorvastatin versus placebo				
ASCOT, 2003 [1]	-1.2 at 1year	-1.34 at 1y		

8.2 Meta-analysis results

The results are detailed in table 8.5 (page 43). This table is followed by the Forest's plot corresponding to each endpoint.

Atorvastatin versus placebo

The single study eligible for this comparison provided data on **cardiovascular death**. No statistically significant difference between the groups was found in cardiovascular death, with a RR of 0.90 (95% CI 0.66 to 1.23, p=0.4947).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of atorvastatin in stroke (fatal and non fatal), with a RR of 0.73 (95% CI 0.56 to 0.96, p=0.0235).
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 atorvastatin in coronary death and non fatal MI, with a RR of 0.65 (95% CI 0.50 to 0.83, 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 atorvastatin in coronary event, with a RR of 0.72 (95% CI 0.59 to 0.87, p=0.0000).
The single study eligible for this comparison provided data on **MACE**. The analysis detected a statistically significant difference in favor of atorvastatin in MACE, with a RR of 0.80 (95% CI 0.70 to 0.90, p=0.0000).

Table 8.5: *Results details - statins - atorvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
atorvastatin versus placebo						
cardiovascular death	RR=0.90	[0.66;1.23]	0.4947	1.0000 (I^2=0.00)	1	10305
stroke (fatal and non fatal)	RR=0.73	[0.56;0.96]	0.0235	1.0000 (I^2=0.00)	1	10305
coronary death and non fatal MI	RR=0.65	[0.50;0.83]	0.0000	1.0000 (I^2=0.00)	1	10305
coronary event	RR=0.72	[0.59;0.87]	0.0000	1.0000 (I^2=0.00)	1	10305
MACE	RR=0.80	[0.70;0.90]	0.0000	1.0000 (I^2=0.00)	1	10305
rhabdomyolysis	RR=1.99	[0.07;59.25]	0.6916	1.0000 (I^2=0.00)	1	10305
all cause death	RR=0.87	[0.71;1.05]	0.1494	1.0000 (I^2=0.00)	1	10305

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 cardiovascular death*

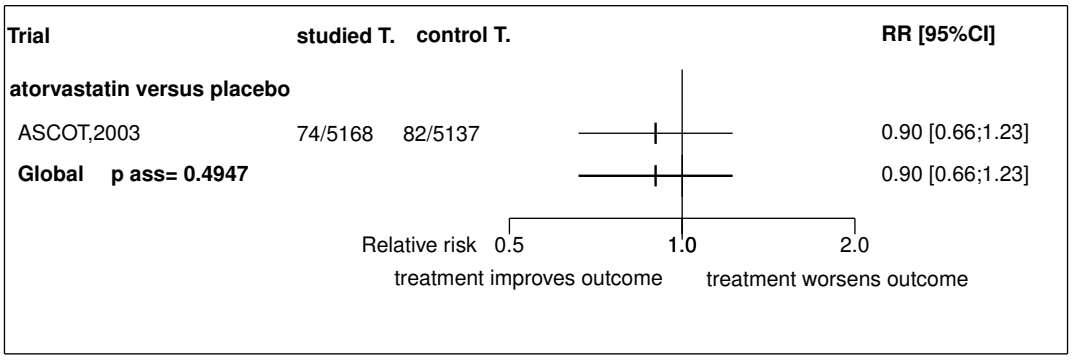


Figure 8.2: *Forest's plot for stroke (fatal and non fatal)*

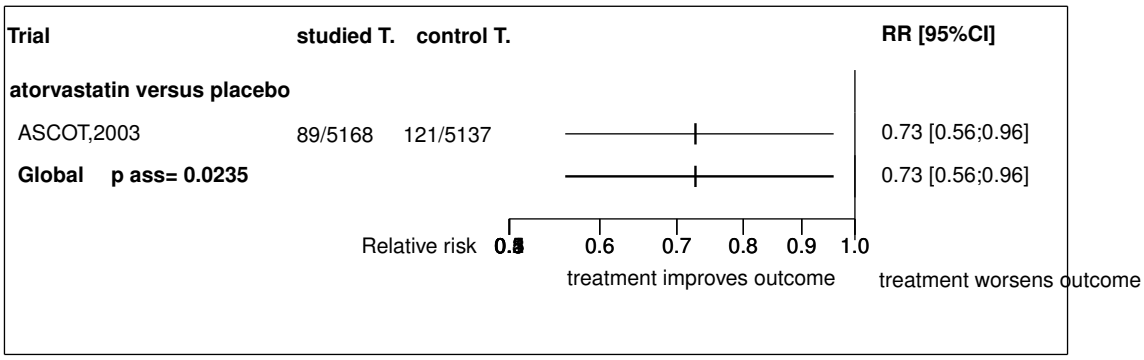


Figure 8.3: *Forest's plot for coronary death and non fatal MI*

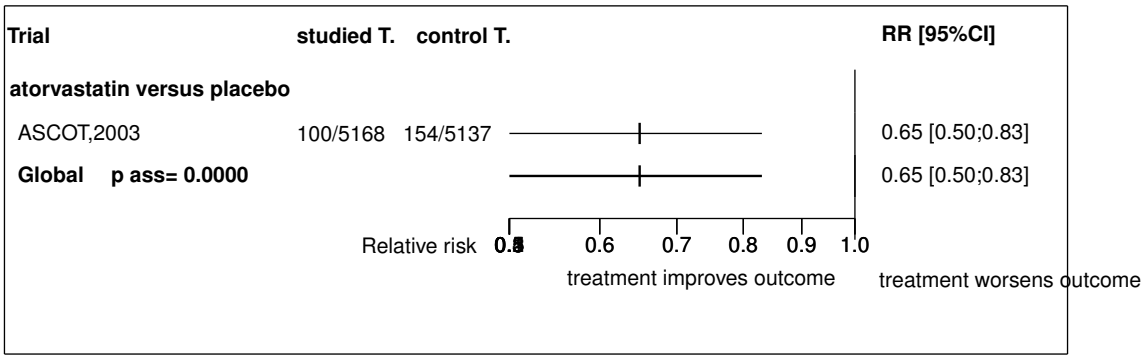


Figure 8.4: *Forest's plot for coronary event*

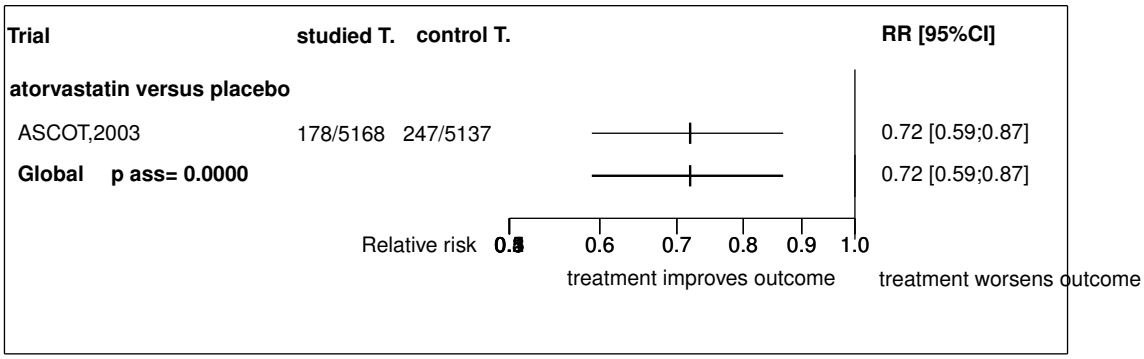


Figure 8.5: *Forest's plot for MACE*

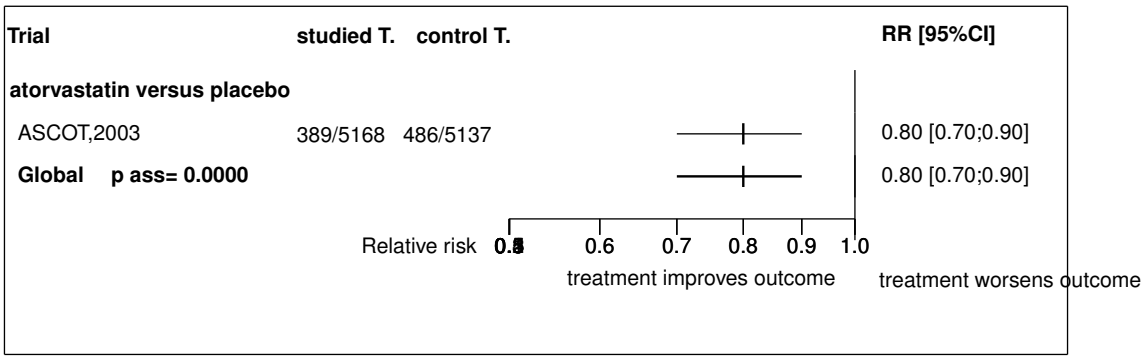


Figure 8.6: *Forest's plot for rhabdomyolysis*

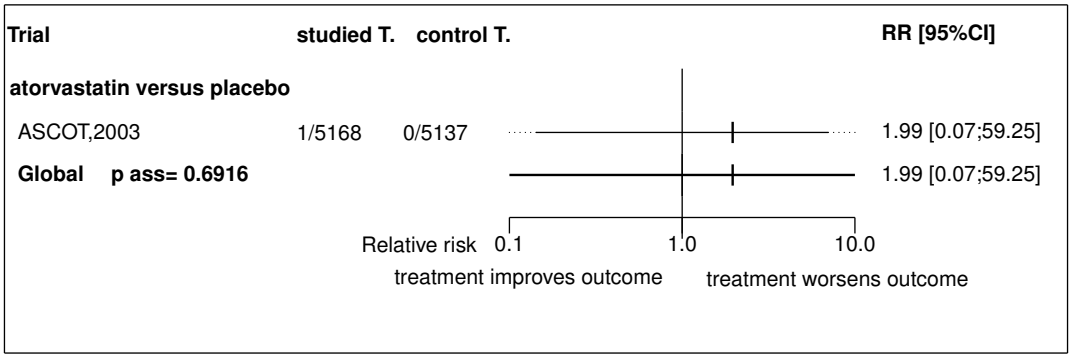
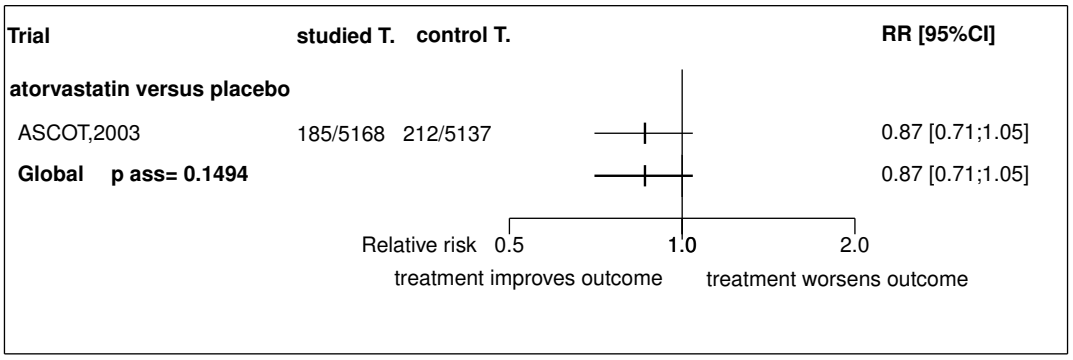


Figure 8.7: *Forest's plot for all cause death*



References

[1] Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J,. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361:1149-58. [PMID=12686036]

8.3 Individual trial summaries

Table 8.6: *ASCOT, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=10305 (5168 vs. 5137) **Follow-up duration:** 3.3 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias UK et Scandinavie, multicentre **Inclusion period:** feb 1998, May 2000	Hypertensive patients aged 40-79 years with at least three other cardiovascular risk factors **Inclusion criteria:** men and women aged between 40 and 79 years; either untreated hypertension, defined as systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, or both, or treated hypertension with systolic blood pressure of 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or both; total cholesterol concentrations of 65 mmol/L or lower; not currently be taking a statin or a fibrate; at least three of the following risk factors for cardiovascular disease: left-ventricular hypertrophy, other specified abnormalities on electrocardiogram, type 2 diabetes, peripheral **Exclusion criteria:** previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglycerides higher than 45 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important haematological or biochemical abnormality	**Studied treatment:** atorvastatin 10mg/d **Control treatment:** placebo	Cardiovascular death RR=0.90 [0.66;1.23] Stroke (fatal and non fatal) RR=0.73 [0.56;0.96] Coronary death and non fatal MI RR=0.65 [0.50;0.83] Coronary event RR=0.72 [0.59;0.87] MACE RR=0.80 [0.70;0.90]

Reference

Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J,. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361:1149-58 [PMID=12686036]

9 Detailed results for pravastatin

9.1 Available trials

A total of 4 RCTs which randomized 18106 patients were identified: 3 trials compared pravastatin with placebo and it compared pravastatin with usual care.
The average study size was 4526 patients (range 885 to 10355). The first study was published in 1993, and the last study was published in 2002.
A total of 3 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Coronary death data was reported in 3 trials; 3 trials reported data on coronary event; 3 trials reported data on coronary death and non fatal MI; 3 trials reported data on cardiovascular events; 2 trials reported data on cardiovascular death; 2 trials reported data on stroke (fatal and non fatal); 2 trials reported data on MACE; 1 trials reported data on non fatal MI; 1 trials reported data on non cardiovascular death; 2 trials reported data on death from cancer; 2 trials reported data on rhabdomyolysis; 1 trials reported data on myopathy; 1 trials reported data on cancer; and 3 trials reported data on all cause death.
Following tables 9.1 (page 49), 9.2 (page 49), 9.4 (page 52), and 9.3 (page 50) summarized the main characteristics of the trials including in this systematic review of randomized trials of pravastatin.

Table 9.1: *Treatment description - statins - pravastatin*

Trial	Studied treatment	Control treatment
Pravastatin versus placebo		
PMSG (1993) [1]	pravastatin 20 mg once daily	placebo
PROSPER (2002) [2]	pravastatin 40mg daily	placebo
REGRESS (1995) [3, 4]	pravastatin 40 mg daily	placebo
Pravastatin versus usual care		
ALLHAT (2002) [5] [a]	pravastatin 40mg/d	usual care

a) factorial design with 4 antihypertensive treament (amlodipine, lisinopril, doxazosin compared with chlorthalidone)

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

Trial	Patients
Pravastatin versus placebo	

continued...

Trial	Patients	
PMSG (1993) [1]	Patients with hypercholesterolemia(serum total cholesterol concentrations of 5.2 to 7.8 mmol/liter) and >or = 2 additional risk factors for atherosclerotic coronary artery disease	
PROSPER (2002) [2]	Men and women aged 70-82 years with a history of, or risk factors for, vascular disease	
	Inclusion criteria: men and women aged 7082 years; either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes; total cholesterol between 4090 mmol/L; triglyceride less than 60 mmol/L	**Exclusion criteria:** poor cognitive function (mini mentalstate examination score <24)
REGRESS (1995) [3, 4]	Symptomatic men with normal to moderately elevated serum cholesterol levels	
Pravastatin versus usual care		
ALLHAT (2002) [5]	Older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor	
	Inclusion criteria: age >=55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor; fasting LDL-C level of 120 to 189 mg/dL (3.1 to 4.9 mmol/L) for those with no known CHD, or 100 to 129 mg/dL (2.6 to 3.3 mmol/L) for those with known CHD (the upper limit was 159 mg/dL [4.1 mmol/L] prior to April 5, 1994, but was changed in light of 4S4 findings); and fasting triglyceride levels lower than 350 mg/dL (3.9 mmol/L)	**Exclusion criteria:** current lipid-lowering therapy, large doses of niacin, or probucol in the last year; intolerance of statins; significant liver or kidney disease (serum alanine aminotransferase [ALT] >100 IU/L or serum creatinine >2.0 mg/dL [176.8 mol/L]); other contraindications for statin therapy; secondary cause of hyperlipidemia. Enrollment was discouraged for participants whose personal physicians recommended cholesterollowering medications.

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

Trial	Design	Duration	Centre	Primary endpoint
Pravastatin versus placebo				
PMSG, 1993 [1] n=1062	Parallel groups double blind exploratory trial	26 weeks		not defined
PROSPER, 2002 [2] n=5804	Parallel groups double blind confirmatory trial at low risk of bias	3.2 years inclusion period: dec 1997, May 1999	Ecosse, Irelande, Pays bas multicenter	death, MI , stroke
REGRESS, 1995 [3, 4] n=885	Parallel groups double blind exploratory trial	2 years	Netherlands	change in average mean segment diameter
Pravastatin versus usual care				

continued...

Trial	Design	Duration	Centre	Primary endpoint
ALLHAT, 2002 [5] n=10355	Factorial plan open confirmatory trial at risk of bias	4.8 years inclusion period: feb 1994, mar 2002	USA, Puerto Rico, Canada 513 centres	all cause death

Table 9.4: *Trial characteristics - statins - pravastatin*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Pravastatin versus placebo				
PMSG, 1993 [1]	-1.3			
PROSPER, 2002 [2]	-1.1			
REGRESS, 1995 [3, 4]	-1.2			
Pravastatin versus usual care				
ALLHAT, 2002 [5]	-0.6			

9.2 Meta-analysis results

The results are detailed in table 9.5 (page 54). This table is followed by the Forest's plot corresponding to each endpoint.

Pravastatin versus placebo

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 0.74 (95% CI 0.51 to 1.08, p=0.1156). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0306, I^2 = 0.79%).
Only one of the 3 studies 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 0.87 (95% CI 0.69 to 1.08, p=0.2101).
Only one of the 3 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 1.04 (95% CI 0.82 to 1.31, p=0.7533).
A total of 2 of the 3 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 0.82 (95% CI 0.71 to 0.95, p=0.0066). No heterogeneity was detected (p = 0.5435, I^2 = 0.00%).
A total of 2 of the 3 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 0.82 (95% CI 0.71 to 0.95, p=0.0081). No heterogeneity was detected (p = 0.7284, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **coronary death**. When pooled together, there was no statistically significant difference between the groups in coronary death, with a RR of 0.78 (95% CI 0.60 to 1.01, p=0.0610). No heterogeneity was detected (p = 0.8785, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **MACE**. When pooled together, there was no statistically significant difference between the groups in MACE, with a RR of 0.74 (95% CI 0.50 to 1.09, p=0.1257). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0269, I^2 = 0.80%).
Only one of the 3 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 0.88 (95% CI 0.74 to 1.05, p=0.1489).
Only one of the 3 studies eligible for this comparison provided data on **non cardiovascular death**. No statistically significant difference between the groups was found in non cardiovascular death, with a RR of 0.96 (95% CI 0.14 to 6.82, p=0.9711).

Pravastatin versus usual care

The single study eligible for this comparison provided data on **cardiovascular events**. No statistically significant difference between the groups was found in cardiovascular events, with a RR of 0.91 (95% CI 0.79 to 1.03, p=0.1430).
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 0.99 (95% CI 0.84 to 1.15, p=0.8613).
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 0.91 (95% CI 0.76 to 1.09, p=0.2982).

The single study eligible for this comparison provided data on **coronary death and non fatal MI**. No statistically significant difference between the groups was found in coronary death and non fatal MI, with a RR of 0.91 (95% CI 0.79 to 1.03, p=0.1430).
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 0.91 (95% CI 0.79 to 1.03, p=0.1430).
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 0.99 (95% CI 0.80 to 1.23, p=0.9308).

Table 9.5: *Results details - statins - pravastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pravastatin versus placebo						
cardiovascular events	RR=0.74	[0.51;1.08]	0.1156	0.0306 (I^2=0.79)	2	6689
cardiovascular death	RR=0.87	[0.69;1.08]	0.2101	1.0000 (I^2=0.00)	1	5804
stroke (fatal and non fatal)	RR=1.04	[0.82;1.31]	0.7533	1.0000 (I^2=0.00)	1	5804
coronary death and non fatal MI	RR=0.82	[0.71;0.95]	0.0066	0.5435 (I^2=0.00)	2	6689
coronary event	RR=0.82	[0.71;0.95]	0.0081	0.7284 (I^2=0.00)	2	6689
coronary death	RR=0.78	[0.60;1.01]	0.0610	0.8785 (I^2=0.00)	2	6688
MACE	RR=0.74	[0.50;1.09]	0.1257	0.0269 (I^2=0.80)	2	6689
death from cancer	RR=1.27	[0.97;1.67]	0.0795	1.0000 (I^2=0.00)	1	5804
rhabdomyolysis	RR=0.99	[0.06;15.76]	0.9926	0.9883 (I^2=0.00)	2	6689
myopathy	RR=1.13	[0.71;1.82]	0.6037	1.0000 (I^2=0.00)	1	5804
non fatal MI	RR=0.88	[0.74;1.05]	0.1489	1.0000 (I^2=0.00)	1	5804
all cause death	RR=0.97	[0.84;1.13]	0.7160	0.3937 (I^2=0.00)	2	6688
non cardiovascular death	RR=0.96	[0.14;6.82]	0.9711	1.0000 (I^2=0.00)	1	884
pravastatin versus usual care						
cardiovascular events	RR=0.91	[0.79;1.03]	0.1430	1.0000 (I^2=0.00)	1	10355
cardiovascular death	RR=0.99	[0.84;1.15]	0.8613	1.0000 (I^2=0.00)	1	10355
stroke (fatal and non fatal)	RR=0.91	[0.76;1.09]	0.2982	1.0000 (I^2=0.00)	1	10355
coronary death and non fatal MI	RR=0.91	[0.79;1.03]	0.1430	1.0000 (I^2=0.00)	1	10355
coronary event	RR=0.91	[0.79;1.03]	0.1430	1.0000 (I^2=0.00)	1	10355
coronary death	RR=0.99	[0.80;1.23]	0.9308	1.0000 (I^2=0.00)	1	10355
death from cancer	RR=1.10	[0.89;1.38]	0.3739	1.0000 (I^2=0.00)	1	10355
cancer	RR=1.03	[0.89;1.18]	0.7018	1.0000 (I^2=0.00)	1	10355

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
all cause death	RR=0.99	[0.89;1.09]	0.8071	1.0000 (I^2=0.00)	1	10355

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

Figure 9.1: *Forest's plot for cardiovascular events*

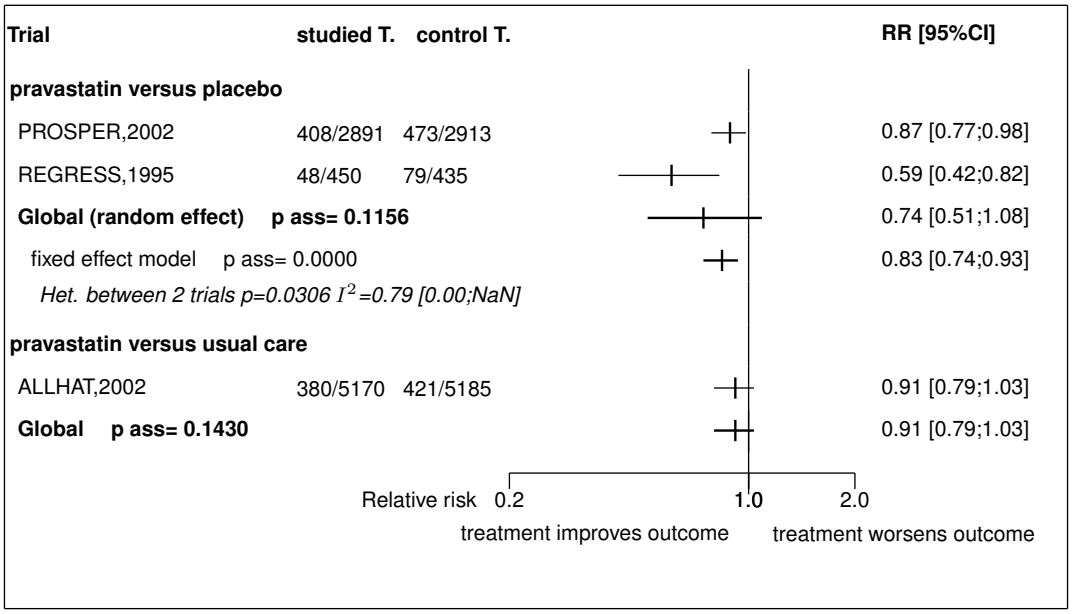


Figure 9.2: *Forest's plot for cardiovascular death*

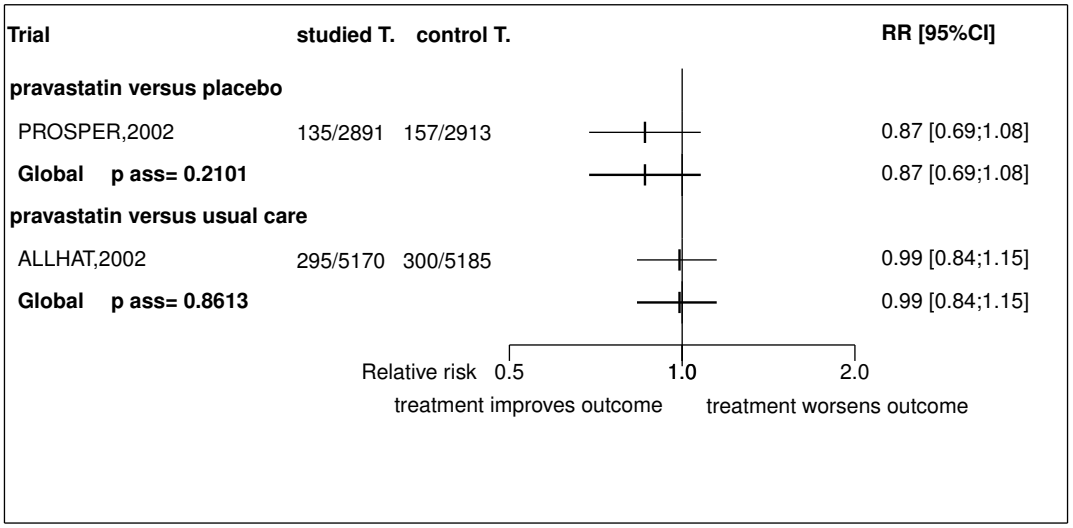


Figure 9.3: *Forest's plot for stroke (fatal and non fatal)*

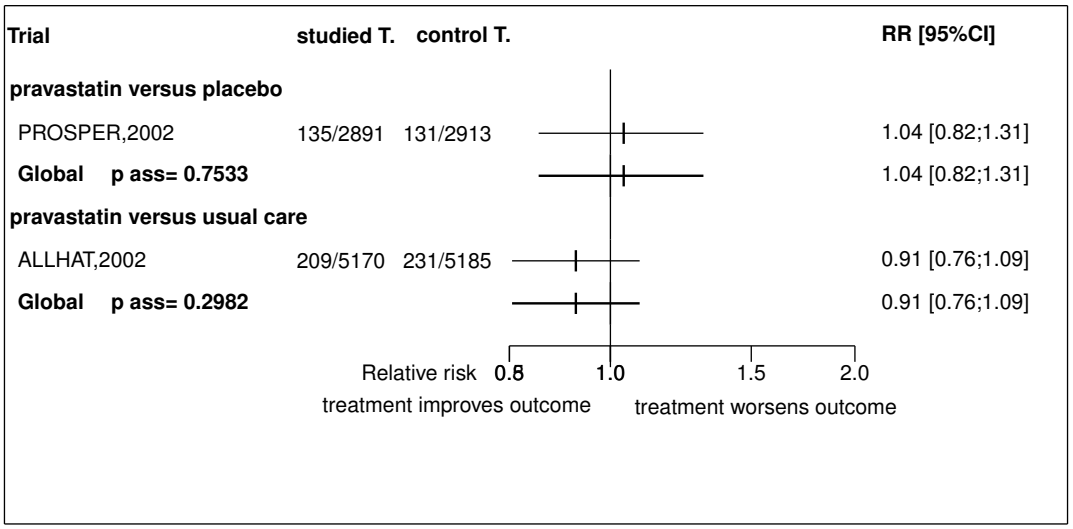


Figure 9.4: *Forest's plot for coronary death and non fatal MI*

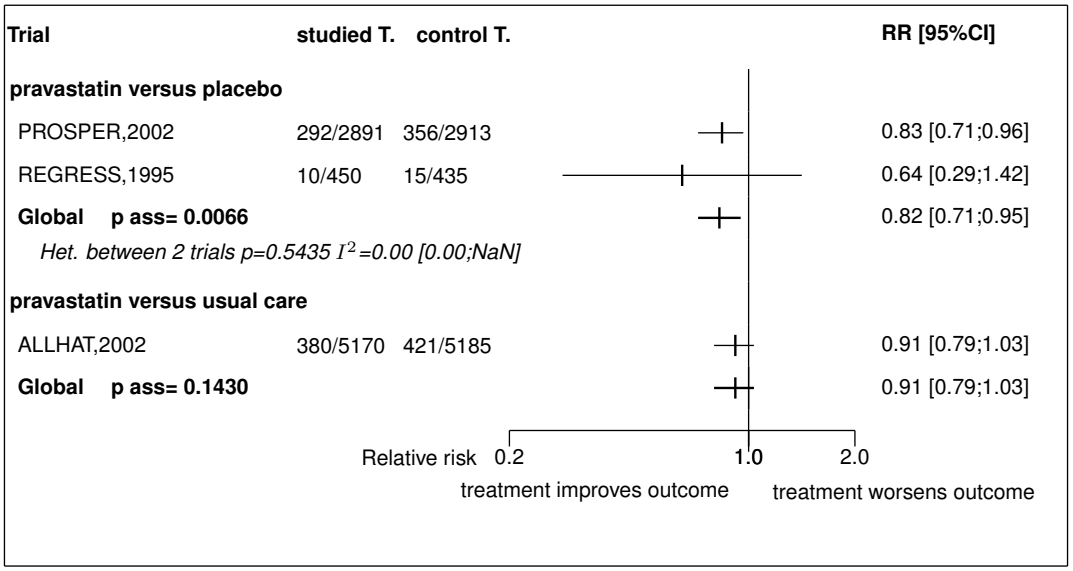


Figure 9.5: *Forest's plot for coronary event*

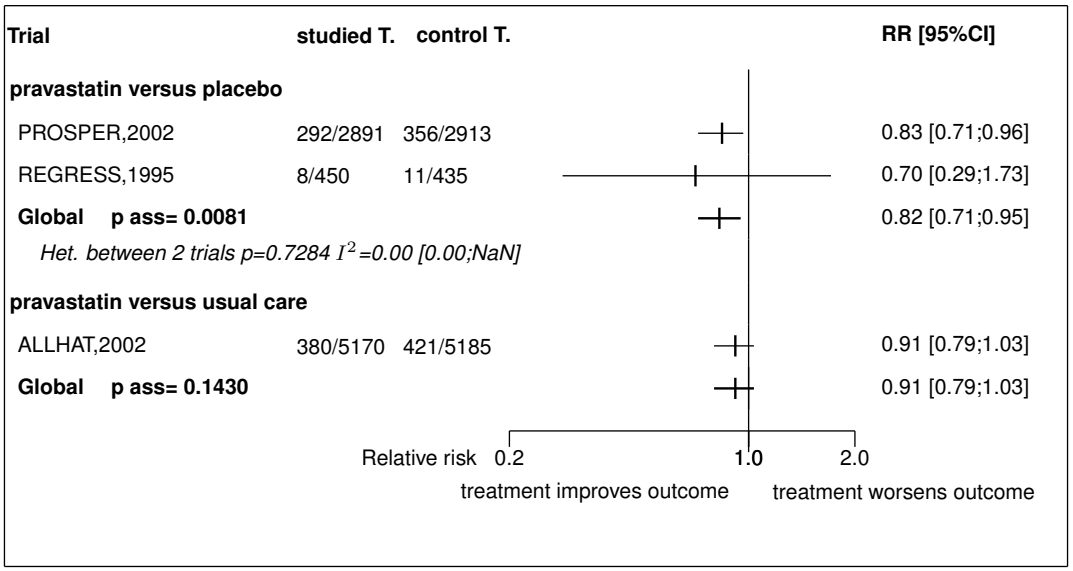


Figure 9.6: *Forest's plot for coronary death*

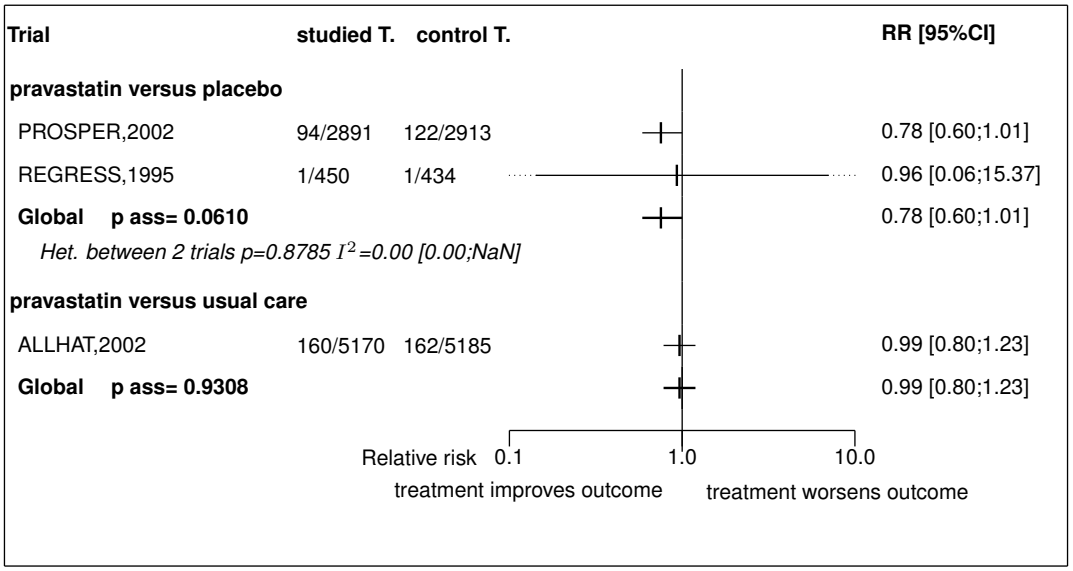


Figure 9.7: *Forest's plot for MACE*

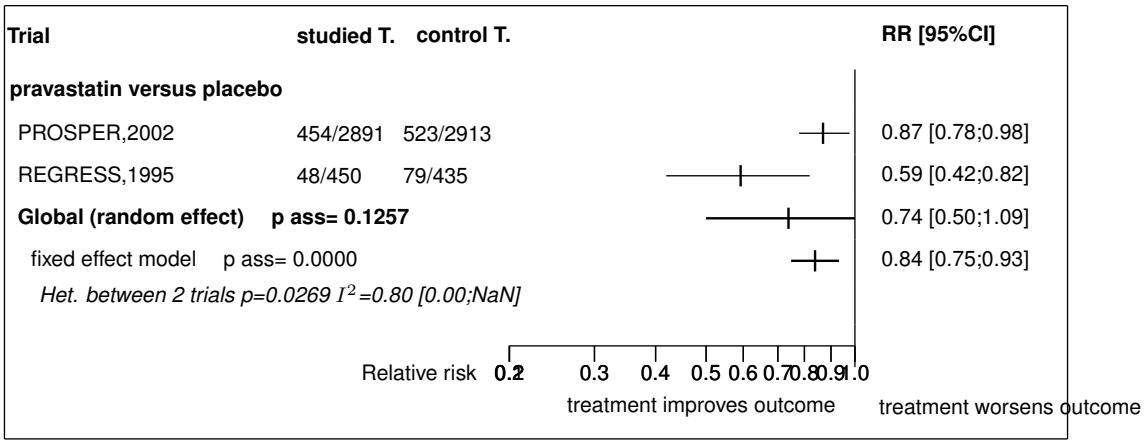


Figure 9.8: *Forest's plot for death from cancer*

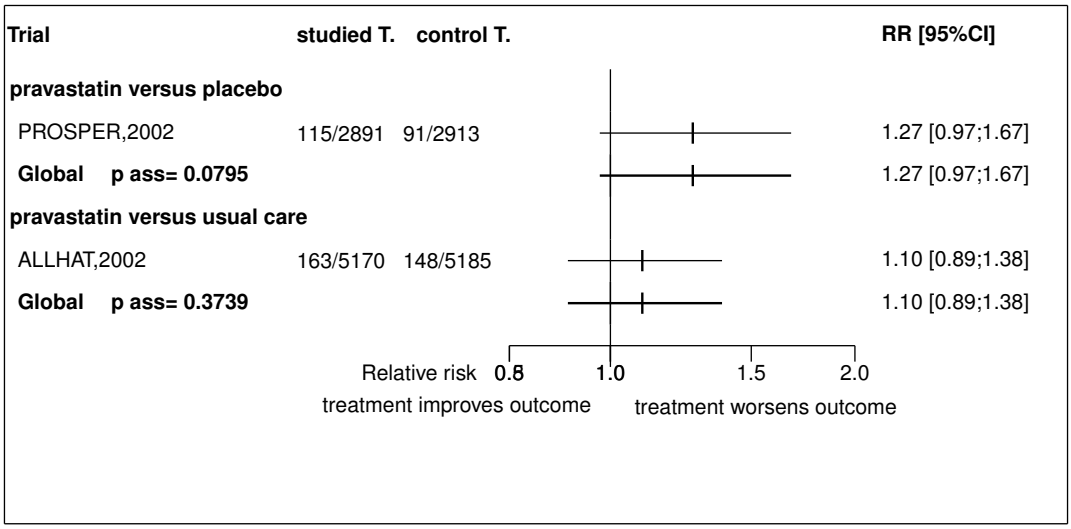


Figure 9.9: *Forest's plot for rhabdomyolysis*

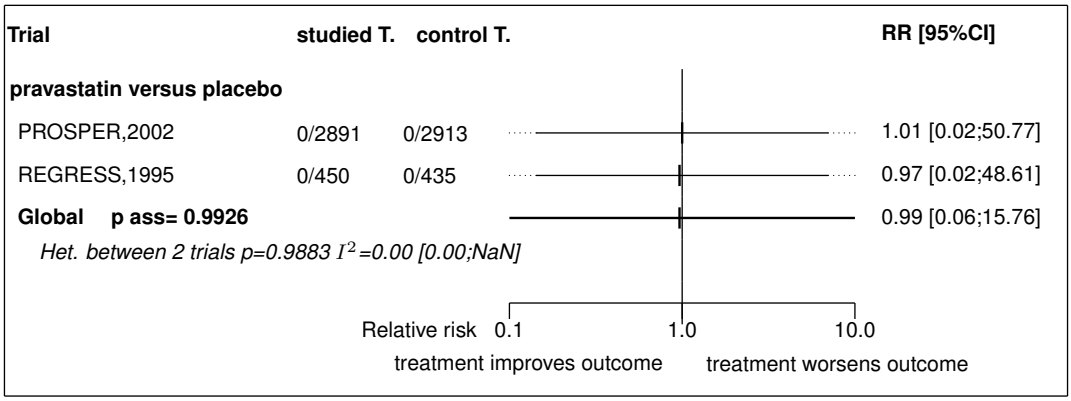


Figure 9.10: *Forest's plot for myopathy*

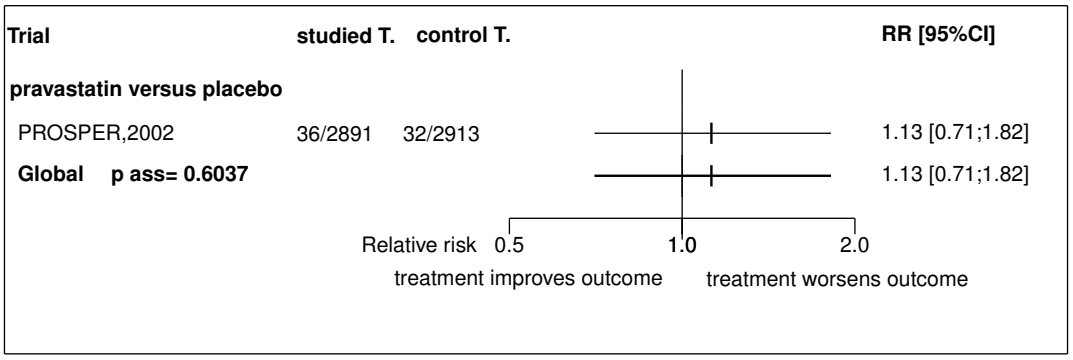


Figure 9.11: *Forest's plot for non fatal MI*

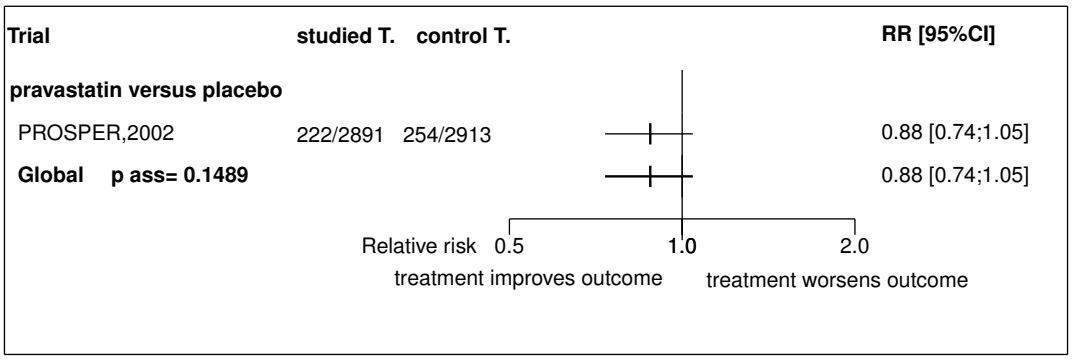


Figure 9.12: *Forest's plot for cancer*

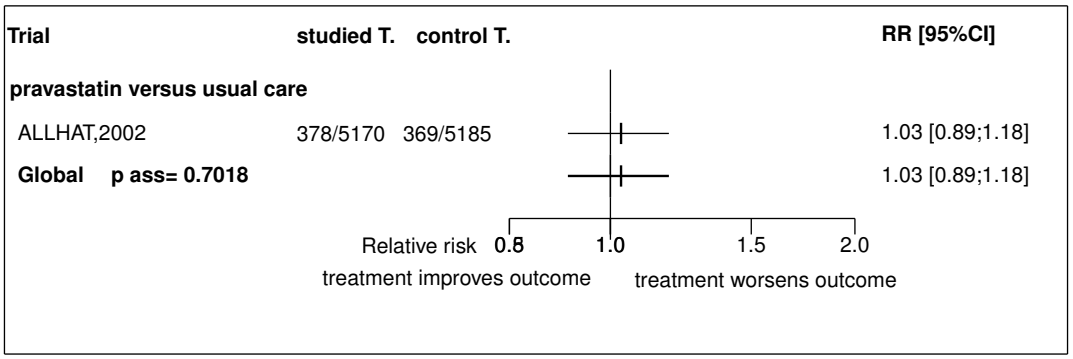


Figure 9.13: *Forest's plot for all cause death*

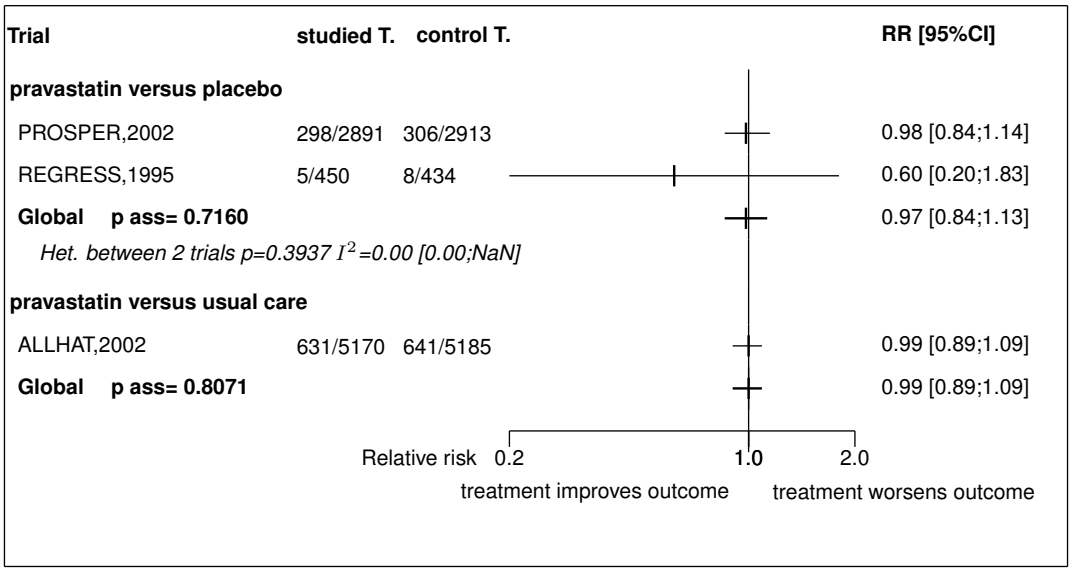
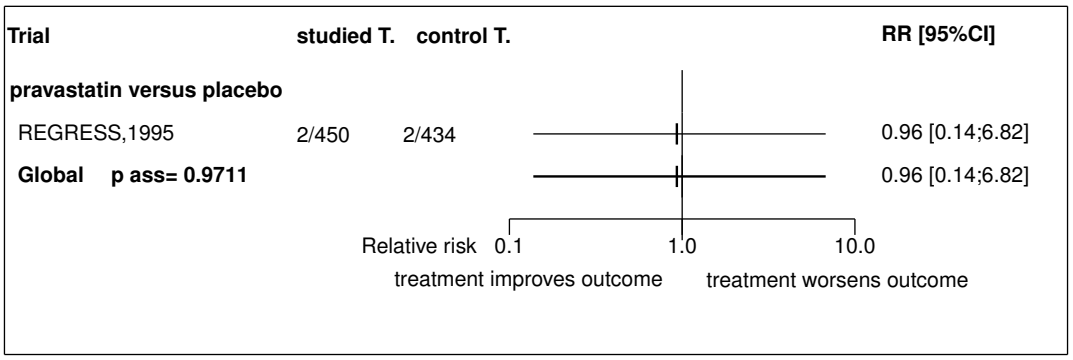


Figure 9.14: *Forest's plot for non cardiovascular death*



References

[1] . Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. The Pravastatin Multinational Study Group for Cardiac Risk Patients. Am J Cardiol 1993;72:1031-7. [PMID=8213583]

[2] Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG,. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360:1623-30. [PMID=12457784]

[3] Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH, Jansen H, Boerma GJ, van Rappard FM, Lie KI. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). Circulation 1995;91:2528-40. [PMID=7743614]

[4] van Boven AJ, Jukema JW, Zwinderman AH, Crijns HJ, Lie KI, Bruschke AV. Reduction of transient myocardial ischemia with pravastatin in addition to the conventional treatment in patients with angina pectoris. REGRESS Study Group. Circulation 1996;94:1503-5. [PMID=8840836]

[5] ,. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002; 288:2998-3007. [PMID=12479764]

9.3 Individual trial summaries

Table 9.6: *PMSG, 1993 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1062 (530 vs. 532) **Follow-up duration:** 26 weeks **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Patients with hypercholesterolemia(serum total cholesterol concentrations of 5.2 to 7.8 mmol/liter) and >or = 2 additional risk factors for atherosclerotic coronary artery disease	**Studied treatment:** pravastatin 20 mg once daily **Control treatment:** placebo	

Reference

. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. The Pravastatin Multinational Study Group for Cardiac Risk Patients. Am J Cardiol 1993;72:1031-7 [PMID=8213583]

Table 9.7: *PROSPER, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=5804 (2891 vs. 2913) **Follow-up duration:** 3.2 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Ecosse, Irelande, Pays bas, multicenter **Inclusion period:** dec 1997, May 1999	Men and women aged 70-82 years with a history of, or risk factors for, vascular disease **Inclusion criteria:** men and women aged 7082 years; either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes; total cholesterol between 4090 mmol/L; triglyceride less than 60 mmol/L **Exclusion criteria:** poor cognitive function (mini mentalstate examination score <24)	**Studied treatment:** pravastatin 40mg daily **Control treatment:** placebo	Cardiovascular events RR=0.87 [0.77;0.98] Cardiovascular death RR=0.87 [0.69;1.08] Stroke (fatal and non fatal) RR=1.04 [0.82;1.31] Coronary death and non fatal MI RR=0.83 [0.71;0.96] Coronary event RR=0.83 [0.71;0.96] Coronary death RR=0.78 [0.60;1.01] MACE RR=0.87 [0.78;0.98] Death from cancer RR=1.27 [0.97;1.67]

Reference
Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG,. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360:1623-30 [PMID=12457784]

Table 9.8: *REGRESS, 1995 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=885 (450 vs. 435) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Netherlands	Symptomatic men with normal to moderately elevated serum cholesterol levels	**Studied treatment:** pravastatin 40 mg daily **Control treatment:** placebo	Cardiovascular events RR=0.59 [0.42;0.82] Coronary death and non fatal MI RR=0.64 [0.29;1.42] Coronary event RR=0.70 [0.29;1.73] Coronary death RR=0.96 [0.06;15.37] MACE RR=0.59 [0.42;0.82]

References

Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH, Jansen H, Boerma GJ, van Rappard FM, Lie KI. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). Circulation 1995;91:2528-40 [PMID=7743614]
van Boven AJ, Jukema JW, Zwinderman AH, Crijns HJ, Lie KI, Bruschke AV. Reduction of transient myocardial ischemia with pravastatin in addition to the conventional treatment in patients with angina pectoris. REGRESS Study Group. Circulation 1996;94:1503-5 [PMID=8840836]

Table 9.9: *ALLHAT, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=10355 (5170 vs. 5185) **Follow-up duration:** 4.8 years **Study design:** Randomized controlled trial Factorial plan Open Confirmatory trial at risk of bias USA, Puerto Rico, Canada, 513 centres **Inclusion period:** feb 1994, mar 2002	Older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor **Inclusion criteria:** age >=55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor; fasting LDL-C level of 120 to 189 mg/dL (3.1 to 4.9 mmol/L) for those with no known CHD, or 100 to 129 mg/dL (2.6 to 3.3 mmol/L) for those with known CHD (the upper limit was 159 mg/dL [4.1 mmol/L] prior to April 5, 1994, but was changed in light of 4S4 findings); and fasting triglyceride levels lower than 350 mg/dL (3.9 mmol/L) **Exclusion criteria:** current lipid-lowering therapy, large doses of niacin, or probucol in the last year; intolerance of statins; significant liver or kidney disease (serum alanine aminotransferase [ALT] >100 IU/L or serum creatinine >2.0 mg/dL [176.8 mol/L]); other contraindications for statin therapy; secondary cause of hyperlipidemia. Enrollment was discouraged for participants whose personal physicians recommended cholesterollowering medications.	**Studied treatment:** pravastatin 40mg/d **Control treatment:** usual care **note:** factorial design with 4 antihypertensive treament (amlodipine, lisinopril, doxazosin compared with chlorthalidone)	Cardiovascular events RR=0.91 [0.79;1.03] (Fatal CHD and nonfatal MI) Cardiovascular death RR=0.99 [0.84;1.15] Stroke (fatal and non fatal) RR=0.91 [0.76;1.09] Coronary death and non fatal MI RR=0.91 [0.79;1.03] Coronary event RR=0.91 [0.79;1.03] Coronary death RR=0.99 [0.80;1.23] Death from cancer RR=1.10 [0.89;1.38]

Reference

,. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002; 288:2998-3007 [PMID=12479764]

10 Detailed results for rosuvastatin

10.1 Available trials

Only one trial which randomized 17802 patients was identified: it compared rosuvastatin with placebo.
This trial included 17802 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 10.1 (page 67), 10.2 (page 67), 10.4 (page 69), and 10.3 (page 68) summarized the main characteristics of the trial including in this systematic review of randomized trials of rosuvastatin.

Table 10.1: *Treatment description - statins - rosuvastatin*

Trial	Studied treatment	Control treatment
Rosuvastatin versus placebo		
JUPITER (2008) [1]	rosuvastatin 20 mg daily	placebo

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

Trial	Patients
Rosuvastatin versus placebo	

continued...

Trial	Patients	
JUPITER (2008) [1]	Apparently healthy individuals with low LDL-cholesterol levels of less than 130 mg per deciliter but elevated C-reactive-protein (high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher)	
	Inclusion criteria: males aged 50 years and older and females aged 60 years and older with no history of MI, stroke, or arterial revascularisation; LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter); high-sensitivity C-reactive protein level of 2.0 mg per liter or more; triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter)	**Exclusion criteria:** previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatine kinase level that was more than three times the upper limit of the normal range, a creatinine level that was higher than 2.0 mg per deciliter (176.8 mol per liter), diabetes, uncontrolled hypertension (systolic blood pressure $>$190 mm Hg or diastolic blood pressure $>$100 mm Hg), cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), uncontrolled hypothyroidism (a thyroid-stimulating hormone level that was more than 1.5 times the upper limit of the normal range), and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study

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

Trial	Design	Duration	Centre	Primary endpoint
Rosuvastatin versus placebo				
JUPITER, 2008 [1] n=17802	Parallel groups double blind confirmatory trial at low risk of bias	median 1.9 year inclusion period: feb 2003 - dec 2006	26 countries 1200 centres	MI, stroke, arterial revascularization, hospitalization for unstable angina, cardiovascular death

Table 10.4: *Trial characteristics - statins - rosuvastatin*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Rosuvastatin versus placebo				
JUPITER, 2008 [1]				

10.2 Meta-analysis results

The results are detailed in table 10.5 (page 70). This table is followed by the Forest's plot corresponding to each endpoint.

Rosuvastatin versus placebo

No data were presented in the 1 trial identified

Table 10.5: *Results details - statins - rosuvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
rosuvastatin 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] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med 2008 Nov 9;:. [PMID=18997196]

10.3 Individual trial summaries

Table 10.6: *JUPITER, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=17802 (8901 vs. 8901) **Follow-up duration:** median 1.9 year **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 26 countries, 1200 centres **Inclusion period:** feb 2003 - dec 2006	Apparently healthy individuals with low LDL-cholesterol levels of less than 130 mg per deciliter but elevated C-reactive-protein (high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher) **Inclusion criteria:** males aged 50 years and older and females aged 60 years and older with no history of MI, stroke, or arterial revascularisation; LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter); high-sensitivity C-reactive protein level of 2.0 mg per liter or more; triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter) **Exclusion criteria:** previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatine kinase level that was more than three times the upper limit of the normal range, a creatinine level that was higher than 2.0 mg per deciliter (176.8 mol per liter), diabetes, uncontrolled hypertension (systolic blood pressure >190 mm Hg or diastolic blood pressure >100 mm Hg), cancer within 5 years before enrollment (with	**Studied treatment:** rosuvastatin 20 mg daily **Control treatment:** placebo	

Reference

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med 2008 Nov 9;: [PMID=18997196]

11 Detailed results for simvastatin

11.1 Available trials

Only one trial which randomized 20536 patients was identified: it compared simvastatin with placebo.
This trial included 20536 patients and was published in 2002.
This trial was double blind in design.
It was reported in English language.
Coronary death and non fatal MI data was reported in 1 trials; 1 trials reported data on coronary death; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on cardiovascular death; 1 trials reported data on coronary event; 1 trials reported data on non fatal MI; 1 trials reported data on myopathy; 1 trials reported data on death from cancer; 1 trials reported data on rhabdomyolysis; and 1 trials reported data on all cause death.
Following tables 11.1 (page 73), 11.2 (page 73), 11.4 (page 75), and 11.3 (page 74) summarized the main characteristics of the trial including in this systematic review of randomized trials of simvastatin.

Table 11.1: *Treatment description - statins - simvastatin*

Trial	Studied treatment	Control treatment
Simvastatin versus placebo		
HPS (2002) [1, 2, 3]	simvastatin 40 mg/d	placebo
	Concomittant treatment: diet	

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

Trial	Patients
Simvastatin versus placebo	

continued...

Trial	Patients	
HPS (2002) [1, 2, 3]	Adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabete	
	Inclusion criteria: men and women aged about 4080 years with non-fasting blood total cholesterol concentrations of at least 35 mmol/L (135 mg/dL); considered to be at substantial 5-year risk of death from coronary heart disease because of a past medical history of: (i) coronary disease (ie, myocardial infarction, unstable or stable angina, coronary artery bypass graft, or angioplasty); or (ii) occlusive disease of non-coronary arteries (ie, non-disabling stroke not thought to be haemorrhagic, transient cerebral ischaemia, leg artery stenosis [eg, intermittent claudication], carotid endarterectomy, other arterial surgery or angioplasty); or (iii) diabetes mellitus (whether type 1 or type 212,25); or (iv) treated hypertension (if also male and aged at least 65 years, in order to be at similar risk to the other disease categories)	**Exclusion criteria:** chronic liver disease (cirrhosis or hepatitis) or evidence of abnormal liver function (eg, alanine aminotransferase >67 IU/L [15 times the ULN]); severe renal disease or evidence of impaired renal function (creatinine >200 micromol/L); inflammatory muscle disease (eg, dermatomyositis or polymyositis) or evidence of muscle problems (creatine kinase >750 IU/L [3ULN]); concurrent treatment with ciclosporin, fibrates, or high-dose niacin; child-bearing potential (premenopausal woman not sterilised or using reliable contraception); severe heart failure; some lifethreatening condition other than vascular disease or diabetes (eg, severe chronic airways disease or any cancer other than non-melanoma skin cancer); or conditions that might limit long-term compliance (eg, severely disabling stroke, dementia, or psychiatric disorder).

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

Trial	Design	Duration	Centre	Primary endpoint
Simvastatin versus placebo				
HPS, 2002 [1, 2, 3] n=20536	Factorial plan double blind confirmatory trial at low risk of bias	5 years inclusion period: Jul 1994, may 1997	UK multicentrique	all cause death

Table 11.4: *Trial characteristics - statins - simvastatin*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Simvastatin versus placebo				
HPS, 2002 [1, 2, 3]	-1			

11.2 Meta-analysis results

The results are detailed in table 11.5 (page 76). This table is followed by the Forest's plot corresponding to each endpoint.

Simvastatin versus placebo

The single study eligible for this comparison provided data on **cardiovascular death**. The analysis detected a statistically significant difference in favor of simvastatin in cardiovascular death, with a RR of 0.83 (95% CI 0.76 to 0.91, p=0.0000).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of simvastatin in stroke (fatal and non fatal), with a RR of 0.76 (95% CI 0.67 to 0.86, p=0.0000).
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 simvastatin in coronary death and non fatal MI, with a RR of 0.74 (95% CI 0.68 to 0.80, 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 simvastatin in coronary event, with a RR of 0.74 (95% CI 0.68 to 0.80, p=0.0000).
The single study eligible for this comparison provided data on **coronary death**. The analysis detected a statistically significant difference in favor of simvastatin in coronary death, with a RR of 0.83 (95% CI 0.75 to 0.92, 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 simvastatin in non fatal MI, with a RR of 0.62 (95% CI 0.55 to 0.71, p=0.0000).

Table 11.5: *Results details - statins - simvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
simvastatin versus placebo						
cardiovascular death	RR=0.83	[0.76;0.91]	0.0000	1.0000 (I^2=0.00)	1	20536
stroke (fatal and non fatal)	RR=0.76	[0.67;0.86]	0.0000	1.0000 (I^2=0.00)	1	20536
coronary death and non fatal MI	RR=0.74	[0.68;0.80]	0.0000	1.0000 (I^2=0.00)	1	20536
coronary event	RR=0.74	[0.68;0.80]	0.0000	1.0000 (I^2=0.00)	1	20536
coronary death	RR=0.83	[0.75;0.92]	0.0000	1.0000 (I^2=0.00)	1	20536
death from cancer	RR=1.04	[0.90;1.20]	0.5932	1.0000 (I^2=0.00)	1	20536
rhabdomyolysis	RR=1.67	[0.40;6.97]	0.4843	1.0000 (I^2=0.00)	1	20536
myopathy	RR=2.50	[0.78;7.97]	0.1214	1.0000 (I^2=0.00)	1	20536
non fatal MI	RR=0.62	[0.55;0.71]	0.0000	1.0000 (I^2=0.00)	1	20536
all cause death	RR=0.88	[0.82;0.94]	0.0000	1.0000 (I^2=0.00)	1	20536

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

Figure 11.1: *Forest's plot for cardiovascular death*

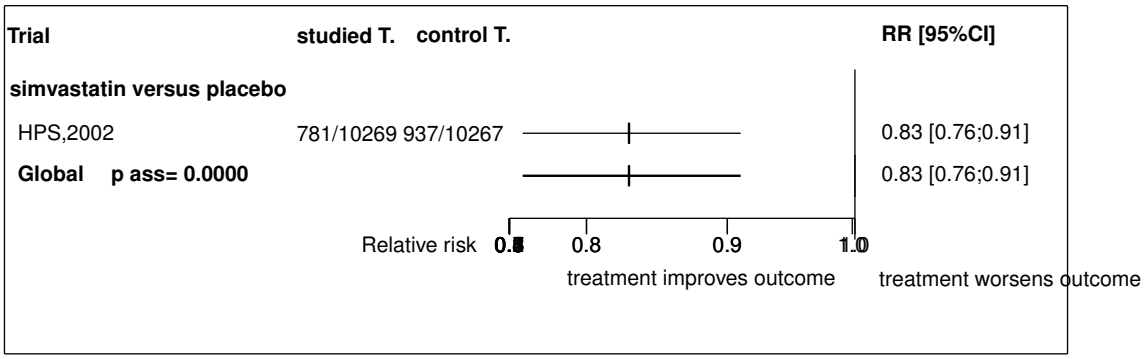


Figure 11.2: *Forest's plot for stroke (fatal and non fatal)*

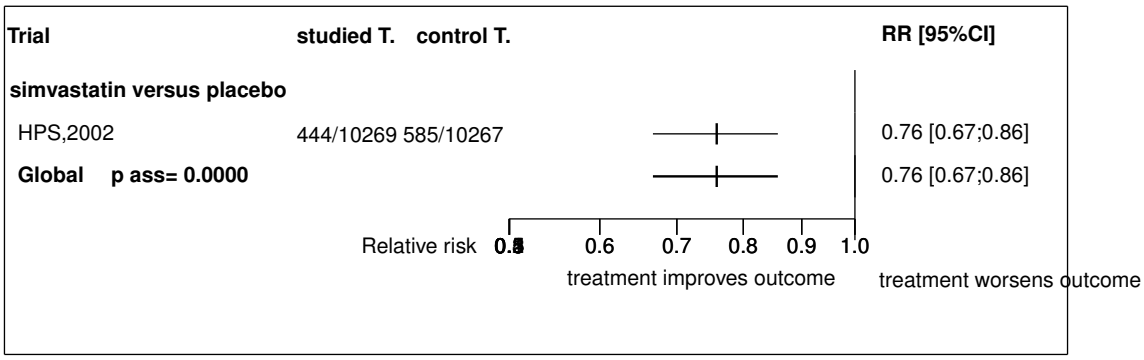


Figure 11.3: *Forest's plot for coronary death and non fatal MI*

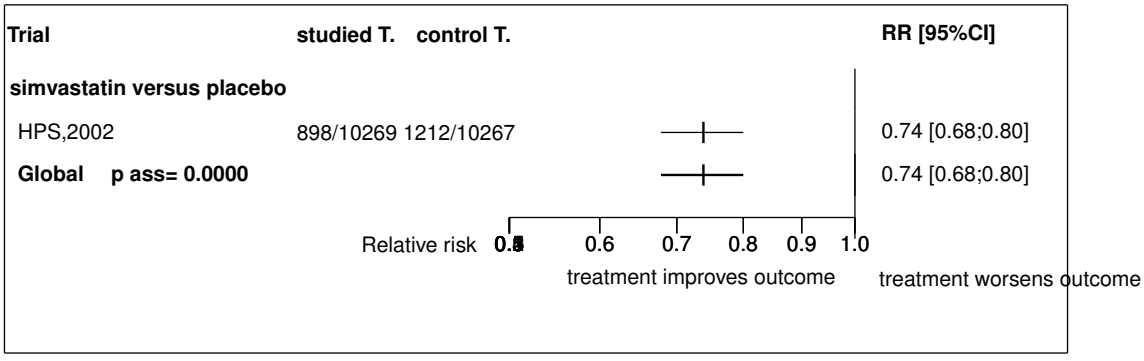


Figure 11.4: *Forest's plot for coronary event*

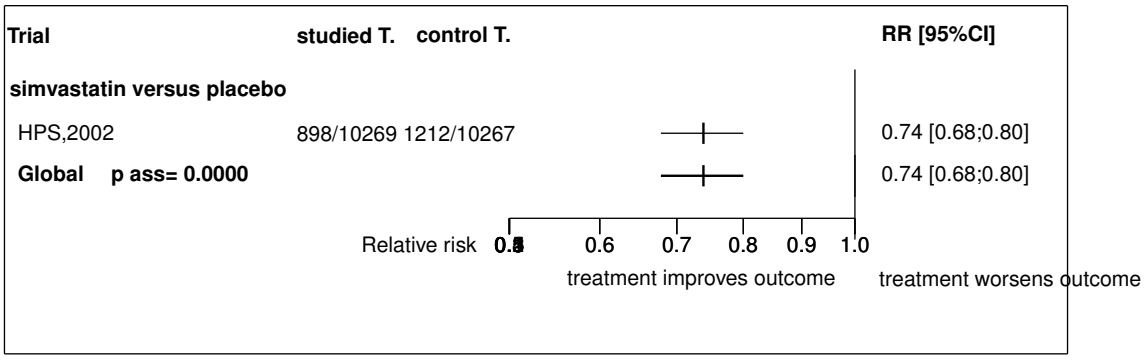


Figure 11.5: *Forest's plot for coronary death*

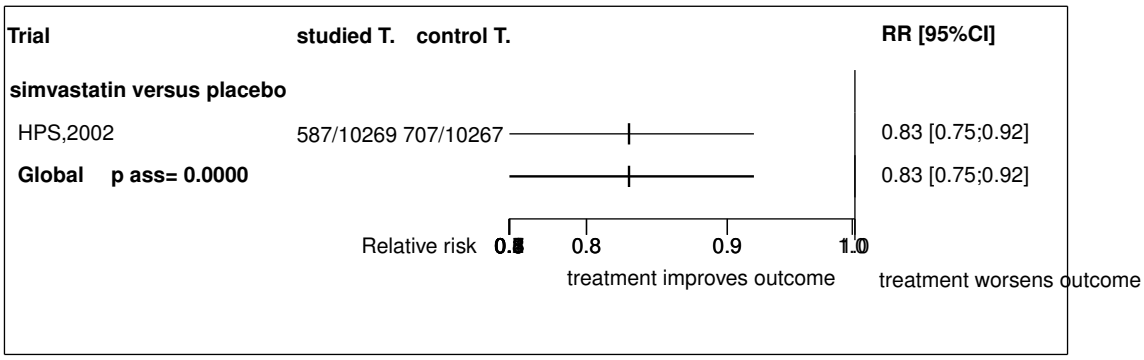


Figure 11.6: *Forest's plot for death from cancer*

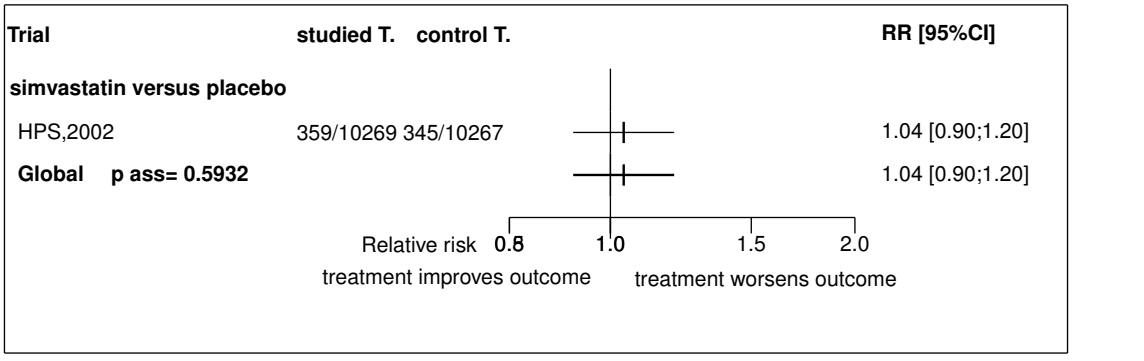


Figure 11.7: *Forest's plot for rhabdomyolysis*

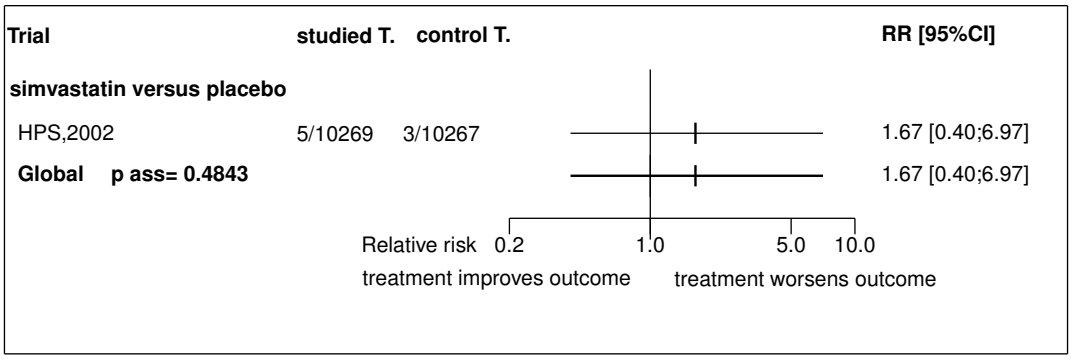


Figure 11.8: *Forest's plot for myopathy*

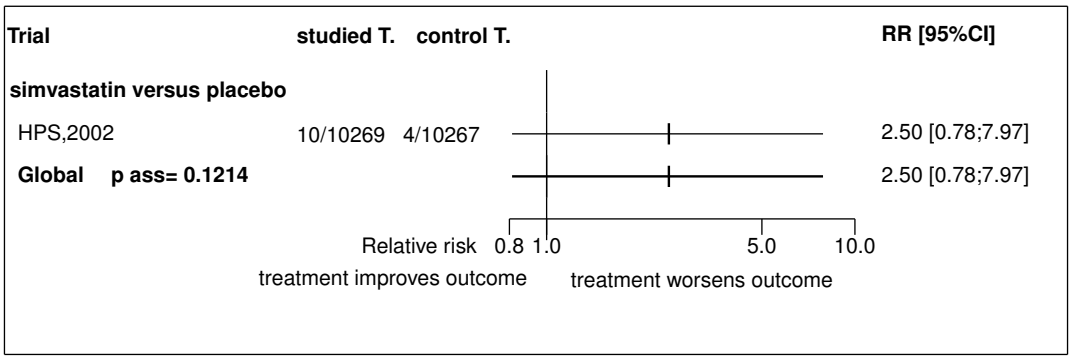


Figure 11.9: *Forest's plot for non fatal MI*

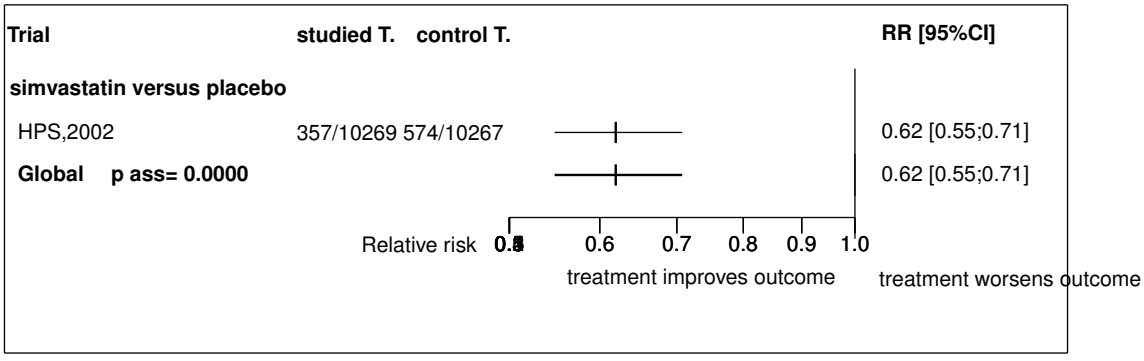
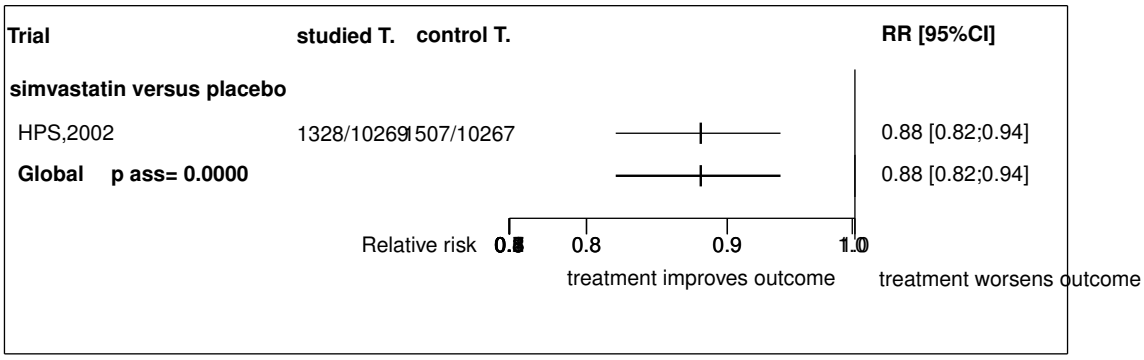


Figure 11.10: *Forest's plot for all cause death*



References

[1] ,. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7-22. [PMID=12114036]

[2] Armitage J, Collins R. Need for large scale randomised evidence about lowering LDL cholesterol in people with diabetes mellitus: MRC/BHF heart protection study and other major trials. Heart 2000;84:357-60. [PMID=10995396]

[3] . MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. Eur Heart J 1999;20:725-41. [PMID=10329064]

11.3 Individual trial summaries

Table 11.6: *HPS, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=20536 (10269 vs. 10267) **Follow-up duration:** 5 years **Study design:** Randomized controlled trial Factorial plan Double blind Confirmatory trial at low risk of bias UK, multicentrique **Inclusion period:** Jul 1994, may 1997	Adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabete **Inclusion criteria:** men and women aged about 4080 years with non-fasting blood total cholesterol concentrations of at least 35 mmol/L (135 mg/dL); considered to be at substantial 5-year risk of death from coronary heart disease because of a past medical history of: (i) coronary disease (ie, myocardial infarction, unstable or stable angina, coronary artery bypass graft, or angioplasty); or (ii) occlusive disease of non-coronary arteries (ie, non-disabling stroke not thought to be haemorrhagic, transient cerebral ischaemia, leg artery stenosis [eg, intermittent claudication], carotid endarterectomy, other arterial **Exclusion criteria:** chronic liver disease (cirrhosis or hepatitis) or evidence of abnormal liver function (eg, alanine aminotransferase >67 IU/L [15 times the ULN]); severe renal disease or evidence of impaired renal function (creatinine >200 micromol/L); inflammatory muscle disease (eg, dermatomyositis or polymyositis) or evidence of muscle problems (creatine kinase >750 IU/L [3ULN]); concurrent treatment with ciclosporin, fibrates, or high-dose niacin; child-bearing potential (premenopausal woman not sterilised or using reliable contraception); severe heart failure; some l	**Studied treatment:** simvastatin 40 mg/d **Control treatment:** placebo **Concomitant treat.:**diet	Cardiovascular death RR=0.83 [0.76;0.91] Stroke (fatal and non fatal) RR=0.76 [0.67;0.86] Coronary death and non fatal MI RR=0.74 [0.68;0.80] Coronary event RR=0.74 [0.68;0.80] Coronary death RR=0.83 [0.75;0.92] Death from cancer RR=1.04 [0.90;1.20] Rhabdomyolysis RR=1.67 [0.40;6.97]

continued...

trial details	Patients	Treatments	Outcomes

References

,. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7-22 [PMID=12114036]
Armitage J, Collins R. Need for large scale randomised evidence about lowering LDL cholesterol in people with diabetes mellitus: MRC/BHF heart protection study and other major trials. Heart 2000;84:357-60 [PMID=10995396]
. MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. Eur Heart J 1999;20:725-41 [PMID=10329064]

12 Global meta-analysis: all statins

12.1 Global meta-analysis: all statins versus placebo

Table 12.1: *All statinsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.74 [1]	0.51;1.08	0.1156	0.0306 (0.79) †	2	6689
cardiovascular death	RR=0.84	0.78;0.91	0.0000	0.8736 (0.00)	3	36645
stroke (fatal and non fatal)	RR=0.83	0.67;1.01	0.0644	0.0522 (0.66)	3	36645
coronary death and non fatal MI	RR=0.75	0.69;0.81	0.0000	0.3437 (0.10)	4	37530
coronary event	RR=0.75	0.71;0.81	0.0000	0.5715 (0.00)	4	37530
coronary death	RR=0.82	0.75;0.91	0.0000	0.8934 (0.00)	3	27224
MACE	RR=0.79	0.68;0.92	0.0027	0.0715 (0.62)	3	16994
non fatal MI	RR=0.74 [2]	0.52;1.04	0.0786	0.0000 (0.90) †	2	26340
non cardiovascular death	RR=0.96	0.14;6.82	0.9711	1.0000 (0.00)	1	884

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

12.2 Global meta-analysis: all statins versus usual care

Table 12.2: *All statinsversus usual care*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.91	0.79;1.03	0.1430	1.0000 (0.00)	1	10355
cardiovascular death	RR=0.99	0.84;1.15	0.8613	1.0000 (0.00)	1	10355
stroke (fatal and non fatal)	RR=0.91	0.76;1.09	0.2982	1.0000 (0.00)	1	10355
coronary death and non fatal MI	RR=0.91	0.79;1.03	0.1430	1.0000 (0.00)	1	10355
coronary event	RR=0.91	0.79;1.03	0.1430	1.0000 (0.00)	1	10355
coronary death	RR=0.99	0.80;1.23	0.9308	1.0000 (0.00)	1	10355

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

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.83 95% CI 0.74;0.93
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.70 95% CI 0.64;0.78

13 Ongoing studies of statins

No ongoing trial was identified.

14 Excluded studies for statins

No trial was excluded.

References