Cholesterol lowering intervention for cardiovascular prevention in diabetic patients

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 diabetic patients .

Contents

0.1 Synthesis of the meta-analysis results

In all 29 randomised controlled trials (RCTs) were included. These included 10 studies of **fibrates** involving 19,056 patients, 18 studies of **statins** involving 24,269 patients and 1 studie of **strategy** involving 499 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 Fibrates

Reports of 9 trials (including 19,074 patients) were identified .
Among these comparisons, one trial are about bezafibrate,two about clofibrate,one about etofibrate,4 about fenofibrate and two about gemfibrozil.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Bezafibrate

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

Table 1: *Results summary - Bezafibrate*

Benefit	Harmful	No evidence
	Bezafibrate versus placebo	

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

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

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	

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

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

Etofibrate

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

Table 3: *Results summary - Etofibrate*

Benefit	Harmful	No evidence
	Etofibrate 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)

Fenofibrate

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

Table 4: *Results summary - Fenofibrate*

Benefit	Harmful	No evidence
	Fenofibrate versus placebo	
	Fenofibrate versus placebo (on top simvastatine)	

* 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 5.

Table 5: *Results summary - Gemfibrozil*

Benefit	Harmful	No evidence
	Gemfibrozil 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)

0.1.2 Statins

Reports of 18 trials (including 24,287 patients) were identified .
Among these comparisons, one trial are about aggressive cholesterol-lowering,4 about atorvastatin,one about atorvastatin high dose,two about fluvastatin,one about lovastatin,6 about pravastatin,one about pravastatin high dose and two about simvastatin.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation

of results. No ongoing trial was found.

Aggressive cholesterol-lowering

Results obtained with aggressive cholesterol-lowering for all the endpoints with data in at least one trial are summarized table 6.

Table 6: *Results summary - Aggressive cholesterol-lowering*

Benefit	Harmful	No evidence
Aggressive cholesterol-lowering versus moderate cholesterol-lowering		

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ 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 7.

Table 7: *Results summary - Atorvastatin*

Benefit	Harmful	No evidence
Atorvastatin versus placebo		
↓ cardiovascular events RR=0.70† [0.55;0.88] k=2 ↓ stroke (fatal and non fatal) RR=0.60† [0.42;0.86] k=2 ↓ coronary event RR=0.72* [0.55;0.94] k=2 ↓ MACE RR=0.65¶ [0.49;0.84] k=1 ↓ non fatal MI RR=0.60* [0.37;0.99] k=1		→ cardiovascular death RR=0.65^{NS} [0.36;1.15] k=1 → coronary death RR=0.74^{NS} [0.40;1.36] k=1 → death from cancer RR=0.66^{NS} [0.38;1.15] k=1 → rhabdomyolysis RR=0.99^{NS} [0.02;49.77] k=1 → myopathy RR=0.99^{NS} [0.06;15.78] k=1 → all cause death RR=0.74^{NS} [0.53;1.02] k=1 → adverse events RR=0.94^{NS} [0.50;1.75] k=1

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

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

Atorvastatin high dose

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

Table 8: *Results summary - Atorvastatin high dose*

Benefit	Harmful	No evidence
Atorvastatin high dose versus atorvastatin		

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

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

Fluvastatin

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

Table 9: *Results summary - Fluvastatin*

Benefit	Harmful	No evidence
Fluvastatin 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)

Lovastatin

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

Table 10: *Results summary - Lovastatin*

Benefit	Harmful	No evidence
Lovastatin 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)

Pravastatin

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

Table 11: *Results summary - Pravastatin*

Benefit	Harmful	No evidence
	Pravastatin versus placebo	
		→ cardiovascular events RR=0.80^{NS} [0.59;1.09] k=1 → stroke (fatal and non fatal) RR=0.85^{NS} [0.48;1.52] k=1 → coronary event RR=0.85^{NS} [0.69;1.05] k=2
	Pravastatin versus usual care	

* 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 high dose

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

Table 12: *Results summary - Pravastatin high dose*

Benefit	Harmful	No evidence
	Pravastatin high dose versus pravastatin	

* 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 13.

Table 13: *Results summary - Simvastatin*

Benefit	Harmful	No evidence
	Simvastatin versus placebo	
↓ cardiovascular events RR=0.81¶ [0.73;0.89] k=1 ↓ stroke (fatal and non fatal) RR=0.77* [0.63;0.95] k=1		→ all cause death RR=0.79^{NS} [0.49;1.28] k=1

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

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

0.1.3 Strategy

Only one trials including 499 patients was found.
Among these comparisons, one trial are about aggressive treatment.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with aggressive treatment for all the endpoints with data in at least one trial are summarized table 14.

Table 14: *Results summary - Aggressive treatment*

Benefit	**Harmful**	**No evidence**
	Aggressive treatment versus standard teatment	
		→ cardiovascular events RR=1.35^{NS} [0.55;3.29] k=1 → non cardiovascular death RR=0.49^{NS} [0.09;2.65] k=1 → adverse events RR=1.32^{NS} [0.98;1.78] 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 diabetic patients . The following classes of treatment are considered:

1. fibrates
2. statins
3. strategy

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 diabetic patients .

1.2.1 Sources searched

The following electronic databases were searched for relevant published literature for the period up to 2017 - 7 - 1:

- MEDLINE,
- EMBASE,
- Cochrane Database of Systematic Reviews (CDSR),
- Cochrane Central Register of Controlled Trials (CCTR),
- Health Technology Assessment (HTA) database,
- ISI Web of Science Proceedings (Index to Scientific and Technical Proceedings),
- ISI Web of Science Science Citation Index Expanded,

Each database was searched as far back as possible, with no language restrictions.
Search strategies of relevant clinical keywords were developed through reference to published strategies, and by iterative searching, whereby keywords identified in references retrieved by initial scoping searches were used to extend the search strategy and so increase the sensitivity of retrieval.
In addition, the reference lists of relevant articles were handsearched.
Attempts to identify further studies were made by consulting health technology assessment and guideline producing agencies, and research and trials registers via the Internet.
Titles and, when available, abstracts of all studies identified in the searches were assessed by a single researcher for relevance to the review. In cases of doubt, the full article was obtained.

1.2.2 Search restrictions

No language, study/publication or date restrictions were applied to the main searches.

1.3 Inclusion criteria

Participants only those studies were included in which the participants had been diagnosed as having established 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 fibrates, statins, strategy,
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

Fibrates

2 Overview of fibrates

2.1 Included trials

A total of 10 randomized comparisons which enrolled 19074 patients were identified. In all, 1 randomized comparison concerned bezafibrate , two clofibrate , one etofibrate , 4 fenofibrate and two gemfibrozil.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 23) for bezafibrate, in section 4 (page 28) for clofibrate, in section 5 (page 35) for etofibrate, in section 6 (page 40) for fenofibrate and in section 7 (page 51) for gemfibrozil.

The average study size was 2119 patients (range 63 to 9795). The first study was published in 1969, and the last study was published in 2010.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 2.1 (page 19) 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 fibrates provide the results listed in tables 2.2 to 2.6 (page 21) and in the following graphs.

2.2.1 Bezafibrate

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

2.2.2 Clofibrate

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

2.2.3 Etofibrate

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

2.2.4 Fenofibrate

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

Data were insufficient to compare **fenofibrate** to **placebo (on top simvastatine)**. There were 2 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis.

2.2.5 Gemfibrozil

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

Table 2.1: *Main study characteristics - fibrates*

Trial	Patients	Treatments	Trial design and method
Bezafibrate			
Bezafibrate versus placebo			
SENDCAP, 1998 [1] n = 81 vs. 83	type 2 diabetic subjects without a history of clinical cardiovascular	bezafibrate 400 mg daily **versus** placebo	double blind parallel groups Primary endpoint: B-mode ultrasound UK
Clofibrate			
Clofibrate versus placebo			
Hanefeld, 1991 [1] n = 379 vs. 382	newly diagnosed middle-aged (30- to 55-yr-old) patients with non-insulin-dependent diabetes mellitus	clofibric acid 1.6 g/day **versus** placebo	double-blind parallel groups Primary endpoint: NA Germany
Harrold, 1969 [2] n = 30 vs. 33	diabetic retinopathy	clofibrate **versus** placebo	double-blind parallel groups
Etofibrate			
Etofibrate versus placebo			
Emmerich, 2009 [1] n = NA vs. NA	patients with type 2 diabetes mellitus and concomitant diabetic retinopathy	etofibrate 1g/j **versus** placebo	double-blind parallel groups Primary endpoint: not defined Germany
Fenofibrate			
Fenofibrate versus placebo			

continued...

Trial	Patients	Treatments	Trial design and method
FIELD, 2005 [1] n = 4895 vs. 4900	aged 50-75 years, with type 2 diabetes mellitus, and not taking statin therapy at study entry	fenofibrate 200 mg daily **versus** placebo	Primary endpoint: coronary events
DAIS, 2001 [2] n = 207 vs. 211	men and women with type 2 diabetes and coronary atherosclerosis	fenofibrate 200 mg/day **versus** placebo	double-blind parallel groups Primary endpoint: QCA (minimum lumen diameter) Canada, Finland, France, Sweden
Fenofibrate versus placebo (on top simvastatine)			
ACCORD lipid, 2010 [3, 4, 5] n = 2765 vs. 2753	high-risk patients with type 2 diabetes	fenofibrate on top simvastatin **versus** placebo (on top simvastatine)	double-blind factorial plan Primary endpoint: fatal cardiovascular events, nonfatal MI, or nonfatal stroke 77 centres, United States and Canada
ACCORD lipid (subgroup Eye study), 2010 [6] n = 806 vs. 787	high-risk patients with type 2 diabetes	fenofibrate on top simvastatin **versus** placebo (on top simvastatine)	double-blind factorial plan Primary endpoint: fatal cardiovascular events, nonfatal MI, or nonfatal stroke 77 centres, United States and Canada
Gemfibrozil			
Gemfibrozil versus placebo			
HHS (sub group), 1987 [1] n= 135	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	gemfibrozil 600mg twice daily **versus** placebo	double blind
VA-HIT (sub group), 1999 [2] n = 309 vs. 318	men with coronary heart disease, an HDL cholesterollevel of 40 mg per deciliter (1.0 mmol per liter)or less, and an LDL cholesterol level of 140 mgper deciliter (3.6 mmol per liter) or less.	gemfibrozil 1200 mg per day **versus** placebo	double blind parallel groups

Table 2.2: *Summary of all results for bezafibrate*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
bezafibrate 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 2.3: *Summary of all results for clofibrate*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
clofibrate 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 2.4: *Summary of all results for etofibrate*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
etofibrate 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 2.5: *Summary of all results for fenofibrate*

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

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

Table 2.6: *Summary of all results for gemfibrozil*

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

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n

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

3 Detailed results for bezafibrate

3.1 Available trials

Only one trial which randomized 164 patients was identified: it compared bezafibrate with placebo.
This trial included 164 patients and was published in 1998.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 3.1 (page 23), 3.2 (page 23), 3.4 (page 24), and 3.3 (page 23) summarized the main characteristics of the trial including in this systematic review of randomized trials of bezafibrate.

Table 3.1: *Treatment description - fibrates - bezafibrate*

Trial	Studied treatment	Control treatment
Bezafibrate versus placebo		
SENDCAP (1998) [1]	bezafibrate 400 mg daily	placebo

Table 3.2: *Descriptions of participants - fibrates - bezafibrate*

Trial	Patients
Bezafibrate versus placebo	
SENDCAP (1998) [1]	Type 2 diabetic subjects without a history of clinical cardiovascular

Table 3.3: *Design and methodological quality of trials - fibrates - bezafibrate*

Trial	Design	Duration	Centre	Primary end-point
Bezafibrate versus placebo				
SENDCAP, 1998 [1] n=164	Parallel groups double blind exploratory trial	3.0 years	UK	B-mode ultra-sound

Table 3.4: *Trial characteristics - fibrates - bezafibrate*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Bezafibrate versus placebo				
SENDCAP, 1998 [1]		-0.3 mmol/L		

3.2 Meta-analysis results

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

Bezafibrate versus placebo

No data were presented in the 1 trial identified

Table 3.5: *Results details - fibrates - bezafibrate*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
bezafibrate 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] Elkeles RS, Diamond JR, Poulter C, Dhanjil S, Nicolaides AN, Mahmood S, Richmond W, Mather H, Sharp P, Feher MD. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. Diabetes Care 1998;21:641-8. [PMID=9571357]

3.3 Individual trial summaries

Table 3.6: *SENDCAP, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=164 (81 vs. 83) **Follow-up duration:** 3.0 years **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial UK	Type 2 diabetic subjects without a history of clinical cardiovascular	**Studied treatment:** bezafibrate 400 mg daily **Control treatment:** placebo	

Reference

Elkeles RS, Diamond JR, Poulter C, Dhanjil S, Nicolaides AN, Mahmood S, Richmond W, Mather H, Sharp P, Feher MD. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. Diabetes Care 1998;21:641-8 [PMID=9571357]

4 Detailed results for clofibrate

4.1 Available trials

A total of 2 RCTs which randomized 824 patients were identified: all compared clofibrate with placebo.
The average study size was 412 patients (range 63 to 761). The first study was published in 1969, and the last study was published in 1991.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
data was reported in trials;
Following tables 4.1 (page 28), 4.2 (page 28), 4.4 (page 30), and 4.3 (page 29) summarized the main characteristics of the trials including in this systematic review of randomized trials of clofibrate.

Table 4.1: *Treatment description - fibrates - clofibrate*

Trial	Studied treatment	Control treatment
Clofibrate versus placebo		
Hanefeld (1991) [1]	clofibric acid 1.6 g/day	placebo
Harrold (1969) [2]	clofibrate	placebo

Table 4.2: *Descriptions of participants - fibrates - clofibrate*

Trial	Patients
Clofibrate versus placebo	
Hanefeld (1991) [1]	Newly diagnosed middle-aged (30- to 55-yr-old) patients with non-insulin-dependent diabetes mellitus
Harrold (1969) [2]	Diabetic retinopathy

Table 4.3: *Design and methodological quality of trials - fibrates - clofibrate*

Trial	Design	Duration	Centre	Primary end-point
Clofibrate versus placebo				
Hanefeld, 1991 [1] n=761	Parallel groups double-blind confirmatory trial at low risk of bias	5 years	Germany	NA
Harrold, 1969 [2] n=63	Parallel groups double-blind confirmatory trial at low risk of bias	1 years		

Table 4.4: *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				
Hanefeld, 1991 [1]	NA			
Harrold, 1969 [2]				

4.2 Meta-analysis results

The results are detailed in table 4.5 (page 31). This table is followed by the Forest's plot corresponding to each endpoint.

Clofibrate versus placebo

No data were presented in the 2 trials identified

Table 4.5: *Results details - fibrates - clofibrate*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
clofibrate 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] Hanefeld M, Fischer S, Schmechel H, Rothe G, Schulze J, Dude H, Schwanebeck U, Julius U. Diabetes Intervention Study. Multi-intervention trial in newly diagnosed NIDDM. Diabetes Care 1991;14:308-17. [PMID=2060433]

[2] Harrold BP, Marmion VJ, Gough KR. A double-blind controlled trial of clofibrate in the treatment of diabetic retinopathy. Diabetes 1969;18:285-91. [PMID=4894161]

4.3 Individual trial summaries

Table 4.6: *Hanefeld, 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=761 (379 vs. 382) **Follow-up duration:** 5 years **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias Germany	Newly diagnosed middle-aged (30- to 55-yr-old) patients with non-insulin-dependent diabetes mellitus	**Studied treatment:** clofibric acid 1.6 g/day **Control treatment:** placebo	

Reference

Hanefeld M, Fischer S, Schmechel H, Rothe G, Schulze J, Dude H, Schwanebeck U, Julius U. Diabetes Intervention Study. Multi-intervention trial in newly diagnosed NIDDM. Diabetes Care 1991;14:308-17 [PMID=2060433]

Table 4.7: *Harrold, 1969 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=63 (30 vs. 33) **Follow-up duration:** 1 years **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias	Diabetic retinopathy	**Studied treatment:** clofibrate **Control treatment:** placebo	

Reference

Harrold BP, Marmion VJ, Gough KR. A double-blind controlled trial of clofibrate in the treatment of diabetic retinopathy. Diabetes 1969;18:285-91 [PMID=4894161]

5 Detailed results for etofibrate

5.1 Available trials

Only one trial which randomized 0 patients was identified: it compared etofibrate with placebo.
This trial included NaN patients and was published in 2009.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 5.1 (page 35), 5.2 (page 35), 5.4 (page 36), and 5.3 (page 35) summarized the main characteristics of the trial including in this systematic review of randomized trials of etofibrate.

Table 5.1: *Treatment description - fibrates - etofibrate*

Trial	Studied treatment	Control treatment
Etofibrate versus placebo		
Emmerich (2009) [1]	etofibrate 1g/j	placebo

Table 5.2: *Descriptions of participants - fibrates - etofibrate*

Trial	Patients
Etofibrate versus placebo	
Emmerich (2009) [1]	Patients with type 2 diabetes mellitus and concomitant diabetic retinopathy

Table 5.3: *Design and methodological quality of trials - fibrates - etofibrate*

Trial	Design	Duration	Centre	Primary endpoint
Etofibrate versus placebo				
Emmerich, 2009 [1] n=NaN	Parallel groups double-blind exploratory trial	12 months	Germany	not defined

Table 5.4: *Trial characteristics - fibrates - etofibrate*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Etofibrate versus placebo				
Emmerich, 2009 [1]				

5.2 Meta-analysis results

The results are detailed in table 5.5 (page 37). This table is followed by the Forest's plot corresponding to each endpoint.

Etofibrate versus placebo

No data were presented in the 1 trial identified

Table 5.5: *Results details - fibrates - etofibrate*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
etofibrate 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] Emmerich KH, Poritis N, Stelmane I, Klindzane M, Erbler H, Goldsteine J, Görtelmeyer R. [Efficacy and safety of etofibrate in patients with non-proliferative diabetic retinopathy]. Klin Monbl Augenheilkd 2009;226:561-7. [PMID=19644802]

5.3 Individual trial summaries

Table 5.6: *Emmerich, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** 12 months **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial Germany	Patients with type 2 diabetes mellitus and concomitant diabetic retinopathy	**Studied treatment:** etofibrate 1g/j **Control treatment:** placebo	

Reference

Emmerich KH, Poritis N, Stelmane I, Klindzane M, Erbler H, Goldsteine J, Görtelmeyer R. [Efficacy and safety of etofibrate in patients with non-proliferative diabetic retinopathy]. Klin Monbl Augenheilkd 2009;226:561-7 [PMID=19644802]

6 Detailed results for fenofibrate

6.1 Available trials

A total of 4 RCTs which randomized 17324 patients were identified: 2 trials compared fenofibrate with placebo and 2 trials compared fenofibrate with placebo (on top simvastatine).
The average study size was 4331 patients (range 418 to 9795). The first study was published in 2001, and the last study was published in 2010.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
data was reported in trials;
Following tables 6.1 (page 40), 6.2 (page 40), 6.4 (page 43), and 6.3 (page 41) summarized the main characteristics of the trials including in this systematic review of randomized trials of fenofibrate.

Table 6.1: *Treatment description - fibrates - fenofibrate*

Trial	Studied treatment	Control treatment
Fenofibrate versus placebo		
FIELD (2005) [1]	fenofibrate 200 mg daily	placebo
DAIS (2001) [2]	fenofibrate 200 mg/day	placebo
Fenofibrate versus placebo (on top simvastatine)		
ACCORD lipid (2010) [3, 4, 5] [a]	fenofibrate on top simvastatin 160 mg per day adjusted according to the estimated glomerular filtration rate	placebo (on top simvastatine)
ACCORD lipid (subgroup Eye study) (2010) [6] [b]	fenofibrate on top simvastatin 160 mg per day adjusted according to the estimated glomerular filtration rate	placebo (on top simvastatine)

a) participants were also randomized to either intensive or standard glycemic control and to either intensive or standard blood-pressure control. Glycemic-control ACCORD study was stopped early, in February 2008, because of higher mortality in the intensive-glycemic-control group. All patients were then transferred to a standard glycemia-control regimen b) participants were also randomized to either intensive or standard glycemic control and to either intensive or standard blood-pressure control. Glycemic-control ACCORD study was stopped early, in February 2008, because of higher mortality in the intensive-glycemic-control group. All patients were then transferred to a standard glycemia-control regimen

Table 6.2: *Descriptions of participants - fibrates - fenofibrate*

Trial	Patients
Fenofibrate versus placebo	
FIELD (2005) [1]	Aged 50-75 years, with type 2 diabetes mellitus, and not taking statin therapy at study entry

continued...

Trial	Patients	
DAIS (2001) [2]	Men and women with type 2 diabetes and coronary atherosclerosis	
Fenofibrate versus placebo (on top simvastatine)		
ACCORD lipid (2010) [3, 4, 5]	High-risk patients with type 2 diabetes **Inclusion criteria:** type 2 diabetes; glycated hemoglobin level of 7.5% or more; LDL cholesterol level of 60 to 180 mg per deciliter; HDL cholesterol level below 55 mg per deciliter for women and blacks or below 50 mg per deciliter for all other groups, and a triglyceride level below 750 mg per deciliter if they were not receiving lipid therapy or below 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy; age between 40 to 79 y in case of evidence of clinical cardiovascular disease;	**Exclusion criteria:**
ACCORD lipid (subgroup Eye study) (2010) [6]	High-risk patients with type 2 diabetes **Inclusion criteria:** type 2 diabetes; glycated hemoglobin level of 7.5% or more; LDL cholesterol level of 60 to 180 mg per deciliter; HDL cholesterol level below 55 mg per deciliter for women and blacks or below 50 mg per deciliter for all other groups, and a triglyceride level below 750 mg per deciliter if they were not receiving lipid therapy or below 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy; age between 40 to 79 y in case of evidence of clinical cardiovascular disease;	**Exclusion criteria:** proliferative diabeticretinopathy that had been treated with laserphotocoagulation or vitrectomy

Table 6.3: *Design and methodological quality of trials - fibrates - fenofibrate*

Trial	Design	Duration	Centre	Primary endpoint
Fenofibrate versus placebo				
FIELD, 2005 [1] n=9795	confirmatory trial at low risk of bias	5y		coronary events
DAIS, 2001 [2] n=418	Parallel groups double-blind exploratory trial	3.3 years	Canada, Finland, France, Sweden	QCA (minimum lumen diameter)
Fenofibrate versus placebo (on top simvastatine)				
ACCORD lipid, 2010 [3, 4, 5] n=5518	Factorial plan double-blind confirmatory trial at low risk of bias	4.7y inclusion period: jan 2001 - oct 2005	United States and Canada 77 centres	fatal cardiovascular events, nonfatal MI, or nonfatal stroke

continued...

Trial	Design	Duration	Centre	Primary endpoint
ACCORD lipid (subgroup Eye study), 2010 [6] n=1593	Factorial plan double-blind exploratory trial	4.7y inclusion period: jan 2001 - oct 2005	United States and Canada 77 centres	fatal cardiovascular events, nonfatal MI, or nonfatal stroke

Table 6.4: *Trial characteristics - fibrates - fenofibrate*

Trial
Fenofibrate versus placebo
FIELD, 2005 [1]
DAIS, 2001 [2]
-0.2
Fenofibrate versus placebo (on top simvastatine)
ACCORD lipid, 2010 [3, 4, 5]
ACCORD lipid (subgroup Eye study), 2010 [6]

6.2 Meta-analysis results

The results are detailed in table 6.5 (page 44). This table is followed by the Forest's plot corresponding to each endpoint.

Fenofibrate versus placebo

No data were presented in the 2 trials identified

Fenofibrate versus placebo (on top simvastatine)

No data were presented in the 2 trials identified

Table 6.5: *Results details - fibrates - fenofibrate*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fenofibrate versus placebo						
No data were presented in the trial identified						
fenofibrate versus placebo (on top simvastatine)						
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] Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849-61. [PMID=16310551]

[2] . Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet 2001;357:905-10. [PMID=11289345]

[3] . Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. N Engl J Med 2010 Mar 14;:. [PMID=20228404]

[4] . Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. N Engl J Med 2010 Jun 29;:. [PMID=20587587]

[5] Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010 Jun 29;:. [PMID=20594588]

[6] . Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. N Engl J Med 2010 Jun 29;:. [PMID=20587587]

6.3 Individual trial summaries

Table 6.6: *FIELD, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=9795 (4895 vs. 4900) **Follow-up duration:** 5y **Study design:** Randomized controlled trial Confirmatory trial at low risk of bias	Aged 50-75 years, with type 2 diabetes mellitus, and not taking statin therapy at study entry	**Studied treatment:** fenofibrate 200 mg daily **Control treatment:** placebo	

Reference

Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849-61 [PMID=16310551]

Table 6.7: *DAIS, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=418 (207 vs. 211) **Follow-up duration:** 3.3 years **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial Canada, Finland, France, Sweden	Men and women with type 2 diabetes and coronary atherosclerosis	**Studied treatment:** fenofibrate 200 mg/day **Control treatment:** placebo	

Reference

. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet 2001;357:905-10 [PMID=11289345]

Table 6.8: *ACCORD lipid, 2010 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=5518 (2765 vs. 2753) **Follow-up duration:** 4.7y **Study design:** Randomized controlled trial Factorial plan Double-blind Confirmatory trial at low risk of bias United States and Canada, 77 centres **Inclusion period:** jan 2001 - oct 2005	High-risk patients with type 2 diabetes **Inclusion criteria:** type 2 diabetes; glycated hemoglobin level of 7.5% or more; LDL cholesterol level of 60 to 180 mg per deciliter; HDL cholesterol level below 55 mg per deciliter for women and blacks or below 50 mg per deciliter for all other groups, and a triglyceride level below 750 mg per deciliter if they were not receiving lipid therapy or below 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy; age between 40 to 79 y in case of evidence of clinical cardiovascular disease;	**Studied treatment:** fenofibrate on top simvastatin 160 mg per day adjusted according to the estimated glomerular filtration rate **Control treatment:** placebo (on top simvastatine) **note:** participants were also randomized to either intensive or standard glycemic control and to either intensive or standard blood-pressure control. Glycemic-control ACCORD study was stopped early, in February 2008, because of higher mortality in the intensive-glycemic-control group. All patients were then transferred to a standard glycemia-control regimen	

References

. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. N Engl J Med 2010 Mar 14;: [PMID=20228404]

. Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. N Engl J Med 2010 Jun 29;: [PMID=20587587]

Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010 Jun 29;: [PMID=20594588]

Table 6.9: *ACCORD lipid (subgroup Eye study), 2010 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1593 (806 vs. 787) **Follow-up duration:** 4.7y **Study design:** Randomized controlled trial Factorial plan Double-blind Exploratory trial United States and Canada, 77 centres **Inclusion period:** jan 2001 - oct 2005	High-risk patients with type 2 diabetes **Inclusion criteria:** type 2 diabetes; glycated hemoglobin level of 7.5% or more; LDL cholesterol level of 60 to 180 mg per deciliter; HDL cholesterol level below 55 mg per deciliter for women and blacks or below 50 mg per deciliter for all other groups, and a triglyceride level below 750 mg per deciliter if they were not receiving lipid therapy or below 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy; age between 40 to 79 y in case of evidence of clinical cardiovascular disease; **Exclusion criteria:** proliferative diabeticretinopathy that had been treated with laserphotocoagulation or vitrectomy	**Studied treatment:** fenofibrate on top simvastatin 160 mg per day adjusted according to the estimated glomerular filtration rate **Control treatment:** placebo (on top simvastatine) **note:** participants were also randomized to either intensive or standard glycemic control and to either intensive or standard blood-pressure control. Glycemic-control ACCORD study was stopped early, in February 2008, because of higher mortality in the intensive-glycemic-control group. All patients were then transferred to a standard glycemia-control regimen	

Reference

. Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. N Engl J Med 2010 Jun 29;: [PMID=20587587]

7 Detailed results for gemfibrozil

7.1 Available trials

A total of 2 RCTs which randomized 762 patients were identified: all compared gemfibrozil with placebo.
The average study size was 381 patients (range 135 to 627). The first study was published in 1987, and the last study was published in 1999.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
data was reported in trials;
Following tables 7.1 (page 51), 7.2 (page 51), 7.4 (page 53), and 7.3 (page 52) summarized the main characteristics of the trials including in this systematic review of randomized trials of gemfibrozil.

Table 7.1: *Treatment description - fibrates - gemfibrozil*

Trial	Studied treatment	Control treatment
Gemfibrozil versus placebo		
HHS (sub group) (1987) [1]	gemfibrozil 600mg twice daily	placebo
VA-HIT (sub group) (1999) [2]	gemfibrozil 1200 mg per day	placebo

Table 7.2: *Descriptions of participants - fibrates - gemfibrozil*

Trial	Patients
Gemfibrozil versus placebo	
HHS (sub group) (1987) [1]	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
VA-HIT (sub group) (1999) [2]	Men with coronary heart disease, an HDL cholesterollevel of 40 mg per deciliter (1.0 mmol per liter)or less, and an LDL cholesterol level of 140 mgper deciliter (3.6 mmol per liter) or less.

Table 7.3: *Design and methodological quality of trials - fibrates - gemfibrozil*

Trial	Design	Duration	Centre	Primary end-point
Gemfibrozil versus placebo				
HHS (sub group), 1987 [1] n=135	double blind exploratory trial			
VA-HIT (sub group), 1999 [2] n=627	Parallel groups double blind exploratory trial	5.1 y		

Table 7.4: *Trial characteristics - fibrates - gemfibrozil*

Trial
Gemfibrozil versus placebo
HHS (sub group), 1987 [1]
VA-HIT (sub group), 1999 [2]

7.2 Meta-analysis results

The results are detailed in table 7.5 (page 54). This table is followed by the Forest's plot corresponding to each endpoint.

Gemfibrozil versus placebo

No data were presented in the 2 trials identified

Table 7.5: *Results details - fibrates - gemfibrozil*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
gemfibrozil 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] Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. . N Engl J Med 1987;317:1237-45. [PMID=3313041]

[2] Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. . N Engl J Med 1999;341:410-8. [PMID=10438259]

7.3 Individual trial summaries

Table 7.6: *HHS (sub group), 1987 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (135 vs. 0) **Follow-up duration:** **Study design:** Randomized controlled trial Double blind Exploratory trial	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	**Studied treatment:** gemfibrozil 600mg twice daily **Control treatment:** placebo	

Reference

Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. . N Engl J Med 1987;317:1237-45 [PMID=3313041]

Table 7.7: *VA-HIT (sub group), 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=627 (309 vs. 318) **Follow-up duration:** 5.1 y **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Men with coronary heart disease, an HDL cholesterollevel of 40 mg per deciliter (1.0 mmol per liter)or less, and an LDL cholesterol level of 140 mgper deciliter (3.6 mmol per liter) or less.	**Studied treatment:** gemfibrozil 1200 mg per day **Control treatment:** placebo	

Reference

Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. . N Engl J Med 1999;341:410-8 [PMID=10438259]

8 Global meta-analysis: all fibrates

8.1 Global meta-analysis: all fibrates versus placebo

Table 8.1: *All fibratesversus 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

8.2 Global meta-analysis: all fibrates versus placebo (on top simvastatine)

Table 8.2: *All fibratesversus placebo (on top simvastatine)*

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

9 Ongoing studies of fibrates

No ongoing trial was identified.

10 Excluded studies for fibrates

No trial was excluded.

References

Part II

Statins

11 Overview of statins

11.1 Included trials

A total of 18 randomized comparisons which enrolled 24287 patients were identified. In all, 1 randomized comparison concerned aggressive cholesterol-lowering , 4 atorvastatin , one atorvastatin high dose , two fluvastatin , one lovastatin , 6 pravastatin , one pravastatin high dose and two simvastatin.
The detailed descriptions of trials and meta-analysis results is given in section 12 (page 77) for aggressive cholesterol-lowering, in section 13 (page 83) for atorvastatin, in section 14 (page 98) for atorvastatin high dose, in section 15 (page 104) for fluvastatin, in section 16 (page 111) for lovastatin, in section 17 (page 116) for pravastatin, in section 18 (page 130) for pravastatin high dose and in section 19 (page 136) for simvastatin.

The average study size was 1428 patients (range 70 to 5963). The first study was published in 1996, and the last study was published in 2006.
A total of 14 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 11.1 (page 63) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

11.2 Summary of meta-analysis results

The meta-analysis of the available trials about statins provide the results listed in tables 11.2 to 11.9 (page 67) and in the following graphs.

11.2.1 Aggressive cholesterol-lowering

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

11.2.2 Atorvastatin

Atorvastatin was superior to **placebo** in terms of cardiovascular events (RR=0.70, 95% CI 0.55 to 0.88, p=0.0021, 2 trials), stroke (fatal and non fatal) (RR=0.60, 95% CI 0.42 to 0.86, p=0.0050, 2 trials), coronary event (RR=0.72, 95% CI 0.55 to 0.94, p=0.0172, 2 trials), MACE (RR=0.65, 95% CI 0.49 to 0.84, p=0.0000, 1 trial)and non fatal MI (RR=0.60, 95% CI 0.37 to 0.99, p=0.0435, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.65, 95% CI 0.36 to 1.15, p=0.1375, 1 trial), coronary death (RR=0.74, 95% CI 0.40 to 1.36, p=0.3330, 1 trial)and all cause death (RR=0.74, 95% CI 0.53 to 1.02, p=0.0619, 1 trial).

11.2.3 Atorvastatin high dose

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

11.2.4 Fluvastatin

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

11.2.5 Lovastatin

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

11.2.6 Pravastatin

No significant difference was found between **pravastatin** and **placebo** in terms of cardiovascular events (RR=0.80, 95% CI 0.59 to 1.09, p=0.1522, 1 trial), stroke (fatal and non fatal) (RR=0.85, 95% CI 0.48 to 1.52, p=0.5920, 1 trial)and coronary event (RR=0.85, 95% CI 0.69 to 1.05, p=0.1402, 2 trials).

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

11.2.7 Pravastatin high dose

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

11.2.8 Simvastatin

Simvastatin was superior to **placebo** in terms of cardiovascular events (RR=0.81, 95% CI 0.73 to 0.89, p=0.0000, 1 trial)and stroke (fatal and non fatal) (RR=0.77, 95% CI 0.63 to 0.95, p=0.0155, 1 trial). However, no significant difference was found on all cause death (RR=0.79, 95% CI 0.49 to 1.28, p=0.3359, 1 trial).

Table 11.1: *Main study characteristics - statins*

Trial	Patients	Treatments	Trial design and method
Aggressive cholesterol-lowering			
Aggressive cholesterol-lowering versus moderate cholesterol-lowering			
Post CABG (sub group), 1999 [1] n= 116	patients 1-11 years after CABG	aggressive cholesterol-lowering **versus** moderate cholesterol-lowering	double blind Primary endpoint: angiographic end points
Atorvastatin			
Atorvastatin versus placebo			
ASCOT (diabetics sub group), 2003 [1] n = 1258 vs. 1274	hypertensive patients with nohistory of coronary heart disease (CHD) but at least three cardiovascular risk factors	10 mg atorvastatin **versus** placebo	
Deutsche Diabetes Dialyse Studie (4D), 2005 [2] n = 619 vs. 636	patients with type 2 diabetes mellitus on maintenance hemodialysis	atorvastatin 20mg daily **versus** matching placebo	double blind parallel groups Primary endpoint: cardiac death, stroke, MI
ASPEN, 2006 [3] n = 1211 vs. 1199	patients s with type 2 diabetes and LDL cholesterol levels below contemporaryguideline targets	atorvastatin 10mg daily **versus** placebo	double blind parallel groups Primary endpoint: CV death, mI, stroke, re-canalization, CABG, worsening
CARDS, 2004 [4] n = 1429 vs. 1412	patients with type 2 diabetes without high concentrations of LDL-cholesterol and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension.	atorvastatin 10mg/d **versus** placebo	double blind parallel groups Primary endpoint: ev coronariens aigus, revascularisation ou AVC 132 centres, UK, Irelande
Atorvastatin high dose			
Atorvastatin high dose versus atorvastatin			

continued...

Trial	Patients	Treatments	Trial design and method
TNT (sub group), 2006 [1] n = 748 vs. 753	patients with stable coronary heart disease	atorvastatin 80 mg daily **versus** atorvastatin 10 mg daily	double blind Primary endpoint: major cardiovascular event
Fluvastatin			
Fluvastatin versus placebo			
LIPS (sub group), 2002 [1] n = 120 vs. 82	patients (aged 18-80 years) with stable or unstable angina or silent ischemia following successful completion of their first PCI who had baseline total cholesterol levels between 135 and 270 mg/dL	fluvastatin **versus** placebo	double blind parallel groups Primary endpoint: MACE
ALERT (sub group), 2003 [2] n = 197 vs. 199	renal transplant recipients withtotal cholesterol 4090 mmol/L	fluvastatin **versus** placebo	double blind parallel groups
Lovastatin			
Lovastatin versus placebo			
AFCAPS/TexCAPS (sub group), 1998 [1] n = 84 vs. 71	men and women without clinically evident atherosclerotic cardiovasculardisease with average total cholesterol (TC) and LDL-C levels and below-average high-densitylipoprotein cholesterol (HDL-C) levels	lovastatin **versus** placebo	double blind parallel groups
Pravastatin			
Pravastatin versus placebo			
PROSPER (sub group), 2002 [1] n = 320 vs. 303	mena and women aged7082 years with a history of, or risk factors for, vasculardisease	pravastatin 40mg daily **versus** placebo	double blind parallel groups Primary endpoint: CV events

continued...

Trial	Patients	Treatments	Trial design and method
LIPID (sub group), 1998 [2] n = 396 vs. 386	patients with a history of myocardial infarction or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg per deciliter	pravastatin 40 mg daily **versus** placebo	double blind parallel groups Primary endpoint: mortality from coronary heart disease 87 centres, Australia, New Zealand
CARE (sub group), 1998 [3] n = 282 vs. 304	men and postmenopausal women between 21 to 75 years of age, with MI between 3 and 20 months before randomization and plasma total cholesterol values <240mg/dL, LDL-C levelsbetween 115 and 174mg/dL, and triglycerides <350mg/dL	pravastatin **versus** placebo	parallel groups
WOSCOPS (sub group), 1996 [4, 5] n= 70	men aged 45-64 years with no history of myocardial infarction and plasma total cholesterol concentrations of 6.5-8.0 mmol/L at initial screening	pravastatin 40 mg daily **versus** placebo	double blind
Pravastatin versus usual care			
GISSI P (sub group), 2000 [6] n = NA vs. NA	recent acute myocardial infarction patients (<or = 6 months) with total blood cholesterol >or = 200 mg/dl	pravastatin 20 mg daily **versus** usual care	open
ALLHAT-LLT (sub group), 2002 [7] n = 1855 vs. 1783	ambulatory persons aged 55 years or older, with lowdensitylipoprotein cholesterol (LDL-C) of 120 to 189 mg/dL (100 to 129 mg/dL ifknown CHD) and triglycerides lower than 350 mg/dL	pravastatin **versus** usual care	open parallel groups
Pravastatin high dose			
Pravastatin high dose versus pravastatin			
PROVE IT TIMI 22 (diabetic sub group), 2006 [1] n = 373 vs. 361	patients hospitalized for an acute coronary syndrome within the preceding 10 days	pravastatin 80mg daily **versus** pravastatin 40mg daily	double blind parallel groups Primary endpoint: cv events

continued...

Trial	Patients	Treatments	Trial design and method
Simvastatin			
Simvastatin versus placebo			
HPS (sub group), 2002 [1] n = 2978 vs. 2985	men and women diabetes aged about 4080 years with non-fastingblood total cholesterol concentrations of at least35 mmol/L (135 mg/dL)	simvastatin 40mg daily **versus** placebo	double blind parallel groups
4S (sub group), 1999 [2] n = 251 vs. 232	diabetic menand women aged 35 to 70 years with previous MI or active,stable angina pectoris and with serum total cholesterollevel between 5.5 to 8.0 mmol/L and serumtriglyceride level <=2.5 mmol/L	simvastatin **versus** placebo	double blind parallel groups 94 centres, Denmark, Finland, Iceland, Norway, and Sweden

Table 11.2: *Summary of all results for aggressive cholesterol-lowering*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
aggressive cholesterol-lowering versus moderate cholesterol-lowering						
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 11.3: *Summary of all results for atorvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
atorvastatin versus placebo						
cardiovascular events	RR=0.70	0.55;0.88	0.0021	0.3098 (0.03)	2	5373
cardiovascular death	RR=0.65	0.36;1.15	0.1375	1.0000 (0.00)	1	2841
stroke (fatal and non fatal)	RR=0.60	0.42;0.86	0.0050	0.5336 (0.00)	2	5373
coronary event	RR=0.72	0.55;0.94	0.0172	0.3783 (0.00)	2	5373
coronary death	RR=0.74	0.40;1.36	0.3330	1.0000 (0.00)	1	2841
MACE	RR=0.65	0.49;0.84	0.0000	1.0000 (0.00)	1	2841
death from cancer	RR=0.66	0.38;1.15	0.1447	1.0000 (0.00)	1	2841
rhabdomyolysis	RR=0.99	0.02;49.77	0.9952	1.0000 (0.00)	1	2841
myopathy	RR=0.99	0.06;15.78	0.9932	1.0000 (0.00)	1	2841
non fatal MI	RR=0.60	0.37;0.99	0.0435	1.0000 (0.00)	1	2841
all cause death	RR=0.74	0.53;1.02	0.0619	1.0000 (0.00)	1	2841
adverse events	RR=0.94	0.50;1.75	0.8424	1.0000 (0.00)	1	2841

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 11.4: *Summary of all results for atorvastatin high dose*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
atorvastatin high dose 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 11.5: *Summary of all results for fluvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
fluvastatin 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 11.6: *Summary of all results for lovastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
lovastatin 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 11.7: *Summary of all results for pravastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
pravastatin versus placebo						
cardiovascular events	RR=0.80	0.59;1.09	0.1522	1.0000 (0.00)	1	623
stroke (fatal and non fatal)	RR=0.85	0.48;1.52	0.5920	1.0000 (0.00)	1	586
coronary event	RR=0.85	0.69;1.05	0.1402	0.8840 (0.00)	2	1368
pravastatin versus usual care						
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 11.8: *Summary of all results for pravastatin high dose*

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

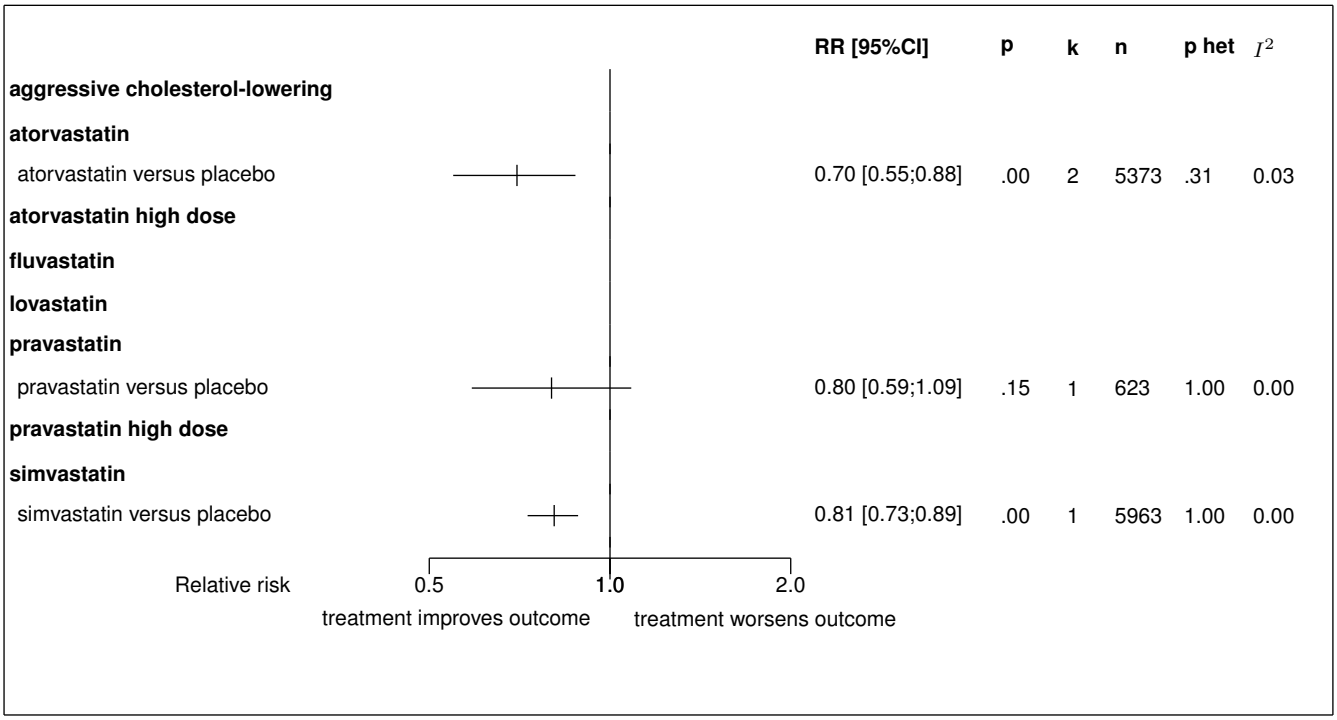
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 11.9: *Summary of all results for simvastatin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
simvastatin versus placebo						
cardiovascular events	RR=0.81	0.73;0.89	0.0000	1.0000 (0.00)	1	5963
stroke (fatal and non fatal)	RR=0.77	0.63;0.95	0.0155	1.0000 (0.00)	1	5963
all cause death	RR=0.79	0.49;1.28	0.3359	1.0000 (0.00)	1	483

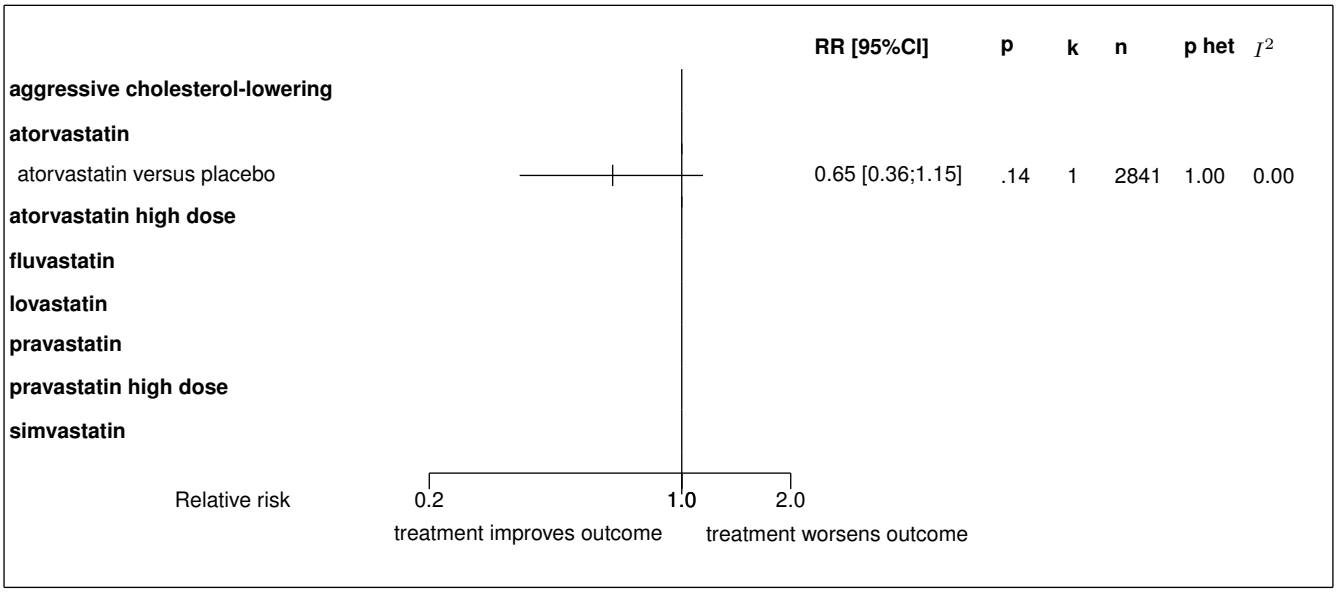
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



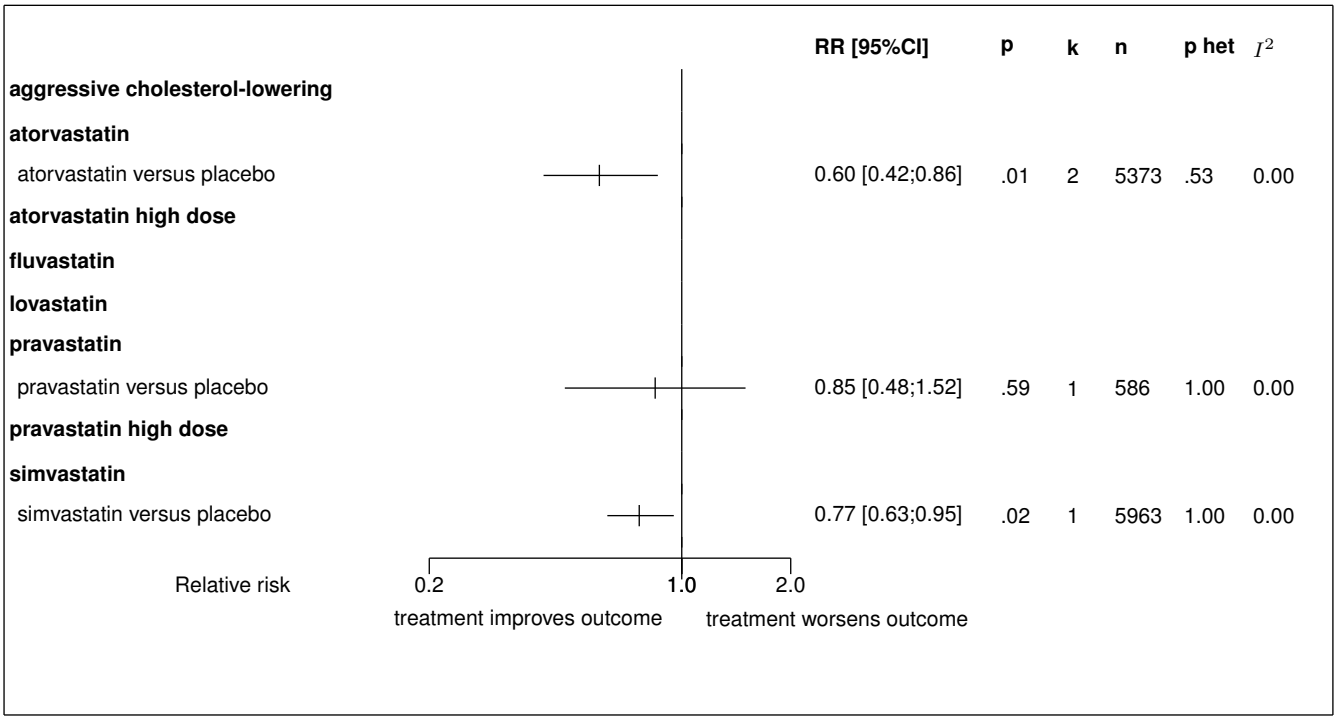
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 11.2: *Forest's plot for cardiovascular death*



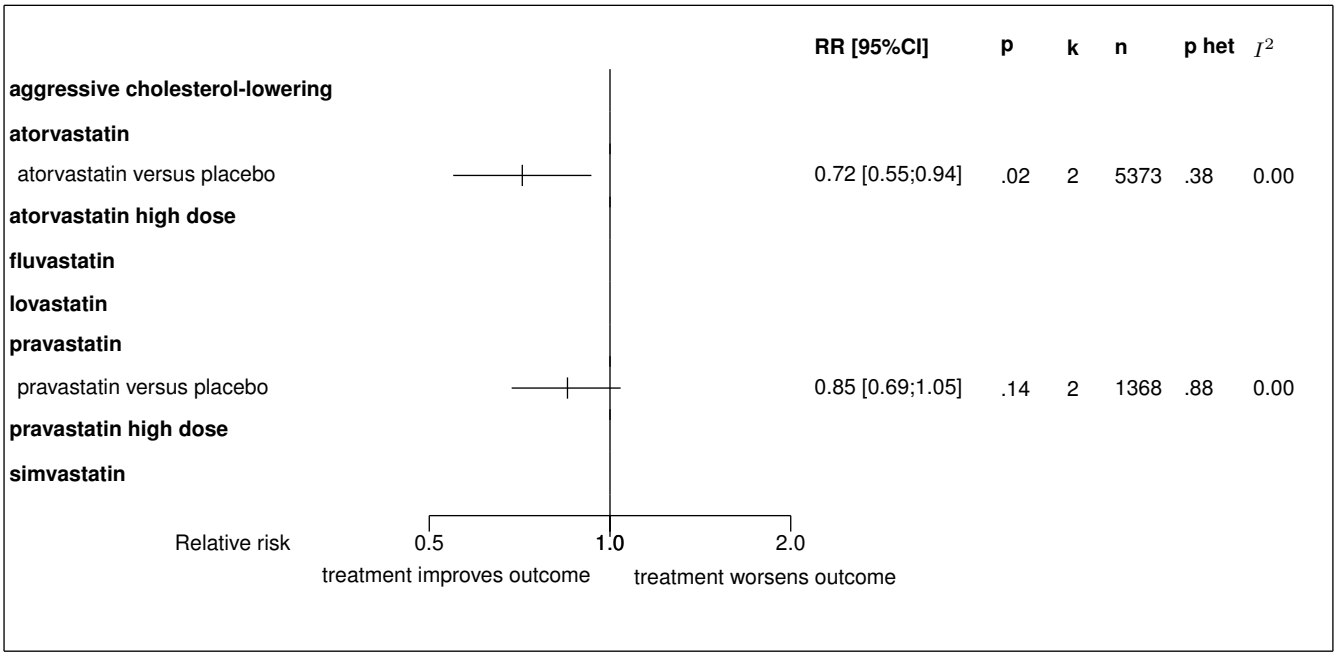
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 11.3: *Forest's plot for stroke (fatal and non fatal)*



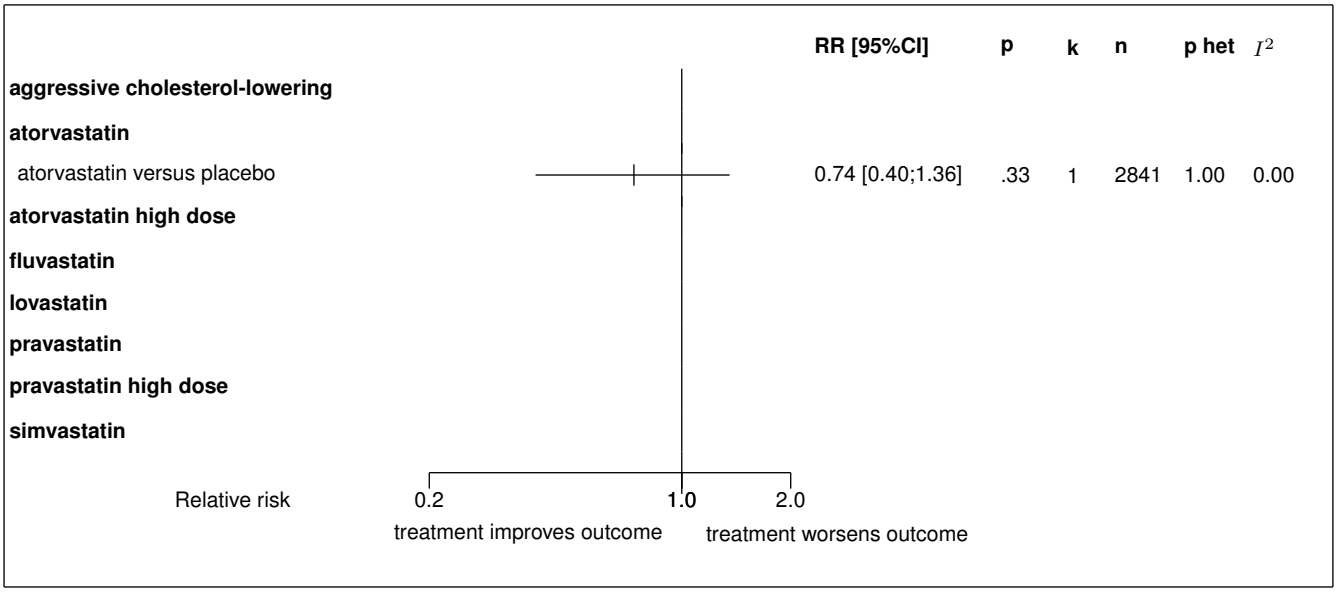
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



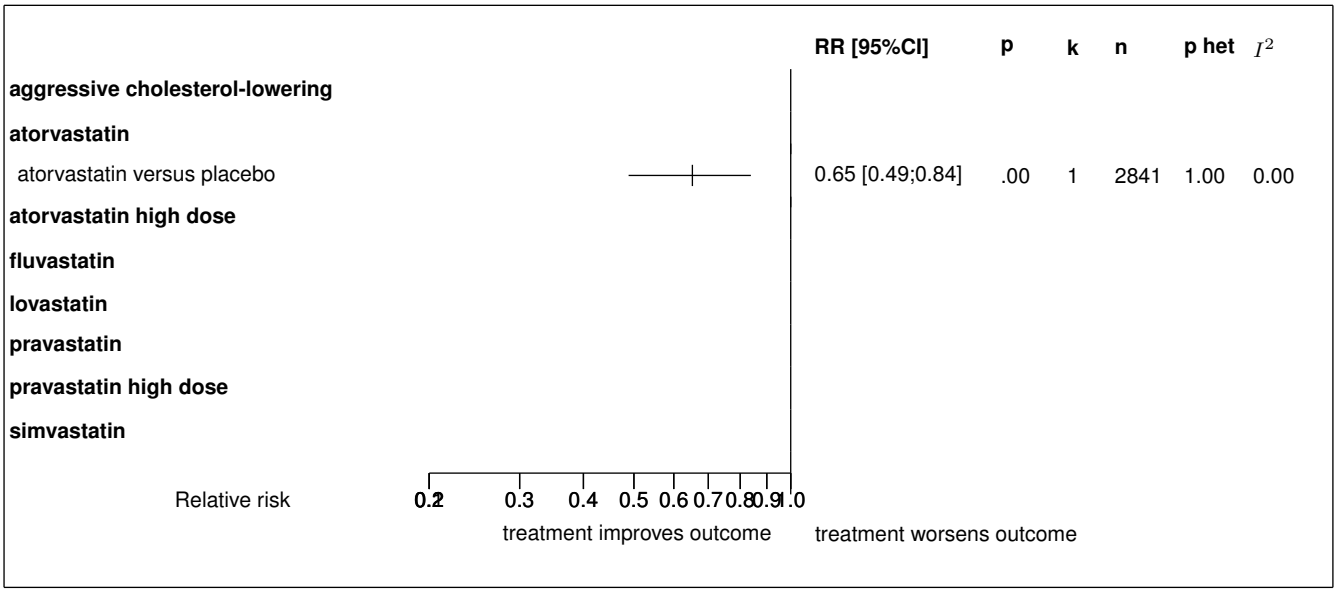
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



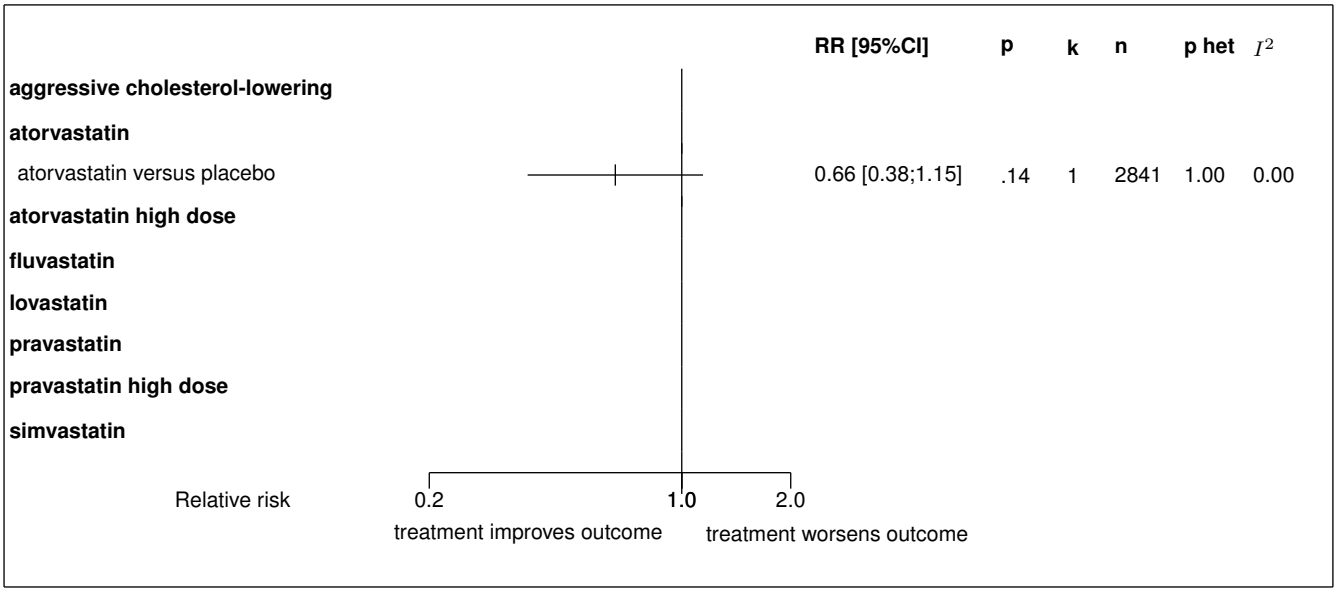
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 11.6: *Forest's plot for MACE*



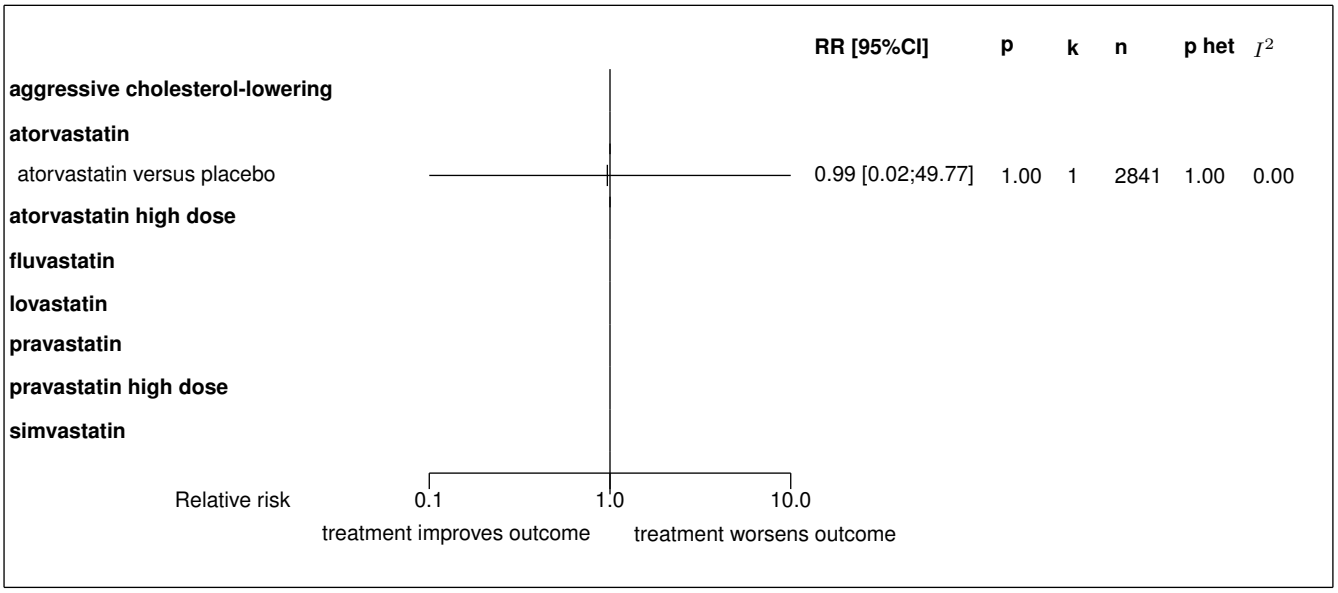
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 11.7: *Forest's plot for death from cancer*



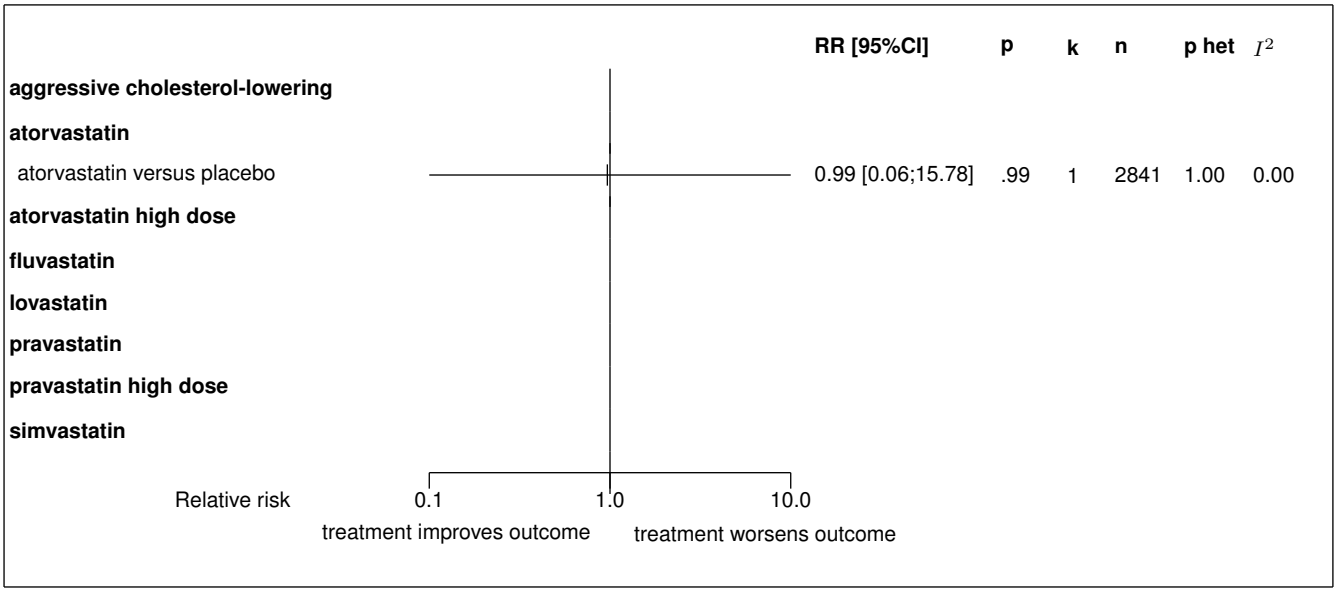
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 11.8: *Forest's plot for rhabdomyolysis*



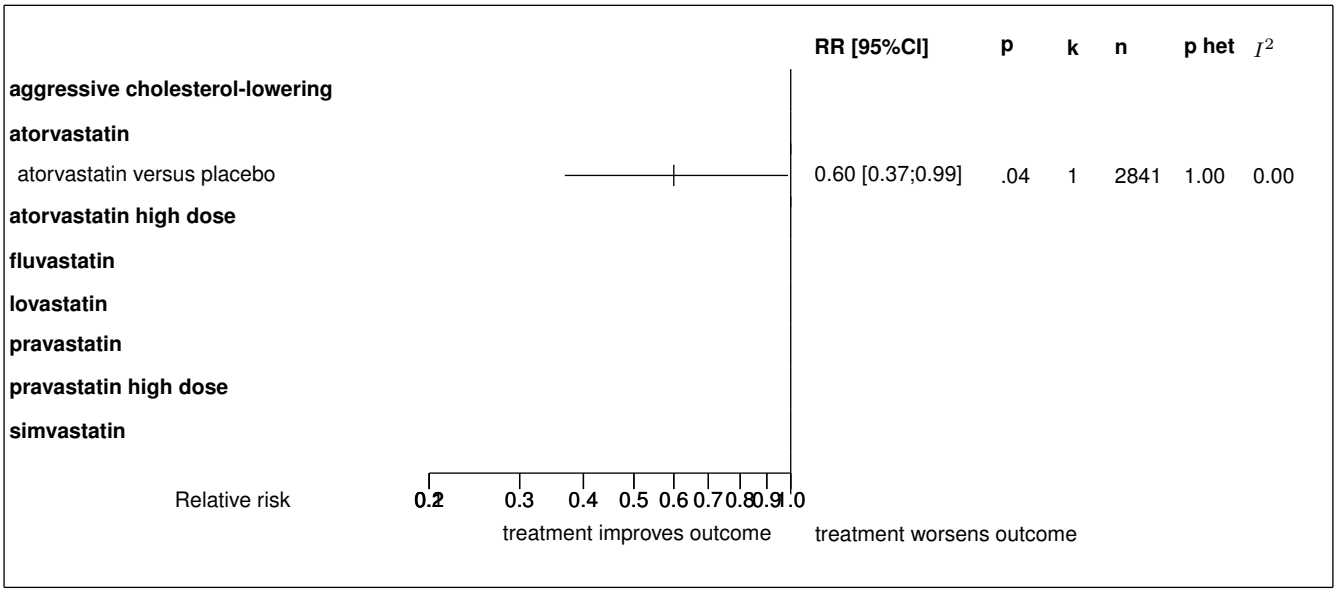
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 11.9: *Forest's plot for myopathy*



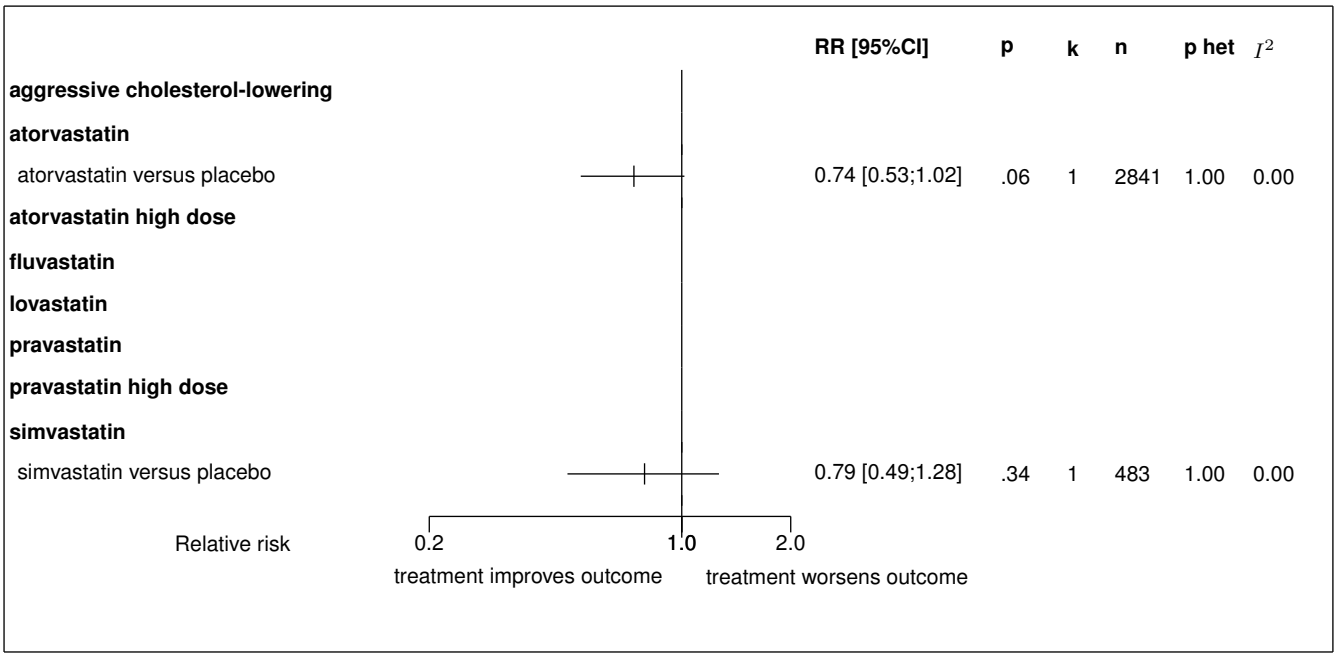
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



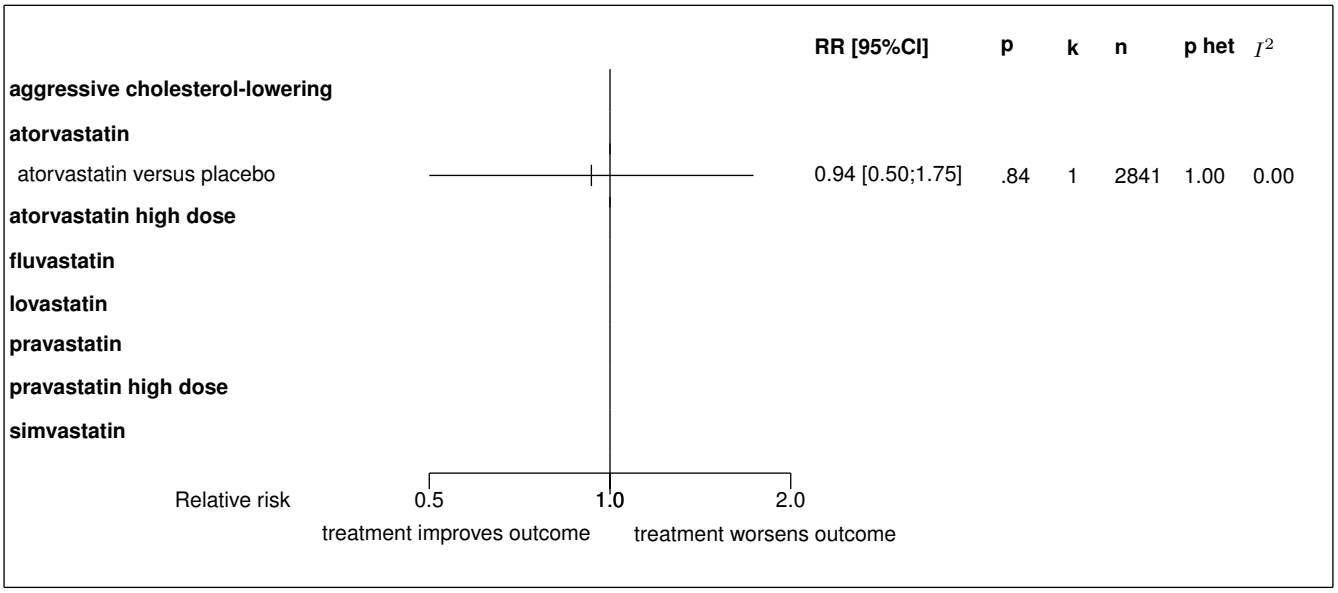
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 11.11: *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

Figure 11.12: *Forest's plot for adverse events*



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

12 Detailed results for aggressive cholesterol-lowering

12.1 Available trials

Only one trial which randomized 116 patients was identified: it compared aggressive cholesterol-lowering with moderate cholesterol-lowering.
This trial included 116 patients and was published in 1999.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 12.1 (page 77), 12.2 (page 77), 12.4 (page 79), and 12.3 (page 77) summarized the main characteristics of the trial including in this systematic review of randomized trials of aggressive cholesterol-lowering.

Table 12.1: *Treatment description - statins - aggressive cholesterol-lowering*

Trial	Studied treatment	Control treatment
Aggressive cholesterol-lowering versus moderate cholesterol-lowering		
Post CABG (sub group) (1999) [1]	aggressive cholesterol-lowering	moderate cholesterol-lowering

Table 12.2: *Descriptions of participants - statins - aggressive cholesterol-lowering*

Trial	Patients
Aggressive cholesterol-lowering versus moderate cholesterol-lowering	
Post CABG (sub group) (1999) [1]	Patients 1-11 years after CABG

Table 12.3: *Design and methodological quality of trials - statins - aggressive cholesterol-lowering*

Trial	Design	Duration	Centre	Primary end-point
Aggressive cholesterol-lowering versus moderate cholesterol-lowering				

continued...

Trial	Design	Duration	Centre	Primary end-point
Post CABG (sub group), 1999 [1] n=116	double blind exploratory trial			angiographic end points

Table 12.4: *Trial characteristics - statins - aggressive cholesterol-lowering*

Trial
Aggressive cholesterol-lowering versus moderate cholesterol-lowering
Post CABG (sub group), 1999 [1]

12.2 Meta-analysis results

The results are detailed in table 12.5 (page 80). This table is followed by the Forest's plot corresponding to each endpoint.

Aggressive cholesterol-lowering versus moderate cholesterol-lowering

No data were presented in the 1 trial identified

Table 12.5: *Results details - statins - aggressive cholesterol-lowering*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
aggressive cholesterol-lowering versus moderate cholesterol-lowering						
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] Hoogwerf BJ, Waness A, Cressman M, Canner J, Campeau L, Domanski M, Geller N, Herd A, Hickey A, Hunninghake DB, Knatterud GL, White C. Effects of aggressive cholesterol lowering and low-dose anticoagulation on clinical and angiographic outcomes in patients with diabetes: the Post Coronary Artery Bypass Graft Trial. Diabetes 1999;48:1289-94. [PMID=10342818]

12.3 Individual trial summaries

Table 12.6: *Post CABG (sub group), 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (116 vs. 0) **Follow-up duration:** **Study design:** Randomized controlled trial Double blind Exploratory trial	Patients 1-11 years after CABG	**Studied treatment:** aggressive cholesterol-lowering **Control treatment:** moderate cholesterol-lowering	

Reference

Hoogwerf BJ, Waness A, Cressman M, Canner J, Campeau L, Domanski M, Geller N, Herd A, Hickey A, Hunninghake DB, Knatterud GL, White C. Effects of aggressive cholesterol lowering and low-dose anticoagulation on clinical and angiographic outcomes in patients with diabetes: the Post Coronary Artery Bypass Graft Trial. Diabetes 1999;48:1289-94 [PMID=10342818]

13 Detailed results for atorvastatin

13.1 Available trials

A total of 4 RCTs which randomized 9038 patients were identified: all compared atorvastatin with placebo.
The average study size was 2259 patients (range 1255 to 2841). The first study was published in 2003, and the last study was published in 2006.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Stroke (fatal and non fatal) data was reported in 2 trials; 2 trials reported data on cardiovascular events; 2 trials reported data on coronary event; 1 trials reported data on cardiovascular death; 1 trials reported data on non fatal MI; 1 trials reported data on MACE; 1 trials reported data on coronary death; 1 trials reported data on myopathy; 1 trials reported data on death from cancer; 1 trials reported data on rhabdomyolysis; 1 trials reported data on adverse events; and 1 trials reported data on all cause death.
Following tables 13.1 (page 83), 13.2 (page 83), 13.4 (page 86), and 13.3 (page 84) summarized the main characteristics of the trials including in this systematic review of randomized trials of atorvastatin.

Table 13.1: *Treatment description - statins - atorvastatin*

Trial	Studied treatment	Control treatment
Atorvastatin versus placebo		
ASCOT (diabetics sub group) (2003) [1]	10 mg atorvastatin	placebo
Deutsche Diabetes Dialyse Studie (4D) (2005) [2]	atorvastatin 20mg daily	matching placebo
ASPEN (2006) [3]	atorvastatin 10mg daily	placebo
CARDS (2004) [4]	atorvastatin 10mg/d	placebo

Table 13.2: *Descriptions of participants - statins - atorvastatin*

Trial	Patients
Atorvastatin versus placebo	

continued...

Trial	Patients
ASCOT (diabetics sub group) (2003) [1]	Hypertensive patients with nohistory of coronary heart disease (CHD) but at least three cardiovascular risk factors
Deutsche Diabetes Dialyse Studie (4D) (2005) [2]	Patients with type 2 diabetes mellitus on maintenance hemodialysis
ASPEN (2006) [3]	Patients s with type 2 diabetes and LDL cholesterol levels below contemporaryguideline targets
CARDS (2004) [4]	Patients with type 2 diabetes without high concentrations of LDL-cholesterol and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension. **Inclusion criteria:** men and women aged 4075 years; with type 2 diabetes mellitus (defined with 1985 WHO criteria) diagnosed at least 6 months before; at least one or more of the following: a history of hypertension, defined as receiving antihypertensive treatment or having systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater on at least two successive occasions; retinopathyie, any retinopathy, maculopathy, or previous photocoagulation; microalbuminuria or macroalbuminuria, defined as a positive Micral or other strip test, an albumin creatinine ratio of 25 mg/mmol or greater, or an albumin excretion rate on timed collection of 20 g/min or more, all on at least two successive occasions; or currently smoking (no minimum number of cigarettes per day was required); serum LDL-cholesterol concentration 414 mmol/L or lower; serum triglycerides 678 mmol/L or less **Exclusion criteria:** any past history of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery); plasma creatinine concentration greater than 150 micromol/L, glycated haemoglobin (HbA1c) of more than 12%, or if during the baseline phase they had less than 80% compliance with placebo

Table 13.3: *Design and methodological quality of trials - statins - atorvastatin*

Trial	Design	Duration	Centre	Primary endpoint
Atorvastatin versus placebo				
ASCOT (diabetics sub group), 2003 [1] n=2532	exploratory trial			
Deutsche Diabetes Dialyse Studie (4D), 2005 [2] n=1255	Parallel groups double blind confirmatory trial at low risk of bias	4 y (median) inclusion period: mar 1998 - oct 2002		cardiac death, stroke, MI

continued...

Trial	Design	Duration	Centre	Primary endpoint
ASPEN, 2006 [3] n=2410	Parallel groups double blind confirmatory trial at low risk of bias	4y		CV death, mI, stroke, recanalization, CABG, worsening
CARDS, 2004 [4] n=2841	Parallel groups double blind confirmatory trial at low risk of bias	3.9 years inclusion period: nov 1997 - Juin 2001	UK, Irelande 132 centres	Ev coronariens aigus, revascularisation ou AVC

Table 13.4: *Trial characteristics - statins - atorvastatin*

Trial
Atorvastatin versus placebo
ASCOT (diabetics sub group), 2003 [1]
Deutsche Diabetes Dialyse Studie (4D), 2005 [2]
ASPEN, 2006 [3]
CARDS, 2004 [4]

13.2 Meta-analysis results

The results are detailed in table 13.5 (page 87). This table is followed by the Forest's plot corresponding to each endpoint.

Atorvastatin versus placebo

A total of 2 of the 4 studies 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 0.70 (95% CI 0.55 to 0.88, p=0.0021). No heterogeneity was detected (p = 0.3098, I^2 = 0.03%).
Only one of the 4 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 0.65 (95% CI 0.36 to 1.15, p=0.1375).
A total of 2 of the 4 studies 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 0.60 (95% CI 0.42 to 0.86, p=0.0050). No heterogeneity was detected (p = 0.5336, I^2 = 0.00%).
A total of 2 of the 4 studies 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 0.55 to 0.94, p=0.0172). No heterogeneity was detected (p = 0.3783, I^2 = 0.00%).
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 0.74 (95% CI 0.40 to 1.36, p=0.3330).
Only one of the 4 studies 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 0.65 (95% CI 0.49 to 0.84, p=0.0000).
Only one of the 4 studies eligible for this comparison provided data on **non fatal MI**. The analysis detected a statistically significant difference in favor of atorvastatin in non fatal MI, with a RR of 0.60 (95% CI 0.37 to 0.99, p=0.0435).
Only one of the 4 studies eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.74 (95% CI 0.53 to 1.02, p=0.0619).

Table 13.5: *Results details - statins - atorvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
atorvastatin versus placebo						
cardiovascular events	RR=0.70	[0.55;0.88]	0.0021	0.3098 (I^2=0.03)	2	5373
cardiovascular death	RR=0.65	[0.36;1.15]	0.1375	1.0000 (I^2=0.00)	1	2841
stroke (fatal and non fatal)	RR=0.60	[0.42;0.86]	0.0050	0.5336 (I^2=0.00)	2	5373
coronary event	RR=0.72	[0.55;0.94]	0.0172	0.3783 (I^2=0.00)	2	5373
coronary death	RR=0.74	[0.40;1.36]	0.3330	1.0000 (I^2=0.00)	1	2841
MACE	RR=0.65	[0.49;0.84]	0.0000	1.0000 (I^2=0.00)	1	2841
death from cancer	RR=0.66	[0.38;1.15]	0.1447	1.0000 (I^2=0.00)	1	2841

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
rhabdomyolysis	RR=0.99	[0.02;49.77]	0.9952	1.0000 (I^2=0.00)	1	2841
myopathy	RR=0.99	[0.06;15.78]	0.9932	1.0000 (I^2=0.00)	1	2841
non fatal MI	RR=0.60	[0.37;0.99]	0.0435	1.0000 (I^2=0.00)	1	2841
all cause death	RR=0.74	[0.53;1.02]	0.0619	1.0000 (I^2=0.00)	1	2841
adverse events	RR=0.94	[0.50;1.75]	0.8424	1.0000 (I^2=0.00)	1	2841

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 13.1: *Forest's plot for cardiovascular events*

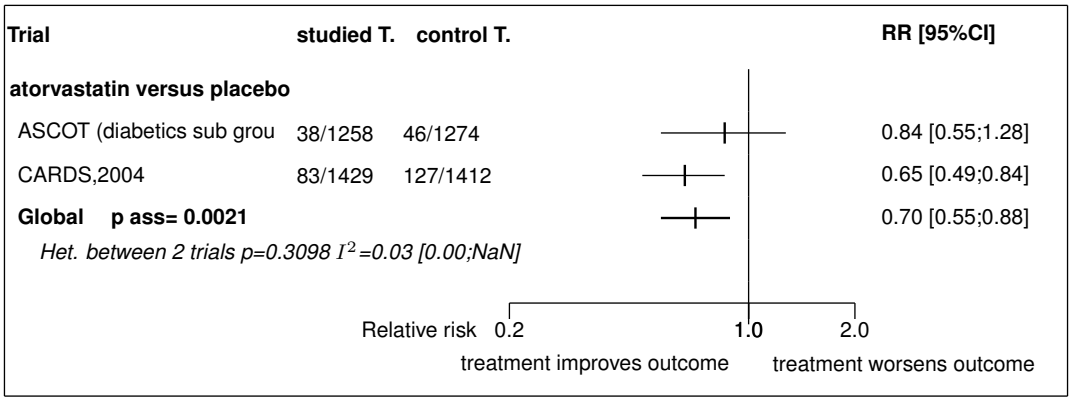


Figure 13.2: *Forest's plot for cardiovascular death*

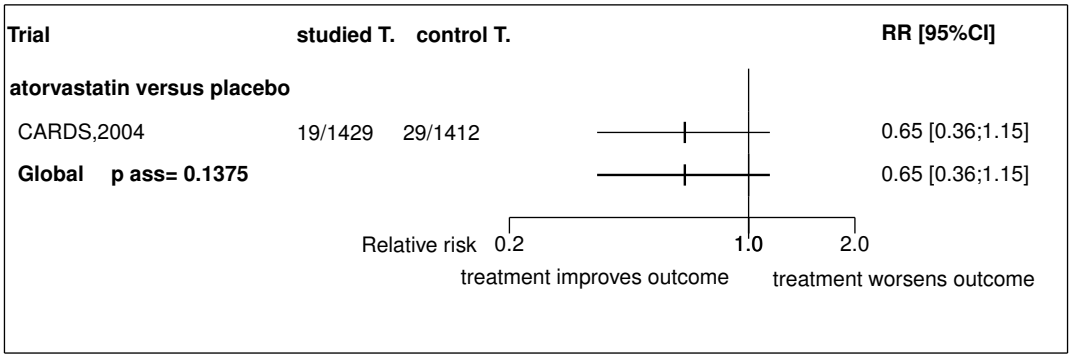


Figure 13.3: *Forest's plot for stroke (fatal and non fatal)*

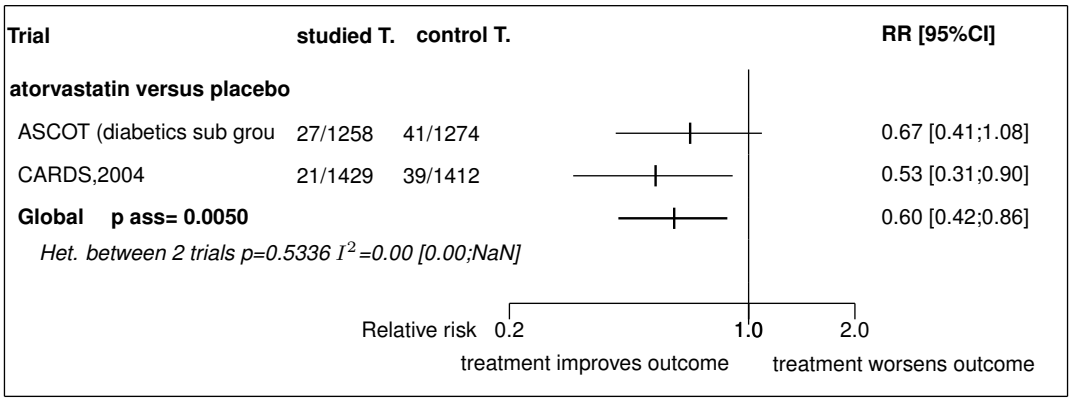


Figure 13.4: *Forest's plot for coronary event*

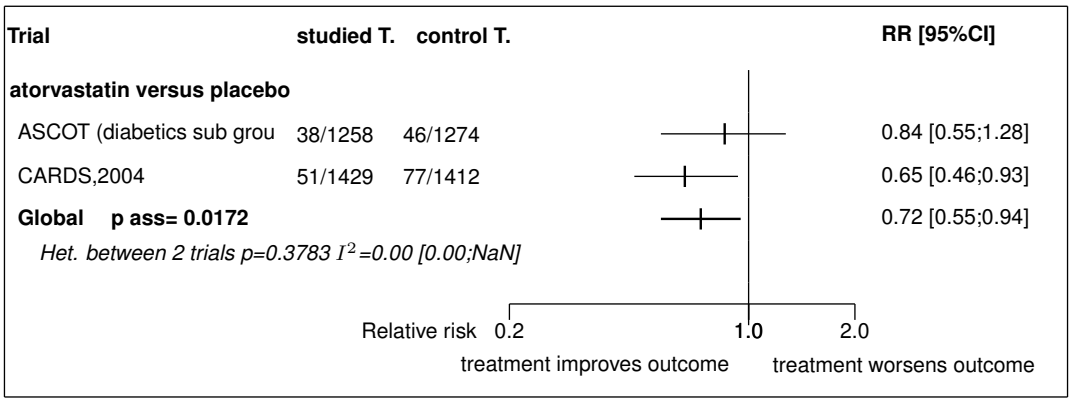


Figure 13.5: *Forest's plot for coronary death*

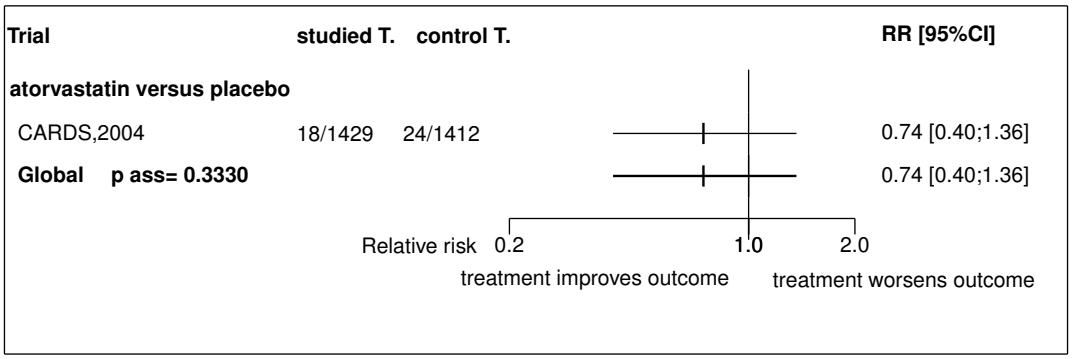


Figure 13.6: *Forest's plot for MACE*

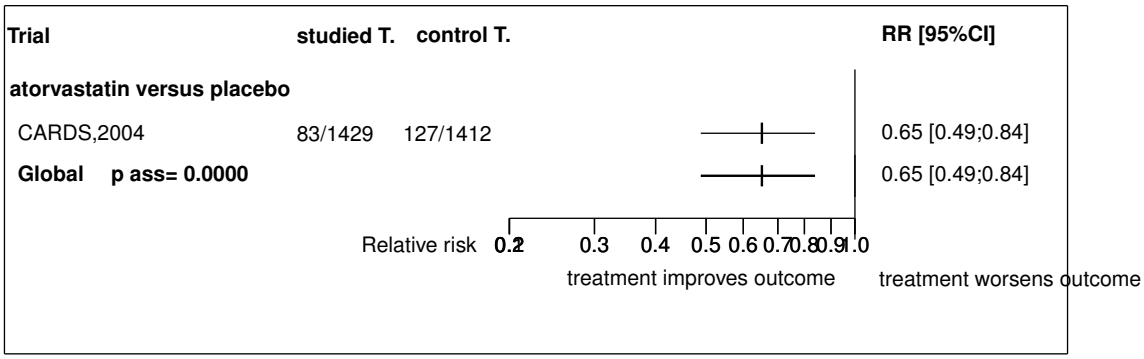


Figure 13.7: *Forest's plot for death from cancer*

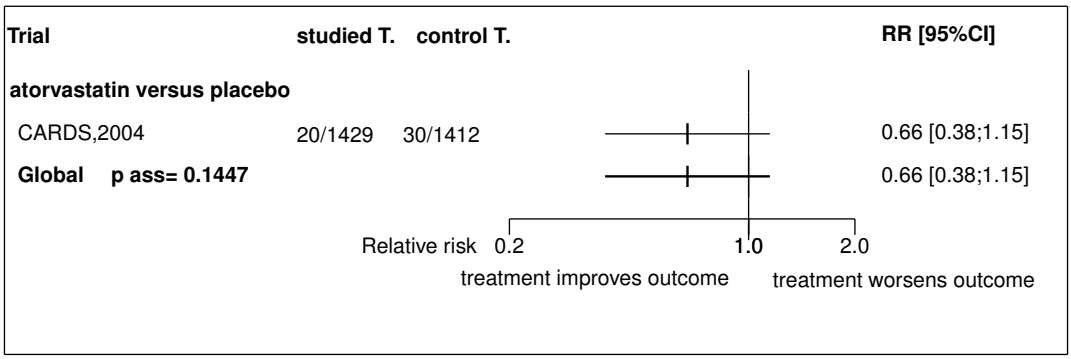


Figure 13.8: *Forest's plot for rhabdomyolysis*

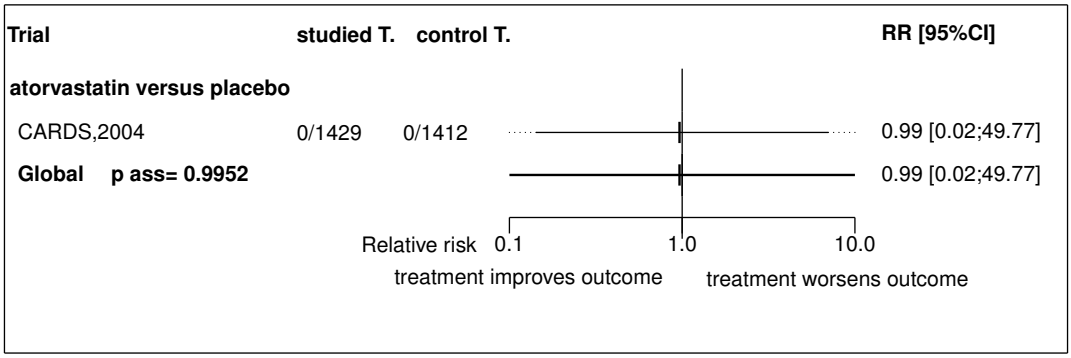


Figure 13.9: *Forest's plot for myopathy*

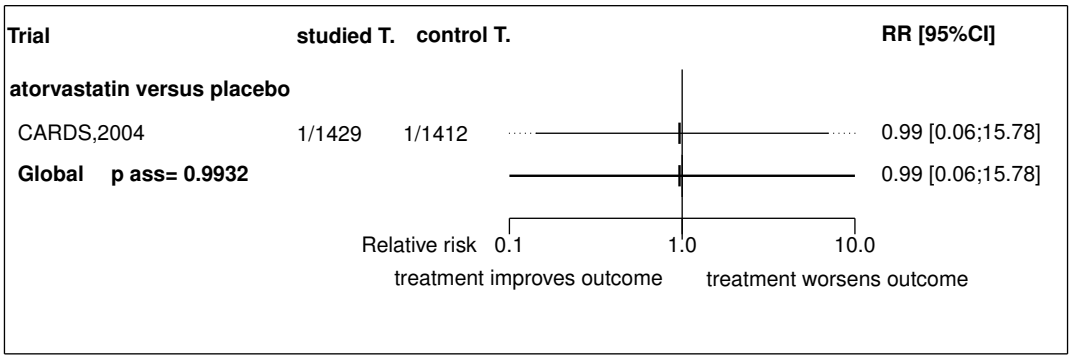


Figure 13.10: *Forest's plot for non fatal MI*

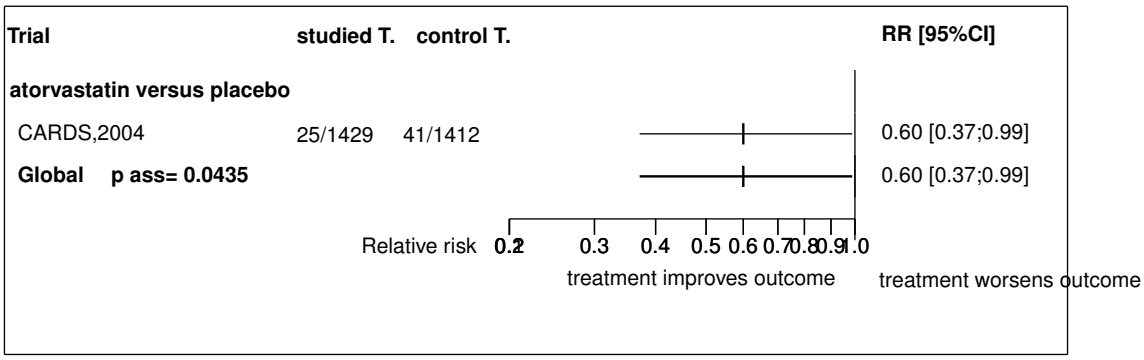


Figure 13.11: *Forest's plot for all cause death*

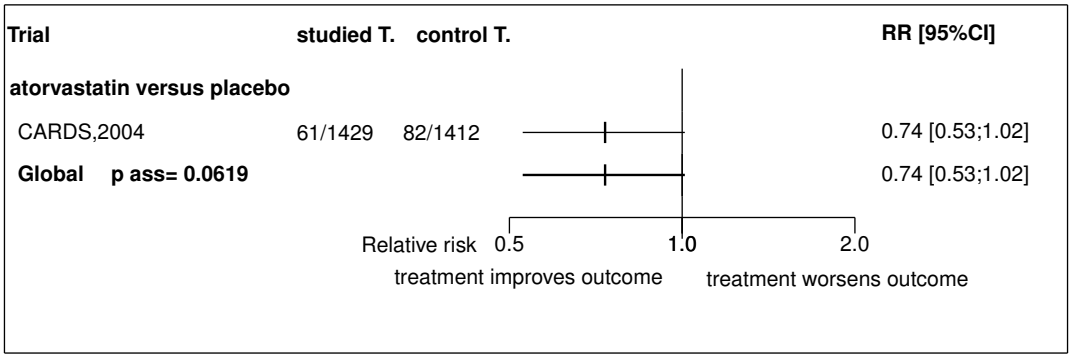
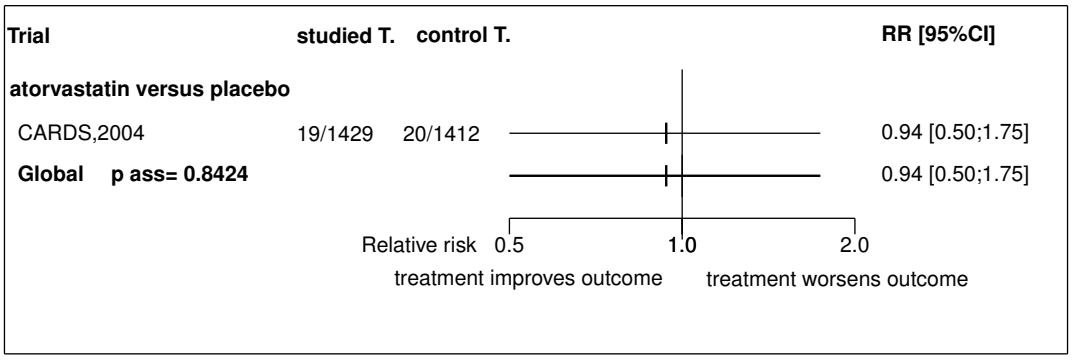


Figure 13.12: *Forest's plot for adverse events*



References

[1] Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005 May;28:1151-7. [PMID=15855581]

[2] Wanner C, Krane V, Mrz W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005 Jul 21;353:238-48. [PMID=16034009]

[3] Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care 2006 Jul;29:1478-85. [PMID=16801565]

[4] Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004 Aug 21;364:685-96. [PMID=15325833]

13.3 Individual trial summaries

Table 13.6: *ASCOT (diabetics sub group), 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2532 (1258 vs. 1274) **Follow-up duration:** **Study design:** Randomized controlled trial Exploratory trial	Hypertensive patients with nohistory of coronary heart disease (CHD) but at least three cardiovascular risk factors	**Studied treatment:** 10 mg atorvastatin **Control treatment:** placebo	Cardiovascular events RR=0.84 [0.55;1.28] (including procedure) Stroke (fatal and non fatal) RR=0.67 [0.41;1.08] (fatal and non fatal stroke) Coronary event RR=0.84 [0.55;1.28]

Reference

Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005 May;28:1151-7 [PMID=15855581]

Table 13.7: *Deutsche Diabetes Dialyse Studie (4D), 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1255 (619 vs. 636) **Follow-up duration:** 4 y (median) **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias **Inclusion period:** mar 1998 - oct 2002	Patients with type 2 diabetes mellitus on maintenance hemodialysis	**Studied treatment:** atorvastatin 20mg daily **Control treatment:** matching placebo	

Reference

Wanner C, Krane V, Mrz W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005 Jul 21;353:238-48 [PMID=16034009]

Table 13.8: *ASPEN, 2006 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2410 (1211 vs. 1199) **Follow-up duration:** 4y **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias	Patients s with type 2 diabetes and LDL cholesterol levels below contemporaryguideline targets	**Studied treatment:** atorvastatin 10mg daily **Control treatment:** placebo	

Reference

Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care 2006 Jul;29:1478-85 [PMID=16801565]

Table 13.9: *CARDS, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2841 (1429 vs. 1412) **Follow-up duration:** 3.9 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias UK, Irelande, 132 centres **Inclusion period:** nov 1997 - Juin 2001	Patients with type 2 diabetes without high concentrations of LDL-cholesterol and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension. **Inclusion criteria:** Men and women aged 4075 years; with type 2 diabetes mellitus (defined with 1985 WHO criteria) diagnosed at least 6 months before; at least one or more of the following: a history of hypertension, defined as receiving antihypertensive treatment or having systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater on at least two successive occasions; retinopathyie, any retinopathy, maculopathy, or previous photocoagulation; microalbuminuria or macroalbuminuria, defined as a positive Micral or other strip test, an albumin creatinine ratio of 25 mg/mmol or g **Exclusion criteria:** any past history of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery); plasma creatinine concentration greater than 150 micromol/L, glycated haemoglobin (HbA1c) of more than 12%, or if during the baseline phase they had less than 80% compliance with placebo	**Studied treatment:** atorvastatin 10mg/d **Control treatment:** placebo	Cardiovascular events RR=0.65 [0.49;0.84] Cardiovascular death RR=0.65 [0.36;1.15] Stroke (fatal and non fatal) RR=0.53 [0.31;0.90] Coronary event RR=0.65 [0.46;0.93] Coronary death RR=0.74 [0.40;1.36] MACE RR=0.65 [0.49;0.84] Death from cancer RR=0.66 [0.38;1.15]

Reference

Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004 Aug 21;364:685-96 [PMID=15325833]

14 Detailed results for atorvastatin high dose

14.1 Available trials

Only one trial which randomized 1501 patients was identified: it compared atorvastatin high dose with atorvastatin.
This trial included 1501 patients and was published in 2006.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 14.1 (page 98), 14.2 (page 98), 14.4 (page 100), and 14.3 (page 98) summarized the main characteristics of the trial including in this systematic review of randomized trials of atorvastatin high dose.

Table 14.1: *Treatment description - statins - atorvastatin high dose*

Trial	Studied treatment	Control treatment
Atorvastatin high dose versus atorvastatin		
TNT (sub group) (2006) [1]	atorvastatin 80 mg daily	atorvastatin 10 mg daily

Table 14.2: *Descriptions of participants - statins - atorvastatin high dose*

Trial	Patients
Atorvastatin high dose versus atorvastatin	
TNT (sub group) (2006) [1]	Patients with stable coronary heart disease

Table 14.3: *Design and methodological quality of trials - statins - atorvastatin high dose*

Trial	Design	Duration	Centre	Primary endpoint
Atorvastatin high dose versus atorvastatin				
TNT (sub group), 2006 [1] n=1501	double blind exploratory trial	4.9 y		major cardiovascular event

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 14.4: *Trial characteristics - statins - atorvastatin high dose*

Trial
Atorvastatin high dose versus atorvastatin
TNT (sub group), 2006 [1]

14.2 Meta-analysis results

The results are detailed in table 14.5 (page 101). This table is followed by the Forest's plot corresponding to each endpoint.

Atorvastatin high dose versus atorvastatin

No data were presented in the 1 trial identified

Table 14.5: *Results details - statins - atorvastatin high dose*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
atorvastatin high dose 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] Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, Hsia J, Breazna A, LaRosa J, Grundy S, Waters D. . Diabetes Care 2006;29:1220-6. [PMID=16731999]

14.3 Individual trial summaries

Table 14.6: *TNT (sub group), 2006 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1501 (748 vs. 753) **Follow-up duration:** 4.9 y **Study design:** Randomized controlled trial Double blind Exploratory trial	Patients with stable coronary heart disease	**Studied treatment:** atorvastatin 80 mg daily **Control treatment:** atorvastatin 10 mg daily	

Reference

Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, Hsia J, Breazna A, LaRosa J, Grundy S, Waters D. . Diabetes Care 2006;29:1220-6 [PMID=16731999]

15 Detailed results for fluvastatin

15.1 Available trials

A total of 2 RCTs which randomized 598 patients were identified: all compared fluvastatin with placebo.
The average study size was 299 patients (range 202 to 396). The first study was published in 2002, and the last study was published in 2003.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
data was reported in trials;
Following tables 15.1 (page 104), 15.2 (page 104), 15.4 (page 106), and 15.3 (page 105) summarized the main characteristics of the trials including in this systematic review of randomized trials of fluvastatin.

Table 15.1: *Treatment description - statins - fluvastatin*

Trial	Studied treatment	Control treatment
Fluvastatin versus placebo		
LIPS (sub group) (2002) [1]	fluvastatin	placebo
ALERT (sub group) (2003) [2]	fluvastatin	placebo

Table 15.2: *Descriptions of participants - statins - fluvastatin*

Trial	Patients
Fluvastatin versus placebo	
LIPS (sub group) (2002) [1]	Patients (aged 18-80 years) with stable or unstable angina or silent ischemia following successful completion of their first PCI who had baseline total cholesterol levels between 135 and 270 mg/dL
ALERT (sub group) (2003) [2]	Renal transplant recipients withtotal cholesterol 4090 mmol/L

Table 15.3: *Design and methodological quality of trials - statins - fluvastatin*

Trial	Design	Duration	Centre	Primary end-point
Fluvastatin versus placebo				
LIPS (sub group), 2002 [1] n=202	Parallel groups double blind exploratory trial	3.9y		MACE
ALERT (sub group), 2003 [2] n=396	Parallel groups double blind exploratory trial			

Table 15.4: *Trial characteristics - statins - fluvastatin*

Trial
Fluvastatin versus placebo
LIPS (sub group), 2002 [1]
ALERT (sub group), 2003 [2]

15.2 Meta-analysis results

The results are detailed in table 15.5 (page 107). This table is followed by the Forest's plot corresponding to each endpoint.

Fluvastatin versus placebo

No data were presented in the 2 trials identified

Table 15.5: *Results details - statins - fluvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
fluvastatin 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] Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B. . JAMA 2002;287:3215-22. [PMID=12076217]

[2] Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambhl P, Olsson AG, Hartmann A, Solbu DO, Pedersen TR. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet 2003;361:2024-31. [PMID=12814712]

15.3 Individual trial summaries

Table 15.6: *LIPS (sub group), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=202 (120 vs. 82) **Follow-up duration:** 3.9y **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Patients (aged 18-80 years) with stable or unstable angina or silent ischemia following successful completion of their first PCI who had baseline total cholesterol levels between 135 and 270 mg/dL	**Studied treatment:** fluvastatin **Control treatment:** placebo	

Reference

Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B. . JAMA 2002;287:3215-22 [PMID=12076217]

Table 15.7: *ALERT (sub group), 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=396 (197 vs. 199) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Renal transplant recipients withtotal cholesterol 4090 mmol/L	**Studied treatment:** fluvastatin **Control treatment:** placebo	

Reference

Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambhl P, Olsson AG, Hartmann A, Solbu DO, Pedersen TR. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet 2003;361:2024-31 [PMID=12814712]

16 Detailed results for lovastatin

16.1 Available trials

Only one trial which randomized 155 patients was identified: it compared lovastatin with placebo.
This trial included 155 patients and was published in 1998.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 16.1 (page 111), 16.2 (page 111), 16.4 (page 112), and 16.3 (page 111) summarized the main characteristics of the trial including in this systematic review of randomized trials of lovastatin.

Table 16.1: *Treatment description - statins - lovastatin*

Trial	Studied treatment	Control treatment
Lovastatin versus placebo		
AFCAPS/TexCAPS (sub group) (1998) [1]	lovastatin	placebo

Table 16.2: *Descriptions of participants - statins - lovastatin*

Trial	Patients
Lovastatin versus placebo	
AFCAPS/TexCAPS (sub group) (1998) [1]	Men and women without clinically evident atherosclerotic cardiovasculardisease with average total cholesterol (TC) and LDL-C levels and below-average high-densitylipoprotein cholesterol (HDL-C) levels

Table 16.3: *Design and methodological quality of trials - statins - lovastatin*

Trial	Design	Duration	Centre	Primary end-point
Lovastatin versus placebo				
AFCAPS/TexCAPS (sub group), 1998 [1] n=155	Parallel groups double blind exploratory trial			

Table 16.4: *Trial characteristics - statins - lovastatin*

Trial
Lovastatin versus placebo
AFCAPS/TexCAPS (sub group), 1998 [1]

16.2 Meta-analysis results

The results are detailed in table 16.5 (page 113). This table is followed by the Forest's plot corresponding to each endpoint.

Lovastatin versus placebo

No data were presented in the 1 trial identified

Table 16.5: *Results details - statins - lovastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
lovastatin 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] Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. . JAMA 1998;279:1615-22. [PMID=9613910]

16.3 Individual trial summaries

Table 16.6: *AFCAPS/TexCAPS (sub group), 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=155 (84 vs. 71) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Men and women without clinically evident atherosclerotic cardiovasculardisease with average total cholesterol (TC) and LDL-C levels and below-average high-densitylipoprotein cholesterol (HDL-C) levels	**Studied treatment:** lovastatin **Control treatment:** placebo	

Reference

Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. . JAMA 1998;279:1615-22 [PMID=9613910]

17 Detailed results for pravastatin

17.1 Available trials

A total of 6 RCTs which randomized 5699 patients were identified: 4 trials compared pravastatin with placebo and 2 trials compared pravastatin with usual care.
The average study size was 1139 patients (range 70 to 3638). The first study was published in 1996, and the last study was published in 2002.
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.
Coronary event data was reported in 4 trials; 1 trials reported data on stroke (fatal and non fatal); and 1 trials reported data on cardiovascular events.
Following tables 17.1 (page 116), 17.2 (page 117), 17.4 (page 119), and 17.3 (page 117) summarized the main characteristics of the trials including in this systematic review of randomized trials of pravastatin.

Table 17.1: *Treatment description - statins - pravastatin*

Trial	Studied treatment	Control treatment
Pravastatin versus placebo		
PROSPER (sub group) (2002) [1]	pravastatin 40mg daily	placebo
LIPID (sub group) (1998) [2]	pravastatin 40 mg daily	placebo
CARE (sub group) (1998) [3]	pravastatin	placebo
WOSCOPS (sub group) (1996) [4, 5]	pravastatin 40 mg daily	placebo
Pravastatin versus usual care		
GISSI P (sub group) (2000) [6]	pravastatin 20 mg daily	usual care
ALLHAT-LLT (sub group) (2002) [7]	pravastatin	usual care

Table 17.2: *Descriptions of participants - statins - pravastatin*

Trial	Patients
Pravastatin versus placebo	
PROSPER (sub group) (2002) [1]	Mena and women aged7082 years with a history of, or risk factors for, vasculardisease
LIPID (sub group) (1998) [2]	Patients with a history of myocardial infarction or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg per deciliter
CARE (sub group) (1998) [3]	Men and postmenopausal women between 21 to 75 years of age, with MI between 3 and 20 months before randomization and plasma total cholesterol values <240mg/dL, LDL-C levelsbetween 115 and 174mg/dL, and triglycerides <350mg/dL
WOSCOPS (sub group) (1996) [4, 5]	Men aged 45-64 years with no history of myocardial infarction and plasma total cholesterol concentrations of 6.5-8.0 mmol/L at initial screening
Pravastatin versus usual care	
GISSI P (sub group) (2000) [6]	Recent acute myocardial infarction patients (<or = 6 months) with total blood cholesterol >or = 200 mg/dl
ALLHAT-LLT (sub group) (2002) [7]	Ambulatory persons aged 55 years or older, with lowdensitylipoprotein cholesterol (LDL-C) of 120 to 189 mg/dL (100 to 129 mg/dL ifknown CHD) and triglycerides lower than 350 mg/dL

Table 17.3: *Design and methodological quality of trials - statins - pravastatin*

Trial	Design	Duration	Centre	Primary endpoint
Pravastatin versus placebo				
PROSPER (sub group), 2002 [1] n=623	Parallel groups double blind exploratory trial	3.2y mean		CV events
LIPID (sub group), 1998 [2] n=782	Parallel groups double blind exploratory trial	mean 6.1y inclusion period: Jun 1990 - Dec 1992	Australia, New Zealand 87 centres	mortality from coronary heart disease
CARE (sub group), 1998 [3] n=586	Parallel groups exploratory trial			
WOSCOPS (sub group), 1996 [4, 5] n=70	double blind exploratory trial	mean 4.9y		

continued...

Trial	Design	Duration	Centre	Primary endpoint
Pravastatin versus usual care				
GISSI P (sub group), 2000 [6] n=NaN	open exploratory trial	median 24.3 months		
ALLHAT-LLT (sub group), 2002 [7] n=3638	Parallel groups open exploratory trial			

Table 17.4: *Trial characteristics - statins - pravastatin*

Trial
Pravastatin versus placebo
PROSPER (sub group), 2002 [1]
LIPID (sub group), 1998 [2]
CARE (sub group), 1998 [3]
WOSCOPS (sub group), 1996 [4, 5]
Pravastatin versus usual care
GISSI P (sub group), 2000 [6]
ALLHAT-LLT (sub group), 2002 [7]

17.2 Meta-analysis results

The results are detailed in table 17.5 (page 120). This table is followed by the Forest's plot corresponding to each endpoint.

Pravastatin versus placebo

Only one of the 4 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 0.80 (95% CI 0.59 to 1.09, p=0.1522).
Only one of the 4 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 0.85 (95% CI 0.48 to 1.52, p=0.5920).
A total of 2 of the 4 studies eligible for this comparison provided data on **coronary event**. When pooled together, there was no statistically significant difference between the groups in coronary event, with a RR of 0.85 (95% CI 0.69 to 1.05, p=0.1402). No heterogeneity was detected (p = 0.8840, I^2 = 0.00%).

Pravastatin versus usual care

No data were presented in the 2 trials identified

Table 17.5: *Results details - statins - pravastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pravastatin versus placebo						
cardiovascular events	RR=0.80	[0.59;1.09]	0.1522	1.0000 (I^2=0.00)	1	623
stroke (fatal and non fatal)	RR=0.85	[0.48;1.52]	0.5920	1.0000 (I^2=0.00)	1	586
coronary event	RR=0.85	[0.69;1.05]	0.1402	0.8840 (I^2=0.00)	2	1368
pravastatin versus usual care						
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

Figure 17.1: *Forest's plot for cardiovascular events*

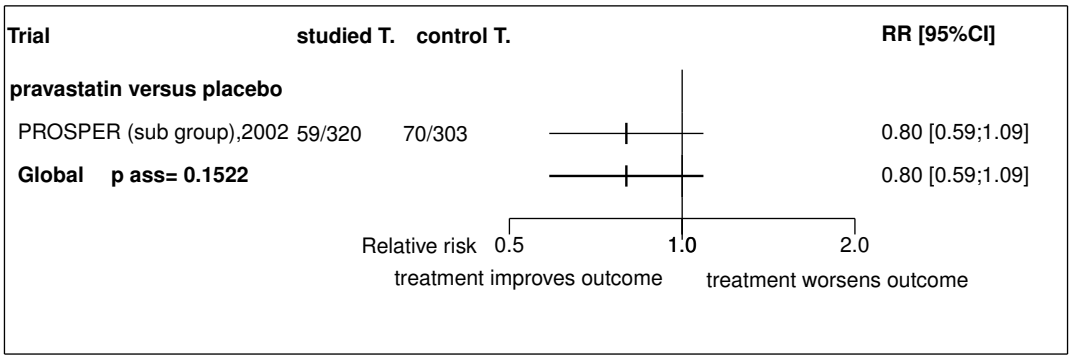


Figure 17.2: *Forest's plot for stroke (fatal and non fatal)*

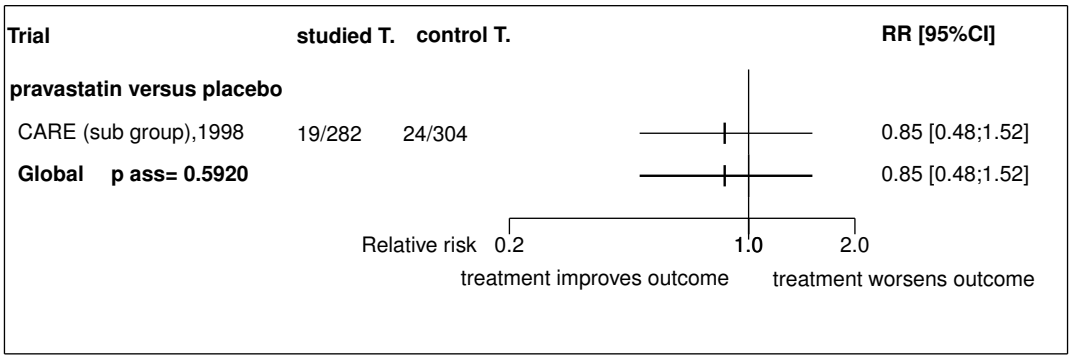
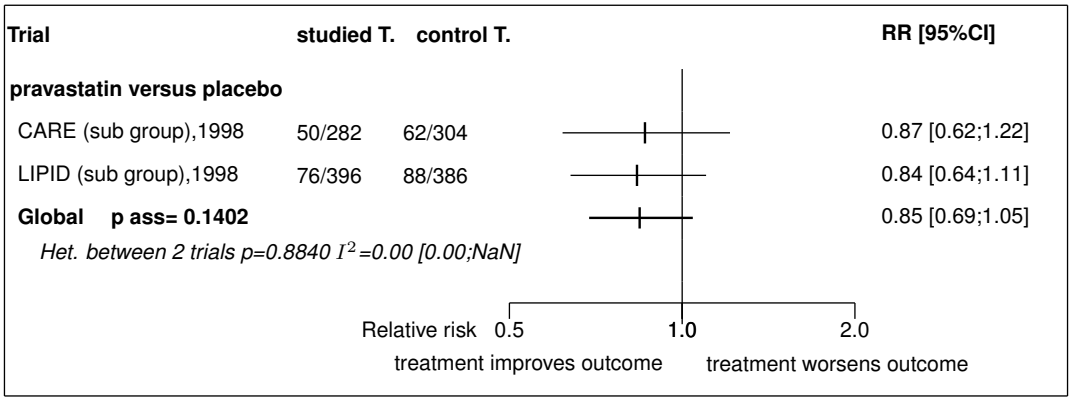


Figure 17.3: *Forest's plot for coronary event*



References

[1] 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. . Lancet 2002;360:1623-30. [PMID=12457784]

[2] . . N Engl J Med 1998;339:1349-57. [PMID=9841303]

[3] Goldberg RB, Mellies MJ, Sacks FM, Moy LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. Circulation 1998;98:2513-9. [PMID=9843456]

[4] . West of Scotland Coronary Prevention Study: identification of high-risk groups and comparison with other cardiovascular intervention trials. Lancet 1996 Nov 16;348:1339-42. [PMID=8918276]

[5] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. . N Engl J Med 1995;333:1301-7. [PMID=7566020]

[6] . Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). Ital Heart J 2000;1:810-20. [PMID=11302109]

[7] . . JAMA 2002;288:2998-3007. [PMID=12479764]

17.3 Individual trial summaries

Table 17.6: *PROSPER (sub group), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=623 (320 vs. 303) **Follow-up duration:** 3.2y mean **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Mena and women aged7082 years with a history of, or risk factors for, vasculardisease	**Studied treatment:** pravastatin 40mg daily **Control treatment:** placebo	Cardiovascular events RR=0.80 [0.59;1.09]

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. . Lancet 2002;360:1623-30 [PMID=12457784]

Table 17.7: *LIPID (sub group), 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=782 (396 vs. 386) **Follow-up duration:** mean 6.1y **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Australia, New Zealand, 87 centres **Inclusion period:** Jun 1990 - Dec 1992	Patients with a history of myocardial infarction or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg per deciliter	**Studied treatment:** pravastatin 40 mg daily **Control treatment:** placebo	Coronary event RR=0.84 [0.64;1.11]
Reference . . N Engl J Med 1998;339:1349-57 [PMID=9841303]			

Table 17.8: *CARE (sub group), 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=586 (282 vs. 304) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Exploratory trial	Men and postmenopausal women between 21 to 75 years of age, with MI between 3 and 20 months before randomization and plasma total cholesterol values <240mg/dL, LDL-C levelsbetween 115 and 174mg/dL, and triglycerides <350mg/dL	**Studied treatment:** pravastatin **Control treatment:** placebo	Stroke (fatal and non fatal) RR=0.85 [0.48;1.52] Coronary event RR=0.87 [0.62;1.22]

Reference

Goldberg RB, Mellies MJ, Sacks FM, Moy LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. Circulation 1998;98:2513-9 [PMID=9843456]

Table 17.9: *WOSCOPS (sub group), 1996 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (70 vs. 0) **Follow-up duration:** mean 4.9y **Study design:** Randomized controlled trial Double blind Exploratory trial	Men aged 45-64 years with no history of myocardial infarction and plasma total cholesterol concentrations of 6.5-8.0 mmol/L at initial screening	**Studied treatment:** pravastatin 40 mg daily **Control treatment:** placebo	

References

. West of Scotland Coronary Prevention Study: identification of high-risk groups and comparison with other cardiovascular intervention trials. Lancet 1996 Nov 16;348:1339-42 [PMID=8918276]
Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. . N Engl J Med 1995;333:1301-7 [PMID=7566020]

Table 17.10: *GISSI P (sub group), 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** median 24.3 months **Study design:** Randomized controlled trial Open Exploratory trial	Recent acute myocardial infarction patients (<or = 6 months) with total blood cholesterol >or = 200 mg/dl	**Studied treatment:** pravastatin 20 mg daily **Control treatment:** usual care	

Reference

. Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). Ital Heart J 2000;1:810-20 [PMID=11302109]

Table 17.11: *ALLHAT-LLT (sub group), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3638 (1855 vs. 1783) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial	Ambulatory persons aged 55 years or older, with lowdensitylipoprotein cholesterol (LDL-C) of 120 to 189 mg/dL (100 to 129 mg/dL ifknown CHD) and triglycerides lower than 350 mg/dL	**Studied treatment:** pravastatin **Control treatment:** usual care	

Reference

. . JAMA 2002;288:2998-3007 [PMID=12479764]

18 Detailed results for pravastatin high dose

18.1 Available trials

Only one trial which randomized 734 patients was identified: it compared pravastatin high dose with pravastatin.
This trial included 734 patients and was published in 2006.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 18.1 (page 130), 18.2 (page 130), 18.4 (page 132), and 18.3 (page 130) summarized the main characteristics of the trial including in this systematic review of randomized trials of pravastatin high dose.

Table 18.1: *Treatment description - statins - pravastatin high dose*

Trial	Studied treatment	Control treatment
Pravastatin high dose versus pravastatin		
PROVE IT TIMI 22 (diabetic sub group) (2006) [1]	pravastatin 80mg daily	pravastatin 40mg daily

Table 18.2: *Descriptions of participants - statins - pravastatin high dose*

Trial	Patients
Pravastatin high dose versus pravastatin	
PROVE IT TIMI 22 (diabetic sub group) (2006) [1]	Patients hospitalized for an acute coronary syndrome within the preceding 10 days

Table 18.3: *Design and methodological quality of trials - statins - pravastatin high dose*

Trial	Design	Duration	Centre	Primary endpoint
Pravastatin high dose versus pravastatin				

continued...

Trial	Design	Duration	Centre	Primary end-point
PROVE IT TIMI 22 (diabetic sub group), 2006 [1] n=734	Parallel groups double blind exploratory trial	24 months mean		Cv events

Table 18.4: *Trial characteristics - statins - pravastatin high dose*

Trial
Pravastatin high dose versus pravastatin
PROVE IT TIMI 22 (diabetic sub group), 2006 [1]

18.2 Meta-analysis results

The results are detailed in table 18.5 (page 133). This table is followed by the Forest's plot corresponding to each endpoint.

Pravastatin high dose versus pravastatin

No data were presented in the 1 trial identified

Table 18.5: *Results details - statins - pravastatin high dose*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
pravastatin high dose versus pravastatin						
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] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. . N Engl J Med 2004;350:1495-504. [PMID=15007110]

18.3 Individual trial summaries

Table 18.6: *PROVE IT TIMI 22 (diabetic sub group), 2006 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=734 (373 vs. 361) **Follow-up duration:** 24 months mean **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Patients hospitalized for an acute coronary syndrome within the preceding 10 days	**Studied treatment:** pravastatin 80mg daily **Control treatment:** pravastatin 40mg daily	

Reference

Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. . N Engl J Med 2004;350:1495-504 [PMID=15007110]

19 Detailed results for simvastatin

19.1 Available trials

A total of 2 RCTs which randomized 6446 patients were identified: all compared simvastatin with placebo.
The average study size was 3223 patients (range 483 to 5963). The first study was published in 1999, 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.
Coronary event data was reported in 2 trials; 1 trials reported data on cardiovascular events; and 1 trials reported data on stroke (fatal and non fatal).
Following tables 19.1 (page 136), 19.2 (page 136), 19.4 (page 138), and 19.3 (page 137) summarized the main characteristics of the trials including in this systematic review of randomized trials of simvastatin.

Table 19.1: *Treatment description - statins - simvastatin*

Trial	Studied treatment	Control treatment
Simvastatin versus placebo		
HPS (sub group) (2002) [1]	simvastatin 40mg daily	placebo
4S (sub group) (1999) [2]	simvastatin	placebo

Table 19.2: *Descriptions of participants - statins - simvastatin*

Trial	Patients
Simvastatin versus placebo	
HPS (sub group) (2002) [1]	Men and women diabetes aged about 4080 years with non-fastingblood total cholesterol concentrations of at least35 mmol/L (135 mg/dL)
4S (sub group) (1999) [2]	Diabetic menand women aged 35 to 70 years with previous MI or active,stable angina pectoris and with serum total cholesterollevel between 5.5 to 8.0 mmol/L and serumtriglyceride level <=2.5 mmol/L

Table 19.3: *Design and methodological quality of trials - statins - simvastatin*

Trial	Design	Duration	Centre	Primary end-point
Simvastatin versus placebo				
HPS (sub group), 2002 [1] n=5963	Parallel groups double blind exploratory trial	inclusion period: Jul 1994 - may 1997		
4S (sub group), 1999 [2] n=483	Parallel groups double blind exploratory trial	5.4y inclusion period: May 1988 - Aug 1989	Denmark, Finland, Iceland, Norway, and Sweden 94 centres	

Table 19.4: *Trial characteristics - statins - simvastatin*

Trial
Simvastatin versus placebo
HPS (sub group), 2002 [1]
4S (sub group), 1999 [2]

19.2 Meta-analysis results

The results are detailed in table 19.5 (page 139). 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**. The analysis detected a statistically significant difference in favor of simvastatin in cardiovascular events, with a RR of 0.81 (95% CI 0.73 to 0.89, p=0.0000).
Only one of the 2 studies 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 0.77 (95% CI 0.63 to 0.95, p=0.0155).
Only one of the 2 studies eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.79 (95% CI 0.49 to 1.28, p=0.3359).

Table 19.5: *Results details - statins - simvastatin*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
simvastatin versus placebo						
cardiovascular events	RR=0.81	[0.73;0.89]	0.0000	1.0000 (I^2=0.00)	1	5963
stroke (fatal and non fatal)	RR=0.77	[0.63;0.95]	0.0155	1.0000 (I^2=0.00)	1	5963
all cause death	RR=0.79	[0.49;1.28]	0.3359	1.0000 (I^2=0.00)	1	483

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

Figure 19.1: *Forest's plot for cardiovascular events*

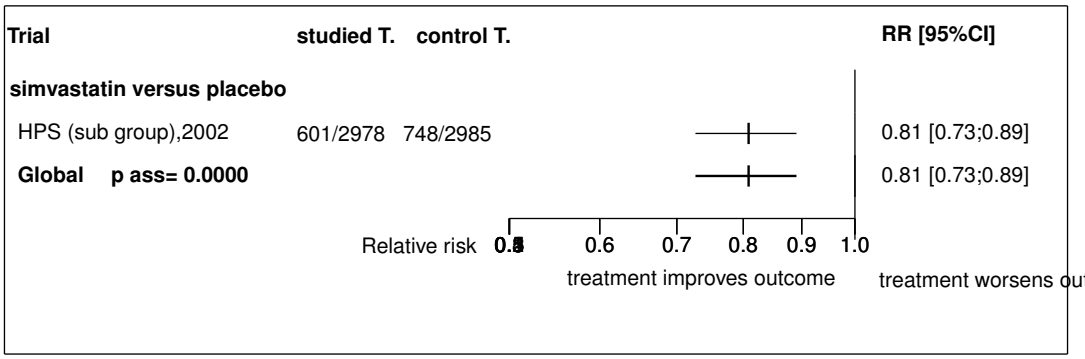


Figure 19.2: *Forest's plot for stroke (fatal and non fatal)*

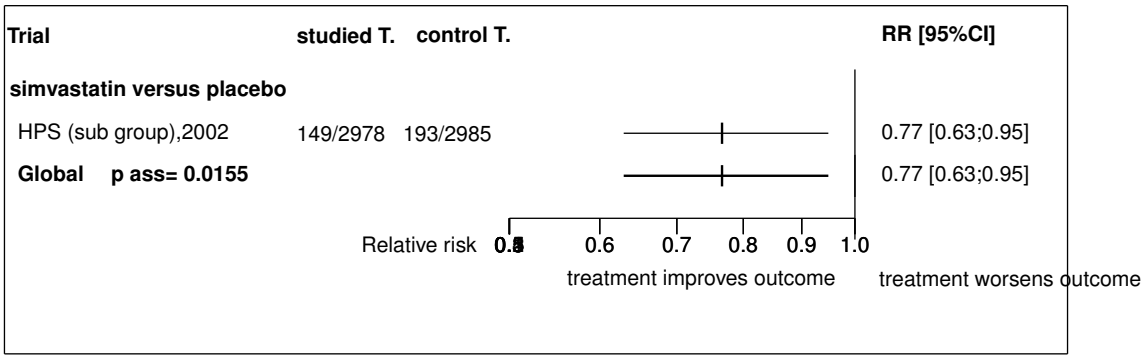
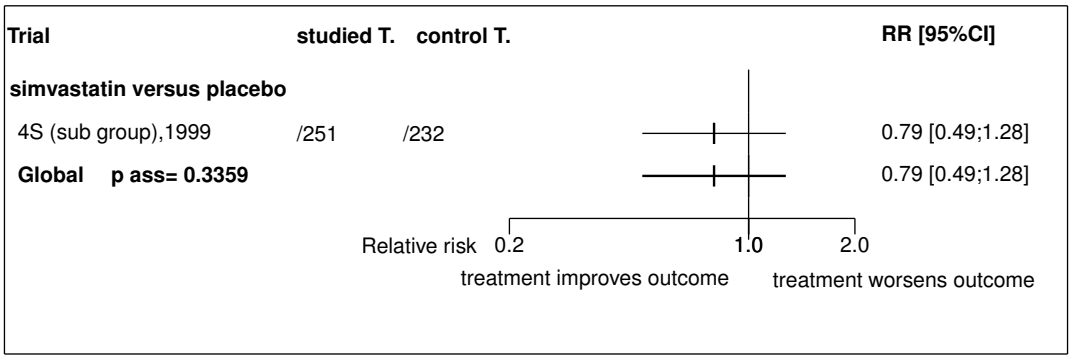


Figure 19.3: *Forest's plot for all cause death*



References

[1] Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003 Jun 14;361:2005-16. [PMID=12814710]

[2] Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyörl K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. Arch Intern Med 1999 Dec 13-27;159:2661-7. [PMID=10597756]

19.3 Individual trial summaries

Table 19.6: *HPS (sub group), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=5963 (2978 vs. 2985) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial **Inclusion period:** Jul 1994 - may 1997	Men and women diabetes aged about 4080 years with non-fastingblood total cholesterol concentrations of at least35 mmol/L (135 mg/dL)	**Studied treatment:** simvastatin 40mg daily **Control treatment:** placebo	Cardiovascular events RR=0.81 [0.73;0.89] Stroke (fatal and non fatal) RR=0.77 [0.63;0.95]

Reference

Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003 Jun 14;361:2005-16 [PMID=12814710]

Table 19.7: *4S (sub group), 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=483 (251 vs. 232) **Follow-up duration:** 5.4y **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Denmark, Finland, Iceland, Norway, and Sweden, 94 centres **Inclusion period:** May 1988 - Aug 1989	Diabetic menand women aged 35 to 70 years with previous MI or active,stable angina pectoris and with serum total cholesterollevel between 5.5 to 8.0 mmol/L and serumtriglyceride level <=2.5 mmol/L	**Studied treatment:** simvastatin **Control treatment:** placebo	

Reference

Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyörl K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. Arch Intern Med 1999 Dec 13-27;159:2661-7 [PMID=10597756]

20 Global meta-analysis: all statins

20.1 Global meta-analysis: all statins versus atorvastatin

Table 20.1: *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

20.2 Global meta-analysis: all statins versus moderate cholesterol-lowering

Table 20.2: *All statinsversus moderate cholesterol-lowering*

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

20.3 Global meta-analysis: all statins versus placebo

Table 20.3: *All statinsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.79	0.73;0.86	0.0000	0.4886 (0.00)	4	11959
cardiovascular death	RR=0.65	0.36;1.15	0.1375	1.0000 (0.00)	1	2841
stroke (fatal and non fatal)	RR=0.74	0.62;0.87	0.0000	0.5515 (0.00)	4	11922
coronary event	RR=0.80	0.68;0.94	0.0084	0.6356 (0.00)	4	6741
coronary death	RR=0.74	0.40;1.36	0.3330	1.0000 (0.00)	1	2841
MACE	RR=0.65	0.49;0.84	0.0000	1.0000 (0.00)	1	2841
non fatal MI	RR=0.60	0.37;0.99	0.0435	1.0000 (0.00)	1	2841
all cause death	RR=0.75	0.57;0.98	0.0370	0.8071 (0.00)	2	3324

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

20.4 Global meta-analysis: all statins versus pravastatin

Table 20.4: *All statinsversus pravastatin*

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

20.5 Global meta-analysis: all statins versus usual care

Table 20.5: *All statinsversus usual care*

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 statins

No ongoing trial was identified.

22 Excluded studies for statins

No trial was excluded.

References

Part III

Strategy

23 Overview of strategy

23.1 Included trials

Only one trial which randomized 499 patients was identified. In all, 1 randomized comparison concerned aggressive treatment.
The detailed descriptions of trials and meta-analysis results is given in section 24 (page 153) for aggressive treatment.

This trial included 499 patients and was published in 2008.
This trial was open-label in design.
It was reported in English language.
The table 23.1 (page 150) 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 strategy provide the results listed in tables 23.2 to 23.2 (page 151) and in the following graphs.

23.2.1 Aggressive treatment

No significant difference was found between **aggressive treatment** and **standard teatment** in terms of cardiovascular events (RR=1.35, 95% CI 0.55 to 3.29, p=0.5128, 1 trial)and non cardiovascular death (RR=0.49, 95% CI 0.09 to 2.65, p=0.4077, 1 trial).

Table 23.1: *Main study characteristics - strategy*

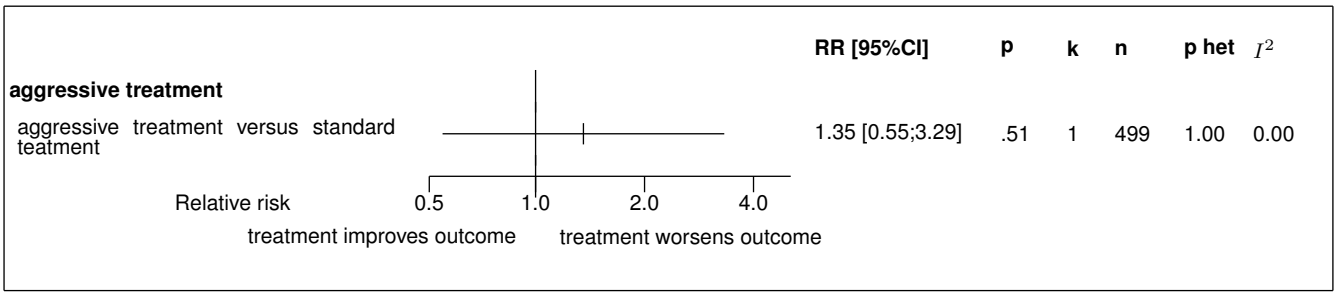
Trial	Patients	Treatments	Trial design and method
Aggressive treatment			
Aggressive treatment versus standard teatment			
SANDS, 2008 [1, 2] n = 252 vs. 247	adults with type 2 diabetes	aggressive targets of LDL-C of 70 mg/dL or lower and SBP of 115 mm Hg or lower **versus** standard targets of LDL-C of 100 mg/dL or lower and SBP of 130 mm Hg or lower	open parallel groups Primary endpoint: common carotid artery intimal medial thickness (IMT) 4 centres, US

Table 23.2: *Summary of all results for aggressive treatment*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
aggressive treatment versus standard teatment						
cardiovascular events	RR=1.35	0.55;3.29	0.5128	1.0000 (0.00)	1	499
non cardiovascular death	RR=0.49	0.09;2.65	0.4077	1.0000 (1.00)	1	499
adverse events	RR=1.32	0.98;1.78	0.0722	1.0000 (0.00)	1	499

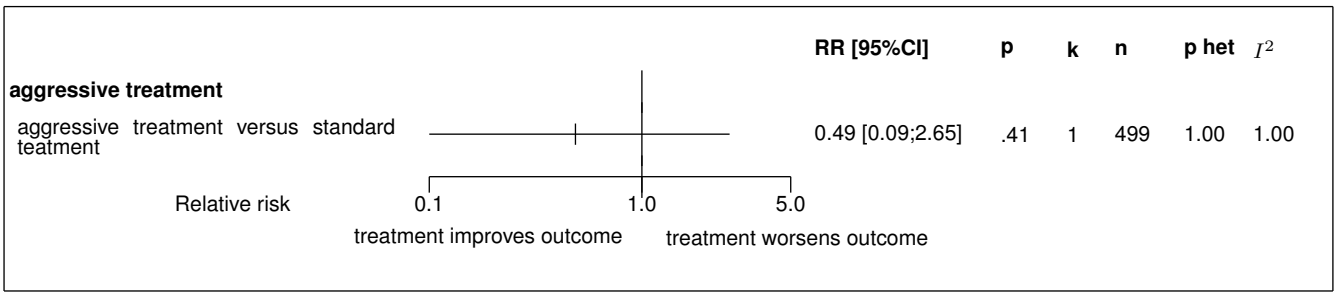
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 23.1: *Forest's plot for cardiovascular events*



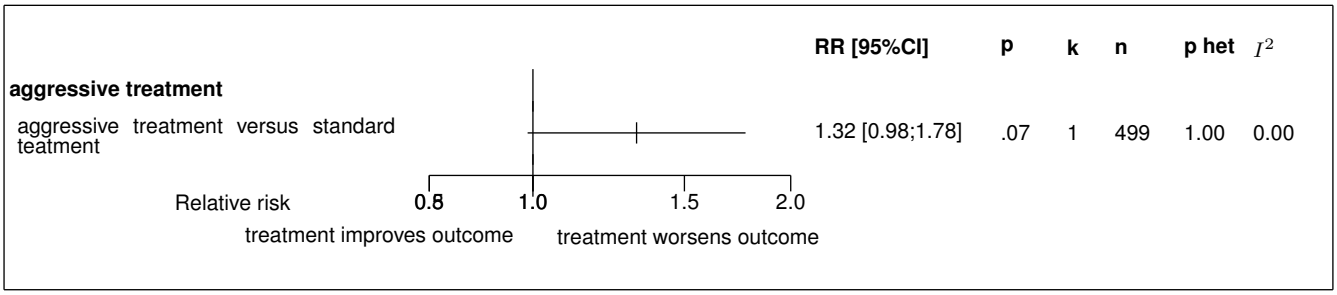
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 23.2: *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

Figure 23.3: *Forest's plot for adverse events*



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

24 Details

24.1 Available trials

Only one trial which randomized 499 patients was identified: it compared aggressive treatment with standard teatment.
This trial included 499 patients and was published in 2008.
This trial was open-label in design.
It was reported in English language.
Cardiovascular events data was reported in 1 trials; 1 trials reported data on non cardiovascular death; and 1 trials reported data on adverse events.
Following tables 24.1 (page 153), 24.2 (page 153), 24.4 (page 155), and 24.3 (page 154) summarized the main characteristics of the trial including in this systematic review of randomized trials of aggressive treatment.

Table 24.1: *Treatment description - strategy - aggressive treatment*

Trial	Studied treatment	Control treatment
Aggressive treatment versus standard teatment		
SANDS (2008) [1, 2]	aggressive targets of LDL-C of 70 mg/dL or lower and SBP of 115 mm Hg or lower for achieving lipid goals, if lifestyle modification was unsuccessful, use of a statin drug was initiated. If the LDL-C goal was not reached with statin use, combination therapy with ezetimibe was initiated. In addition, the nonHDL-C goals were addressed using fish oil, fenofibrate, or niacin. For achieving BP goals, step 1 drugs were angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), in case of intolerance to ACE inhibitors. Step 2 was use of hydrochlorothiazide. Steps 3 to 5 added calcium channel blockers, -blockers, and then -blockers and other vasodilators.	standard targets of LDL-C of 100 mg/dL or lower and SBP of 130 mm Hg or lower

Table 24.2: *Descriptions of participants - strategy - aggressive treatment*

Trial	Patients	
Aggressive treatment versus standard teatment		
SANDS (2008) [1, 2]	Adults with type 2 diabetes	
	Inclusion criteria: men and women with type 2 diabetes; aged 40 years or older; documented type 2 diabetes, plus LDL-C of at least 100 mg/dL and SBP greater than 130 mm Hg within the previous 12 months	**Exclusion criteria:** new York Heart Association class III or IV heart failure, SBP greater than 180mmHg, liver transaminase levels more than twice the upper limit of normal, or diagnosis of primary hyperlipidemia or hypercholesterolemia due to hyperthyroidism or nephrotic syndrome

continued...

Trial	Patients

Table 24.3: *Design and methodological quality of trials - strategy - aggressive treatment*

Trial	Design	Duration	Centre	Primary endpoint
Aggressive treatment versus standard teatment				
SANDS, 2008 [1, 2] n=499	Parallel groups open exploratory trial	3 years inclusion period: may 2003 - jul 2004	US 4 centres	common carotid artery intimal medial thickness (IMT)

Table 24.4: *Trial characteristics - strategy - aggressive treatment*

Trial	LDL change, end of study (mg/DL)	cholesterol change (mmol/L)	CRP change	LDL change, at 1 y (mg/dL)
Aggressive treatment versus standard teatment				
SANDS, 2008 [1, 2]	-0.82			

24.2 Meta-analysis results

The results are detailed in table 24.5 (page 156). This table is followed by the Forest's plot corresponding to each endpoint.

Aggressive treatment versus standard teatment

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 1.35 (95% CI 0.55 to 3.29, p=0.5128).
The single study 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 0.49 (95% CI 0.09 to 2.65, p=0.4077).

Table 24.5: *Results details - strategy - aggressive treatment*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
aggressive treatment versus standard teatment						
cardiovascular events	RR=1.35	[0.55;3.29]	0.5128	1.0000 (I^2=0.00)	1	499
non cardiovascular death	RR=0.49	[0.09;2.65]	0.4077	1.0000 (I^2=1.00)	1	499
adverse events	RR=1.32	[0.98;1.78]	0.0722	1.0000 (I^2=0.00)	1	499

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 cardiovascular events*

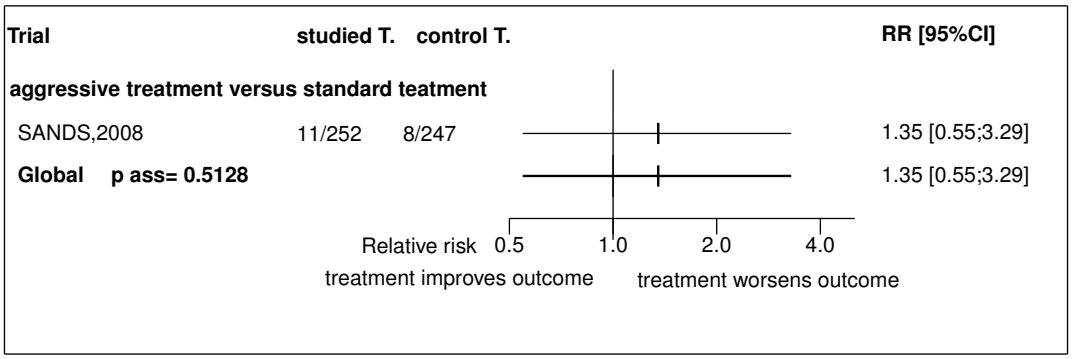


Figure 24.2: *Forest's plot for non cardiovascular death*

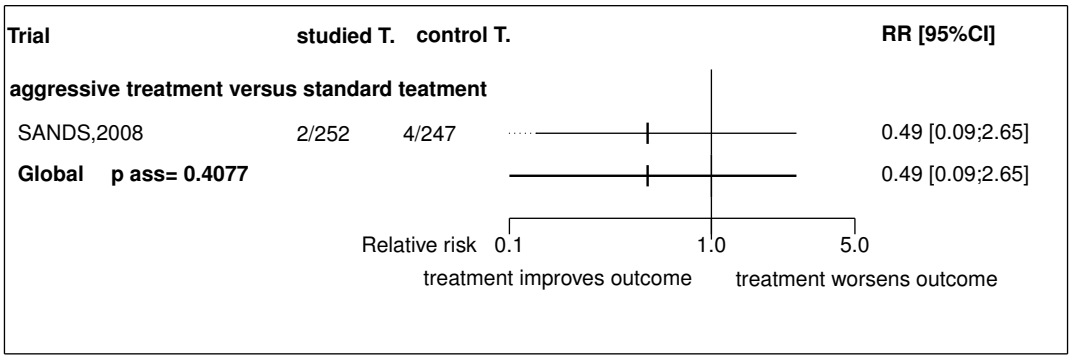
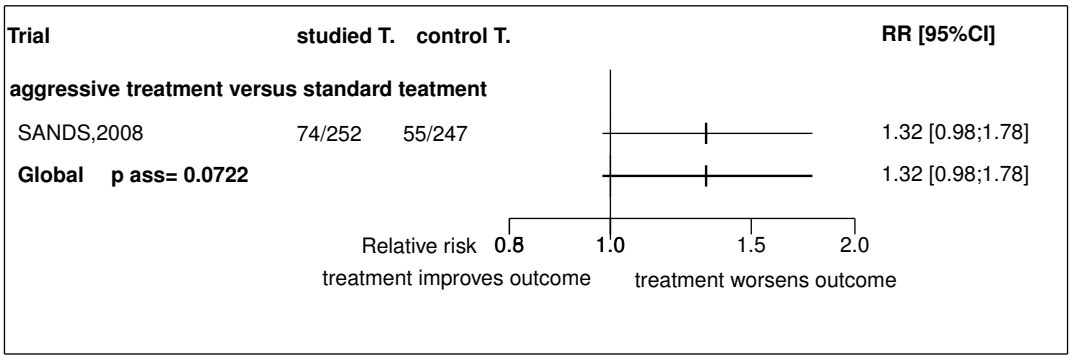


Figure 24.3: *Forest's plot for adverse events*



References

[1] Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, Silverman A, Galloway JM, Henderson JA, Weir MR, Wilson C, Stylianou M, Howard WJ. Effect of Statins Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes The SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial. J Am Coll Cardiol 2008 Dec 16;52:2198-205. [PMID=19095139]

[2] Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, Howard WJ, Lee ET, Mete M, Poolaw B, Ratner RE, Russell M, Silverman A, Stylianou M, Umans JG, Wang W, Weir MR, Weissman NJ, Wilson C, Yeh F, Zhu J. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA 2008;299:1678-89. [PMID=18398080]

24.3 Individual trial summaries

Table 24.6: *SANDS, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=499 (252 vs. 247) **Follow-up duration:** 3 years **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial US, 4 centres **Inclusion period:** may 2003 - jul 2004	Adults with type 2 diabetes **Inclusion criteria:** men and women with type 2 diabetes; aged 40 years or older; documented type 2 diabetes, plus LDL-C of at least 100 mg/dL and SBP greater than 130 mm Hg within the previous 12 months **Exclusion criteria:** New York Heart Association class III or IV heart failure, SBP greater than 180mmHg, liver transaminase levels more than twice the upper limit of normal, or diagnosis of primary hyperlipidemia or hypercholesterolemia due to hyperthyroidism or nephrotic syndrome	**Studied treatment:** aggressive targets of LDL-C of 70 mg/dL or lower and SBP of 115 mm Hg or lower for achieving lipid goals, if lifestyle modification was unsuccessful, use of a statin drug was initiated. If the LDL-C goal was not reached with statin use, combination therapy with ezetimibe was initiated. In addition, the nonHDL-C goals were addressed using fish oil, fenofibrate, or niacin. For achieving BP goals, step 1 drugs were angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), in case of intolerance to ACE inhibitors. Step 2 was use of hydrochlorot **Control treatment:** standard targets of LDL-C of 100 mg/dL or lower and SBP of 130 mm Hg or lower	Cardiovascular events RR=1.35 [0.55;3.29]

References

Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, Silverman A, Galloway JM, Henderson JA, Weir MR, Wilson C, Stylianou M, Howard WJ. Effect of Statins Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes The SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial. J Am Coll Cardiol 2008 Dec 16;52:2198-205 [PMID=19095139]
Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, Howard WJ, Lee ET, Mete M, Poolaw B, Ratner RE, Russell M, Silverman A, Stylianou M, Umans JG, Wang W, Weir MR, Weissman NJ, Wilson C, Yeh F, Zhu J. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA 2008;299:1678-89 [PMID=18398080]

25 Global meta-analysis: all strategy

25.1 Global meta-analysis: all strategy versus standard teatment

Table 25.1: *All strategyversus standard teatment*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=1.35	0.55;3.29	0.5128	1.0000 (0.00)	1	499
non cardiovascular death	RR=0.49	0.09;2.65	0.4077	1.0000 (1.00)	1	499

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

26 Ongoing studies of strategy

No ongoing trial was identified.

27 Excluded studies for strategy

No trial was excluded.

References