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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Evaluation of the effects of statins (with particular consideration of atorvastatin)

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Aim of the evaluation

In 2004 and 2005, public statements were repeatedly made and controversially discussed in respect of the therapeutic superiority of atorvastatin (Sortis®) over other statins.

In particular, statements with regard to:

- greater benefits of atorvastatin in patients with stable coronary heart disease;

- greater benefits of atorvastatin in patients with acute coronary syndrome;

- greater benefits of atorvastatin in patients with diabetes mellitus;

- fewer adverse drug effects with atorvastatin during high-dose statin therapy;

- overall superiority of atorvastatin due to its LDL cholesterol-lowering potency.

Statin therapy is one of the main interventions in patients with cardiovascular disease, the main cause of death in men and women in Germany. Statements regarding the superiority of a particular statin are therefore of vital importance for patients and physicians.

The aim of this systematic literature review is to describe and evaluate the current evidence available on the therapeutic effects of statins, focussing on the aspects described above, and to relay the results to physicians, patients, and the Federal Joint Committee.

This evaluation was conducted according to the valid published scientific methods of the Institute.

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Summary of results

In patients with stable coronary heart disease, only simvastatin and pravastatin showed a benefit of statin therapy with regard to a life-prolonging effect. No such evidence of a benefit was shown for atorvastatin, fluvastatin, and lovastatin.

Studies on patient-relevant benefits of statins in patients with acute coronary syndrome were available for atorvastatin, pravastatin, and simvastatin. Flaws in study design and study reporting make interpretation of data difficult with regard to comparative evaluations. The superiority of a specific statin over another with regard to patient-relevant endpoints was not demonstrated.

In patients with diabetes mellitus, only simvastatin showed a benefit of statin therapy with regard to a life-prolonging effect. No such evidence of a benefit was shown for atorvastatin, fluvastatin, lovastatin, and pravastatin.

In studies conducted with the highest approved dose, discontinuations of therapy due to adverse events occurred more frequently in patients treated with atorvastatin than in patients treated with simvastatin. In addition, liver enzyme elevations occurred more frequently with atorvastatin than with simvastatin or pravastatin.

It cannot be inferred from the available long-term intervention studies on different statins that the degree of LDL cholesterol lowering is appropriate to generally demonstrate or quantify benefits with regard to patient-relevant endpoints.

1 Background

Randomised, controlled trials (RCTs) have repeatedly shown that treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduces the risk of first or recurrent myocardial infarction in patients with pre-existing coronary heart disease (CHD) [106,421,466]. This also applies in part to patients without manifest vascular disease, but with an increased risk of vascular events [466].

The effects of statins are varied. Besides their primary effect, the lowering of serum cholesterol levels (in particular low-density lipoprotein [LDL] cholesterol) through inhibition of HMG-CoA reductase, statins are associated with other potentially beneficial effects on parameters that can be linked to the risk of coronary or other vascular events and are regarded as risk markers or risk factors for such events. These effects of statins are referred to as pleitropic effects [423]. Examples include the effects on platelet function and on high-density lipoprotein (HDL) cholesterol and C-reactive protein (CRP) levels [2,60,330,422]. However, it is still unclear which of these versatile effects are ultimately relevant for treatment benefits in high-risk patients, and which additional pathophysiological mechanisms are involved. It is a matter of controversy whether and to what extent the lowering of LDL cholesterol is causally responsible for these benefits; previous studies have even disproved a benefit of treatment with other cholesterol-lowering drugs [426, 459]. Intervention studies have shown that certain cholesterol-lowering interventions do not reduce cardiac risks but may even increase them [426,459]. LDL cholesterol cannot therefore be generally regarded as a valid surrogate parameter of a benefit with regard to cardiac events. Other markers, including CRP, have recently been described as potent indicators of an outcome-orientated treatment of cardiovascular high-risk patients [208,213,424]; however, their clinical relevance is also unclear.

Furthermore, the isolated investigation of specific cardiovascular risk markers does not consider the spectrum of adverse effects of individual substances and substance classes, and is therefore inappropriate for a balanced appraisal of beneficial and harmful effects. For example, the statin cerivastatin (Lipobay®) was withdrawn from the international market in 2001 after several incidents of serious adverse effects, including deaths [427]. Regarding cholesterol-lowering effects, daily treatment with 0.4 mg cerivastatin daily vs. 40 mg pravastatin daily is approximately comparable [330]. In contrast to therapy with cerivastatin,

the available evidence shows a positive benefit-harm ratio for daily treatment with 40 mg pravastatin [66].

In a large-scale intervention study, clofibrate led to an increase in total mortality despite lowering cholesterol levels [467]. The assessment of total mortality is therefore the most important parameter to describe the benefit of cholesterol-lowering drugs and non-drug interventions in high-risk patients.

Experiences with clofibrate and numerous other examples have shown that evidence of the positive effect of a particular therapy on a surrogate parameter (e.g. laboratory values or results of medical-technical tests) does not suffice as evidence of a benefit of this therapy with regard to patient-relevant endpoints [452,453]. The opposite effect, namely more harm than benefit, may be the case.

In summary, statins have numerous known and possibly also unknown effects on known and unknown, important and less important cardiac risk markers; LDL cholesterol is only one of these markers. LDL cholesterol, according to the results of available intervention studies on different cholesterol-lowering therapies, is neither a valid surrogate marker for cardiovascular events nor for total mortality. Serious adverse effects led to the withdrawal of cerivastatin from the market, a statin which effectively lowers elevated serum cholesterol levels. To assess the effects of statin therapy on patient-relevant endpoints, long-term studies that investigate exactly these endpoints as well as adverse effects are necessary for all statins, not studies that investigate effects on surrogate markers (e.g. LDL- and HDL-cholesterol, CRP, blood coagulation parameters etc.). This also applies without reservation to the question as to whether a particular statin has a superior benefit-risk ratio compared with other statins.

2 Research questions

The aim of this review is to answer the following research questions on statins.[*]

Section 4.1

1a) Does statin therapy in patients with stable CHD lead to a reduction in total mortality and/or coronary morbidity and mortality?

1b) In this context, can a superior effect of atorvastatin (Sortis®) over other statins be inferred from the intervention studies available?

Section 4.2

2a) Does the prompt initiation of statin therapy in patients with acute coronary syndrome lead to a reduction in total mortality and/or coronary morbidity and mortality?

2b) In this context, can a superior effect of atorvastatin (Sortis®) over other statins be inferred from the intervention studies available?

Section 4.3

3a) Does statin therapy in patients with diabetes mellitus lead to a reduction in total mortality and/or coronary morbidity and mortality?

3b) In this context, can a superior effect of atorvastatin (Sortis®) over other statins be inferred from the intervention studies available?

Section 4.4

4) In studies conducted with the highest approved dose, do adverse drug effects (especially hepatic or myopathic effects) occur more frequently or more rarely with atorvastatin (Sortis®) than with other statins?

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[*] In the following text, the term "statins" refers to all currently approved and available HMG-CoA-reductase inhibitors in Germany (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin).

Section 4.5

5) Is there an association between the degree of statin-induced LDL cholesterol lowering and the degree of reduction of total mortality or coronary morbidity and mortality?

3 Methods

Specific literature searches for topic-related scientific publications (the basic procedures are outlined in Appendix B), and the systematic evaluation of these publications form the basis of the conclusions made in this review. Specific inclusion and exclusion criteria, the corresponding search date, as well as other topic-related methodological details are described in the respective section.

Information on the randomisation process, allocation concealment[†] and blinding of the assessment of endpoints in the individual studies was extracted from the available publications and is presented in this review. Insofar as it can be assumed with sufficient probability from the information provided that randomisation, allocation concealment, and assessment of endpoints were devised so that the probability of systematic distortion was minimised, these procedures are referred to as "adequate".[‡] If the information provided was insufficient, then the relevant information available is presented for each case. Insofar as it is inferred from the information provided that randomisation, allocation concealment and/or assessment of endpoints were conducted in a way that systematic distortion was possible or probable, this is noted separately and taken into account in the summarised evaluation of the statin (e.g. by conducting a sensitivity analysis).

In the following, results are described as "statistically significant" if their error probability is less than 5% ($p < 0.05$ [two-sided]).

The results of the relevant individual studies are presented in a summary. If no clear conclusions on a particular substance could be made from the results of the individual studies, meta-analyses were conducted additionally, provided that this was a meaningful procedure and possible on the basis of the information available.

[†] Concealment of treatment allocation at study entry.

[‡] Examples for this purpose are: a) for randomisation: block randomisation using a computer-generated list with variable block sizes; b) for allocation concealment: centralised telephone randomisation, issue of medication in neutral packaging coded with a randomisation number; c) for blinded assessment of endpoints: evaluation by an independent committee (blinded towards the type of treatment) on the basis of patient files.

In order to assess the relevance of the exclusion of patients from the evaluation who were lost to follow-up, best case/worst case analyses were conducted with regard to the overall conclusion of the respective study. The results of these analyses are presented in Sections 4.1 to 4.3 for efficacy endpoints (total mortality, coronary morbidity and mortality), and in Section 4.4 for safety endpoints. A prerequisite for these analyses in each case was that, according to the publication of the study, a statistically significant difference was shown between treatment groups, and event rates were reported in the publications. The following procedure was adopted:

a) Best case analysis: For all patients lost to follow-up in the intervention group, it was assumed that the respective event had not occurred. For all patients lost to follow-up in the control group, it was assumed that the respective event had occurred.

b) Worst case analysis: for all patients lost to follow-up in the intervention group, it was assumed that the respective event had occurred. For all patients lost to follow-up in the control group, it was assumed that the respective event had not occurred

If in both analyses a difference in the event rate continued to be shown between treatment groups, and this was in accordance with the results reported in the publication (e.g. fewer events with Therapy A than with Therapy B), the study result is described as "robust" in this review.

Insofar as only a predefined subgroup analysis in a study was relevant for a particular question, but details on the number of patients lost to follow-up were only available for the overall study population, it was assumed that the proportion of patients lost to follow-up in the subgroup population was analogous to the proportion of patients lost to follow-up in the overall study population.

Examples of best case/worst case analyses are presented in Appendix C.

The specific applicable methodological aspects for Section 4.5 are described in Section 4.5.3.

In addition to these aspects, the methods published by the Institute on 01.03.2005 apply [479].

4 Results

The results for the individual research questions stated in Section 2 are presented in the following sections.

4.1 Stable coronary heart disease

4.1.1 Research questions

1a)   Does statin therapy in patients with stable CHD lead to a reduction in total mortality and/or coronary morbidity and mortality?

1b)   In this context, can a superior effect of atorvastatin (Sortis[®]) over other statins be inferred from the intervention studies available?

4.1.2 Conclusion

In patients with stable CHD, only simvastatin and pravastin showed a benefit of statin therapy with regard to a life-prolonging effect. No such evidence of a benefit was shown for atorvastatin, fluvastatin, and lovastatin.

4.1.3 Search strategy

The general methodology of the literature search is described in Appendix B.

Studies fulfilling all the following inclusion criteria and none of the exclusion criteria were included in the evaluation.

Inclusion criteria:

I-1.   **Patients:** Adults with stable CHD (as defined in the respective study), with or without previous myocardial infarction, and who were not included in the study as a result of an acute cardiac event. Studies where, in addition to patients with stable CHD, other patients were also investigated, were only included in the evaluation if predefined subgroup analyses were available for patients with stable CHD.

I-2.   **Intervention:** Statin therapy in a dose approved in Germany.

I-3.   **Control treatment:** Treatment with placebo or another statin in a dose approved in Germany.

I-4.   **Additional lipid-lowering therapy:** The evaluation included studies in which an additional lipid-lowering treatment, depending on cholesterol levels, was possible. The evaluation did not include studies in which a priori a lipid-lowering combination therapy represented the intervention or control treatment (e.g. therapy with a statin and a fibrate).

I-5.   **Endpoints:** Total mortality, coronary morbidity and mortality. Mortality data from studies which were not primarily designed to investigate these endpoints are presented additionally, insofar as only patients with stable CHD were investigated.

I-6.   **Study design:** Double-blind RCT.

I-7.   **Duration:** > 1 year.

I-8.   **Language of publication:** German or English.

Exclusion criteria:

E-1.   Studies in patients who had undergone heart transplantation.

E-2.   No full-text publication available.

4.1.4 Search results

The systematic literature search identified six studies that corresponded to the inclusion/ exclusion criteria and were designed to provide evidence of an effect with regard to one of the endpoints stated under I-5:

-   the Scandinavian Simvastatin Survival Study (4S) [70];
-   the Cholesterol and Recurrent Events (CARE) Study [72];
-   the Heart Protection Study (HPS) [100];
-   the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study [66];
-   the Lescol Intervention Prevention Study (LIPS) [99,198];
-   the Lescol in Severe Atherosclerosis (LiSA) Study [71].

All studies were placebo-controlled. Direct comparison studies between different statins were not found.

In addition to these six studies, the Treating to New Targets (TNT) Study [436] was identified as the only double-blind, long-term, dose-comparison study on atorvastatin that assessed patient-relevant endpoints in patients with stable CHD (see inclusion criterion I-5). Despite not fulfilling inclusion criterion I-3 (atorvastatin was also used as a control intervention in a low dose), the TNT study is presented in this section.

Nine additional double-blind, long-term studies were identified [43,82-85,89,90,438,455], these studies were not primarily designed to prove an effect with regard to the endpoints listed under inclusion criterion I-5, but reported mortality rates. These mortality rates are presented separately.

4.1.5 Description of the studies included

Information on the design of the six studies included and on the TNT study is presented in Table 1. Main patient characteristics and inclusion/exclusion criteria are presented in Table 2.

For atorvastatin, no relevant placebo-controlled study or direct comparative study on statins was identified (except the TNT dose-comparison study).

Two relevant placebo-controlled studies on fluvastatin, the LIPS study and the LiSA study, were found. In the LIPS study, which only included patients following successful percutaneous coronary intervention (PCI), the predefined subgroup analysis of patients with stable angina pectoris was relevant for the research question posed. This subgroup represented approx. 50% of the whole study population. The second relevant study was the LiSA study, which included patients with CHD confirmed by a positive exercise-ECG.

No relevant study on lovastatin was found.

Two relevant placebo-controlled studies on pravastatin were found; the CARE and LIPID studies. Only patients with previous myocardial infarction were included in the CARE study. The LIPID study also included patients with a history of unstable angina pectoris.

Two relevant placebo-controlled studies on simvastatin, the 4S-study and the HPS study, were found. The 4S-study included patients with previous myocardial infarction or stabile angina pectoris. In the HPS study, a mixed primary and secondary prevention study, the predefined subgroup evaluation of CHD patients was relevant for the research question posed. This subgroup represented approx. 65% of the overall study population.

Table 1: Long-term studies in patients with stable coronary heart disease - Overview

Statin Study	Follow-up [years]	Number of patients [intervention] [control]	Primary endpoint	Total mortality reported
Atorvastatin				
TNT [436] 2005	4.9[a]	5006 [atorvastatin 80 mg] 4995 [atorvastatin 10 mg]	Combined endpoint: death from CHD, non-fatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, fatal or non-fatal stroke.	yes (secondary endpoint).
Fluvastatin				
LIPS [198][b] 2004	3.9[a]	418 [fluvastatin 80 mg] 416 [placebo]	Combined endpoint: cardiac death, non-fatal myocardial infarction, repeat coronary intervention procedure.	yes (secondary endpoint); not reported separately for patients with stable angina pectoris.
LiSA [71] 1999	1	187 [fluvastatin 40-80 mg] 178 [placebo]	Combined endpoint: death from cardiovascular cause (fatal myocardial infarction, sudden cardiac death) non-fatal myocardial infarction, coronary artery bypass graft, unstable angina pectoris.	no
Pravastatin				
CARE [72] 1996	5[a]	2081 [pravastatin 40 mg] 2078 [placebo]	Combined endpoint: death from CHD (fatal myocardial infarction [either definite or probable], sudden death, death during a coronary intervention, death from other coronary causes), symptomatic (unless during non-cardiac surgery) non-fatal myocardial infarction.	yes (tertiary endpoint).
LIPID [66] 1998	6.1[c]	4512 [pravastatin 40 mg] 4502 [placebo]	Death from CHD (fatal myocardial infarction, sudden death, death in the hospital after possible myocardial infarction, death due to heart failure or another coronary cause).	yes (secondary endpoint).
Simvastatin				
4S [70] 1994	5.4[a]	2221 [simvastatin 20-40 mg][d] 2223 [placebo]	Total mortality.	yes (primary endpoint).
HPS [100][e] 2002	5[c,f]	6694 [simvastatin 40 mg] 6692 [placebo]	Outcome criteria for overall population: deaths from all causes, from CHD, and from all other causes. Combined endpoints for subgroup of patients with CHD: major vascular and major coronary events.	yes (primary endpoint); not reported separately for patients with CHD.

Table 1: Long-term studies in patients with stable coronary heart disease – Overview (continued)

a: Median.
b: Predefined subgroup (patients with stable angina pectoris). Further information applies to this subgroup, unless otherwise stated.
c: Mean.
d: A dose of 10 mg simvastatin daily was also possible, but only affected two patients (< 0.1%).
e: Predefined subgroup (patients with known CHD). Further information applies to this subgroup, unless otherwise stated.
f: Data for overall population; separate data on patients with CHD are lacking.
CHD: coronary heart disease.

Table 2: Long-term studies in patients with stable coronary heart disease – Patient characteristics

Statin Study	Age [years][a]	Sex f[%]	m[%]	Previous myocardial infarction [%]	Main inclusion criteria	Main exclusion criteria
Atorvastatin						
TNT [436]					Myocardial infarction / coronary revascularisation > 1 month before study entry; angina pectoris.	Congestive heart failure (EF < 30%), uncontrolled hypertension, uncontrolled diabetes mellitus, liver disease.
Atorvastatin 80	61±9	19	81	59		
Atorvastatin 10	61±9	19	81	58		
Fluvastatin						
LIPS [198]					Stable angina following successful completion of first PCI 0-6 months before study entry.	Congestive heart failure (EF < 30%), uncontrolled hypertension, renal dysfunction (serum creatinine > 1.8 mg/dl).
Fluvastatin	60±10	14	86	43		
Placebo	60±10	16	84	46		
LiSA [71]					Stable CHD confirmed by positive exercise-ECG.	Congestive heart failure (NYHA III or NYHA IV), liver disease.
Fluvastatin	59±8	37	63	35		
Placebo	60±7	40	60	36		
Pravastatin						
CARE [72]					Myocardial infarction 3-20 months before study entry.	Symptomatic congestive heart failure
Pravastatin	59±9	14	86	100		
Placebo	59±9	14	86	100		
LIPID [66]					Myocardial infarction or hospitalisation for unstable angina pectoris 3-36 months before study entry.	Cardiac failure, hepatic disease, renal disease.
Pravastatin	62 (55-67)	17	83	64		
Placebo	62 (55-68)	17	83	64		

Table 2: Long-term studies in patients with stable coronary heart disease – Patient characteristics (continued)

Statin Study	Age [years][a]		Sex f [%]	m[%]	Previous myocardial infarction [%]	Main inclusion criteria	Main exclusion criteria
Simvastatin							
4S [70]	women	men				Myocardial infarction > 6 months before study entry, stable angina pectoris.	Congestive heart failure requiring treatment with digitalis, stroke.
Simvastatin	61±6	58±7	18	82	79		
Placebo	61±6	58±7	19	81	79		
HPS [100] Simvastatin Placebo	64±8[b]		23	77[c]	64[b]	Myocardial infarction / coronary artery bypass graft / unstable angina pectoris > 6 months before study entry; stable angina pectoris.	Severe heart failure, liver disease, renal disease (serum creatinine > 2.3 mg/dl).

a: Mean (rounded off where necessary) with standard deviation (±), or median (with interquartile range, if available).
b: Data for overall population of the HPS Study (n = 20536) from [443].
c: Data from [67]; sum of patients with CHD in [67] is discrepant to information in [100]: n = 13379 vs. n = 13386.
EF: ejection fraction; ECG: electrocardiogram; CHD: coronary heart disease; NYHA III / IV: classification of the degree of congestive heart failure of the New York Heart Association; PCI: percutaneous coronary intervention; m: male; f: female.

Criteria for study and publication quality are presented in Table 3.

No detailed information on the randomisation process and allocation concealment was found for the LiSA and TNT studies, even after perusal of additional publications (e.g. publications on study design or on results in specific subgroups), so it cannot be judged whether randomisation and allocation concealment were adequate in these studies. The randomisation in the CARE study was performed centrally by telephone by a Data Coordinating Centre [457]. The mechanisms that ensured a random distribution cannot be identified from the information provided. Randomisation was adequate in the LIPID study, but no details were provided on allocation concealment. The randomisation process and allocation concealment were adequate in the 4S, HPS, and LIPS studies.

In all studies, the assessment of main endpoints (mortality and/or vascular morbidity) was blinded.

Sample size planning was described comprehensibly in all seven studies.

In all studies except for the LiSA study, the rate of patients in relation to the overall study population who were lost to follow-up during the study was under 3%. Insofar as statistically significant differences between treatment groups were found with regard to the endpoints reported in Table 4, these results remained robust after a best case/worst case analysis was conducted; i.e., the tendency of the results was not altered by extreme assumptions. In the LiSA study 87 patients (approx. 24% of the overall study population) discontinued prematurely. It was not described in the publication, whether and to what extent these patients were taken into account in the evaluation. Due to the overall low event rate in the LiSA study, the reported results did not remain robust in the best case/worst case analysis (with consideration of these 87 patients). The results of the LiSA study are therefore fraught with great uncertainty.

Table 3: Long-term studies in patients with stable coronary heart disease – Quality of studies and publications

Statin Study	Randomisation	Allocation concealment	Blinded assessment of endpoints[a]	Sample size planning	Lost to follow-up [n]	Discrepant information on patients lost to follow-up	ITT-analysis robust[b]
Atorvastatin							
TNT [436]	n.d.	n.d.	yes, adequate	described adequately	47 (atorvastatin 80) 37 (atorvastatin 10)	no	yes
Fluvastatin							
LIPS [198]	adequate	adequate	yes, adequate	described adequately	7 (fluvastatin)[c] 10 (placebo)[c]	no	no relevant endpoint statistically significantly different
LiSA [71]	n.d.	n.d.	yes, adequate	described adequately	41 (fluvastatin) 46 (placebo)	no	no
Pravastatin							
CARE [72]	n.d.	adequate	yes, adequate	described adequately	1 (regarding mortality)	no	yes
LIPID [66]	adequate	n.d.	yes, adequate	described adequately	1 (regarding mortality)	no	yes
Simvastatin							
4S [70]	adequate	adequate	yes, adequate	described adequately	0 (regarding mortality)	no	yes
HPS [100]	adequate	adequate	yes, adequate	described adequately	7 (mortality)[d] 60 (morbidity)[d]	no	yes

Table 3: Long-term studies in patients with stable coronary heart disease – Quality of studies and publications (continued)

a: Regarding coronary morbidity/mortality and/or total mortality.
b: After a best case/worst case analysis was conducted with consideration of the patients not followed up. See also previous text.
c: Data for the overall study population from [99]; no separate data provided for the population with CHD.
d: Data for the overall study population; no separate data provided for the population with CHD.
ITT: Intention to treat; n.d.: no details provided; CHD: coronary heart disease.

Table 4: Long-term studies in patients with stable coronary heart disease - Results

Statin Study	Total mortality	Coronary mortality	Non-fatal myocardial infarction	Primary endpoint[a]	Duration of observation [patient years]
Atorvastatin					
TNT [436]	HR: 1.01 (0.85-1.19)	HR: 0.8 (0.61-1.03)	**HR: 0.78 (0.66-0.93)**	**HR: 0.78 (0.69-0.89)**	48900[b]
Atorvastatin 80	284 (5.7%)	101 (2%)	**243 (4.9%)**	**434 (8.7%)**	
Atorvastatin 10	282 (5.6%)	127 (2.5%)	**308 (6.2%)**	**548 (10.9%)**	
Fluvastatin					
LIPS [198]	HR: 0.69 (0.45-1.07)[c]	n.d.	n.d.	HR: 0.8 (0.6-1.07)	3200[b]
Fluvastatin	36 (4.3%)			n.d.	
Placebo	49 (5.9%)			n.d.	
LiSA [71]	n.d.	HR: n.d.	HR: n.d.	p < 0.05 (HR: n.d.)	350[b]
Fluvastatin		2 (1.1%)	0 (0%)	3 (1.6%)	
Placebo		4 (2.2%)	1 (0.6%)	10 (5.6%)	
Pravastatin					
CARE [72]	HR: 0.91 (0.74-1.12)	HR: 0.8 (0.61-1.05)	**HR: 0.77 (0.61-0.96)**	**HR: 0.76 (0.64-0.91)**	20700[b]
Pravastatin	180 (8.6%)	96 (4.6%)	**135 (6.5%)**	**212 (10.2%)**	
Placebo	196 (9.4%)	119 (5.7%)	**173 (8.3%)**	**274 (13.2%)**	
LIPID [66]	**HR: 0.78 (0.69-0.87)**	**HR: 0.76 (0.65-0.88)**	HR: 0.71 (0.62-0.82)	**corresponds to "coronary mortality"**	54900[b]
Pravastatin	**498 (11%)**	**287 (6.4%)**	7.5%		
Placebo	**633 (14.1%)**	**373 (8.3%)**	10.3%		
Simvastatin					
4S [70]	**HR: 0.7 (0.58-0.85)**	**HR: 0.58 (0.46-0.73)**	**HR: 0.63 (0.54-0.73)[d]**	**corresponds to "total mortality"**	23900[b]
Simvastatin	**182 (8.2%)**	**111 (5%)**	279 (12.6%)		
Placebo	**256 (11.5%)**	**189 (8.5%)**	418 (18.8%)		
HPS [100]	HR: 0.87 (0.81-0.94)[c]	HR: 0.8 (0.75-0.9)[c,e]	HR: 0.6 (0.55-0.7)[c,e]	**HR: 0.76 (0.69-0.84)[f]**	66100[g]
Simvastatin	1328 (12.9%)	587 (5.7%)	357 (3.5%)	**717 (10.7%)**	
Placebo	1507 (14.7%)	707 (6.9%)	574 (5.6%)	**927 (13.9%)**	

Table 4: Long-term studies in patients with stable coronary heart disease – Results (continued)

a: As defined in the respective study; see also Table 1.
b: Approximate calculation from number of patients * duration of observation (mean or median, according to study); rounded off.
c: Data for overall population, no separate data for patients with CHD provided.
d: Endpoint "definite or probable acute myocardial infarction". For endpoint: "definite acute myocardial infarction", no hazard ratio provided. Event rate with simvastatin: 7.4%; with placebo: 12.1%.
e: Read off and rounded off from figure in [100].
f: Endpoint: "major coronary events".
g: Approximate calculation from patient years in [100] * 65% (corresponds to proportion of patients with CHD in the overall study population); rounded off.
Data presented as hazard ratio (with 95% confidence interval, if available).
Statistically significant events are in bold print, insofar as only patients with stable CHD were included in the respective analysis and the result remained robust after a best case/worst case analysis was conducted.
For studies where not only patients with stable CHD were investigated, the results of the subgroup of patients with stable CHD are presented (if available). Insofar as results were only available for the overall study population, these are presented if the predefined subgroup of patients with stable CHD represented approx. 50% or more of the overall study population.
HR: hazard ratio; n.d.: no details provided; CHD: coronary heart disease.

Table 5: Long-term studies in patients with stable coronary heart disease – Adverse effects

Statin Study	Discontinuations of therapy due to AEs	Liver enzyme elevations[a]	Creatinine kinase elevations[b]	Rhabdomyolysis	New cancers[c]
Atorvastatin					
TNT [436]	p < 0.001	p < 0.001[d]	p: n.d.	p: n.d.	p = 0.42[e]
Atorvastatin 80	7.2%	1.2%[d]	0%[d]	2 (0.04%)	1.7%[e]
Atorvastatin 10	5.3%	0.2%[d]	0%[d]	3 (0.06%)	1.5%[e]
Fluvastatin					
LIPS [99][f]	p: n.d.	p: n.d.	p: n.d.		p: n.d.
Fluvastatin	21.2%	1.2%[d]	0%[g]	0 (0%)	5.5%
Placebo	24%	0.4%[d]	0.4%[g]	n.d.	5.9%
LiSA [71]	p: n.d.	n.d.	p: n.d.	n.d.	n.d.
Fluvastatin	6.1%		0%[g]		
Placebo	4.5%		0.6%[g]		
Pravastatin					
CARE [72]	p = 0.007	p: n.d.	p: n.d.	n.d.	p: n.d.
Pravastatin	2.2%	3.2%[g]	0.6%[g]		8.3%
Placebo	3.6%	3.5%[g]	0.3%[g]		7.7%
LIPID [66]	n.d.	p = 0.41	p: "not significant"	n.d.	p = 0.43
Pravastatin		2.1%	n.d.		8.4%
Placebo		1.9%	n.d.		8.9%

Table 5: Long-term studies in patients with stable coronary heart disease – Adverse effects (continued)

Statin Study	Discontinuations of therapy due to AEs	Liver enzyme elevations[a]	Creatinine kinase elevations[b]	Rhabdomyolysis	New cancers[c]
Simvastatin					
4S [70]	p: n.d.	p: n.d.	p: n.d.	p: n.d.	p: n.d.
Simvastatin	5.7%	2.2%[g,h]	0.3%[i]	1 (0.04%)	4.1%
Placebo	5.8%	1.5%[g,h]	0.04%[i]	0 (0%)	4.3%
HPS [100][f]	p: n.d.	p = 0.3[j]	p=0.07[k]	p: n.d.	p: n.d.
Simvastatin	4.8%	0.09%[j]	0.07%[k]	5 (0.05%)	10.3%
Placebo	5.1%	0.04%[j]	0.01%[k]	3 (0.03%)	9.8%

a: According to definition in the respective study, mostly more than 3-fold increase over the respective normal value.
b: More than 10-fold increase over the respective normal value.
c: Fatal and non-fatal cancers.
d: Persistent enzyme elevations; rate of non-persistent enzyme elevations not clear.
e: Only fatal cancers; non-fatal cancers not reported.
f: Data available only for the overall population.
g: No data provided as to whether persistent.
h: Minimum rate. Separate data provided for different liver enzymes. No data provided on rate of patients with one or more elevations of liver enzymes.
i: Single elevation, not persistent.
j: Persistent elevation. Rate of patients with at least one elevation more than 4 times the normal value: 0.42% (simvastatin) vs. 0.31% (placebo).
k: Persistent elevation (more than 4 times the normal value). Rate of patients with at least one elevation: 0.11% (simvastatin) vs. 0.06% (placebo).
For studies where not only patients with stable CHD were investigated, the results of the subgroup of patients with stable CHD are presented, if available. Insofar as results are only available for the overall study population, these are presented if the predefined subgroup of patients with stable CHD represented approx. 50% or more of the overall study population.
AE: adverse event; CHD: coronary heart disease.

Table 6: Mortality in studies not primarily designed to show evidence of a benefit with regard to morbidity/mortality.

Statin Study	Follow-up [years][a]	Number of patients [intervention] [control]	Myocardial-infarction[b] [%]	Total mortality	Duration of observation [patient years][c]
Atorvastatin					
REVERSAL 2004 [43]	1.5	Atorvastatin 80 mg [327] Pravastatin 40 mg [327]	n.d.	1 (0.3%) 1 (0.3%)	1000
VBS 2005 [455]	1	Atorvastatin 80 mg [96][d] Lovastatin 5 mg [103][d]	42 36	1 (1%) 0 (0%)	200
Lovastatin[e]					
CCAIT 1994 [82]	2	Lovastatin 20-80 mg [165] Placebo [166]	58 51	2 (1.2%) 2 (1.2%)	700
MARS 1993 [83]	2.2	Lovastatin 80 mg [123] Placebo [124]	60[f]	2 (1.6%) 1 (0.8%)	500
Pravastatin[g]					
PLAC I 1995 [84]	3	Pravastatin 40 mg [206] Placebo [202]	46 41	4 (1.9%) 6 (3%)	1200
PLAC II 1995 [85]	3	Pravastatin 20-40 mg [75] Placebo [76]	n.d.	3 (4%) 5 (6.7%)	500
REGRESS 1995 [88]	2	Pravastatin 40 mg [450] Placebo [434]	50 45	5 (1.1%) 7 (1.6%)	1700
Simvastatin					
CIS 1997 [90]	2.3	Simvastatin 40 mg [129] Placebo [125]	n.d.	1 (0.8%) 4 (3.2%)	600
MAAS 1994 [89]	4	Simvastatin 20 mg [193] Placebo [188]	55 54	4 (2.1%) 11 (5.9%)	1500
				Total duration of observation (patient years): 7900	

a: As noted in the respective study (e.g. mean or median).
b: Rate of patients with previous myocardial infarction at study entry.
c: Approximate calculation from number of patients * follow-up (as noted in the respective study); rounded off.
d: Treatment aim: LDL cholesterol < 80 mg/dl in the atorvastatin group; < 130 mg/dl in the lovastatin group. Data for median dose.
e: In addition: VBS study (see under atorvastatin).
f: Data for overall study population.
g: In addition: REVERSAL study (see under atorvastatin).
n.d.: no details provided.

4.1.6 Discussion of study results

4.1.6.1   Total mortality

A statistically significant reduction in mortality following treatment with statins was only shown in studies on pravastatin and simvastatin (pravastatin: LIPID study; simvastatin: 4S study).

In the CARE study (pravastatin), a statistically insignificant difference was shown between treatment groups with fewer mortalities (absolute numbers) reported with pravastatin.

In the meta-analytical summary of results of the LIPID and CARE studies, all in all, a significant effect of pravastatin was shown with regard to a reduction in total mortality (Figure 1).

The results of the 4S (simvastatin) study were confirmed, with reservations, by the HPS study. Information on mortality was only available for the overall study population in the HPS study; no separate details for the subgroup of patients with stable CHD were provided. Under consideration of results available to date from intervention studies on primary and secondary prophylaxis with statins, it can be assumed that a mortality-lowering effect of simvastatin can be expected, particularly in secondary prophylaxis (i.e. in patients with manifest CHD) [421]. However, reliable evidence of a reduction in mortality in patients with stable CHD was lacking in the HPS study.

No statistically significant evidence of a life-prolonging effect was shown in the available intervention studies on fluvastatin and atorvastatin. No relevant studies were available on lovastatin.

The results on total mortality in the studies that were not primarily designed to show a benefit with regard to morbidity/mortality do not contradict the previous statements regarding the effects of individual statins on total mortality (Table 6). The total sum of patient years over all of these nine studies lay, at 7900, clearly below the observation periods for each study on atorvastatin, pravastatin, and simvastatin (20700 to 66100 patient years, [Table 4]).

Figure 1: Meta-analysis of the pravastatin studies in patients with stable CHD – total mortality

Meta-analysis pravastatin
Total mortality
Random effects, logarithm of the hazard ratio

Study	Effect 95% CI	Weight %	Effect 95% CI	
CARE 1996		33.84	0.91	[0.74, 1.12]
LIPID 1998		66.16	0.78	[0.69, 0.88]
Total (95% CI)		100.00	0.82	[0.71, 0.95]

0.50   0.71   1.00   1.41   2.00
favours pravastatin   favours placebo

Heterogeneity: Q=1.62, df=1 (p=0.203), I²=38.2%
Overall effect: Z Score=-2.69 (p=0.007), tau²=0.005
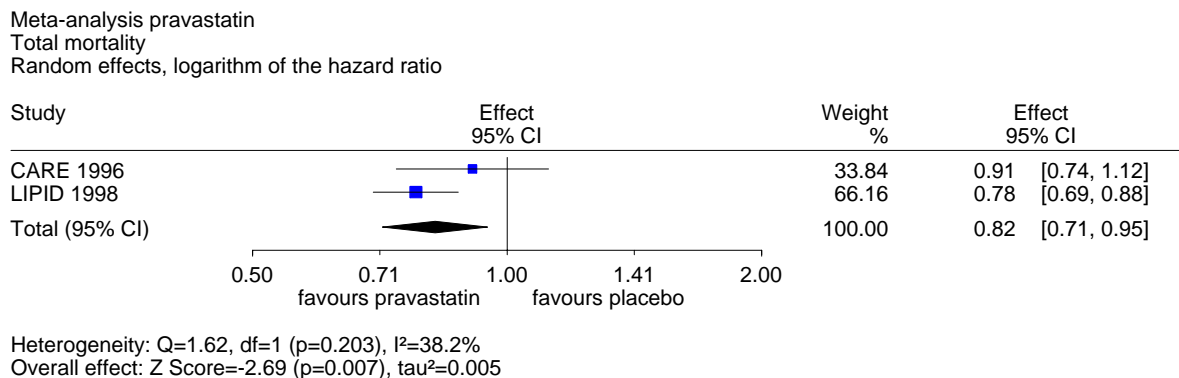
The confidence intervals stated in this figure and the following figures for the meta-analyses may deviate slightly from the confidence intervals stated in the results tables due to the conversion of the standard errors and widths of confidence intervals.

Figure 2: Meta-analysis of the pravastatin studies in patients with stable CHD – coronary mortality.

Meta-analysis pravastatin
Coronary mortality
Random effects, logarithm of the hazard ratio

Study	Effect 95% CI	Weight %	Effect 95% CI	
CARE 1996		23.73	0.80	[0.61, 1.05]
LIPID 1998		76.27	0.76	[0.65, 0.88]
Total (95% CI)		100.00	0.77	[0.67, 0.88]

0.50   0.71   1.00   1.41   2.00
favours pravastatin   favours placebo

Heterogeneity: Q=0.1, df=1 (p=0.746), I²=0%
Overall effect: Z Score=-3.89 (p=0.000), tau²=0.000
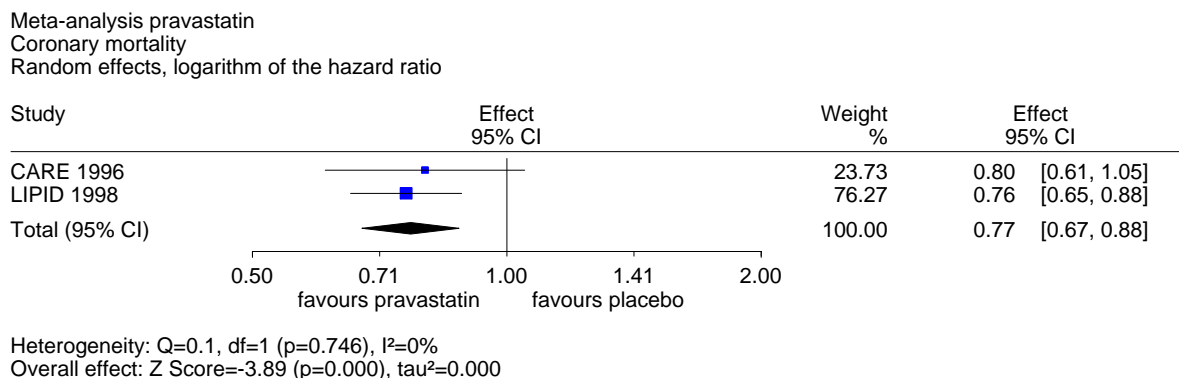
4.1.6.2   Coronary mortality

Consideration of the results available (Table 4) and of the meta-analytical summary of the results on pravastatin (Figure 2) indicates that the conclusions on individual statins with regard to total mortality can also be applied to coronary mortality. The available evidence showed a statistically significant effect of pravastatin and simvastatin with regard to a reduction in coronary mortality; this did not apply to other statins.

4.1.6.3   Non-fatal myocardial infarctions

No statistically significant difference was shown in the LiSA study between patients treated with fluvastatin and patients treated with placebo with regard to non-fatal myocardial infarctions. In the LIPS study, no separate data were provided with regard to occurrence of non-fatal myocardial infarctions.

Both the CARE and the LIPID studies showed a statistically significant difference in respect of non-fatal myocardial infarctions in favour of pravastatin [316].

In the 4S study, statistically significantly fewer non-fatal myocardial infarctions occurred with simvastatin than with placebo. In the HPS study, the event rate in the overall study population (patients with and without CHD) treated with simvastatin was statistically significantly lower than with placebo. Separate data for the subgroup of patients with CHD were not available.

In the TNT study, a statistically significant difference in favour of atorvastatin 80 mg daily was shown. Assuming that no more fatal myocardial infarctions occur with atorvastatin 10 mg than with placebo, evidence of a benefit of treatment with atorvastatin 80 mg with regard to non-fatal myocardial infarctions can be inferred indirectly from the TNT study.

4.1.6.4   Primary study endpoints

In all studies except for the 4S study, the primary endpoint was a combined endpoint including aspects of coronary morbidity and/or mortality. In the 4S study, total mortality was the primary endpoint.

With regard to the different combination endpoints, a statistically significant difference between pravastatin vs. placebo or simvastatin vs. placebo in favour of statin therapy was shown in all studies available.

This also applies to treatment with atorvastatin 80 mg daily vs. atorvastatin 10 mg daily. Assuming that no more cardiac and/or vascular events occur with atorvastatin 10 mg than with placebo, evidence of a benefit of treatment with atorvastatin 80 mg with regard to cardiac and vascular events can be indirectly inferred from the TNT study.

No such evidence of a benefit can be inferred from the two intervention studies on fluvastatin. In the LIPS study, no statistically significant difference was shown between treatment groups in patients with stable CHD. The results of the LiSA study should be regarded as extremely uncertain (see Section 4.1.5) and are not sufficiently robust to show definite evidence of a benefit of fluvastatin therapy.

4.1.6.5   Adverse drug effects

From the intervention studies available, no superiority of one statin over another can be inferred with regard to hepatic or myopathic adverse drug effects (including rhabdomyolysis). Equally, no clear result in favour of or against a particular statin was shown regarding the occurrence of new cancers. A substantially higher risk of statin therapy compared with placebo with respect to the reported adverse drug effects cannot be inferred from the placebo comparison studies.

4.1.6.6 Summary

In patients with stable CHD, evidence of a life-prolonging effect was shown for pravastatin 40 mg vs. placebo and simvastatin 20-40 mg vs. placebo. No such evidence was available for other statins. This was also the case for coronary mortality, non-fatal myocardial infarctions, and the combined endpoints for cardiac and/or vascular events as defined in the respective study.

For atorvastatin 80 mg, evidence of a benefit was shown for cardiac and vascular events compared with atorvastatin 10 mg.

The available data on fluvastatin were insufficient to show certain evidence of a benefit.

No relevant study on lovastatin was available.

All in all, the superiority of atorvastatin over other statins cannot be inferred from the data available.

4.2 Acute coronary syndrome

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4.2.1 Research questions

2a) Does the prompt initiation of statin therapy in patients with acute coronary syndrome lead to a reduction in total mortality and/or coronary morbidity and mortality?

2b) In this context, can a superior effect of atorvastatin (Sortis[®]) over other statins be inferred from the intervention studies available?

4.2.2 Conclusion

No evidence for any statin showed that the initiation of treatment in patients with acute coronary syndrome reduced total mortality, coronary mortality, or the rate of non-fatal myocardial infarctions compared with placebo. All in all, no evidence of the superiority of atorvastatin over other statins can be inferred from the available data. Atorvastatin 80 mg daily in a subgroup of patients with unstable angina pectoris without ST-elevation myocardial infarction was shown to reduce the risk of the occurrence of a combined cardiac endpoint compared with placebo.

For simvastatin 40-80 mg daily and pravastatin 20-40 mg daily, no statistically significant effect was shown for the mixed collective of patients with acute ST-elevation myocardial infarction and unstable angina pectoris compared with placebo or a sequential therapy of placebo and low-dose simvastatin (20 mg).

No relevant studies were available on fluvastatin and lovastatin.

Valid direct comparative studies between different statins were not available.The placebo-controlled studies available cannot be validly compared because of different patient collectives (inclusion of patients with ST-elevation myocardial infarction in the A-Z and PACT studies, but not in the MIRACL study), different study periods (PACT: 30 days vs MIRACL: 16 weeks), and insufficient power of the PACT and the A to Z studies.

4.2.3 Search strategy

The general methodology of the literature search is described in Appendix B.

Studies fulfilling all the following inclusion criteria and none of the exclusion criteria were included in the evaluation.

Inclusion criteria:

I-1.   **Patients:** Adults with acute coronary syndrome (ST-elevation infarction, non-ST-elevation infarction, unstable angina pectoris); study entry during an acute event (within 7 days of the event or during the resulting hospital stay). Studies where, in addition to patients with acute coronary syndrome, other patients were also investigated were only included in the evaluation if predefined subgroup analyses for patients with acute coronary syndrome were available.

I-2.   **Intervention**: Statin therapy in a dose approved in Germany.

I-3.   **Control treatment:** Treatment with placebo or another statin in a dose approved in Germany.

I-4.   **Additional lipid-lowering therapy:** The evaluation included studies in which an additional lipid-lowering treatment, depending on cholesterol levels, was possible. The evaluation did not include studies in which a priori a lipid-lowering combination therapy represented the intervention or control treatment (e.g. therapy with a statin and a fibrate).

I-5.   **Endpoints**: Total mortality, coronary morbidity and mortality. Mortality data for studies that were not primarily designed to investigate one of these endpoints are presented additionally (insofar as only patients with acute coronary syndrome were investigated).

I-6.   **Study design**: Double-blind RCT.

I-7.   **Duration**: > 4 weeks (to describe effects of acute treatment)

I-8.   **Language of publication:** German or English.

Exclusion criteria:

E-1.   Studies in patients who had undergone heart transplantation.

E-2.   No full-text publication available.

4.2.4 Search results

The systematic literature search identified four studies that corresponded to the inclusion/ exclusion criteria and were designed to provide evidence of an effect with regard to one of the endpoints stated under I-5:

- the A-to-Z (Phase Z) Study [182];
- the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study [78];
- the Pravastatin in Acute Coronary Treatment (PACT) Study [223];
- the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) Study [64].

The MIRACL and PACT studies were placebo-controlled.

In the A to Z study, a sequential therapy of simvastatin (initially 40 mg daily for 30 days, then 80 mg daily) was compared with a sequential therapy comprising a 4-month treatment period with placebo and subsequent therapy with simvastatin 20 mg daily. With reference to the mean study duration of 2 years, the A to Z study is to be regarded for the most part as a dose and not as a placebo comparative study. However, the A to Z study, analogously to the TNT study in Section 4.1, is presented here, as it was the only available study on simvastatin in patients with acute coronary syndrome.

The PROVE-IT study was the only direct comparative study on statins (atorvastatin 80 mg vs. pravastatin 40 mg).

Three additional double-blind, long-term studies were found [77,79,460]; these studies were not primarily designed to find evidence of an effect regarding the endpoints listed under inclusion criteria I-5, but reported mortality rates. These mortality rates are presented separately.

4.2.5 Description of the studies included

Details of the design of the four studies included are presented in Table 7. Main patient characteristics and inclusion/exclusion criteria are presented in Table 8.

Two relevant studies on atorvastatin were found; a direct comparative study (PROVE-IT) and a placebo-controlled study (MIRACL).

No relevant studies on fluvastatin and lovastatin were identified.

Two relevant studies on pravastatin were found; a placebo-controlled study, and the direct comparative study vs. atorvastatin (PROVE-IT).

One relevant study on simvastatin was found; the combined placebo and dose-comparison study A to Z (Phase Z).

All studies, apart from MIRACL, also included patients with acute ST-elevation myocardial infarction.

Table 7: Endpoint studies in patients with acute coronary syndrome - Overview

Statin Study	Follow-up	Number of patients [intervention] [control]	Primary endpoint	Total mortality reported
Atorvastatin				
MIRACL 2001 [78]	16 weeks	1538 [atorvastatin 80 mg] 1548 [placebo]	Combined endpoint: death, non-fatal acute myocardial infarction, cardiac arrest with resuscitation, recurrent symptomatic myocardial ischaemia with objective evidence and requiring emergency rehospitalisation.	yes (secondary endpoint).
PROVE-IT 2004 [64]	2 years[a]	2099 [atorvastatin 80 mg][b] 2063 [pravastatin 40 mg][b]	Combined endpoint: death from any cause, myocardial infarction, documented unstable angina requiring rehospitalisation, revascularisation (> 30 days after randomisation), stroke.	yes (secondary endpoint).
Pravastatin[c]				
PACT 2004 [223]	30 days	1710 [pravastatin 20-40 mg] 1698 [placebo]	Combined endpoint: death, recurrence of myocardial infarction, readmission to hospital for unstable angina.	yes (not a predefined endpoint).
Simvastatin				
A-to-Z 2004 [182]	2 years[d]	2265 [simvastatin 40/80 mg][e] 2232 [placebo / simvastatin 20 mg][f]	Combined endpoint: cardiovascular death, non-fatal myocardial infarction, readmission for acute coronary syndrome, stroke.	yes (secondary endpoint).

a: Mean.
b: According to the study protocol, a halving of the dose (in both groups) or dose increase (only pravastatin) was possible. These changes in dose affected less than 10% of all patients.
c: In addition: PROVE-IT study (see under atorvastatin).
d: Median: 721 days.
e: At start of study: 40 mg simvastatin daily; after 30 days: switch to 80 mg daily.
f: At start of study: placebo; after 4 months: switch to 20 mg simvastatin daily.

Table 8: Endpoint studies in patients with acute coronary syndrome – Patient characteristics

Statin Study	Age [years][a]	Sex f[%]	Sex m[%]	Reason for inclusion Myocardial infarction [%]	Reason for inclusion unstable AP / non-ST-MI [%]	Initiation of statin therapy[b]	Main exclusion criteria
Atorvastatin							
MIRACL [78]						24-96 hours after acute event; mean: 63 hours.	Planned coronary revascularisation, severe congestive heart failure (NYHA IIIb/IV), hepatic dysfunction.
Atorvastatin	65±12	36	64	0	100		
Placebo	65±12	34	66	0	100		
PROVE-IT [64]						Up to 10 days after acute event.[c]	Therapy with any statin at a dose of 80 mg per day at the time of the index event, serious hepatic disease, renal dysfunction (creatinine > 2.0 mg/dl).
Atorvastatin	58±11	22	78	36	64		
Pravastatin	58±11	22	78	33	67		
Pravastatin[d]							
PACT [223]	61±12[e]			65[e]	35[e]	Within 24 hours after acute event.	Statin therapy before event, planned coronary revascularisation, severe hepatic or renal disease.
Pravastatin		24	76				
Placebo		24	76				
Simvastatin							
A-to-Z [182]						Within 5 days after acute event.[c]	Statin therapy at the time of randomisation, planned coronary revascularisation, liver dysfunction.
Simvastatin 40/80	61 (52-69)	24	76	40	60		
Placebo / Sim. 20	61 (53-69)	25	75	40	60		

a: Mean (rounded off where necessary) with standard deviation (±), or median (with interquartile range, if available).
b: Latency period between the acute event leading to study entry and the start of treatment.
c: Only clinically stable patients were included in the study.
d: In addition: PROVE-IT study (see under atorvastatin).
e: Data available only for the overall study population.
AP: angina pectoris; Non-ST-MI: Non-ST-elevation-myocardial infarction; NYHA IIIb/IV: Classification of the degree of congestive heart failure according to the New York Heart Association; m: male; f: female.

The quality criteria for studies and publications are presented in Table 9.

For the MIRACL and PACT studies, no detailed information on randomisation process and allocation concealment was found, even after perusal of additional publications (e.g. publications on study design or results in specific subgroups). For these studies, it therefore cannot be judged whether randomisation and allocation concealment were adequate. In the PROVE-IT and A to Z study, the randomisation process and allocation concealment were adequate.

In the MIRACL, PACT and A to Z studies, the assessment of main endpoints (coronary morbidity/mortality and/or total mortality) was blinded. For the PROVE-IT study, the information provided on this issue was insufficient.

Sample size planning was described adequately in all four studies. In the MIRACL study, fewer events occurred than estimated at the time of sample size planning, for which reason the study was extended and conducted with more patients than originally planned (3086 patients; 2100 patients were originally planned).
The PACT study was terminated prematurely upon the sponsor's recommendation because of recruitment problems; in total, 3408 patients were included (10 000 were originally planned). The PACT study therefore has a low power for the primary endpoint with regard to showing a statistically significant difference between treatment groups.
In the A to Z study, fewer events occurred than originally estimated (625 events; 970 were estimated); the same applies to the MIRACL study. In contrast to the MIRACL study, the A to Z study was not extended but, under acceptance of a lower power to show a statistically significant difference between treatment groups, was conducted with the originally planned number of patients. A main reason for this decision by the investigators was, according to the publication, the fact that after publication of the results of the MIRACL study, the recruitment of patients became more difficult.

The rate of patients in relation to the overall study population who were lost to follow-up during the study was under 4% in all studies (apart from the PROVE-IT study). The MIRACL study results remained robust after a best case/worst case analysis was conducted.

In the PROVE-IT study, the information on the number of patients lost to follow-up was discrepant between text and figure in the original publication [64] and the additional publication by the authors [429]. According to the information in the text [64], only 8 patients were lost to follow-up. It can be concluded from Figure 2 in the publication [64], that after 12 months (i.e., 6 months before the minimum observation period of 18 months), a primary endpoint event had occurred in approx. 17% of the patients in the atorvastatin group (an estimated 356 patients), and in approx. 20% of patients in the pravastatin group (an estimated 412 patients). The "No. at risk" in the same figure shows that after 12 months, 508 patients in the atorvastatin group and 527 patients in the pravastatin group were no longer included in the evaluation. As the primary endpoint included the "death from any cause" component, premature exclusion (censoring) as a result of a concurrent event is not conceivable. Exclusion from further evaluation was therefore possible for two reasons: a) a primary endpoint event had occurred; b) the patient could, for whatever reason, no longer be investigated, and was therefore lost to follow-up. Therefore, according to Figure 2, approx. 152 patients in the atorvastatin group and approx. 155 patients in the pravastatin group should be regarded as lost to follow-up 12 months after the start of the study. These numbers outweigh by far the difference observed at this point of approx. 60 events (absolute difference of approx. 3%), and the overall difference observed after 2 years of approx. 80 events (absolute difference of 3.9% between treatment groups [64]) for the primary endpoint. Furthermore, in an additional publication by the authors, 63 patients were reported to have withdrawn consent to follow-up [429]. This clearly contradicts the statement made in the original publication [64] that only 8 patients were lost to follow-up.

On the one hand, it remains unclear how many patients were lost to follow-up and if, as maintained in the publication, an intent-to-treat analysis was performed; on the basis of the information provided in Figure 2 [64], this seems unlikely. On the other hand, a best case/worst case analysis for the primary endpoint (assuming that the number of patients prematurely lost to follow-up according to Figure 2 and explicitly referring to the primary endpoint was correct) showed that the results were not robust.

In addition, the interpretation of the results is made more difficult by the subsequent change (which was not originally planned) of the statistical hypothesis to be tested (from non-inferiority [pravastatin] to superiority [atorvastatin]), as aspects of study design (including the use of planning instruments, e.g. ITT strategy) may differ for the respective underlying hypotheses.

Furthermore, in the PROVE-IT study, doses of atorvastatin and pravastatin were used whose equipotency with regard to known and unknown risk markers has not been demonstrated [60]. Finally, it cannot be concluded from the available publications whether a blinded assessment of study endpoints was made.

With consideration of all of the noted individual aspects of the PROVE-IT study, the results of this trial cannot be safely interpreted, as they are not sufficiently valid or robust. They do not provide evidence of the substance-specific superiority of atorvastatin over pravastatin.

Table 9: Endpoint studies in patients with acute coronary syndrome – Quality of studies and publications

Statin Study	Randomisation	Allocation concealment	Assessment of endpoints blinded[a]	Sample size planning	Lost to follow-up [n]	Discrepant details on patients lost to follow-up	ITT-analysis robust[b]
Atorvastatin							
MIRACL [78]	Stratification, otherwise n.d.	n.d.	yes, adequate	described adequately [c]	8 (atorvastatin) 3 (placebo)	no	yes
PROVE-IT [64]	adequate	adequate	n.d.	described adequately [d]	unclear[e]	yes	no
Pravastatin[f]							
PACT [223]	n.d.	n.d.	yes, adequate	described adequately [g]	40 (pravastatin) 45 (placebo)	no	no relevant endpoint statistically significantly different
Simvastatin							
A-to-Z [182]	adequate	adequate	yes, adequate	described adequately [h]	68 (simvastatin 40/80) 69 (placebo / simvastatin 20)	no	no relevant endpoint statistically significantly different

a: Regarding coronary morbidity/mortality and/or total mortality.
b: After conducting a best case/worst case analysis with consideration of patients not followed up; only for endpoints with a statistically significant difference between treatment groups.
c: The event rate in the study lay below the originally estimated event rate. The study was therefore extended and conducted with more patients than originally planned (3086 instead of 2100).
d. The study was originally designed as a non-inferiority study (pravastatin 40 mg vs. atorvastatin 80 mg).
e: Discrepant details in text and figure of publication [64] and in additional publication [429]; see also previous text.
f: In addition: PROVE-IT study (see under atorvastatin).
g: Premature end of study due to recruitment problems (according to publication).
h: In total, fewer events than planned occurred (652 vs. 970); however, no study extension due to recruitment problems (according to publication).
ITT: Intention-to-treat; n.d.: no details provided.

Table 10: Endpoint studies in patients with acute coronary syndrome – Results

Statin Study	Total mortality	Coronary mortality	Non-fatal myocardial infarction	Primary endpoint[a]	Observation period [patient years]
Atorvastatin					
MIRACL [78] Atorvastatin Placebo	HR 0.94 (0.67-1.31) 64 (4.2%) 68 (4.4%)	n.d.	HR: 0.9 (0.69-1.16) 101 (6.6%) 113 (7.3%)	**HR: 0.84 (0.7-1.0)** **228 (14.8%)** **269 (17.4%)**	1000[b]
PROVE-IT [64] Atorvastatin Pravastatin	HR: 0.72 (0.5-1.05)[c] 2.2% 3.2%	HR: 0.7 (0.4-1.15)[c] 1.1% 1.4%	HR: 0.87 (0.7-1.1)[c] 6.6% 7.4%	HR: 0.84 (0.74-0.95) 22.4% 26.3%	8300[b]
Pravastatin[d]					
PACT [223] Pravastatin Placebo	HR: n.d. 24 (1.4%) 37 (2.2%)	n.d.	p: n.s.; HR: n.d. 52 (3.1%) 48 (2.8%)	HR: 0.94 (0.72-1.13) 199 (11.6%) 211 (12.4%)	250[b]
Simvastatin					
A-to-Z [182] Simvastatin 40/80 Placebo / Sim. 20	HR: 0.79 (0.61-1.02) 104 (5.5%) 130 (6.7%)	n.d.	HR: 0.96 (0.77-1.21) 151 (7.1%) 155 (7.4%)	HR: 0.89 (0.76-1.04) 309 (14.4%) 343 (16.7%)	8900[b]

a: As defined in the respective study, see also Table 7.
b: Approximate calculation from number of patients * duration of observation (mean or median, according to study); rounded off.
c. Confidence interval estimated from Figure 4 [64].
d: In addition: PROVE-IT study (see under atorvastatin).
Data presented as hazard ratio (with 95% confidence interval, if available).
Statistically significant results are in bold print insofar as only patients with acute coronary syndrome were included in the respective analysis.
HR: hazard ratio; n.d.: no details provided; n.s.: not significant.

Table 11: Long-term studies in patients with acute coronary syndrome – Adverse drug effects

Statin Study	Discontinuation of therapy due to AEs	Liver enzyme elevations[a]	Creatinine kinase elevations[b]	Rhabdomyolysis	New cancers[c]
Atorvastatin					
MIRACL [78]	p: n.d.	p < 0.001	n.d.	n.d.	n.d.
Atorvastatin	2.6%	2.5%[d]			
Placebo	2.1%	0.6%[d]			
PROVE-IT [64]	p = 0.23	p < 0.001	n.d.		n.d.
Atorvastatin	3.3%[e]	3.3%[d]		0 (0%)	
Pravastatin	2.7%[e]	1.1%[d]		0 (0%)	
Pravastatin[f]					
PACT [223]	n.d.	p: n.s.			n.d.
Pravastatin		1.5%[g]	0%[h]	0 (0%)	
Placebo		1.1%[g]	0%[h]	0 (0%)	
Simvastatin					
A-to-Z [182]	p=0.49	p=0.05	p = 0.02	p: n.d.	n.d.
Simvastatin 40/80	1.8%[h]	0.9%[g]	0.4%[i]	3 (0.1%)	
Placebo / Sim. 20	1.5%[h]	0.4%[g]	0.04%[i]	n.d.	

a: According to the definition in the respective study, mostly more than 3-fold increase over the respective normal value.
b: More than 10-fold increase over the respective normal value.
c: Fatal and non-fatal cancers.
d: Unclear, whether persistent or non-persistent.
e: Only for discontinuations of therapy by the investigator because of muscle symptoms or creatinine kinase elevations.
f: In addition: PROVE-IT study (see under atorvastatin).
g: Persistent enzyme elevations; rate of non-persistent enzyme elevations unclear.
h: For subsidiary point "muscle-related", otherwise n.d.
i: Only for symptomatic enzyme elevations (with muscle symptoms).
AE: adverse event; n.d.: no details provided; n.s. not significant.

Table 12: Mortality in studies not primarily designed to show evidence of a benefit with regard to morbidity and mortality

Statin Study	Follow-up[a]	Number of patients [intervention] [control]	Myocardial infarction[b] [%]	Total mortality	Duration of observation [patient years][c]
Atorvastatin					
Macin et al. 2005 [460]	30 days			p = 0.34	7
		Atorvastatin 40 mg [44]	52	1 (2.3%)	
		Placebo [46]	67	3 (6.5%)	
Fluvastatin					
FLORIDA 2002 [77]	1 year			p: n.d.	500
		Fluvastatin 80 mg [265]	100	7 (2.6%)	
		Placebo [275]	100	11 (4%)	
Pravastatin					
PAIS 2001 [79]	3 months			p: n.d.	20
		Pravastatin 40 mg [50]	n.d.	2 (4%)	
		Placebo [49]		2 (4.1%)	
			Total duration of observation in patient years: 527 patient years		

a: As noted in the respective study (e.g. mean or median).
b: Rate of patients included in the respective study because of an acute myocardial infarction.
c: Approximate calculation from number of patients * follow-up (as noted in the respective study); rounded off.
n.d.: no details provided.

4.2.6 Discussion of study results

4.2.6.1 Total mortality

None of the available studies showed a statistically significant difference between treatment groups with regard to total mortality.

The results on total mortality in the studies that were not primarily designed to find evidence of a benefit in respect of morbidity/mortality do not contradict this statement (Table 12).

4.2.6.2 Coronary mortality

None of the studies available showed a statistically significant difference between treatment groups with regard to coronary mortality.

4.2.6.3 Non-fatal myocardial infarction

None of the studies available showed a statistically significant difference between treatment groups with regard to the endpoint "non-fatal myocardial infarction".

4.2.6.4 Primary study endpoints

A statistically significant difference between treatment groups in favour of atorvastatin regarding the primary combined endpoint (death, non-fatal myocardial infarction, cardiac arrest with resuscitation, recurrent myocardial ischaemia requiring rehospitalisation) was shown in the MIRACL study. Only patients with unstable angina pectoris and non-ST-elevation myocardial infarction were included in the MIRACL study. It is unclear whether the results of the MIRACL study can be transferred to patients with acute ST-elevation myocardial infarction.

The results of the PROVE-IT study are characterised by substantial uncertainty, and are not sufficiently valid or robust to show clear evidence of a benefit of treatment with atorvastatin or pravastatin (see also Section 4.2.5).

In the PACT and A to Z studies, no statistically significant difference was shown between treatment groups (pravastatin or simvastatin vs. placebo). It remains unclear whether this was due to the limited power of the studies described above. The 95% confidence interval of the hazard ratio for the respective primary endpoint in both studies included the effect estimate of the MIRACL study (see Table 10).

4.2.6.5 Adverse drug effects

From the intervention studies available in patients with acute coronary syndrome, the superiority of one statin over another cannot be inferred with regard to hepatic or myopathic adverse drug effects (including rhabdomyolysis). No information was provided in the publications on the incidence of new cancers.

A more frequent occurrence of liver enzyme elevations in patients treated with atorvastatin and of creatinine kinase elevations in patients treated with simvastatin may be assumed on the basis of the placebo comparative studies. However, it is unclear how far the data on patients lost to follow-up also apply to the evaluation in respect of adverse drug effects, i.e., whether the respective results are robust (see also Section 4.4).

4.2.6.6   Summary

No evidence was found for any statin that initiation of treatment during an acute coronary syndrome reduced total mortality, coronary mortality, and/or the rate of non-fatal myocardial infarctions compared with placebo. Overall, no evidence of the superiority of atorvastatin over other statins can be inferred from the data available.

Atorvastatin 80 mg daily, in the subgroup of patients with unstable angina pectoris without ST-elevation myocardial infarction, reduced the risk of the occurrence of a combined cardiac endpoint compared with placebo.

For simvastatin 40-80 mg daily and pravastatin 20-40 mg daily, no statistically significant effect was shown in the combined collective of patients with acute ST-elevation myocardial infarction and unstable angina pectoris compared with placebo, or a sequential therapy of placebo and low-dose simvastatin (20 mg).

No relevant studies on fluvastatin and lovastatin were available.

Valid direct comparative studies between different statins were not available. The placebo-controlled studies available cannot be validly compared due to different patient collectives (inclusion of patients with ST-elevation myocardial infarction in the A to Z and PACT studies, but not in the MIRACL study), different study periods (PACT: 30 days vs. MIRACL: 16 weeks), and insufficient power of the PACT and A to Z studies.

4.3 Diabetes mellitus

4.3.1 Research questions

3a) Does statin therapy in patients with diabetes mellitus lead to a reduction in total mortality and/or coronary morbidity and mortality?

3b) In this context, can a superior effect of atorvastatin (Sortis[®]) over other statins be inferred from the intervention studies available?

4.3.2 Conclusion

In patients with diabetes mellitus, only simvastatin showed a benefit of statin therapy with regard to a life-prolonging effect. No such evidence of a benefit was shown for atorvastatin, fluvastatin, lovastatin, and pravastatin.

4.3.3 Search strategy

The general methodology of the literature search is described in Appendix B. Studies fulfilling all the following inclusion criteria and none of the exclusion criteria were included in the evaluation.

Inclusion criteria:

I-1.   **Patients**: Adults with manifest diabetes mellitus type 1 or type 2 as defined in the respective study. Studies which, in addition to including patients with diabetes mellitus, also included other patients, were only considered in the evaluation if predefined subgroup analyses of patients with diabetes mellitus were available.

I-2.   **Intervention**: Statin therapy in a dose approved in Germany.

I-3.   **Comparator treatment:** Treatment with placebo or another statin in a dose approved in Germany.

I-4.   **Additional lipid-lowering therapy:** The evaluation included studies in which an additional lipid-lowering treatment, depending on cholesterol levels, was possible. The evaluation did not include studies in which a priori a lipid-lowering combination therapy represented the intervention or control treatment (e.g. therapy with a statin and a fibrate).

I-5.   **Endpoints:** Total mortality, coronary morbidity and mortality. Mortality data for studies which were not primarily designed to investigate one of these endpoints are presented additionally, insofar as only patients with stable CHD were investigated.

I-6.   **Study design:** Double-blind RCT.

I-7.   **Duration:** > 1 year.

I-8.   **Language of publication**: German or English.

Exclusion criteria:

E-1.   Studies in patients who had undergone heart transplantation.

E-2.   No full-text publication available.

4.3.4 Search results

The systematic literature search identified eight studies that corresponded to the inclusion/ exclusion criteria and were designed to show evidence of an effect with regard to one of the endpoints stated in I-5:

- the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA) [73,437];
- the Collaborative Atorvastatin Diabetes Study (CARDS) [176];
- the German Diabetes und Dialysis (4D) Study [442];
- the Heart Protection Study (HPS) [100,101];
- the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study [66,322];
- the Lescol Intervention Prevention Study (LIPS) [99,475];
- the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [75];
- the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) Study [64].

Apart from the PROVE-IT study, all of these studies were placebo-controlled. PROVE-IT was a direct comparative study between atorvastatin (80 mg daily) and pravastatin (40 mg daily).

The A to Z study [182] described in Section 4.2 did not fulfil the inclusion criteria, as the placebo treatment period only lasted four months.

No additional long-term studies reporting mortality rates and fulfilling the inclusion/exclusion criteria were found.

4.3.5 Description of the studies included

Information on the study design of the eight trials included is presented in Table 13. Main patient characteristics and inclusion/exclusion criteria are presented in Table 14.

Four relevant studies on atorvastatin were found; three placebo-controlled studies (ASCOT-LLA, CARDS, 4D) and the direct comparative study PROVE-IT. The CARDS study was conducted in patients with diabetes mellitus type 2 without diagnosed CHD but with coexistence of additional risk factors/markers for vascular diseases. The 4D study was conducted in patients with diabetes mellitus type 2 with kidney failure requiring haemodialysis. In the ASCOT-LLA and PROVE-IT studies, the respective predefined subgroup analysis of patients with diabetes mellitus was relevant for the research question posed. These subgroups represented approx. 25% (ASCOT-LLA) and 18% (PROVE-IT) of the respective overall study population. The ASCOT-LLA study included patients with hypertension and coexistence of other cardiac risk factors/markers. The PROVE-IT study included patients with an acute coronary syndrome.

One relevant placebo-controlled study on fluvastatin, the LIPS study, was found. In this study, which only included CHD patients following successful percutaneous coronary intervention, the predefined subgroup analysis of patients with diabetes mellitus was relevant for the research question posed. This subgroup represented approx. 12% of the overall study population.

No relevant study was found on lovastatin.

Three relevant studies on pravastatin were found; the PROVE-IT study, and two placebo-controlled studies, the LIPID and PROSPER studies. In the LIPID study, which only included patients with stable CHD, the predefined subgroup analysis of patients with diabetes mellitus was relevant for the research question posed. This subgroup represented approx. 12% of the overall study population. In the PROSPER study, which included patients from 70 years upwards with a history of, or risk factors for vascular disease, the predefined subgroup analysis of patients with diabetes mellitus was relevant for the research question posed. This subgroup represented approx. 11% of the overall study population.

One relevant placebo-controlled study on simvastatin, the HPS study, was found. In this combined primary and secondary prevention study, the predefined subgroup analysis of patients with diabetes mellitus was relevant for the research question posed. This subgroup represented approx. 29% of the overall study population.

Table 13: Long-term studies in patients with diabetes mellitus - Overview

Statin Study	Follow-up [years]	Number of patients [intervention] [control]	Primary endpoint	Total mortality reported
Atorvastatin				
ASCOT-LLA 2005 [437]	3.3[a]	1258 [atorvastatin 10 mg] 1274 [placebo]	Combined endpoint: fatal CHD, non-fatal myocardial infarction.	no (but predefined endpoint, also for the group of patients with diabetes mellitus).
CARDS 2004 [176]	3.9[a]	1428 [atorvastatin 10 mg] 1410 [placebo]	Combined endpoint: myocardial infarction including silent infarction, unstable angina, acute coronary heart disease death, resuscitated cardiac arrest, coronary revascularisation procedure, stroke.	yes (secondary endpoint).
4D 2005 [442]	4[a]	619 [atorvastatin 20 mg] 636 [placebo]	Combined endpoint: death from cardiac causes, non-fatal myocardial infarction, fatal or non-fatal stroke.	yes (secondary endpoint).
PROVE-IT[b] 2004 [64]	2[c,d]	373 [atorvastatin 80 mg][e] 361 [pravastatin 40 mg][e]	Combined endpoint: death from any cause, myocardial infarction, documented unstable angina requiring rehospitalisation, revascularisation (> 30 days after randomisation), stroke.	yes (secondary endpoint); not reported separately for patients with diabetes mellitus.
Fluvastatin				
LIPS 2002 [99][b]	3.9[a, d]	120 [fluvastatin 80 mg] 82 [placebo]	Combined endpoint: cardiac death, non-fatal myocardial infarction, coronary reintervention procedure.	yes (secondary endpoint); not reported separately for patients with diabetes mellitus.
Pravastatin[f]				
LIPID 2003 [322][b]	6[a]	542 [pravastatin 40 mg] 535 [placebo]	Combined endpoint: CHD death (fatal myocardial infarction, sudden cardiac death, death in the hospital after possible myocardial infarction, death due to heart failure or another coronary cause), non-fatal myocardial infarction.	yes (secondary endpoint); not reported separately for patients with diabetes mellitus.
PROSPER 2002 [75][b]	3.2[c,d]	303 [pravastatin 40 mg] 320 [placebo]	Combined endpoint: coronary death, non-fatal myocardial infarction, fatal or non-fatal stroke.	yes (not a predefined endpoint); not reported separately for patients with diabetes mellitus.

Table 13: Long-term studies in patients with diabetes mellitus – Overview (continued)

Statin Study	Follow-up [years]	Number of patients [intervention] [control]	Primary endpoint	Total mortality reported
Simvastatin				
HPS 2003 [101][b]	4.8[a]	2978 [simvastatin 40 mg] 2985 [placebo]	Outcome criteria for the overall population: deaths from all causes, from CHD, from all other causes. Combined endpoints for subgroup of patients with diabetes mellitus: major vascular and major coronary events.	yes (primary endpoint); separately reported in [468].

a: Median.
b: Predefined subgroup (patients with diabetes mellitus); data presented for this subgroup, unless otherwise noted.
c: Mean.
d: Data for overall study population, separate data for patients with diabetes mellitus are lacking.
e: According to the study protocol, a halving of the dose (in both groups) or an increase in dose (only pravastatin) was possible. These dose changes affected less than 10% of patients (in relation to the overall study population).
f: In addition: PROVE-IT study (see under atorvastatin).
CHD: coronary heart disease.

Table 14: Long-term studies in patients with diabetes mellitus – Patient characteristics

Statin Study	Age [years][a]	Sex f[%]	Sex m[%]	Known CHD [%]	Main inclusion criteria	Main exclusion criteria
Atorvastatin						
ASCOT-LLA [437]					Hypertension, diabetes mellitus type 2 and at least two further cardiac risk factors.	Previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, heart failure.
Atorvastatin	64±9	23	77	0		
Placebo	64±8	24	76	0		
CARDS [176]					Diabetes mellitus type 2 and at least one further cardiac risk factor	Past history of: myocardial infarction, angina pectoris, coronary vascular surgery, cerebrovascualar accident, severe peripheral vascular disease.
Atorvastatin	62±8	32	68	0		
Placebo	62±8	32	68	0		
4D [442]					Patients with diabetes mellitus type 2 who had been receiving haemodialysis for less than two years.	Liver dysfunction, congestive heart failure, myocardial infarction within 3 months preceding the period of enrolment, hypertension resistant to therapy.
Atorvastatin	66±8	46	54	28		
Placebo	66±8	46	54	31		
PROVE-IT [64]					Patients with acute coronary syndrome.	Therapy with any statin at a dose of 80 mg per day at the time of the index event, serious liver disease, renal dysfunction (creatinine > 2.0 mg/dl).
Atorvastatin	58±11[b]	22	78[b]	100		
Pravastatin	58±11[b]	22	78[b]	100		
Fluvastatin						
LIPS [99,475]					Stable or unstable angina or silent ischaemia following successful completion of first PCI 0-6 months before study entry.	Congestive heart failure (EF < 30%), uncontrolled hypertension, renal dysfunction (serum creatinine 1.8 mg/dl).
Fluvastatin	63±8	20	80	100		
Placebo	62±9	20	80	100		
Pravastatin[d]						
LIPID [322]	64 (57-68)[c]	19	81[c]		Myocardial infarction or hospital admission for unstable angina pectoris 3-36 months before study entry.	Cardiac failure, renal or hepatic disease.
Pravastatin				100		
Placebo				100		
PROSPER [75]					Age: 70-82 years, pre-existing vascular disease or raised risk of such disease because of smoking, hypertension, diabetes.	Poor cognitive function.
Pravastatin	75±3[b]	52	48	13[e]		
Placebo	75±3[b]	52	48	14[e]		

Table 14: Long-term studies in patients with diabetes mellitus – Patient characteristics (continued)

Statin Study	Age [years][a]	Sex f[%]	m[%]	Known CHD [%]	Main inclusion criteria	Main exclusion criteria
Simvastatin						
HPS [101] Simvastatin Placebo	62±9[c]	30	70[c]	33[c]	Diabetes mellitus (sufficient as a criterion for increased cardiovascular risk).	Severe heart failure, liver disease, renal disease (serum creatinine > 2.3 mg/dl).

a: Mean (rounded off where necessary) with standard deviation (±), or median (with interquartile range, if available).
b: Data for overall study population, separate details for patients with diabetes mellitus are lacking.
c: No separate details for intervention and control group.
d: In addition: PROVE-IT study (see under atorvastatin).
e: Rate of patients with previous myocardial infarction, otherwise no data provided.
EF: ejection fraction; n.d.: no details provided; m: male; w: female; PCI: percutaneous coronary intervention.

Criteria for study and publication quality are described in Table 15.

In the LIPID study, randomisation was adequate. No information was found on allocation concealment. In the other studies, randomisation and allocation concealment were adequate.

In contrast to all other included studies, no information was found in the PROVE-IT study as to whether the investigation of main endpoints (mortality and/or vascular morbidity) was blinded.

Sample size planning was comprehensibly described in all eight studies. In studies where patients with diabetes mellitus represented a predefined subgroup, no statements on the issue of power for this subgroup were found (except in the HPS study). According to the authors, the size of the HPS study was planned so that the study results would also be sufficiently meaningful with regard to subgroups (e.g. patients with diabetes mellitus).

For the LIPS, LIPID and HPS studies, information on the number of patients lost to follow-up was only available for the overall study population, but not for the subgroup of patients with diabetes mellitus. This was not relevant for the LIPID study, as in total only one patient was lost to follow-up, and, in addition, no statistically significant differences were shown with regard to the endpoints reported in Table 16. As described in Section 4, a best case/worst case analysis was conducted for the LIPID and HPS studies, assuming that the rate of patients lost to follow-up did not differ between the overall study population and the subgroup of patients with diabetes mellitus. Under this assumption the results of both studies were robust.
No information was available on the rate of patients lost to follow-up in the PROSPER study. The discrepancies in the PROVE-IT study with regard to the data on patients lost to follow-up are described in detail in Section 4.2.5.
In the ASCOT-LLA, the CARDS and the 4D studies, the rate of patients lost to follow-up was under 2% in each study. The results of the CARDS study remained robust after a best/worst case analysis was conducted.

Table 15: Long-term studies in patients with diabetes mellitus – Quality of studies and publications

Statin Study	Randomisation	Allocation concealment	Assessment of endpoints blinded[a]	Sample size planning	Lost to follow-up [n]	Discrepant information on patients lost to follow-up	ITT-analysis robust[b]
Atorvastatin							
ASCOT-LLA [437]	adequate	adequate	yes, adequate	described adequately	30 (total) 4 (regarding mortality)	no	no relevant endpoint statistically significantly different
CARDS [176]	adequate	adequate	yes, adequate	described adequately	atorvastatin: 1 (mortality) / 7 (morbidity) placebo: 4 (mortality) / 12 (morbidity)	no	yes
4D [442]	adequate	adequate	yes, adequate	described adequately	atorvastatin: 0 placebo: 1	no	no relevant endpoint statistically significantly different
PROVE-IT [64]	adequate	adequate	n.d.	described adequately[c]	unclear[d]	yes	no relevant endpoint statistically significantly different
Fluvastatin							
LIPS [99]	adequate	adequate	yes, adequate	described adequately	7 (fluvastatin)[e] 10 (placebo)[e]	no	yes
Pravastatin[f]							
LIPID [322]	adequate	n.d.	yes, adequate	described adequately	1 (mortality)[e]	no	no relevant endpoint statistically significantly different
PROSPER [75]	adequate	adequate	yes, adequate	described adequately	n.d.	n.d.	no relevant endpoint statistically significantly different

Table 15: Long-term studies in patients with diabetes mellitus – Quality of studies and publications (continued)

Statin Study	Randomisation	Allocation concealment	Assessment of endpoints blinded[a]	Sample size planning	Lost to follow-up [n]	Discrepant information on patients lost to follow-up	ITT-analysis robust[b]
Simvastatin							
HPS [101]	adequate	adequate	yes, adequate	described adequately	7 (mortality)[e] 60 (morbidity)[e]	no	yes
a: Regarding coronary morbidity/mortality and/or total mortality b: After conducting a best case/worst case analysis with consideration of the patients lost to follow-up. See also previous text. c: The study was originally designed as a non-inferiority study (pravastatin 40 mg vs. atorvastatin 80 mg). d: Discrepant details in text and figure [64] as well as in additional publication [429]; see also Section 4.2.5. e: Data for the overall study population, no separate data provided for patients with diabetes mellitus. f: In addition: PROVE-IT study (see under atorvastatin). ITT: Intention to treat; n.d.: no details provided.							

Table 16: Long-term studies in patients with diabetes mellitus - Results

Statin Study	Total mortality	Coronary mortality	Non-fatal myocardial infarction	Primary endpoint[a]	Observation period [patient years][b]
Atorvastatin					
ASCOT-LLA [437] Atorvastatin Placebo	n.d.	HR: 1.72 (0.79-3.76) 17 (1.4%) 10 (0.8%)	HR: 0.62 (0.37-1.06) 22 (1.7%) 36 (2.8%)	HR: 0.84 (0.55-1.29) 38 (3%) 46 (3.6%)	8300
CARDS [176] Atorvastatin Placebo	HR: 0.73 (0.52-1.01) 61 (4.3%) 82 (5.8%)	HR: n.d. 18 (1.3%) 24 (1.7%)	HR: n.d. 25 (1.8%) 41 (2.9%)	**HR: 0.63 (0.48-0.83) 83 (5.8%) 127 (9%)**	10550[c]
4D [442] Atorvastatin Placebo	HR: 0.93 (0.79-1.08) 297 (48%) 320 (50.3%)	n.d.	HR: 0.88 (0.64-1.21) 70 (11.3%) 79 (12.4%)	HR: 0.92 (0.77-1.1) 226 (36.7%) 243 (38.2%)	4900
PROVE-IT [64] Atorvastatin Pravastatin	n.d.	n.d.	n.d.	HR: 0.8 (0.6-1.05)[d] 28.8% 34.6%	1400
Fluvastatin					
LIPS [99,475] Fluvastatin Placebo	n.d.	n.d.	n.d.	**HR: 0.53 (0.29-0.97)[e] 26 (21.7%) 31 (37.8%)**	1100
Pravastatin[f]					
LIPID [322] Pravastatin Placebo	n.d.	n.d.	n.d.	HR: 0.81 (0.6-1.05)[g] 106 (19.6%) 125 (23.4%)	6400
PROSPER [75] Pravastatin Placebo	n.d.	n.d.	n.d.	HR: 1.27 (0.9-1.8) 70 (23.1%) 59 (18.4%)	1900

Table 16: Long-term studies in patients with diabetes mellitus – Results (continued)

Statin Study	Total mortality	Coronary mortality	Non-fatal myocardial infarction	Primary endpoint[a]	Observation period [patient years][b]
Simvastatin					

HPS [101]
  Simvastatin
  Placebo
	HR: 0.85 (0.75-0.95)[h]
	384 (12.9%)
	446 (14.9%)
		HR: 0.8 (0.66-0.96)
		193 (6.5%)
		239 (8%)
			HR: 0.63 (0.5-0.8)
			105 (3.5%)
			164 (5.5%)
				HR: 0.73 (0.66-0.81)
				279 (9.4%)
				377(12.6%)
					28600

a: As defined in the respective study; see also Table 13.
b: Approx. calculation from number of patients with diabetes mellitus * duration of observation (mean or median, according to study); rounded off.
c: Exact specification of primary endpoint from [176].
d: Read off Figure 5 in [64]; rounded off.
e: Data from [99]. Discrepant data between [99] and [475]. Data in [475]: HR: 0.49 (0.29-0.84). Statistical significance in both cases.
f: In addition: PROVE-IT study (see under atorvastatin).
g: Confidence interval read off Figure 3 in [322] and rounded off.
h: From figure in [468].
Data presented as hazard ratio (with 95% confidence interval, if available).
Statistically significant results are in bold print, insofar as exclusively patients with diabetes mellitus were included in the respective analysis and the results remained robust after conduct of a best case/worst case analysis.
For studies where not only patients with diabetes mellitus were investigated, the results of the subgroup of patients with diabetes mellitus are presented (if available).
Insofar as results were only available for the overall study population, these are presented if the predefined subgroup of patients with diabetes mellitus represented approx. 50% or more of the overall study population.
HR: hazard ratio; n.d.: no details provided.

Table 17: Long-term studies in patients with diabetes mellitus – Adverse drug effects

Statin Study	Discontinuations of therapy due to AEs	Liver enzyme elevations[a]	Creatinine kinase elevations[b]	Rhabdomyolysis	New cancers[c]
Atorvastatin					
ASCOT-LLA [437] Atorvastatin Placebo	n.d.	p: n.s.[d] n.d. n.d.	n.d.	 0 (0%) 0 (0%)	n.d.
CARDS [176] Atorvastatin Placebo	p: n.d. 122 (8.5%) 145 (10.3%)	p: n.d. 17 (1.2%)[e] 14 (1.0%)[e]	p: n.d. 10 (0.7%)[e] 2 (0.1%)[e]	 0 (0%) 0 (0%)	p = 0.14 20 (1.4%)[f] 30 (2.1%)[f]
4D [442] Atorvastatin Placebo	p: n.d. 73 (11.8%) 52 (8.2%)	p: n.d. 5 (0.8%) 1 (0.2%)	p: n.d. 1 (0.2%)[d,g] 1 (0.2%)[d,g]	 0 (0%) 0 (0%)	p: n.d. 39 (6.3%) 44 (6.9%)
PROVE-IT [64] Atorvastatin Pravastatin	n.d.	n.d.	n.d.	 0 (0%) 0 (0%)	n.d.
Fluvastatin					
LIPS [99] Fluvastatin Placebo	n.d.	n.d.	n.d.	n.d.	n.d.
Pravastatin[h]					
LIPID [322] Pravastatin Placebo	n.d.	n.d.	n.d.	n.d.	n.d.
PROSPER [75] Pravastatin Placebo	n.d.	n.d.	 0% 0%	 0 (0%) 0 (0%)	n.d.

Table 17: Long-term studies in patients with diabetes mellitus – Adverse drug effects (continued)

Statin Study	Discontinuations of therapy due to AEs	Liver enzyme elevations[a]	Creatinine kinase elevations[b]	Rhabdomyolysis	New cancers[c]
Simvastatin					

HPS [101]
  Simvastatin
  Placebo
	n.d.	p: n.d.
		14 (0.5%)[d]
		11 (0.4%)[d]
			p: n.d.
			4 (0.13%)
			2 (0.07%)
				n.d.	n.d.

a: According to definition in the respective study, mostly more than 3-fold increase over the respective normal value.
b: More than 10-fold increase over the respective normal value.
c: Fatal and non-fatal cancers.
d: Unclear whether persistent or non-persistent.
e: Persistent and non-persistent enzyme elevations.
f. Only fatal cancers; non-fatal cancers not reported.
g: 5 to 10-fold increase over the normal value.
h: In addition: PROVE-IT study (see under atorvastatin).
AE: Adverse event; n.d.: no details provided; n.s.: not significant.

4.3.6 Discussion of study results

4.3.6.1   *Total mortality*

In the HPS study, a significant reduction in total mortality was shown following treatment with simvastatin 40 mg versus placebo in patients with diabetes mellitus. No such evidence was shown for any other statin (Table 16).

For atorvastatin, both the CARDS and 4D studies showed no statistically significant difference with regard to total mortality. A meta-analytical summary of the results of these studies (conducted with reservations about the heterogeneity of their content: different patient collectives with substantially differing mortality rates with placebo) showed no statistically significant effect of atorvastatin on total mortality (Figure 3). For the ASCOT-LLA study, no information on total mortality in the subgroup of patients with diabetes mellitus was provided. According to the study protocol, the evaluation of all major endpoints was planned for the subgroup of patients with diabetes mellitus [441]. In the publication [437], only information on selected endpoints was found (e.g. stroke, combined endpoint of cardiovascular events and interventions). As the endpoint "coronary mortality" occurred even more often with atorvastatin than with placebo, the ASCOT-LLA study also did not provide any evidence to support the statement that atorvastatin reduces total mortality in patients with diabetes mellitus.

For fluvastatin and pravastatin, studies were only available where patients with diabetes mellitus represented a predefined subgroup. No publication of these studies provided information on total mortality for the respective subgroup of patients with diabetes mellitus. In the LIPS study (fluvastatin), there was no evidence of an effect of fluvastatin on total mortality in the overall study population.

Such an effect was shown in the LIPID study (pravastatin), see also Section 4.1.6.1; however, the subgroup of patients with diabetes mellitus represented only approx. 12% of the overall study population, so that the benefit of statin therapy in patients with diabetes mellitus in respect of total mortality remains unclear.

Figure 3: Meta-analysis of atorvastatin studies in patients with diabetes mellitus – total mortality

Meta-analysis atorvastatin
Total mortality
Random effects, logarithm of the hazard ratio

Study	Effect 95% CI	Weight %	Effect 95% CI	
CARDS 2004		30.97	0.73	[0.52, 1.02]
4D 2005		69.03	0.93	[0.80, 1.09]
Total (95% CI)		100.00	0.86	[0.69, 1.07]

0.50   0.71   1.00   1.41   2.00
favours atorvastatin   favours placebo
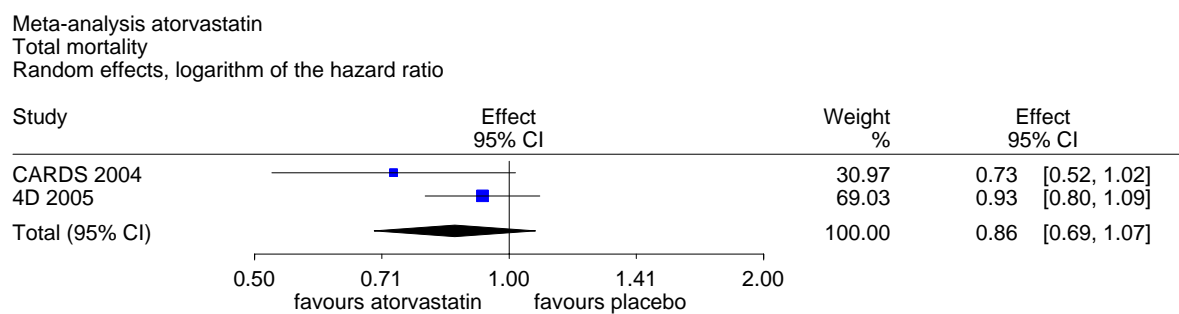
Heterogeneity: Q=1.67, df=1 (p=0.196), I²=40.2%
Overall effect: Z Score=-1.32 (p=0.188), tau²=0.012

4.3.6.2   Coronary mortality

Information on coronary mortality in patients treated with atorvastatin was only found in publications on the ASCOT-LLA and CARDS studies. In the ASCOT-LLA study, no statistically significant difference between treatment groups was shown. The rate with atorvastatin was even higher than with placebo. In the CARDS study, event rates were reported, but hazard ratios were not. The event rate with atorvastatin was lower than with placebo.

The statements made in Section 4.3.6.1 apply correspondingly for the statins fluvastatin and pravastatin.

In the HPS study, a statistically significant difference in favour of simvastatin was also shown with regard to coronary mortality.

4.3.6.3   Non-fatal myocardial infarctions

None of the studies on atorvastatin showed a statistically significant difference for the endpoint "non-fatal myocardial infarctions". In all three placebo-controlled studies (ASCOT-LLA, CARDS and 4D), the rate of non-fatal myocardial infarctions in patients treated with atorvastatin was lower than in patients treated with placebo. A meta-analytical summary of the results of the ASCOT-LLA and 4D studies (conducted with reservations about the heterogeneity of the studies: different patient collectives with substantially differing mortality rates with placebo) showed no statistically significant effect in respect of the rate of non-fatal myocardial infarctions. The CARDS study was not included in this analysis as no hazard ratio was provided.

No relevant studies on fluvastatin were found for the endpoint "non-fatal myocardial infarction".

The statements made in Section 4.3.6.1 in respect of the endpoint "non-fatal myocardial infarction" apply correspondingly for pravastatin.

In the HPS study, a statistically significant difference in favour of simvastatin with regard to non-fatal myocardial infarctions was shown.

Figure 4: Meta-analysis of the atorvastatin studies in patients with diabetes mellitus – non-fatal myocardial infarctions

Meta-analysis atorvastatin
Non-fatal myocardial infarction
Random effects, logarithm of the hazard ratio

Study	Effect 95% CI	Weight %	Effect 95% CI
ASCOT-LLA 2005		31.37	0.62 [0.37, 1.05]
4D 2005		68.63	0.88 [0.64, 1.21]
Total (95% CI)		100.00	0.79 [0.57, 1.08]

favours atorvastatin   favours placebo

Heterogeneity: Q=1.25, df=1 (p=0.264), I²=19.7%
Overall effect: Z Score=-1.46 (p=0.144), tau²=0.012
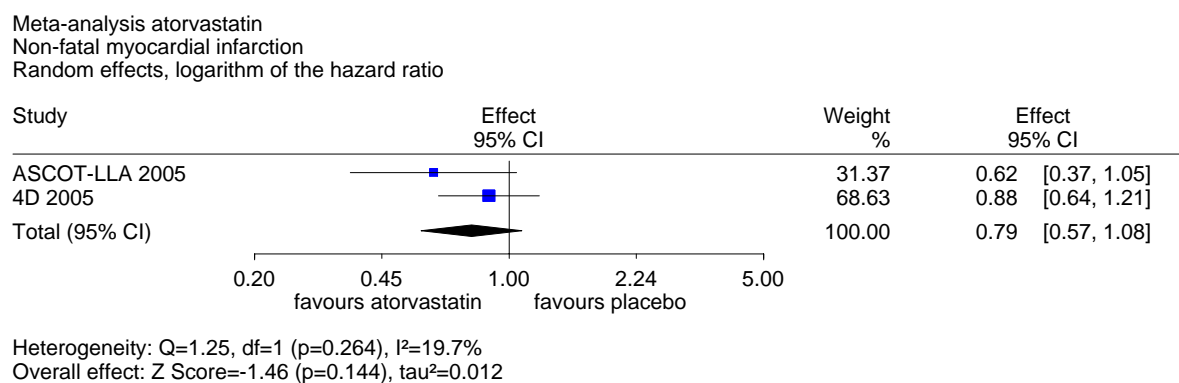
4.3.6.4   Primary study endpoints

In the CARDS study, the combined primary endpoint (see Table 13) occurred statistically significantly more rarely in patients treated with atorvastatin than in patients treated with placebo. In both the ASCOT–LLA and 4D studies, no statistically significant differences were shown between atorvastatin and placebo. The results of the PROVE-IT study (which also showed no statistically significant difference in the subgroup of patients with diabetes mellitus) are not sufficiently valid or robust, for the reasons stated in Section 4.1.5.

In the LIPS study, a statistically significant difference between treatment groups in favour of fluvastatin was shown with regard to the combined primary endpoint. However, the data provided in the two publications [99,475] are discrepant (see Table 16). No statistically significant difference between pravastatin and placebo was shown in the LIPID study or in the PROSPER study with regard to the combined primary endpoint as defined in the respective study. The event rate in the LIPID study was lower with pravastatin than with placebo, whereas in the PROSPER study the opposite was the case. With regard to cardiac or cardiovascular morbidity (independently of the presence of CHD), no evidence of a benefit was shown for pravastatin in patients with diabetes mellitus.

In the HPS study, a statistically significant difference in favour of simvastatin was shown for the combined primary endpoint "major coronary events".

4.3.6.5   Adverse drug effects

For the subgroup of patients with diabetes mellitus, very little information on adverse drug effects can be gained from the relevant publications available. No superiority of one statin over another can be inferred from the data available, neither regarding hepatic nor myopathic adverse drug effects (including rhabdomyolysis). Likewise, no clear result in advantage or disadvantage of a particular statin was shown in respect of the occurrence of new cancers. In the PROSPER study [75], which only included patients over 70 years, a higher cancer rate was shown in patients treated with pravastatin than in patients treated with placebo in the overall study population; it is unclear whether this also applies to the subgroup of patients with diabetes mellitus.

4.3.6.6   Summary

Simvastatin 40 mg daily reduced total mortality and the risk of severe coronary events (including coronary mortality and non-fatal myocardial infarctions) in patients with diabetes mellitus (with or without pre-existing CHD).

Atorvastatin 10 mg daily reduced the risk of a combined endpoint of cardio- and cerebrovascular events in patients with diabetes mellitus without pre-existing CHD, but with a high risk of vascular disease. A benefit with regard to total mortality, coronary mortality, and/or non-fatal myocardial infarctions was not shown.

Fluvastatin 80 mg daily reduced the risk of the occurrence of a combined endpoint of coronary mortality, non-fatal myocardial infarction, and recurrent revascularisation procedure in patients with diabetes mellitus and coexisting CHD following successful coronary revascularisation. A benefit with regard to total mortality, coronary mortality, and/or non-fatal myocardial infarctions was not shown.

No certain evidence of a benefit of pravastatin therapy in the subgroup of patients with diabetes mellitus was shown in the studies available.

No relevant study on lovastatin was available.

All in all, no evidence of the superiority of atorvastatin over other statins in patients with diabetes mellitus can be inferred from the available data. Valid direct comparative studies are lacking.

4.4 Adverse effects with high-dose therapy

4.4.1 Research question

4)   In studies conducted with the highest approved dose, do adverse drug effects (especially hepatic or myopathic effects) occur more frequently or more rarely with atorvastatin (Sortis®) than with other statins?

4.4.2 Conclusion

In studies conducted with the highest approved dose, discontinuations of therapy due to adverse events occurred more frequently in patients treated with atorvastatin than in patients treated with simvastatin, and liver enzyme elevations occurred more frequently in patients treated with atorvastatin than in patients treated with simvastatin or pravastatin.

4.4.3 Search strategy

The general methodology of the literature search is described in Appendix B.

Studies fulfilling all the following inclusion criteria and none of the exclusion criteria were included in the evaluation:

I-1. **Patients:** No limitations.

I-2. **Intervention:** Atorvastatin therapy with the highest dose approved in Germany (80 mg daily [140]). Studies where the daily dose was not specified and where the dose-specific frequency of adverse effects could not be determined were not taken into account.

I-3. **Control treatment:** Fluvastatin, lovastatin, pravastatin, or simvastatin therapy with the highest approved dose in Germany (fluvastatin: 80 mg daily [141]; lovastatin: 80 mg daily [144]; pravastatin: 40 mg daily [142]; simvastatin: 80 mg daily [143]). Studies where the daily dose was not specified and where the dose-specific frequency of adverse effects could not be determined were not taken into account.

I-4. **Additional lipid-lowering therapy:** The evaluation included studies in which an additional lipid-lowering treatment, depending on cholesterol levels, was possible. The evaluation did not include studies in which a priori a lipid-lowering combination therapy represented the intervention or control treatment (e.g. therapy with a statin and a fibrate).

I-5. **Endpoints:** Adverse drug effects

I-6. **Study design**: Double-blind RCT.

I-7. **Duration:** > 4 weeks.

I-8. **Language of publication**: German or English.

Exclusion criteria:

E-1. No full-text publication available.

4.4.4 Search results

The systematic literature search identified five studies that fulfilled the inclusion/exclusion criteria and included data on adverse drug effects:

- the Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES) Study [464];
- the Comparative HDL Efficacy and Safety Study (CHESS) [9];
- the Simvastatin Atorvastatin HDL Study (Illingworth et al.) [27];
- the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) Study [64];
- the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Study [43].

4.4.5 Description of the studies included

An overview of the five studies, including demographic information, is shown in Table 18.

No relevant comparative studies on atorvastatin vs. fluvastatin or atorvastatin vs. lovastatin were found.

Three relevant comparative studies on atorvastatin vs. pravastatin were found; the BELLES study in post-menopausal women with diagnosed coronary calcification, the PROVE-IT study in patients with acute coronary syndrome, and the REVERSAL study in patients with CHD.

Two relevant comparative studies were found on atorvastatin vs. simvastatin; the CHESS study and the study by Illingworth et al., which both included patients with hypercholesterolaemia (with or without CHD).

None of the studies had sufficient power to show significant differences with regard to rare or very rare adverse events between treatment groups.

Table 18: Direct dose-comparison studies with the highest approved dose (atorvastatin vs. other statins) – Overview and patient characteristics

Statin comparison Study	Follow-up	Number of patients [intervention] [control]	Age [years][a]	Sex f[%]	m[%]	Indication	Main exclusion criteria
Atorvastatin 80 mg vs. Pravastatin 40 mg							
BELLES 2005 [464]	12 months	305 [A] 309 [P]	64±7 65±6	100 100	0 0	Postmenopausal women with evidence of coronary calcification,[b] hypercholesterolaemia.	Existing statin therapy, hepatic dysfunction, renal dysfunction (creatinine > 1.5 mg/dl).
PROVE-IT 2004 [64]	2 years[c]	2099 [A][d] 2063 [P][d]	58±11 58±11	22 22	78 78	Acute coronary syndrome	Therapy with any statin at a dose of 80 mg per day at the time of the index event, serious hepatic disease, renal dysfunction (creatinine > 2.0 mg/dl).
REVERSAL 2004 [43]	18 months	327 [A] 327 [P]	56±10 57±9	29 27	71 73	Coronary stenosis diagnosed by angiography, hypercholesterolaemia.	n.d.
Atorvastatin 80 mg vs. Simvastatin 80 mg							
CHESS 2003 [9]	24 weeks	464 [A] 453 [S]	57±10 57±11	45 44	55 56	Hypercholesterolaemia	Liver disease, kidney dysfunction, diabetes mellitus type 1, uncontrolled diabetes mellitus type 2.
Illingworth et al. 2001 [27]	24 weeks[e]	394 [A][f] 385 [S][f]	n.d.	52 43	48[g] 57[g]	Hypercholesterolaemia	Existing statin or fibrate therapy.

a: Mean (rounded off where necessary), with standard deviation (±).
b: Defined as coronary Calcium Volume Score (CVS) > 30, measured with electron beam tomography.
c: Mean.
d: According to the study protocol, a halving of the dose (in both groups) or dose increase (only pravastatin) was possible. These changes in dose affected less than 10% of all patients.
e: A total of three study phases: 6 weeks [A] 20 mg vs. [S] 40 mg; 6 weeks [A] 40 mg vs. [S] 80 mg; 24 weeks [A] 80 mg vs. [S] 80 mg.
f: Number of patients in the 3rd study phase. Number of patients randomised: n = 412 [A]; n = 414 [S].
g: Data for intent-to-treat population according to publication (n = 408 [A]; n = 405 [S]).
n.d.: no details provided; m: male; f: female; [A]: atorvastatin; [P]: pravastatin; [S]: simvastatin.

Criteria for study and publication quality are shown in Table 19.

No detailed information on the randomisation process was found for the BELLES, CHESS, and Illingworth et al. studies, even after perusal of additional publications (e.g. publications on the study design or on results in specific subgroups), so it cannot be assessed whether randomisation and allocation concealment were adequate in these studies.

In the REVERSAL study the randomisation process was adequate. No information on allocation concealment was found.

In the PROVE-IT study, randomisation and allocation concealment were adequate.

No information was found in any of the five studies on whether the assessment of safety data was blinded or not.

In relation to the overall study population, the rate of patients lost to follow-up in the BELLES, CHESS, Illingworth et al. and REVERSAL studies was under 10%. Table 19 presents which results with regard to adverse drug effects remained robust after a best case/worst case analysis was conducted.

In the PROVE-IT study, the number of patients lost to follow-up is unclear. The reasons for this are explained in detail in Section 4.1.5. For the following analyses, it is assumed that patients whose LDL cholesterol was measured on the final study visit were also followed up with regard to the occurrence of adverse drug effects. Figure 1 [64] shows that this was the case for nearly all the patients who had not died.

For this reason, the number (n=8) stated in the text in [64] is assumed to be the number lost to follow-up for the following analyses.

Table 19: Direct dose-comparison studies with the highest approved dose (atorvastatin vs. other statins) – Quality of studies and publications

Statin comparison Study	Randomisation	Allocation concealment	Assessment of endpoint blinded[a]	Lost to follow-up [n]	Discrepant information on patients lost to follow-up	ITT-analysis robust[a,b]
Atorvastatin 80 mg vs. Pravastatin 40 mg						
BELLES [464]	n.d.	n.d.	n.d.	[A]: 12 (3.9%) [P]: 10 (3.2%)	no	no statistically significant results
PROVE-IT [64]	adequate	adequate	n.d.	unclear[c]	yes	no
REVERSAL [43]	adequate	n.d.	n.d.	[A]: 16 (4.9%) [P]: 11 (3.4%)	no	no statistically significant results
Atorvastatin 80 mg vs. Simvastatin 80 mg						
CHESS [9]	n.d.	n.d.	n.d.	[A]: 8 (1.7%) [S]: 6 (1.3%)	no	yes
Illingworth et al. [27]	n.d.	n.d.	n.d.	[A]: 18 (4.4%)[d] [S]: 29 (7%)[d]	no	in part[e]

a: Regarding adverse drug effects.
b: After conducting a best/worst case analysis with consideration of patients who were not followed up; only for endpoints with a statistically significant difference between treatment groups.
c: Discrepant information in text and figure [64] as well as in additional publication [429]; see also previous text.
d: Drop outs in the first two treatment phases. These were the basis for the best case/worst case analysis for the parameter "discontinuations of therapy". For liver enzyme elevations: additionally one patient lost to follow-up with simvastatin and three patients with atorvastatin.
e: See Section 4.4.6.5.
ITT: intent-to-treat; n.d.: no details provided; [A]: atorvastatin; [P]: pravastatin; [S]: simvastatin.

Table 20: Direct dose-comparison studies with the highest approved dose (atorvastatin vs. other statins) – Adverse drug effects

Statin Study	Discontinuations of therapy due to AEs	Liver enzyme elevations[a]	Creatinine kinase elevations[b]	Rhabdomyolysis	New cancers[c]
Atorvastatin 80 mg vs. Pravastatin 40 mg					
BELLES [464]	p: n.d.	p: n.d.		p: n.d.	n.d.
Atorvastatin	14.1%[d]	2.7%[e]	0%[e]	1 (0.3%)	
Pravastatin	6.8%[d]	0%[e]	0%[e]	0 (0%)	
PROVE-IT [64]	p = 0.23	p < 0.001	n.d.		n.d.
Atorvastatin	3.3%[f]	3.3%[g]		0 (0%)	
Pravastatin	2.7%[f]	1.1%[g]		0 (0%)	
REVERSAL [43]	p: n.d.	p: n.d.			p: n.d.
Atorvastatin	6.4%	2.3%[g,h]	0%[g]	0 (0%)	0%[i]
Pravastatin	6.7%	1.6%[g,h]	0%[g]	0 (0%)	0.6%[i]
Atorvastatin 80 mg vs. Simvastatin 80 mg					
CHESS [9]	p: n.d.	p = 0.007	p: n.d.		n.d.
Atorvastatin	14%	2.8%[e]	0.2%	0 (0%)	
Simvastatin	6%	0.4%[e]	0%	0 (0%)	
Illingworth et al. [27]	p: n.d.	p = 0.002			n.d.
Atorvastatin	6.9%	3.8%[e]	0%[j]	0 (0%)	
Simvastatin	3.1%	0.5%[e]	0%[j]	0 (0%)	

Table 20: Direct dose-comparison studies with the highest approved dose (atorvastatin vs. other statins) – Adverse drug effects (continued)

a: According to the definition in the respective study, mostly more than 3-fold increase compared with the respective normal value.
b: More than 10-fold increase over the respective normal value.
c: Fatal and non-fatal cancers.
d: According to Figure 1 in [464].
e: Persistent enzyme elevations; rate of non-persistent enzyme elevations not clear.
f: Only for discontinuations of therapy by the investigator because of muscle symptoms or creatinine kinase elevations.
g: Unclear, whether persistent or non-persistent.
h: Alanine aminotransferase. Rate of patients with an elevation of at least one liver enzyme unclear.
i: Only rate of cancers leading to discontinuations of therapy, otherwise n.d.
j: Only symptomatic creatinine kinase elevations.
AE: adverse event; n.d.: no details provided.

4.4.6 Discussion of study results

4.4.6.1 Discontinuations of therapy due to adverse events

Atorvastatin vs. pravastatin

In the PROVE-IT study, no statistically significant difference was shown between treatment groups with regard to discontinuations of therapy. In the REVERSAL study, the rate of discontinuations of therapy was comparable between treatment groups. A significance test was not conducted. In the BELLES study, discontinuations of therapy occurred more frequently in patients treated with atorvastatin than in patients treated with pravastatin (14.1% vs. 6.8%). Assuming statistical significance (Fisher's exact test, 2-sided: $p = 0.004$), this result remained robust after a best/worst case analysis was conducted.

A meta-analytical summary of the study results showed no statistically significant difference between atorvastatin and pravastatin with regard to the endpoint "discontinuations of therapy due to adverse events" (Figure 5). Marked heterogeneity between studies was shown.

Atorvastatin vs. simvastatin

In the CHESS study, more discontinuations of therapy occurred in patients treated with atorvastatin than in patients treated with simvastatin (14% vs. 6%). Assuming statistical significance (Fisher's exact test, 2-sided: $p < 0.001$), this result remained robust after a best case/worst case analysis was conducted.

Likewise, in the Illingworth et al. study, more discontinuations of therapy due to adverse events occurred with atorvastatin than with simvastatin (6.9% vs. 3.1%). Assuming statistical significance (Fisher's exact test, 2-sided: $p = 0.025$), this result did not remain robust after a best case/worst case analysis was conducted.

A meta-analytical summary of both studies showed that discontinuations of therapy due to adverse events occurred statistically significantly more frequently with atorvastatin than with simvastatin (Figure 6).

Figure 5: Meta-analysis of direct comparative studies between atorvastatin and pravastatin in the highest approved dose – Discontinuations of therapy

Meta-analysis atorvastatin vs. pravastatin
Comparison of discontinuations of therapy due to AEs
Distance measure: relative risk, random effects

Study	Atorvastatin n/N	Pravastatin n/N	RR 95% CI	Weight %	RR 95% CI
BELLES 2005	43/305	21/309		31.52	2.07 [1.26, 3.41]
PROVE-IT 2004	69/2099	56/2063		41.38	1.21 [0.86, 1.71]
REVERSAL 2004	21/327	22/327		27.10	0.95 [0.54, 1.70]
Total (95% CI)	133/2731	99/2699		100.00	1.35 [0.89, 2.03]

```
          0.20  0.33 0.50   1.00   2.00 3.00  5.00
          favours atorvastatin    favours pravastatin
```
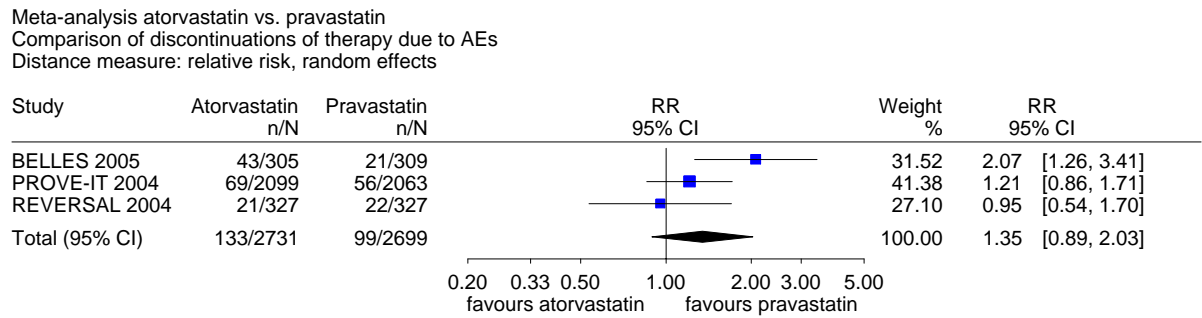
Heterogeneity: Q=4.62, df=2 (p=0.099), I²=56.7%
Overall effect: Z Score=1.42 (p=0.156), tau²=0.074

Figure 6: Meta-analysis of direct comparative studies between atorvastatin and simvastatin in the highest approved dose – Discontinuations of therapy

Meta-analysis atorvastatin vs. simvastatin
Comparison of discontinuations of therapy due to AEs
Distance measure: relative risk, random effects

Study	Atorvastatin n/N	Simvastatin n/N	RR 95% CI	Weight %	RR 95% CI
CHESS 2003	65/464	27/453		70.57	2.35 [1.53, 3.61]
Illingworth 2001	27/394	12/385		29.43	2.20 [1.13, 4.28]
Total (95% CI)	92/858	39/838		100.00	2.30 [1.61, 3.31]

```
          0.20   0.33 0.50   1.00   2.00 3.00  5.00
          favours atorvastatin    favours simvastatin
```
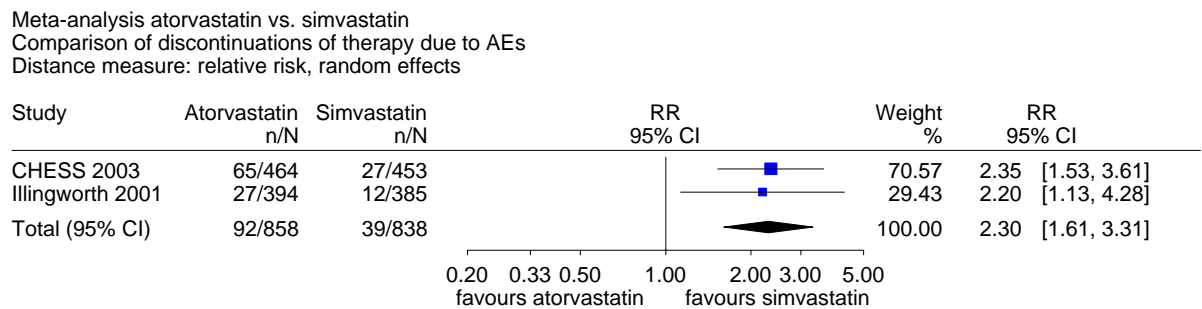
Heterogeneity: Q=0.03, df=1 (p=0.869), I²=0%
Overall effect: Z Score=4.53 (p=0.000), tau²=0.000

4.4.6.2   Liver enzyme elevations

Atorvastatin vs. pravastatin

In the PROVE-IT study, liver enzyme elevations occurred statistically significantly more frequently in patients treated with atorvastatin than in patients treated with pravastatin. This result remained robust after a best case/worst case analysis was conducted.

In both the BELLES and REVERSAL studies, more liver enzyme elevations occurred with atorvastatin than with pravastatin. Assuming statistical significance (Fisher's exact test, 2-sided: $p = 0.014$), the result of the BELLES study did not remain robust after a best case/worst case analysis was conducted. The difference between treatment groups in the REVERSAL study was not statistically significant (Fisher's exact test, two-sided: $p = 0.77$).

A meta-analytical summary of study results showed that following treatment with the highest approved dose, statistically significantly more liver enzyme elevations occurred with atorvastatin than with pravastatin (Figure 7).

Atorvastatin vs. simvastatin

In the CHESS study, statistically significantly more liver enzyme elevations occurred in patients treated with atorvastatin than in patients treated with simvastatin. This result remained robust after a best case/worst case analysis was conducted. Likewise, in the Illingworth et al. study, statistically significantly more liver enzyme elevations occurred with atorvastatin than with simvastatin. This result did not remain robust after a best case/worst case analysis was conducted. A meta-analytical summary of the study results showed that following treatment with the highest approved dose, statistically significantly more liver enzyme elevations occurred with atorvastatin than with simvastatin (Figure 8).
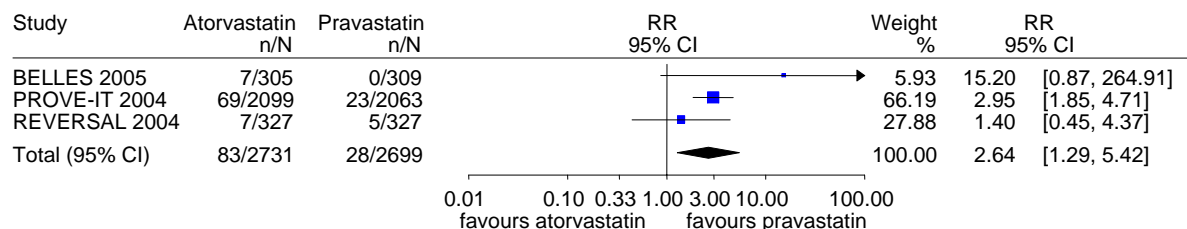
Figure 7: Meta-analysis of direct comparative studies between atorvastatin and pravastatin in the highest approved dose – Liver enzyme elevations

Meta-analysis atorvastatin vs. pravastatin
Comparison of liver enzyme elevations
Distance measure: relative risk, random effects

Study	Atorvastatin n/N	Pravastatin n/N	RR 95% CI	Weight %	RR 95% CI
BELLES 2005	7/305	0/309		5.93	15.20 [0.87, 264.91]
PROVE-IT 2004	69/2099	23/2063		66.19	2.95 [1.85, 4.71]
REVERSAL 2004	7/327	5/327		27.88	1.40 [0.45, 4.37]
Total (95% CI)	83/2731	28/2699		100.00	2.64 [1.29, 5.42]

```
0.01      0.10 0.33 1.00 3.00 10.00     100.00
     favours atorvastatin      favours pravastatin
```

Heterogeneity: Q=2.86, df=2 (p=0.239), I²=30.1%
Overall effect: Z Score=2.64 (p=0.008), tau²=0.147

Figure 8: Meta-analysis of direct comparative studies between atorvastatin and simvastatin in the highest approved dose – Liver enzyme elevations

Meta-analysis atorvastatin vs. simvastatin
Comparison of liver enzyme elevations
Distance measure: relative risk, random effects

Study	Atorvastatin n/N	Simvastatin n/N	RR 95% CI	Weight %	RR 95% CI
CHESS 2003	13/464	2/453		49.51	6.35 [1.44, 27.96]
Illingworth 2001	15/391	2/384		50.49	7.37 [1.70, 31.99]
Total (95% CI)	28/855	4/837		100.00	6.84 [2.41, 19.43]

```
0.01      0.10 0.33 1.00 3.00 10.00     100.00
     favours atorvastatin      favours simvastatin
```
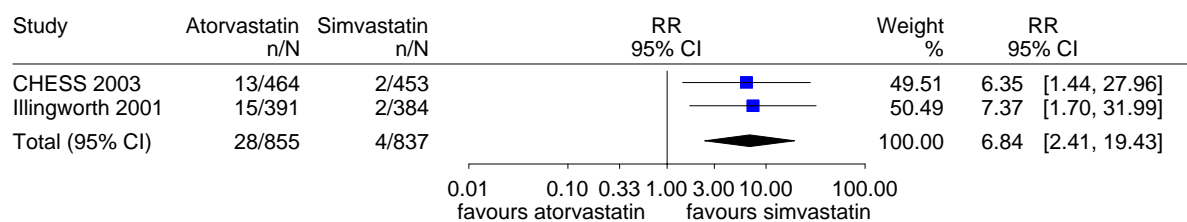
Heterogeneity: Q=0.02, df=1 (p=0.889), I²=0%
Overall effect: Z Score=3.61 (p=0.000), tau²=0.000

4.4.6.3 Muscle-related adverse drug effects

With regard to persistent or non-persistent creatinine kinase elevations, the available randomised controlled studies showed no relevant differences between atorvastatin and pravastatin or atorvastatin and simvastatin.

Cases of rhabdomyolysis were rare in the available intervention studies, which were not large enough to show differences between treatment groups for this adverse effect.

Results from case reports are presented in Section 4.4.7.

4.4.6.4 Cancers

The incidence of new cancers was only reported in the REVERSAL study. No clear difference was shown between treatment groups. On the basis of their size and duration, the studies were not designed to show a difference between treatment groups with regard to the occurrence of new cancers.

4.4.6.5 Other adverse drug effects

In the study by Illingworth et al., gastrointestinal adverse drug effects occurred statistically significantly more frequently in patients treated with atorvastatin than in patients treated with simvastatin. This result did not remain robust after a best case/worst case analysis was conducted. In the CHESS study, according to the publication, no statistically significant difference was shown between atorvastatin and simvastatin with regard to the overall incidence of gastrointestinal adverse drug effects. However, no detailed information was provided. Diarrhoea occurred more frequently with atorvastatin (3% vs. 1.3%), nausea more frequently with simvastatin (1.8% vs. 0.9%).

In both the CHESS study and the study by Illingworth et al., the incidence of any clinical adverse drug effect was higher with atorvastatin than with simvastatin (CHESS: 18.3% vs. 14.8 [not statistically significant]; Illingworth et al.: 23.4% vs. 11.9% [$p < 0.001$]).

This also applied to adverse laboratory changes (CHESS: 10.6% vs. 3.3% [$p < 0.001$]; Illingworth et al.: 12.2% vs. 3.9% [$p < 0.001$]). All the quoted statistically significant differences remained robust after a best case/worst case analysis was conducted.

4.4.7 Case reports on rhabdomyolysis

On the basis of their size and duration, the few direct comparative studies presented in the analyses described in the previous sections were insufficient to show differences between statins with regard to rare adverse drug effects, i.e. adequate randomised controlled statin trials were not available. Such events can only be detected after a sufficiently long observation period with a very high number of treated patients.

For this reason, retrospective collections of case reports, e.g. of the U.S. approval agency FDA (Food and Drug Administration) are occasionally referred to as evidence of the superiority of one particular statin over another. FDA reports include voluntary reports by physicians and patients, and reports from post-marketing surveillance studies. These reports may be a first indicator of differences between various treatment options with regard to serious and rare adverse effects. Due also to their voluntary nature, realistic event rates cannot be inferred from such reports,.

Bias in FDA reports is also possible for the following reasons:

- Controlling for known and unknown confounders is hardly possible, even after consultation of medical records.

- The sooner a drug is associated with a particular adverse effect (e.g. through media coverage), the more likely an adverse effect will be reported.

- The reported adverse effects may differ in their severity and time of occurrence compared with unreported cases.

- Outside the setting of a study, the assessment of adverse drug effects is prone to great subjectivity. For example, an adverse effects report is classified as "rhabdomyolysis" in the database if the reporting person (physician or patient) uses this term. However, this diagnosis is not verified. In a retrospective analysis by Graham et al., case reports were evaluated using hospital records; in the majority of cases, the reported diagnosis did not accord with the definition of this diagnosis or the hospital records [435].

- Duplicate reporting is possible (e.g. by both the physician and the patient).

In 2003, Staffa et al. [434] published findings from case reports of fatal rhabdomyolysis, based on data recorded in the FDA database until June 2001 (Table 21).

Table 21: Case reports of rhabdomyolysis (FDA database)

Statin	Number of fatal cases of rhabdomyolysis	Number of prescriptions between approval and May 2001 (in 1000)	Reporting rate (reports per one million prescriptions)
Atorvastatin	6	140360	0.04
Fluvastatin	0	37392	0.0
Lovastatin	19	99197	0.19
Pravastatin	3	81364	0.04
Simvastatin	14	116145	0.12
Cerivastatin	31	9815	3.16

This analysis is occasionally referred to as evidence of the superiority of atorvastatin over simvastatin with regard to the occurrence of fatal cases of rhabdomyolysis [259]. However, the authors of the analysis explicitly state that, apart from an obvious indicator with regard to cerivastatin, no rigorous comparisons between statins can be made: "Rigorous comparisons between drugs that are based on these data are not recommended, since many factors can affect reporting and an unknown number of cases may not be attributed to the drug or reported to the FDA. Reporting rates are not incidence rates."

In December 2004, Graham et al. [435] estimated the incidence of rhabdomyolysis in patients treated with statins or fibrates (alone or in combination) using reports from 11 managed care health plans across the United States. Cohorts of patients who were treated with statins and/or fibrates between January 1998 and June 2001 were established retrospectively. A case of rhabdomyolysis was assumed if the diagnosis "rhabdomyolysis" was made by the treating physician and, according to the reports, serious muscle damage existed or creatinine kinase was more than 10-fold the normal value.

Unlike reports in the FDA database, reports on potential cases of rhabdomyolyis were evaluated by three authors, who were blinded with regard to the type of therapy (statin and/or fibrate). Hospital records were also used for this evaluation; consequently, only 31 reports out of 194 reports of potential rhabdomyolysis cases were assessed to be actual rhabdomyolysis cases. This is important information to evaluate the quality and validity of case reports, e.g. on the basis of the FDA database.

Of the 31 cases of rhabdomyolysis, 13 occurred in patients treated with statin monotherapy, 8 with combined therapy with fibrates and 3 with fibrate monotherapy. Seven cases were not included in the analysis because at the time of occurrence of rhabdomyolysis, no lipid-lowering medication had been prescribed. Due to the low prescription numbers for fluvastatin and lovastatin, both drugs were excluded from the further analysis. Cases of rhabdomyolysis with different statin monotherapies are presented in Table 22.

The reported estimates of incidence were based on treatment years (estimated treatment period per patient on the basis of the prescription data) and not on the number of prescriptions. No clear differences between simvastatin and atorvastatin were shown for the resulting incidence estimates of rhabdomyolysis. No cases of rhabdomyolysis occurred in the cohorts treated with pravastatin. In Graham's analysis, there was also an indicator of an increased risk of rhabdomyolysis with cerivastatin.

In summary, an indicator of an increased incidence of rhabdomyolysis with cerivastatin can be inferred from the available retrospective case reports. Cerivastatin was withdrawn from the market in 2001. Due to their underlying methodology, these types of analyses are not appropriate for robust comparative conclusions on other statins.

Table 22: Cases of rhabdomyolysis in patients receiving monotherapy with different statins – Data from 11 US managed care health plans

	Atorvastatin (n = 130865)	Cerivastatin (n = 12695)	Fluvastatin (n = 4706)	Lovastatin (n = 1207)	Pravastatin (n = 35713)	Simvastatin (n = 46799)
Patient characteristics						
$\geq$ 65 years (%)	25	34	49	50	27	31
Women (%)	44	50	55	52	47	45
Diabetes (%)	14	13	12	11	13	13
Liver disease (%)	1	1	1	1	1	1
Kidney disease (%)	1	0	0	1	1	1
Treatment years	129367	7486	3292	775	331149	40940
Cases of rhabdomyolysis (n)	7	4	0	0	0	2
Cases of rhabdomyolysis / 10000 treatment years 95% confidence interval	0.54 (0.22-1.12)	5.34 (1.46-13.68)	0 No details provided	0 No details provided	0 (0-1.11)	0.49 (0.06-1.76)

4.4.8 Summary

Statistically significantly more discontinuations of therapy due to adverse events occurred in patients treated with atorvastatin 80 mg daily than in patients treated with simvastatin 80 mg daily. Liver enzyme elevations occurred more frequently with atorvastatin than with simvastatin.

In studies conducted with the highest approved dose, more clinical adverse drug effects occurred with atorvastatin and more adverse laboratory changes were reported with simvastatin. The studies available had an observation period of 24 weeks. Conclusions on differences between statins with regard to long-term therapy cannot be made on the basis of these studies.

More liver enzyme elevations occurred with atorvastatin 80 mg daily than with pravastatin 40 mg daily.

Direct comparative studies with the highest approved dose between atorvastatin and fluvastatin or atorvastatin and lovastatin were not available.

Retrospective analyses from case reports showed an indicator for rhabdomyolysis to the disadvantage of cerivastatin, which was withdrawn from the market in 2001. Due to their underlying methodology, these types of analyses are not appropriate for robust comparisons between other statins.

In summary, no evidence of the superiority of atorvastatin over other statins with regard to the occurrence of adverse drug effects was found.

4.5 LDL cholesterol-lowering potency

4.5.1 Research question

5) Is there an association between the degree of statin-induced LDL cholesterol lowering and the degree of reduction of total mortality or coronary morbidity and mortality?

4.5.2 Conclusion

It cannot be inferred from the available long-term intervention studies on different statins that the extent of LDL cholesterol lowering is appropriate to generally prove or quantify a benefit with regard to patient-relevant endpoints.

4.5.3 Methods

The results of the studies described in Sections 4.1 to 4.3 with regard to total mortality, coronary mortality, and non-fatal myocardial infarctions were correlated to the LDL cholesterol lowering shown in these studies by means of meta-regression analysis. The difference in the relative lowering of LDL cholesterol between intervention and control group (x-axis) was plotted against the relative event reduction, measured by the hazard ratio (y-axis). In the respective analysis, studies were included where sufficient information was provided, including a 95% confidence interval of the hazard ratio. Further adjusting factors were not considered in the meta-regression.

4.5.4 Results

The relevant information on the studies included in the meta-regression is presented in Table 23.

For the HPS study, the results of the overall population were used, as the study populations described in Sections 4.1 and 4.3 overlap, and in addition, though no information on the relevant endpoints for the CHD subgroup was provided, this group represented the majority (approx. 65%) of the overall study population. According to [67], 3172 patients in the HPS study had neither CHD nor diabetes mellitus. The subgroups of patients with CHD and/or diabetes mellitus considered in this review therefore represented 85% of the overall study population in the HPS study.

An additional meta-regression of all three endpoints was conducted. The results of the PROVE-IT study were not taken into account, as serious doubts exist as to their validity (Section 4.1.5.) (sensitivity analysis).

Figures 9 to 11 show the results for the assessed endpoints. Each study is represented in the respective figure by a circle whose surface area reflects the weight of the respective study in the analysis.

None of the analyses showed a statistically significant association between the degree of the relative difference of LDL cholesterol lowering and the relative degree of event reduction.

Table 23: LDL-lowering and event rates in relevant intervention studies

Study	Δ Relative lowering of LDL cholesterol[a]	Total mortality[b]	Coronary mortality[b]	Non-fatal myocardial infarctions[b]
4D	37%	0.93 (0.79-1.08)	n.d.	0.88 (0.64-1.21)
4S	36%	0.7 (0.58-0.85)	0.58 (0.46-0.73)	0.63 (0.54-0.73)
ASCOT	27%	n.d.	1.72 (0.79-3.76)	0.62 (0.37-1.06)
A-to-Z	14%	0.79 (0.61-1.02)	n.d.	0.96 (0.77-1.21)
CARDS	44%	0.73 (0.52-1.01)	n.d.	n.d.
CARE	28%	0.91 (0.74-1.12)	0.8 (0.61-1.05)	0.77 (0.61-0.96)
HPS[c]	30%	0.87 (0.81-0.94)	0.8 (0.75-0.9)	0.6 (0.55-0.7)
LIPID	25%	0.78 (0.69-0.87)	0.76 (0.65-0.88)	0.71 (0.62-0.82)
LIPS	38%	0.69 (0.45-1.07)	n.d.	n.d.
LiSA	n.r.	n.d.	n.d.	n.d.
MIRACL	50%	0.94 (0.67-1.31)	n.d.	0.9 (0.69-1.16)
PACT	n.r.	n.d.	n.d.	n.d.
PROVE-IT	31%	0.72 (0.5-1.05)	0.7 (0.4-1.15)	0.87 (0.7-1.1)
TNT	24%	1.01 (0.85-1.19)	0.8 (0.61-1.03)	0.78 (0.66-0.93)

a: Difference between treatment groups; rounded off where necessary.
b: Hazard ratio (with 95% confidence interval).
c: Data for overall study population. Respective data for the subgroup of patients with diabetes mellitus: Relative lowering of LDL cholesterol: 28%; total mortality (HR): 0.85 (0.75-0.95); coronary mortality (HR): 0.8 (0.66-0.96); non-fatal myocardial infarction (HR): 0.63 (0.5-0.8).
HR: hazard ratio; n.d.: no details provided; n.r.: not relevant (no endpoint data).

Figure 9: Meta-regression of the endpoint: "total mortality"
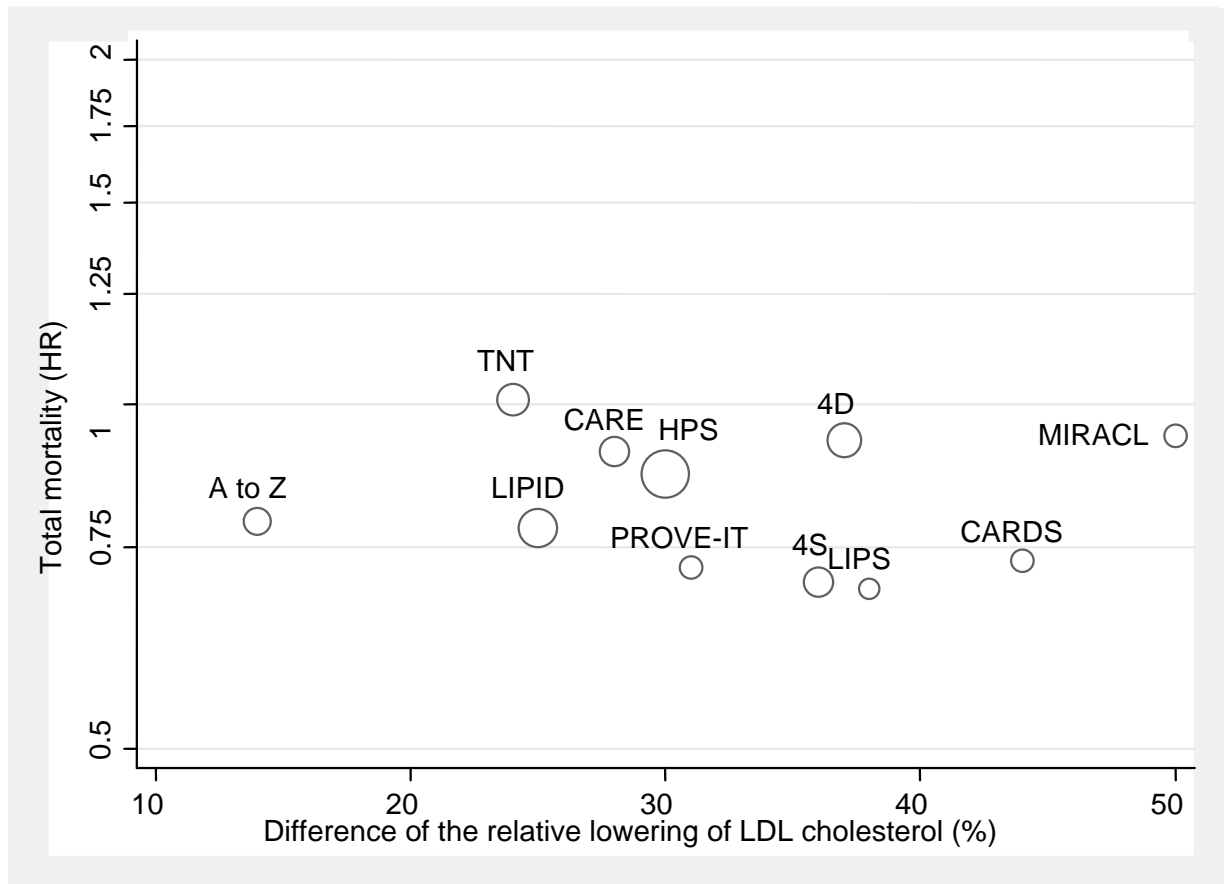
p = 0.81 for the effect of the difference of the relative lowering of LDL cholesterol on the hazard ratio; change of the hazard ratio per 1%-point difference of the relative lowering of LDL cholesterol (95% confidence interval): 1.00 (0.99-1.01).

Sensitivity analysis (meta-regression excluding the PROVE-IT study)

p = 0.81 for the effect of the difference of the relative lowering of LDL cholesterol on the hazard ratio; change of the hazard ratio per 1%-point difference of the relative lowering of LDL cholesterol (95% confidence interval): 1.00 (0.99-1.01).

Figure 10: Meta-regression of the endpoint "coronary mortality"

p = 0.12 for the effect of the difference of the relative lowering of LDL cholesterol on the hazard ratio; change of the hazard ratio per 1%-point difference of the relative lowering of LDL cholesterol (95% confidence interval): 0.98 (0.95-1.01).

Sensitivity analysis (meta-regression excluding the PROVE-IT study)

p = 0.13 for the effect of the difference of the relative lowering of LDL cholesterol on the hazard ratio; change of the hazard ratio per 1%-point difference of the relative lowering of LDL cholesterol (95% confidence interval): 0.98 (0.95-1.01).

Figure 11: Meta-regression for the endpoint "non-fatal myocardial infarction"
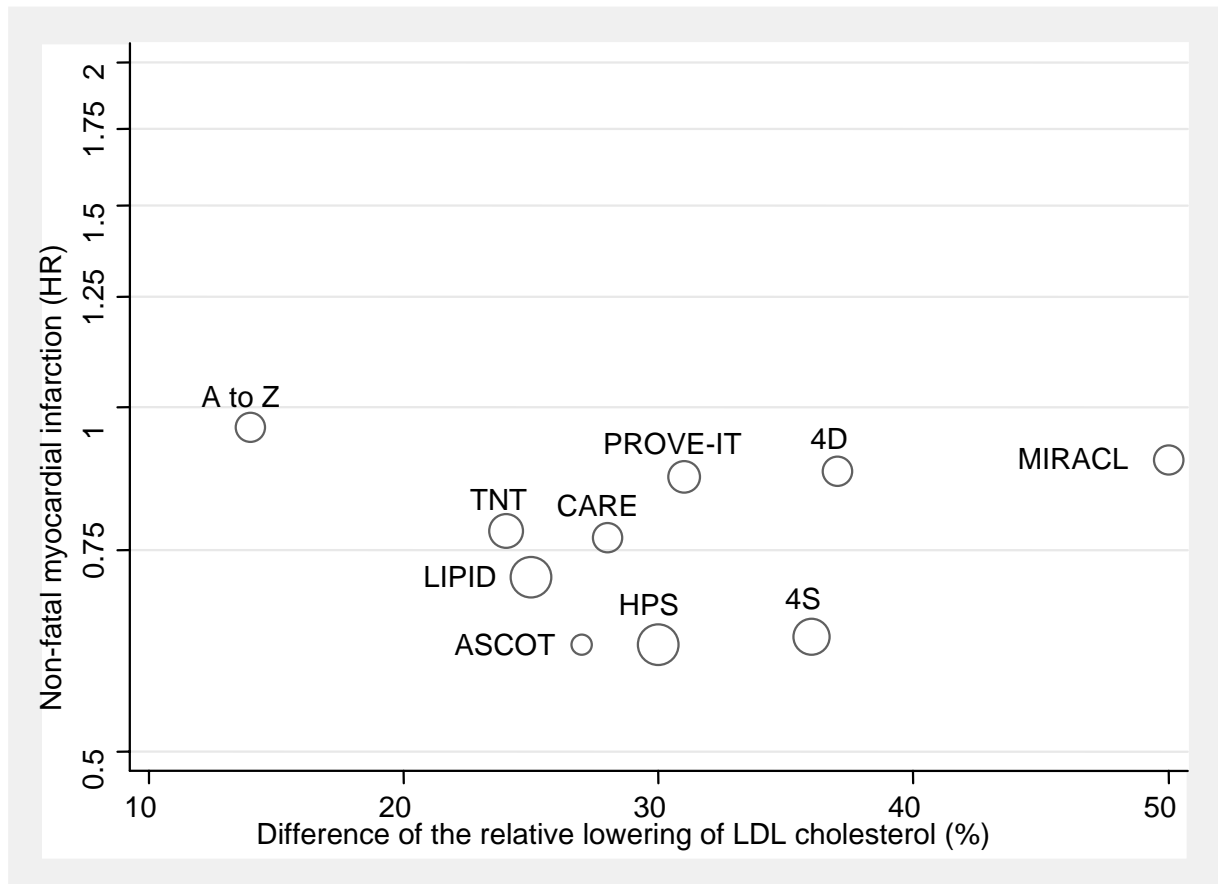
p = 0.95 for the effect of the difference of the relative lowering of LDL cholesterol on the hazard ratio; change of the hazard ratio per 1%-point difference of the relative lowering of LDL cholesterol (95% confidence interval): 1.00 (0.99-1.01).

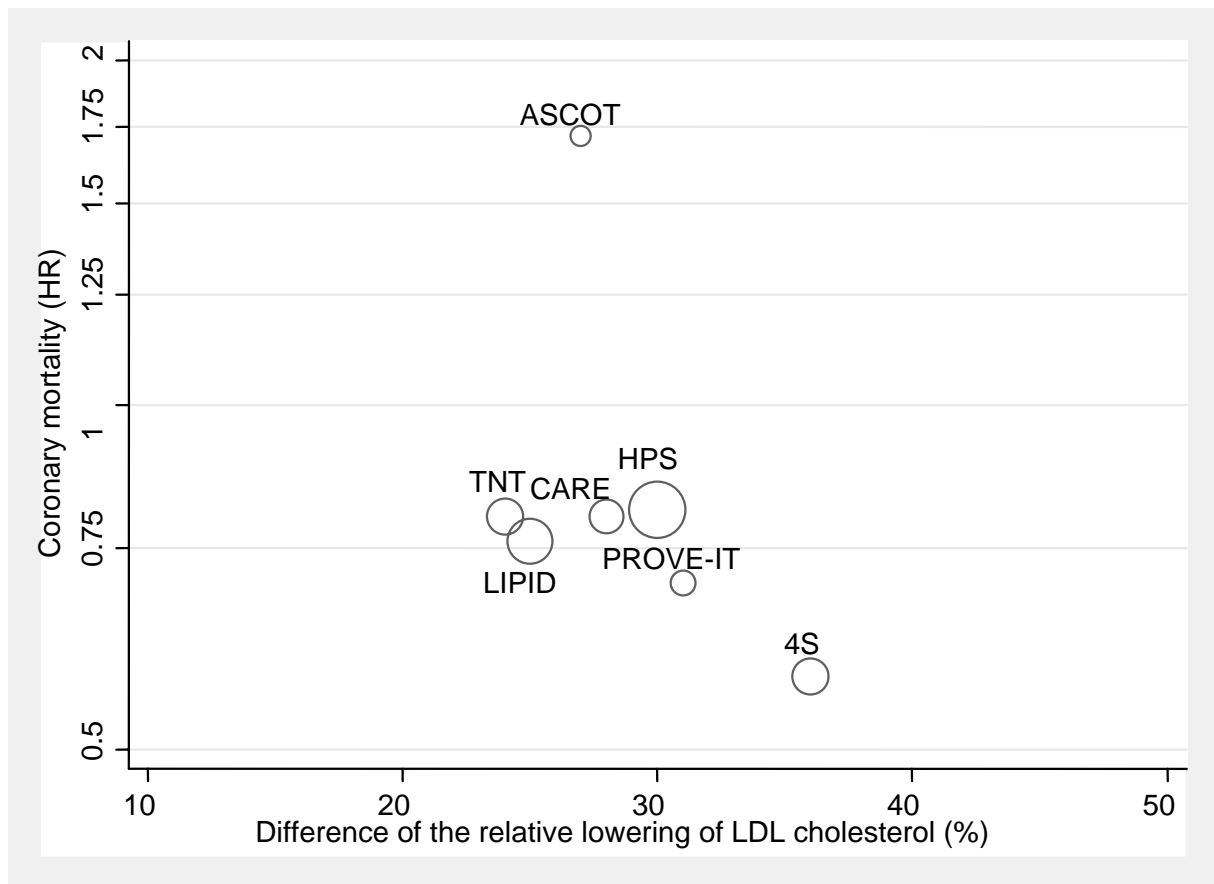Sensitivity analysis (meta-regression excluding the PROVE-IT study)

p = 0.96 for the effect of the difference of the relative lowering of LDL cholesterol on the hazard ratio; change of the hazard ratio per 1%-point difference of the relative lowering of LDL cholesterol (95% confidence interval): 1.00 (0.99-1.01).

4.5.5 Conclusion

No statistically significant association was shown between the degree of the difference of relative LDL cholesterol lowering and the degree of event reduction, neither for total mortality, nor for coronary mortality, nor for non-fatal myocardial infarctions.

It cannot be inferred from the long-term intervention studies available on different statins that the degree of LDL cholesterol lowering is appropriate to generally prove or quantify a benefit with regard to patient-relevant endpoints.

Appendix A: References

This reference list includes publications that were considered and evaluated in the production of the review on hand.

No.	Authors	Title	Published by
1	American Heart Association.	Heart Disease and Stroke Statistics — 2005 Update	Dallas, Tex.: American Heart Association; 2004.
2	Balk EM, Lau J, Goudas LC, et al.	Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review.	Ann Intern Med 2003; 139: 670-682.
3	National Cholesterol Education Program.	Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 2002.	http://www.nhlbi.nih.gov; Access on 1.8.2005
4	Centre for Reviews and Dissemination.	Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews	http://www.york.ac.uk; Access on 1.8.2005
5	Harris RP, Helfand M, Woolf SH, et al.	Current methods of the US Preventive Services Task Force: a review of the process.	Am J Prev Med 2001; 20(Suppl. 3): 21-35.
6	Andrews TC, Ballantyne CM, Hsia JA, Kramer JH.	Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins.	Am J Med 2001; 111: 185-191.
7	The Lovastatin Pravastatin Study Group.	A multicenter comparative trial of lovastatin and pravastatin in the treatment of hypercholesterolemia. The Lovastatin Pravastatin Study Group.	Am J Cardiol 1993; 71: 810-815.
8	Assmann G, Huwel D, Schussman KM, et al.	Efficacy and safety of atorvastatin and pravastatin in patients with hypercholesterolemia.	Eur J Intern Med 1999; 10: 33-39.
9	Ballantyne CM, Blazing MA, Hunninghake DB, et al.	Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hypercholesterolemia: Results of the Comparative HDL Efficacy and Safety Study (CHESS).	Am Heart J 2003; 146: 862-869.
10	Berger ML, Wilson HM, Liss CL.	A comparison of the tolerability and efficacy of lovastatin 20 mg and fluvastatin 20 mg in the treatment of primary hypercholesterolemia.	J Cardiovasc Pharmacol Ther 1996; 1: 101-106.

Evaluation of the effects of statins (with particular consideration of atorvastatin)

No.	Authors	Title	Published by
11	Bertolini S, Bon GB, Campbell LM, et al.	Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia.	Atherosclerosis 1997; 130: 191-197.
12	Blasetto JW, Stein EA, Brown WV, Chitra R, Raza A.	Efficacy of rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups.	Am J Cardiol 2003; 91: 3C-10C.
13	Branchi A, Fiorenza AM, Torri A, et al.	Effects of atorvastatin 10 mg and simvastatin 20 mg on serum triglyceride levels in patients with hypercholesterolemia.	Curr Ther Res Clin Exp 2001; 62: 408-415.
14	Brown AS, Bakker-Arkema RG, Yellen L, et al.	Treating patients with documented atherosclerosis to National Cholesterol Education Program recommended low density lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin.	J Am Coll Cardiol 1998; 32: 665-672.
15	Brown WV, Bays HE, Hassman DR, et al.	Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial.	Am Heart J 2002; 144: 1036-1043.
16	Crouse JRI, Frohlich J, Ose L, Mercuri M, Tobert JA.	Effects of high doses of simvastatin and atorvastatin on high density lipoprotein cholesterol and apolipoprotein A I.	Am J Cardiol 1999; 83: 1476-1477.
17	Dart A, Jerums G, Nicholson G, et al.	A multicenter, double blind, one year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia.	Am J Cardiol 1997; 80: 39-44.
18	Davidson M, Ma P, Stein EA, et al.	Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia.	Am J Cardiol 2002; 89: 268-275.
19	Davidson M, McKenney J, Stein E, Schrott H, Bakker-Arkema R, Fayyad R, et al.	Comparison of one year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia.	Am J Cardiol 1997; 79: 1475-1481.
20	Davidson MH, Palmisano J, Wilson H, Liss C, Dicklin MR.	A multicenter, randomized, double-blind clinical trial comparing the low-density lipoprotein cholesterol-lowering ability of lovastatin 10, 20, and 40 mg/d with fluvastatin 20 and 40 mg/d.	Clin Ther 2003; 25: 2738-2753.
21	Douste-Blazy P, Ribeiro VG, Seed M, et al.	Comparative study of the efficacy and tolerability of simvastatin and pravastatin in patients with primary hypercholesterolaemia.	Drug Invest 1993; 6: 353-361.

Evaluation of the effects of statins (with particular consideration of atorvastatin)

No.	Authors	Title	Published by
22	Farmer JA, Washington LC, Jones PH, Shapiro DR, Gotto AM, Mantell G.	Comparative effects of simvastatin and lovastatin in patients with hypercholesterolemia.	Clin Ther 1992; 14: 708-717.
23	Farnier M, Portal JJ, Maigret P.	Efficacy of atorvastatin compared with simvastatin in patients with hypercholesterolemia.	J Cardiovasc Pharmacol Ther 2000; 5: 27-32.
24	Frohlich J, Brun LD, Blank D, Campeau L, Crockford P, Curnew G, et al.	Comparison of the short term efficacy and tolerability of lovastatin and simvastatin in the management of primary hypercholesterolemia.	Can J Cardiol 1993; 9: 405-412.
25	Gentile S, Turco S, Guarino G, et al.	Comparative efficacy study of atorvastatin vs simvastatin, pravastatin, lovastatin and placebo in type 2 diabetic patients with hypercholesterolaemia.	Diabetes Obes Metab 2000; 2: 355-362.
26	Hunninghake D, Bakker-Arkema RG, Wigand JP, et al.	Treating to meet NCEP recommended LDL cholesterol concentrations with atorvastatin, fluvastatin, lovastatin, or simvastatin in patients with risk factors for coronary heart disease.	J Fam Pract 1998; 47: 349-356.
27	Illingworth RD, Crouse IJ, Hunninghake DB, et al.	A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial.	Curr Med Res Opin 2001; 17: 43-50.
28	Insull W, Kafonek S, Goldner D, Zieve F.	Comparison of efficacy and safety of atorvastatin (10mg) with simvastatin (10mg) at six weeks. ASSET Investigators.	Am J Cardiol 2001; 87: 554-559.
29	Jacotot B, Benghozi R, Pfister P, Holmes D.	Comparison of fluvastatin versus pravastatin treatment of primary hypercholesterolemia. French Fluvastatin Study Group.	Am J Cardiol 1995; 76: 54A-56A.
30	Jones P, Kafonek S, Laurora I, Hunninghake D.	Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study).	Am J Cardiol 1998; 81: 582-587.
31	Jones PH, Davidson MH, Stein EA, et al.	Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial).	Am J Cardiol 2003; 92: 152-160.
32	Kadikoylu G, Yukselen V, Yavasoglu I, Bolaman Z.	Hemostatic effects of atorvastatin versus simvastatin.	Ann Pharmacother 2003; 37: 478-484.

No.	Authors	Title	Published by
33	Karalis DG, Ross AM, Vacari RM, Zarren H, Scott R.	Comparison of efficacy and safety of atorvastatin and simvastatin in patients with dyslepidemia with and without coronary heart disease.	Am J Cardiol 2002; 89: 667-671.
34	Kastelein JJ, Isaacsohn JL, Ose L, et al.	Comparison of effects of simvastatin versus atorvastatin on high density lipoprotein cholesterol and apolipoprotein A I levels.	Am J Cardiol 2000; 86: 221-223.
35	Lambrecht LJ, Malini PL, Berthe C, et al.	Efficacy and tolerability of simvastatin 20 mg vs pravastatin 20 mg in patients with primary hypercholesterolemia.	Acta Cardiol 1993; 48: 541-554.
36	Lefebvre P, Scheen A, Materne P, et al.	Efficacy and tolerability of simvastatin and pravastatin in patients with primary hypercholesterolemia (multicountry comparative study).	Am J Cardiol 1992; 70: 1281-1286.
37	Lintott CJ, Scott RS, Sutherland WH, Bremer JM.	Treating hypercholesterolaemia with HMG CoA reductase inhibitors a direct comparison of simvastatin and pravastatin.	Aust N Z J Med 1993; 23: 381-386.
38	Lukacsko P, Walters EJ, Cullen EI, Niecestro R, Friedhoff LT.	Efficacy of once-daily extended-release lovastatin as compared to immediate-release lovastatin in patients with hypercholesterolemia.	Curr Med Res Opin 2004; 20: 13-18.
39	Malini PL, Ambrosioni E, De Divitiis O, Di Somma S, Rosiello G, Trimarco B.	Simvastatin versus pravastatin efficacy and tolerability in patients with primary hypercholesterolemia.	Clin Ther 1991; 13: 500-510.
40	März W, Wollschläger H, Klein G, Neiss A, Wehling M.	Safety of low density lipoprotein cholestrol reduction with atorvastatin versus simvastatin in a coronary heart disease population (the TARGET TANGIBLE trial).	Am J Cardiol 1999; 84: 7-13.
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No.	Authors	Title	Published by
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Appendix B: Methodology of the literature search

The objective of the literature search was to identify full-text published clinical studies on the topics assessed in this systematic review.

The following sources were consulted to find relevant full-text published studies in German or English:

- bibliographic databases: MEDLINE,[§] EMBASE,[**] CENTRAL.[††]
- Reference lists in publications of relevant studies.
- Reference lists in relevant secondary publications (HTA[‡‡] reports, systematic reviews, meta-analyses). These were identified as follows:
    1. in parallel by the database search mentioned above (MEDLINE, EMBASE and CENTRAL);
    2. by a search in specialised databases (CDSR[§§], DARE[***] and HTA-Database);
    3. by an internet search.

The search in the bibliographical databases was conducted in 2 steps:

1. First search in January 2005,
2. Additional search in August 2005 for the publication period between 01.1.2005 and 31.7.2005.

An example of a search strategy in the database MEDLINE is presented in Table 24. The search strategies for the other databases followed the same pattern except for adaptations specific to the respective database.

Two reviewers assessed the potential relevance of the publications on the basis of their titles and, if available, their abstracts. Publications which both reviewers assessed as potentially relevant were then assessed on the basis of the full text with regard to their relevance for the topic(s) investigated. Publications which initially only one reviewer assessed as potentially relevant were then assessed again by both reviewers and subsequently, after discussion, either

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[§] Medical Literature Analysis and Retrieval System Online
[**] Excerpta Medica Database
[††] Cochrane Central Register of Controlled Trials
[‡‡] Health technology assessment
[§§] Cochrane Database of Systematic Reviews
[***] Database of Abstracts of Reviews of Effects

assessed as irrelevant or were also assessed on the basis of their full-text with regard to their relevance for the investigated topic(s).

The assessment of the relevance of the publications on the basis of the full text was also performed independently by two reviewers. After this step, publications assessed as relevant for this systematic review on hand were defined as:

- Publications that were assessed as relevant by both reviewers.
- Publications that were initially assessed as relevant by only one reviewer, but after subsequent discussion were assessed as relevant by both reviewers.

The search for relevant secondary publications in the specialised databases CDSR, DARE and HTA was also performed in January 2005 and in August 2005.

Internet searches were repeatedly conducted during the production of the review on hand. No additional relevant publications were identified.

Table 24: Example of a search strategy

Search step	Search text
#16	Search #14 AND #12 NOT #15
#15	Search #13 AND #12
#14	Search (meta-analy*[ti] OR metaanaly*[ti] OR meta analy*[ti]) OR ((review[tiab] OR search*[tiab]) AND (medical database*[tiab] OR medline[tiab] OR pubmed[tiab] OR embase[tiab] OR cochrane[tiab] OR systemat*[tiab]))
#13	Search (randomized controlled trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh]) OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab]) AND (mask*[tiab] OR blind*[tiab])) OR ((randomis*[tiab] OR randomiz*[tiab]) AND controlled[tiab] AND (trial[tiab] OR study[tiab]))
#12	Search #9 NOT (#10 OR #11)
#11	Search Bibliography[pt] OR Biography[pt] OR Case Reports[pt] OR Clinical Conference[pt] OR Comment[pt] OR Congresses[pt] OR Consensus Development Conference[pt] OR Consensus Development Conference, NIH[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR Festschrift[pt] OR Interview[pt] OR Lectures[pt] OR Legal Cases[pt] OR Legislation[pt]
#10	Search animal[mh] NOT human[mh]
#9	Search #1 OR #2 OR #3 OR #4 OR #4 OR #5 OR #6 OR #7 OR #8
#8	Search fluvastatin[substance same] OR fluvastatin[mh] OR fluvastatin[tw]
#7	Search atorvastatin[substance same] OR atorvastatin[mh] OR atorvastatin[tw]
#6	Search lovastatin[substance name] OR lovastatin[mh] OR lovastatin[tw]
#5	Search pravastatin[substance name] OR pravastatin[mh] OR pravastatin[tw]
#4	Search simvastatin[substance name] OR simvastatin[mh] OR simvastatin[tw]
#3	Search statin[tw] OR statins[tw] OR statine[tw] OR statines[tw]
#2	Search hmg[tiab] AND coa[tiab] AND reductase[tiab] AND inhibitor*[tiab]
#1	Search "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR Hydroxymethylglutaryl-CoA Reductase Inhibitors[tiab]

Appendix C: Examples of best case/worst case analyses

Example A

- Randomised patients: 1000 patients per intervention group and per control group.
- Lost to follow-up: 50 patients per intervention group and per control group.
- Event rate in the intervention group according to publication: 60 / 1000 patients = 6%.
- Event rate in the control group according to publication: 100 / 1000 patients = 10%.
- Difference between events = 6% - 10% = -4% (fewer events in the intervention group).
- Best case analysis: Event rate in the intervention group unchanged (6%); event rate in the control group = (100 + 50) / 1000 = 150 / 1000 = 15%. Difference between events = 6% - 15% = -9%. This does not lead to a change of the overall conclusion (fewer events in the intervention group).
- Worst case analysis: Event rate in the intervention group = (60 + 50) / 1000 = 110 / 1000 = 11%; event rate in the control group unchanged (10%). Difference between events = 11% - 10% = 1%. This leads to a change in the overall conclusion (more events in the intervention group assuming the worst case).

The results of this fictitious study are therefore not robust.

Example B

- Randomised patients: 1000 patients per intervention group and per control group.
- Lost to follow-up: 30 patients per intervention group and per control group.
- Event rate in the intervention group according to the publication: 60 / 970 patients = 6.2% (in the publication, patients lost to follow-up were already excluded from the reference population).
- Event rate in the control group according to the publication: 100 / 970 patients = 10.3%.
- Difference between events = 6.2% - 10.3% = -4.1% (fewer events in the intervention group).
- Best case analysis: event rate in the intervention group = 60 / (970 + 30) = 60 / 1000 patients = 6% (number of events unchanged, but reference population extended due to patients lost to follow-up; event rate in the control group = (100 + 30) / (970 + 30) =

130 / 1000 = 13%. Difference between events = 6% - 13% = -7%. This does not lead to a change in the overall conclusion (fewer events in the intervention group).

- Worst case analysis: event rate in the intervention group = (60 + 30) / (970 + 30) = 90 / 1000 = 9%; event rate in the control group = 100 / (970 + 30) = 10%. Difference between events = 9% - 10% = -1%. This also does not lead to a change in the overall conclusion (fewer events in the intervention group).

The results of this fictitious study are therefore robust.

Appendix D: List of abbreviations

Abbreviation	Definition
AE	Adverse event
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
DARE	Database of Reviews of Effects
ECG	Electrocardiogram
EF	Ejection fraction
EMBASE	Excerpta Medica Database
FDA	Food and Drug Administration
HDL	High-density lipoprotein
HR	Hazard ratio
HTA	Health technology assessment
ITT	Intention to treat
LDL	Low-density lipoprotein
MEDLINE	Medical Literature Analysis and Retrieval System Online
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
RCT	Randomised controlled trial
RR	Relative risk