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Review

ATORVASTATIN: GOLD STANDARD FOR PROPHYLAXIS OF MYOCARDIAL ISCHEMIA AND STROKE

COMPARISON OF THE CLINICAL BENEFIT OF STATINS ON THE BASIS OF RANDOMIZED CONTROLLED ENDPOINT STUDIES

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Abstract

Aim: of this study was to compare the clinical benefit - reduction of heart attacks, strokes or deaths - of the different statins applying the results of randomized controlled endpoint studies.

Method: We analyzed 11 published randomized controlled endpoint studies statin-to-placebo looking for the cardiovasculoprotective benefit of the 5 statins (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin) tested: AFCAPS/TexCAPS, ASCOT, CARE, FLORIDA, HPS, PROSPER, LIPID, LIPS, MIRACL, 4S, WOSCOPS.

Results:

1. Statins produced substantial benefit for the patients, reducing the rate of cardiovascular morbidity and mortality.
2. This benefit was independent of the patient´s initial cholesterol or LDL-cholesterol concentrations and could also be demonstrated in patients who had average or low cholesterol levels.
3. Men and women showed a comparable benefit from statin treatment, elderly patients a little more than younger patients.
4. The statins did not have like effects. There were clear differences in potency as well as in the interval between initiation of treatment and the onset of clinical benefit.
5. Estimating 5 years of treatment, cardiac morbidity decreased with atorvastatin up to 44 %, with pravastatin up to 36 %, with fluva- or simvastatin up to 32 % and with lovastatin up to 24 %, approximately.
6. Estimating 5 years of treatment, morbidity of suffering from stroke decreased with atorvastatin up to 41 %, with simvastatin up to 34 % and with pravastatin up to 31 %, approximately. For fluva- and lovastatin there are no comparable data. Within the first 16 weeks of treatment following an acute coronary syndrome relative risk for suffering a non-lethal stroke was reduced with atorvastatin 80 mg/day up to 59 % compared to placebo, the relative risk for stroke up to 50 %.
7. The fastest onset of clinical benefit - reduction of fatal and non-fatal cardiovascular events, hospitalization and necessity of invasive interventions - was demonstrated by treatment with atorvastatin (rapid, within some weeks), followed by lovastatin (after one year), fluva-, prava- and simvastatin (after 1 1/2 - 2 years).
8. These results were achieved with atorvastatin 10 mg/day (80 mg/day used in MIRACL), lovastatin 20 to 40 mg/day (caused by dosage titration), pravastatin 40 mg/day, simvastatin 20 to 80 mg/day (caused by dosage titration) or fluvastatin 80 mg/day.
9. The advantage of atorvastatin may be due to its ability to reduce cardiovascular disease by stopping the growth of plaques in artery walls.
10. Atorvastatin was the most powerful compound in the group of statins, improving patients´ health and expectation of life.

Conclusions: The authors of the studies agree, that patients at risk for cardiovascular diseases should be treated with a statin irrespective of initial cholesterol concentrations, sex or age. If an acute cardiovascular event has happened, statin treatment should be initiated early to improve the prognosis of these patients at high risk, independent from initial LDL cholesterol values.

Summing-up of these 11 trials, the best results and the greatest benefit for the patients were achieved with atorvastatin, which might be considered to be the gold standard for prophylaxis of cardiac ischemia and stroke.

Key words: HMG-CoA Reductase Inhibitors; Atorvastatin; Fluvastatin; Lovastatin; Pravastatin; Rosuvastatin; Simvastatin; Coronary Heart Disease; Stroke; Benefit; Major Coronary Event

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Introduction

Cardiovascular disease is the most common non-infective cause of death worldwide with ever increasing frequency. In Germany every second death is caused by cardiovascular disease like acute myocardial infarction or stroke.

Statins originally have been developed as lipid-regulating agents. They have now been accepted as the gold standard for the treatment of patients with hypercholesterolemia. During recent years intervention studies have confirmed that statins have a clear cardiovascular benefit in primary and secondary prevention and acute coronary syndromes across a wide age range and among patients with total cholesterol or LDL cholesterol concentrations below average as well.

In addition to the lowering of total cholesterol and LDL cholesterol statins have salutary physiologic effects. They improve endothelial function, decrease platelet aggregability and thrombus deposition and reduce vascular inflammation. Most recently it has been reported that statins may reduce (pravastatin) or stop (atorvastatin) the growth of plaques in artery walls (Nissen 2003).

The aim of this study was to compare the clinical benefit - reduction of heart attacks, strokes or deaths - of the different statins applying the results of randomized controlled endpoint studies.

We analyzed 11 randomized controlled endpoint studies statin-to-placebo looking for the cardiovasculoprotective benefit of the 5 statins (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin) tested: AFCAPS/TexCAPS, ASCOT, CARE, FLORIDA, HPS, PROSPER, LIPID, LIPS, MIRACL, 4S, WOSCOPS.

It is difficult to compare the results of the studies, because each study had its own design. The goal of the trials evaluated is the proof of the clinical benefit of the study medication compared to placebo. For this purpose in advance all important parameters of the study design were calculated to provide the study with optimal power: study sample size, time of reviewing the participants, dosage of the study medication, inclusion and exclusion criteria, definition of primary and secondary endpoints, breaking down of the results. None of the 11 evaluated trials is comparable to the others with respect to these parameters. As long as there are such fundamental differences - and these differences are also useful - meta-analyzes are scarcely helpful (Moher et al. 1998), it is more expressive to analyze the trials individually. Our highly esteemed teacher Nepomuk Zöllner, educated by Siegfried J. Thannhauser in Boston, taught us to not only to look to the statistics, but also to look at each single case in detail (Gresser 2003).

Some of the trials are published more than once. We have consciously limited our analyzes to the data published in the main manuscript.

The studies are decribed chronologically according to the year of publication; data and results of the studies are summarized in Tables 1 to 4.

Scandinavian Simvastatin Survival Study (4S). Lancet 1994

(Scandinavian Simvastatin Survival Study Group 1994)

Study design

Patients were recruited at 94 clinical centres in Scandinavia. 4,444 patients with angina pectoris or previous myocardial infarction and serum cholesterol 213-309 mg/dl (5.5-8.0 mmol/L) on a lipid-lowering diet were randomized to double-blind treatment with simvastatin 20 to 40 mg/day or placebo. The two treatment groups were well matched at baseline and the exclusion criteria were extensive. The study was stopped after a median follow-up time of 5.4 years because interim analysis showed, that the predefined aim of the study was reached.

Results

Noncardiovascular mortality was similiar in both treatment groups (simvastatin 2.1 %, placebo 2.2 %), cardiovascular mortality differed significantly (simvastin 136 = 6.1 %; placebo 207 = 11.5 %). Compared to placebo relative risk for cardiovascular death was 0.65 for the patients treated with simvastatin, for suffering heart attack it was 0.73, and for undergoing coronary artery bypass surgery or angioplasty it was 0.63.

In patients aged 60 years and more (simvastatin 52 %, placebo 51 % of participants) there was a significant difference between the simvastatin and the placebo group. The observed relative risk reductions produced by simvastatin were somewhat less when compared with the younger patients. In the simvastatin group the mortality of patients aged 60 years and more was 11.0 % compared to 5.2 % in younger patients, in the placebo group it was 14.8 % compared to 8.1 %.

Mortality in women was less than in men (simvastatin 6.6 % for women, 8.5 % for men, placebo 6.0 % compared to 12.8 % respectively), with a relative risk of 1.12 for the simvastatin group compared to placebo. In this trial simvastatin showed no positive effect in women.

The impact of simvastatin on coronary heart disease seemed to begin after about one year of therapy and increased steadily thereafter. The Kaplan-Meier curves for simvastatin or placebo separated after 1 to 2 years, latest after 2 years for the relative risk of undergoing revascularization procedures.

The authors concluded, that addition of simvastatin 20 to 40 mg/day to the treatment regimen of 100 coronary heart disease patients could preserve the lives of 4 of the 9 patients who otherwise would die from coronary heart disease within the first 6 years of treatment.

A single case of rhabdomyolysis occurred in a woman taking simvastatin 20 mg/day; she recovered when treatment was stopped.

The study was supported by Merck Research Laboratories USA.

SUMMARY

The 4S-trial was the first longterm endpoint study designed to evaluate the clinical benefit of simvastatin treatment on cardiovascular morbidity and mortality. Compared to placebo, simvastatin 20 to 40 mg/day reduced significantly cardiovascular morbidity and mortality and the risk of undergoing myocardial revascularization procedures. After two years of treatment there was a 26 % reduction of symptomatic myocardial infarction.

WOSCOP-STUDY. N ENGL J MED 1995

(Shepherd et al. 1995)

STUDY DESIGN

6,595 male patients from primary medical care facilities throughout the West of Scotland district were randomized and treated with pravastatin 40 mg/day or placebo for an average follow-up period of 4.9 years. Inclusion criteria were no history of myocardial infarction, no serious ECG abnormalities or arrhythmia and cholesterol ≥ 251 mg/dl (≥ 6.5 mmol/L).

The treatment groups were well balanced. Exclusion criteria were serious cardiac and non-cardiac illness.

RESULTS

The authors classified the endpoints as "definite" or "definite and suspected". Death from coronary heart disease occurred in 1.2 % of the pravastatin treated patients (definite and suspected cases 1.3 %) and in 1.7 % (1.9 %) of the placebo treated patients with a relative risk of 0.72 (0.67) for the pravastatin patients. Cardiovascular mortality was 1.6 % in the pravastatin group and 2.3 % in the placebo group with a relative risk for the pravastatin treated patients of 0.68.

1.39 % of the patients in the pravastatin group and 1.55 % in the placebo group suffered from stroke, relative risk was 0.89.

There are only few data about reduction in lipid levels. Pravastatin was found to have lowered plasma levels of cholesterol by 20 %, and triglycerides by 12 %, whereas HDL cholesterol was increased by 5 %. There were no such changes with placebo.

There were neither statistically significant differences between the subgroups (e.g. sex, age), nor severe adverse events.

The study was supported by Bristol-Myers Squibb Pharmaceutical Research Institute.

SUMMARY

Treatment with pravastatin 40 mg/day reduced the incidence of myocardial infarction and death from cardiovascular causes in men with moderate hypercholesterolemia and no history of myocardial infarction. The time-to-event curves began to diverge within six months to one year of the initiation of treatment.

CARE-STUDY. N ENGL J MED 1996

(Sacks et al. 1996)

STUDY DESIGN

From 80 participating centers, 13 in Canada and 67 in the United States, 4,159 patients with a history of acute myocardial infarction between 3 and 20 months before randomization, plasma total cholesterol levels of less than 240 mg/dl (62 mmol/L) and LDL cholesterol levels between 115-174 mg/dl (3.0-4.5 mmol/L) were recruited. After randomization participants were treated with pravastatin 40 mg/day or placebo, the median duration of follow-up was 5.0 years.

The characteristics of the two groups were similar. The primary endpoint of the trial was death from coronary heart disease or a symptomatic non-fatal myocardial infarction.

RESULTS

Pravastatin lowered the mean LDL cholesterol level of 139 mg/dl (3.6 mmol/L) by 32 % to about 97-98 mg/dl (2.5 mmol/L), this was 28 % lower than in the placebo group. Total cholesterol level was 20 % lower with pravastatin, HDL cholesterol 5 % higher compared to placebo.

The rate of fatal myocardial infarction was 37 % lower in the pravastatin group than in the placebo group, the rate of non-fatal myocardial infarction was 23 % lower. The pravastatin group had a 27 % lower rate of coronary bypass surgery or angioplasty. Of the patients with pravastatin treatment 2.6 % suffered from stroke compared to 3.8 % in the placebo group, the relative risk was 0.69.

The lower incidence of the primary end point showed a slight correlation to the total cholesterol level, the LDL cholesterol level, smoking and age over 60 years. Women had slightly better results with pravastatin than men.

For comparison of the results with simvastatin, the authors applied the methodical characteristics of the "Scandinavian Simvastatin Survival Study (4S)" (Scandinavian Simvastatin Survival Study Group 1994) to the participants of the CARE-study. In the 2,221 4S-patients simvastatin led to a reduction of coronary events of 37 % compared to placebo, in the 544 analog CARE-patients pravastatin led to a reduction of 43 % compared to placebo.

The time-to-event curves began to diverge about two years after initiation of treatment.

The study was supported by Bristol-Myers Squibb.

SUMMARY

In patients with a history of acute myocardial infarction and total cholesterol below 240 mg/dl

(6.2 mmol/L) pravastatin 40 mg/day led to a reduction in coronary events and in the necessity of invasive intervention.

LIPID-Study. N Engl J Med 1998

(The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998)

Study Design

9,014 patients with a history of acute myocardial infarction or unstable angina 3 to 36 months before study entry and initial total cholesterol of 155-271 mg/dl (4.0-7.0 mmol/L) were recruited at 87 centers in Australia and New Zealand, and randomized to pravastatin 40 mg/day or placebo.

The groups were well balanced. Exclusion criteria included severe medical or surgical events within three months before study entry, cardiac failure or running cholesterol lowering medication. The primary study outcome was death from coronary heart disease.

The study was stopped after a mean follow-up of 6.1 years because the prespecific boundary for a difference in overall mortality had been crossed.

Results

The incidence of the primary study endpoint "death from coronary heart disease" was 6.4 % in the pravastatin group and 8.3 % in the placebo group, with a relative risk of 0.76 for the pravastatin treated patients. Cardiovascular mortality was 7.3 % in the pravastatin group and 9.6 % in the placebo group, relative risk was 0.75.

Averaged over the first 5 years of follow-up total cholesterol level fell by 39 mg/dl (1 mmol/L) from 218 mg/dl (5.6 mmol/L), this was 18 % greater than in the placebo group. LDL cholesterol level fell by 25 % more than in the placebo group, HDL cholesterol increased by 5 % more than in the placebo group.

At the end of the study 19 % of the patients in the pravastatin group had stopped taking the study drug and 24 % of the patients in the placebo group had begun open-labelled therapy with a cholesterol-lowering drug.

There were no significant or clinically relevant differences between the subgroups. Significant reductions in the risk of coronary events were also observed in patients with initial total cholesterol levels below 213 mg/dl (5.5 mmol/L).

The authors estimate, that over a period of 6.1 years there could be avoided 30 deaths, 28 non-fatal myocardial infarctions, 9 non-fatal strokes, 23 episodes of coronary-artery bypass surgery, 20 cases of coronary angioplasty and 82 hospital admissions for unstable angina in 48 patients for every 1,000 patients randomly assigned to treatment with pravastatin 40 mg/day.

The time-to-event curves began to diverge about one to two years after initiation of treatment. There were no severe adverse effects.

The study was supported by Bristol-Myers Squibb Pharmaceutical Research Institute.

Summary

Pravastatin 40 mg/day compared to placebo reduced overall mortality, mortality from coronary heart disease and cardiovascular events in patients with a history of myocardial infarction or unstable angina, including patients with initial total cholesterol levels below 213 mg/dl (5.5 mmol/L).

AFCAPS/TexCAPS-Study. JAMA 1998

(Downs et al. 1998)

Study Design

About two-thirds of deaths from coronary heart disease occur in patients with average or below-average total cholesterol levels. The goal of this study was to compare the effect of lovastatin vs. placebo on the incidence of first acute major coronary events in patients without clinically evident atherosclerotic disease and average total cholesterol and LDL cholesterol levels and below average HDL cholesterol.

6,605 persons from 2 centers in Texas who fulfilled the lipid entry criteria without history, signs or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident or transient ischemic attack were randomized to lovastatin 20 mg/day or placebo. Follow-up was 5.2 years.

Baseline characteristics were similar in both groups; in the lovastatin group there were more smokers (lovastatin 13.0 %, placebo 11.8 %) and less patients with a family history of premature coronary heart disease (lovastatin 15.0 %, placebo 16.3 %).

Exclusion criteria included uncontrolled hypertension, insulin-dependent or uncontrolled diabetes mellitus, and adipositas permagna. The primary endpoint was defined as first acute major coronary event: fatal or non-fatal myocardial infarction, unstable angina or sudden cardiac death.

Results

During follow-up 50 % of the participants in the lovastatin group were titrated to lovastatin 40 mg/day because the LDL cholesterol level was more than 110 mg/dl (2.84 mmol/L).

After an average follow-up of 5.2 years the incidence of first major coronary events was reduced by 37 % (lovastatin 116, placebo 183 cases), of myocardial infarction by 40 % (lovastatin 57, placebo 95), unstable angina by 32 % (lovastatin 60, placebo 87), necessity of coronary revascularization procedures by 33 % (lovastatin 106, placebo 157), coronary events by 25 % (lovastatin 163, placebo 215) and cardiovascular events by 25 % (lovastatin 194, placebo 255).

After the first year of treatment lovastatin 20 to 40 mg/day reduced total cholesterol by 18 % to 184 mg/dl (4.75 mmol/L), LDL cholesterol by 25 % to 115 mg/dl (2.96 mmol/L) and increased HDL cholesterol by 6 % to 39 mg/dl (1.02 mmol/L). In the placebo group maximal changes were by ± 2.3 %.

None of the subgroups differed significantly in treatment benefit; the effect of lovastatin on the incidence of first major coronary events was numerically greater in women than in men. The time-to-event curves began to diverge about end of first year of treatment. There are no data about the incidence of stroke.

In the lovastatin group 1 patient developed non-fatal Stevens-Johnson-Syndrome after approximately 9 months of treatment, 1 patient reversible rhabdomyolysis. In the placebo group there were 2 cases of reversible rhabdomyolysis.

The study was supported by Merck & Co..

Summary

Lovastatin 20 to 40 mg/day reduced the risk for the first major coronary event in patients without clinically evident atherosclerotic disease and average total cholesterol and LDL cholesterol levels and below-average HDL cholesterol levels. The clinical benefit was obvious at the end of the first year of treatment. There were 1 case of non-fatal Stevens-Johnson-Syndrome and 1 case of reversible rhabdomyolysis (2 in the placebo group) in the lovastatin group.

MIRACL Study. JAMA 2001

(Schwartz et al. 2001)

Study Design

Patients experience the highest rate of death and recurrent ischemic events during the early period after an acute coronary event. The MIRACL trial was done to observe, whether early initiation of atorvastatin treatment in patients with an acute coronary syndrome could improve prognosis of these high risk patients, which had been excluded in the other endpoint trials with statins.

From 122 centers in Europe, North Amerika, South Africa and Australasia 3,086 patients with acute coronary syndrome and total cholesterol up to 270 mg/dl (7.0 mmol/L) - in Poland and South Africa up to 310 mg/dl (8 mmol/L) - were randomly assigned to double-blind treatment with atorvastatin 80 mg/day or placebo. Treatment was initiated 24 to 96 hours (mean 63 hours in both groups) following hospital admission and monitored for 16 weeks.

The groups were similar at baseline, also according to concurrent medications. Exclusion criteria are limited to patients, in which it would have been unethical or impractical to include them in a double-blind study vs. placebo like total cholesterol > 270/310 mg/dl (> 7/8 mmol/L); concurrent treatment with other lipid lowering drugs, necessity of invasive revascularization procedures or severe arrhythmia or heart failure.

Primary combined endpoint was death, non-fatal acute myocardial infarction, cardiac arrest with resuscitation or recurrent symptomatic myocardial ischemia requiring rehospitalisation.

Results

Six weeks after initiation of atorvastatin treatment the lipid lowering effect was at a maximum. After 16 weeks with atorvastatin 80 mg/day LDL cholesterol was decreased 40 % from 124 mg/dl to 72 mg/dl (3.2 mmol/L to 1.9 mmol/L), whereas it was increased with placebo 12 % from 124 mg/dl to 135 mg/dl (3.2 mmol/L to 3.5 mmol/L).

A primary endpoint event occured in 14.8 % (228 patients) of the atorvastatin patients and in 17.4 % (269 patients) of the placebo patients. Relative risk was 0.84, there was no correlation to the initial LDL cholesterol level or its decrease. The atorvastatin group had a lower risk according to total mortality, non-fatal acute myocardial infarction or cardiac arrest. In the atorvastatin group there was a 26 % statistically significant lowered risk of a symptomatic acute myocardial ischemia requiring rehospitalisation.

In the atorvastatin group 12 (3 fatal) strokes occurred, in the placebo group 24 (2 fatal) strokes. The relative risk for suffering a non-fatal stroke was 59 % lower in the atorvastatin patients than in the placebo patients, the relative risk for suffering a fatal or non-fatal stroke was 50 % lower.

The study was supported by Pfizer Inc..

Summary

In the MIRACL trial treatment with atorvastatin 80 mg/day, initiated in the early period after an acute coronary syndrome, recurrent ischemic events were significantly reduced compared to placebo. Within the first 16 weeks of treatment atorvastatin led to a decrease in primary endpoint events of 16 %, a decrease in total mortality of 6 % and a decrease of cardiovascular morbidity of 18 % compared to placebo.

In the atorvastatin group the relative risk for suffering a non-fatal stroke was 59 % lower than in the placebo group, the relative risk for suffering a fatal or non-fatal stroke was 50 % lower.

Treatment with atorvastatin 80 mg/day initiated early after an acute cardiac event improved the prognosis of these patients at high risk, independent from of LDL cholesterol values.

Heart Protection Study (HPS). Lancet 2002

(Heart Protection Study Collaborative Group 2002a)

We focused our analyzes to the data published in the main manuscript (Heart Protection Study

Collaborative Group 2002a) limited to first events.

Previous publications were "early" or "preliminary" (Heart Protection Study Collaborative Group 1999, Armitage and Collins 2000, Collins et al. 2002), others give data about the second study medication antioxidant vitamins (Heart Protection Study Collaborative Group 2002b) or the subgroup of patients with diabetes (Collins et al. 2003). The authors announce a future report dealing with subsequent events.

Study Design

20,536 patients were recruited at 69 hospitals in the United Kingdom and randomized to simvastatin 40 mg/day or placebo. Inclusion criteria were total cholesterol concentrations of at least 135 mg/dl (3.5 mmol/L) combined with a substantial risk of death from coronary heart disease because of coronary disease, occlusive disease of non-coronary arteries, diabetes mellitus or treated hypertension: 8,510 patients with previous myocardial infarction; 4,876 with a history of coronary disease; 7,150 without a history of coronary disease.

The groups were well balanced. Randomization was done between July 1994 and May 1997. In early 1998 the study design was changed: participants, who were prescribed a non-study statin could continue the study, taking both prescriptions, up to a total statin dose equivalent to simvastatin 80 mg/day.

Exclusion criteria were angina, myocardial infarction or stroke during the 8 to 10 weeks lasting run-in-phase and severe organic or psychiatric disorders. Patients with running statin therapy were not randomized.

Analyzes of lipid profiles were done in a selected sample of about 5 % of the participants. Information about major vascular events, cancers or deaths was recorded at each follow-up and sought from the participant´s general practitioner.

Before randomization there was a run-in phase involving 4 weeks of placebo followed by 4-6 weeks of a fixed dose of simvastatin 40 mg/day, to allow a prerandomization assessment of the LDL-lowering "responsiveness" of each participant. Of those, who entered run-in, 36 % were not subsequently randomized, 3/4 of these participants did not want to enter the trial or seemed to be non-compliant.

The study was initiated directly following the 4-6 weeks´ duration statin-phase. There was no wash-out in between. There are no data, whether the statin-phase was added or subtracted to the length of the treatment phase of the groups. If not, there would be a difference in length of the treatment phase between the placebo group and the simvastatin group.

The publication is limited to the first events, subsequent events are omitted. There were no data about concomitant medication.

Results

The mean duration of follow-up was 5.0 years for all participants, 5.3 years for those who were still alive at the end of the study, about half of that for those who died during the study.

After one year of follow-up compliance in the simvastatin group was 89 %, use of a non-study statin in the placebo group was 4 %. After 5 years of follow-up this grew to 82 % non-compliance in the statin group, and 32 % use of a non-study statin in the placebo group. Study average (analysis restricted to those who had not yet suffered a major vascular event) was 85 % respectively 17 %. The authors subtract these data (85 % minus 17 % = 67 %) and conclude, that the intention-to-treat comparisons in their report assess the effects of about two-thirds of simvastatin-allocated patients. This construction lowers the expressiveness of the data. It would have been better, if the results would have been differentiated between patients with or without additional medication, too.

4,002 participants, 19.5 % of all participants, were taking a non-study statin at the final follow-up: 53 % simvastatin, 28 % atorvastatin, 10 % pravastatin, 5 % cerivastatin, 4 % fluvastatin. This means, that about 5.5 % of all study participants in addition or instead of simvastatin or placebo took atorvastatin.

The average difference in total cholesterol (simvastatin minus placebo, 5 years of follow-up) was about 46 mg/dl (1.2 mmol/L), in LDL cholesterol about 39 mg/dl (1.0 mmol/L).

All data are limited to first events following randomization.

The coronary death rate was 5.7 % in the simvastatin group and 6.9 % in the placebo group with a relative risk of 0.83. Cardiovascular mortality was 7.6 % in the simvastatin group respectively 9.1 % in the placebo group with a relative risk of 0.83.

In the simvastatin group 444 patients suffered a first stroke after randomization (96 fatal), in the placebo group 585 (119 fatal). The difference is statistically significant. Relative risk for suffering a stroke was 0.75, relative risk to die from stroke was 0.81 for the simvastatin allocated patients.

Reduction of acute first events in the simvastatin group compared to placebo was independent from age or sex or subgroup and measured approximately 25 %. In patients aged 75-80 years at entry, the benefit was somewhat more compared to the younger patients (event rate 23.1 % in the simvastatin group and 32.3 % in the placebo group).

The authors give a short summary of the information, that the antioxidant vitamins, whose effect was studied versus placebo in parallel in the same participants, did not influence the effects of simvastatin on blood lipids or on vascular disease outcome. There are no data according to the subgroups statin plus vitamins, statin without vitamins, placebo plus vitamins, placebo without vitamins.

5 patients in the simvastatin group and 3 patients in the placebo group developed a non-fatal rhabdomyolysis. There are not data about the concomitant medication, especially according to statin medication. 19.5 % of all participants were taking a non-study statin at the final follow-up, 32 % of the patients in the placebo group were taking a non-study statin. Without case related data it is not possible, to assign the undesired side effect to simvastatin or placebo.

The study was supported by Merck & Co. and Roche Vitamins Ltd..

Summary

The authors concluded, that simvastatin treatment could lower cardiovascular morbidity and mortality. Within 5 years of treatment simvastatin allocated patients had a decrease in risk for suffering from myocardial infarction or stroke or the necessity for invasive revascularization by about 25 %. This benefit is independent from initial total cholesterol.

Some of the benefit might not be caused by simvastatin, but caused by one of the other statins like atorvastatin, which was taken by 5.5 % of all participants.

PROSPER-Study. Lancet 2002

(Shepherd et al. 2002)

Study Design

The study was designed to evaluate the benefits of pravastatin treatment in elderly men and women with - or at high risk of developing - cardiovascular events.

5,804 patients (2,804 men, 3,000 women) from Scotland, Ireland and the Netherlands, aged between 70-82 years, were included in the study. They had either vascular disease (coronary, cerebral, peripheral) or raised risk of such disease because of smoking, hypertension or diabetes. After randomization the patients received pravastatin 40 mg/day or placebo for a mean follow-up of 3.2 years.

Primary endpoints were coronary heart disease death or non-fatal myocardial infarction, or fatal or non-fatal stroke. The characteristics of the groups are similar, in both groups more than 50 % were women.

Results

Compared to placebo pravastatin 40 mg/day lowered LDL cholesterol levels by 34 %. In the pravastatin group there were 408 primary endpoint events, in the placebo group 473, relative risk for suffering from a primary endpoint event was 0.85. The relative risk for coronary heart disease death and for non-fatal myocardial infarction was reduced to 0.81.

All cause mortality fell only by 3 %, based on a shift from cardiovascular death to other causes of death. In the pravastatin group there were more new diagnosed cancers than in the placebo group, with a relative risk of 1.25. This might probably be caused by the age structure of the study collective.

The relative risk for transient ischemic attack was 0.75, for coronary events it was 0.77, for necessity of invasive intervention it was 0.82 and for heart failure hospitalisation it was 0.91. There were no differences in risk and outcome of stroke. Coronary risk reduction seemed more pronounced in men. Cognitive function was unaffected. There were no severe adverse events.

Summary

In these elderly individuals pravastatin 40 mg/day was well tolerated. It reduced the risk of coronary disease including the necessity of invasive intervention, but not the risk of stroke. The slightly reduced total mortality might be based on the age of the participants between 73-85 years at the end of the study.

LIPS-Study. JAMA 2002

(Serruys et al. 2002)

Study Design

From 57 international interventional centers in Belgium, France, Germany, Italy, United Kingdom, the Netherlands, Spain, Switzerland, Canada and Brazil 1,677 patients with stable or unstable angina or silent ischemia following successful completion of their first percutaneous coronary intervention and total cholesterol levels between 135-270 mg/dl (3.5-7.0 mmol/L) were recruited. They were randomized to fluvastatin 80 mg/day (2 x 40 mg/day) or placebo, follow-up was done at 77 referral centers.

Median time from percutaneous coronary intervention to initiation of study medication was 2.0 days, median follow-up was 3.9 years in both groups.

The groups were well balanced except for a difference in the incidence of diabetes mellitus (fluvastatin group 14.2 %, placebo group 9.8 %). The primary endpoint included cardiac death, non-fatal myocardial infarction, and a reintervention procedure.

Results

In the fluvastatin group survival time without a major cardiac event was significantly longer than in the placebo group. At least one major cardiac event occurred in 181 out of 844 patients in the fluvastatin group (21.4 %) and 222 out of 833 patients in the placebo group (26.7 %), relative risk was 0.78.

Cardiac death happened in 1.5 % of the fluvastatin patients and in 2.9 % of the placebo patients, relative risk was 0.53, statistically not significant.

Patients in the fluvastatin group with a multivessel disease (relative risk 0.66) or diabetes (relative risk 0.53) had a lower risk to suffer a major cardiac event compared to placebo. The influence on the clinical benefit of fluvastatin was independent of baseline total cholesterol levels: The risk of major cardiac events among patients with baseline cholesterol levels below 200 mg/dl (5.2 mmol/L) was 20.9 % for patients taking fluvastatin and 25.3 % for patients receiving placebo; for patients with baseline cholesterol levels above 200 mg/dl (5.2 mmol/L) the risk of major cardiac events was 20.5 % in the fluvastatin group and 27.5 % in the placebo group.

In the fluvastatin group 2 patients suffered from stroke (0.24 %), in the placebo group 1 patient (0.12 %).

Six weeks after initiation of treatment there was a decrease of 27 % in LDL cholesterol in the fluvastatin group and an increase of 11 % in the placebo group. These effects continued throughout follow-up.

At the end of the study after a median follow-up of 3.9 years compliance in the fluvastatin group was 80.7 %, in the placebo group 24 % of the patients had started an additional lipid lowering medication.

Time-to-event curves diverged about 1 1/2 years after initiation of treatment. There were no severe adverse events.

The study was supported by Novartis.

Summary

The study included patients with average cholesterol levels following successful completion of their first percutaneous coronary intervention. In all endpoints patients with fluvastatin 80 mg/day had better results compared to placebo. The survival time without a major cardiac event was significantly longer in the fluvastatin group.

FLORIDA-Study. Eur Heart J 2002

(Liem et al. 2002)

Study Design

From centers in the Netherlands 540 patients early after acute myocardial infarction and total cholesterol levels below 251 mg/dl (6.5 mmol/L) were randomized to fluvastation 2 x 40 mg/day or placebo. The medication was started no later than 14 days (mean 8 days) after diagnosis of acute myocardial infarction. The follow-up was 1 year.

The main exclusion criteria were use of lipid-lowering agents within the previous 3 months, severe heart failure or arrhythmia or severe organic disease.

The two study groups were similar in their baseline characteristics. Primary endpoints were ischemia on 48-hours ambulatory electrocardiographic monitoring (AECG) at 12 months, or the occurrence of a major clinical event: cardiovascular death, non-cardiovascular death, recurrent acute myocardial infarction or recurrent ischemia necessitating hospitalization or revascularization.

Results

After 12 months of treatment with fluvastatin or placebo LDL cholesterol was lowered by 21 % from 135 mg/dl (3.5 mmol/L) to 104 mg/dl (2.7 mmol/L) with fluvastatin 2 x 40 mg/day, whereas it was increased by 9 % from 139 mg/dl (3.6 mmol/L) to 151 mg/dl (3.9 mmol/L) with placebo. Total cholesterol was lowered by 13 % with fluvastatin and increased by 9 % with placebo.

Major clinical events were evenly distributed in both groups. In the fluvastatin group 62 out of 265 patients (23.4 %) had at least one major clinical event, in the placebo group 68 out of 275 patients (24.7 %), relative risk was 0.95, statistically not significant. Total mortality was 2.6 % in the fluvastatin group and 4.0 % in the placebo group. There were 2 fatal strokes in the fluvastatin group and 1 in the placebo group. The composite endpoint was reached in 32.5 % of the fluvastatin patients and 35.8 % of the placebo patients, relative risk was 0.91, statistically not significant. The presence of ischemia at baseline was predictive for composite endpoints.

The study was supported by AstraZeneca.

Summary

In total there was a positive trend in clinical benefit for the fluvastatin treated patients, but there were no statistically significant differences between the fluvastatin group and the placebo group. This might be caused by the relatively small number of participants, the authors conclude that the study was underpowered.

ASCOT-Study. Lancet 2003

(Sever et al. 2003)

Study Design

The goal of this study was to look for the influence of atorvastatin treatment on cardiovascular morbidity and mortality in patients at risk for cardiovascular diseases and total cholesterol below 251 mg/dl (6.5 mmol/L).

10,305 hypertensive patients were recruited from 686 family practices and 32 regional centers in United Kingdom, Sweden, Norway, Iceland, Denmark, Finland and Ireland and randomized to atorvastatin 10 mg/day or placebo. Inclusion criteria were hypertension in combination with at least three additional risk factors for cardiovascular disease and total cholesterol concentrations of 251 mg/dl (6.5 mmol/L) or lower. The planned average follow-up was 5 years.

The groups were well matched. Exclusion criteria included previous myocardial infarction, currently treated angina, a cerebrovascular event

within the previous 3 months, heart failure or uncontrolled arrhythmias.

Primary endpoint was the combined incidence of non-fatal myocardial infarction and fatal coronary heart disease.

Results

The data safety monitoring board recommended early termination of the trial and the study was stopped prematurely after a median follow-up of 3.3 years. By that time atorvastatin 10 mg/day had resulted in a highly significant reduction in the primary endpoint of coronary heart disease events compared with placebo and a significant reduction in the incidence of stroke.

Within these 3.3. years 100 primary events had occurred in the atorvastatin group (1.9 %) compared to 154 in the placebo group (3.0 %), the difference was statistically significant, relative risk was 0.64. There were also significant reductions in the incidence of total cardiovascular events including revascularization procedures (atorvastatin 389 cases, placebo 486 cases, relative risk 0.79), total coronary events (atorvastatin 178 cases, placebo 247 cases, relative risk 0.71), fatal and non-fatal stroke (atorvastatin 89 cases, placebo 121 cases, relative risk 0.73).

At the end of follow-up in the atorvastatin group there was a 23.34 % decrease of total cholesterol from 212 mg/dl (5.48 mmol/L) by 49 mg/dl (1.27 mmol/L) to 163 mg/dl (4.21 mmol/L), in the placebo group there was a 4.96 % decrease from 212 mg/dl (5.48 mmol/L) by 10 mg/dl (0.27 mmol/L) to 201 mg/dl (5.21 mmol/L). LDL cholesterol was lowered 32.56 % with atorvastatin from 133 mg/dl (3.44 mmol/L) by 43 mg/dl (1.12 mmol/L) to 90 mg/dl (2.32 mmol/L), and 5.23 % with placebo from 133 mg/dl (3.44 mmol/L) by 7 mg/dl (0.18 mmol/L) to 126 mg/dl (3.27 mmol/L).

After 3 years of follow-up 87 % of the patients in the atorvastatin group were still taking the statin, and 9 % of the patients in the placebo group had been prescribed open-label statins.

Time-to-event curves diverged within the 1st year after initiation of treatment, beginning after some weeks.

In the atorvastatin group there was one case of reversible rhabdomyolysis in a male patient who had had a very high alcohol intake and a recent febrile illness.

The study was supported by Pfizer, Servier Research Group and Leo Laboratories.

Summary

With atorvastatin there was a 36 % reduction in the incidence of the primary endpoint - fatal and non-fatal coronary heart disease events - during the average follow-up of 3.3 years. The authors concluded that if the study would have been continued for an average follow-up of 5 years, as it was planned, the reduction might have approached 50 % or more.

In the atorvastatin group there were also significant reductions in the incidence of total cardiovascular events including revascularization procedures (relative risk 0.79), total coronary events (relative risk 0.71) and stroke (relative risk 0.73).

The benefit emerged in the first year of follow-up, beginning after some weeks.

Summarizing Conclusion

There are innumerable publications dealing with the effects of statins. We have consciously limited our analyzes to the published randomized controlled endpoint studies statin-to-placebo looking for the cardiovasculoprotective benefit of the statins tested, with the aim to create a scientifically correct, readable and comprehensible paper.

All studies included are of high quality, considerably fulfilling the CONSORT-statement (Moher et al. 2001). It is important also to take note of the smaller studies, which have a lower chance to reach highly significant differences in results, but show many worthwhile trends and observations. "Highly significant" does not mean, that the medication is highly potent, it only means that possible differences in results are less likely to be by chance. The differences between the trials concerning study design and definitions are so large, that the p-values calculated on this individual basis may lead to misinterpretations, and we decided to leave them out.

None of these clinically relevant studies could have been done without sponsorship by the pharmaceutical industry. In a study about potential effects of commercialization of research 100 randomized controlled trials were investigated and no significant association between funding source, trial outcome and reporting quality was found (Clifford et al. 2002).

Patients experience the highest rate of death and recurrent ischemic events during the early period after an acute coronary event. In most of the studies patients in this period were excluded. Only 2 out of the 11 trials (MIRACL, FLORIDA) were done to determine whether early initiation of atorvastatin or fluvastatin treatment in patients with an acute coronary syndrome could improve prognosis of these high risk patients.

In the FLORIDA trial there was a positive trend in clinical benefit for the fluvastatin treated patients, but there were no statistically significant differences between the fluvastatin group and the placebo group. In the MIRACL trial treatment with atorvastatin 80 mg/day, initiated in the early period after an acute coronary syndrome, significantly reduced recurrent ischemic events compared to placebo. Within the first 16 weeks of treatment atorvastatin led to a decrease in primary endpoint events of 16 %, a decrease in total mortality of 6 % and a decrease of cardiovascular morbidity of 18 % compared to placebo. In the atorvastatin group the relative risk for suffering a non-fatal stroke was 59 %

lower than in the placebo group, the relative risk for suffering a fatal or non-fatal stroke was 50 % lower.

At the American Heart Association Meeting in Orlando in November 2003 Nissen reported the results of the REVERSAL trial which compared the effects of pravastatin vs. atorvastatin on plaque progression-regression in patients with coronary artery disease. 18 months after initiation of treatment atorvastatin allocated patients had no change in the plaques in their arteries, whereas pravastatin allocated patients showed a plaque increase by 2.7 % (Nissen 2003).

The differences between the statins according to the clinical benefit are too large to be due to chance. The potent and fast action of atorvastatin might be based on special characteristics in metabolism. Clearing up of this question is of fundamental interest for all patients at risk for cardiovascular diseases, and will be topic of a future report.

According to the development of new and potent statins, the market shares of different statins have changed during the last decade. The market release of pravastatin and simvastatin led to a dramatic decrease of the prescription rate of lovastatin, and since 1997 - when atorvastatin was released - the prescription rates of prava- and simvastatin decreased, while atorvastatin prescriptions grew constantly (Mamdani and Tu 2001). The safety data reported about atorvastatin confirm that this potent statin 6 years after market release is remarkably safe, making it an excellent therapeutic choice (Newman et al. 2003, Waters 2003).

In conclusion

Statins produced substantial benefit for the patients, reducing the rate of cardiovascular morbidity and mortality. This benefit was independent of the patient´s initial cholesterol or LDL-cholesterol concentrations and could also be demonstrated in patients who had average or low cholesterol levels. Men and women showed a comparable benefit from statin treatment, elderly patients a little more than younger patients.

The statins did not have like effects. There were clear differences in potency as well as in the interval between initiation of treatment and the onset of clinical benefit.

Estimating 5 years of treatment, cardiac morbidity decreased with atorvastatin up to 44 %, with pravastatin up to 36 %, with fluva- or simvastatin up to 32 % and with lovastatin up to 24 %, approximately.

Estimating 5 years of treatment, the long term morbidity of suffering from stroke decreased with atorvastatin up to 41 %, with simvastatin up to 34 % and with pravastatin up to 31 %, approximately. For fluva- and lovastatin there are no comparable data available.

Within the first 16 weeks of treatment following an acute coronary syndrome relative risk for suffering a non-lethal stroke was reduced with atorvastatin 80 mg/day up to 59 % compared to placebo, the relative risk for stroke up to 50 %.

The fastest onset of clinical benefit - reduction of fatal and non-fatal cardiovascular events, hospitalization and necessity of invasive interventions - was demonstrated by treatment with atorvastatin (rapid, within some weeks), followed by lovastatin (after one year), fluva-, prava- and simvastatin (after $1\,1/2$ - 2 years).

These results were achieved with atorvastatin 10 mg/day (80 mg/day used in MIRACL), lovastatin 20 to 40 mg/day (caused by dosage titration), pravastatin 40 mg/day, simvastatin 20 to 80 mg/day (caused by dosage titration) or fluvastatin 80 mg/day.

Atorvastatin was the most powerful compound in the group of statins, improving patients´ health and expectation of life. The advantage of atorvastatin may be due to its ability to reduce cardiovascular disease by stopping the growth of plaques in artery walls.

The authors agree, that patients at risk for cardiovascular diseases should be treated with a statin irrespective of initial cholesterol concentrations, sex or age. If an acute cardiovascular event has happened, statin treatment should be initiated early to improve the prognosis of these patients at high risk, independent from initial LDL cholesterol values.

Summing-up of these 11 trials, the best results and the greatest benefit for the patients were achieved with atorvastatin, which might be considered to be the gold standard for prophylaxis of cardiac ischemia and stroke.

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Table 1. Study design, inclusion and exclusion criteria, severe adverse events.

Study	**Statin** **Study design**	**Number of participants** **Age** **Median follow-up time**	**Initial cholesterol** **Inclusion criteria**	**Major cardiovascular** **exclusion criteria**	**Severe adverse events**
1994					
Scandinavian Simvastatin Survival Study (4S). Lancet 1994 (Scandinavian Simvastatin Survival Study Group 1994)	simvastatin 20 to 40 mg/day placebo double-blind randomized	4,444 35-70 years 5.4 years	5.5-8.0 mmol/L 213-309 mg/dl angina pectoris or previous myocardial infarction	myocardial infarction during the preceding 6 months	**Simvastatin:** reversible rhabdomyolysis 1x
1995					
WOSCOP-Study. N Engl J Med 1995 (Shepherd et al. 1995)	pravastatin 40 mg/day placebo double-blind randomized	6,595 45-64 years 4.9 years	≥ 6.5 mmol/L ≥ 252 mg/dl moderate hypercholesterolemia and no history of myocardial infarction	history of myocardial infarction, serious ECG abnormalities or arrhythmia	None
1996					
CARE-Study. N Engl J Med 1996 (Sacks et al. 1996)	pravastatin 40 mg/day placebo double-blind randomized	4,159 21-75 years 5.0 years	< 6.2 mmol/L < 240 mg/dl LDL 115-174 mg/dl LDL 3.0-4.5 mmol/L acute myocardial infarction between 3 and 20 months before randomisation	acute myocardial infarction during the preceding 3 months	None
1998					
LIPID-Study. N Engl J Med 1998 (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998)	pravastatin 40 mg/day placebo double-blind randomized	9,014 31-75 years 6.1 years	4.0-7.0 mmol/L 155-271 mg/dl history of acute myocardial infarction or unstable angina 3 to 36 months before study entry	severe event within three months before study entry, cardiac failure	None
AFCAPS/TexCAPS-Study. JAMA 1998 (Downs et al. 1998)	lovastatin 20 to 40 mg/day placebo double-blind randomized	6,605 45-73 years 5.2 years	4.65-6.82 mmol/L 180-264 mg/dl LDL 3.36-4.91 mmol/L LDL 130-190 mg/dl no cardiovascular disease	uncontrolled hypertension, insulin-dependent or uncontrolled diabetes mellitus, adipositas permagna	**Lovastatin:** Stevens-Johnson-Syndrome, non-fatal 1 x reversible rhabdomyolysis 1 x **Placebo:** reversible rhabdomyolysis 2 x

2001					
MIRACL Study. JAMA 2001 (Schwartz et al. 2001)	atorvastatin 80 mg/day placebo double-blind randomized	3,086 > 18 years 16 weeks	≤ 7.0 mmol/L ≤ 270 mg/dl Poland and South Africa: ≤ 8.0 mmol/L ≤ 310 mg/dl unstable angina or non-Q-wave acute myocardial infarction	necessity of revascularization, history of Q-wave acute myocardial infarction (preceding 4 weeks), coronary artery bypass surgery (3 month), percutaneous coronary intervention (6 months), severe heart failure or arrhythmia, treatment with other lipid regulating agents	None
2002					
Heart Protection Study. Lancet 2002 (Heart Protection Study Collaborative Group 2002)	simvastatin 40 to 80 mg/day placebo randomized	20,536 40-80 years 5.3 years	≥ 3.5 mmol/L ≥ 135 mg/dl coronary disease, occlusive disease of non-coronary arteries, diabetes mellitus or treated hypertension	angina, myocardial infarction or stroke during the 8-10 weeks lasting run-in-phase; severe heart failure	**simvastatin:** reversible rhabdomyolysis 5 x **placebo:** reversible rhabdomyolysis 3 x. There are no data whether these patients have had a statin outside the protocol
PROSPER-Study. Lancet 2002 (Shepherd et al. 2002)	pravastatin 40 mg/day placebo double-blind randomized	5,804 70-82 years 3.2 years	4.0 bis 9.0 mmol/L 155-348 mg/dl vascular disease or raised risk of such disease because of smoking, hypertension or diabetes	no data	None
LIPS-Study. JAMA 2002 (Serruys et al. 2002)	fluvastatin 80 mg/day placebo double-blind randomized	1,677 18-80 years 3.9 years	3.5-7.0 mmol/L 135-270 mg/dl stable or unstable angina or silent ischemia following successful completion of their first percutaneous coronary intervention	systolic blood pressure > 180 mmHg, diastolic blood pressure > 100 mmHg, LVEF < 30 %, severe valvular disease, cardiomyopathy or congenital heart disease, previous invasive intervention	None
FLORIDA-Study. Eur Heart J 2002 (Liem et al. 2002)	fluvastatin 80 mg/day placebo double-blind randomized	540 > 18 years 1 year	< 6.5 mmol/L < 251 mg/dl early (average 8 days) after acute myocardial infarction	severe heart failure or arrhythmia	None
2003					
ASCOT-Study. Lancet 2003 (Sever et al. 2003)	atorvastatin 10 mg/day placebo double-blind randomized	10.305 40-79 years 3.3 years	< 6.5 mmol/L < 251 mg/dl hypertension in combination with at least three additional risk factors for cardiovascular disease	previous myocardial infarction, currently treated angina, cerebrovascular event within the previous 3 months, hypertriglyceridemia, heart failure or uncontrolled arrhythmias	**Atorvastatin:** reversible rhabdomyolysis 1 x

Table 2. Influence of statin treatment on morbidity and mortality compared to placebo.
Results: We list all results independent from statistical significance, to show the trend, too. For comparison of the results it should be considered, that the definitions are similar, but not identical. The differences between the trials concerning study design and definitions are so large, that the p-values calculated on this individual basis may lead to misinterpretations, and we decided to leave them out.
Relative Risk: during median follow-up compared to placebo.
Median follow-up: median follow-up appropriate to study design. Three studies were stopped prematurely, because the prespecific boundary for a difference in primary endpoint events had been crossed: Scandinavian Simvastatin Survival-Study (simvastatin vs. placebo, after 5.4 years), LIPID-Study (pravastatin vs. placebo, after 6.1 years) and ASCOT-Study (atorvastatin vs. placebo, after 3.3 years).

Study	Statin Dosage Median follow-up time	Primary endpoint Frequency Relative risk Definition	Mortality non coronary	Mortality cardiovas-cular	Relative risk for death from any cause	Relative risk for death from coronary heart dis-ease	Relative risk for death from cardiovas-cular causes	Relative risk for suffering a cardiac event	Relative risk for suffering a cardiovas-cular event	Relative necessity for under-going in-vasive interven-tions like bypass, an-gioplasty
Atorvastatin										
MIRACL Study. JAMA 2001 (Schwartz et al. 2001)	Atorvastatin 80 mg/day Placebo **16 weeks**	Ator 14.8 % Plac 17.4 % **0.84** death, non-fatal acute myocardial infarction, cardiac arrest with resus-citation or recurrent symptomatic myocardial ischemia requiering re-hospitalisation	not reported	Ator 4.3 % Plac 4.5 %	0.94	0.94	0.96	0.84	0.82 Stroke 0.50	1.02
ASCOT-Study. Lancet 2003 (Sever et al. 2003)	Atorvastatin 10 mg/day Placebo **3.3 years**	Ator 1.9 % Plac 3.0 % **0.64** non-fatal myocardial in-farction, fatal coronary heart disease	Ator 2.1 % Plac 2.5 % non cardio-vascular	Ator 1.4 % Plac 1.6 %	0.87	not reported	0.90	0.71	0.79 Stroke 0.73	not reported
Fluvastatin										
LIPS-Study. JAMA 2002 (Serruys et al. 2002)	Fluvastatin 80 mg/day Placebo **3.9 years**	Fluva 21.4 % Plac 26.7 % **0.78** cardiac death, non-fatal myocardial infarction, reintervention procedure	Fluva 2.7 % Plac 3.0 %	Fluva 1.5 % Plac 2.9 % without stroke	0.69	0.53	not reported	0.75	not reported	0.85
FLORIDA-Study. Eur Heart J 2002 (Liem et al. 2002)	Fluvastatin 80 mg/day Placebo **1 year**	Fluva 32.5 % Plac 35.8 % **0.91** ischemia on AECG moni-toring at 12 months, car-diovascular or non-cardiovascular death, recurrent acute myocar-dial infarction or ischemia necessitating hospitaliza-tion or revascularization	Fluva 2.6 % Plac 2.9 %	Fluva 2.3 % Plac 4.0 %	0.66	not reported	0.57	not reported	0.91	0.94

Lovastatin										
AFCAPS/TexCAPS-Study. **JAMA 1998** (Downs et al. 1998)	Lovastatin 20 to 40 mg/day Placebo **5.2 years**	Lova 6.8 % Plac 10.9 % **0.63** first acute major coronary event: fatal or non-fatal myocardial infarction, unstable angina, sudden cardiac death	Lova 1.6 % Plac 1.1 %	Lova 0.5 % Plac 0.8 %	- 0.96	0.73	0.68	0.75	0.75	0.67
Pravastatin										
WOSCOP-Study. **N Engl J Med 1995** (Shepherd et al. 1995)	Pravastatin 40 mg/day Placebo **4.9 years** definite - definite and suspected	Prav 5.5 % Plac 7.9 % **0,69** definite non-fatal myocardial infarction or death from coronary heart disease as a first event	Prav 1.7 % Plac 1.9 %	Prav 1.6 % Plac 2.3 %	0.78	0.67 - 0.72	0.68	0.69 - 0.71	0.74 - 0.75	0.63
CARE-Study. **N Engl J Med 1996** (Sacks et al. 1996)	Pravastatin 40 mg/day Placebo **5.0 years**	Prav 10.2 % Plac 13.2 % **0.76** death from coronary heart disease or a symptomatic non-fatal myocardial infarction	Prav 4.0 % Plac 3.6 %	Prav 5.4 % Plac 6.4 %	0.91	0.80	0.84	0.76	Myocardial infarction 0.76 Stroke 0.69	0.73
LIPID-Study. **N Engl J Med 1998** (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998)	Pravastatin 40 mg/day Placebo **6.1 years**	Prav 6.4 % Plac 8.3 % **0.76** death from coronary heart disease	Prav 3.7 % Plac 4.4 %	Prav 7.3 % Plac 9.6 %	0.78	0.76	0.75	0.71	Myocardial infarction 0.71 Stroke 0.81	0.80
PROSPER-Study. **Lancet 2002** (Shepherd et al. 2002)	Pravastatin 40 mg/day Placebo **3.2 years**	Prav 14.1 % Plac 16.2 % **0.85** coronary heart disease death or non-fatal myocardial infarction, or fatal or non-fatal stroke	Prav 7.1 % Plac 6.3 %	Prav 4.7 % Plac 5.4 %	0.97	0.76	0.85	0.77	0.85	0.82
Simvastatin										
Scandinavian Simvastatin Survival Study (4S). **Lancet 1994.** (Scandinavian Simvastatin Survival Study Group 1994)	Simvastatin 20 to 40 mg/day Placebo **5.4 years**	Simv 8.2 % Plac 11.5 % **0.70** total mortality	Sim 2.1 % Plac 2.2 %	Sim 6.1 % Plac 9.3 %	0.70	0.58	0.65	0.66	0.73 Stroke 0.63	0.63
Heart Protection Study. **Lancet 2002** (Heart Protection Study Collaborative Group 2002)	Simvastatin 40 to 80 mg/day Placebo **5.3 years**	Simv 12.9 % Plac 14.7 % **0.87** total mortality limited to first events	Sim 7.2 % Plac 7.8 %	Sim 7.6 % Plac 9.1 %	0.87	0.83	0.83	0.73	0.76 Stroke 0.75	0.76

Table 3. Study data, subgroups, divergence of the time-to-event curves, compliance.

Study	Statin	Divergence of the time-to-event curves	Difference between men and women	Difference between elderly and younger patients	Changes in non-vascular morbidity and mortality	Taking of study-statin in the statin group	Taking of a statin in the placebo group
Atorvastatin							
MIRACL Study. JAMA 2001 Schwartz et al. 2001	Atorvastatin 80 mg/day Placebo double-blind randomized	after 4 weeks of treatment	no difference	no difference	no difference	88.8 % after 16 weeks	1.7 % after 16 weeks
ASCOT-Study. Lancet 2003 Sever et al. 2003	Atorvastatin 10 mg/day Placebo double-blind randomized	in the first year of follow-up, beginning after some weeks	benefit was somewhat less in women	no difference	no difference	87 % after 3 years	9 % after 3 years
Fluvastatin							
LIPS-Study. JAMA 2002 Serruys et al. 2002	Fluvastatin 80 mg/day Placebo double-blind randomized	about 1½ years after initiation of treatment	no difference	no data	no difference	80.7 % after 3.9 years	24 % (lipid lowering drug) after 3.9 years
FLORIDA-Study. Eur Heart J 2002 Liem et al. 2002	Fluvastatin 80 mg/day Placebo double-blind randomized	no divergence within 1 year of follow-up	no difference	no difference	no difference	88.7 % after 1 year	13.5 % after 1 year
Lovastatin							
AFCAPS/TexCAPS-Study. JAMA 1998 Downs et al. 1998	Lovastatin 20 to 40 mg/day Placebo double-blind randomized	end of first year of treatment	benefit was somewhat more in women	no difference	no data	71 % after 5.2 years	no data (non-compliance 37 % after 5.2 years)
Pravastatin							
WOSCOP-Study. N Engl J Med 1995 Shepherd et al. 1995	Pravastatin 40 mg/day Placebo double-blind randomized	end of first year of treatment	only men included	no difference	no difference	70.4 % after 5 years	no data (non-compliance 30.8 % after 5 years)
Care-Study. N Engl J Med 1996 Sacks et al. 1996	Pravastatin 40 mg/day Placebo double-blind randomized	about two years after initiation of treatment	benefit was somewhat more in women	no difference	no difference	94 % in the 5th year	8 % (lipid lowering drug) in the 5th year
LIPID-Study. N Engl J Med 1998 The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998	Pravastatin 40 mg/day Placebo double-blind randomized	one to two years after initiation of treatment	no difference	no difference	no difference	81 % after 6.1 years	24 % (cholesterol lowering drug) after 6.1 years
PROSPER-Study. Lancet 2002 Shepherd et al. 2002	Pravastatin 40 mg/day Placebo double-blind randomized	about two years after initiation of treatment	benefit was somewhat more in men	only elderly patients included	new cancer diagnosis was 25 % more frequent in the pravastatin-group	94 % after 3.2 years	10 % after 3.2 years

Simvastatin							
Scandinavian Simvastatin Survival Study (4S). Lancet 1994 Scandinavian Simvastatin Survival Study Group 1994	Simvastatin 20 to 40 mg/day Placebo double-blind randomized	after 1 to 2 years	no difference	in patients aged 60 years and more the benefit was somewhat less compared to the younger patients	no difference	90 % after 5.4 years	no data (non-compliance 13 % after 5.4 years)
Heart Protection Study. Lancet 2002 Heart Protection Study Collaborative Group 2002	Simvastatin 40 to 80 mg/day Placebo randomized	after 1st year	no difference	in patients aged 75-80 years the benefit was somewhat more compared to the younger patients	no difference	82 % after 5.3 years	32 % after 5.3 years

Table 4. Study, statin, industrial sponsor, journal.

Study	Statin	Industrial sponsor	Journal
Atorvastatin			
MIRACL Study. JAMA 2001 (Schwartz et al. 2001)	atorvastatin vs. placebo double-blind randomized	Pfizer	JAMA
ASCOT-Study. Lancet 2003 (Sever et al. 2003)	atorvastatin vs. placebo double-blind randomized	Pfizer Servier Research Group Leo Laboratories	Lancet
Fluvastatin			
LIPS-Study. JAMA 2002 (Serruys et al. 2002)	fluvastatin vs. placebo double-blind randomized	Novartis	JAMA
FLORIDA-Study. Eur Heart J 2002 (Liem et al. 2002)	fluvastatin vs. placebo double-blind randomized	Astra Zeneca	Eur Heart J
Lovastatin			
AFCAPS/TexCAPS-Study. JAMA 1998 (Downs et al. 1998)	lovastatin vs. placebo double-blind randomized	Merck	JAMA
Pravastatin			
WOSCOPS-Study. N Engl J Med 1995 (Shepherd et al. 1995)	pravastatin vs. placebo double-blind randomized	Bristol-Myers Squibb	N Engl J Med
Care-Study. N Engl J Med 1996 (Sacks et al. 1996)	pravastatin vs. placebo double-blind randomized	Bristol-Myers Squibb	N Engl J Med
LIPID-Study. N Engl J Med 1998 (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998)	pravastatin vs. placebo double-blind randomized	Bristol-Myers Squibb	N Engl J Med
PROSPER-Study. Lancet 2002 (Shepherd et al. 2002)	pravastatin vs. placebo double-blind randomized	Bristol-Myers Squibb	Lancet
Simvastatin			
Scandinavian Simvastatin Survival Study (4S). Lancet 1994 (Scandinavian Simvastatin Survival Study Group 1994)	simvastatin vs. placebo double-blind randomized	Merck	Lancet
HPS Heart Protection Study. Lancet 2002 (Heart Protection Study Collaborative Group 2002)	simvastatin vs. placebo randomized	Merck Roche	Lancet