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Statins for acute coronary syndrome (Review)

Vale N, Nordmann AJ, Schwartz GG, de Lemos J, Colivicchi F, den Hartog F, Ostadal P, Macin SM, Liem AH, Mills EJ, Bhatnagar N, Bucher HC, Briel M

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[Intervention Review]

Statins for acute coronary syndrome

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ABSTRACT

Background

The early period following the onset of acute coronary syndrome (ACS) represents a critical stage of coronary heart disease, with a high risk of recurrent events and deaths. The short-term effects of early treatment with statins on patient-relevant outcomes in patients suffering from ACS are unclear. This is an update of a review previously published in 2011.

Objectives

To assess the effects, both harms and benefits, of early administered statins in patients with ACS, in terms of mortality and cardiovascular events.

Search methods

We updated the searches of CENTRAL (2013, Issue 3), MEDLINE (Ovid) (1946 to April Week 1 2013), EMBASE (Ovid) (1947 to 2013 Week 14), and CINAHL (EBSCO) (1938 to 2013) on 12 April 2013. We applied no language restrictions. We supplemented the search by contacting experts in the field, by reviewing the reference lists of reviews and editorials on the topic, and by searching trial registries.

Selection criteria

Randomized controlled trials (RCTs) comparing statins with placebo or usual care, with initiation of statin therapy within 14 days following the onset of ACS, follow-up of at least 30 days, and reporting at least one clinical outcome.

Data collection and analysis

Two authors independently assessed risk of bias and extracted data. We calculated risk ratios (RRs) for all outcomes in the treatment and control groups and pooled data using random-effects models.

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Main results

Eighteen studies (14,303 patients) compared early statin treatment versus placebo or no treatment in patients with ACS. The new search did not identify any new studies for inclusion. There were some concerns about risk of bias and imprecision of summary estimates. Based on moderate quality evidence, early statin therapy did not decrease the combined primary outcome of death, non-fatal myocardial infarction, and stroke at one month (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.80 to 1.08) or four months (RR 0.93, 95% CI 0.81 to 1.06) of follow-up when compared to placebo or no treatment. There were no statistically significant risk reductions from statins for total death, total myocardial infarction, total stroke, cardiovascular death, revascularization procedures, and acute heart failure at one month or at four months, although there were favorable trends related to statin use for each of these endpoints. Moderate quality evidence suggests that the incidence of unstable angina was significantly reduced at four months following ACS (RR 0.76, 95% CI 0.59 to 0.96). There were nine individuals with myopathy (elevated creatinine kinase levels more than 10 times the upper limit of normal) in statin-treated patients (0.13%) versus one (0.015%) in the control groups. Serious muscle toxicity was mostly limited to patients treated with simvastatin 80 mg.

Authors' conclusions

Based on moderate quality evidence, due to concerns about risk of bias and imprecision, initiation of statin therapy within 14 days following ACS does not reduce death, myocardial infarction, or stroke up to four months, but reduces the occurrence of unstable angina at four months following ACS. Serious side effects were rare.

PLAIN LANGUAGE SUMMARY

Statins for acute coronary syndrome

Long-term therapy with statins (for at least one year) has been shown to reduce the risk of heart attack, stroke, and all-cause mortality in patients with and without established coronary heart disease. The early period following an acute coronary syndrome is a critical stage of coronary heart disease, with a high risk of recurrent events and death. We aimed to determine if early initiation of statins improves patient-relevant outcomes within the first four months following an acute coronary syndrome. This review is an update of a review previously published in 2011 that included 18 studies, enrolling 14,303 patients. The update of this review did not identify any new studies for inclusion. We did not find a significant risk reduction for all-cause mortality, heart attack, or stroke within the first four months. We had some concerns about risk of bias and imprecision of the results. The risk of unstable angina was reduced by about 25% at four months following acute coronary syndrome. Serious side effects from early treatment with statins were rare (0.1%), and serious muscle toxicity was mostly observed with simvastatin 80 mg.

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Summary of findings for the main comparison. Statins compared to control at 4 months (3 to 6 months) for acute coronary syndrome

Statins compared to control at 4 months (3 to 6 months) for acute coronary syndrome

Patient or population: patients with acute coronary syndrome
Settings: inpatients, developed countries
Intervention: statins
Comparison: control at 4 months (3 to 6 months)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control at 4 months (3 to 6 months)	Statins				
Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths Follow-up: 3 to 6 months	**80 per 1000** [1]	**75 per 1000** (65 to 85)	**RR 0.93** (0.81 to 1.06)	9625 (11 studies)	⊕⊕⊕⊖ **moderate** [2,3]	
Death from all causes Follow-up: 3 to 6 months	**28 per 1000** [1]	**25 per 1000** (20 to 32)	**RR 0.9** (0.7 to 1.14)	9733 (12 studies)	⊕⊕⊕⊖ **moderate** [2,3]	
Fatal and non-fatal myocardial infarction or reinfarction Follow-up: 3 to 6 months	**65 per 1000** [1]	**59 per 1000** (50 to 69)	**RR 0.91** (0.77 to 1.06)	9537 (10 studies)	⊕⊕⊕⊖ **moderate** [2,3]	
Fatal and non-fatal stroke Follow-up: 3 to 6 months	**10 per 1000** [1]	**7 per 1000** (4 to 11)	**RR 0.72** (0.45 to 1.16)	8536 (7 studies)	⊕⊕⊕⊖ **moderate** [2,3]	
Unstable angina Follow-up: 3 to 6 months	**63 per 1000** [1]	**48 per 1000** (37 to 60)	**RR 0.76** (0.59 to 0.96)	8770 (9 studies)	⊕⊕⊕⊖ **moderate** [2,4]	
Acute heart failure Follow-up: mean 4 months	**26 per 1000** [1]	**22 per 1000** (17 to 30)	**RR 0.86** (0.65 to 1.15)	7583 (2 studies)	⊕⊕⊕⊖ **moderate** [3]	
Rhabdomyolysis Follow-up: mean 4 months	**0 per 1000** [1]	**0 per 1000** (0 to 0)	**RR 6.9** (0.36 to 133.47)	4497 (1 study)	⊕⊕⊖⊖ **low** [5]	

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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]The basis of the assumed risk is the average risk of control group patients.
[2]The largest studies had allocation concealment and used blinding for patients, caregivers, and outcome assessors; however for many studies allocation concealment remained unclear and almost half were open-label. Sensitivity analyses with high quality studies did not change the point estimate.
[3]The CI includes effects suggesting benefit as well as no benefit, therefore we decided to downgrade by one level when considering this imprecision together with some concerns about risk of bias.
[4]There is moderate heterogeneity among studies included in the analysis of unstable angina at four months (I^2 = 33%). The subgroup analysis for trials with blinded outcome assessment (because of possible subjective component for diagnosis of unstable angina) was still statistically significant, but the estimated risk reduction was smaller. Overall we decided to downgrade by one level when considering the heterogeneity and remaining concerns about the risk of bias.
[5]The CI includes the possibility of both harms or benefits and there are only three events of rhabdomyolysis in total; therefore we decided to downgrade by two levels for imprecision.

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BACKGROUND

Coronary heart disease accounts for 20% of overall mortality in the United States (AHA 2007). Large trials and meta-analyses have shown that HMG CoA reductase inhibitors (statins) effectively reduce low-density lipoprotein (LDL) cholesterol and clinical endpoints such as cardiovascular events and overall mortality in a large spectrum of patients at varying risk of cardiovascular disease (4S 1994; HPS 2002; Shepherd 1995; Studer 2005). A limitation of most of the trials in secondary prophylaxis after acute myocardial infarction or unstable angina is, however, that statins have been started three or more months after an acute event. Acute coronary syndrome (ACS) is defined as a broad spectrum of manifestations that are due to insufficient coronary blood supply. These include ST-segment elevation myocardial infarction, non-ST-segment elevation ACS with or without myocardial cell necrosis (unstable angina and/or non-ST-segment elevation myocardial infarction), and ST-segment depression (non-Q-wave) myocardial infarction. The early period following an ACS represents a critical stage of coronary heart disease with a high risk of recurrent events and death due to vessel occlusions from vulnerable coronary plaques (Wood 1998). Therefore, strategies to stabilize vulnerable coronary plaques during this high-risk period are paramount.

Experimental data indicate that statins may have early beneficial effects by improving the endothelial function of arteries (RECIFE 1999), decreasing platelet aggregability and thrombus formation (Rosenson 1998), and reducing vascular inflammation (Ridker 1998). Each of these mechanisms plays an important role in ACS and they are targets for existing or new drugs in the management of the ACS (Kumar 2009). Statins may exert these additional effects beyond their cholesterol-lowering effect, which makes them amenable to supplementary therapy of ACS (Sposito 2002).

There is controversial evidence from observational studies that statin therapy prior to or at hospital discharge is associated with reducing short-term mortality among patients after an ACS (Aronow 2001; Fonarow 2005; Newby 2002; Spencer 2004; Stenestrand 2001). Evidence from randomized controlled trials (RCTs) focusing on patients with an ACS indicates that statins may reduce combined endpoints that include recurrent angina, re-angioplasty, and re-hospitalization (Cannon 2004b; L-CAD 2000; MIRACL 2001; Serruys 2002). These endpoints, however, may be less reliable because they depend to a greater extent on clinical judgement and local practices. Therefore information on 'harder' clinical endpoints, such as definite myocardial infarction, stroke, and coronary heart disease-specific mortality, is important.

Why it is important to do this review

This is an update of a Cochrane review previously published in 2011. Morrissey et al have questioned the Level of Evidence: 1A recommendation of the current American College of Cardiology/ American Heart Association (ACC/AHA) guidelines that statin therapy should be initiated in patients before hospital discharge after an episode of ACS regardless of the baseline LDL level because of a mismatch with the underlying evidence (Morrissey 2009). Two previous meta-analyses on the topic suggested that early treatment with statins does not reduce death, myocardial infarction, or stroke up to four months following an ACS (Briel 2006a; Hulten 2006). Hulten et al used slightly different eligibility criteria (e.g. they allowed for head to head comparisons of statins to be included), did not contact investigators of primary trials for unpublished data, and pooled hazard ratios instead of risk ratios (Hulten 2006). They concluded that early statin therapy reduces the combined endpoint of death, recurrent ischemia, and recurrent myocardial infarction at six months of treatment and thereafter.

The purpose of the present study is to comprehensively update previous systematic reviews and meta-analyses of RCTs evaluating the effects of early use of statins on relevant clinical endpoints of cardiovascular morbidity and overall mortality during the early stages at one and four months following the onset of ACS (Briel 2006a; Vale 2011).

OBJECTIVES

To assess the effects, both harms and benefits, of early administered statins in patients with ACS, in terms of mortality and cardiovascular events.

METHODS

Criteria for considering studies for this review

Types of studies

We include randomized controlled trials (RCTs) comparing statin to placebo or no treatment in patients with an ACS (myocardial infarction or unstable angina). We excluded trials comparing two different statins without a placebo or no treatment control. We only considered trials with at least 30 days of follow-up of participants after an ACS, reporting at least one clinical outcome.

Types of participants

Adults with recent ACS, regardless of prior lipid levels and prior lipid-modifying treatment or diet. ACS is defined as a broad spectrum of manifestations that are due to insufficient coronary blood supply. These include ST-segment elevation myocardial infarction, non-ST-segment elevation ACS with or without myocardial cell necrosis (unstable angina and/or non-ST-segment elevation myocardial infarction), and ST-segment depression (non-Q-wave) myocardial infarction. We included patients regardless of previous ACS, percutaneous coronary interventions including stents, or co-morbidities such as atrial fibrillation with or without antithrombotic treatment.

Types of interventions

Initiation of statin therapy (HMG-CoA reductase inhibitors such as pravastatin, simvastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin) administered orally at any dosage within 14 days following the onset of an acute coronary syndrome. We only considered trials using cerivastatin for sensitivity analysis since this compound was withdrawn from the market in 2001 (Staffa 2002).

Types of outcome measures

We assessed the following clinical outcomes at one month, four months (range three to six months), and 12 months of follow-up.

Primary outcome

- Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and death from all causes

Secondary outcomes

- Death from all causes

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- Death from cardiovascular causes
- Fatal and non-fatal myocardial infarction or reinfarction
- Fatal and non-fatal stroke
- Revascularization procedures (bypass grafts, angioplasty with or without stenting)
- Unstable angina (recurrent myocardial ischemia requiring emergency hospitalization)
- Acute (new or worsening) heart failure
- Adverse events (rhabdomyolysis, creatinine kinase levels more than 10 times the upper limit of normal values, and liver aminotransferase levels more than three times the upper limit of normal values)
- Patient-perceived quality of life

We considered outcomes and adverse events irrespective of their putative relation to the treatment. To maximize the statistical power of our primary analysis and to recognize the event hierarchy of fatal and non-fatal events (occurrence of death precludes any other clinical events), we chose a combined primary endpoint to test the most patient-relevant 'hard' outcomes: death, myocardial infarction, and stroke. Each of the components is highly patient-relevant and about equally frequent (Montori 2005).

Search methods for identification of studies

To identify relevant trials we updated the searches from February 2010 by re-running the searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 3), MEDLINE (Ovid, 1946 to April Week 1 2013), EMBASE Classic and EMBASE (Ovid, 1947 to 2013 Week 14), and CINAHL (EBSCO, 1938 to 12 April 2013) on 12 April 2013.

We did not impose any language restrictions. In addition, we searched previous systematic reviews (Briel 2006a; Hulten 2006), reference lists of identified articles, recently published editorials and narrative reviews on the topic, and trial registries (ISRCTN trials registry: isrctn.org/; US National Institute of Health Clinical Trials Registry: www.clinicaltrials.gov/) for further eligible trials. We contacted specialists in the field for any unpublished studies.

The detailed electronic search strategies developed by NB and MB for MEDLINE, EMBASE, CENTRAL, and CINAHL, which include filters for finding RCTs (modified from Dickersin 1994), are listed in Appendix 1. We updated the electronic searches with the help of the Cochrane Heart Group (Appendix 2). We have added some search terms and updated the RCT filter for MEDLINE and EMBASE (Lefebvre 2011).

Data collection and analysis

Selection of studies

Two authors (NV and AJN) independently assessed trial eligibility using a predefined form. We resolved disagreement by discussion and consensus. We excluded double reports. We applied no language restrictions.

Assessment of risk of bias in included studies

Two authors (NV and AJN) independently assessed the risk of bias in the selected trials according to the Cochrane 'Risk of bias' tool (six domains).

We ranked the risk of selection bias with respect to allocation concealment as:

- low risk (i.e. central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description regarding the methods used that warrants a judgement of adequate allocation concealment)
- unclear risk (i.e. unreported)
- high risk (for instance, alternation or reference to case record numbers or to dates of birth)

We resolved disagreements by discussion and consensus. We used our 'Risk of bias' assessment of included trials to explore heterogeneity among trials and to perform subgroup analysis.

Data extraction and management

Two authors (NV and AJN) independently extracted trial data in duplicate using predefined forms. We extracted data on patients' characteristics (age, gender, diabetes, hypertension, current smoker, prior myocardial infarction, lipid values at baseline, myocardial infarction as the index event, concomitant treatment for the index event (fibrinolysis, percutaneous coronary intervention), statin regimen (type of statin, daily dosage, starting time, duration), control group therapy (placebo or conventional treatment), follow-up duration, and measured outcomes for both study groups (proportion of patients with the outcome) at one, four, and 12 months following the onset of the ACS. We resolved any disagreement between authors by discussion and consensus.

Data synthesis

We calculated risk ratios with 95% confidence intervals for all outcomes in the treatment and control groups and pooled them by conducting a random-effects model meta-analysis (DerSimonian 1986). We also calculated Peto odds ratios (fixed-effect model), which are suggested for rare events (Deeks 1998). We investigated the presence of publication bias by means of funnel plots (Sterne 2001). We tested for heterogeneity with the Cochran Q test and measured inconsistency (I^2 statistic: the percentage of total variance across studies that is due to heterogeneity rather than chance) of treatment effects across the primary and secondary outcomes (Higgins 2002; Higgins 2003). We did not include studies without events in either group in the analyses.

Sensitivity analysis

We examined treatment effects according to 'Risk of bias' components (concealed treatment allocation, blinding of patients and caregivers, blinded outcome assessment) for the combined primary outcome death, myocardial infarction, and stroke, for death from all causes, and for unstable angina. We also assessed the effect of time to initiation of statins on the combined primary outcome, and the type of statin on the combined primary outcome. We also conducted a sensitivity analysis by including unpublished data from a trial using cerivastatin on death from all causes, total myocardial infarction, total stroke, and unstable angina (PRINCESS 2004).

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RESULTS

Description of studies

The combined search of CENTRAL, MEDLINE, EMBASE, and CINAHL identified 2324 potentially relevant articles, of which we excluded all but 63 because it was clear from the abstract that they were not eligible (Figure 1). Full-text assessment of the 63 potentially relevant articles resulted in the further exclusion of 39 studies (39 articles) because they were not randomized trials, had a follow-up of less than one month, treatment was given for less than one month, they were head-to-head comparisons of statins, statin therapy was initiated beyond 14 days following the onset of ACS, or no or unclear clinical outcome data were reported. In an update of the electronic search on 12 April 2013 we identified another 2268 potentially relevant articles (Appendix 2). After title and abstract screening we checked 24 full texts but found no new eligible studies for inclusion.

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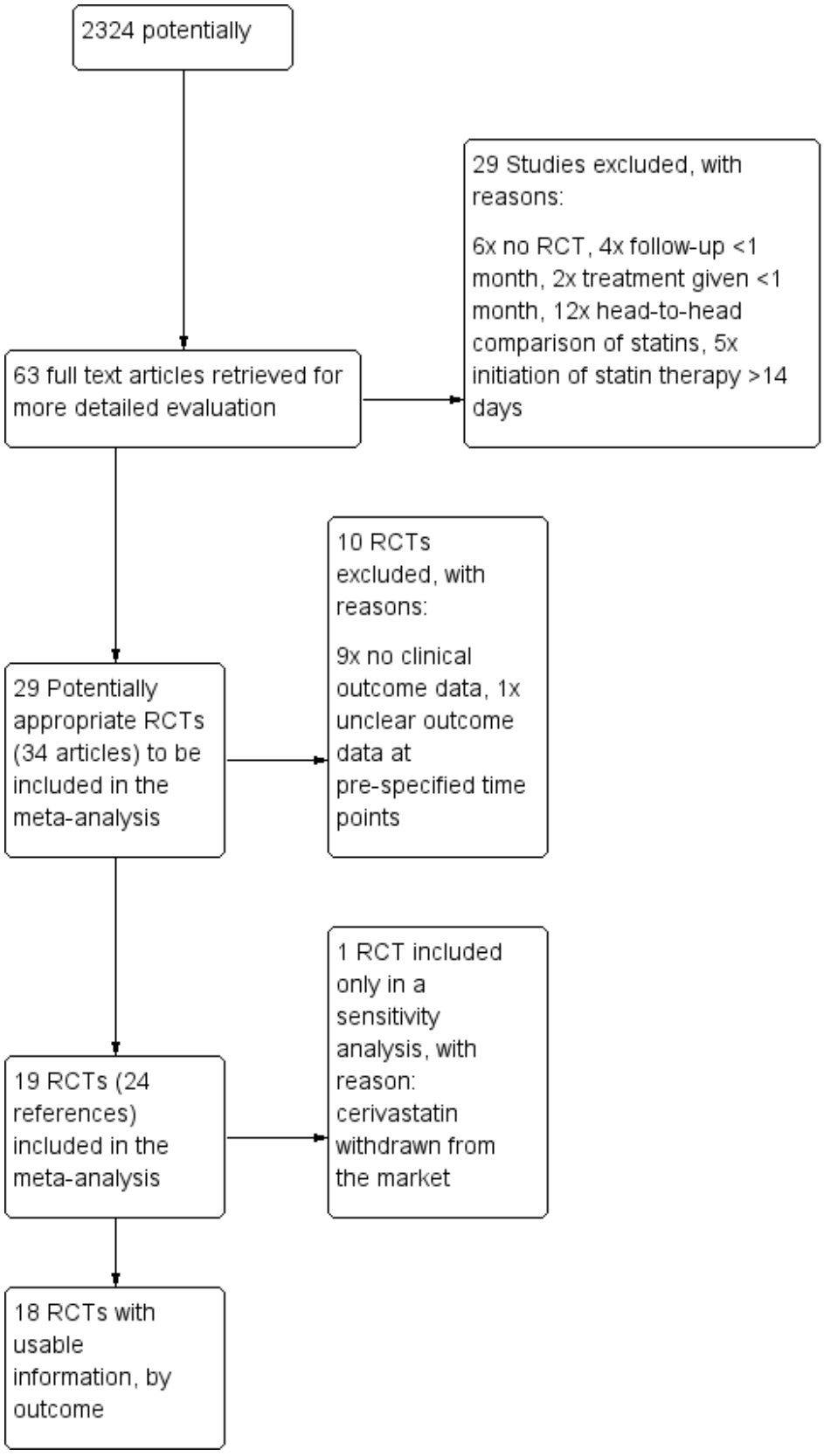
Figure 1. Study flow chart.



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For information on the excluded studies please see Characteristics of excluded studies.

Included in the meta-analysis were 19 RCTs (24 references). One trial using cerivastatin was prematurely stopped because the drug was withdrawn from the market (PRINCESS 2004). We excluded data from the 4.5-month follow-up of this trial from the primary analysis, but included the data in a sensitivity analysis. The remaining 18 RCTs enrolled a total of 14,303 patients (7172 treatment, 7131 control). We found no evidence of ongoing eligible trials. Authors of included primary trials contributed additional data relevant for the purpose of this analysis. We were unable to contact the investigators from three trials (LAMIL 1997; Sakamoto 2005; Shal'nev 2007).

Seventeen of the 19 included trials investigated four different statins: pravastatin (seven trials; LAMIL 1997; L-CAD 2000; OACIS-LIPID 2008; PACT 2004; PAIS 2001; PTT 2002; RECIFE 1999), atorvastatin (four trials; Colivicchi 2002; ESTABLISH 2004; Macin 2005; MIRACL 2001), fluvastatin (three trials; FACS 2010; FLORIDA 2002; LIPS 2002), and simvastatin (three trials; de Lemos 2004; Ren 2009; Shal'nev 2007) (Table 1). One trial allowed any statin to be used in the intervention group (Sakamoto 2005).

In accordance with our eligibility criteria, we only included the subgroup of patients with unstable angina from the Lescol Intervention Prevention Study (LIPS 2002). In the A-to-Z trial we only used data from the placebo comparison during the first four months of follow-up (de Lemos 2004).

Of the 19 included trials, four were international, multicenter trials (de Lemos 2004; LIPS 2002; MIRACL 2001; PRINCESS 2004), three were conducted in Japan (ESTABLISH 2004; OACIS-LIPID 2008; Sakamoto 2005), two in the Netherlands (FLORIDA 2002; PAIS 2001), and one each were conducted in Germany (L-CAD 2000), Belgium (LAMIL 1997), Argentina (Macin 2005), Australia (PACT 2004), Turkey (PTT 2002), Canada (RECIFE 1999), China (Ren 2009), the Czech Republic and Slovakia (FACS 2010), and Russia (Shal'nev 2007). The earliest included trial started recruitment in April 1996 (LIPS 2002), with the latest concluding in July 2006 (Ren 2009). However, six trials did not specify the recruitment dates (L-CAD 2000; LAMIL 1997; PACT 2004; PRINCESS 2004; RECIFE 1999; Shal'nev 2007). Eleven trials were reported to be industry-sponsored (de Lemos 2004; FLORIDA 2002; L-CAD 2000; LAMIL 1997; LIPS 2002; MIRACL 2001; PACT 2004; PAIS 2001; PRINCESS 2004; RECIFE 1999; FACS 2010). See Characteristics of included studies.

Study population

The reported mean age of participants in the trials ranged from 53 to 69 years (Table 2). All trials enrolled mostly men (range among trials, 59% to 88%). There was considerable variation in the proportion of cardiovascular risk factors and participants with a myocardial infarction prior to the index event (range, 0% to 85%). Due to different trial protocols the proportion of participants with co-interventions for the index event such as fibrinolytic therapy or percutaneous coronary interventions (PCI) varied widely among trials (range, 0% to 100%).

Lipid-lowering effects

The average weighted mean baseline LDL cholesterol level of included participants was 120 mg/dL (3.1 mmol/L) (range, 78 to 178 mg/dL (2.0 to 4.6 mmol/L)) (Table 3). Mean reduction of LDL cholesterol ranged from -15% to -53% and of total cholesterol from -9% to -37%, with higher reductions in trials using higher drug doses and/or more potent drugs. The effects on HDL cholesterol and triglycerides were less pronounced and inconsistent among trials (range of average change for HDL cholesterol, -9.5% to +13%; and for triglycerides, -28% to +10%).

Risk of bias in included studies

Risk of bias varied among studies (see 'Risk of bias' summary, Figure 2). Concealed allocation of participants was reported only for three trials (de Lemos 2004; LIPS 2002; MIRACL 2001). Eight trials were reported to have assessed clinical outcomes in a blinded fashion (Colivicchi 2002; de Lemos 2004; FLORIDA 2002; LIPS 2002; MIRACL 2001; OACIS-LIPID 2008; Sakamoto 2005; Ren 2009), and 11 trials reported blinding of caregivers and patients (de Lemos 2004; FACS 2010; FLORIDA 2002; LAMIL 1997; LIPS 2002; Macin 2005; MIRACL 2001; PACT 2004; PAIS 2001; RECIFE 1999; Ren 2009). Loss to follow-up was under 2% in all but three studies (RECIFE 1999: 8%, Sakamoto 2005: 16%, LAMIL 1997: 19%). One trial was stopped early for benefit (Colivicchi 2002), with potential overestimation of treatment effects (Bassler 2010).

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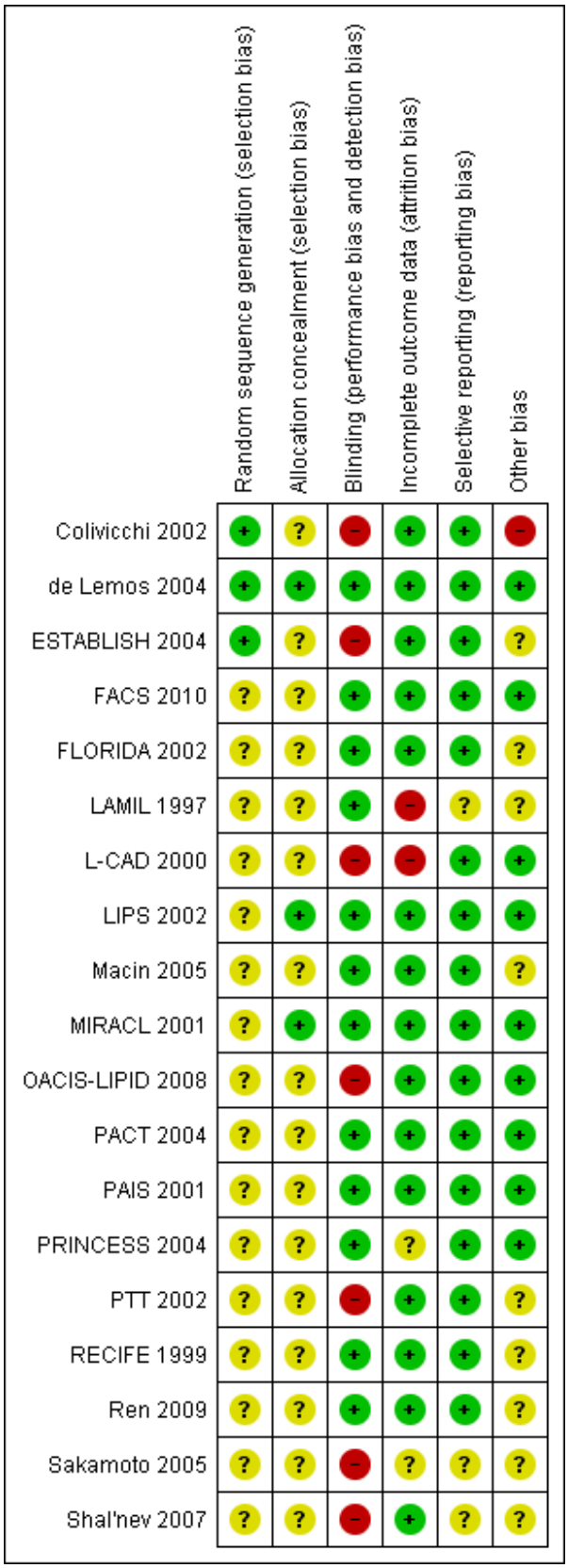
Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Effects of interventions

See: **Summary of findings for the main comparison** Statins compared to control at 4 months (3 to 6 months) for acute coronary syndrome

Statins versus placebo or no treatment

Analyses for publication bias indicated no evidence for such bias (Figure 3; Figure 4; Figure 5). Since there were only minimal differences in the estimates when calculating risk ratios or Peto odds ratios (fixed-effect model), we reported outcomes as risk ratios (RR) only.

Figure 3. Funnel plot of comparison: 1 Statins versus control at 1 month, outcome: 1.1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.

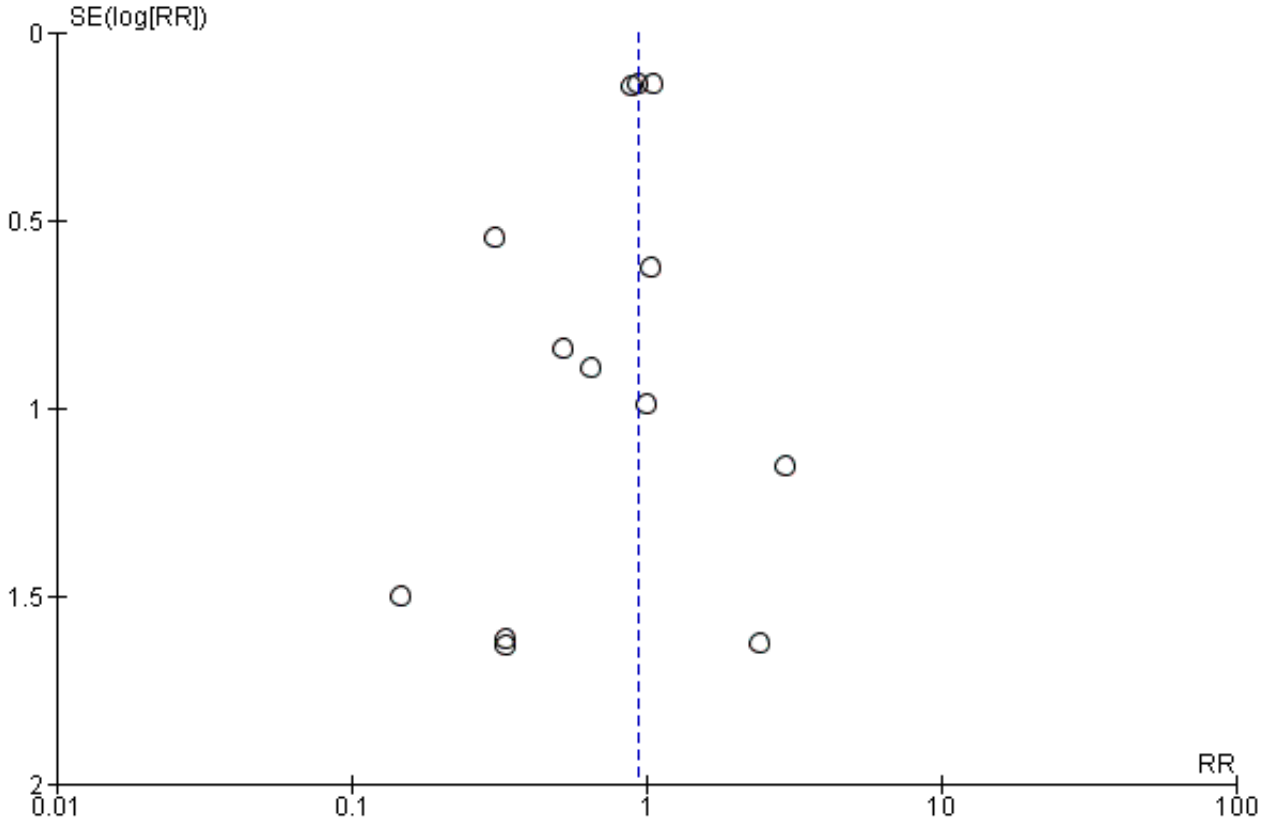

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Figure 4. Funnel plot of comparison: 2 Statins versus control at 4 months (3 to 6 months), outcome: 2.1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.

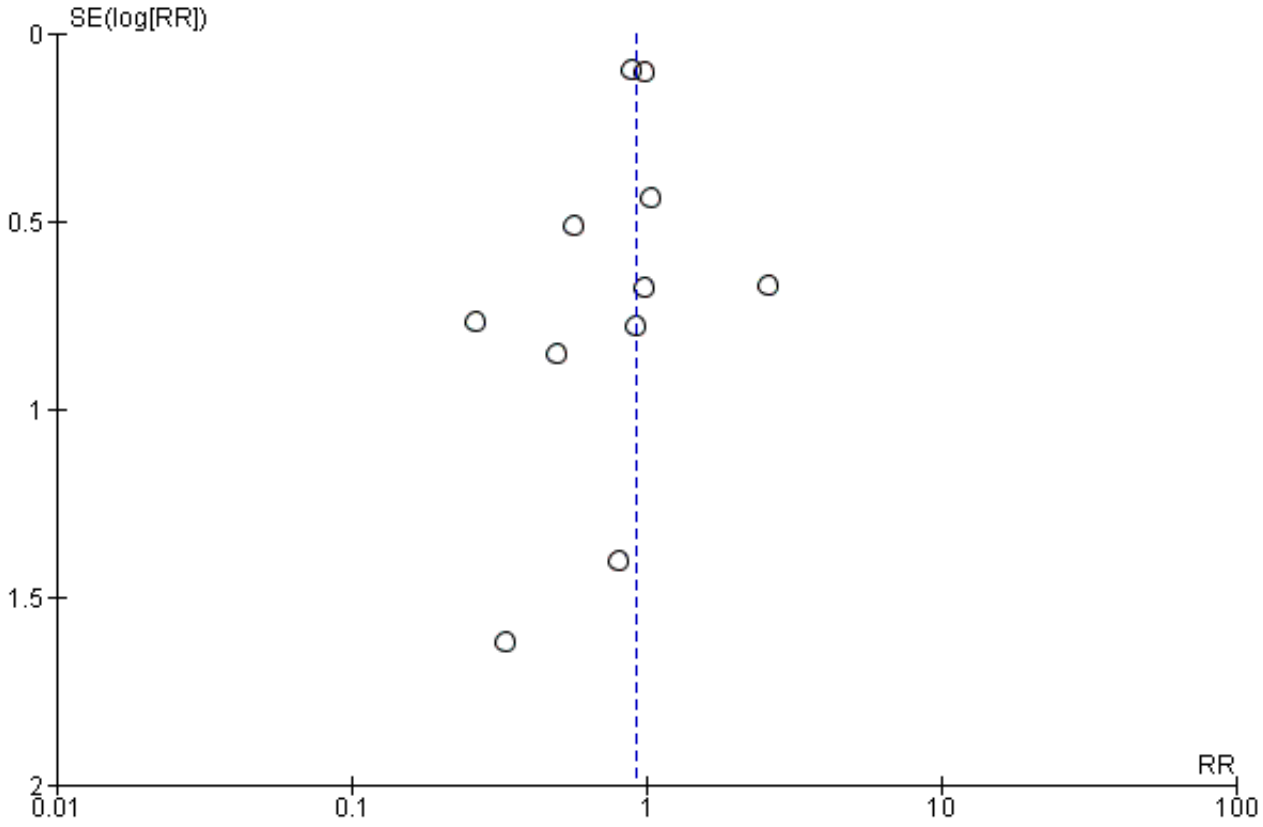

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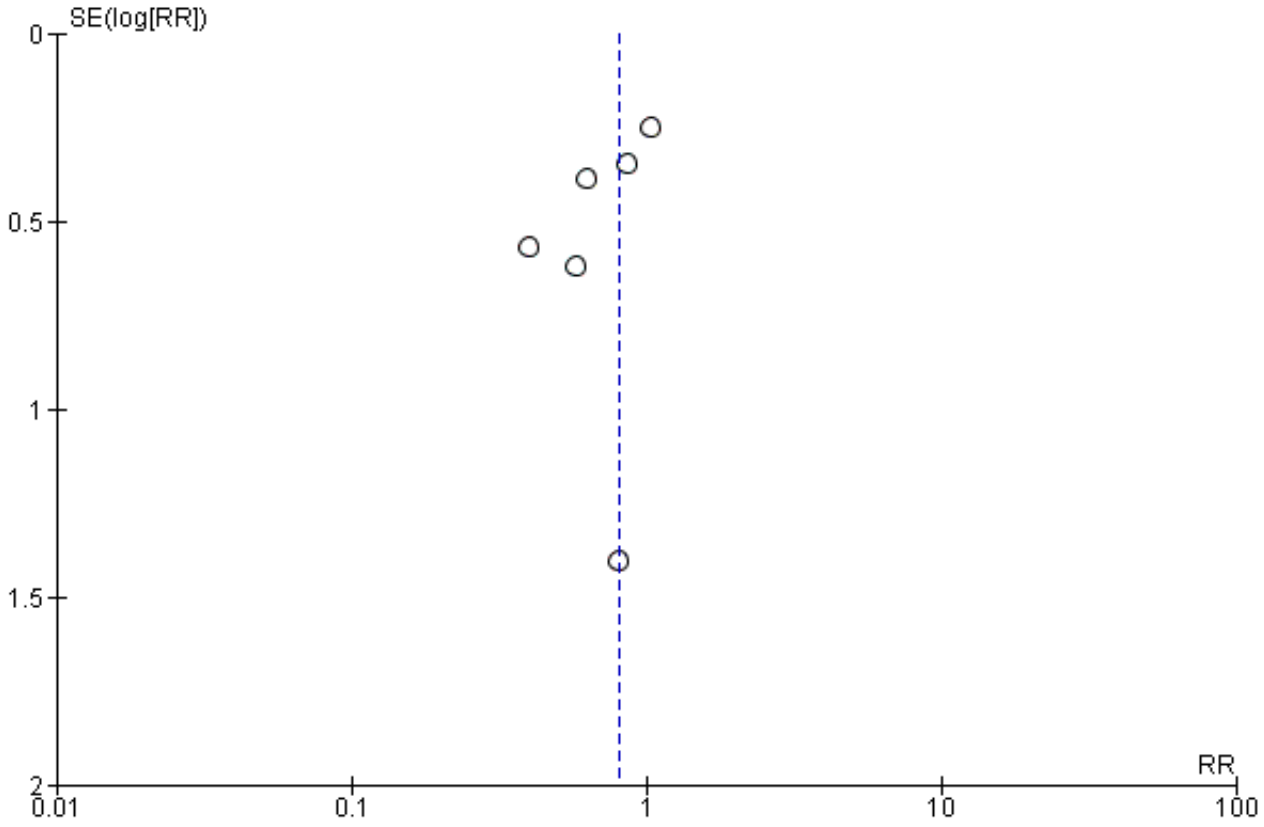
Figure 5. Funnel plot of comparison: 3 Statins versus control at 12 months, outcome: 3.1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.



Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and death from all causes

There was no significant difference in the primary combined outcome with early statin treatment in comparison to placebo or no treatment at one month (RR 0.93, 95% confidence interval (CI) 0.80 to 1.08; 13 studies, 13,484 patients) (Analysis 1.1), four months (RR 0.93, 95% CI 0.81 to 1.06; 11 studies, 9625 participants) (Analysis 2.1), or 12 months (RR 0.80, 95% CI 0.58 to 1.11; six studies, 2080 participants) (Analysis 3.1). We found no evidence of relevant heterogeneity among trials at any follow-up time points (I^2 = 0%).

In sensitivity analyses, summary estimates of the primary endpoint at four months suggested smaller risk reductions for trials with higher methodological quality compared to trials that lacked a respective quality component. In trials with concealed allocation the summary RR for statins compared to control was 0.96 (95% CI 0.79 to 1.16; three studies, 8407 participants) (Analysis 5.1). For trials without concealed allocation the RR was 0.70 (95% CI 0.44 to 1.14; eight studies, 1218 participants) (Analysis 5.1). For trials with blinded outcome assessment the summary RR was 0.94 (95% CI 0.82 to 1.08; five studies, 9028 participants) (Analysis 5.3). For trials without blinded outcome assessment the RR was 0.60 (95% CI 0.30 to 1.22; six studies, 597 participants) (Analysis 5.3). For trials with blinding of patients and caregivers the summary RR was 0.95 (95% CI 0.82 to 1.09; seven studies, 9271 participants; Analysis 5.2). For trials without blinding of patients and caregivers the RR was 0.46 (95% CI 0.21 to 1.00; four studies, 354 participants) (Analysis 5.2).

We did not find different treatment effects for trials with initiation of statin therapy within three days versus up to 14 days (Analysis 5.14), or for trials using different types of statins (Analysis 5.15). Overall, we found moderate quality evidence that early statins provide no relevant risk reduction for the combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total deaths within the first four months following acute coronary syndrome (ACS) (see Summary of findings for the main comparison).

Death from all causes

We found no statistically significant difference in death from all causes with early statin therapy compared to placebo or usual care at one month (RR 0.78, 95% CI 0.59 to 1.03; 13 studies, 13,155 patients) (Analysis 1.2), four months (RR 0.90, 95% CI 0.70 to 1.14; 12 studies, 9733 participants) (Analysis 2.2), or 12 months (RR 0.68, 95% CI 0.39 to 1.20; six studies, 2080 participants) (Analysis 3.2). We found no evidence of relevant heterogeneity among trials at any follow-up time points (I^2 = 0%).

In sensitivity analyses, summary estimates of the primary endpoint at four months suggested smaller risk reductions for trials with higher methodological quality compared to trials that lacked a respective quality component. For trials with concealed allocation the RR for statins compared to control was 0.94 (95% CI 0.72 to 1.21; three studies, 8407 participants) (Analysis 5.4). For trials without concealed allocation the RR was 0.64 (95% CI 0.31 to 1.31; nine studies, 1326 participants) (Analysis 5.4). For trials with blinded outcome assessment the summary RR was 0.91 (95% CI 0.71 to

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1.17; five studies, 9028 participants) (Analysis 5.6). For trials without blinded outcome assessment the RR was 0.77 (95% CI 0.31 to 1.90; seven studies, 705 participants) (Analysis 5.6). For trials with blinding of patients and caregivers the summary RR was 0.93 (95% CI 0.72 to 1.19; seven studies, 9271 participants) (Analysis 5.5). For trials without blinding of patients and caregivers the RR was 0.55 (95% CI 0.21 to 1.44; five studies, 462 participants) (Analysis 5.5). When we additionally included 4.5-month data from 3605 patients with ACS from the PRINCESS study in a sensitivity analysis (Prevention of Ischemic Events by Early Treatment of Cerivastatin Study, PRINCESS 2004), the summary RR for all-cause mortality was 0.95 (95% CI 0.78 to 1.17) (Analysis 5.10).

Overall, we found moderate quality evidence that early statins provide no relevant risk reduction for the combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total deaths within the first four months following ACS (see Summary of findings for the main comparison).

Death from cardiovascular causes

There was no statistically significant difference in deaths from cardiovascular causes with early statin treatment in comparison to placebo or no treatment at one month (RR 0.80, 95% CI 0.60 to 1.07; 10 studies, 12,387 participants) (Analysis 1.3), four months (RR 0.84, 95% CI 0.64 to 1.09; eight studies, 9273 participants) (Analysis 2.3), or 12 months (RR 0.55, 95% CI 0.28 to 1.09; five studies, 1954 participants) (Analysis 3.3). We found no evidence of relevant heterogeneity among trials at any follow-up time points (I^2 = 0%).

Fatal and non-fatal myocardial infarction or reinfarction

We found no statistically significant difference in fatal and non-fatal myocardial infarctions with early statin treatment in comparison to placebo or usual care at one month (RR 0.98, 95% CI 0.82 to 1.16; 12 studies, 13,074 participants) (Analysis 1.4), four months (RR 0.91, 95% CI 0.77 to 1.06; 10 studies, 9537 participants) (Analysis 2.4), or 12 months (RR 0.94, 95% CI 0.61 to 1.45; five studies, 1954 participants) (Analysis 3.4). We found no evidence of relevant heterogeneity among trials at any follow-up time points (I^2 = 0%).

In a sensitivity analysis we included 4.5-month data from 3605 patients with ACS from the PRINCESS study and found a summary RR for fatal and non-fatal myocardial infarctions of 0.90 (95% CI 0.78 to 1.03) (Analysis 5.11).

Due to some concerns about risk of bias and imprecision of results we rated the quality of the available evidence that early statins provide no relevant risk reduction for fatal and non-fatal myocardial infarction within the first four months following ACS as moderate (see Summary of findings for the main comparison).

Fatal and non-fatal stroke

There was no statistically significant difference in fatal and non-fatal strokes with early statin treatment in comparison to placebo or usual care at one month (RR 0.78, 95% CI 0.47 to 1.29; seven studies, 12,147 participants) (Analysis 1.5), four months (RR 0.72, 95% CI 0.45 to 1.16; seven studies, 8536 participants) (Analysis 2.5), or 12 months (RR 0.38, 95% CI 0.13 to 1.10; four studies, 1130 participants) (Analysis 3.5). We found no evidence of relevant heterogeneity among trials at all follow-up time points (I^2 = 0%).

In a sensitivity analysis we included 4.5-month data from 3605 patients with ACS from the PRINCESS study and found a summary RR for fatal and non-fatal strokes of 0.79 (95% CI 0.52 to 1.18) (Analysis 5.12).

Revascularization procedures

There was no statistically significant difference for revascularization procedures (bypass grafts, angioplasty) with early statin treatment compared to placebo or usual care at one month (RR 1.00, 95% CI 0.86 to 1.16; 10 studies, 9668 participants) (Analysis 1.6), or four months (RR 0.92, 95% CI 0.78 to 1.08; nine studies, 9474 participants) (Analysis 2.6). However, at 12 months we found a reduced risk of revascularization procedures with early statins (RR 0.70, 95% CI 0.52 to 0.93; five studies, 1999 participants) (Analysis 3.6). The heterogeneity among treatment effects was low at one month (I^2 = 0%) and four months (I^2 = 21%), but moderate at 12 months (I^2 = 50%). This may be due to differences in settings and definitions of the endpoint of revascularization procedures among trials (Table 4).

Unstable angina

The RR for unstable angina with early statin therapy compared to placebo or no treatment at one month was 0.89 (95% CI 0.76 to 1.05; 10 studies, 12,181 participants) (Analysis 1.7), at four months the RR was 0.76 (95% CI 0.59 to 0.96; nine studies, 8770 participants) (Analysis 2.7), and at 12 months the RR was 0.61 (95% CI 0.33 to 1.12; four studies, 1130 participants) (Analysis 3.7). The heterogeneity among treatment effects was low at one month (I^2 = 0%), but we found moderate heterogeneity at four months (I^2 = 33%) and at 12 months (I^2 = 35%). This may be due to differences in the definition of the endpoint of unstable angina among trials (Table 4).

In sensitivity analyses, summary estimates for unstable angina at four months suggested smaller risk reductions for trials with higher methodological quality compared to trials that lacked a respective quality component. In trials with concealed allocation the summary RR for statins compared to control was 0.79 (95% CI 0.64 to 0.97; two studies, 7583 participants) (Analysis 5.7). For trials without concealed allocation the RR was 0.68 (95% CI 0.44 to 1.04; seven studies, 1187 participants) (Analysis 5.7). For trials with blinded outcome assessment the summary RR was 0.81 (95% CI 0.66 to 0.99; four studies, 8204 participants) (Analysis 5.9). For trials without blinded outcome assessment the RR was 0.59 (95% CI 0.35 to 1.00; five studies, 566 participants) (Analysis 5.9). For trials with blinding of patients and caregivers the summary RR was 0.85 (95% CI 0.64 to 1.14; five studies, 8378 participants) (Analysis 5.8). For trials without blinding of patients and caregivers the RR was 0.51 (95% CI 0.34 to 0.79; four studies, 392 participants) (Analysis 5.8).

When we additionally included 4.5-month data from 3605 patients with ACS from the PRINCESS study in a sensitivity analysis (PRINCESS 2004), the summary RR for unstable angina was 0.78 (95% CI 0.65 to 0.95) (Analysis 5.13).

Overall, we found moderate quality evidence that early statin therapy leads to a relevant risk reduction of unstable angina within the first four months following ACS (see Summary of findings for the main comparison).

Acute heart failure

There was no statistically significant difference for acute (new or worsening) heart failure with early statin treatment compared to placebo or no treatment at one month (RR 0.85, 95% CI 0.63 to 1.14;

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five studies, 11,141 participants) (Analysis 1.8), four months (RR 0.86, 95% CI 0.65 to 1.15; two studies, 7583 participants) (Analysis 2.8), or at 12 months (RR 0.09, 95% CI 0.01 to 1.64; one study, 353 participants) (Analysis 3.8). The heterogeneity among treatment effects was low at one month (I^2 = 0%) and four months (I^2 = 0%); at 12 months there was only one study.

Adverse events

Among all included trials, only three incidents of rhabdomyolysis were reported in patients treated with statins (0.04%); all occurred in the A-to-Z trial (RR 6.90, 95% CI 0.36 to 133.47; 4497 participants) (Analysis 4.1). There were nine individuals with myopathy (elevated creatinine kinase levels more than 10 times the upper limit of normal) in the statin groups versus one in the control groups (0.13% versus 0.015%); the summary RR for myopathy was significantly higher with statins than with control (RR 4.69, 95% CI 1.01 to 21.67; three studies, 4677 participants) (Analysis 4.2). All nine cases occurred beyond the first month of statin treatment and seven of the nine patients were treated with high-dose simvastatin (80 mg/day). None of the nine patients died. The risk of elevated liver aminotransferase levels (ALT more than three times the upper limit of normal) was significantly higher in the early statin groups than the control groups (RR 2.49, 95% CI 1.16 to 5.32; five studies, 11,914 participants) (Analysis 4.3). The heterogeneity in the effects on elevated liver aminotransferase levels was moderate (I^2 = 48%). This may be due to differences in trial settings and included patients (Table 4). Due to serious concerns about the imprecision of the rhabdomyolysis results, we rated the available evidence as low quality (see Summary of findings for the main comparison).

Patient-perceived quality of life

None of the included trials reported patient-perceived quality of life.

DISCUSSION

Key findings

This systematic review of randomized controlled trials in over 14,000 patients with acute coronary syndrome (ACS) investigated whether early statin therapy compared to placebo or no treatment improves patient-relevant outcomes shortly after ACS. The results of our meta-analysis did not show a statistically significant reduction of the composite primary endpoint (death, myocardial infarction, or stroke) for patients treated early with statins at one month, four months, and 12 months following ACS. There was, however, a non-significant trend towards risk reduction and this trend increased with time. There were non-significant trends towards risk reductions for the secondary outcomes of total death, total myocardial infarction, total stroke, cardiovascular death, and acute heart failure at one month, four months, and 12 months following ACS. The only significant relative risk reductions were in unstable angina at four months (estimated relative risk reduction of 24%) and revascularization procedures at 12 months (estimated relative risk reduction of 30%) following ACS. There were few data available from included trials at 12 months. However, the vulnerable coronary situation following ACS usually stabilizes within three to four months and other studies have already shown significant risk reductions for hard clinical outcomes such as myocardial infarction, stroke, or death in patients with stable coronary heart disease (4S 1994; Briel 2004; LIPID Study Group 1998; Studer 2005). Our results at 12 months are compatible with these findings.

In terms of adverse events we found that the risk of elevated liver aminotransferase levels (ALT more than three times the upper limit of normal) was significantly higher in the early statin groups than the control groups, but serious events such as myopathy or rhabdomyolysis were rare (three reported incidents of rhabdomyolysis in patients treated early with simvastatin 80 mg (0.04%) and nine individuals with myopathy (elevated creatinine kinase levels more than 10 times the upper limit of normal) in statin-treated patients (0.13%); seven of these nine individuals took simvastatin 80 mg).

Overall we rated the quality of evidence for all outcomes as moderate due to some concerns about risk of bias and imprecision of results (see Summary of findings for the main comparison), except for rhabdomyolysis for which we only found low quality evidence due to serious concerns about imprecision of results.

Why should effects on unstable angina be stronger than effects on myocardial infarction?

One could argue that statins might ameliorate coronary vascular endothelial function, but that doing so does not directly influence atherothrombosis. One might also posit that there actually are concordant effects on all of these endpoints (trends are all in a favorable direction with statins), but that the composite sample size and duration of observation in this group of trials are inadequate to ascertain an effect with sufficiently low type I error rate. Another important point is the biomarker methods used for ascertainment of myocardial infarction in many of these studies. In the late 1990s or even early 2000s, many sites continued to use CK-MB or even total CK as the biomarker to detect myocardial injury. Multicenter trials generally do not specify one biomarker to define myocardial injury in endpoint events. Thus many endpoint events that would be associated with a small rise in troponin and today be categorized as acute myocardial infarction according to the current International Definition of Myocardial Infarction (Thygesen 2007), were likely to have been considered biomarker-negative and categorized as unstable angina using the older and less sensitive biomarker methods prevalent during the conduct of the trials in question. Therefore, one might reasonably expect that had contemporary diagnostic criteria and methods been applied to the events in these trials, there might have been more events categorized as acute myocardial infarction (and fewer as unstable angina), affording greater power to detect an effect of early statin therapy on acute myocardial infarction.

Strengths and weaknesses

We have conducted an extensive literature search to retrieve all relevant eligible trials and collaborated with the investigators of the primary trials. This collaboration with experts in the field should minimize potential publication bias. In addition, formal testing indicated little evidence for such bias. In searching trial registries we found no evidence of ongoing eligible trials, which means that the trials gathered in this review may constitute the totality of the available evidence on the topic.

We were unable to include one small trial with 151 randomized individuals because the original investigators failed to clarify outcome events (Pedersen 2000). Two other trials including 3468

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patients had a follow-up of only one month (PACT 2004) and 1.5 months (RECIFE 1999). As a consequence, the power of our analysis at four months was compromised.

It may well be that early use of statins in ACS is associated with a beneficial effect on hard clinical outcomes such as total mortality, myocardial infarction, and stroke in the short term; summary estimates for all efficacy outcomes show a trend towards risk reduction with early statin therapy, but this meta-analysis may lack the power to detect a significant risk reduction for hard outcomes. However, our sensitivity analyses indicated even smaller treatment effects when restricting the analysis to trials of adequate methodological quality, or when we additionally included secondary endpoint data from a large, prematurely terminated trial using cerivastatin in 3605 patients (PRINCESS 2004). To rule out effects of 10% risk reduction or less on our combined primary endpoint (death, myocardial infarction, and stroke), more than 34,000 patients with ACS would need to be randomized (Lachin 2000).

As expected, statins lowered low-density lipoprotein (LDL) cholesterol levels more efficiently than placebo or usual care, and there were larger reductions in LDL cholesterol in trials using higher doses of statins. However, available data precluded adequate exploration of an association between clinical outcomes and the lipid-lowering potency of different statin types and doses. It remains an open question whether potent statins at top doses provide clinical benefit that is not achieved with lower-intensity statin therapy, since the only individual trials that have shown significant clinical benefit of statins in the early period following ACS are those that compared atorvastatin 80 mg with placebo (MIRACL 2001) or pravastatin 40 mg (Cannon 2004b). The possibility that high-intensity, but not moderate-intensity statin therapy is beneficial in the early period after ACS is supported by data from a meta-analysis of five randomized controlled trials that compared high-intensity with moderate-intensity statin treatment in a total of 39,612 patients with coronary heart disease (Baigent 2010). Two of the five trials (A-to-Z (de Lemos 2004) and PROVE-IT (Cannon 2004b)) included only ACS patients; two other included trials (SEARCH (Armitage 2010) and IDEAL (Pedersen 2005)) included some patients with recent ACS. The risk ratio (RR) for major vascular events among those treated with a high-intensity regimen was 0.85 (95% confidence interval (CI) 0.82 to 0.89). In part, this finding led to the recent recommendation in the 2013 AHA/ACC Guideline for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults that most patients with established coronary heart disease should be treated with an intensive statin regimen (Stone 2013).

Finally, this systematic review cannot address the benefit of the use of early statins in patients with ACS undergoing early percutaneous coronary intervention (PCI) of culprit lesions, since only a minority of patients in the included trials underwent PCI. Finally, as only one trial specified that it was unfunded (PTT 2002), and 11 trials specified direct industry sponsorship (de Lemos 2004; FACS 2010; FLORIDA 2002; L-CAD 2000; LAMIL 1997; LIPS 2002; MIRACL 2001; PACT 2004; PAIS 2001; PRINCESS 2004; RECIFE 1999), the reader should be cautioned of a potential bias of interpretation of trial results (Als-Nielsen 2003).

Comparison with other studies

Our findings contrast with results from published observational studies on the topic that suggest a lower risk of mortality with early statin therapy within one month following ACS (odds ratios as low as 0.4) (Aronow 2001; Fonarow 2005; Spencer 2004; Stenestrand 2001). Results from these observational studies, however, may be prone to bias due to survivor treatment selection (Glesby 1996), competing medical issues (Redelmeier 1998), or differences in unknown confounders between comparison groups (Laupacis 2004). Another large observational study that found no benefit of early statin initiation in a propensity and covariate-adjusted analysis might have better captured potentially important confounders (Newby 2002). Our meta-analysis of randomized controlled trials demonstrates that observational studies with insufficient control of confounders greatly overestimate the magnitude of effect from early statin therapy in ACS.

On first sight, our findings might appear to contrast with results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial that randomized patients with ACS to atorvastatin 80 mg/day or pravastatin 40 mg/day (Cannon 2004a). In fact, however, there is no obvious discordance. In PROVE-IT, Kaplan-Meier curves of the primary composite endpoint appear to diverge as early as 30 days after ACS in favor of patients treated with atorvastatin, but the difference did not reach statistical significance until six months. It is important to note that the primary composite endpoint of PROVE-IT comprised not only death, myocardial infarction, and stroke, but also recurrent unstable angina requiring re-hospitalization and revascularization. If the more limited composite of death, myocardial infarction, and stroke is considered, there was no significant difference between the two treatment arms of PROVE-IT. Unstable angina and revascularization were the most frequent events in PROVE-IT and appeared to have driven the primary composite endpoint. Similarly, our meta-analysis indicates that statins reduce the risk of unstable angina following ACS at four months. Although endpoints such as unstable angina depend at least in part on clinicians' judgment or action, and therefore may be less reliable (Freemantle 2003), our finding of a risk reduction for unstable angina of 19% (95% CI 1% to 34%) at four months in trials with blinded outcome assessment supports the validity of this result.

AUTHORS' CONCLUSIONS

Implications for practice

Statins impact lipid profiles within days (Correia 2002), and in vitro studies show immediate inhibition of smooth muscle cell proliferation and stimulation of re-endothelialization by statins (Walter 2004). These effects seem to translate into a reduction of unstable angina pectoris at four months following ACS, but not to the same extent into a reduction of death, myocardial infarction, or stroke.

In our meta-analysis we considered only endpoint events that occurred during the period of randomized treatment. It is likely that the beneficial effects of statins are cumulative. In most of the landmark trials of statins in patients with chronic coronary heart disease a benefit of treatment was not evident until one to two years after randomization (4S 1994; LIPID Study Group 1998). Similarly, there appeared to be a delayed benefit of more intensive statin treatment, compared to less intensive statin treatment, in the

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late phase of the A-to-Z trial (de Lemos 2004). Therefore, some of the benefit of statin treatment in the period up to four months after ACS may only become manifest after four months.

This systematic review confirms that early treatment with statins in ACS can, in general, be considered safe and that the highest approved doses of potent statins may be considered in this context (Stone 2013). However, physicians and patients should pay close attention to muscle-related symptoms, especially when maximum available doses - in particular of simvastatin 80 mg - are administered (Ara 2009), or when clinical risk factors for statin myopathy are present (e.g. advanced age, low body mass, impaired renal function).

There are concerns that when administered in clinical practice, long-term adherence to statins among patients with recent onset of ACS is poor (Jackevicius 2002). Evidence from a small randomized trial and from observational studies suggests better adherence to statins when therapy is started in hospital shortly after an acute event (Nordmann 2000; Smith 2005).

In summary, initiation of statin therapy within 14 days following ACS produces favorable trends but does not significantly reduce death, myocardial infarction, or stroke up to four months after the index event. Early initiation of statin therapy does significantly reduce the occurrence of unstable angina at four months following ACS. Serious muscle toxicity was more common with early statin therapy than with placebo, but was rare and mostly limited to treatment with simvastatin 80 mg.

Implications for research

A pooled analysis using individual patient data from eligible trials would be useful since it allows for pooled time-to-event analyses, powerful subgroup analyses, and multivariable regression analyses to clarify further the timing and mechanism by which statins confer cardiovascular benefits.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Colivicchi 2002

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in Italy **Patient recruitment**: January 1999 to July 2001 **Blinding**: outcome adjudicators **Intention-to-treat**: yes **Follow-up period**: 12 months **Lost to follow-up**: 0
Participants	**Number randomized**: statin 40, control 41 **Mean age (SD) in years**: statin 69 (14), control 68 (14) **Men, n (%)**: statin 23 (58%), control 24 (59%) **Diabetes, n (%)**: statin 22 (55%), control 24 (58%) **Hypertension, n (%)**: statin 35 (87%), control 37 (90%) **Current smoker, n (%)**: unspecified **Prior myocardial infarction, n (%)**: statin 34 (85%), control 35 (85%) **Index event, n (%)**: • Myocardial infarction: unspecified • Unstable angina: unspecified • Fibrinolysis therapy: none • Percutaneous coronary intervention (PCI): none

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Colivicchi 2002 *(Continued)*

	Inclusion criteria: (1) angiographic evidence of severe and diffuse coronary artery disease, that was not amenable to direct revascularization by coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, as determined by a cardiac surgeon and an interventional cardiologist during the index admission; (2) objective evidence of symptomatic reversible myocardial ischemia (0.1 mV ST-segment depression on the electrocardiogram) at a low exercise workload while receiving medical treatment (2 antianginal medications at maximal tolerated doses), as assessed by treadmill ergometry (Bruce's protocol) before discharge; and (3) left ventricular ejection fraction 35% **Exclusion criteria**: presence of congestive heart failure, the need for continuous use of intravenous antianginal medications, and the presence of any major concurrent illness
Interventions	Atorvastatin 80 mg initiated on average 12 days of onset of ACS
Outcomes	**Primary**: composite of cardiovascular death, non-fatal MI, readmission for ACS (requiring new electrocardiographic changes or cardiac marker elevation), and stroke **Secondary**: individual components of the primary endpoint
Source	Not reported
Daily intervention	Adherence to the National Cholesterol Education Program Guidelines
Control	Usual care including lipid-lowering therapy
Notes	Outcome data available at 1, 3, 6, and 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random list but no explicit specification on blinding
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or caregivers but outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up of patients
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	High risk	Stopped early for benefit after 5th interim analysis

de Lemos 2004

Methods	**Design**: multi-center randomized controlled trial **Setting**: 322 centers in 41 countries **Patient recruitment**: December 1999 to January 2003

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de Lemos 2004 *(Continued)*

	Blinding: patients, caregivers, and outcome adjudicators **Intention-to-treat**: yes **Follow-up period**: 4 months for comparison simvastatin 40/80 mg versus placebo **Lost to follow-up**: 44 (1%)
Participants	**Number randomized**: statin 2265, control 2232 **Mean age (SD) in years**: statin 60 (11), control 61 (11) **Men, n (%)**: statin 1716 (76%), control 1680 (75%) **Diabetes, n (%)**: statin 529 (23%), control 530 (24%) **Hypertension, n (%)**: statin 1131 (50%), control 1105 (50%) **Current smoker, n (%)**: statin 926 (41%), control 915 (41%) **Prior myocardial infarction, n (%)**: statin 409 (18%), control 355 (16%) **Index event, n (%)**: • Myocardial infarction: statin 1956 (86%), control 1919 (86%) • Unstable angina: statin 309 (14%), control 313 (14%) • Fibrinolysis therapy: statin 483 (21%), control 472 (21%) • Percutaneous coronary intervention (PCI): statin 979 (43%), control 979 (44%) **Inclusion criteria**: patients with ACS, between the ages of 21 and 80 years with either non-ST-elevation ACS; total cholesterol of 250 mg/dL (6.48 mmol/L) or lower; stabilized for at least 12 consecutive hours within 5 days after symptom onset, and meeting at least one of the following high-risk characteristics: age older than 70 years, diabetes mellitus, prior history of coronary artery disease, peripheral arterial disease, or stroke; elevation of serum creatine kinase-MB or troponin levels; recurrent angina with ST-segment changes; electrocardiographic evidence of ischemia on a pre-discharge stress test; or multivessel coronary artery disease determined by coronary angiography **Exclusion criteria**: on statins at time of randomization, coronary artery bypass graft surgery planned, or PCI planned within the following 2 weeks; ALT level higher than 20% above the upper limit of normal; an increased risk of myopathy due to renal impairment (serum creatinine level > 2.0 mg/dL) or concomitant therapy with agents known to enhance myopathy risk, such as fibrates, cyclosporine, macrolide antibiotics, azole antifungals, amiodarone, or verapamil; or a prior history of non exercise-related elevations in creatine kinase level or nontraumatic rhabdomyolysis
Interventions	Simvastatin 40 mg initiated within 5 days of onset of ACS and then titrated to 80 mg at 1 month
Outcomes	**Primary**: composite of cardiovascular death, non-fatal MI, readmission for ACS (requiring new electrocardiographic changes or cardiac marker elevation), and stroke **Secondary**: individual components of the primary endpoint, revascularization due to documented ischemia, death from any cause, new-onset congestive heart failure (requiring admission or initiation of heart failure medications), and cardiovascular rehospitalization
Source	Funded by Merck
Daily intervention	All patients were encouraged to adopt an American Heart Association Step I diet
Control	Placebo
Notes	Outcome data for the review at 1 and 4 months of follow-up provided by original investigators. After 4 months the control group received simvastatin 20 mg

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de Lemos 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization using blinded allocation tables
Allocation concealment (selection bias)	Low risk	Adequate. Central randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded patients, caregivers, and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% of patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided; study protocol available
Other bias	Low risk	Adhered to the intention-to-treat principle; not stopped early for benefit

ESTABLISH 2004

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in Japan **Patient recruitment**: November 2001 to August 2003 **Blinding**: statistician **Intention-to-treat**: unspecified **Follow-up period**: 6 months **Lost to follow-up**: 1 (1%)
Participants	**Number randomized**: statin 35, control 35 **Mean age (SD) in years**: statin 61 (10), control 63 (11) **Men, n (%)**: statin 30 (86%), control 30 (86%) **Diabetes, n (%)**: statin 12 (34%), control 11 (31%) **Hypertension, n (%)**: statin 19 (54%), control 19 (54%) **Current smoker, n (%)**: statin 24 (69%), control 19 (54%) **Prior myocardial infarction, n (%)**: statin 5 (14%), control 5 (14%) **Index event, n (%)**: • Myocardial infarction: statin 22 (63%), control 26 (74%) • Unstable angina: statin 13 (37%), control 9 (26%) • Fibrinolysis therapy: statin 7 (20%), control 3 (9%) • Percutaneous coronary intervention (PCI): statin 35 (100%), control 35 (100%)

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ESTABLISH 2004 *(Continued)*

	Inclusion criteria: ACS with significant stenosis on initial coronary angiography and received PCI. ACS was defined as high-risk unstable angina, non–ST-elevated myocardial infarction (MI) or ST-elevated MI. MI was diagnosed by the rise (2 times) in serum creatine phosphokinase and positivity for troponin T **Exclusion criteria**: failed PCI, diseased bypass graft, recommended CABG, cardiogenic shock, and administration of lipid-lowering drugs (statin, clofibrate, probucol or analog, nicotinic acid, or other prohibited drug) before enrollment
Interventions	Atorvastatin 20 mg initiated within 14 days of ACS
Outcomes	**Primary**: % change in plaque volume **Secondary**: composite of death, non-fatal MI, and non-fatal stroke, death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, revascularization procedures (CABG/PCI), and unstable angina
Source	Not reported
Daily intervention	Aspirin 100 mg daily, ticlopidine 100 mg twice daily
Control	Usual care including lipid-lowering diet
Notes	Outcome data available at 1, 4 and 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Minimization method of randomization
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, caregivers, or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient was lost to follow-up
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Unclear risk	Adherence to the intention-to-treat principle not reported

FACS 2010

Methods	**Design**: multi-center randomized controlled trial **Setting**: 5 centers in Czech Republic and Slovakia **Patient recruitment**: November 2003 to February 2006 **Blinding**: participants, caregivers **Intention-to-treat**: yes

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FACS 2010 *(Continued)*

	Follow-up period: 12 months **Lost to follow-up**: 0
Participants	**Number randomized**: statin 78, control 78 **Mean age (SD) in years**: statin 61 (12), control 63 (11) **Men, n (%)**: statin 55 (71%), control 51 (65%) **Diabetes, n (%)**: statin 14 (18%), control 16 (21%) **Hypertension, n (%)**: statin 40 (51%), control 40 (51%) **Current smoker, n (%)**: statin 33 (42%), control 39 (50%) **Prior myocardial infarction, n (%)**: statin 4 (5%), control 8 (10%) **Index event, n (%)**: • Myocardial infarction: statin > 47 (60%), control > 54 (69%) • Unstable angina: statin < 31 (40%), control < 24 (31%) • Fibrinolysis therapy: none • Percutaneous coronary intervention (PCI): statin 68 (87%), control 71 (91%) **Inclusion criteria**: ST elevation ACS must have resting chest pain less than 12 hours before admission and either ≥ 1 mm ST-segment elevation in 2 or more continuous leads or new left bundle branch block on ECG. Those with non-ST elevation ACS must have resting chest pain during the previous 48 hours and either ≥ 1 mm ST segment depression or negative T waves in 2 or more continuous leads **Exclusion criteria**: < 18 years of age or if they have concomitant active liver disease or persistent elevation of transaminases (> 3 times the upper limit of normal), a history of lipid-lowering therapy less than 30 days before the index event or a known allergy to fluvastatin or to any additives present in the drug. Other exclusions include inability to ingest oral medication, unwillingness to be followed for the duration of the study, muscle disease (e.g. myositis), and creatine kinase ≥ 5 times the upper limit of normal due to conditions other than myocardial infarction. Women of childbearing potential who are pregnant, nursing or who are not using effective contraception
Interventions	Fluvastatin 80 mg within 1 hour of ACS
Outcomes	**Primary**: levels of C-reactive protein and IL-6 **Secondary**: composite of death, non-fatal MI, and non-fatal stroke, death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, revascularization procedures (CABG/PCI)
Source	Medication and Clinical Monitoring by Novartis Pharma CR, Laboratory investigations by grant from Czech Ministry of Health
Daily intervention	Usual care
Control	Placebo
Notes	Outcome data available at 1, 3, and 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomization - method of sequence generation unclear

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FACS 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported blinding of participants and caregivers, but not outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up of patients
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided; study protocol available
Other bias	Low risk	Adherence to the intention-to-treat principle; not stopped early for benefit

FLORIDA 2002

Methods	**Design**: multi-center randomized controlled trial **Setting**: 28 centers in The Netherlands **Patient recruitment**: July 1997 to May 1999 **Blinding**: patients, caregivers, and outcome adjudicators **Intention-to-treat**: unspecified **Follow-up period**: 12 months **Lost to follow-up**: 0
Participants	**Number randomized**: statin 265, control 275 **Mean age (SD) in years**: statin 61 (12), control 60 (11) **Men, n (%)**: statin 214 (81%), control 234 (85%) **Diabetes, n (%)**: statin 29 (11%), control 31 (11%) **Hypertension, n (%)**: statin 67 (25%), control 65 (24%) **Current smoker, n (%)**: statin 140 (53%), control 139 (51%) **Prior myocardial infarction, n (%)**: statin 31 (12%), control 31 (11%) **Index event, n (%)**: • Myocardial infarction: statin 265 (100%), control 275 (100%) • Unstable angina: none • Fibrinolysis therapy: statin 137 (52%), control 133 (48%) • Percutaneous coronary intervention (PCI): statin 8 (3%), control 10 (4%) **Inclusion criteria**: new or markedly increased chest pain lasting longer than 30 minutes, or a new pathological Q wave of 0.04 s duration, or 25% of the corresponding R wave amplitude, both in at least 2 contiguous leads **Exclusion criteria**: age < 18 years, use of lipid-lowering agents within the previous 3 months, a high triglyceride level of > 4.5 mmol/l, known familial dyslipidemia, severe renal failure, known hepatic disease, signs and symptoms of severe heart failure (New York Heart Association class IV), a scheduled

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FLORIDA 2002 *(Continued)*

	percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and co-medication that influences the ST-segment (digoxin, quinidine or tricyclic antidepressants), atrial fibrillation, Wolff-Parkinson-White syndrome, complete left bundle-branch block, known pre-existent ST-segment deviations before the qualifying MI, left ventricular hypertrophy with a pattern of strain or presence of a permanent pacemaker
Interventions	Fluvastatin 80 mg within 14 days of ACS
Outcomes	**Primary**: composite of death, non-fatal MI, and non-fatal stroke, death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, revascularization procedures (CABG/PCI), unstable angina requiring emergency hospitalization **Secondary**: ischemia on the ambulatory ECG (without taking clinical events into account), change in ischemic burden, the time to a major clinical event and the 12-month change in lipid profile
Source	Unrestricted Grant from AstraZeneca, The Netherlands
Daily intervention	At discretion of attending cardiologist for starting standard medication including aspirin, beta-blocking agents, and/or ACE-inhibitors
Control	Placebo
Notes	Outcome data available at 1, 4, 6, and 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported blinding of participants, caregivers, and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete patient follow-up
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Unclear risk	Adherence to intention-to-treat principle not reported

L-CAD 2000

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in Germany **Patient recruitment**: unspecified **Blinding**: none

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L-CAD 2000 *(Continued)*

	Intention-to-treat: yes **Follow-up period**: 24 months **Lost to follow-up**: 0
Participants	**Number randomized**: statin 70, control 56 **Mean age (SD) in years**: statin 55 (10), control 59 (11) **Men, n (%)**: statin 57 (81%), control 44 (79%) **Diabetes, n (%)**: none **Hypertension, n (%)**: statin 22 (31%), control 18 (32%) **Current smoker, n (%)**: statin 49 (70%), control 36 (64%) **Prior myocardial infarction, n (%)**: statin 45 (64%), control 39 (70%) **Index event, n (%)**: • Myocardial infarction: statin 32 (46%), control 23 (41%) • Unstable angina: statin 38 (54%), control 33 (59%) • Fibrinolysis therapy: unspecified • Percutaneous coronary intervention (PCI): statin 58 (83%), control 50 (89%) **Inclusion criteria**: total cholesterol of > 200 to < 400 mg/dL and low-density lipoprotein (LDL) cholesterol of > 130 to < 300 mg/dL (after exclusion of secondary forms of hyperlipidemia) with an acute myocardial infarction (defined by new Q waves and increase of enzymes of > 3-fold the normal value) and/or who underwent emergency percutaneous transluminal coronary balloon angioplasty due to severe or unstable angina pectoris (defined by clinical symptoms and electrocardiographic (ECG) alterations **Exclusion criteria**: > 75 years old, diabetics (fasting blood glucose > 125 mg/dL), patients with post-coronary artery bypass graft, known malignant disease, serious kidney or liver dysfunction (creatinine > 1.5 mg/dL, alanine aminotransferase and aspartate aminotransferase > 2 times normal value), or women of child-bearing age not using a reliable contraception
Interventions	Pravastatin 20 to 40 mg (8 of 70 individuals received additionally cholestyramine or nicotinic acid) within 1 to 11 days of ACS
Outcomes	**Primary**: composite of death, non-fatal MI, and non-fatal stroke **Secondary**: non-fatal myocardial infarction, coronary balloon angioplasty or bypass grafting, stroke, new onset of occlusive peripheral vascular disease, cardiovascular death, and all-cause mortality
Source	Bristol-Myers Squibb Company, Munich, Germany
Daily intervention	All patients received dietary counseling per the standards of the European Atherosclerosis Society
Control	Usual care (including lipid-lowering therapy)
Notes	Outcome data available at 1, 4, 6,12, and 24 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomization - sequence generation unspecified

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L-CAD 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, caregivers, or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Complete patient follow-up
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Low risk	Adherence to intention-to-treat principle; no stopping early for benefit

LAMIL 1997

Methods	**Design**: multi-center randomized controlled trial **Setting**: 10 centers in Belgium **Patient recruitment**: unspecified **Blinding**: participants and caregivers, but not outcome assessors **Intention-to-treat**: not reported **Follow-up period**: 3 months **Lost to follow-up**: 14 (20%)
Participants	**Number randomized**: statin 36, control 33 **Mean age (SD) in years**: unspecified **Men, n (%)**: unspecified **Diabetes, n (%)**: unspecified **Hypertension, n (%)**: unspecified **Current smoker, n (%)**: unspecified **Prior myocardial infarction, n (%)**: unspecified **Index event, n (%)**: • Myocardial infarction: statin 36 (100%), control 33 (100%) • Unstable angina: none • Fibrinolysis therapy: unspecified • Percutaneous coronary intervention (PCI): unspecified **Inclusion criteria**: definite cases of acute MI using ECG and enzymatic criteria **Exclusion criteria**: unspecified
Interventions	Pravastatin 10 to 20 mg 3 days after ACS
Outcomes	**Primary**: lipid profile

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LAMIL 1997 *(Continued)*

	Secondary: composite of death, non-fatal MI, and non-fatal stroke, death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, and revascularization procedures (CABG/PCI)
Source	Bristol-Myers-Squibb Pharmaceutical Company who also played a role in co-ordinating the study
Daily intervention	None specified, no other lipid-lowering drugs allowed
Control	Placebo
Notes	Outcome data available at 1 and 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported blinding of participants and caregivers, but not outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	It remains unclear how many patients were lost to follow-up for clinical events; 14 patients (20%) were not available for a follow-up lipid profile
Selective reporting (reporting bias)	Unclear risk	Author contact failed; no protocol available
Other bias	Unclear risk	Adherence to the intention-to-treat principle not reported

LIPS 2002

Methods	**Design**: multi-center randomized controlled trial **Setting**: 57 centers in 10 countries **Patient recruitment**: April 1996 to October 1998 **Blinding**: patients, caregivers, and outcome adjudicators **Intention-to-treat**: yes **Follow-up period**: median of 3.9 years **Lost to follow-up**: 0 up to 12 months of follow-up
Participants	**Number randomized**: statin 417, control 407 (these individuals just represent the subgroup of patients with unstable angina; the LIPS trial originally included another 853 individuals with stable angina) **Mean age (SD) in years**: statin 61 (10), control 60 (10) **Men, n (%)**: statin 344 (83%), control 336 (83%) **Diabetes, n (%)**: statin 65 (16%), control 34 (8%)

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LIPS 2002 *(Continued)*

	Hypertension, n (%): statin not available, control not available **Current smoker, n (%)**: statin not available, control not available **Prior myocardial infarction, n (%)**: statin 184 (44%), control 172 (42%) **Index event, n (%)**: • Myocardial infarction: statin 0, control 0 • Unstable angina: statin 417 (100%), control 407 (100%) • Fibrinolysis therapy: statin 0, control 0 • Percutaneous coronary intervention (PCI): statin 417 (100%), control 407 (100%) **Inclusion criteria**: patients with unstable angina, who had successfully undergone their first PCI of 1 or more lesions in the native coronary arteries. Successful PCI was defined as a reduction of the stenosis diameter to less than 50% in the target lesion without evidence of myocardial necrosis, need for repeat PCI or CABG, or death before hospital discharge. Any type of PCI was allowed and included balloon angioplasty with or without stent placement, rotational or directional atherectomy, laser ablation, transluminal extraction catheter, or cutting balloon. Patients further needed to have a total cholesterol level between 135 and 270 mg/dL (3.5 to 7.0 mmol/L), with fasting triglyceride levels of less than 400 mg/dL (4.5 mmol/L) before the index procedure. The upper total cholesterol limit for eligibility was 212 mg/dL (5.5 mmol/L) for patients whose baseline lipids were measured from blood drawn 24 hours to 4 weeks following MI and 232 mg/dL (6.0 mmol/L) for patients with type 1 or 2 diabetes mellitus **Exclusion criteria**: sustained systolic blood pressure of more than 180 mmHg and diastolic blood pressure of more than 100 mmHg despite medical therapy, left ventricular ejection fraction of less than 30%, a history of previous PCI or CABG, severe valvular disease, idiopathic cardiomyopathy or congenital heart disease, severe renal dysfunction (defined as serum creatinine level > 1.8 mg/dL, obesity (defined as a body mass index > 35 kg/m^2), and the presence of malignant or other disease with a life expectancy of less than 4 years
Interventions	Fluvastatin 80 mg initiated at a median of 2 days after the index PCI
Outcomes	**Primary**: development of a major adverse cardiac event (MACE), defined as cardiac death (any death unless an unequivocal noncardiac cause could be established); non-fatal MI (appearance of pathological Q waves that were absent at baseline or a total creatine kinase level > 2 times the upper limit of normal (ULN) with presence of CK isoenzyme MB higher than the ULN); or a re-intervention procedure (CABG, repeat PCI, or PCI for a new lesion). Angiographic assessments without interventions were not included **Secondary**: MACE, excluding re-intervention procedures (surgical or PCI) occurring in the first 6 months of follow-up for lesions treated at the index procedure, cardiac mortality, non-cardiac mortality, all-cause mortality, combined cardiac mortality and MI, and combined all-cause mortality and MI
Source	Funded by Novartis Pharma AG who also provided the fluvastatin and matching placebo
Daily intervention	Dietary and lifestyle counseling
Control	Placebo
Notes	Outcome data for the subgroup of patients with unstable angina at 1, 4, and 12 months of follow-up were provided by original investigators

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomization - sequence generation unclear

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LIPS 2002 *(Continued)*

Allocation concealment (selection bias)	Low risk	Adequate. Coded medication containers
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded patients, caregivers, and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete patient follow-up within first 12 months
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Low risk	Adherence to intention-to-treat principle; not stopped early for benefit

Macin 2005

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in Argentina **Patient recruitment**: December 1999 to November 2000 **Blinding**: patients and caregivers, but not outcome adjudicators **Intention-to-treat**: unspecified **Follow-up period**: 1 month **Lost to follow-up**: 0
Participants	**Number randomized**: statin 44, control 46 **Mean age (SD) in years**: statin 59 (13), control 61 (12) **Men, n (%)**: statin 34 (77%), control 33 (72%) **Diabetes, n (%)**: statin 10 (23%), control 11 (24%) **Hypertension, n (%)**: statin 29 (66%), control 31 (67%) **Current smoker, n (%)**: statin 18 (41%), control 19 (41%) **Prior myocardial infarction, n (%)**: statin 5 (11%), control 7(15%) **Index event, n (%)**: • Myocardial infarction: statin 23 (52%), control 31 (67%) • Unstable angina: statin 21 (48%), control 15 (33%) • Fibrinolysis therapy: statin 7 (16%), control 8 (17%) • Percutaneous coronary intervention (PCI): none **Inclusion criteria**: > 21 years old who fulfilled both of the following criteria: ACS within 48 hours of onset and CRP levels ≥ 1.4 mg/dl within 24 hours. Acute coronary syndrome was diagnosed in the presence of ischemic chest pain at rest lasting ≥ 20 minutes and at least 1 of the following: new or presumably new ST-segment deviations on electrocardiogram (electrocardiographic evidence of ST-segment elevation or depression), enzyme abnormalities (creatine kinase–MB above upper limit of reference in ≥ 2 samples obtained with an interval of > 6 hours), and/or troponin T ≥ 0.02 ng/mL

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Macin 2005 *(Continued)*

	Exclusion criteria: (1) use of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor or another lipid-lowering agent at any time during the preceding 1 month; (2) history of active liver disease; (3) untreated endocrine disorder; (4) history of systemic inflammatory disease or cancer; (5) known hypersensitivity to statins; (6) patients judged to be unlikely to comply with the study drug regimen or study process; (7) known infectious disease in the last 30 days; (8) unwilling to provide written informed consent; and (9) cardiogenic shock or acute pulmonary edema
Interventions	Atorvastatin 40 mg within 96 hours of ACS
Outcomes	**Primary**: C-reactive protein levels **Secondary**: lipid profile, acute phase reactants, composite of death, non-fatal MI, and non-fatal stroke, death from any cause, fatal MI, non-fatal MI and unstable angina
Source	Unspecified. Laboratorio Elea Sacifya provided active drug and placebo
Daily intervention	All patients received dietary counseling to promote compliance with National Cholesterol Education Program (NCEP) diet
Control	Placebo
Notes	Outcome data available at 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded participants and caregivers, but not outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete patient follow-up for clinical events
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Unclear risk	Adherence to the intention-to-treat principle not reported

MIRACL 2001

Methods	**Design**: multi-center randomized controlled trial **Setting**: 122 centers in Europe, North America, South Africa, Australasia **Patient recruitment**: May 1997 to September 1999 **Blinding**: patients, caregivers, and outcome adjudicators **Intention-to-treat**: yes

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MIRACL 2001 *(Continued)*

	Follow-up period: 4 month **Lost to follow-up**: 9 (0.4%)
Participants	**Number randomized**: statin 1538, control 1548 **Mean age (SD) in years**: statin 65 (12), control 65 (12) **Men, n (%)**: statin 992 (64%), control 1020 (66%) **Diabetes, n (%)**: statin 342 (22%), control 373 (24%) **Hypertension, n (%)**: statin 843 (55%), control 846 (55%) **Current smoker, n (%)**: statin 429 (28%), control 430 (28%) **Prior myocardial infarction, n (%)**: statin 382 (25%), control 392 (25%) **Index event, n (%)**: • Myocardial infarction: statin 812 (53%), control 843 (55%) • Unstable angina: statin 726 (47%), control 705 (45%) • Fibrinolysis therapy: statin 109 (7%), control 139 (9%) • Percutaneous coronary intervention (PCI): none **Inclusion criteria**: 18 years or older with chest pain or discomfort of at least 15 minutes' duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and represented a change from their usual anginal pattern **Exclusion criteria**: serum total cholesterol level at screening exceeded 270 mg/dL (7 mmol/L) (sites in Poland and South Africa used levels of 310 mg/dL (8 mmol/L)), coronary revascularization was planned or anticipated at the time of screening, evidence of Q-wave acute MI within the preceding 4 weeks; coronary artery bypass surgery within the preceding 3 months; percutaneous coronary intervention within the preceding 6 months; left bundle-branch block or paced ventricular rhythm; severe congestive heart failure (New York Heart Association class IIIb or IV); concurrent treatment with other lipid-regulating agents (except niacin at doses of 500 mg/d), vitamin E (except at doses #400 IU/d), or drugs associated with rhabdomyolysis in combination with statins; severe anemia; renal failure requiring dialysis; hepatic dysfunction (alanine aminotransferase greater than 2 times ULN); insulin-dependent diabetes; pregnancy or lactation
Interventions	Atorvastatin 80 mg daily, starting at a mean of 3 days after onset of ACS
Outcomes	**Primary**: composite of death, non-fatal MI, and non-fatal stroke **Secondary**: death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, revascularization procedures (CABG/PCI), unstable angina requiring emergency hospitalization
Source	Grant from Pfizer Inc.
Daily intervention	All participants received instruction and counseling to promote compliance with NCEP step 1 diet
Control	Placebo
Notes	Outcome data available at 1 and 4 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomization - sequence generation unspecified

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MIRACL 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central randomization stratified by study center
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported blinding of participants, caregivers, and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	0.4% of patients lost to follow-up
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided; study protocol available
Other bias	Low risk	Adherence to the intention-to-treat principle; not stopped early for benefit

OACIS-LIPID 2008

Methods	**Design**: multi-center randomized controlled trial **Setting**: 14 centers in Japan **Patient recruitment**: May 2000 to December 2003 **Blinding**: outcome adjudicators **Intention-to-treat**: yes **Follow-up period**: 9 months **Lost to follow-up**: 5 (1%)
Participants	**Number randomized**: statin 176, control 177 **Mean age (SD) in years**: statin 64 (10), control 63 (11) **Men, n (%)**: statin 129 (73%), control 142 (80%) **Diabetes, n (%)**: statin 52 (30%), control 59 (34%) **Hypertension, n (%)**: statin 81 (46%), control 87 (49%) **Current smoker, n (%)**: statin 98 (56%), control 105 (59%) **Prior myocardial infarction, n (%)**: statin 16 (9%), control 19 (10%) **Index event, n (%)**: • Myocardial infarction: unspecified • Unstable angina: unspecified • Fibrinolysis therapy: unspecified • Percutaneous coronary intervention (PCI): statin 161 (91%), control 161 (91)% **Inclusion criteria**: (1) clinical history of central chest pressure, pain, or tightness lasting for 30 minutes or more, (2) typical electrocardiographic changes (i.e. ST-segment elevation > 0.1 mV in at least 1 standard or 2 precordial leads, ST-segment depression > 0.1 mV in at least 2 leads, abnormal Q wave, or T wave inversion in at least 2 leads), and (3) an increase in the serum creatine kinase activity more than twice the normal laboratory value. All patients presenting within 1 week after the onset of acute MI were registered prospectively

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OACIS-LIPID 2008 *(Continued)*

	Exclusion criteria: concurrent therapy with any statins or had a history of side effects associated with any statin. Evidence of life-threatening arrhythmia, severe chronic congestive heart failure (New York Heart Association class III–IV), hepatic dysfunction, renal failure, cerebrovascular disease, poorly controlled diabetes, pregnancy, lactation, age < 20 years, and unable to take medication or absence of written informed consent. Patients whom the doctors consider inappropriate for any other reason were also not included
Interventions	Pravastatin 10 mg initiated on average within 7 days after onset of ACS
Outcomes	**Primary**: combination of death, non-fatal myocardial infarction, unstable angina, revascularization and non-fatal stroke, and re-hospitalization because of other cardiovascular diseases
Source	Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science, Tokyo, Japan and from Japan Arteriosclerosis Prevention Fund, Tokyo, Japan
Daily intervention	All patients received instructions and counseling to promote compliance with the National Cholesterol Education Program (NCEP) Step I diet
Control	Usual care
Notes	Outcome data available at 1 and 9 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or caregivers, but blinded outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% of participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	Author contact partially established; data on relevant outcomes provided
Other bias	Low risk	Adherence to intention-to-treat principle; not stopped early for benefit

PACT 2004

Methods	**Design**: multi-center randomized controlled trial **Setting**: 6 centers in Australia **Patient recruitment**: unspecified **Blinding**: patients and caregivers, but not outcome adjudicators **Intention-to-treat**: yes

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PACT 2004 *(Continued)*

	Follow-up period: 1 month **Lost to follow-up**: 85 (2%)
Participants	**Number randomized**: statin 1710, control 1698 **Mean age (SD) in years**: statin 62 (12), control 61 (12) **Men, n (%)**: statin 1308 (76%), control 1285 (76%) **Diabetes, n (%)**: statin 244 (14%), control 234 (14%) **Hypertension, n (%)**: statin 700 (41%), control 714 (42%) **Current smoker, n (%)**: statin 608 (36%), control 575 (34%) **Prior myocardial infarction, n (%)**: statin 236 (14%), control 197 (12%) **Index event, n (%)**: • Myocardial infarction: statin 1109 (65%), control 1111 (65%) • Unstable angina: statin 601 (35%), control 587 (35%) • Fibrinolysis therapy: statin 651 (38%), control 671 (40%) • Percutaneous coronary intervention (PCI): statin 414 (24%), control 406 (24%) **Inclusion criteria**: 24 hours of the onset of symptoms if they had electrocardiographic changes suggestive of an acute MI or unstable angina **Exclusion criteria**: taking statin therapy before their event (other lipid-lowering therapies were permitted), participation in any other clinical trial or the taking of an investigational drug within the previous 30 days, planned coronary revascularization or cardiac transplantation, severe renal or hepatic disease or other severe disease, drug- or alcohol-related problems, gastrointestinal disease or a history of gastrointestinal surgery that might affect drug absorption, and known hypersensitivity or previous serious adverse reactions to statin therapy Women of child-bearing potential
Interventions	Pravastatin 20 to 40 mg
Outcomes	**Primary**: composite of death, non-fatal MI, and non-fatal stroke, death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, unstable angina requiring emergency hospitalization
Source	Bristol-Myers Squibb, Australia
Daily intervention	Usual care
Control	Placebo
Notes	Outcome data available at 1 month; trial stopped early due to recruitment difficulties

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias)	Low risk	Reported blinding of participants and caregivers, but not outcome assessors

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PACT 2004 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% of participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Low risk	Adherence to intention-to-treat principle; not stopped early for benefit

PAIS 2001

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in The Netherlands **Patient recruitment**: April 1997 to- January 1998 **Blinding**: patients and caregivers, but not outcome adjudicators **Intention-to-treat**: yes **Follow-up period**: 3 months **Lost to follow-up**: 2 (2%)
Participants	**Number randomized**: statin 50, control 49 **Mean age (SD) in years**: statin 64 (1), control 63 (2) **Men, n (%)**: statin 35 (70%), control 37 (76%) **Diabetes, n (%)**: statin 8 (16%), control 5 (10%) **Hypertension, n (%)**: statin 12 (24%), control 16 (33%) **Current smoker, n (%)**: statin 17 (34%), control 17 (35%) **Prior myocardial infarction, n (%)**: statin 14 (28%), control 12 (25%) **Index event, n (%)**: • Myocardial infarction: statin 35 (70%), control 31 (63%) • Unstable angina: statin 15 (30%), control 18 (37%) • Fibrinolysis therapy: statin 17 (34%), control 14 (29%) • Percutaneous coronary intervention (PCI): none **Inclusion criteria**: men aged 18 to 80 or postmenopausal women with serum total cholesterol levels > 5.2 mmol/l and LDL cholesterol levels > 3.5 mmol/l; signs of either UA or acute MI (defined as ST segment elevations ≥ 1 mm in 2 leads or T-wave inversion) **Exclusion criteria**: history of hypersensitivity to statins, severe congestive heart failure, cardiomyopathy, significant liver disease, significant gastrointestinal disease or abdominal surgery that might adversely influence drug absorption, substance or alcohol abuse, history or present use of any other lipid-lowering or investigational agent, uncontrolled diabetes, thyroid disease, severe renal impairment, dysproteinemia, primary muscle disease
Interventions	Pravastatin 40 mg/d

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PAIS 2001 *(Continued)*

Outcomes	**Primary**: composite of death, non-fatal MI, and non-fatal stroke, death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, revascularization procedures (CABG/PCI), "recurrent angina pectoris"
Source	Funded by Bristol-Myers Squibb, Woerden, The Netherlands
Daily intervention	"Dispensed educational materials on appropriate dietary modification"
Control	Placebo
Notes	Outcome data available at 1 and 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported blinding of participants and caregivers, but not outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% of patients lost to follow-up
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Low risk	Adherence to intention-to-treat principle; not stopped early for benefit

PRINCESS 2004

Methods	**Design**: multi-center randomized controlled trial **Setting**: 280 centers in 8 countries **Patient recruitment**: unspecified **Blinding**: patients, caregivers, and outcome adjudicators **Intention-to-treat**: yes **Follow-up period**: 4.5 months (44% of the participants completed the 4.5 months of follow-up at trial termination) **Lost to follow-up**: unclear
Participants	**Number randomized**: statin 1795, control 1810 **Mean age (SD) in years**: not available **Men, n (%)**: not available

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PRINCESS 2004 *(Continued)*

	Diabetes, n (%): not available **Hypertension, n (%)**: not available **Current smoker, n (%)**: not available **Prior myocardial infarction, n (%)**: not available **Index event, n (%)**: • Myocardial infarction: not available • Unstable angina: not available • Fibrinolysis therapy: not available • Percutaneous coronary intervention (PCI): not available **Inclusion criteria**: patients with ACS (myocardial infarction or unstable angina), no lower LDL cholesterol limit
Interventions	Cerivastatin 0.4 mg initiated within 2 days of onset of ACS
Outcomes	**Primary**: composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina or heart failure **Secondary**: recurrent coronary ischemia including ischemic coronary revascularization, fatal and non-fatal reinfarction and unstable angina, all-cause mortality, myocardial infarction, and stroke
Source	Funded by Bayer
Daily intervention	Unclear
Control	Placebo (after 3 months the control group received cerivastatin 0.4 mg)
Notes	The trial was prematurely interrupted on 8 August 2001 when Bayer withdrew cerivastatin from the worldwide market. Outcome data on mortality from any cause, fatal and non-fatal myocardial infarction, and fatal and non-fatal stroke at 4.5 months of follow-up were provided by the original investigators

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded patients, caregivers, and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No full publication available
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Low risk	Adherence to intention-to-treat principle; not stopped early for benefit

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PTT 2002

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in Turkey **Patient recruitment**: June 1997 to September 1998 **Blinding**: none **Intention-to-treat**: unclear **Follow-up period**: 6 months **Lost to follow-up**: 0
Participants	**Number randomized**: statin 79, control 85 **Mean age (SD) in years**: statin 53 (11), control 52 (10) **Men, n (%)**: statin 65 (82%), control 69 (81%) **Diabetes, n (%)**: statin 14 (18%), control 13 (15%) **Hypertension, n (%)**: statin 16 (20%), control 21 (25%) **Current smoker, n (%)**: statin 63 (80%), control 66 (78%) **Prior myocardial infarction, n (%)**: statin none, control none **Index event, n (%)**: • Myocardial infarction: statin 79 (100%), control 85 (100%) • Unstable angina: none • Fibrinolysis therapy: statin 79 (100%), control 85 (100%) • Percutaneous coronary intervention (PCI): none **Inclusion criteria**: patients receiving fibrinolysis therapy within 6 hours of ST-segment elevated acute MI **Exclusion criteria**: contraindications for thrombolytic therapy, age > 75 years, history of myocardial infarction, previous percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, congestive heart failure, secondary hyperlipidemia, uncontrolled hypertension or diabetes mellitus, liver disease, thyroid dysfunction, use of anticoagulant drugs other than aspirin, use of steroids or hormone replacement therapy, women of childbearing potential and patients with physical or psychosocial disorders that could interfere with protocol adherence
Interventions	Pravastatin 40 mg/d
Outcomes	**Primary**: composite of death, non-fatal MI, and non-fatal stroke, death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, revascularization procedures (CABG/PCI), "recurrent angina pectoris"
Source	Not funded
Daily intervention	All patients received fibrinolysis therapy, intravenous nitrates, heparin infusions, a AHA step II diet and a daily 100 mg aspirin
Control	Usual care

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PTT 2002 *(Continued)*

Notes	Outcome data available at 1 and 6 months. Note: only a subgroup of 77 patients (40 intervention, 37 control, those who received additional coronary angioplasty) were followed up for 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, caregivers, or clinical outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up for clinical outcomes
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Unclear risk	Adherence to the intention-to-treat principle not reported

RECIFE 1999

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in Canada **Patient recruitment**: unspecified **Blinding**: participants and caregivers, but not outcome assessors **Intention-to-treat**: unclear **Follow-up period**: 6 weeks **Lost to follow-up**: 0 for clinical events
Participants	**Number randomized**: statin 30, control 30 **Mean age (SD) in years**: statin 55 (2), control 56 (2) **Men, n (%)**: statin 26 (93%), control 22 (81%) **Diabetes, n (%)**: statin 1 (4%), control 0 (0%) **Hypertension, n (%)**: statin 5 (18%), control 8 (29%) **Current smoker, n (%)**: statin 14 (50%), control 17 (63%) **Prior myocardial infarction, n (%)**: statin 1 (4%), control 2 (7%) **Index event, n (%)**: • Myocardial infarction: statin 11 (39%), control 12 (44%)

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RECIFE 1999 *(Continued)*

	• Unstable angina: statin 19 (61%), control 18 (66%) • Fibrinolysis therapy: none • Percutaneous coronary intervention (PCI): statin 16 (57%), control 17 (63%) **Inclusion criteria**: diagnosis of acute myocardial infarction or unstable angina and admission total serum cholesterol ?5.2 mmol/L or LDL cholesterol ?3.4 mmol/L and serum triglycerides ?4.5 mmol/L **Exclusion criteria**: presence of heart failure with an ejection fraction of < 40%, administration of lipid-lowering agents in the preceding 8 weeks, renal failure with serum creatinine level > 200 mmol/L, and patients requiring coronary artery bypass surgery, premenopausal women, postmenopausal women on hormone replacement therapy
Interventions	Pravastatin 40 mg/d
Outcomes	**Primary**: brachial artery flow **Secondary**: composite of death, non-fatal MI, and non-fatal stroke, death from any cause, cardiovascular death, fatal MI, non-fatal MI, total stroke, revascularization procedures (CABG/PCI), unstable angina requiring emergency hospitalization
Source	Funded by Bristol-Myers Squibb, Canada
Daily intervention	American Heart Association step 2 diet
Control	Placebo
Notes	Outcome data available at 1.5 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported blinding of participants and caregivers, but not outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up for clinical events
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Unclear risk	Adherence to the intention-to-treat principle not reported

Ren 2009

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in China

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Ren 2009 *(Continued)*

	Patient recruitment: March 2004 to July 2006 **Blinding**: probable blinding of participants and caregivers; blinding of outcome assessors not reported **Intention-to-treat**: unclear **Follow-up period**: 4 weeks **Lost to follow-up**: 0
Participants	**Number randomized**: statin 43, control 43 **Mean age (SD) in years**: statin 58 (11), control 59 (10) **Men, n (%)**: statin 27 (63%), control 30 (70%) **Diabetes, n (%)**: statin 12 (28%), control 10 (23%) **Hypertension, n (%)**: statin 21 (49%), control 18 (42%) **Current smoker, n (%)**: not available **Prior myocardial infarction, n (%)**: statin 1 (4%), control 2 (7%) **Index event, n (%)**: • Myocardial infarction: none • Unstable angina: statin 43 (100%), control 43 (100%) • Fibrinolysis therapy: none • Percutaneous coronary intervention (PCI): none **Inclusion criteria**: newly diagnosed unstable angina, age > 18 years, ischemic symptoms < 72 h, absence of cardiogenic shock, and not previously treated with statin **Exclusion criteria**: severe renal dysfunction, primary cardiomyopathy or COPD, taking inflammatory drugs other than aspirin, elevated cardiac markers
Interventions	Simvastatin 40 mg/d
Outcomes	**Primary**: plasma IL-6 **Secondary**: death from any cause, cardiovascular death, fatal MI, non-fatal MI, heart failure, revascularization procedures (CABG/PCI)
Source	Not reported
Daily intervention	Not reported
Control	Placebo
Notes	Outcome data available at 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported

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Ren 2009 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and caregivers probable; blinding of clinical outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up for clinical events
Selective reporting (reporting bias)	Low risk	Author contact established; data on relevant outcomes provided
Other bias	Unclear risk	Adherence to the intention-to-treat principle not reported

Sakamoto 2005

Methods	**Design**: multi-center randomized controlled trial **Setting**: 28 centers in Japan **Patient recruitment**: February 2002 to September 2004 **Blinding**: no blinding of participants or caregivers, but blinding of outcome assessors **Intention-to-treat**: unclear **Follow-up period**: 24 months **Lost to follow-up**: 35 (7%)
Participants	**Number randomized**: statin 241, control 245 **Mean age (SD) in years**: statin 63 (11), control 65 (12) **Men, n (%)**: statin 190 (80%), control 193 (79%) **Diabetes, n (%)**: statin 83 (35%), control 61 (25%) **Hypertension, n (%)**: statin 149 (63%), control 142 (58%) **Current smoker, n (%)**: statin 131 (55%), control 130 (53%) **Prior myocardial infarction, n (%)**: statin 10 (4%), control 15 (6%) **Index event, n (%)**: • Myocardial infarction: statin 241 (100%), control 245 (100%) • Unstable angina: none • Fibrinolysis therapy: statin 45 (19%), control 50 (20%) • Percutaneous coronary intervention (PCI): statin 215 (91%), control 220 (90%) **Inclusion criteria**: qualifying AMI (increased creatinine phosphokinase-MB and/or total creatinine phosphokinase level ≥ 2 times the upper limit of normal) and prolonged chest pain (> 30 minutes), objective evidence of myocardial ischemia based on dynamic or interval ST- or T-wave changes in ≥ 2 contiguous electrocardiographic leads (≥ 0.1 mV ST elevation, ≥ 0.05 mV flat or downsloping ST depression at the J point and 80 ms after the J point, or ≥ 0.3 mV T-wave inversion), or new left bundle branch block; serum total cholesterol levels were required to be 180 to 240 mg/dL on admission **Exclusion criteria**: < 18 years of age, use of lipid-lowering agents within the previous 3 months,known familial dyslipidemia, severe renal failure, known hepatic disease, signs and symptoms of severe heart failure (Killip's class III or IV), a scheduled PCI or coronary artery bypass grafting (CABG), previous

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Sakamoto 2005 *(Continued)*

	PCI (within 6 months) or CABG (within 3 months), and the presence of malignant disease or allergy to statins
Interventions	Any statin (pravastatin, atorvastatin, fluvastatin, simvastatin, or pitavastatin) Note: statin and dose at discretion of treating physician and could be switched or adjusted at any time but prohibited from using any other lipid-lowering agent
Outcomes	**Primary**: combination of cardiovascular death, non-fatal MI, recurrent symptomatic myocardial ischemia with objective evidence that required emergency rehospitalization, congestive heart failure that required emergency rehospitalization, and non-fatal stroke **Secondary**: CABG, PCI for a new lesion, and repeat PCI procedures for restenosis of infarct-related or non-infarct-related lesions
Source	Funded by the Japan Heart Foundation and the Ministry of Health, Labour and Welfare, Tokyo, Japan
Daily intervention	All patients received instruction and counseling to promote compliance with the Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases Step I diet
Control	Usual care excluding statins
Notes	Outcome data available at 1 and 24 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or caregivers, but blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Follow-up information was sought for all patients who were withdrawn early from the study." 35 patients (7%) dropped out (unclear if followed up or not)
Selective reporting (reporting bias)	Unclear risk	Author contact failed; no study protocol available
Other bias	Unclear risk	Adherence to intention-to-treat not reported

Shal'nev 2007

Methods	**Design**: single-center randomized controlled trial **Setting**: 1 center in Russia **Patient recruitment**: unspecified **Blinding**: none **Intention-to-treat**: unclear

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Shal'nev 2007 *(Continued)*

	Follow-up period: 6 months **Lost to follow-up**: 2 (2%)
Participants	**Number randomized**: statin 55, control 53 **Mean age (SD) in years**: not available **Men, n (%)**: not available **Diabetes, n (%)**: not available **Hypertension, n (%)**: not available **Current smoker, n (%)**: not available **Prior myocardial infarction, n (%)**: not available **Index event, n (%)**: • Myocardial infarction: not available • Unstable angina: not available • Fibrinolysis therapy: not available • Percutaneous coronary intervention (PCI): not available **Inclusion criteria**: patients with acute coronary syndrome (myocardial infarction or unstable angina)
Interventions	Simvastatin 40 mg/d
Outcomes	**Primary**: total death, unstable angina (hospitalized and non-hospitalized), MI (acute and in later follow-up)
Source	Unspecified
Daily intervention	Unspecified
Control	Usual care
Notes	Outcome data available at 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation unspecified
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, caregivers, or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% of participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Author contact failed; no study protocol available

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Shal'nev 2007 *(Continued)*

Other bias	Unclear risk	Adherence to intention-to-treat not reported

ACE: angiotensin-converting enzyme
ACS: acute coronary syndrome
AHA: American Heart Association
ALT: aminotransferase
CABG: coronary artery bypass grafting
COPD: chronic obstructive pulmonary disease
CRP: C-reactive protein
d: day
ECG: electrocardiogram
IL-6: interleukin-6
LDL: low-density lipoprotein
MACE: major adverse cardiac event
MI: myocardial infarction
NCEP: National Cholesterol Education Program
PCI: percutaneous coronary intervention
UA: unstable angina

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akasaka 2012	Head to head comparison of statins (atorvastatin 20 mg versus atorvastatin 5 mg); no clinical outcomes reported
Barderas 2009	No clinical outcomes reported
Bermejo 2006	Not a randomized trial
Cannon 2004a	Head to head comparison of statins (atorvastatin 80 mg versus pravastatin 40 mg)
Chi 2007	Treatment not initiated within 14 days
Chiodini 2007	Treatment not initiated within 14 days
Chyrchel 2011	Only 7 days of statin treatment and follow-up; no clinical outcomes
Colivicchi 2010	Comparison of high-dose (80 mg/d) versus low-dose (20 mg/d) atorvastatin
Colivicchi 2010a	Head to head comparison of statins (atorvastatin 80 mg versus atorvastatin 20 mg)
Colivicchi 2011	Head to head comparison of statins (atorvastatin 80 mg versus atorvastatin 20 mg)
Correia 2002	Follow-up less than 30 days (only 5 days)
de Winter 2005	Not a randomized trial
Dohi 2010	Extended follow-up of the already included ESTABLISH trial
FLAME 2006	Head to head comparison of statins (simvastatin 20 mg versus simvastatin 40 mg)
Ge 2010	Statin versus placebo only for pretreatment of PCI; after PCI both groups received statins
Guazzi 2007	No clinical outcomes reported

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Study	Reason for exclusion
Gómez-Doblas 2006	Follow-up less than 30 days (only 8 days)
Gómez-Hernández 2008	No clinical outcomes reported
Hall 2009	Head to head comparison of statins (simvastatin versus rosuvastatin)
He 2011	Head to head comparison of statins (atorvastatin 40 mg versus atorvastatin 10 mg)
Hiro 2009	Head to head comparison of statins (pitavastatin versus atorvastatin)
Hiro 2009a	Head to head comparison of statins (pitavastatin versus atorvastatin)
Hiro 2010	Head to head comparison of statins (pitavastatin versus atorvastatin)
Kanadasi 2006	Not a randomized trial
Kashima 2009	Protocol for a head to head comparison of statins
Kuznetsova 2010	Head to head comparison of statins (atorvastatin versus rosuvastatin)
Lablanche 2008	Head to head comparison of statins
LAVA 2005	No clinical outcomes reported; fluvastatin 80 mg within 12 hours versus 4 to 5 days following ACS
Lemos 2005	Treatment not initiated within 14 days
Leone 2008	Head to head comparison of statins (atorvastatin 80 mg versus atorvastatin 20 mg)
Li 2005	No clinical outcomes reported
Li 2006	Follow-up less than 30 days (only 14 days)
Lim 2012	Not a randomized trial
Link 2006	No clinical outcomes reported
Link 2006a	No clinical outcomes reported
Link 2011	No clinical outcomes reported
Liu 2012	Head to head comparison of statins (atorvastatin 80 mg versus "usual care statin dose")
Miyauchi 2006	Head to head comparison of statins (pitavastatin versus atorvastatin); design and rationale paper for Hiro T et al
Monteiro 2008	No clinical outcomes reported
Nakamura 2008	No clinical outcomes reported
Nakaya 2005	Not a randomized trial
Ordulu 2008	Head to head comparison of statins
Ostadal 2003	Follow-up less than 30 days (only 1 day)

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Study	Reason for exclusion
Patti 2007	Treatment not given for 30 days (only twice)
PEACE 2005	Head to head comparison of statins (pravastatin 20 mg versus pravastatin 40 mg)
Pedersen 2000	Outcome data not available per treatment group for the comparison simvastatin 40 mg versus usual care
Pedersen 2005	Treatment not initiated within 14 days
Pitt 2008	Head to head comparison of statins
Pitt 2012	Head to head comparison of statins
Post 2012	Only statin versus placebo for pretreatment of PCI; no clinical outcomes
Sakata 2005	Not a randomized trial
Shah 2007	Head to head comparison of statin combinations
Stefanadi 2009	No clinical outcomes reported
Suh 2011	Not a randomized trial
Teshima 2009	Not a randomized trial
Tousoulis 2006	No clinical outcomes reported
Tousoulis 2006a	No clinical outcomes assessed
Tousoulis 2006b	Treatment not initiated within 14 days
Xin-wei 2009	High versus low-dose statin therapy in pre-PCI in ACS patients
Yun 2009	Only pre-procedural comparison (rosuvastatin versus no statin); after PCI all patients received rosuvastatin
Zhang 2013	Head to head comparison of statins (atorvastatin 80 mg versus atorvastatin 20 mg)
Zhao 2009	Head to head comparison of statins
Zheng 2009	Atorvastatin versus atorvastatin plus probucol
Zheng 2009a	Atorvastatin versus atorvastatin plus probucol

ACS: acute coronary syndrome
PCI: percutaneous coronary intervention

DATA AND ANALYSES

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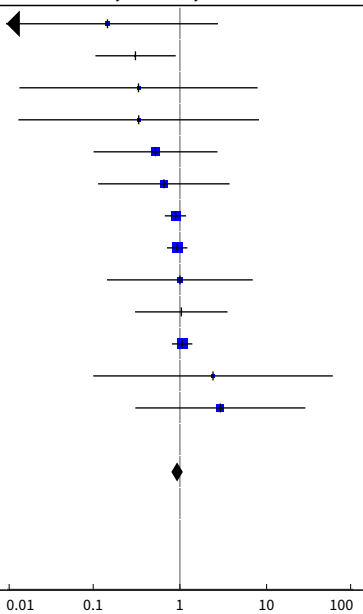
Comparison 1. Statins versus control at 1 month

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths	13	13484	Risk Ratio (IV, Random, 95% CI)	0.93 [0.80, 1.08]
2 Death from all causes	13	13155	Risk Ratio (IV, Random, 95% CI)	0.78 [0.59, 1.03]
3 Death from cardiovascular causes	10	12387	Risk Ratio (IV, Random, 95% CI)	0.80 [0.60, 1.07]
4 Fatal and non-fatal myocardial infarction or reinfarction	12	13074	Risk Ratio (IV, Random, 95% CI)	0.98 [0.82, 1.16]
5 Fatal and non-fatal stroke	7	12147	Risk Ratio (IV, Random, 95% CI)	0.78 [0.47, 1.29]
6 Revascularization procedures (bypass grafts, angioplasty)	10	9668	Risk Ratio (IV, Random, 95% CI)	1.00 [0.86, 1.16]
7 Unstable angina	10	12181	Risk Ratio (IV, Random, 95% CI)	0.89 [0.76, 1.05]
8 Acute heart failure	5	11141	Risk Ratio (IV, Random, 95% CI)	0.85 [0.63, 1.14]

Analysis 1.1. Comparison 1 Statins versus control at 1 month, Outcome 1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	0/40	3/41		0.27%	0.15[0.01,2.75]
PTT 2002	4/79	14/85		2.03%	0.31[0.11,0.89]
RECIFE 1999	0/30	1/30		0.23%	0.33[0.01,7.87]
OACIS-LIPID 2008	0/176	1/177		0.23%	0.34[0.01,8.17]
Macin 2005	2/44	4/46		0.85%	0.52[0.1,2.71]
PAIS 2001	2/50	3/49		0.76%	0.65[0.11,3.74]
PACT 2004	86/1710	96/1698		28.89%	0.89[0.67,1.18]
de Lemos 2004	99/2265	105/2232		32.19%	0.93[0.71,1.22]
FACS 2010	2/78	2/78		0.62%	1[0.14,6.92]
FLORIDA 2002	5/265	5/275		1.54%	1.04[0.3,3.54]
MIRACL 2001	101/1538	96/1548		31.7%	1.06[0.81,1.39]
L-CAD 2000	1/70	0/56		0.23%	2.41[0.1,58.01]
LIPS 2002	3/417	1/407		0.45%	2.93[0.31,28.03]
Total (95% CI)	**6762**	**6722**		**100%**	**0.93[0.8,1.08]**
Total events: 305 (Statin), 331 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.43, df=12(P=0.67); I^2=0%					
Test for overall effect: Z=0.96(P=0.34)					



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Analysis 1.2. Comparison 1 Statins versus control at 1 month, Outcome 2 Death from all causes.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	0/40	1/41		0.74%	0.34[0.01,8.14]
de Lemos 2004	20/2265	29/2232		23.31%	0.68[0.39,1.2]
FACS 2010	1/78	0/78		0.74%	3[0.12,72.53]
FLORIDA 2002	1/265	3/275		1.47%	0.35[0.04,3.3]
L-CAD 2000	1/70	0/56		0.74%	2.41[0.1,58.01]
LAMIL 1997	1/36	0/33		0.75%	2.76[0.12,65.41]
Macin 2005	1/44	3/46		1.51%	0.35[0.04,3.23]
MIRACL 2001	32/1538	30/1548		30.79%	1.07[0.66,1.76]
OACIS-LIPID 2008	0/176	1/177		0.73%	0.34[0.01,8.17]
PACT 2004	27/1710	39/1698		31.68%	0.69[0.42,1.12]
PAIS 2001	1/50	2/49		1.33%	0.49[0.05,5.23]
PTT 2002	3/79	9/85		4.64%	0.36[0.1,1.28]
Sakamoto 2005	4/241	1/245		1.57%	4.07[0.46,36.12]
Total (95% CI)	**6592**	**6563**		**100%**	**0.78[0.59,1.03]**
Total events: 92 (Statin), 118 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.19, df=12(P=0.69); I^2=0%					
Test for overall effect: Z=1.77(P=0.08)					

Analysis 1.3. Comparison 1 Statins versus control at 1 month, Outcome 3 Death from cardiovascular causes.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	0/40	1/41		0.86%	0.34[0.01,8.14]
de Lemos 2004	20/2265	29/2232		26.87%	0.68[0.39,1.2]
FLORIDA 2002	1/265	3/275		1.69%	0.35[0.04,3.3]
LAMIL 1997	1/36	0/33		0.86%	2.76[0.12,65.41]
Macin 2005	1/44	3/46		1.74%	0.35[0.04,3.23]
MIRACL 2001	27/1538	21/1548		26.94%	1.29[0.73,2.28]
OACIS-LIPID 2008	0/176	1/177		0.85%	0.34[0.01,8.17]
PACT 2004	26/1710	34/1698		33.67%	0.76[0.46,1.26]
PAIS 2001	1/50	2/49		1.54%	0.49[0.05,5.23]
PTT 2002	3/79	7/85		4.97%	0.46[0.12,1.72]
Total (95% CI)	**6203**	**6184**		**100%**	**0.8[0.6,1.07]**
Total events: 80 (Statin), 101 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.18, df=9(P=0.72); I^2=0%					
Test for overall effect: Z=1.49(P=0.14)					

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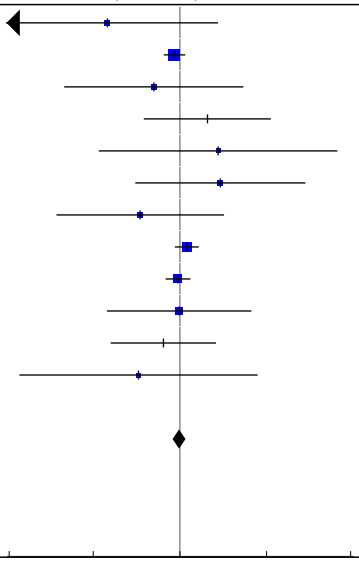
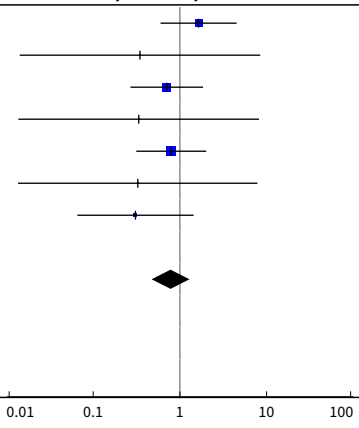
Analysis 1.4. Comparison 1 Statins versus control at 1 month, Outcome 4 Fatal and non-fatal myocardial infarction or reinfarction.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	0/40	3/41		0.35%	0.15[0.01,2.75]
de Lemos 2004	86/2265	98/2232		36.88%	0.86[0.65,1.15]
FACS 2010	1/78	2/78		0.52%	0.5[0.05,5.4]
FLORIDA 2002	4/265	2/275		1.04%	2.08[0.38,11.24]
LAMIL 1997	1/36	0/33		0.3%	2.76[0.12,65.41]
LIPS 2002	3/417	1/407		0.58%	2.93[0.31,28.03]
Macin 2005	1/44	3/46		0.6%	0.35[0.04,3.23]
MIRACL 2001	80/1538	67/1548		29.56%	1.2[0.88,1.65]
PACT 2004	67/1710	70/1698		27.55%	0.95[0.68,1.32]
PAIS 2001	2/50	2/49		0.8%	0.98[0.14,6.68]
PTT 2002	3/79	5/85		1.52%	0.65[0.16,2.61]
RECIFE 1999	0/30	1/30		0.3%	0.33[0.01,7.87]
Total (95% CI)	**6552**	**6522**		**100%**	**0.98[0.82,1.16]**
Total events: 248 (Statin), 254 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.98, df=11(P=0.71); I^2=0%					
Test for overall effect: Z=0.26(P=0.79)					



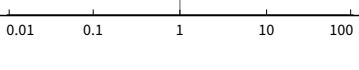
Analysis 1.5. Comparison 1 Statins versus control at 1 month, Outcome 5 Fatal and non-fatal stroke.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
de Lemos 2004	10/2265	6/2232		24.88%	1.64[0.6,4.51]
FLORIDA 2002	0/265	1/275		2.49%	0.35[0.01,8.45]
MIRACL 2001	7/1538	10/1548		27.38%	0.7[0.27,1.85]
OACIS-LIPID 2008	0/176	1/177		2.49%	0.34[0.01,8.17]
PACT 2004	8/1710	10/1698		29.55%	0.79[0.31,2.01]
PAIS 2001	0/50	1/49		2.52%	0.33[0.01,7.83]
PTT 2002	2/79	7/85		10.69%	0.31[0.07,1.44]
Total (95% CI)	**6083**	**6064**		**100%**	**0.78[0.47,1.29]**
Total events: 27 (Statin), 36 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.34, df=6(P=0.63); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					



Analysis 1.6. Comparison 1 Statins versus control at 1 month, Outcome 6 Revascularization procedures (bypass grafts, angioplasty).

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
de Lemos 2004	19/2265	22/2232		6.02%	0.85[0.46,1.57]
FACS 2010	3/78	4/78		1.05%	0.75[0.17,3.24]



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Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
FLORIDA 2002	16/265	12/275		4.23%	1.38[0.67,2.87]
L-CAD 2000	0/70	2/56		0.25%	0.16[0.01,3.28]
LIPS 2002	77/417	87/407		29.81%	0.86[0.66,1.14]
Macin 2005	8/44	8/46		2.85%	1.05[0.43,2.54]
MIRACL 2001	162/1538	147/1548		50.09%	1.11[0.9,1.37]
PAIS 2001	4/50	2/49		0.82%	1.96[0.38,10.22]
PTT 2002	12/79	15/85		4.66%	0.86[0.43,1.72]
Ren 2009	0/43	1/43		0.22%	0.33[0.01,7.96]
Total (95% CI)	**4849**	**4819**		**100%**	**1[0.86,1.16]**
Total events: 301 (Statin), 300 (Control)					
Heterogeneity: Tau²=0; Chi²=5.89, df=9(P=0.75); I²=0%					
Test for overall effect: Z=0.03(P=0.98)					

Analysis 1.7. Comparison 1 Statins versus control at 1 month, Outcome 7 Unstable angina.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	1/40	1/41		0.34%	1.02[0.07,15.83]
de Lemos 2004	27/2265	30/2232		9.53%	0.89[0.53,1.49]
FACS 2010	2/78	6/78		1.03%	0.33[0.07,1.6]
FLORIDA 2002	6/265	5/275		1.84%	1.25[0.38,4.03]
Macin 2005	7/44	8/46		2.96%	0.91[0.36,2.31]
MIRACL 2001	72/1538	87/1548		27.49%	0.83[0.61,1.13]
PACT 2004	123/1710	126/1698		44.46%	0.97[0.76,1.23]
PAIS 2001	16/50	11/49		5.86%	1.43[0.74,2.75]
PTT 2002	11/79	25/85		6.22%	0.47[0.25,0.9]
RECIFE 1999	0/30	1/30		0.25%	0.33[0.01,7.87]
Total (95% CI)	**6099**	**6082**		**100%**	**0.89[0.76,1.05]**
Total events: 265 (Statin), 300 (Control)					
Heterogeneity: Tau²=0; Chi²=8.58, df=9(P=0.48); I²=0%					
Test for overall effect: Z=1.4(P=0.16)					

Analysis 1.8. Comparison 1 Statins versus control at 1 month, Outcome 8 Acute heart failure.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
de Lemos 2004	27/2265	31/2232		33.31%	0.86[0.51,1.43]
Macin 2005	4/44	10/46		7.46%	0.42[0.14,1.24]
MIRACL 2001	21/1538	21/1548		24.25%	1.01[0.55,1.84]
PACT 2004	28/1710	31/1698		34.11%	0.9[0.54,1.49]
RECIFE 1999	0/30	1/30		0.88%	0.33[0.01,7.87]
Total (95% CI)	**5587**	**5554**		**100%**	**0.85[0.63,1.14]**

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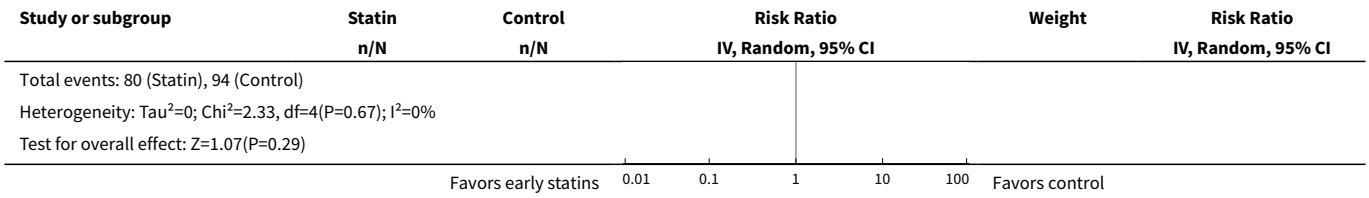
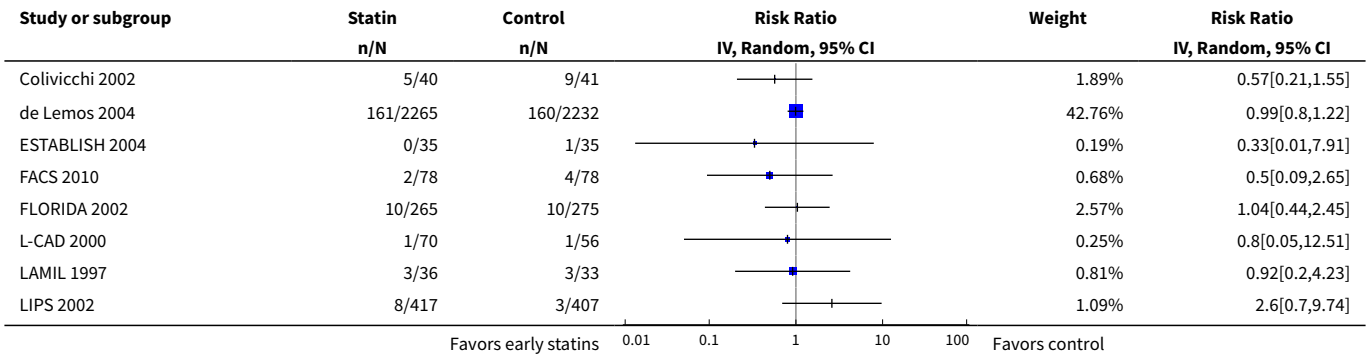


Comparison 2. Statins versus control at 4 months (3 to 6 months)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths	11	9625	Risk Ratio (IV, Random, 95% CI)	0.93 [0.81, 1.06]
2 Death from all causes	12	9733	Risk Ratio (IV, Random, 95% CI)	0.90 [0.70, 1.14]
3 Death from cardiovascular causes	8	9273	Risk Ratio (IV, Random, 95% CI)	0.84 [0.64, 1.09]
4 Fatal and non-fatal myocardial infarction or reinfarction	10	9537	Risk Ratio (IV, Random, 95% CI)	0.91 [0.77, 1.06]
5 Fatal and non-fatal stroke	7	8536	Risk Ratio (IV, Random, 95% CI)	0.72 [0.45, 1.16]
6 Revascularization procedures (bypass grafts, angioplasty)	9	9474	Risk Ratio (IV, Random, 95% CI)	0.92 [0.78, 1.08]
7 Unstable angina	9	8770	Risk Ratio (IV, Random, 95% CI)	0.76 [0.59, 0.96]
8 Acute heart failure	2	7583	Risk Ratio (IV, Random, 95% CI)	0.86 [0.65, 1.15]

Analysis 2.1. Comparison 2 Statins versus control at 4 months (3 to 6 months), Outcome 1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.



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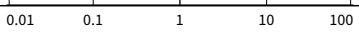
Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
MIRACL 2001	162/1538	183/1548		47.84%	0.89[0.73,1.09]
PAIS 2001	4/50	4/49		1.08%	0.98[0.26,3.7]
PTT 2002	2/40	7/37		0.84%	0.26[0.06,1.19]
Total (95% CI)	**4834**	**4791**		**100%**	**0.93[0.81,1.06]**
Total events: 358 (Statin), 385 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.48, df=10(P=0.68); I^2=0%					
Test for overall effect: Z=1.1(P=0.27)					

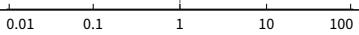
Analysis 2.2. Comparison 2 Statins versus control at 4 months (3 to 6 months), Outcome 2 Death from all causes.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	2/40	3/41		1.94%	0.68[0.12,3.88]
de Lemos 2004	44/2265	48/2232		35.63%	0.9[0.6,1.35]
ESTABLISH 2004	0/35	1/35		0.58%	0.33[0.01,7.91]
FACS 2010	1/78	0/78		0.58%	3[0.12,72.53]
FLORIDA 2002	2/265	6/275		2.31%	0.35[0.07,1.7]
L-CAD 2000	1/70	1/56		0.77%	0.8[0.05,12.51]
LAMIL 1997	1/36	0/33		0.58%	2.76[0.12,65.41]
LIPS 2002	1/417	0/407		0.57%	2.93[0.12,71.67]
MIRACL 2001	64/1538	68/1548		52.36%	0.95[0.68,1.32]
PAIS 2001	2/50	2/49		1.58%	0.98[0.14,6.68]
PTT 2002	1/40	3/37		1.19%	0.31[0.03,2.83]
Shal'nev 2007	2/55	3/53		1.91%	0.64[0.11,3.69]
Total (95% CI)	**4889**	**4844**		**100%**	**0.9[0.7,1.14]**
Total events: 121 (Statin), 135 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.56, df=11(P=0.95); I^2=0%					
Test for overall effect: Z=0.88(P=0.38)					



Analysis 2.3. Comparison 2 Statins versus control at 4 months (3 to 6 months), Outcome 3 Death from cardiovascular causes.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	1/40	2/41		1.23%	0.51[0.05,5.43]
de Lemos 2004	42/2265	48/2232		40.89%	0.86[0.57,1.3]
FLORIDA 2002	2/265	6/275		2.71%	0.35[0.07,1.7]
LAMIL 1997	1/36	0/33		0.69%	2.76[0.12,65.41]
LIPS 2002	1/417	0/407		0.67%	2.93[0.12,71.67]
MIRACL 2001	51/1538	60/1548		51.14%	0.86[0.59,1.23]
PAIS 2001	2/50	2/49		1.86%	0.98[0.14,6.68]
PTT 2002	0/40	3/37		0.8%	0.13[0.01,2.48]



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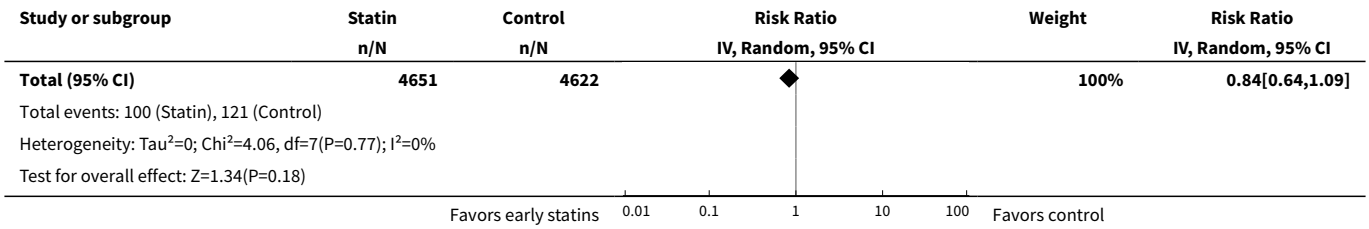
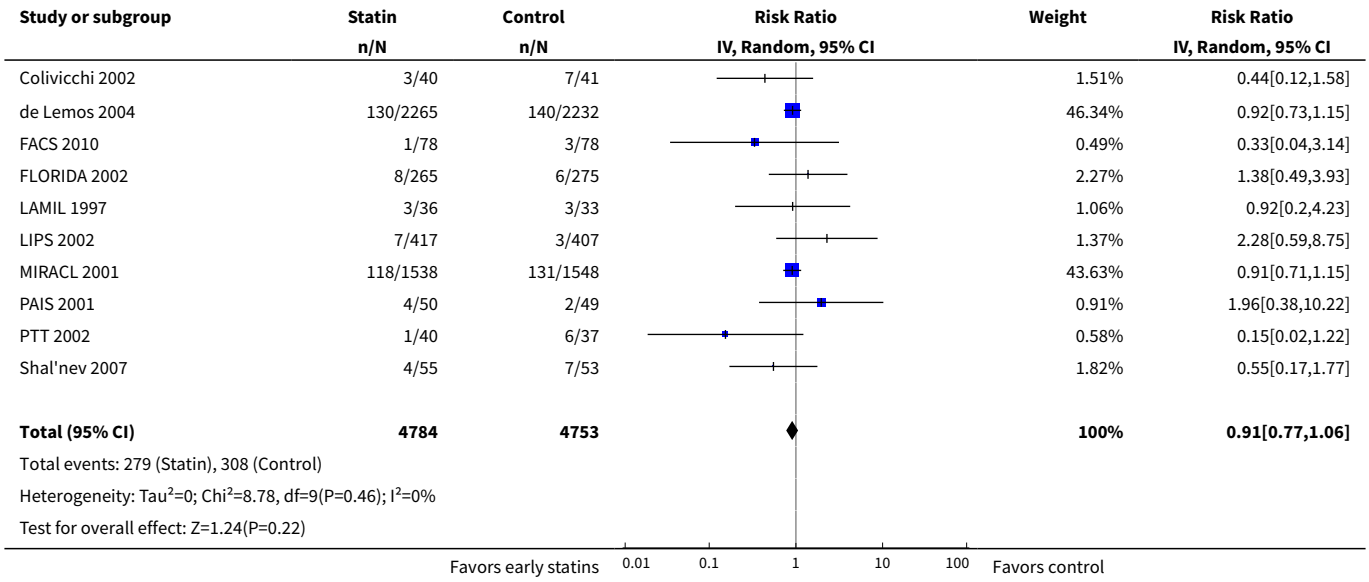
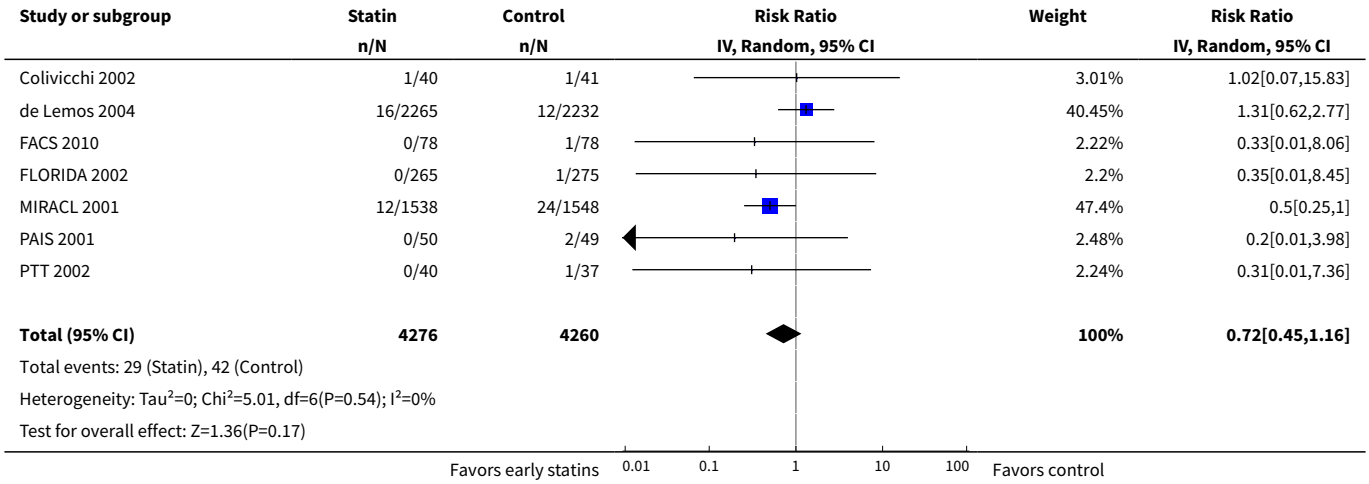


Analysis 2.4. Comparison 2 Statins versus control at 4 months (3 to 6 months), Outcome 4 Fatal and non-fatal myocardial infarction or reinfarction.



Analysis 2.5. Comparison 2 Statins versus control at 4 months (3 to 6 months), Outcome 5 Fatal and non-fatal stroke.



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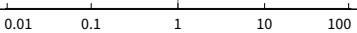
Analysis 2.6. Comparison 2 Statins versus control at 4 months (3 to 6 months), Outcome 6 Revascularization procedures (bypass grafts, angioplasty).

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
de Lemos 2004	60/2265	60/2232		15.92%	0.99[0.69,1.4]
FACS 2010	3/78	8/78		1.59%	0.38[0.1,1.36]
FLORIDA 2002	30/265	32/275		10.24%	0.97[0.61,1.55]
L-CAD 2000	2/70	9/56		1.2%	0.18[0.04,0.79]
LAMIL 1997	1/36	1/33		0.36%	0.92[0.06,14.07]
LIPS 2002	78/417	88/407		22.55%	0.87[0.66,1.14]
MIRACL 2001	254/1538	250/1548		37.81%	1.02[0.87,1.2]
PAIS 2001	11/50	9/49		4.08%	1.2[0.54,2.63]
PTT 2002	11/40	16/37		6.25%	0.64[0.34,1.19]
Total (95% CI)	**4759**	**4715**		**100%**	**0.92[0.78,1.08]**
Total events: 450 (Statin), 473 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=10.09, df=8(P=0.26); I^2=20.72%					
Test for overall effect: Z=1.03(P=0.3)					

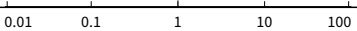
Analysis 2.7. Comparison 2 Statins versus control at 4 months (3 to 6 months), Outcome 7 Unstable angina.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	2/40	3/41		1.83%	0.68[0.12,3.88]
de Lemos 2004	56/2265	61/2232		21.07%	0.9[0.63,1.29]
FACS 2010	3/78	12/78		3.51%	0.25[0.07,0.85]
FLORIDA 2002	11/265	9/275		6.47%	1.27[0.53,3.01]
L-CAD 2000	6/70	10/56		5.52%	0.48[0.19,1.24]
MIRACL 2001	95/1538	130/1548		27.35%	0.74[0.57,0.95]
PAIS 2001	24/50	21/49		17.31%	1.12[0.73,1.73]
PTT 2002	12/40	22/37		13.11%	0.5[0.29,0.87]
Shal'nev 2007	4/55	7/53		3.82%	0.55[0.17,1.77]
Total (95% CI)	**4401**	**4369**		**100%**	**0.76[0.59,0.96]**
Total events: 213 (Statin), 275 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=11.9, df=8(P=0.16); I^2=32.78%					
Test for overall effect: Z=2.27(P=0.02)					



Analysis 2.8. Comparison 2 Statins versus control at 4 months (3 to 6 months), Outcome 8 Acute heart failure.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
de Lemos 2004	45/2265	55/2232		54.3%	0.81[0.55,1.19]
MIRACL 2001	40/1538	43/1548		45.7%	0.94[0.61,1.43]



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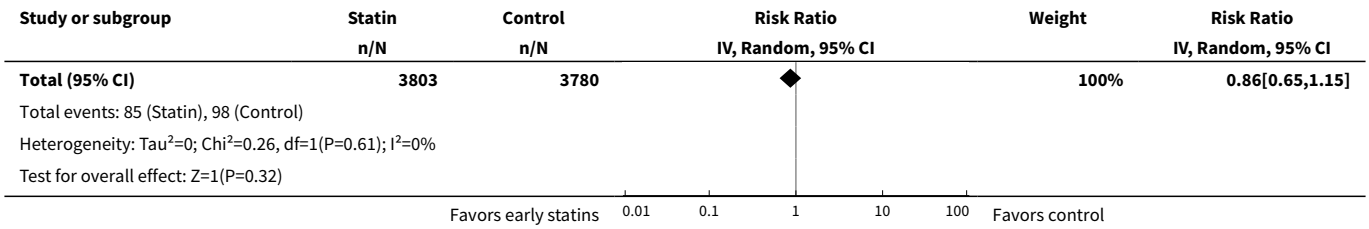
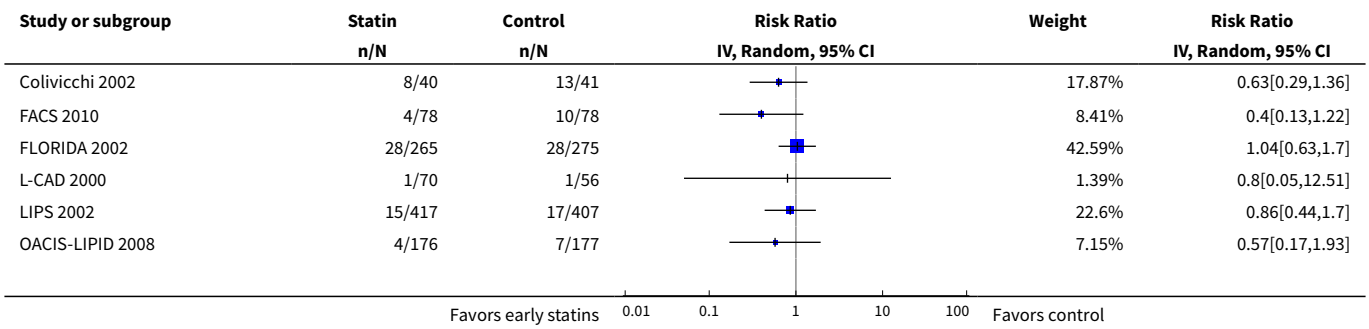


Comparison 3. Statins versus control at 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths	6	2080	Risk Ratio (IV, Random, 95% CI)	0.80 [0.58, 1.11]
2 Death from all causes	6	2080	Risk Ratio (IV, Random, 95% CI)	0.68 [0.39, 1.20]
3 Death from cardiovascular causes	5	1954	Risk Ratio (IV, Random, 95% CI)	0.55 [0.28, 1.09]
4 Fatal and non-fatal myocardial infarction or reinfarction	5	1954	Risk Ratio (IV, Random, 95% CI)	0.94 [0.61, 1.45]
5 Fatal and non-fatal stroke	4	1130	Risk Ratio (IV, Random, 95% CI)	0.38 [0.13, 1.10]
6 Revascularization procedures (bypass grafts, angioplasty)	5	1999	Risk Ratio (IV, Random, 95% CI)	0.70 [0.52, 0.93]
7 Unstable angina	4	1130	Risk Ratio (IV, Random, 95% CI)	0.61 [0.33, 1.12]
8 Acute heart failure	1	353	Risk Ratio (IV, Random, 95% CI)	0.09 [0.01, 1.64]

Analysis 3.1. Comparison 3 Statins versus control at 12 months, Outcome 1 Combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.



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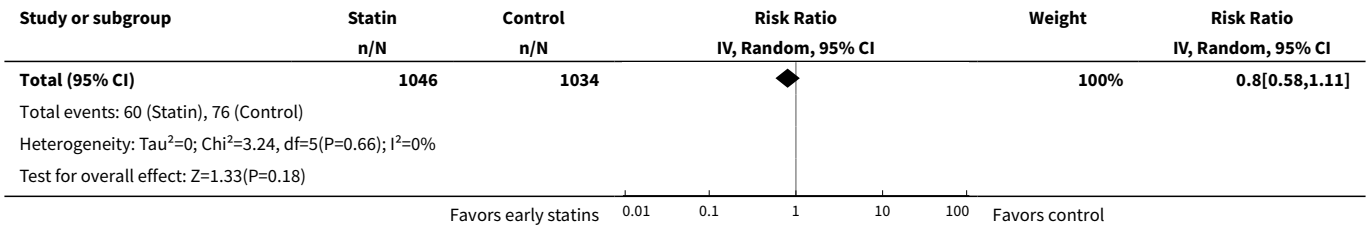
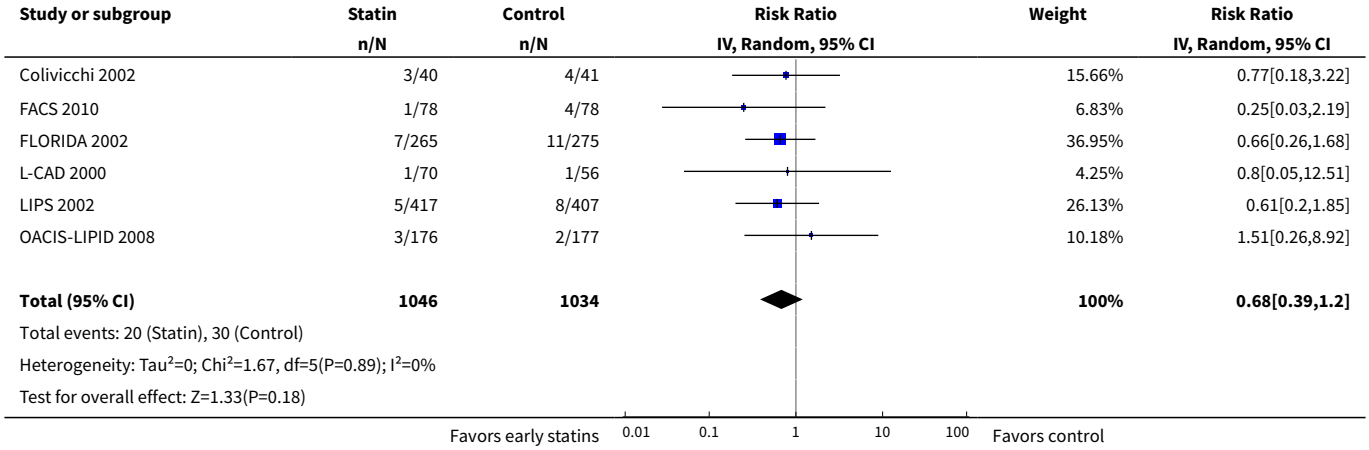
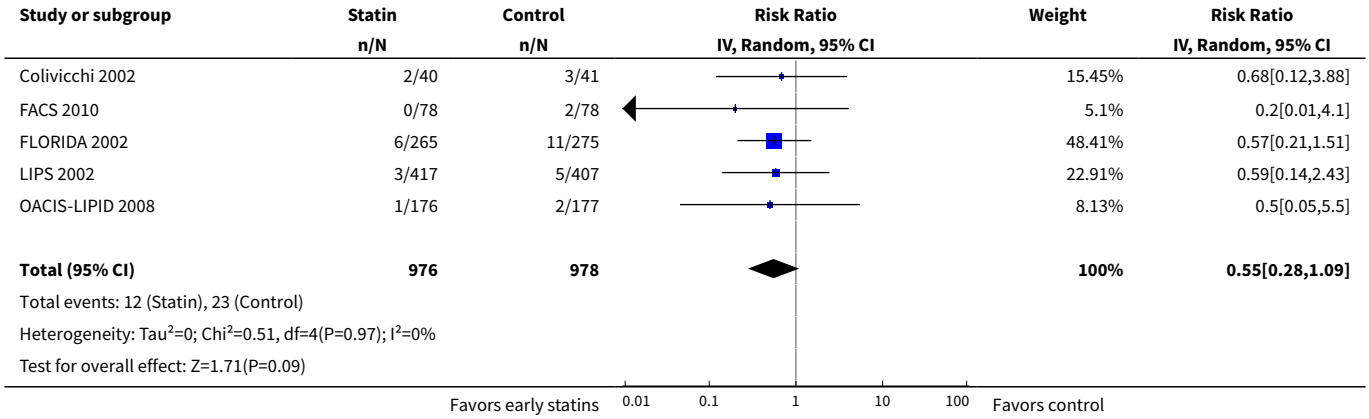


Analysis 3.2. Comparison 3 Statins versus control at 12 months, Outcome 2 Death from all causes.



Analysis 3.3. Comparison 3 Statins versus control at 12 months, Outcome 3 Death from cardiovascular causes.



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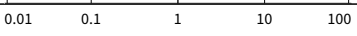
Analysis 3.4. Comparison 3 Statins versus control at 12 months, Outcome 4 Fatal and non-fatal myocardial infarction or reinfarction.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	6/40	10/41		21.35%	0.62[0.25,1.53]
FACS 2010	2/78	5/78		7.08%	0.4[0.08,2]
FLORIDA 2002	21/265	16/275		43.16%	1.36[0.73,2.55]
LIPS 2002	11/417	10/407		24.76%	1.07[0.46,2.5]
OACIS-LIPID 2008	1/176	3/177		3.64%	0.34[0.04,3.19]
Total (95% CI)	**976**	**978**		**100%**	**0.94[0.61,1.45]**
Total events: 41 (Statin), 44 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=4.14, df=4(P=0.39); I^2=3.48%					
Test for overall effect: Z=0.26(P=0.79)					



Analysis 3.5. Comparison 3 Statins versus control at 12 months, Outcome 5 Fatal and non-fatal stroke.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	1/40	2/41		20.79%	0.51[0.05,5.43]
FACS 2010	1/78	3/78		23.06%	0.33[0.04,3.14]
FLORIDA 2002	2/265	5/275		43.53%	0.42[0.08,2.12]
OACIS-LIPID 2008	0/176	2/177		12.62%	0.2[0.01,4.16]
Total (95% CI)	**559**	**571**		**100%**	**0.38[0.13,1.1]**
Total events: 4 (Statin), 12 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.26, df=3(P=0.97); I^2=0%					
Test for overall effect: Z=1.78(P=0.08)					

Analysis 3.6. Comparison 3 Statins versus control at 12 months, Outcome 6 Revascularization procedures (bypass grafts, angioplasty).

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
FACS 2010	6/78	15/78		8.45%	0.4[0.16,0.98]
FLORIDA 2002	46/265	51/275		25.81%	0.94[0.65,1.34]
L-CAD 2000	12/70	22/56		14.82%	0.44[0.24,0.8]
LIPS 2002	80/417	91/407		31.51%	0.86[0.66,1.12]
OACIS-LIPID 2008	22/176	36/177		19.4%	0.61[0.38,1]
Total (95% CI)	**1006**	**993**		**100%**	**0.7[0.52,0.93]**
Total events: 166 (Statin), 215 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=7.96, df=4(P=0.09); I^2=49.78%					
Test for overall effect: Z=2.44(P=0.01)					

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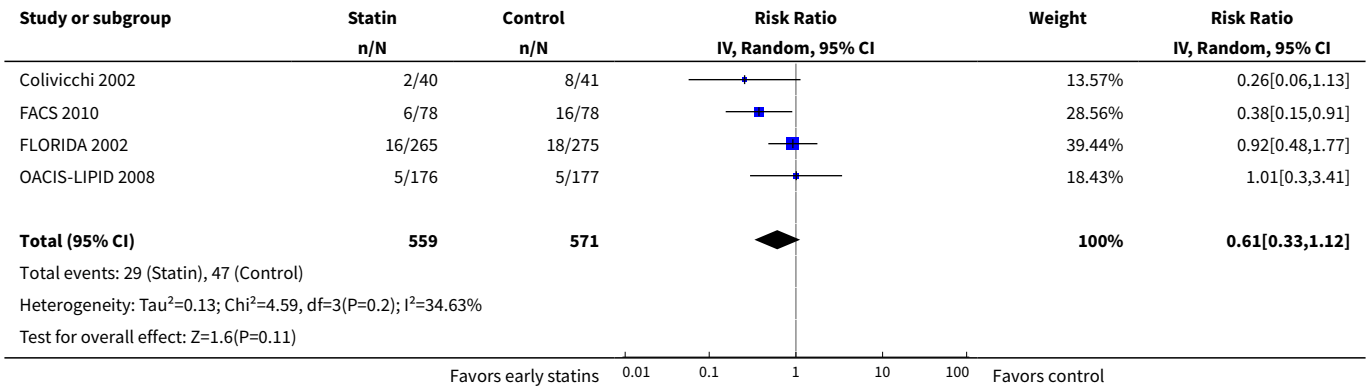
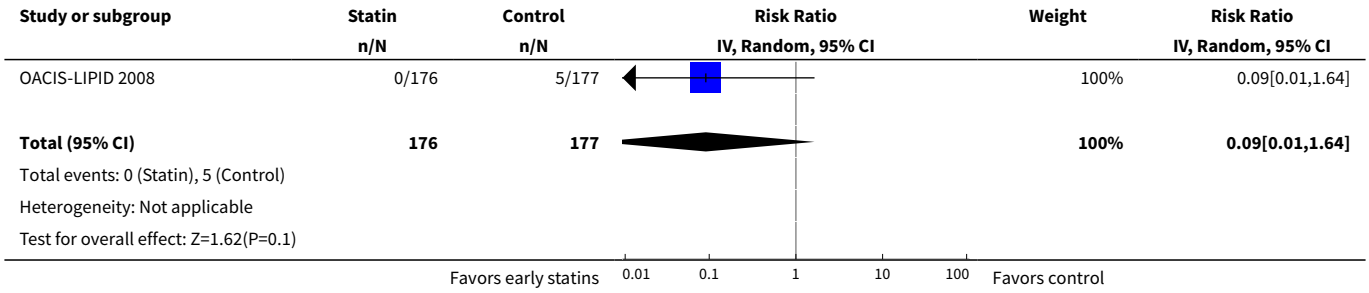
Analysis 3.7. Comparison 3 Statins versus control at 12 months, Outcome 7 Unstable angina.



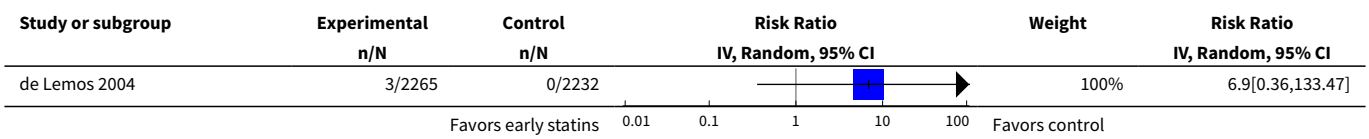
Analysis 3.8. Comparison 3 Statins versus control at 12 months, Outcome 8 Acute heart failure.



Comparison 4. Statins versus control: adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rhabdomyolysis	1	4497	Risk Ratio (IV, Random, 95% CI)	6.90 [0.36, 133.47]
2 Elevated CK > 10x upper-limit of normal	3	4677	Risk Ratio (IV, Random, 95% CI)	4.69 [1.01, 21.67]
3 Elevated ALT > 3x upper-limit of normal	5	11914	Risk Ratio (IV, Random, 95% CI)	2.49 [1.16, 5.32]

Analysis 4.1. Comparison 4 Statins versus control: adverse events, Outcome 1 Rhabdomyolysis.



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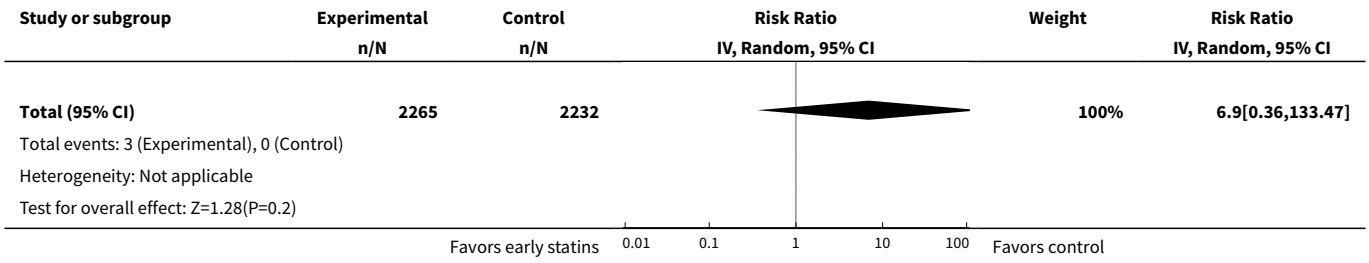
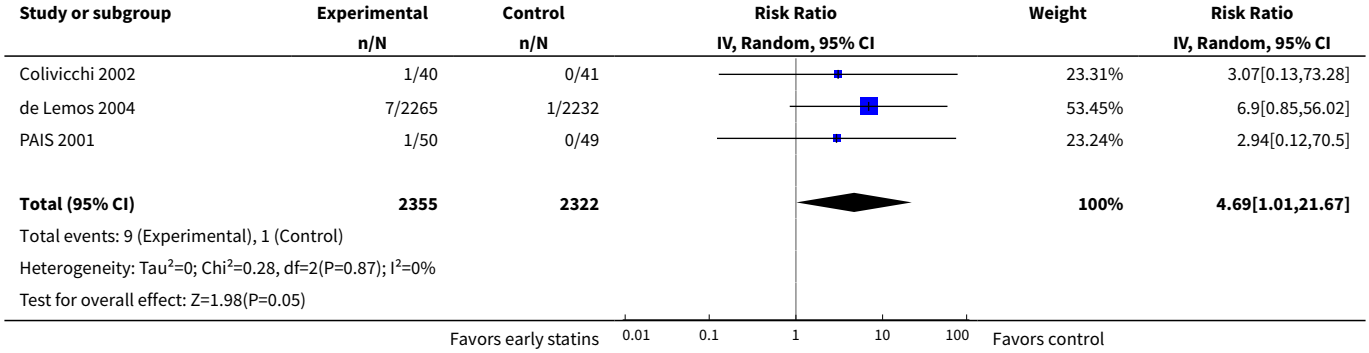
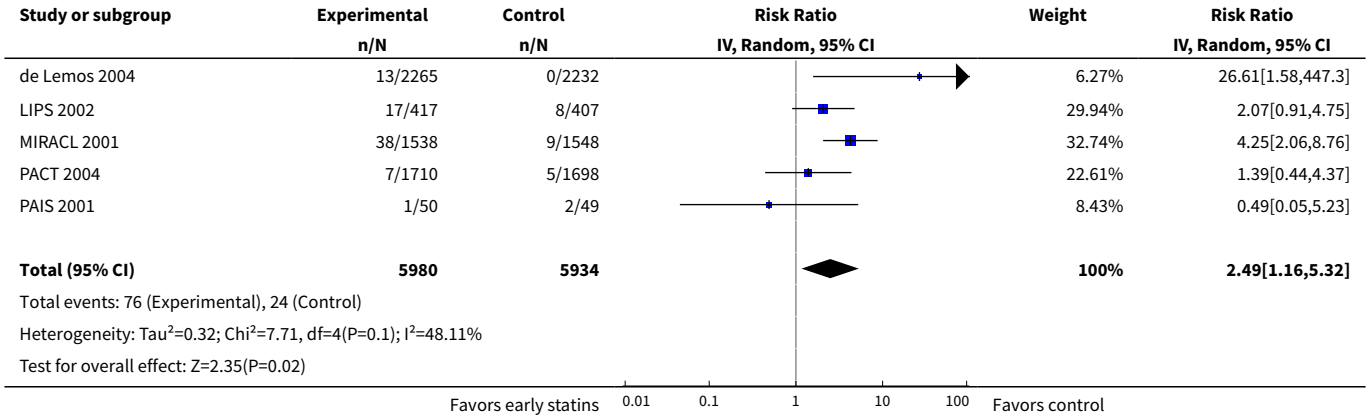


Analysis 4.2. Comparison 4 Statins versus control: adverse events, Outcome 2 Elevated CK > 10x upper-limit of normal.



Analysis 4.3. Comparison 4 Statins versus control: adverse events, Outcome 3 Elevated ALT > 3x upper-limit of normal.



Comparison 5. Statins versus control at 4 months: sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allocation concealment - combined outcome of non-fatal myocardial in-	11	9625	Risk Ratio (IV, Random, 95% CI)	0.93 [0.81, 1.06]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
farction, non-fatal stroke, and total number of deaths				
1.1 Reported allocation concealment	3	8407	Risk Ratio (IV, Random, 95% CI)	0.96 [0.79, 1.16]
1.2 No reported allocation concealment	8	1218	Risk Ratio (IV, Random, 95% CI)	0.70 [0.44, 1.14]
2 Blinded patients and caregivers - combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths	11	9625	Risk Ratio (IV, Random, 95% CI)	0.93 [0.81, 1.06]
2.1 Blinded patients and caregivers	7	9271	Risk Ratio (IV, Random, 95% CI)	0.95 [0.82, 1.09]
2.2 No blinded patients and caregivers	4	354	Risk Ratio (IV, Random, 95% CI)	0.46 [0.21, 1.00]
3 Blinded assessment - combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths	11	9625	Risk Ratio (IV, Random, 95% CI)	0.93 [0.81, 1.06]
3.1 Blinded outcome assessors	5	9028	Risk Ratio (IV, Random, 95% CI)	0.94 [0.82, 1.08]
3.2 No blinded outcome assessors	6	597	Risk Ratio (IV, Random, 95% CI)	0.60 [0.30, 1.22]
4 Allocation concealment - death from all causes	12	9733	Risk Ratio (IV, Random, 95% CI)	0.90 [0.70, 1.14]
4.1 Reported allocation concealment	3	8407	Risk Ratio (IV, Random, 95% CI)	0.94 [0.72, 1.21]
4.2 No reported allocation concealment	9	1326	Risk Ratio (IV, Random, 95% CI)	0.64 [0.31, 1.31]
5 Blinded patients and caregivers - death from all causes	12	9733	Risk Ratio (IV, Random, 95% CI)	0.90 [0.70, 1.14]
5.1 Blinded patients and caregivers	7	9271	Risk Ratio (IV, Random, 95% CI)	0.93 [0.72, 1.19]
5.2 No blinded patients and caregivers	5	462	Risk Ratio (IV, Random, 95% CI)	0.55 [0.21, 1.44]
6 Blinded assessment - death from all causes	12	9733	Risk Ratio (IV, Random, 95% CI)	0.90 [0.70, 1.14]
6.1 Blinded outcome assessors	5	9028	Risk Ratio (IV, Random, 95% CI)	0.91 [0.71, 1.17]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 No blinded outcome assessors	7	705	Risk Ratio (IV, Random, 95% CI)	0.77 [0.31, 1.90]
7 Allocation concealment - unstable angina	9	8770	Risk Ratio (IV, Random, 95% CI)	0.76 [0.59, 0.96]
7.1 Reported allocation concealment	2	7583	Risk Ratio (IV, Random, 95% CI)	0.79 [0.64, 0.97]
7.2 No reported allocation concealment	7	1187	Risk Ratio (IV, Random, 95% CI)	0.68 [0.44, 1.04]
8 Blinded patients and caregivers - unstable angina	9	8770	Risk Ratio (IV, Random, 95% CI)	0.76 [0.59, 0.96]
8.1 Blinded patients and caregivers	5	8378	Risk Ratio (IV, Random, 95% CI)	0.85 [0.64, 1.14]
8.2 No blinded patients and caregivers	4	392	Risk Ratio (IV, Random, 95% CI)	0.51 [0.34, 0.79]
9 Blinded assessment - unstable angina	9	8770	Risk Ratio (IV, Random, 95% CI)	0.76 [0.59, 0.96]
9.1 Blinded outcome assessors	4	8204	Risk Ratio (IV, Random, 95% CI)	0.81 [0.66, 0.99]
9.2 No blinded outcome assessors	5	566	Risk Ratio (IV, Random, 95% CI)	0.59 [0.35, 1.00]
10 Death from all causes including PRINCESS	13	13338	Risk Ratio (IV, Random, 95% CI)	0.95 [0.78, 1.17]
11 Fatal and non-fatal myocardial infarction or reinfarction including PRINCESS	11	13142	Risk Ratio (IV, Random, 95% CI)	0.90 [0.78, 1.03]
12 Fatal and non-fatal stroke including PRINCESS	8	12141	Risk Ratio (IV, Random, 95% CI)	0.79 [0.52, 1.18]
13 Unstable angina including PRINCESS	10	12375	Risk Ratio (IV, Random, 95% CI)	0.78 [0.65, 0.95]
14 Initiation of statins	11	9625	Risk Ratio (IV, Random, 95% CI)	0.93 [0.81, 1.06]
14.1 Statin initiated within 3 days	6	1295	Risk Ratio (IV, Random, 95% CI)	0.82 [0.41, 1.64]
14.2 Initiation of statins up to 14 days	5	8330	Risk Ratio (IV, Random, 95% CI)	0.93 [0.81, 1.07]
15 Types of statins	11	9625	Risk Ratio (IV, Random, 95% CI)	0.93 [0.81, 1.06]

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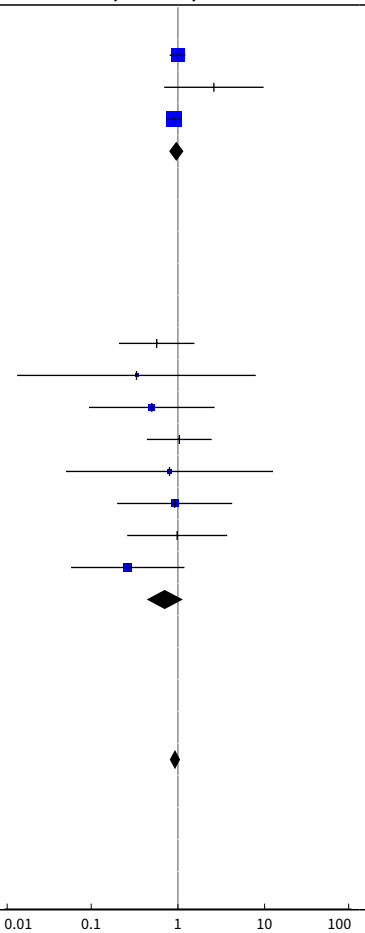
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Pravastatin	4	371	Risk Ratio (IV, Random, 95% CI)	0.65 [0.29, 1.45]
15.2 Fluvastatin	3	1520	Risk Ratio (IV, Random, 95% CI)	1.17 [0.54, 2.53]
15.3 Atorvastatin	3	3237	Risk Ratio (IV, Random, 95% CI)	0.87 [0.72, 1.06]
15.4 Simvastatin	1	4497	Risk Ratio (IV, Random, 95% CI)	0.99 [0.80, 1.22]

Analysis 5.1. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 1 Allocation concealment - combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
5.1.1 Reported allocation concealment					
de Lemos 2004	161/2265	160/2232		42.76%	0.99[0.8,1.22]
LIPS 2002	8/417	3/407		1.09%	2.6[0.7,9.74]
MIRACL 2001	162/1538	183/1548		47.84%	0.89[0.73,1.09]
Subtotal (95% CI)	**4220**	**4187**		**91.69%**	**0.96[0.79,1.16]**
Total events: 331 (Statin), 346 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=2.8, df=2(P=0.25); I^2=28.46%					
Test for overall effect: Z=0.44(P=0.66)					
5.1.2 No reported allocation concealment					
Colivicchi 2002	5/40	9/41		1.89%	0.57[0.21,1.55]
ESTABLISH 2004	0/35	1/35		0.19%	0.33[0.01,7.91]
FACS 2010	2/78	4/78		0.68%	0.5[0.09,2.65]
FLORIDA 2002	10/265	10/275		2.57%	1.04[0.44,2.45]
L-CAD 2000	1/70	1/56		0.25%	0.8[0.05,12.51]
LAMIL 1997	3/36	3/33		0.81%	0.92[0.2,4.23]
PAIS 2001	4/50	4/49		1.08%	0.98[0.26,3.7]
PTT 2002	2/40	7/37		0.84%	0.26[0.06,1.19]
Subtotal (95% CI)	**614**	**604**		**8.31%**	**0.7[0.44,1.14]**
Total events: 27 (Statin), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.31, df=7(P=0.85); I^2=0%					
Test for overall effect: Z=1.44(P=0.15)					
Total (95% CI)	**4834**	**4791**		**100%**	**0.93[0.81,1.06]**
Total events: 358 (Statin), 385 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.48, df=10(P=0.68); I^2=0%					
Test for overall effect: Z=1.1(P=0.27)					
Test for subgroup differences: Chi^2=1.37, df=1 (P=0.24), I^2=27.22%					



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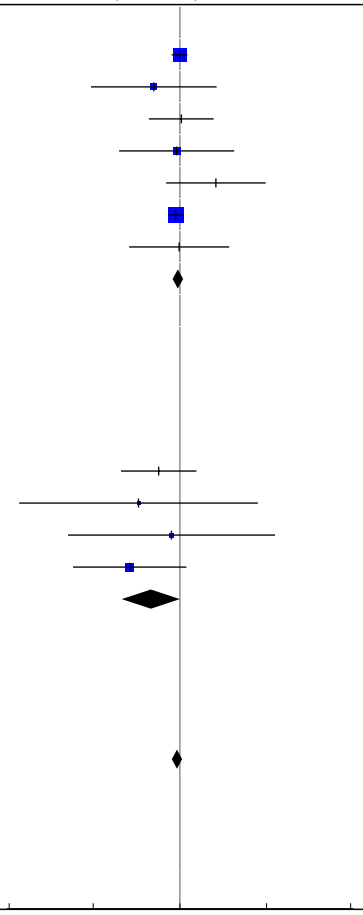
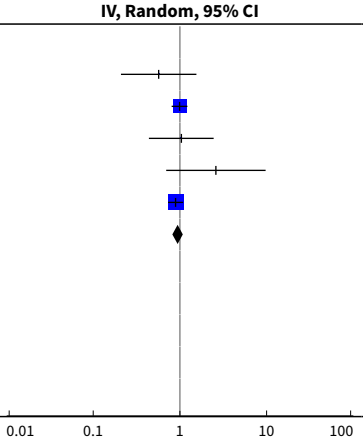
Analysis 5.2. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 2 Blinded patients and caregivers - combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
5.2.1 Blinded patients and caregivers					
de Lemos 2004	161/2265	160/2232		42.76%	0.99[0.8,1.22]
FACS 2010	2/78	4/78		0.68%	0.5[0.09,2.65]
FLORIDA 2002	10/265	10/275		2.57%	1.04[0.44,2.45]
LAMIL 1997	3/36	3/33		0.81%	0.92[0.2,4.23]
LIPS 2002	8/417	3/407		1.09%	2.6[0.7,9.74]
MIRACL 2001	162/1538	183/1548		47.84%	0.89[0.73,1.09]
PAIS 2001	4/50	4/49		1.08%	0.98[0.26,3.7]
Subtotal (95% CI)	**4649**	**4622**		**96.83%**	**0.95[0.82,1.09]**
Total events: 350 (Statin), 367 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.41, df=6(P=0.76); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					
5.2.2 No blinded patients and caregivers					
Colivicchi 2002	5/40	9/41		1.89%	0.57[0.21,1.55]
ESTABLISH 2004	0/35	1/35		0.19%	0.33[0.01,7.91]
L-CAD 2000	1/70	1/56		0.25%	0.8[0.05,12.51]
PTT 2002	2/40	7/37		0.84%	0.26[0.06,1.19]
Subtotal (95% CI)	**185**	**169**		**3.17%**	**0.46[0.21,1]**
Total events: 8 (Statin), 18 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=3(P=0.83); I^2=0%					
Test for overall effect: Z=1.95(P=0.05)					
Total (95% CI)	**4834**	**4791**		**100%**	**0.93[0.81,1.06]**
Total events: 358 (Statin), 385 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.48, df=10(P=0.68); I^2=0%					
Test for overall effect: Z=1.1(P=0.27)					
Test for subgroup differences: Chi^2=3.18, df=1 (P=0.07), I^2=68.56%					



Analysis 5.3. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 3 Blinded assessment - combined outcome of non-fatal myocardial infarction, non-fatal stroke, and total number of deaths.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
5.3.1 Blinded outcome assessors					
Colivicchi 2002	5/40	9/41		1.89%	0.57[0.21,1.55]
de Lemos 2004	161/2265	160/2232		42.76%	0.99[0.8,1.22]
FLORIDA 2002	10/265	10/275		2.57%	1.04[0.44,2.45]
LIPS 2002	8/417	3/407		1.09%	2.6[0.7,9.74]
MIRACL 2001	162/1538	183/1548		47.84%	0.89[0.73,1.09]
Subtotal (95% CI)	**4525**	**4503**		**96.15%**	**0.94[0.82,1.08]**
Total events: 346 (Statin), 365 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.82, df=4(P=0.43); I^2=0%					
Test for overall effect: Z=0.84(P=0.4)					
5.3.2 No blinded outcome assessors					



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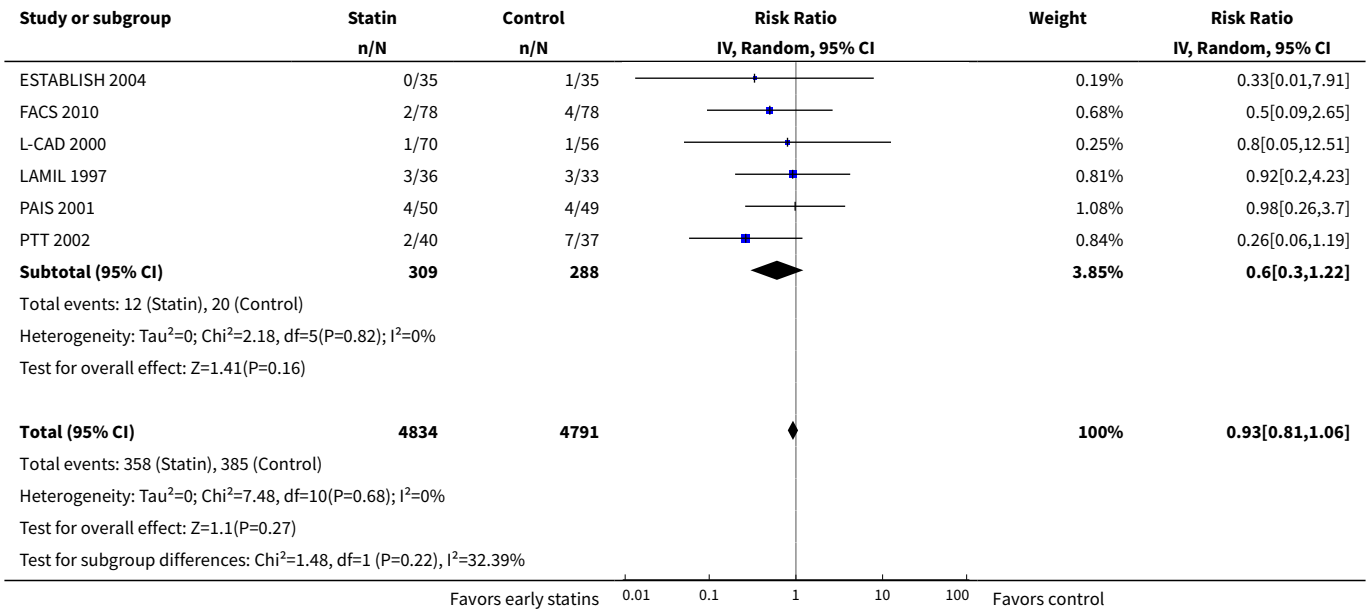
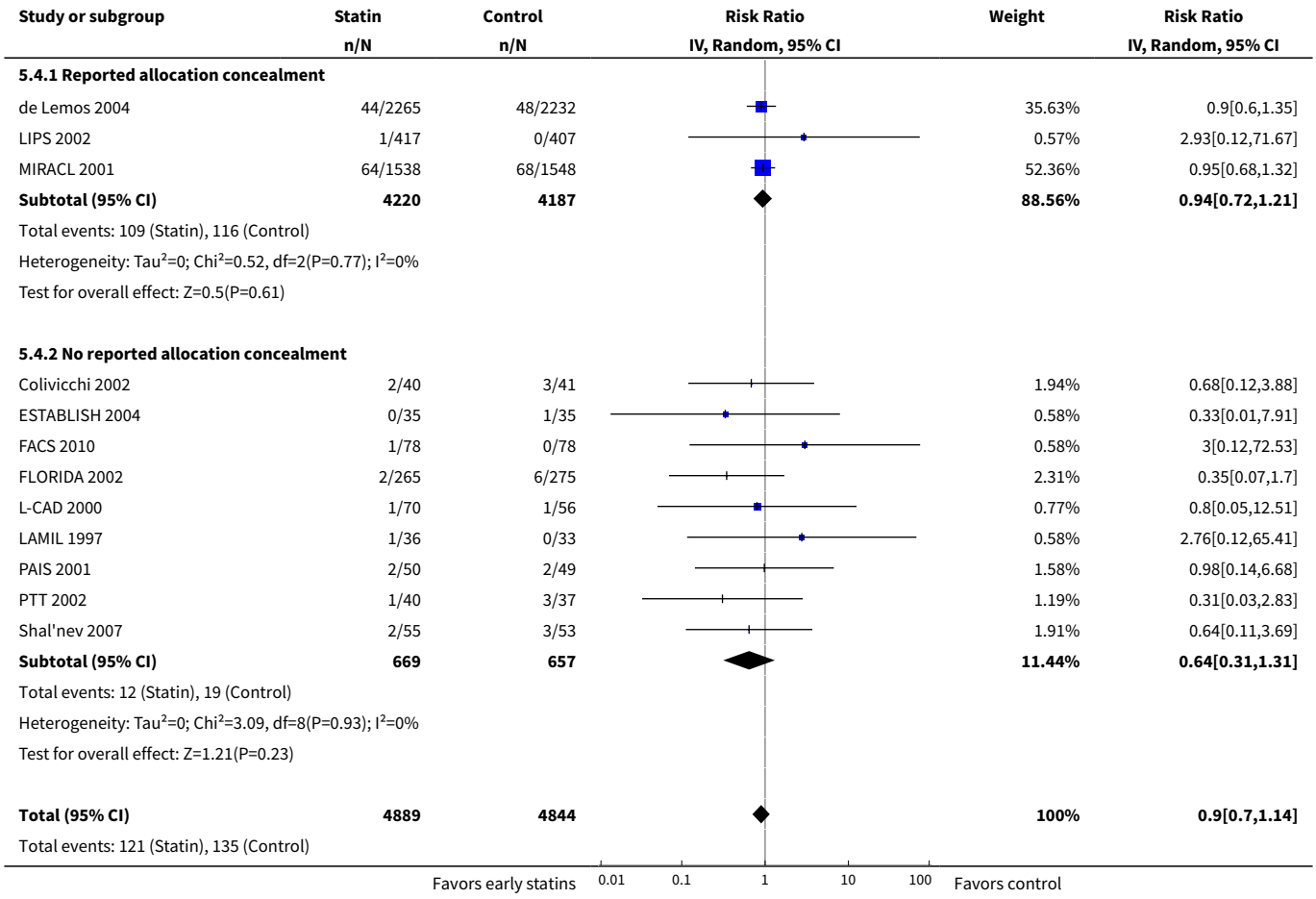


Analysis 5.4. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 4 Allocation concealment - death from all causes.



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Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=4.56, df=11(P=0.95); I²=0%					
Test for overall effect: Z=0.88(P=0.38)					
Test for subgroup differences: Chi²=0.94, df=1 (P=0.33), I²=0%					

Analysis 5.5. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 5 Blinded patients and caregivers - death from all causes.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
5.5.1 Blinded patients and caregivers					
de Lemos 2004	44/2265	48/2232		35.63%	0.9[0.6,1.35]
FACS 2010	1/78	0/78		0.58%	3[0.12,72.53]
FLORIDA 2002	2/265	6/275		2.31%	0.35[0.07,1.7]
LAMIL 1997	1/36	0/33		0.58%	2.76[0.12,65.41]
LIPS 2002	1/417	0/407		0.57%	2.93[0.12,71.67]
MIRACL 2001	64/1538	68/1548		52.36%	0.95[0.68,1.32]
PAIS 2001	2/50	2/49		1.58%	0.98[0.14,6.68]
Subtotal (95% CI)	**4649**	**4622**		**93.61%**	**0.93[0.72,1.19]**
Total events: 115 (Statin), 124 (Control)					
Heterogeneity: Tau²=0; Chi²=2.98, df=6(P=0.81); I²=0%					
Test for overall effect: Z=0.6(P=0.55)					
5.5.2 No blinded patients and caregivers					
Colivicchi 2002	2/40	3/41		1.94%	0.68[0.12,3.88]
ESTABLISH 2004	0/35	1/35		0.58%	0.33[0.01,7.91]
L-CAD 2000	1/70	1/56		0.77%	0.8[0.05,12.51]
PTT 2002	1/40	3/37		1.19%	0.31[0.03,2.83]
Shal'nev 2007	2/55	3/53		1.91%	0.64[0.11,3.69]
Subtotal (95% CI)	**240**	**222**		**6.39%**	**0.55[0.21,1.44]**
Total events: 6 (Statin), 11 (Control)					
Heterogeneity: Tau²=0; Chi²=0.52, df=4(P=0.97); I²=0%					
Test for overall effect: Z=1.22(P=0.22)					
Total (95% CI)	**4889**	**4844**		**100%**	**0.9[0.7,1.14]**
Total events: 121 (Statin), 135 (Control)					
Heterogeneity: Tau²=0; Chi²=4.56, df=11(P=0.95); I²=0%					
Test for overall effect: Z=0.88(P=0.38)					
Test for subgroup differences: Chi²=1.05, df=1 (P=0.3), I²=5.09%					

Analysis 5.6. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 6 Blinded assessment - death from all causes.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
5.6.1 Blinded outcome assessors					

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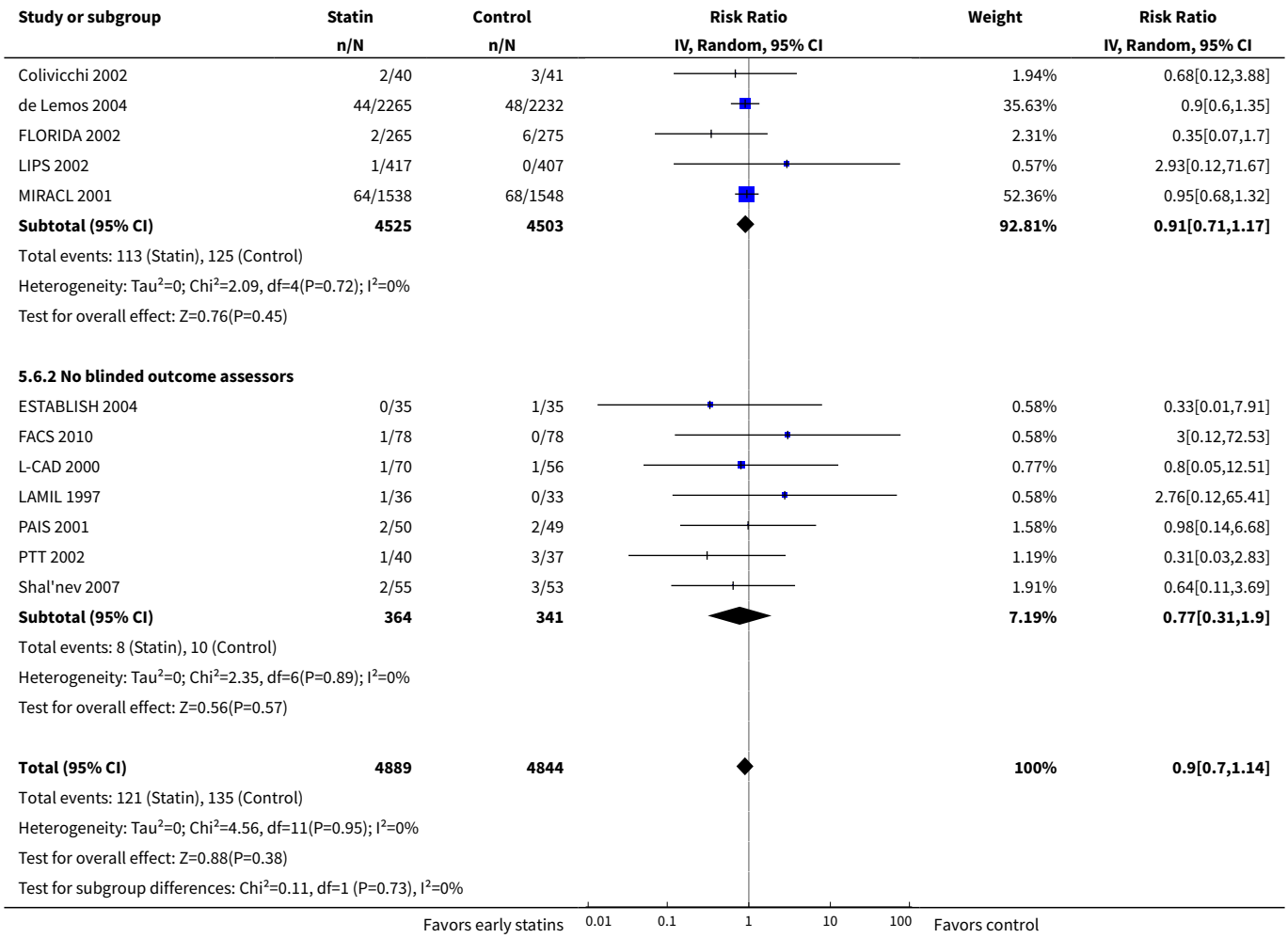
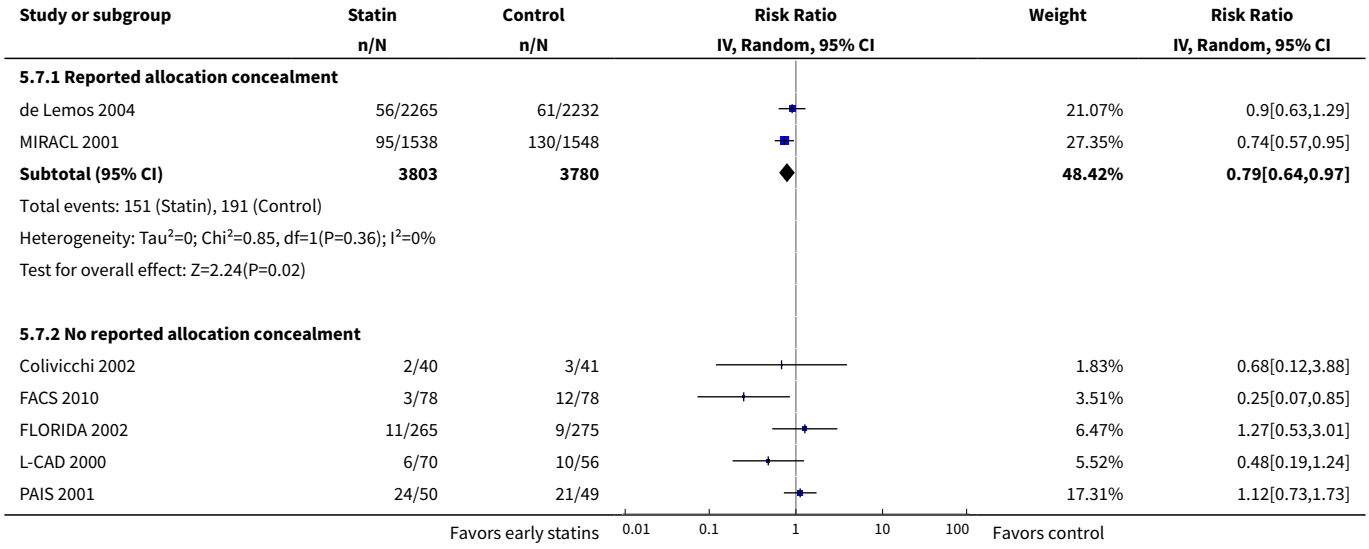


Analysis 5.7. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 7 Allocation concealment - unstable angina.



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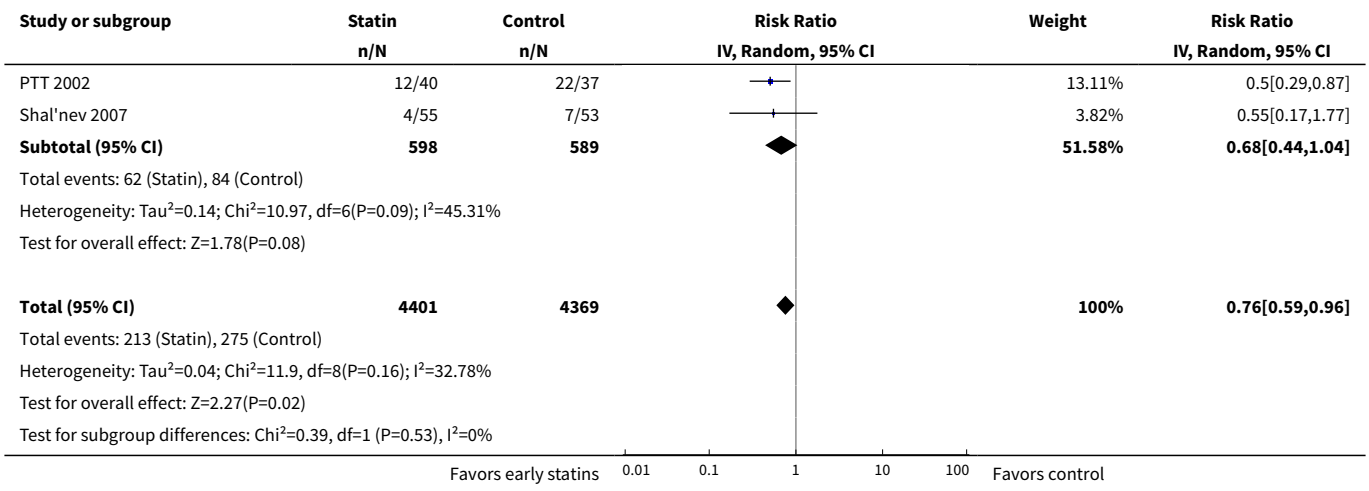
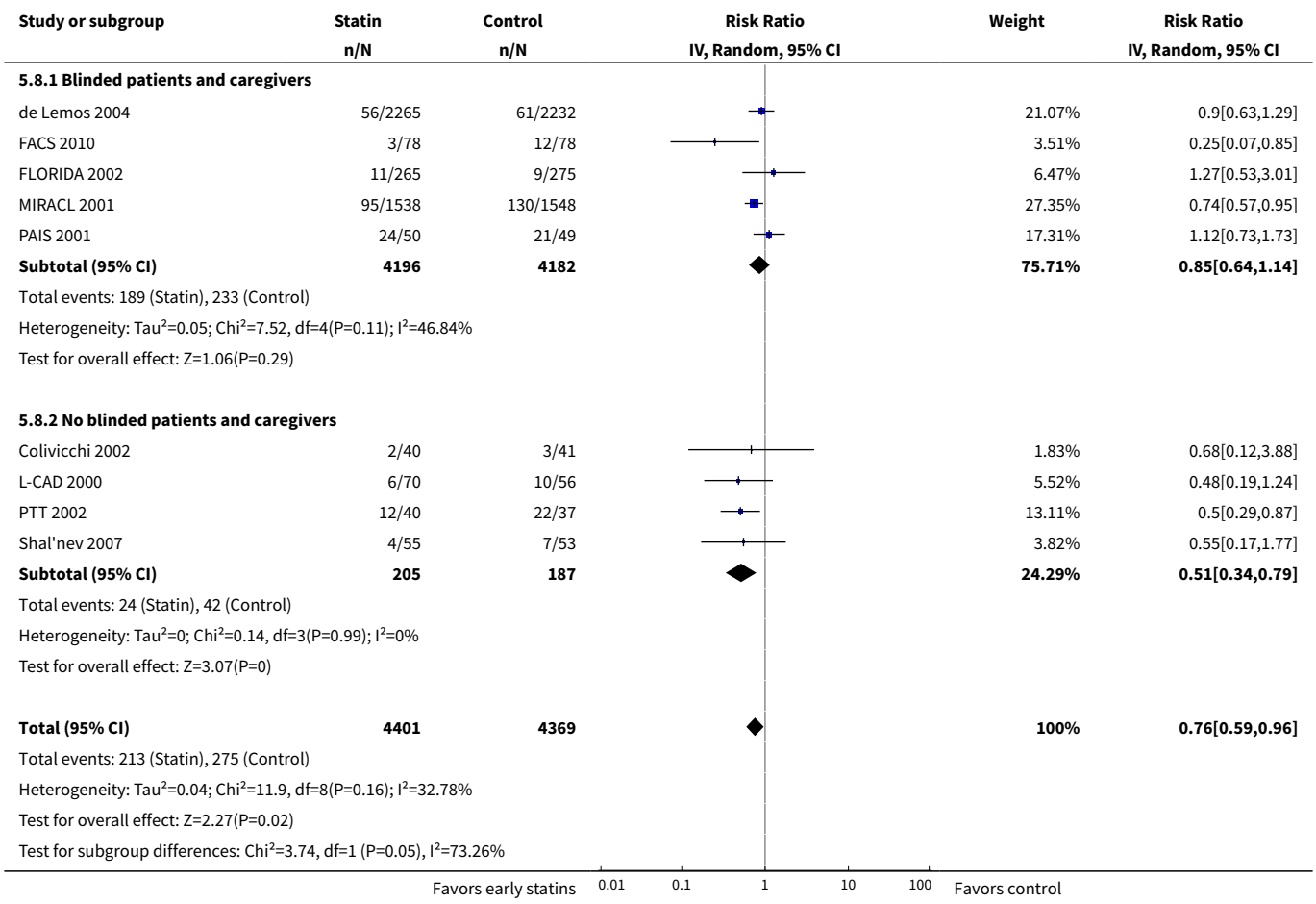


Analysis 5.8. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 8 Blinded patients and caregivers - unstable angina.



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Analysis 5.9. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 9 Blinded assessment - unstable angina.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
5.9.1 Blinded outcome assessors					
Colivicchi 2002	2/40	3/41		1.83%	0.68[0.12,3.88]
de Lemos 2004	56/2265	61/2232		21.07%	0.9[0.63,1.29]
FLORIDA 2002	11/265	9/275		6.47%	1.27[0.53,3.01]
MIRACL 2001	95/1538	130/1548		27.35%	0.74[0.57,0.95]
Subtotal (95% CI)	**4108**	**4096**		**56.72%**	**0.81[0.66,0.99]**
Total events: 164 (Statin), 203 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.99, df=3(P=0.58); I^2=0%					
Test for overall effect: Z=2.09(P=0.04)					
5.9.2 No blinded outcome assessors					
FACS 2010	3/78	12/78		3.51%	0.25[0.07,0.85]
L-CAD 2000	6/70	10/56		5.52%	0.48[0.19,1.24]
PAIS 2001	24/50	21/49		17.31%	1.12[0.73,1.73]
PTT 2002	12/40	22/37		13.11%	0.5[0.29,0.87]
Shal'nev 2007	4/55	7/53		3.82%	0.55[0.17,1.77]
Subtotal (95% CI)	**293**	**273**		**43.28%**	**0.59[0.35,1]**
Total events: 49 (Statin), 72 (Control)					
Heterogeneity: Tau^2=0.19; Chi^2=9.39, df=4(P=0.05); I^2=57.41%					
Test for overall effect: Z=1.97(P=0.05)					
Total (95% CI)	**4401**	**4369**		**100%**	**0.76[0.59,0.96]**
Total events: 213 (Statin), 275 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=11.9, df=8(P=0.16); I^2=32.78%					
Test for overall effect: Z=2.27(P=0.02)					
Test for subgroup differences: Chi^2=1.19, df=1 (P=0.28), I^2=15.82%					

Analysis 5.10. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 10 Death from all causes including PRINCESS.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	2/40	3/41		1.39%	0.68[0.12,3.88]
de Lemos 2004	44/2265	48/2232		25.56%	0.9[0.6,1.35]
ESTABLISH 2004	0/35	1/35		0.42%	0.33[0.01,7.91]
FACS 2010	1/78	0/78		0.41%	3[0.12,72.53]
FLORIDA 2002	2/265	6/275		1.65%	0.35[0.07,1.7]
L-CAD 2000	1/70	1/56		0.55%	0.8[0.05,12.51]
LAMIL 1997	1/36	0/33		0.42%	2.76[0.12,65.41]
LIPS 2002	1/417	0/407		0.41%	2.93[0.12,71.67]
MIRACL 2001	64/1538	68/1548		37.56%	0.95[0.68,1.32]
PAIS 2001	2/50	2/49		1.14%	0.98[0.14,6.68]
PRINCESS 2004	53/1795	48/1810		28.26%	1.11[0.76,1.64]
PTT 2002	1/40	3/37		0.85%	0.31[0.03,2.83]
Shal'nev 2007	2/55	3/53		1.37%	0.64[0.11,3.69]

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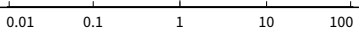
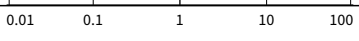
Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Total (95% CI)	**6684**	**6654**		**100%**	**0.95[0.78,1.17]**
Total events: 174 (Statin), 183 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.43, df=12(P=0.94); I^2=0%					
Test for overall effect: Z=0.46(P=0.65)					



Analysis 5.11. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 11 Fatal and non-fatal myocardial infarction or reinfarction including PRINCESS.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	3/40	7/41		1.27%	0.44[0.12,1.58]
de Lemos 2004	130/2265	140/2232		38.87%	0.92[0.73,1.15]
FACS 2010	1/78	3/78		0.41%	0.33[0.04,3.14]
FLORIDA 2002	8/265	6/275		1.91%	1.38[0.49,3.93]
LAMIL 1997	3/36	3/33		0.89%	0.92[0.2,4.23]
LIPS 2002	7/417	3/407		1.15%	2.28[0.59,8.75]
MIRACL 2001	118/1538	131/1548		36.6%	0.91[0.71,1.15]
PAIS 2001	4/50	2/49		0.76%	1.96[0.38,10.22]
PRINCESS 2004	53/1795	63/1810		16.12%	0.85[0.59,1.22]
PTT 2002	1/40	6/37		0.49%	0.15[0.02,1.22]
Shal'nev 2007	4/55	7/53		1.52%	0.55[0.17,1.77]
Total (95% CI)	**6579**	**6563**		**100%**	**0.9[0.78,1.03]**
Total events: 332 (Statin), 371 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.89, df=10(P=0.54); I^2=0%					
Test for overall effect: Z=1.5(P=0.13)					



Analysis 5.12. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 12 Fatal and non-fatal stroke including PRINCESS.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	1/40	1/41		2.22%	1.02[0.07,15.83]
de Lemos 2004	16/2265	12/2232		29.87%	1.31[0.62,2.77]
FACS 2010	0/78	1/78		1.64%	0.33[0.01,8.06]
FLORIDA 2002	0/265	1/275		1.63%	0.35[0.01,8.45]
MIRACL 2001	12/1538	24/1548		35%	0.5[0.25,1]
PAIS 2001	0/50	2/49		1.83%	0.2[0.01,3.98]
PRINCESS 2004	12/1795	12/1810		26.15%	1.01[0.45,2.24]
PTT 2002	0/40	1/37		1.66%	0.31[0.01,7.36]
Total (95% CI)	**6071**	**6070**		**100%**	**0.79[0.52,1.18]**
Total events: 41 (Statin), 54 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.52, df=7(P=0.6); I^2=0%					
Test for overall effect: Z=1.16(P=0.25)					

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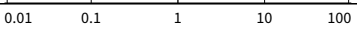
Analysis 5.13. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 13 Unstable angina including PRINCESS.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Colivicchi 2002	2/40	3/41		1.14%	0.68[0.12,3.88]
de Lemos 2004	56/2265	61/2232		16.76%	0.9[0.63,1.29]
FACS 2010	3/78	12/78		2.22%	0.25[0.07,0.85]
FLORIDA 2002	11/265	9/275		4.24%	1.27[0.53,3.01]
L-CAD 2000	6/70	10/56		3.58%	0.48[0.19,1.24]
MIRACL 2001	95/1538	130/1548		23.98%	0.74[0.57,0.95]
PAIS 2001	24/50	21/49		13.05%	1.12[0.73,1.73]
PRINCESS 2004	96/1795	114/1810		23.27%	0.85[0.65,1.11]
PTT 2002	12/40	22/37		9.34%	0.5[0.29,0.87]
Shal'nev 2007	4/55	7/53		2.43%	0.55[0.17,1.77]
Total (95% CI)	**6196**	**6179**		**100%**	**0.78[0.65,0.95]**
Total events: 309 (Statin), 389 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=12.23, df=9(P=0.2); I^2=26.42%					
Test for overall effect: Z=2.54(P=0.01)					



Favors early statins — Favors control

Analysis 5.14. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 14 Initiation of statins.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
5.14.1 Statin initiated within 3 days					
ESTABLISH 2004	0/35	1/35		0.19%	0.33[0.01,7.91]
FACS 2010	2/78	4/78		0.68%	0.5[0.09,2.65]
LAMIL 1997	3/36	3/33		0.81%	0.92[0.2,4.23]
LIPS 2002	8/417	3/407		1.09%	2.6[0.7,9.74]
PAIS 2001	4/50	4/49		1.08%	0.98[0.26,3.7]
PTT 2002	2/40	7/37		0.84%	0.26[0.06,1.19]
Subtotal (95% CI)	**656**	**639**		**4.69%**	**0.82[0.41,1.64]**
Total events: 19 (Statin), 22 (Control)					
Heterogeneity: Tau^2=0.11; Chi^2=5.85, df=5(P=0.32); I^2=14.47%					
Test for overall effect: Z=0.57(P=0.57)					
5.14.2 Initiation of statins up to 14 days					
Colivicchi 2002	5/40	9/41		1.89%	0.57[0.21,1.55]
de Lemos 2004	161/2265	160/2232		42.76%	0.99[0.8,1.22]
FLORIDA 2002	10/265	10/275		2.57%	1.04[0.44,2.45]
L-CAD 2000	1/70	1/56		0.25%	0.8[0.05,12.51]
MIRACL 2001	162/1538	183/1548		47.84%	0.89[0.73,1.09]
Subtotal (95% CI)	**4178**	**4152**		**95.31%**	**0.93[0.81,1.07]**
Total events: 339 (Statin), 363 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.53, df=4(P=0.82); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					

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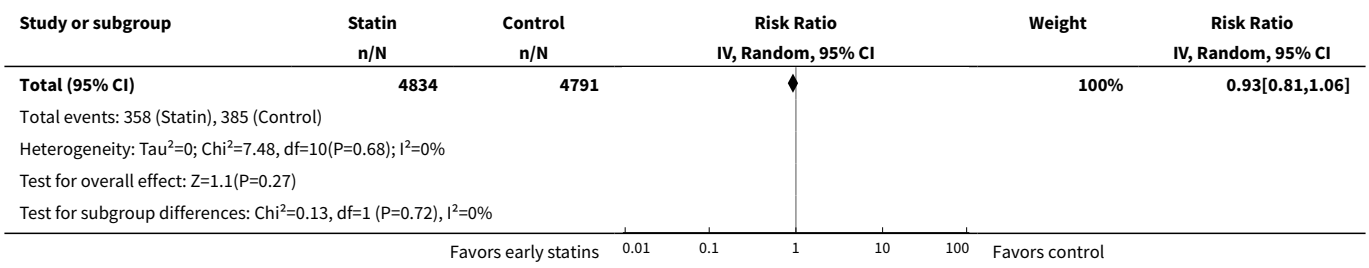
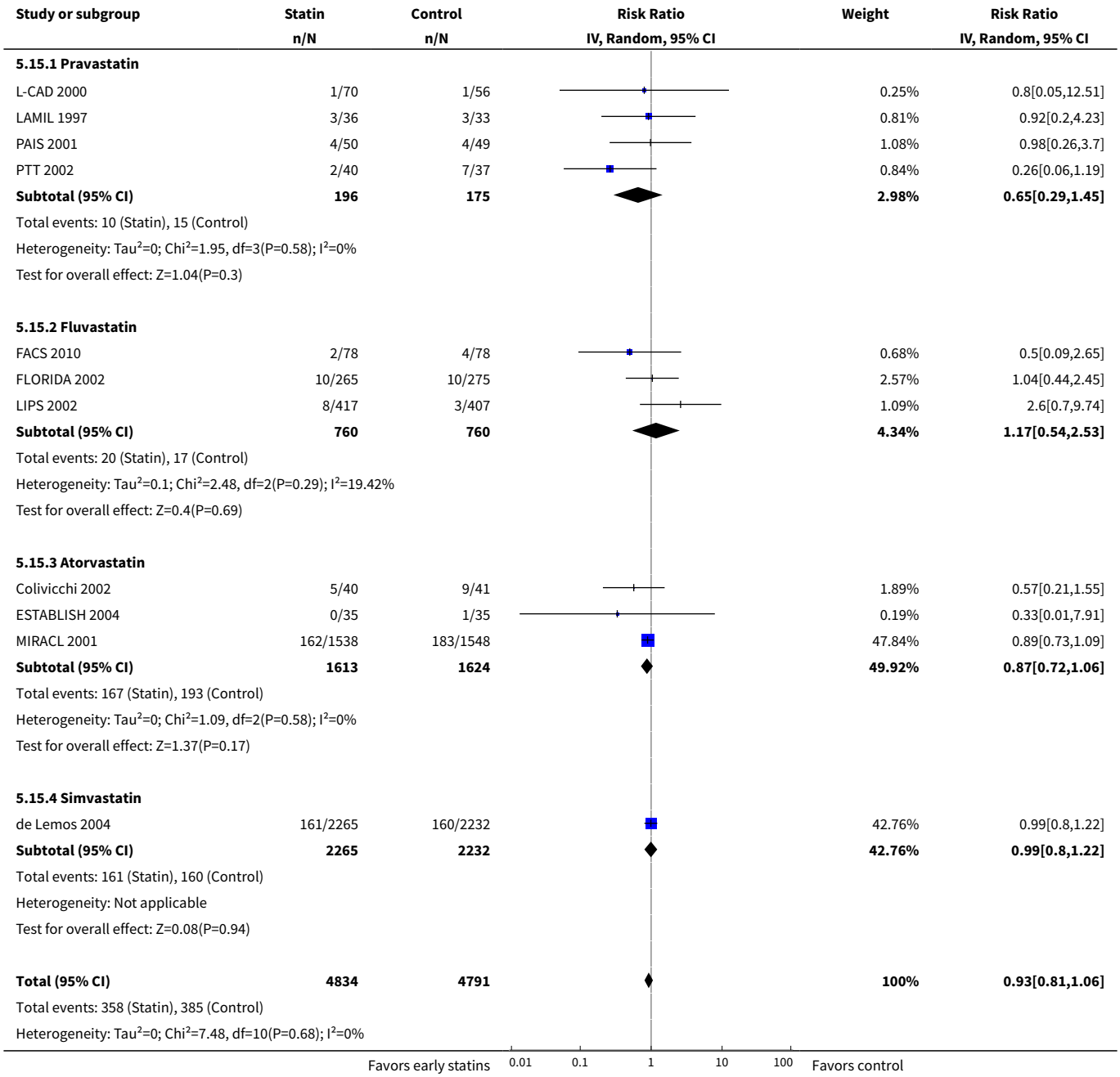


Analysis 5.15. Comparison 5 Statins versus control at 4 months: sensitivity analyses, Outcome 15 Types of statins.



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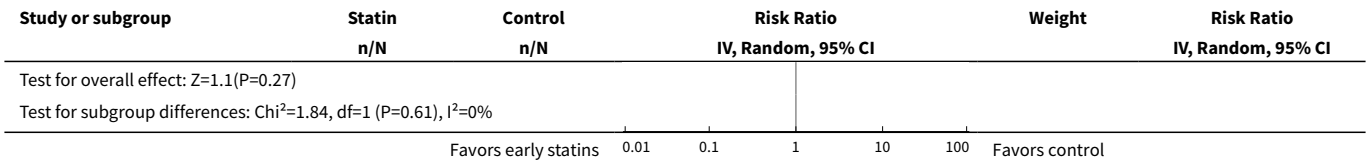

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ADDITIONAL TABLES

Table 1. Baseline characteristics of included patients

Trial (reference)	Randomized individuals, n		Mean age, years (SD)		Men, n (%)		Diabetes, n (%)		Hypertension, n (%)		Current smoker, n (%)		Prior MI, n (%)		MI as index event, n (%)		Fibrinolysis for index event, n (%)		PCI for index event, n (%)	
	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
LAMIL 1997	36	33	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	36 (100)	33 (100)	NA	NA	NA	NA
RECIFE 1999	30	30	55 (2)	56 (2)	26 (93)	22 (81)	1 (4)	0 (0)	5 (18)	8 (29)	14 (50)	17 (63)	1 (4)	2 (7)	11 (39)	12 (44)	0 (0)	0 (0)	16 (57)	17 (63)
L-CAD 2000	70	56	55 (10)	59 (11)	57 (81)	44 (79)	0 (0)	0 (0)	22 (31)	18 (32)	49 (70)	36 (64)	45 (64)	39 (70)	32 (46)	23 (41)	NA	NA	58 (83)	50 (89)
PAIS 2001	50	49	64 (1)	63 (2)	35 (70)	37 (76)	8 (16)	5 (10)	12 (24)	16 (33)	17 (34)	17 (35)	14 (28)	12 (25)	35 (70)	31 (63)	17 (34)	14 (29)	0 (0)	0 (0)
PTT 2002	79	85	53 (11)	52 (10)	65 (82)	69 (81)	14 (18)	13 (15)	16 (20)	21 (25)	63 (80)	66 (78)	0 (0)	0 (0)	79 (100)	85 (100)	79 (100)	85 (100)	0 (0)	0 (0)
PACT 2004	1710	1698	62 (12)	61 (12)	1308 (76)	1285 (76)	244 (14)	234 (14)	700 (41)	714 (42)	608 (36)	575 (34)	236 (14)	197 (12)	1109 (65)	1111 (65)	651 (38)	671 (40)	414 (24)	406 (24)
LIPS 2002	417*	407*	61 (10)	60 (10)	344 (83)	336 (83)	65 (16)	34 (8)	NA	NA	NA	NA	184 (44)	172 (42)	0 (0)	0 (0)	0 (0)	0 (0)	417 (100)	407 (100)
FLORIDA 2002	265	275	61 (12)	60 (11)	214 (81)	234 (85)	29 (11)	31 (11)	67 (25)	65 (24)	140 (53)	139 (51)	31 (12)	31 (11)	265 (100)	275 (100)	137 (52)	133 (48)	8 (3)	10 (4)
MIRACL 2001	1538	1548	65 (12)	65 (12)	992 (64)	1020 (66)	342 (22)	373 (24)	843 (55)	846 (55)	429 (28)	430 (28)	382 (25)	392 (25)	812 (53)	843 (55)	109 (7)	137 (9)	0 (0)	0 (0)
Colivicchi 2002	40	41	69 (14)	68 (14)	23 (58)	24 (59)	22 (55)	24 (59)	35 (88)	37 (90)	NA	NA	34 (85)	35 (85)	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)
ESTABLISH 2004	35	35	61 (10)	63 (11)	30 (86)	30 (86)	12 (34)	11 (31)	19 (54)	19 (54)	24 (69)	19 (54)	5 (14)	5 (14)	22 (63)	26 (74)	7 (20)	3 (9)	35 (100)	35 (100)

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Table 1. Baseline characteristics of included patients *(Continued)*

A-to-Z 2004	2265	2232	60 (11)	61 (11)	1716 (76)	1680 (75)	529 (23)	530 (24)	1131 (50)	1105 (50)	926 (41)	915 (41)	409 (18)	355 (16)	1956 (86)	1919 (86)	483 (21)	472 (21)	979 (43)	979 (44)
Sakamoto 2005	237	244	63 (11)	65 (12)	190 (80)	193 (79)	83 (35)	61 (25)	149 (63)	142 (58)	131 (55)	130 (53)	10 (4)	15 (6)	208 (88)	219 (90)	45 (19)	50 (20)	215 (91)	220 (90)
Macin 2005	44	46	59 (13)	61 (12)	34 (77)	33 (72)	10 (23)	11 (24)	29 (65.9)	31 (67.4)	18 (41)	19 (41)	5 (11)	7 (15)	23 (52)	31 (67)	7 (15.9)	8 (17.4)	0 (0)	0 (0)
Sato 2008	176	177	64 (10)	63 (11)	129 (73)	142 (80)	52 (30)	59 (34)	81 (46)	87 (49)	98 (56)	105 (59)	16 (9)	19 (10)	NA	NA	NA	NA	161 (91)	161 (91)
Shal'nev 2007	55	55	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FACS 2005	78	78	61 (12)	63 (11)	55 (71)	51 (65)	14 (18)	16 (21)	40 (51)	40 (51)	33 (42)	39 (50)	4 (5)	8 (10)	> 47 (60)	> 54 (69)	0 (0)	0 (0)	68 (87)	71 (91)
Ren 2009	43	43	58 (11)	59 (10)	27 (63)	30 (70)	12 (28)	10 (23)	21 (49)	18 (42)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

* These individuals make up the subgroup of patients with unstable angina (n=824).
MI: myocardial infarction
NA: not applicable
PCI: percutaneous coronary intervention
SD: standard deviation

Table 2. General characteristics of included trials

Source	Daily intervention	Control	No. of individuals randomized	Mean initiation of statin after onset of ACS, days	Duration of follow-up available, months	No. (%) of individuals followed up	Reported concealed allocation/masked patients/caregiver/assessor
LAMIL 1997	Pravastatin 10 to 20 mg	Placebo	69	2	1 and 3	55 (80)	No/yes/yes/no
RECIFE 1999	Pravastatin 40 mg	Placebo	60	10	1.5	55 (92)	No/yes/yes/no

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Table 2. General characteristics of included trials *(Continued)*

L-CAD 2000	Pravastatin 20 to 40 mg*	Usual care†	126	6	1, 4, and 6	126 (100)	No/no/no/no
PAIS 2001	Pravastatin 40 mg	Placebo	99	2	1 and 3	97 (98)	No/yes/yes/no
PTT 2002	Pravastatin 40 mg	Usual care†	164‡	1	1 and 6‡	164 (100)	No/no/no/no
PACT 2004	Pravastatin 20 to 40 mg	Placebo	3408	1	1	3323 (98)	No/yes/yes/no
LIPS 2002	Fluvastatin 80 mg	Placebo	824§	2	1, 4, and 6	824 (100)	No/yes/yes/yes
FLORIDA 2002	Fluvastatin 80 mg	Placebo	540	8	1, 4, and 6	540 (100)	No/yes/yes/yes
MIRACL 2001	Atorvastatin 80 mg	Placebo	3086	3	1 and 4	3075 (99.6)	Yes/yes/yes/yes
Colivicchi 2002	Atorvastatin 80 mg	Usual care†	81	12	1, 3, and 6	81 (100)	No/no/no/yes
ESTABLISH 2004	Atorvastatin 20 mg	Usual care†	70	1	1, 4, and 6	69 (99)	No/no/no/no
A-to-Z 2004	Simvastatin 40 to 80 mg	Placebo	4497	4	1 and 4‖	4453 (99)	Yes/yes/yes/yes
Sakamoto 2005	Any statin**	Usual care	486	4	12	407 (84)	No/No/No/Yes
Macin 2005	Atorvastatin 40 mg	Placebo	90	1	1	89 (99)	No/Yes/Yes/No
Sato 2008	Pravastatin 10 mg	Usual care†	353	7	1 and 12	348 (99)	No/No/No/Yes

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Table 2. General characteristics of included trials *(Continued)*

Shal'nev 2007	Simvastatin 40 mg	Usual care	110	1	6	108 (98)	No/No/No/No
FACS 2005	Fluvastatin 80 mg	Placebo	156	1	1, 3, and 12	156 (100)	No/Yes/Yes/No
Ren 2009	Simvastatin 40 mg	Placebo	86	3	1	86 (100)	No/Yes/Yes/Yes

* 8 of 70 individuals received additionally cholestyramine or nicotinic acid.
† Individuals in the control group were allowed conventional medical treatment including lipid-lowering therapy.
‡ All 164 individuals were followed-up for 1 month, a subgroup of 77 (40/37) individuals with additional coronary angioplasty were followed-up for 6 months.
§ These 824 individuals represent just the subgroup with unstable angina; the LIPS [Lescol Intervention Prevention Study]-trial originally included another 853 individuals with stable angina.
|| After 4 months individuals in the control group received simvastatin 20mg.
ACS: acute coronary syndrome

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Table 3. Lipid values at baseline and changes during follow-up

Trial (reference)	Intervention	Follow-up*	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
			Baseline mean, mg/dL (% mean change in difference between treatment and control groups)†			
LAMIL 1997	Pravastatin 10 to 20 mg	3 months	228 (-13)	158 (-23)	36 (+5.3)	NA
RECIFE 1999	Pravastatin 40 mg	1.5 months	247 (-21)	164 (-27)	42 (+13)	194 (-21)
L-CAD 2000‡	Pravastatin 20 to 40 mg	1 month	237 (-24)	178 (-25)	32 (-6.0)	142 (±0)
PAIS 2001	Pravastatin 40 mg	3 months	255 (-23)	176 (-24)	43 (+9.1)	199 (-13)
PTT 2002‡	Pravastatin 40 mg	1 month	230 (-12)	133 (-25)	39 (+3.0)	214 (-5.8)
PACT 2004	Pravastatin 20 to 40 mg	NA	219 (NA)	NA	NA	NA
LIPS 2002	Fluvastatin 80 mg	1.5 months	201 (-28)	131 (-39)	39 (-2.0)	155 (-21)
FLORIDA 2002	Fluvastatin 80 mg	12 months	207 (-22)	137 (-31)	46 (+3.3)	146 (-22)
MIRACL 2001	Atorvastatin 80 mg	1.5 months	206 (-37)	124 (-53)	47 (±0)	183 (-28)
Colivicchi 2002‡	Atorvastatin 80 mg	2 months	220 (-9)	131 (-15)	39 (+1.0)	167 (-13)
ESTABLISH 2004‡	Atorvastatin 20 mg	6 months	191 (-28)	124 (-41)	44 (-8.7)	109 (+4.9)
A-to-Z 2004	Simvastatin 40 to 80 mg	1 month	184 (-33)	112 (-49)	39 (+2.0)	149 (-22)
Sakamoto 2005	Any statin	3 months	207 (-12)	134 (-23)	47 (+2.2)	135 (-5.2)
Macin 2005	Atorvastatin 40 mg	1 month	194 (-19)	124 (-30)	37 (+11)	189 (+0.8)
Sato 2008‡	Pravastatin 10 mg	9 months	220 (NA)	49 (NA)	117 (NA)	148 (NA)
Shal'nev 2007	Simvastatin 40 mg	0.5 months	212 (-29)	131 (-46)	49 (-9.5)	146 (-15)
FACS 2005	Fluvastatin 80 mg	1 month	212 (-26)	135 (-31)	47 (-4.1)	162 (+10)
Ren 2009	Simvastatin 40 mg	1 month	228 (-23%)	139 (-31)	40 (+9.6)	NA

* Lipid values in individual trials were measured at different time points during follow-up; we report those closest to the 4 months follow-up date.
† Baseline lipid levels were defined as the average (mean) before treatment in intervention and control groups. The percentage of change for each trial was calculated as the difference in the mean change in lipid levels from baseline to follow-up in the intervention and the control groups. To convert from mg/dL to mmol/L, multiply by 0.02586 for cholesterol and by 0.01129 for triglycerides.
‡ Individuals in the control group were allowed conventional medical treatment including lipid-lowering therapy.
HDL: high-density lipoprotein
LDL: low-density lipoprotein
NA: not applicable

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Table 4. Clinical endpoints in trials of early statin therapy versus control in acute coronary syndromes

Trial (reference)	Total death, MI, stroke, n (%) *		Total death, n (%)		Cardiovascular death, n (%)		Total MI, n (%)		Total stroke, n (%)		Revascularization (CABG/PCI), n (%)		Unstable angina, n (%)		Adverse events, n (%)						Acute heart failure		QOL	
															Rhabdomyolysis		CK > 10x ULN		ALT > 3x ULN					
	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
LAMIS 1997	NA	NA	1 (2.8)	0 (0)	1 (2.8)	0 (0)	1 (2.8)	0 (0.0)	NA	NA	NA	NA	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
	3 (8.3)	3 (9.1)	1 (2.8)	0 (0)	1 (2.8)	0 (0)	3 (8.3)	3 (9.1)	0 (0)	0 (0)	1 (2.8)	1 (3.0)	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
RECIFE 1999	1 (0)	1 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)	1 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.3)	NA	NA
L-CAD 2000	1 (1.4)	0 (0)	1 (1.4)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)	0 (0)	2 (3.6)	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
	1 (1.4)	1 (1.9)	1 (1.4)	1 (1.9)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)	2 (2.9)	9 (16.1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	1 (1.4)	1 (1.9)	1 (1.4)	1 (1.9)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)	6 (8.6)	12 (21.4)	6 (8.6)	10 (17.9)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PAIS 2001	2 (4.0)	3 (6.1)	1 (2.0)	2 (4.1)	1 (2.0)	2 (4.1)	2 (4.0)	2 (4.1)	0 (0)	1 (2.0)	4 (8.0)	2 (4.1)	16 (32.0) †	11 (22.4) †	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
	4 (8.0)	4 (8.2)	2 (4.0)	2 (4.1)	2 (4.0)	2 (4.1)	4 (8.0)	2 (4.1)	0 (0)	2 (4.1)	11 (22.0)	9 (18.4)	24 (48.0) †	21 (42.9) †	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
PTT 2002	4 (5.1)	14 (16.5)	3 (3.8)	9 (10.6)	3 (3.8)	7 (8.2)	3 (3.8)	5 (5.9)	2 (2.5)	7 (8.2)	12 (15.2)	15 (17.6)	11 (13.9) †	25 (29.4) †	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
	2 (5.0)	7 (18.9)	1 (2.5)	3 (8.1)	0 (0)	3 (8.1)	1 (2.5)	6 (16.2)	0 (0)	1 (2.7)	11 (27.5)	16 (43.2)	12 (30.0) †	22 (59.4) †	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA

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Table 4. Clinical endpoints in trials of early statin therapy versus control in acute coronary syndromes *(Continued)*

PACT 2004	86 (5.0)	96 (5.7)	27 (1.6)	39 (2.3)	26 (1.5)	34 (2.0)	67 (3.9)	70 (4.1)	8 (0.5)	10 (0.6)	NA	NA	123 (7.2)	126 (7.4)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0.4)	5 (0.3)	28 (1.6)	31 (1.8)	NA	NA
LIPS 2002	3 (0.7)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.7)	1 (0.2)	0 (0) ‖	0 (0) ‖	77 (18.5)	87 (21.4)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	8 (1.9)	3 (0.7)	1 (0.2)	0 (0)	1 (0.2)	0 (0)	7 (1.7)	3 (0.7)	0 (0) ‖	0 (0) ‖	78 (18.7)	88 (21.6)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	11 (2.6)	10 (2.5)	3 (0.7)	4 (1.0)	2 (0.5)	3 (0.7)	8 (1.9)	6 (1.5)	0 (0) ‖	0 (0) ‖	79 (18.9)	88 (21.6)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FLORIDA 2002	5 (1.9)	5 (1.8)	1 (0.4)	3 (1.1)	1 (0.4)	3 (1.1)	4 (1.5)	2 (0.7)	0 (0)	1 (0.4)	16 (6.0)	12 (4.4)	6 (2.3) ¶	5 (1.8) ¶	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10 (3.8)	10 (3.6)	2 (0.8)	6 (2.2)	2 (0.8)	6 (2.2)	8 (3.0)	6 (2.2)	0 (0)	1 (0.4)	30 (11.3)	32 (11.6)	11 (4.2) ¶	9 (3.3) ¶	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	14 (5.3)	14 (5.1)	3 (1.1)	6 (2.2)	3 (1.1)	6 (2.2)	11 (4.2)	10 (3.6)	0 (0)	1 (0.4)	36 (13.6)	41 (14.9)	14 (5.3) ¶	14 (5.1) ¶	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	28 (10.6)	28 (10.2)	7 (2.6)	11 (4.0)	6 (2.3)	11 (4.0)	21 (7.9)	16 (5.8)	2 (0.8)	5 (1.8)	46 (17.4)	51 (18.5)	16 (6.0)¶	18 (6.5)¶	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MIR-A-CL 2001	101 (6.6)	96 (6.2)	32 (2.1)	30 (1.9)	27 (1.8)	21 (1.4)	80 (5.2)	67 (4.3)	7 (0.5)	10 (0.6)	162 (10.5)	147 (9.5)	72 (4.7) #	87 (5.6) #	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA	NA	NA
	162 (10.5)	183 (11.8)	64 (4.2)	68 (4.4)	51 (3.3)	60 (3.9)	118 (7.7)	131 (8.5)	12 (0.8)	24 (1.6)	254 (16.5)	250 (16.1)	95 (6.2) #	130 (8.4) #	0 (0)	0 (0)	0 (0)	0 (0)	38 (2.5)	9 (0.6)	43 (2.8)	40 (2.6)	NA	NA
Colivic-	0 (0)	3 (7.3)	0 (0)	1 (2.4)	0 (0)	1 (2.4)	0 (0.0)	3 (7.3)	0 (0)	0 (0)	0 (0) **	0 (0) **	1 (2.5) #	1 (2.4) #	0 (0)	0 (0)	1 (2.5)##	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA

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Table 4. Clinical endpoints in trials of early statin therapy versus control in acute coronary syndromes *(Continued)*

chi 2002																								
	5 (12.5)	9 (22.0)	2 (5.0)	3 (7.3)	1 (2.5)	2 (4.9)	3 (7.5)	7 (17.1)	1 (2.5)	1 (2.4)	0 (0) **	0 (0) **	2 (5.0) #	3 (7.3) #	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
	7 (17.5)	13 (31.7)	3 (7.5)	4 (9.8)	2 (5.0)	3 (9.8)	5 (12.5)	10 (24.4)	1 (2.5)	2 (4.9)	0 (0) **	0 (0) **	2 (5.0) #	6 (14.6) #	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
ESTABLISH 2004	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
	0 (0)	1 (2.9)	0 (0)	1 (2.9)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
	0 (0)	1 (2.9)	0 (0)	1 (2.9)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)	8 (22.9)	8 (22.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
A-to-Z 2004	99 (4.4)	105 (4.7)	20 (0.9)	29 (1.3)	20 (0.9)	29 (1.3)	86 (3.8)	98 (4.4)	10 (0.4)	6 (0.3)	19 (0.8) ††	22 (1.0) ††	27 (1.2) ‡‡	30 (1.3) ‡‡	3 (0.1)	0 (0)	0 (0)	1 (0.04)	1 (0.04)	27 (1.2) §§	31 (1.4) §§	NA	NA	NA
	161 (7.1)	160 (7.2)	44 (1.9)	48 (2.2)	42 (1.9)	48 (2.2)	130 (5.7)	140 (6.3)	16 (0.7)	12 (0.5)	60 (2.6) ††	60 (2.7) ††	56 (2.5) ‡‡	61 (2.7) ‡‡	3 (0.1)	0 (0)	7 (0.3)	1 (0.04)	13 (5.7)	45 (2.0) §§	55 (2.5) §§	98 (5.0) §§	NA	NA
Sakamoto 2005	4 (1.7)	1 (0.4)	4 (1.7)	1 (0.4)	4 (1.7)	1 (0.4)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	12 (5.0)	4 (1.6)	6 (2.5)	2 (0.8)	6 (2.5)	2 (0.8)	NA	NA	3 (1.2)	2 (0.8)	18 (7.5)	24 (9.8)	6 (2.5)	17 (6.9)	NA	NA	NA	NA	NA	NA	1 (0.4)	9 (3.7)	NA	NA
Macin 2005	3 (6.8)	5 (10.9)	1 (2.3)	3 (6.5)	1 (2.3)	3 (6.5)	1 (2.3)	3 (6.5)	0 (0)	0 (0)	8 (18.2) ¶	8 (17.4) ¶	7 (1.6)	8 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (9.3)	10 (21.7)	NA	NA
Sato 2008	0 (0)	1 (0.6)	0	1 (0.6)	0 (0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA

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Table 4. Clinical endpoints in trials of early statin therapy versus control in acute coronary syndromes *(Continued)*

	4 (2.3)	7 (4.0)	3 (1.7)	2 (1.1)	1 (0.6)	2 (1.1)	NA	NA	0 (0)	2 (1.1)	22 (12.7)	36 (20.6)	5 (2.9)	5 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2.8)	NA	NA
Shal'Nev 2007	NA	NA	2 (3.6)	3 (5.5)	NA	NA	NA	NA	NA	NA	NA	NA	4 (7.3)	7 (12.7)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FACS 2005	2 (2.6)	2 (2.6)	1 (1.3)	0 (0)	0 (0)	0 (0)	1 (1.3)	2 (2.6)	0 (0)	0 (0)	3 (3.8)	4 (5.1)	2 (2.6)	6 (7.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
	2 (2.6)	4 (5.1)	1 (1.3)	0 (0)	0 (0)	0 (0)	1 (1.3)	3 (3.8)	0 (0)	1 (1.3)	3 (3.8)	8 (10.3)	3 (3.8)	12 (15.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
	4 (5.1)	10 (12.8)	1 (1.3)	4 (5.1)	0 (0)	2 (2.6)	2 (2.6)	5 (6.4)	1 (1.3)	3 (3.8)	6 (7.7)	15 (19.2)	6 (7.7)	16 (20.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA
Ren 2009	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	NA	NA	0 (0)	1 (2.3)	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

* Combined primary endpoint; unique patients.
† Patients with "recurrent angina pectoris".
‡ All 164 individuals were followed-up for 1 month, a subgroup of 77 individuals with additional coronary angioplasty were followed-up for 6 months.
§ These 824 individuals represent just the subgroup with unstable angina; the LIPS [Lescol Intervention Prevention Study]-trial originally included another 853 individuals with stable angina.
|| Fatal strokes only; non-fatal strokes were not recorded.
¶ Patients with "recurrent ischemia necessitating hospitalization".
# Patients with "recurrent symptomatic myocardial ischemia with objective evidence and emergency hospitalization".
** Individuals enrolled into the trial were not amenable for direct revascularization by coronary artery bypass grafting or percutaneous coronary intervention.
†† Revascularization procedures had to be urgent, occur more than 14 days after randomization, and were not allowed to be planned prior to enrollment.
‡‡ Patients with "readmission for acute coronary syndrome".
§§ Patients with "new onset congestive heart failure requiring admission or initiation of heart failure medications".
ALT: aminotransferase
CABG: coronary artery bypass grafting
CK: creatin kinase
MI: myocardial infarction
NA: not applicable
PCI: percutaneous coronary intervention
QOL: quality of life
ULN: upper limit of normal values

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APPENDICES

Appendix 1. Search strategies 2010

Cochrane Central Register of Controlled Trials

1 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2 exp Hydroxymethylglutaryl CoA Reductases/
3 (hydroxymethylglutaryl$ adj5 inhibitor$).mp.
4 (hmg coa$ adj5 inhibit$).mp.
5 statin$.mp.
6 simvastatin.mp.
7 fluvastatin.mp.
8 cerivastatin.mp.
9 lovastatin.mp.
10 pravastatin.mp.
11 atorvastatin.mp.
12 rosuvastatin.mp.
13 lipostat.mp.
14 lipitor.mp.
15 crestor.mp.
16 zocor.mp.
17 pravachol.mp.
18 baycol.mp.
19 lescol.mp.
20 mevacor.mp.
21 mevinolin.mp.
22 exp Anticholesteremic Agents/ or hypocholesterolemic agent:.mp.
23 or/1-22
24 exp Myocardial Infarction/
25 exp Coronary Thrombosis/ or coronary thrombosis.mp.
26 acute coronary.mp.
27 exp Angina, Unstable/
28 Myocardial infarct$.mp.
29 heart infarct:.mp.
30 acs.mp.
31 ami.mp.
32 (coronary adj3 syndrome$).mp.
33 acute angina.mp.
34 (unstable adj3 angina).mp.
35 unstable coronary.mp.
36 or/24-35
37 36 and 23

Ovid MEDLINE

1 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2 exp Hydroxymethylglutaryl CoA Reductases/
3 (hydroxymethylglutaryl$ adj5 inhibitor$).mp.
4 (hmg coa$ adj5 inhibit$).mp.
5 statin$.mp.
6 simvastatin.mp.
7 fluvastatin.mp.
8 cerivastatin.mp.
9 lovastatin.mp.
10 pravastatin.mp.
11 atorvastatin.mp.
12 rosuvastatin.mp.
13 lipostat.mp.
14 lipitor.mp.
15 crestor.mp.
16 zocor.mp.

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17 pravachol.mp.
18 baycol.mp.
19 lescol.mp.
20 mevacor.mp.
21 mevinolin.mp.
22 exp Anticholesteremic Agents/
23 or/1-22
24 exp Myocardial Infarction/
25 exp Coronary Thrombosis/
26 acute coronary.mp.
27 exp Angina, Unstable/
28 Myocardial infarct$.mp.
29 heart infarct:.mp.
30 acs.mp.
31 ami.mp.
32 (coronary adj3 syndrome$).mp.
33 acute angina.mp.
34 (unstable adj3 angina).mp.
35 unstable coronary.mp.
36 or/24-35
37 36 and 23
38 randomized controlled trial$.mp.
39 randomized controlled trial.pt.
40 double-blind method/
41 single-blind method/
42 controlled clinical trial.pt.
43 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp.
44 or/38-43
45 clinical trials.pt. or comparative study/ or follow-up studies/ or comparative study.pt.
46 prospective studies/ or 45
47 (random: adj5 (controlled or clinical)).mp.
48 random$.mp.
49 46 and (47 or 48)
50 49 or 44
51 50 and 37
52 animals/ not humans/
53 51 not 52

EMBASE

1 exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
2 exp Hydroxymethylglutaryl Coenzyme a Reductase/
3 (hydroxymethylglutaryl$ adj5 inhibitor$).mp.
4 (hmg coa$ adj5 inhibit$).mp.
5 statin$.mp.
6 simvastatin.mp.
7 fluvastatin.mp.
8 cerivastatin.mp.
9 lovastatin.mp.
10 pravastatin.mp.
11 atorvastatin.mp.
12 rosuvastatin.mp.
13 lipostat.mp.
14 lipitor.mp.
15 crestor.mp.
16 zocor.mp.
17 pravachol.mp.
18 baycol.mp.
19 lescol.mp.
20 mevacor.mp.
21 mevinolin.mp.
22 Anticholesteremic agents.mp. or Hypocholesterolemic Agent/

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23 or/1-22
24 exp Heart Infarction/
25 coronary thrombosis.mp. or exp Coronary Artery Thrombosis/
26 acute coronary.mp.
27 exp Unstable Angina Pectoris/
28 Myocardial infarct$.mp.
29 heart infarct:.mp.
30 acs.mp.
31 ami.mp.
32 (coronary adj3 syndrome$).mp.
33 acute angina.mp.
34 (unstable adj3 angina).mp.
35 unstable coronary.mp.
36 or/24-35
37 Randomized Controlled Trial/
38 double-blind method/
39 single-blind method/
40 randomized controlled trial:.mp.
41 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp.
42 controlled clinical trial/
43 or/37-42
44 Clinical Trial/
45 exp comparative study/
46 follow up/
47 prospective study/
48 or/44-47
49 random:.mp.
50 (random: adj5 (controlled or clinical)).mp.
51 50 or 49
52 51 and 48
53 52 or 43
54 53 and 36 and 23
55 nonhuman/ not human/
56 55 and 54
57 54 not 56

EBSCO host CINAHL

S58 S57 and S36
S57 S55 or S56
S56 S49 or S48 or S47 or S46 or S45 or S44 or S43 or S42 or S41 or S40 or S39 or S38 or S37
S55 S54 and S52
S54 S53 or S52 or S50
S53 PT clinical trial
S52 "random*"
S51 (MH "Prospective Studies+")
S50 (MH "Comparative Studies")
S49 "controlled clinical trial*"
S48 TX trebl* w1 mask*
S47 TX tripl* w1 mask*
S46 TX double* w1 mask*
S45 TX singl* w1 mask*
S44 "singl* w1 mask*"
S43 "doubl* w1 mask*"
S42 doubl* w1 blind*
S41 TX tripl* w1 blind*
S40 TX trebl* w1 blind*
S39 TX singl* w1 blind*
S38 TX randomized controlled trial*
S37 (MH "Clinical Trials+")
S36 S35 and S22
S35 S34 or S33 or S32 or S31 or S30 or S29 or S28 or S27 or S26 or

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S25 or S24 or S23
S34 TX unstable coronary
S33 TX unstable n3 angina
S32 TX acute angina
S31 TX coronary n3 syndrome*
S30 TX ami
S29 TX acs
S28 TX Myocardial infarct*
S27 (MH "angina, unstable+")
S26 (MH "angina unstable+")
S25 TX acute coronary
S24 (MH "coronary thrombosis+")
S23 (MH "Myocardial Infarction+")
S22 S21 or S20 or S19 or S18 or S17 or S16 or S15 or S14 or S13 or
S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1
S21 TX Anticholesteremic
S20 TX mevinolin
S19 TX mevacor
S18 TX lescol
S17 TX baycol
S16 TX Pravachol
S15 TX zocor
S14 TX crestor
S13 TX lipitor
S12 TX lipostat
S11 TX rosuvastatin
S10 TX atorvastatin
S9 TX pravastatin
S8 TX lovastatin
S7 TX cerivastatin
S6 TX fluvastatin
S5 TX simvastatin
S4 TX statin*
S3 TX hmg coa* N5 inhibit*
S2 TX hydroxymethylglutaryl* N5 inhibitor*
S1 (MH "Statins+")

Appendix 2. Search strategies 2013

The RCT filter for MEDLINE is the Cochrane sensitivity-maximizing RCT filter and for EMBASE the terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* have been applied. For both the reference is Lefebvre 2011.

CENTRAL

#1 MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#2 hydroxymethylglutaryl*
#3 HMG-CoA*
#4 statin or statins
#5 atorvastatin
#6 cerivastatin
#7 fluvastatin
#8 lovastatin
#9 pravastatin
#10 simvastatin
#11 lipitor
#12 baycol
#13 lescol
#14 mevacor
#15 altocor
#16 pravachol
#17 lipostat
#18 zocor
#19 mevinolin

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#20 compactin
#21 fluindostatin
#22 rosuvastatin
#23 dalvastatin
#24 cranoc
#25 canef
#26 locol
#27 lochol
#28 leucol
#29 lescol
#30 monacolin
#31 medostatin
#32 mevinacor
#33 livalo
#34 pitava
#35 pitavastatin
#36 pravasin
#37 mevalotin
#38 gerosim
#39 lipex
#40 zenas
#41 crestor
#42 meglutol
#43 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#44 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#45 #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
#46 #43 or #44 or #45
#47 MeSH descriptor: [Myocardial Infarction] explode all trees
#48 MeSH descriptor: [Acute Coronary Syndrome] this term only
#49 MeSH descriptor: [Coronary Thrombosis] this term only
#50 coronary next thrombosis
#51 acute next coronary
#52 MeSH descriptor: [Angina, Unstable] explode all trees
#53 myocardial next infarct*
#54 heart next infarct*
#55 acs
#56 ami
#57 coronary near/3 syndrome*
#58 acute next angina
#59 unstable near/3 angina
#60 unstable next coronary
#61 #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60
#62 #46 and #61 from 2010 to 2013

MEDLINE OVID

1. exp Anticholesteremic Agents/
2. exp Hydroxymethylglutaryl CoA Reductases/
3. (hydroxymethylglutaryl* adj5 inhibitor*).mp.
4. (hmg-coa* adj5 statin*).mp.
5. (hmg-coa* adj5 inhibit*).mp.
6. anticholesteremic agent*.mp.
7. hypocholesterolemic agent*.mp.
8. 3-hydroxy-3-methylpentanedioic acid.mp.
9. beta-hydroxy-beta-methylglutarate.mp.
10. 3-hydroxy-3-methylglutaric acid.mp.
11. statin*.mp.
12. (altoc?r or altoprev or artein or atorvastatin).mp.
13. (baycol or bristacol or "bay w 6228" or "bay w6228").mp.
14. (canef or cerivastatin or certa or compactin or cranoc or crestor or ci-981 or ci981 or cs-500 or cs500 or cs-514 or cs514).mp.
15. (dalvastatin or denan).mp.
16. (elisor or epatostantin or eptastatin* or epistatin or fluindostatin or fluvastatin or gerosim or itavastatin).mp.

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17. (lescol or leucol or lipemol or lipitor or lipibec or liplat or lipex or lipobay or lipovas or lipostat or livalo or loc?ol or lodales or lovacol or lovastatin or l-654969 or l-644128 or l644128).mp.
18. (mevastatin or mevastin or mevinolin or mona?olin or methylcompactin or mk-803 or mk803 or mk-0803 or mk0803 or msd-803 or mevacor or mk-733 or mk733 or meglutol or mevalotin or mevinacor or medostatin or ml-236b or ml236b or medipo).mp.
19. (nk-104 or nk104 or nks-104 or nks104 or nisvastatin or neolipid).mp.
20. (pravastatin or prareduct or pravachol or pravacol or pravasin* or pitavastatin or pitava or pravachol).mp.
21. (rms-431 or rms431 or ribar or rivastatin or rosuvastatin or RG-12561).mp.
22. (sanaprav or selektine or simvastatin or sinvacor or s?nvinolin or sortis or sq-31000 or sq31000 sq-31,000 or sq31,000 or sri-62320 or sri62320 or s-4522 or s4522).mp.
23. (tahor or torvast).mp.
24. (vast?n or xu-62320 or xu62320 or ym-548 or ym548 or zarator or zenas or zocor? or zd-4522 or zd4522).mp.
25. or/1-24
26. Acute Coronary Syndrome/
27. exp Myocardial Infarction/
28. exp Coronary Thrombosis/
29. coronary thrombosis.tw.
30. acute coronary.tw.
31. exp Angina, Unstable/
32. myocardial infarct*.tw.
33. heart infarct*.tw.
34. acs.tw.
35. ami.tw.
36. (coronary adj3 syndrome*).tw.
37. acute angina.tw.
38. (unstable adj3 angina).tw.
39. unstable coronary.tw.
40. or/26-39
41. 25 and 40
42. randomized controlled trial.pt.
43. controlled clinical trial.pt.
44. randomized.ab.
45. placebo.ab.
46. clinical trials as topic.sh.
47. randomly.ab.
48. trial.ti.
49. 42 or 43 or 44 or 45 or 46 or 47 or 48
50. exp animals/ not humans.sh.
51. 49 not 50
52. 41 and 51
53. ((2010* or 2011* or 2012* or 2013*) not (201001* or "20100201")).ed.
54. 52 and 53

EMBASE OVID

1. (hydroxymethylglutaryl* adj5 inhibitor*).mp.
2. (hmg-coa* adj5 statin*).mp.
3. (hmg-coa* adj5 inhibit*).mp.
4. anticholesteremic agent*.mp.
5. hypocholesterolemic agent*.mp.
6. 3-hydroxy-3-methylpentanedioic acid.mp.
7. beta-hydroxy-beta-methylglutarate.mp.
8. 3-hydroxy-3-methylglutaric acid.mp.
9. statin*.mp.
10. (altoc?r or altoprev or artein or atorvastatin).mp.
11. (baycol or bristacol or "bay w 6228" or "bay w6228").mp.
12. (canef or cerivastatin or certa or compactin or cranoc or crestor or ci-981 or ci981 or cs-500 or cs500 or cs-514 or cs514).mp.
13. (dalvastatin or denan).mp.
14. (elisor or epatostantin or eptastatin* or epistatin or fluindostatin or fluvastatin or gerosim or itavastatin).mp.
15. (lescol or leucol or lipemol or lipitor or lipibec or liplat or lipex or lipobay or lipovas or lipostat or livalo or loc?ol or lodales or lovacol or lovastatin or l-654969 or l-644128 or l644128).mp.
16. (mevastatin or mevastin or mevinolin or mona?olin or methylcompactin or mk-803 or mk803 or mk-0803 or mk0803 or msd-803 or mevacor or mk-733 or mk733 or meglutol or mevalotin or mevinacor or medostatin or ml-236b or ml236b or medipo).mp.

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17. (nk-104 or nk104 or nks-104 or nks104 or nisvastatin or neolipid).mp.
18. (pravastatin or prareduct or pravachol or pravacol or pravasin* or pitavastatin or pitava or pravachol).mp.
19. (rms-431 or rms431 or ribar or rivastatin or rosuvastatin or RG-12561).mp.
20. (tahor or torvast).mp.
21. exp hypocholesterolemic agent/
22. hydroxymethylglutaryl coenzyme A reductase/
23. or/1-22
24. exp heart infarction/
25. exp acute coronary syndrome/
26. exp coronary artery thrombosis/
27. coronary thrombosis.tw.
28. acute coronary.tw.
29. exp unstable angina pectoris/
30. Myocardial infarct*.tw.
31. heart infarct*.tw.
32. acs.tw.
33. ami.tw.
34. (coronary adj3 syndrome*).tw.
35. acute angina.tw.
36. (unstable adj3 angina).tw.
37. unstable coronary.tw.
38. or/24-37
39. 23 and 38
40. random$.tw.
41. factorial$.tw.
42. crossover$.tw.
43. cross over$.tw.
44. cross-over$.tw.
45. placebo$.tw.
46. (doubl$ adj blind$).tw.
47. (singl$ adj blind$).tw.
48. assign$.tw.
49. allocat$.tw.
50. volunteer$.tw.
51. crossover procedure/
52. double blind procedure/
53. randomized controlled trial/
54. single blind procedure/
55. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. (animal/ or nonhuman/) not human/
57. 55 not 56
58. 39 and 57
59. ((2010* or 2011* or 2012* or 2013*) not ("201001" or "201002" or "201003" or "201004")).em.
60. 58 and 59
61. limit 60 to embase

CINAHL

S26 S24 AND S25
S25 EM 2010-2013
S24 S9 AND S23
S23 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
S22 "unstable coronary"
S21 unstable N3 angina
S20 "acute angina"
S19 coronary N3 syndrome*
S18 acs or ami
S17 "myocardial infarct*"
S16 "myocardial infarct*"
S15 (MH "Angina, Unstable")
S14 "acute coronary"
S13 "coronary thrombosis"

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S12 (MH "Coronary Thrombosis")
S11 (MH "Acute Coronary Syndrome")
S10 (MH "Myocardial Infarction+")
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S8 livalo or pitava or pitavastatin or pravasin or mevalotin or gerosim or lipex or zenas or crestor or meglutol
S7 locol or lochol or leucol or lescol or monacolin or medostatin or mevinacor
S6 fluindostatin or rosuvastatin or dalvastatin or cranoc or canef
S5 pravachol or lipostat or zocor or mevinolin or compactin
S4 simvastatin or lipitor or baycol or lescol or mevacor or altocor
S3 atorvastatin or atorvastatin or fluvastatin or lovastatin or pravastatin
S2 statin* or hydroxymethylglutaryl* or HMG-CoA*
S1 (MH "Statins+")

WHAT'S NEW

Date	Event	Description
21 April 2015	Review declared as stable	No further evidence is expected to change the conclusion of this review.

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 6, 2011

Date	Event	Description
8 April 2014	New citation required but conclusions have not changed	The updated search found no new studies, so the review conclusions remain the same.
8 April 2014	New search has been performed	Search updated on 12 April 2013: no further eligible studies identified.
9 August 2011	Amended	Addition of a 'Summary of findings' (SoF) table. Previous tables erroneously published as SoF tables were moved to the 'Additional tables' section.

CONTRIBUTIONS OF AUTHORS

NV: carried out study selection, quality assessment, and data extraction; drafted the review text.
AJN: carried out study selection, quality assessment and data extraction; drafted the review text.
GGS, JAdL, FC, PO, SMM, AL, EM, FdH, HCB: participated in collection of additional data and critically reviewed the manuscript for important intellectual content.
MB: conceived and designed the review; carried out part of the study selection, quality assessment, and data extraction; drafted the review text.

DECLARATIONS OF INTEREST

Dr Vale declared no interests.

Dr Nordmann declared no interests.

Dr Schwartz has received honoraria and grant support from Pfizer.

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Dr de Lemos has received honoraria from Merck, Pfizer, Merck/Schering, and Bristol-Myers Squibb and grant support from Merck and Pfizer. He has also received consulting fees from Astra Zeneca for participation in an endpoint review committee for a product unrelated to the current manuscript.

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Dr den Hartog declared no interests.

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Dr Macin declared no interests.

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Dr Briel declared no interests.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Coronary Syndrome [*drug therapy] [mortality]; Angina, Unstable [prevention & control]; Cardiovascular Diseases [mortality]; Cause of Death; Drug Administration Schedule; Heart Failure [prevention & control]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [adverse effects] [*therapeutic use]; Myocardial Infarction [prevention & control]; Myocardial Revascularization [statistics & numerical data]; Randomized Controlled Trials as Topic; Stroke [prevention & control]

MeSH check words

Humans

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