

Effects of Early Treatment With Statins on Short-term Clinical Outcomes in Acute Coronary Syndromes

A Meta-analysis of Randomized Controlled Trials

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NUMEROUS CLINICAL TRIALS and meta-analyses show that long-term therapy with statins reduces the risk of myocardial infarction (MI), stroke, and overall mortality in patients at varying risks for cardiovascular disease.¹⁻⁴ These trials typically excluded patients with recent acute coronary syndromes (ACS). The early period following onset of ACS represents a critical stage of coronary heart disease with a high risk for recurrent events and death due to vessel occlusions from vulnerable coronary plaques.⁵ Therefore, strategies to stabilize vulnerable coronary plaques during this high-risk period are arguably paramount.

Context The short-term effects of early treatment with statins in patients after the onset of acute coronary syndromes (ACS) for the outcomes of death, myocardial infarction (MI), and stroke are unclear.

Objective To evaluate relevant outcomes of patients from randomized controlled trials comparing early statin therapy with placebo or usual care at 1 and 4 months following ACS.

Data Sources and Study Selection Systematic search of electronic databases (MEDLINE, EMBASE, PASCAL, Cochrane Central Register) from their inception to August 2005, which was supplemented by contact with experts in the field. Two reviewers independently determined the eligibility of randomized controlled trials that compared treatment with statins with a control, were initiated within 14 days after onset of ACS, and had a minimal follow-up of 30 days. Trials with cerivastatin were only included in a sensitivity analysis.

Data Extraction Information on baseline characteristics of included trials and patients, reported methodological quality, lipid levels, and clinical outcome was independently extracted by 2 investigators. Investigators from each included trial contributed additional data if necessary.

Data Synthesis Twelve trials involving 13 024 patients with ACS were included in the meta-analysis. The risk ratios for the combined end point of death, MI, and stroke for patients treated with early statin therapy compared with control therapy were 0.93 (95% confidence interval [CI], 0.80-1.09; $P=.39$) at 1 month and 0.93 (95% CI, 0.81-1.07; $P=.30$) at 4 months following ACS. There were no statistically significant risk reductions from statins for total death, total MI, total stroke, cardiovascular death, fatal or nonfatal MI, or revascularization procedures (percutaneous coronary intervention or coronary artery bypass graft surgery). Sensitivity analyses with restriction to trials of high quality or with additional data from a large trial using cerivastatin indicated summary risk ratios even closer to 1.

Conclusion Based on available evidence, initiation of statin therapy within 14 days following onset of ACS does not reduce death, MI, or stroke up to 4 months.

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There is growing evidence that statins, beyond their low-density lipoprotein (LDL) cholesterol-lowering effects, reduce vascular inflammation, improve endothelial function, and decrease thrombus formation.⁶ All these mechanisms are expected to have favorable effects on ACS. Several observational studies⁷⁻¹⁰ but not all¹¹ suggest a large reduction in mortality in patients with ACS treated with statins prior to or at hospital discharge. Randomized controlled trials (RCTs) in patients with ACS indicate that statins may reduce composite end points that include recurrent angina, coronary revascularization procedures, and rehospitalization.¹²⁻¹⁵ The latter end points, however, may be less reliable because they depend to a greater extent on clinical judgment and local practices. None of the RCTs have individually shown a clear benefit on death and MI.

The purpose of this meta-analysis of RCTs was to investigate whether early use of statins within 14 days following the onset of ACS reduces relevant clinical end points of cardiovascular morbidity and overall mortality at 1 and 4 months.

METHODS

Eligibility Criteria

Eligible trials had to fulfill the following criteria to be included in this systematic review: (1) RCT design comparing statin therapy with placebo or usual care in patients with ACS (MI or unstable angina); (2) initiation of statin therapy within 14 days following the onset of ACS; and (3) follow-up of at least 30 days. Trials that compared 2 different statins or investigated patients with prior heart transplantation were excluded.¹⁵ Trials using cerivastatin¹⁶ were only considered for sensitivity analysis because this compound was withdrawn from the market in 2001.¹⁷

Data Sources and Study Search

To identify relevant trials, the electronic databases MEDLINE, EMBASE, PASCAL (all from their inception to August 2005) and the Cochrane Central Register of Controlled Trials

(Cochrane Library 2005, issue 2) were searched using the terms *pravastatin*, *atorvastatin*, *fluvastatin*, *simvastatin*, *lovastatin*, *cerivastatin*, *rosuvastatin* and *acute coronary syndrome** as text words and *hydroxymethylglutaryl-CoA reductase inhibitors*, *myocardial ischemia*, *myocardial infarction*, *unstable angina*, and *coronary arteriosclerosis* as Medical Subject Headings. The search was restricted to articles indexed as a clinical trial (publication type) or those that included the words "random" or "placebo" in their titles or abstracts. Language restrictions were not imposed. Reference lists of identified articles, recently published editorials, and reviews on the topic for further eligible trials also were searched. Authors of included primary trials contributed additional data relevant for the purpose of this analysis. We were unable to reach investigators from 1 trial.¹⁸

Selection and Quality Assessment

Two authors (M.B. and A.J.N.) independently assessed trial eligibility and quality. The quality of the trials was assessed according to concealment of treatment allocation; blinding of patients, caregivers, or clinical outcome assessors; and the proportion of patients with complete clinical follow-up.¹⁹ We considered treatment allocation to be concealed if a central independent randomization facility, the use of numbered sealed opaque envelopes, or a central pharmacy, which prepared and distributed numbered containers, was mentioned in the RCT.

End Points and Data Extraction

The primary end point was the combined outcome of nonfatal MI, nonfatal stroke, and total death. Secondary individual end points were total death, total MI, total stroke, cardiovascular death, fatal MI, nonfatal MI, revascularization procedures (coronary artery bypass graft surgery, angioplasty), and unstable angina (recurrent myocardial ischemia requiring emergency hospitalization). We aimed

to assess all end points at 1 and 4 months of follow-up. Adverse events (rhabdomyolysis, creatine kinase levels >10 times upper limit of normal and liver aminotransferase levels >3 times upper limit of normal) were recorded at the end of follow-up for each trial.

Two authors (M.B. and A.J.N.) independently extracted in duplicate all trial data and the additional data provided by the original trial investigators. End points and adverse events were considered irrespective of their putative relationship with the treatment.

Statistical Analysis

We pooled treatment effects and calculated risk ratios (RRs) for all end points in the treatment and control groups by using a random-effects model.²⁰ We also calculated odds ratios²¹ but because of the minimal differences in estimates prefer to report only RRs. The presence of publication bias was investigated by using funnel plots.²² Heterogeneity was tested using the Cochran Q test and inconsistency (the percentage of total variance across studies that is due to heterogeneity rather than chance) of treatment effects was measured across the primary and secondary end points.^{23,24}

Sensitivity analyses were prespecified. The treatment effects were examined according to quality components (concealed treatment allocation, blinding of patients and caregivers, blinded outcome assessment), time to initiation of statins, and the type of statin. One post hoc sensitivity analysis was conducted by including unpublished data from a trial using cerivastatin.¹⁶ For statistical data analysis, Stata software version 9.0 (StataCorp, College Station, Tex) was used. $P < .05$ was set as the level of significance.

RESULTS

Seventeen RCTs were identified that compared early statin therapy with placebo or usual care in individuals with ACS (FIGURE 1). Five trials were excluded from the meta-analysis: 2 reported a follow-up shorter than 30

days,^{25,26} the investigator was unable to provide outcome data according to the prespecified time points in 1 trial,²⁷ and another trial was still ongoing at the time of our analysis.²⁸ One trial using cerivastatin was prematurely stopped because the drug was withdrawn from

the market.¹⁶ Data from this trial for the 4.5 months of follow-up were included only in the sensitivity analysis.

The 12 trials included in the meta-analysis investigated 4 different statins in a total of 13 024 individuals with ACS: pravastatin (6 trials),^{12,18,29-32} atorvastatin (3 trials),^{13,33,34} fluvastatin (2 trials),^{14,35} and simvastatin (1 trial)³⁶ (TABLE 1). In accordance with our eligibility criteria, only the subgroup of patients with unstable angina was included from the Lescol Intervention Prevention Study (LIPS).¹⁴ Only the data from the placebo comparison during the first 4 months of follow-up in the A to Z trial³⁶ were used in this analysis. The analysis for publication bias indicated no evidence of bias for any of the end points. The methodological quality of included trials is summarized in Table 1.

Study Population

The reported mean age of the participants in the trials ranged from 53 to 69 years (TABLE 2). Each trial enrolled mostly men (TABLE 3). Prevalence of individual cardiovascular risk factors and cointerventions for an index event such as fibrinolysis therapy or percu-

taneous coronary intervention (PCI) varied considerably among the included trials.

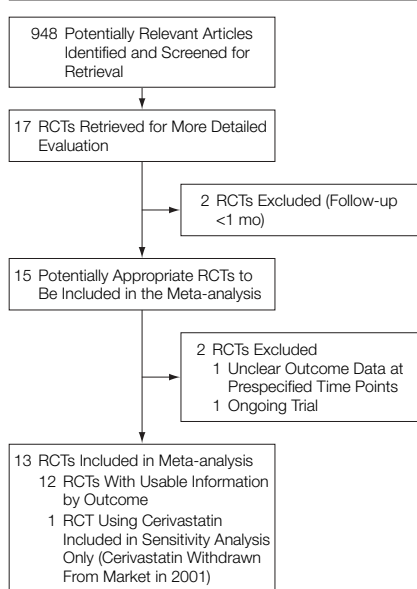
Lipid-Lowering Effects

The average weighted mean baseline LDL cholesterol level of included participants was 123 mg/dL (3.2 mmol/L) (range, 112-178 mg/dL [2.9-4.6 mmol/L]) (TABLE 4). The mean reduction in LDL cholesterol ranged from -15% to -53% and the mean reduction in total cholesterol ranged from -9% to -37%. There were higher reductions in the trials using higher drug doses and/or more potent drugs. The effects on levels of high-density lipoprotein cholesterol and triglycerides were less pronounced and inconsistent among trials.

Combined Primary Outcome

During the first month following onset of ACS, 301 (4.7%) of 6464 individuals in the early statin groups experienced death, MI, or stroke compared with 324 (5.0%) of 6421 individuals in the control groups (RR, 0.93; 95% confidence interval [CI], 0.80-1.09; *P* = .39). At 4 months of follow-up, there were 356 (7.5%) of 4756 in-

Figure 1. Selection of Studies



RCT indicates randomized controlled trial.

Table 1. General Characteristics of Included Trials

Source	Daily Intervention	Control	No. of Individuals Randomized	Mean Initiation of Statin After Onset of ACS, d	Duration of Follow-up Available, mo	No. (%) of Individuals Followed up	Reported Concealed Allocation/Masked Patients/Caregiver/Assessor
LAMIL, ¹⁸ 1997	Pravastatin, 10-20 mg	Placebo	69	2	1 and 3	56 (81)	No/yes/yes/no
RECIFE, ²⁹ 1999	Pravastatin, 40 mg	Placebo	60	10	1.5	55 (92)	No/yes/yes/no
L-CAD, ¹² 2000	Pravastatin, 20-40 mg*	Usual care†	126	6	1, 4, and 6	126 (100)	No/no/no/no
PAIS, ³⁰ 2001	Pravastatin, 40 mg	Placebo	99	2	1 and 3	97 (98)	No/yes/yes/no
PTT, ³¹ 2002	Pravastatin, 40 mg	Usual care†	164	1	1 and 6‡	164 (100)	No/no/no/no
PACT, ³² 2004	Pravastatin, 20-40 mg	Placebo	3408	1	1	3323 (98)	No/yes/yes/no
LIPS, ¹⁴ 2002	Fluvastatin, 80 mg	Placebo	824§	2	1, 4, and 6	824 (100)	No/yes/yes/yes
FLORIDA, ³⁵ 2002	Fluvastatin, 80 mg	Placebo	540	8	1, 4, and 6	540 (100)	No/yes/yes/yes
MIRACL, ¹³ 2001	Atorvastatin, 80 mg	Placebo	3086	3	1 and 4	3075 (99.6)	Yes/yes/yes/yes
Colivicchi et al, ³³ 2002	Atorvastatin, 80 mg	Usual care†	81	12	1, 3, and 6	81 (100)	No/no/no/yes
ESTABLISH, ³⁴ 2004	Atorvastatin, 20 mg	Usual care†	70	1	1, 4, and 6	69 (99)	No/no/no/no
A to Z, ³⁶ 2004	Simvastatin, 40-80 mg	Placebo	4497	4	1 and 4	4453 (99)	Yes/yes/yes/yes

Abbreviations: ACS, acute coronary syndromes; ESTABLISH, Early Statin Treatment in Patients With Acute Coronary Syndrome: Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Serial Volumetric Intravascular Ultrasound Analysis During Half a Year After Coronary Event; FLORIDA, Fluvastatin on Risk Diminishment After Acute Myocardial Infarction; L-CAD, Lipid-Coronary Artery Disease; LAMIL, Lipid Acute Myocardial Infarction Lowering; LIPS, Lescol Intervention Prevention Study; MIRACL, Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering; PACT, Pravastatin in Acute Coronary Treatment; PAIS, Pravastatin in Acute Ischemic Syndromes; PTT, Pravastatin Turkish Trial; RECIFE, Reduction of Cholesterol in Ischemia and Function of the Endothelium.

*Of 70 individuals, 8 also received cholestyramine or nicotinic acid.

†Includes conventional medical treatment and optional lipid-lowering therapy.

‡All 164 individuals were followed up for 1 month; a subgroup of 77 (pravastatin: 40; control: 37) individuals with additional coronary angioplasty were followed up for 6 months.

§These individuals represent just the subgroup with unstable angina; the LIPS trial originally included another 853 individuals with stable angina.

||After 4 months, individuals in the control group received 20 mg/d of simvastatin.

dividuals in the early statin groups with a primary end point event compared with 381 (8.1%) of 4713 individuals in the control groups (RR, 0.93; 95% CI, 0.81-1.07; $P=.30$) (FIGURE 2). We found no evidence for relevant heterogeneity among trials at both follow-up time points. In sensitivity analyses, summary estimates of the primary end point at 1 and 4 months suggested smaller risk reductions for trials with higher methodological quality compared with trials with lower methodological quality (TABLE 5). Different treatment effects were not found for

trials with initiation of statin therapy within 3 days vs up to 14 days after ACS or for trials using different types of statins (TABLE 6).

Individual Secondary Outcomes

There were no statistically significant risk reductions from early statin therapy for total death, total MI, total stroke, cardiovascular death, fatal or nonfatal MI, or revascularization procedures (PCI or coronary artery bypass graft surgery) at 1 and 4 months of follow-up or for unstable angina at 1 month of follow-up (FIGURE 3). At 4 months after

the onset of ACS, unstable angina was reduced: 206 (4.8%) of 4268 individuals experienced unstable angina in the early statin groups compared with 256 (6.0%) of 4238 in the control groups (RR, 0.80; 95% CI, 0.64-1.00; $P=.05$).

The heterogeneity among treatment effects was low except for unstable angina at 4 months, in which moderate heterogeneity was found. This may be due to differences in the definition of the end point of unstable angina among trials (TABLE 7). Absolute numbers of revascularization proce-

Table 2. Baseline Characteristics, Type and Treatment of Index Event

Source	No. of Individuals Randomized		Age, Mean (SD), y		No. (%) of Individuals by Type and Treatment of Index Event					
	Statin	Control	Statin	Control	MI		Fibrinolysis		PCI	
					Statin	Control	Statin	Control	Statin	Control
LAMIL, ¹⁸ 1997	36	33	NA	NA	36 (100)	33 (100)	NA	NA	NA	NA
RECIFE, ²⁹ 1999	30	30	55 (2)	56 (2)	11 (39)	12 (44)	0	0	16 (57)	17 (63)
L-CAD, ¹² 2000	70	56	55 (10)	59 (11)	32 (46)	23 (41)	NA	NA	58 (83)	50 (89)
PAIS, ³⁰ 2001	50	49	64 (1)	63 (2)	35 (70)	31 (63)	17 (34)	14 (29)	0	0
PTT, ³¹ 2002	79	85	53 (11)	52 (10)	79 (100)	85 (100)	79 (100)	85 (100)	0	0
PACT, ³² 2004	1710	1698	62 (12)	61 (12)	1109 (65)	1111 (65)	651 (38)	671 (40)	414 (24)	406 (24)
LIPS, ¹⁴ 2002	417*	407*	61 (10)	60 (10)	0	0	0	0	417 (100)	407 (100)
FLORIDA, ³⁵ 2002	265	275	61 (12)	60 (11)	265 (100)	275 (100)	137 (52)	133 (48)	8 (3)	10 (4)
MIRACL, ¹³ 2001	1538	1548	65 (12)	65 (12)	812 (53)	843 (55)	109 (7)	137 (9)	0	0
Colivicchi et al, ³³ 2002	40	41	69 (14)	68 (14)	NA	NA	0	0	0	0
ESTABLISH, ³⁴ 2004	35	35	61 (10)	63 (11)	22 (63)	26 (74)	7 (20)	3 (9)	35 (100)	35 (100)
A to Z, ³⁶ 2004	2265	2232	60 (11)	61 (11)	1956 (86)	1919 (86)	483 (21)	472 (21)	979 (43)	979 (44)

Abbreviations: MI, myocardial infarction; NA, data not available; PCI, percutaneous coronary intervention. See Table 1 footnote for expansions of trial names.

*These individuals make up the subgroup of patients with unstable angina ($n = 824$).

Table 3. Baseline Characteristics and Cardiovascular Risk Factors

Source	No. (%) of Individuals									
	Men		Diabetes		Hypertension		Current Smoker		Prior MI	
	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
LAMIL, ¹⁸ 1997	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
RECIFE, ²⁹ 1999	26 (93)	22 (81)	1 (4)	0	5 (18)	8 (29)	14 (50)	17 (63)	1 (4)	2 (7)
L-CAD, ¹² 2000	57 (81)	44 (79)	0	0	22 (31)	18 (32)	49 (70)	36 (64)	45 (64)	39 (70)
PAIS, ³⁰ 2001	35 (70)	37 (76)	8 (16)	5 (10)	12 (24)	16 (33)	17 (34)	17 (35)	14 (28)	12 (25)
PTT, ³¹ 2002	65 (82)	69 (81)	14 (18)	13 (15)	16 (20)	21 (25)	63 (80)	66 (78)	0	0
PACT, ³² 2004	1308 (76)	1285 (76)	244 (14)	234 (14)	700 (41)	714 (42)	608 (36)	575 (34)	236 (14)	197 (12)
LIPS, ¹⁴ 2002	344 (83)	336 (83)	65 (16)	34 (8)	NA	NA	NA	NA	184 (44)	172 (42)
FLORIDA, ³⁵ 2002	214 (81)	234 (85)	29 (11)	31 (11)	67 (25)	65 (24)	140 (53)	139 (51)	31 (12)	31 (11)
MIRACL, ¹³ 2001	992 (64)	1020 (66)	342 (22)	373 (24)	843 (55)	846 (55)	429 (28)	430 (28)	382 (25)	392 (25)
Colivicchi et al, ³³ 2002	23 (58)	24 (59)	22 (55)	24 (59)	35 (88)	37 (90)	NA	NA	34 (85)	35 (85)
ESTABLISH, ³⁴ 2004	30 (86)	30 (86)	12 (34)	11 (31)	19 (54)	19 (54)	24 (69)	19 (54)	5 (14)	5 (14)
A to Z, ³⁶ 2004	1716 (76)	1680 (75)	529 (23)	530 (24)	1131 (50)	1105 (50)	926 (41)	915 (41)	409 (18)	355 (16)

Abbreviations: MI, myocardial infarction; NA, data not available. See Table 1 footnote for expansions of trial names.

dures varied among trials not only because of different trial sizes but also because of different trial criteria for revascularization.

In a sensitivity analysis of the secondary end points, trials of adequate methodological quality were associated with smaller risk reductions than trials lacking quality components (Table 5). However, statistically significant risk reductions from statins at 4 months were found for unstable angina in trials that reported concealed allocation and in trials with blinded outcome assessment.

When we additionally included in a sensitivity analysis data from 3605 patients with ACS with only 4.5 months of follow-up in the Prevention of Ischemic Events by Early Treatment of Cerivastatin Study (PRINCESS), the RRs were 0.95 (95% CI, 0.78-1.17; $P=.66$) for total death, 0.91 (95% CI, 0.78-1.05; $P=.19$) for total MI, 0.80 (95% CI, 0.53-1.20; $P=.28$) for total stroke, and 0.81 (95% CI, 0.69-0.96; $P=.02$) for unstable angina.

Adverse Events

Among all included trials, there were 9 individuals (0.1%) receiving statin therapy vs 4 individuals (0.06%)

receiving placebo who developed myopathy (increase of creatine kinase levels >10 times the upper limit of normal). Three individuals (0.05%) with creatine kinase elevations while receiving statin therapy met the definition of rhabdomyolysis (creatin kinase level >10 000 U/L). All 9 cases with myopathy while receiving statins occurred after the first month of treatment and only among patients treated with high-dose simvastatin (80 mg/d).³⁶ None of these patients experienced a fatal outcome. Among all trials, there were 75 individuals (1.1%) treated with statins vs 28 individuals (0.4%) in control groups whose liver aminotransferase levels increased to higher than 3 times the upper limit of normal.

COMMENT

This systematic review of RCTs in patients after the onset of ACS investigated whether early initiation of statin therapy compared with placebo or usual care improves patients' outcomes in the short-term. The results of this meta-analysis failed to demonstrate a reduction in the composite primary end point (death, MI, or stroke) for patients treated early with

statins at 1 and 4 months following ACS. Of the secondary individual end points, evidence for a reduced risk at 4 months following the onset of ACS was found for unstable angina only.

Strengths and Weaknesses

An extensive literature search was conducted to retrieve all relevant eligible trials and investigators of the primary trials were contacted to provide additional information and collaboration. This collaboration with experts in the field should have minimized the potential for publication bias. In addition, formal testing found little evidence for such a bias.

One small trial with 151 randomized individuals was not included because the original investigators failed to clarify outcome events.²⁷ One trial that planned to enroll 1000 individuals was still ongoing at the time of our analysis.²⁸ Two other trials including 3468 patients only had a follow-up of 1 month²⁹ and 1.5 months.³² As a consequence, the power of our analysis, especially at 4 months, was compromised.

We cannot rule out a small beneficial short-term effect with the early

Table 4. Lipid Values at Baseline and Changes During Follow-up

Source	Daily Intervention	Follow-up, mo*	Baseline Mean, mg/dL (% Mean Change in Difference Between Statin and Control Groups)†			
			Total Cholesterol	LDL Cholesterol	HDL Cholesterol	Triglycerides
LAMIL, ¹⁸ 1997	Pravastatin, 10-20 mg	3	228 (-13)	158 (-23)	36 (5.3)	NA
RECIFE, ²⁹ 1999	Pravastatin, 40 mg	1.5	247 (-21)	164 (-27)	42 (13)	194 (-21)
L-CAD, ¹² 2000‡	Pravastatin, 20-40 mg	1	237 (-24)	178 (-25)	32 (-6.0)	NA
PAIS, ³⁰ 2001	Pravastatin, 40 mg	3	255 (-23)	176 (-24)	43 (9.1)	199 (-13)
PTT, ³¹ 2002‡	Pravastatin, 40 mg	1	230 (-12)	133 (-25)	39 (3.0)	214 (-5.8)
PACT, ³² 2004	Pravastatin, 20-40 mg	NA	219 (NA)	NA	NA	NA
LIPS, ¹⁴ 2002	Fluvastatin, 80 mg	1.5	201 (-28)	131 (-39)	39 (-2.0)	155 (-21)
FLORIDA, ³⁵ 2002	Fluvastatin, 80 mg	12	207 (-22)	137 (-31)	46 (3.3)	146 (-22)
MIRACL, ¹³ 2001	Atorvastatin, 80 mg	1.5	206 (-37)	124 (-53)	47 (±0)	183 (-28)
Colivicchi et al, ³³ 2002‡	Atorvastatin, 80 mg	2	220 (-9)	131 (-15)	39 (1.0)	167 (-13)
ESTABLISH, ³⁴ 2004‡	Atorvastatin, 20 mg	6	191 (-28)	124 (-41)	44 (-8.7)	109 (4.9)
A to Z, ³⁶ 2004	Simvastatin, 40-80 mg	1	184 (-33)	112 (-45)	39 (2.0)	149 (-22)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, data not available. See Table 1 footnote for expansions of trial names.

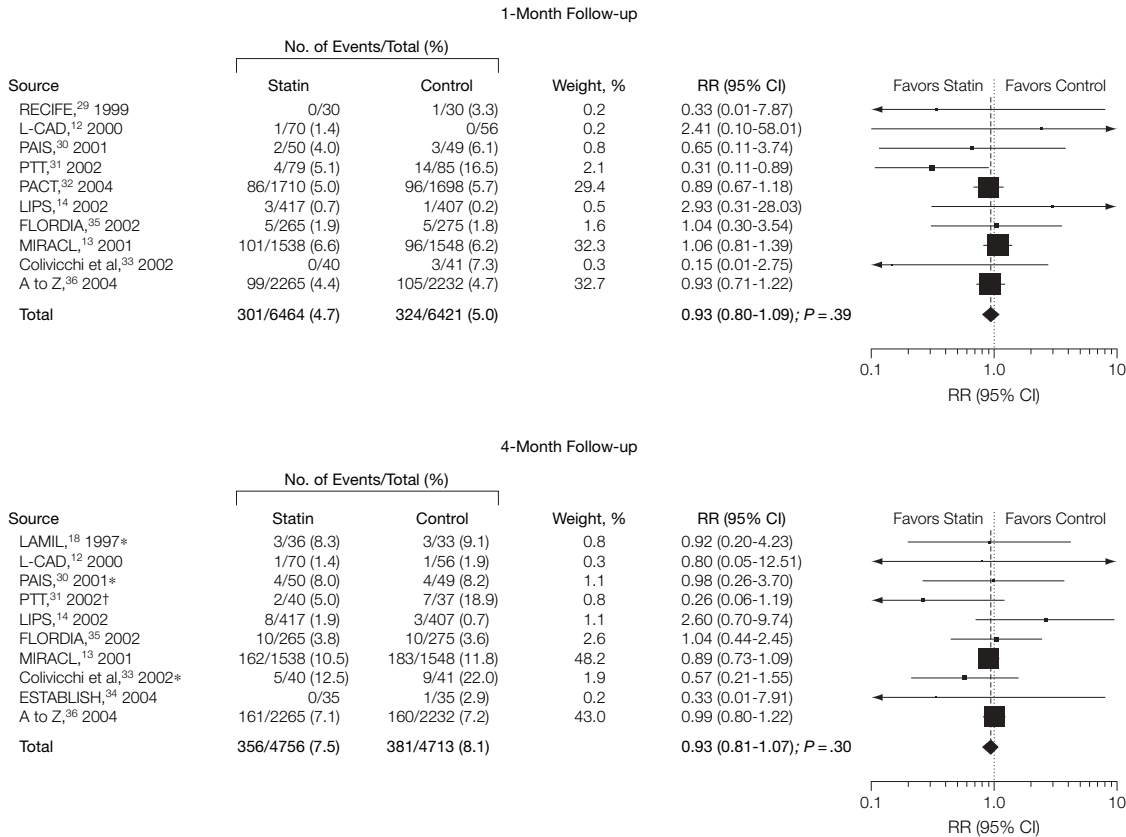
SI conversion factors: To convert HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

*Lipid values in individual trials were measured at different time points during follow-up; the values closest to the 4-month follow-up date are reported.

†Baseline levels were defined as the mean before treatment in statin 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 statin and the control groups.

‡Individuals in the control group were allowed conventional medical treatment including lipid-lowering therapy.

Figure 2. Risk Ratios for the Combined Primary End Point of Death, Nonfatal Myocardial Infarction, and Nonfatal Stroke



At 1 month, LAMIL and ESTABLISH are not presented due to the absence of end point events. Cochran Q test for heterogeneity yielded $P = .48$. Inconsistency measure is 0% (95% uncertainty interval, 0%-62%). At 4 months, RECIFE and PACT were excluded due to follow-up of only 1 month and 1.5 months, respectively. Cochran Q test for heterogeneity yielded $P = .64$. Inconsistency measure is 0% (95% uncertainty interval, 0%-62%). CI indicates confidence interval; RR, risk ratio. See Table 1 footnote for expansions of trial names. The sizes of the data markers relate to study sample size and the inverse of the SE of each study.

*Three months follow-up data used.
 †Six months follow-up data used.

Table 5. Sensitivity Analysis of Quality Components for the Composite End Point, Total Death, and Unstable Angina at 4 Months

Quality Component	Composite of Death, Nonfatal MI, and Stroke*		Total Death		Unstable Angina†	
	RR (95% CI)	P Value	RR (95% CI)	P Value	RR (95% CI)	P Value
Reported concealed allocation						
Yes ^{13,36}	0.94 (0.81-1.08)	.38	0.93 (0.72-1.20)	.58	0.79 (0.64-0.97)	.03
No ^{12,14,18,30,31,33-35}	0.85 (0.53-1.36)	.50	0.64 (0.29-1.40)	.27	0.78 (0.50-1.22)	.28
Blinded patients and caregivers						
Yes ^{13,14,18,30,35,36‡}	0.95 (0.83-1.09)	.48	0.92 (0.72-1.18)	.52	0.88 (0.71-1.09)	.25
No ^{12,31,33,34§}	0.46 (0.21-1.00)	.05	0.52 (0.17-1.62)	.26	0.51 (0.32-0.80)	.004
Blinded outcome assessment						
Yes ^{13,14,33,35,36}	0.94 (0.82-1.08)	.40	0.91 (0.71-1.17)	.45	0.81 (0.66-0.99)	.04
No ^{12,18,30,31,34}	0.63 (0.29-1.36)	.24	0.70 (0.23-2.15)	.54	0.69 (0.37-1.28)	.24

Abbreviations: CI, confidence interval; MI, myocardial infarction; RR, risk ratio.

*Combined primary end point of meta-analysis.

†There were no data available for this end point from the Lescol Intervention Prevention Study (LIPS) and the Lipid Acute Myocardial Infarction Lowering (LAMIL) study.

‡This category is identical to all placebo-controlled trials.

§This category is identical to all trials allowing for concomitant lipid-lowering therapy in control groups.

use of statins after the onset of ACS on total mortality, MI, and stroke and that this meta-analysis may have lacked the power to rule out this effect. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial comparing 80 mg/d of atorvastatin with placebo for 4 months suggested a 16% reduction of a primary composite end point that included recurrent myocardial ischemia with rehospitalization.¹³ In a post hoc calculation, we estimated the power of our meta-analysis to be 73% to detect a 16% difference in our primary combined outcome of death, MI, and stroke at 4 months of follow-up

(1-sided α of .05).³⁷ Thus, a type II error is possible but not likely. To rule out effects of a 10% risk reduction or less on our primary end point, more than 34 000 patients with ACS would be needed in an RCT.³⁸ In addition, our sensitivity analyses indicated even smaller treatment effects when restricting the analysis to trials of adequate methodological quality, or when we additionally included secondary end point data from a large, prematurely terminated trial using cerivastatin in 3605 patients.¹⁶

As expected, statins lowered 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 lipid-lowering potency of different statin types and doses. Because only 2 trials measured ultrasensitive C-reactive protein,^{13,36} we were not able to systematically investigate an association of early statin therapy with a reduction in inflammatory parameters. Finally, this systematic review cannot address the benefit of the early use of statins after onset of ACS in patients undergoing early PCI of culprit lesions because

Table 6. Composite End Point, Total Death, and Cardiovascular Death in Patients With Acute Coronary Syndromes

Source	No. of Individuals Randomized		Follow-up	No. (%) of Individuals					
	Statin	Control		Composite of Death, Nonfatal MI, and Stroke*		Total Death		Cardiovascular Death	
				Statin	Control	Statin	Control	Statin	Control
LAMIL, ¹⁸ 1997	36	33	1 mo	NA	NA	1 (2.8)	0	1 (2.8)	0
			3 mo	3 (8.3)	3 (9.1)	1 (2.8)	0	1 (2.8)	0
RECIFE, ²⁹ 1999	30	30	6 wk	0	1 (3.3)	0	0	0	0
L-CAD, ¹² 2000	70	56	1 mo	1 (1.4)	0	1 (1.4)	0	0	0
			4 mo	1 (1.4)	1 (1.9)	1 (1.4)	1 (1.9)	0	0
			6 mo	1 (1.4)	1 (1.9)	1 (1.4)	1 (1.9)	0	0
PAIS, ³⁰ 2001	50	49	1 mo	2 (4.0)	3 (6.1)	1 (2.0)	2 (4.1)	1 (2.0)	2 (4.1)
			3 mo	4 (8.0)	4 (8.2)	2 (4.0)	2 (4.1)	2 (4.0)	2 (4.1)
PTT, ³¹ 2002	79†	85†	1 mo	4 (5.1)	14 (16.5)	3 (3.8)	9 (10.6)	3 (3.8)	7 (8.2)
			40†	37†	6 mo	2 (5.0)	7 (18.9)	1 (2.5)	3 (8.1)
PACT, ³² 2004	1710	1698	1 mo	86 (5.0)	96 (5.7)	27 (1.6)	39 (2.3)	26 (1.5)	34 (2.0)
LIPS, ¹⁴ 2002	417‡	407‡	1 mo	3 (0.7)	1 (0.2)	0	0	0	0
			4 mo	8 (1.9)	3 (0.7)	1 (0.2)	0	1 (0.2)	0
			6 mo	11 (2.6)	10 (2.5)	3 (0.7)	4 (1.0)	2 (0.5)	3 (0.7)
FLORIDA, ³⁵ 2002	265	275	1 mo	5 (1.9)	5 (1.8)	1 (0.4)	3 (1.1)	1 (0.4)	3 (1.1)
			4 mo	10 (3.8)	10 (3.6)	2 (0.8)	6 (2.2)	2 (0.8)	6 (2.2)
			6 mo	14 (5.3)	14 (5.1)	3 (1.1)	6 (2.2)	3 (1.1)	6 (2.2)
MIRACL, ¹³ 2001	1538	1548	1 mo	101 (6.6)	96 (6.2)	32 (2.1)	30 (1.9)	27 (1.8)	21 (1.4)
			4 mo	162 (10.5)	183 (11.8)	64 (4.2)	68 (4.4)	51 (3.3)	60 (3.9)
Colivicchi et al, ³³ 2002	40	41	1 mo	0	3 (7.3)	0	1 (2.4)	0	1 (2.4)
			3 mo	5 (12.5)	9 (22.0)	2 (5.0)	3 (7.3)	1 (2.5)	2 (4.9)
			6 mo	7 (17.5)	13 (31.7)	3 (7.5)	4 (9.8)	2 (5.0)	3 (9.8)
ESTABLISH, ³⁴ 2004	35	35	1 mo	0	0	0	0	0	0
			4 mo	0	1 (2.9)	0	1 (2.9)	0	0
			6 mo	0	1 (2.9)	0	1 (2.9)	0	0
A to Z, ³⁶ 2004	2265	2232	1 mo	99 (4.4)	105 (4.7)	20 (0.9)	29 (1.3)	20 (0.9)	29 (1.3)
			4 mo	161 (7.1)	160 (7.2)	44 (1.9)	48 (2.2)	42 (1.9)	48 (2.2)

Abbreviations: MI, myocardial infarction; NA, data not available. See Table 1 footnote for expansions of trial names.

*Combined primary end point of meta-analysis.

†These individuals were followed up for 1 month (n = 164); a subgroup of 77 individuals with additional coronary angioplasty were followed up for 6 months.

‡These individuals make up the subgroup with unstable angina (n = 824); the LIPS trial originally included another 853 individuals with stable angina.

only a minority of patients in the included trials underwent PCI.

Comparison With Other Studies

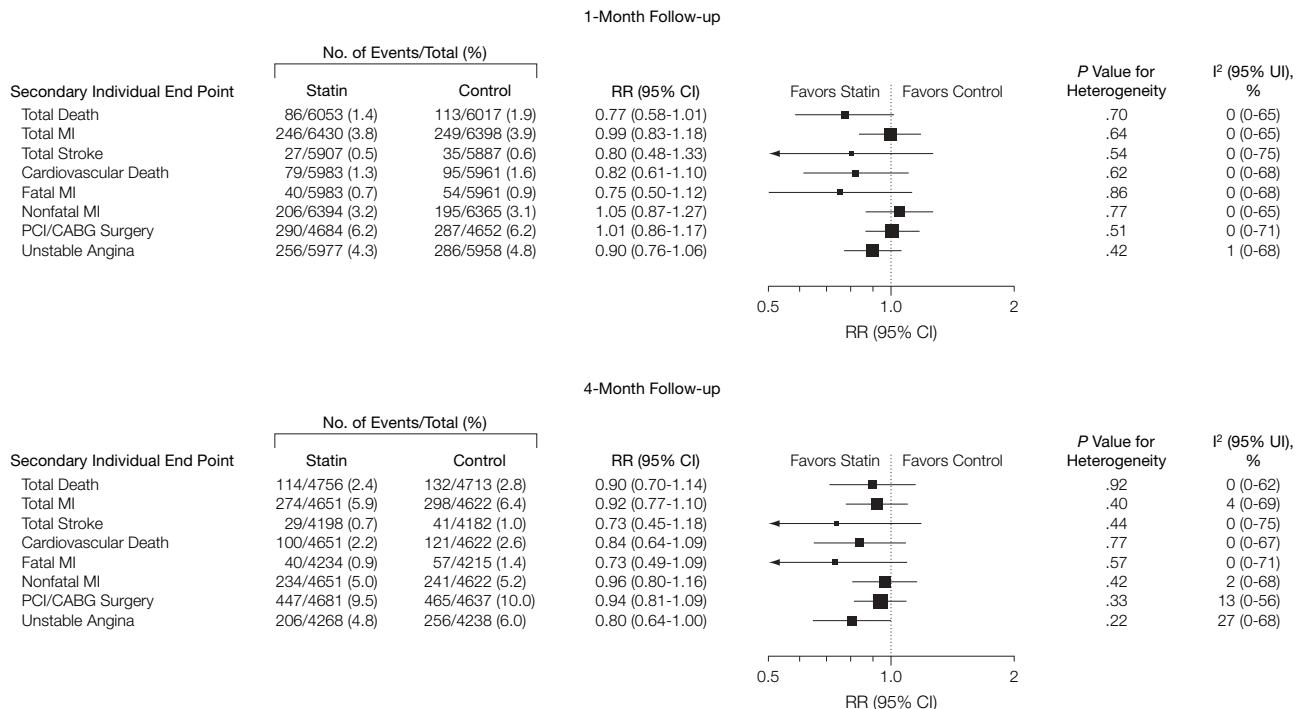
Our findings contrast with results from some recently published observational studies⁸⁻¹⁰ that suggest a lower risk of mortality for early statin therapy within 1 month following onset of ACS (odds ratios as low as 0.4). Results from these observational studies, however, may be prone to bias due to survivor treatment selection,³⁹ competing medical issues,⁴⁰ or differences of unknown confounders between comparison groups.⁴¹ Another large observational study found no benefit of early initiation of statin therapy in a propensity- and covariate-adjusted analysis; this study may have better captured important confounders.¹¹ Our meta-analysis of RCTs demon-

strates that observational studies with insufficient control of confounders greatly overestimate the magnitude of effect from early statin therapy after onset of 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 80 mg/d of atorvastatin or 40 mg/d of pravastatin.¹⁵ In fact, however, there is no obvious discordance. In PROVE IT, Kaplan-Meier curves of the primary composite end point 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 6 months. It is important to note that the primary composite end point of PROVE IT comprised not only death, MI, and

stroke but also recurrent unstable angina requiring rehospitalization and revascularization. If the more limited composite of death, MI, and stroke is considered, there was no significant difference between the 2 treatment groups in PROVE IT. Unstable angina and revascularization were the most frequent events in PROVE IT and appeared to have driven the primary composite end point. Similarly, our meta-analysis indicates that statins reduce the risk of unstable angina following onset of ACS. Although end points such as unstable angina depend at least in part on clinicians' judgment or action and therefore may be less reliable,⁴² our finding of a risk reduction for unstable angina of 19% (95% CI, 1%-44%) at 4 months in trials with blinded outcome assessment supports the validity of this result.

Figure 3. Summary Risk Ratios for Secondary End Points



Trials without events for a specific end point were excluded from the corresponding analysis (different totals for different end points). At 4 months, the Reduction of Cholesterol in Ischemia and Function of the Endothelium (RECIFE) study and the Pravastatin in Acute Coronary Treatment (PACT) study were excluded due to follow-up of only 1.5 months and 1 month, respectively. Cochran Q test was used for heterogeneity. CABG indicates coronary artery bypass graft; CI, confidence interval; I², the percentage of total variance across studies that is due to heterogeneity rather than chance; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, risk ratio; UI, uncertainty interval. The sizes of the data markers relate to study sample size and the inverse of the SE of each study.

Implications for Clinicians, Researchers, and Policy Makers

Statins impact lipid profiles within days,²⁵ and in vitro studies show immediate inhibition of smooth muscle cell proliferation and stimulation of re-endothelialization by statins.⁴³ These effects seem to translate into a reduction of unstable angina pectoris at 4 months following onset of ACS but not into a reduction of death, MI, or stroke.

In our meta-analysis, only end point events that occurred during the period of randomized treatment were con-

sidered. 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 1 to 2 years after randomization.^{2,44} Similarly, there appeared to be a delayed benefit of more intensive statin treatment compared with less intensive statin treatment in the late phase of the A to Z trial.³⁶ Therefore, some of the benefit of statin treatment in the period up to 4 months after ACS may only become manifest after 4 months. This systematic review confirms that

early treatment with statins after the onset of ACS can in general be considered safe even when high doses of statins are used. However, physicians and patients should pay close attention to muscle-related symptoms, especially when maximum available doses—in particular of simvastatin—are administered.

Concern exists that when administered in clinical practice, long-term adherence to statins among patients with recent onset of ACS is poor.⁴⁵ Evidence from a small RCT and from observational studies suggests better ad-

Table 7. Fatal MI, Nonfatal MI, Total Stroke, Revascularization, and Unstable Angina in Patients With Acute Coronary Syndromes*

Source	Follow-up	No. (%) of Individuals									
		Fatal MI		Nonfatal MI		Total Stroke		Revascularization (CABG/PCI)		Unstable Angina	
		Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
LAMIL, ¹⁸ 1997	1 mo	1 (2.8)	0	NA	NA	NA	NA	NA	NA	NA	NA
	3 mo	1 (2.8)	0	2 (5.6)	3 (9.1)	0	0	1 (2.8)	1 (3.0)	NA	NA
RECIFE, ²⁹ 1999	6 wk	0	0	0	1 (3.3)	0	0	0	0	0	1 (3.3)
L-CAD, ¹² 2000	1 mo	0	0	0	0	0	0	0	2 (3.6)	NA	NA
	4 mo	0	0	0	0	0	0	2 (2.9)	9 (16.1)	NA	NA
	6 mo	0	0	0	0	0	0	6 (8.6)	12 (21.4)	6 (8.6)	10 (17.9)
PAIS, ³⁰ 2001	1 mo	1 (2.0)	1 (2.0)	1 (2.0)	1 (2.0)	0	1 (2.0)	4 (8.0)	2 (4.1)	16 (32.0)†	11 (22.4)†
	3 mo	2 (4.0)	1 (2.0)	2 (4.0)	1 (2.0)	0	2 (4.1)	11 (22.0)	9 (18.4)	24 (48.0)†	21 (42.9)†
PTT, ³¹ 2002	1 mo	2 (2.5)	4 (4.7)	1 (1.3)	1 (1.2)	2 (2.5)	7 (8.2)	12 (15.2)	15 (17.6)	11 (13.9)†	25 (29.4)†
	6 mo	0	3 (8.1)	1 (2.5)	3 (8.1)	0	1 (2.7)	11 (27.5)	16 (43.2)	12 (30.0)†	22 (59.4)†
PACT, ³² 2004	1 mo	13 (0.8)	16 (0.9)	54 (3.2)	54 (3.2)	8 (0.5)	10 (0.6)	NA	NA	123 (7.2)	126 (7.4)
LIPS, ¹⁴ 2002	1 mo	0	0	3 (0.7)	1 (0.2)	0‡	0‡	77 (18.5)	87 (21.4)	NA	NA
	4 mo	0	0	7 (1.7)	3 (0.7)	0‡	0‡	78 (18.7)	88 (21.6)	NA	NA
	6 mo	0	0	8 (1.9)	6 (1.5)	0‡	0‡	79 (18.9)	88 (21.6)	NA	NA
FLORIDA, ³⁵ 2002	1 mo	0	1 (0.4)	4 (1.5)	1 (0.4)	0	1 (0.4)	16 (6.0)	12 (4.4)	6 (2.3)§	5 (1.8)§
	4 mo	0	3 (1.1)	8 (3.0)	3 (1.1)	0	1 (0.4)	30 (11.3)	32 (11.6)	11 (4.2)§	9 (3.3)§
	6 mo	0	3 (1.1)	11 (4.2)	7 (2.5)	0	1 (0.4)	36 (13.6)	41 (14.9)	14 (5.3)§	14 (5.1)§
MIRACL, ¹³ 2001	1 mo	10 (0.7)	8 (0.5)	70 (4.6)	59 (3.8)	7 (0.5)	10 (0.6)	162 (10.5)	147 (9.5)	72 (4.7)	87 (5.6)
	4 mo	17 (1.1)	18 (1.2)	101 (6.6)	113 (7.3)	12 (0.8)	24 (1.6)	254 (16.5)	250 (16.1)	95 (6.2)	130 (8.4)
Colivicchi et al, ³³ 2002	1 mo	0	1 (2.4)	0	2 (4.9)	0	0	0¶	0¶	1 (2.5)	1 (2.4)
	3 mo	1 (2.5)	2 (4.9)	2 (5.0)	5 (12.2)	1 (2.5)	1 (2.4)	0¶	0¶	2 (5.0)	3 (7.3)
	6 mo	2 (5.0)	3 (7.3)	3 (7.5)	7 (17.1)	1 (2.5)	2 (4.9)	0¶	0¶	2 (5.0)	6 (14.6)
ESTABLISH, ³⁴ 2004	1 mo	0	0	0	0	0	0	0	0	0	0
	4 mo	0	0	0	0	0	0	0	0	0	0
	6 mo	0	0	0	0	0	0	8 (22.9)	8 (22.9)	0	0
A to Z, ³⁶ 2004	1 mo	13 (0.6)	23 (1.0)	73 (3.2)	75 (3.4)	10 (0.4)	6 (0.3)	19 (0.8)#	22 (1.0)#	27 (1.2)**	30 (1.3)**
	4 mo	19 (0.8)	30 (1.3)	111 (4.9)	110 (4.9)	16 (0.7)	12 (0.5)	60 (2.6)#	60 (2.7)#	56 (2.5)**	61 (2.7)**

Abbreviations: CABG, coronary artery bypass graft surgery; MI, myocardial infarction; NA, data not available; PCI, percutaneous coronary intervention. See Table 1 footnote for expansions of trial names.

*See Table 6 for the number of individuals randomized to statin or control for each study.

†Patients with recurrent angina pectoris.

‡There were no fatal strokes; nonfatal strokes were not recorded in the LIPS trial.

§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 CABG surgery or PCI.

#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 syndromes.

herence to statins when therapy is started while the patient is still in the hospital and shortly after the onset of ACS.^{46,47} Together with our finding of a reduced risk for unstable angina at 4 months, these arguments provide a basis to recommend initiation of statin therapy prior to hospital discharge in all patients with ACS to achieve LDL cholesterol levels of at least less than 100 mg/dL⁴⁸ and preferably less than 70 mg/dL.⁴⁹ Our results support the safety of current guidelines^{48,50} and may help to improve prevailing practices of insufficient lipid-lowering therapy in patients with ACS.⁵¹

CONCLUSIONS

Based on available evidence, early statin therapy is not associated with a relevant reduction of death, MI, or stroke during the first 4 months following ACS. However, early statin therapy may reduce the occurrence of unstable angina at 4 months after the onset of ACS while serious adverse events associated with early initiation of statins are rare.

Author Contributions: Drs Briel, Bucher, and Nordmann had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Briel, Schwartz, Bucher, Nordmann.

Acquisition of data: Briel, Schwartz, Thompson, de Lemos, Blazing, van Es, Kayikçioğlu, Arntz, den Hartog, Veeger, Colivicchi, Dupuis, Okazaki, Wright, Bucher, Nordmann.

Analysis and interpretation of data: Briel, Schwartz, Bucher, Nordmann.

Drafting of the manuscript: Briel, Schwartz, Bucher, Nordmann.

Critical revision of the manuscript for important intellectual content: Briel, Schwartz, Thompson, de Lemos, Blazing, van Es, Kayikçioğlu, Arntz, den Hartog, Veeger, Colivicchi, Dupuis, Okazaki, Wright, Bucher, Nordmann.

Statistical analysis: Briel, Nordmann.

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REFERENCES

- Shepherd J, Cobbe SM, Ford I, et al; West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
- Heart Protection Study Investigators. MRC/BHF Heart Protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
- Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med*. 2005;165:725-730.
- Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. *Eur Heart J*. 1998;19:1434-1503.
- Sposito AC, Chapman MJ. Statin therapy in acute coronary syndromes: mechanistic insight into clinical benefit. *Arterioscler Thromb Vasc Biol*. 2002;22:1524-1534.
- Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA*. 2001;285:430-436.
- Aronow HD, Topol EJ, Roe MT, et al. Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: an observational study. *Lancet*. 2001;357:1063-1068.
- Spencer FA, Allogrè J, Goldberg RJ, et al. Association of statin therapy with outcomes of acute coronary syndromes: the GRACE study. *Ann Intern Med*. 2004;140:857-866.
- Fonarow GC, Wright RS, Spencer FA, et al. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality. *Am J Cardiol*. 2005;96:611-616.
- Newby LK, Kristinsson A, Bhopkar MV, et al. Early statin initiation and outcomes in patients with acute coronary syndromes. *JAMA*. 2002;287:3087-3095.
- Arntz HR, Agrawal R, Wunderlich W, et al. Beneficial effects of pravastatin (+/-colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). *Am J Cardiol*. 2000;86:1293-1298.
- Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711-1718.
- Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following suc-

cessful first percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;287:3215-3222.

15. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504.

16. European Society of Cardiology Web site. PRINCESS: Prevention of Ischaemic Events by Early Treatment of Cerivastatin After Acute Myocardial Infarction: hotline session III, 2004. Available at: <http://cic.escardio.org/SessionDetails.aspx?id=40551>. Accessed August 30, 2005.

17. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med*. 2002;346:539-540.

18. Kesteloot H, Claeys G, Blanckaert N, Lesaffre E. Time course of serum lipids and apolipoproteins after acute myocardial infarction: modification by pravastatin. *Acta Cardiol*. 1997;52:107-116.

19. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA*. 1999;282:1054-1060.

20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.

21. Walter SD. Choice of effect measure for epidemiological data. *J Clin Epidemiol*. 2000;53:931-939.

22. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001;323:101-105.

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.

24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.

25. Correia LC, Sposito AC, Passos LC, et al. Short-term effect of atorvastatin (80 mg) on plasma lipids of patients with unstable angina pectoris or non-Q-wave acute myocardial infarction. *Am J Cardiol*. 2002;90:162-164.

26. Ostadal P, Alan D, Hajek P, et al. The effect of early treatment by cerivastatin on the serum level of C-reactive protein, interleukin-6, and interleukin-8 in the patients with unstable angina and non-Q-wave myocardial infarction. *Mol Cell Biochem*. 2003;246:45-50.

27. Pedersen TR, Jahnsen KE, Vatn S, et al. Benefits of early lipid-lowering intervention in high-risk patients: the lipid intervention strategies for coronary patients study. *Clin Ther*. 2000;22:949-960.

28. Ostadal P, Alan D, Hajek P, et al. Fluvastatin in the therapy of acute coronary syndrome: rationale and design of a multicenter, randomized, double-blind, placebo-controlled trial (the FACS trial). *Curr Control Trials Cardiovasc Med*. 2005;6:4.

29. Dupuis J, Tardif JC, Cernacek P, Theroux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes: the RECIFE (Reduction of Cholesterol in Ischemia and Function of the Endothelium) trial. *Circulation*. 1999;99:3227-3233.

30. den Hartog FR, van Kalmthout PM, van Loenhout TT, et al. Pravastatin in acute ischaemic syndromes: results of a randomised placebo-controlled trial. *Int J Clin Pract*. 2001;55:300-304.

31. Kayikçioğlu M, Can L, Kultursay H, Payzin S, Turkoglu C. Early use of pravastatin in patients with acute myocardial infarction undergoing coronary angioplasty. *Acta Cardiol*. 2002;57:295-302.

32. Thompson PL, Meredith I, Amerena J, et al. Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial. *Am Heart J*. 2004;148:e2.

33. Colivicchi F, Guido V, Tubaro M, et al. Effects of atorvastatin 80 mg daily early after onset of unstable angina pectoris or non-Q-wave myocardial infarction. *Am J Cardiol*. 2002;90:872-874.
34. Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. *Circulation*. 2004;110:1061-1068.
35. Liem AH, van Boven AJ, Veeger NJ, et al. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. *Eur Heart J*. 2002;23:1931-1937.
36. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z Trial. *JAMA*. 2004;292:1307-1316.
37. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. *Psychol Methods*. 2001;6:203-217.
38. Lachin JM. Sample size, power, and efficiency. In: Lachin JM, ed. *Biostatistical Methods*. New York, NY: John Wiley & Sons; 2000:61-86.
39. Glesby MJ, Hoover DR. Survivor treatment selection bias in observational studies: examples from the AIDS literature. *Ann Intern Med*. 1996;124:999-1005.
40. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med*. 1998;338:1516-1520.
41. Laupacis A, Mamdani M. Observational studies of treatment effectiveness: some cautions. *Ann Intern Med*. 2004;140:923-924.
42. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? *JAMA*. 2003;289:2554-2559.
43. Walter DH. Insights into early and rapid effects of statin therapy after coronary interventions. *Curr Pharm Des*. 2004;10:369-373.
44. Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-1357.
45. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA*. 2002;288:462-467.
46. Nordmann A, Blattmann L, Gallino A, et al. Systematic, immediate in-hospital initiation of lipid-lowering drugs during acute coronary events improves lipid control. *Eur J Intern Med*. 2000;11:309-316.
47. Smith CS, Cannon CP, McCabe CH, et al. Early initiation of lipid-lowering therapy for acute coronary syndromes improves compliance with guideline recommendations: observations from the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS-TIMI 16) trial. *Am Heart J*. 2005;149:444-450.
48. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol*. 2004;24:e149-e161.
49. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-1435.
50. Antman EM, Anbe DT, Armstrong PW, et al; Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2004;110:588-636.
51. Foody JM, Roe MT, Chen AY, et al. Lipid management in patients with unstable angina pectoris and non-ST-segment elevation acute myocardial infarction (from CRUSADE). *Am J Cardiol*. 2005;95:483-485.

I studied the lives of great men and famous women, and I found that the men and women who got to the top were those who did the jobs they had in hand, with everything they had of energy and enthusiasm and hard work.

—Harry S Truman (1884-1972)