

Association of Statin Therapy with Outcomes of Acute Coronary Syndromes: The GRACE Study

Frederick A. Spencer, MD; Jeanna Allegrone, BA; Robert J. Goldberg, PhD; Joel M. Gore, MD; Keith A.A. Fox, MB, ChB, FRCP; Christopher B. Granger, MD; Rajendra H. Mehta, MD; and David Brieger, MD, for the GRACE Investigators*

Background: Statins administered early in patients with acute coronary syndromes may lead to modest reductions in recurrent ischemic events.

Objective: To examine the association between previous and early in-hospital statin therapy and the presentation and outcomes of an acute coronary syndrome.

Design: Cohort study.

Setting: 94 hospitals in 14 countries participating in the Global Registry of Acute Coronary Events (GRACE).

Patients: 19 537 patients with an acute coronary syndrome who were enrolled from April 1999 to September 2002.

Measurements: Statin use before and after presentation with an acute coronary syndrome and associated rates of myocardial infarction, hospital complications, and hospital mortality. The composite end point included death, in-hospital myocardial infarction, and stroke.

Results: Patients who were already taking statins when they presented to the hospital were less likely to have ST-segment elevation (odds ratio [OR], 0.79 [95% CI, 0.71 to 0.88]) or myo-

cardial infarction (OR, 0.78 [CI, 0.70 to 0.86]). Patients who continued to take statins in the hospital were less likely to experience complications or die than patients who never received statins (OR, 0.66 [CI, 0.56 to 0.77]). Patients not previously taking statins who began statin therapy in the hospital were less likely to die than patients who never received statin therapy (OR, 0.38 [CI, 0.30 to 0.48]). However, adjustment for the hospital of admission attenuated the association between initiation of statin therapy and the composite end point (OR, 0.84 [CI, 0.65 to 1.10]).

Limitations: This observational study cannot exclude confounding by clinical and hospital factors.

Conclusions: These data support the hypothesis that statin therapy can modulate early pathophysiologic processes in patients with acute coronary syndromes. A randomized trial of statin therapy in acute myocardial infarction is warranted.

Ann Intern Med. 2004;140:857-866.

www.annals.org

For author affiliations, see end of text.

See editorial comment on pp 923-924.

*For a list of the members of the GRACE Scientific Advisory Committee, see the Appendix, available at www.annals.org.

Data from randomized clinical trials support the efficacy of lipid-lowering medications, particularly statins, in the primary and secondary prevention of coronary artery disease (1–3).

The benefits of statins, however, were not readily apparent until after several months of therapy, suggesting that the drugs' lipid-lowering capabilities were largely responsible. In vitro work has suggested that statins may have an abundance of pleiotropic effects (4). These include modulation of inflammation, inhibition of platelet function and thrombosis, and enhancement of endothelial cell function. The demonstrated ability of statins to immediately affect basic pathophysiologic mechanisms has resulted in increased interest in their potential role in the setting of acute coronary syndromes. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial found that early treatment with high-dose atorvastatin modestly reduced event rates of recurrent ischemia in statin-naïve patients presenting with an acute coronary syndrome (5). These observations, while intriguing, did not conclusively establish the role of statins in patients with acute coronary syndromes. In the MIRACL trial, the failure of statins to significantly affect more concrete trial end points (for example, death or recurrent myocardial infarction [MI]) was disappointing. Whether this reflected a true lack of physiologic impact of early statin treatment or merely

indicated that the study was underpowered to detect differences in these end points remains unclear.

In a substudy using data from the Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) trial in patients with acute coronary syndromes, patients already taking statins had better short-term outcomes (decreased risk for death or nonfatal MI) than those not previously receiving statin therapy, unless statin therapy was discontinued in the hospital (6). Initiation of statin therapy after the onset of an acute coronary syndrome appeared to be less effective than treatment with statins before symptom onset.

Using data from the Global Registry of Acute Coronary Events (GRACE) project, a large, multinational, observational study of patients with acute coronary syndromes, we examined the association between previous statin therapy, presentation characteristics of acute coronary syndromes, and hospital outcomes. We also examined the effect of early in-hospital statin therapy (or withdrawal of statins) on important hospital outcomes, including death or the development of recurrent MI or stroke.

METHODS

Full details of the GRACE rationale and methods have been published elsewhere and are outlined below (7–9).

Context

While the benefits of statins in the primary and secondary prevention of coronary artery disease are clear, the value of statin therapy in acute coronary syndromes is uncertain.

Contribution

Analyzing data from a large, international observational study of acute coronary syndromes, these investigators identified associations between statin use before and during acute coronary events and favorable outcomes.

Cautions

While these data suggest a potential benefit of statins during acute coronary events, trials are necessary to determine the most appropriate use of statins in the treatment of acute coronary events.

—The Editors

Site Selection

The GRACE project is designed to reflect an unbiased population of patients with acute coronary syndromes, regardless of geographic region. Currently, 94 hospitals located in 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, the United Kingdom, and the United States) are participating in this observational study.

Patients entered in the registry must be at least 18 years of age and alive at the time of hospital presentation; be admitted with an acute coronary syndrome as a presumptive diagnosis (that is, have symptoms consistent with acute ischemia); and have at least 1 of the following: electrocardiographic changes consistent with an acute coronary syndrome, serial increases in serum biochemical markers of cardiac necrosis, or documentation of coronary artery disease (7–9). The qualifying acute coronary syndrome must not be precipitated by a significant noncardiovascular comorbid condition (for example, trauma or surgery). To ensure the enrollment of an unbiased sample, the first 10 to 20 consecutive patients (depending on each site's patient volume) are recruited from each site on a monthly basis. Where required, study investigators received approval from their local hospital ethics or institutional review board.

Data Collection

At each site, a trained coordinator collected data using a standardized case-report form. Data on demographic characteristics, medical history, presenting symptoms, duration of prehospital delay, biochemical and electrocardiographic findings, treatment practices, and hospital outcome were collected. Standardized definitions of all patient-related variables and clinical diagnoses were used. All cases were assigned to 1 of the following categories: ST-segment elevation MI, non-ST-segment elevation MI, unstable angina, and other cardiac or noncardiac diagnoses that have been previously described (7–9). Standardized definitions

were also used for selected hospital complications and outcomes.

Patient Sample

For the current study, patients who were subsequently found to have noncardiac or other cardiac (nonacute coronary syndrome) primary diagnoses and those who transferred into or out of GRACE registry hospitals were excluded from further consideration. Treatments defined as “previous use” were those taken by the patient on a long-term basis at home and within 7 days of the presenting event, based on the review of information contained in medical records and abstracted by trained study physicians and nurses. Treatments received in the hospital (within the first 24 hours or thereafter) were categorized as “within hospital.” Agents prescribed for use after discharge from participating hospitals were categorized as “at discharge.” Patient treatment categories were defined according to the following groupings: no previous treatment with statins and no treatment with statins during hospitalization, no previous therapy with statins but statin therapy instituted during hospitalization, previous therapy with statins and statin therapy continued during hospitalization, and previous therapy with statins but statin therapy not continued during the index hospitalization.

Statistical Analysis

We used the chi-square tests for discrete variables to analyze differences in demographic and clinical characteristics, treatment practices, clinical presentation (ST-segment elevation vs. non-ST-segment elevation, large infarct [creatinine phosphokinase level > 2 times the upper limit of normal] vs. small infarct), subsequent diagnosis (ST-segment elevation MI, non-ST-segment elevation MI, unstable angina), and hospital complications (death, congestive heart failure or pulmonary edema, cardiogenic shock, stroke, ventricular tachycardia or ventricular fibrillation, and cardiac arrest) in relation to statin use. The Wilcoxon rank-sum test was used to analyze differences between respective comparison groups for continuous variables.

While controlling for potentially confounding variables, we performed multivariate regression analyses to examine the association between previous statin therapy and hospital presentation (ST-segment elevation vs. no ST-segment elevation, creatine phosphokinase level ≥ 2 times normal vs. creatine phosphokinase level < 2 times the upper limit of normal), as well as any association between previous or in-hospital statin therapy and hospital outcomes (death, recurrent MI or MI after 24 hours, and stroke) or a composite end point of all 3 outcomes. Candidate variables for inclusion in the regression models evaluating previous statin use and hospital presentation included patient age, sex, smoking status, diabetes, history of vascular disease (previous MI, stroke, positive angiogram, peripheral vascular disease, percutaneous coronary intervention, or coronary artery bypass graft surgery), hypertension, hyperlipidemia, and previous therapies (aspirin,

angiotensin-converting enzyme [ACE] inhibitors, β -blockers, and other lipid-lowering agents). Candidate variables for regression models evaluating previous or in-hospital statin use and hospital outcomes included all of the previously listed characteristics plus characteristics present at the time of hospital admission (heart rate, systolic blood pressure, Killip class, ST-segment elevation or left bundle-branch block pattern, and positive cardiac enzymes) and receipt of in-hospital therapies (aspirin and other antiplatelet agents, β -blockers, unfractionated heparin, low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, cardiac catheterization, percutaneous coronary intervention, or coronary artery bypass graft surgery). Candidate variables possibly associated with the outcomes of interest ($P < 0.25$ after univariate analysis) were included in the multivariate models. Variables for which the P value exceeded 0.05 were eliminated in a stepwise fashion so that only those that had a statistically significant association with the outcome of interest were included in the final regression models. Because of their clinical relevance and potential importance, age, sex, and history of hyperlipidemia were retained in the final multivariable models for clinical outcomes regardless of statistical significance. Final models were evaluated for goodness of fit by the Hosmer–Lemeshow test.

Because between-hospital variation in use of statin treatment could be considerable and potentially affect our study results, we adjusted for hospital random effects on the observed outcomes. We used a generalized estimating equation modeling technique, assuming patients were repeated measures within each hospital. Variable estimates were generated and were then converted to odds ratios (ORs) for comparison with ORs from the final regression models.

Given the potential impact of a history of hyperlipidemia on patterns of statin use, as well as its possible effect on the hospital outcomes examined, we also tested for any potential interaction between this medical history variable and statin groups for each outcome of interest. All multivariate models were repeated, including the calculated interaction term.

Role of the Funding Source

Funding and sponsorship for the GRACE study are provided by Aventis Pharmaceuticals (Bridgewater, New Jersey). The funding source helped refine the study design and assisted with data collection, management, and analysis. The scientific conduct of the study and manuscript preparation were independent of the funding source. The GRACE Scientific Advisory Committee initiated the present study, independently confirmed all statistical analyses, and supported the preparation of this manuscript for publication.

RESULTS

The study sample consisted of 19 537 men and women with an acute coronary syndrome who were en-

rolled in GRACE from April 1999 to September 2002. Of these, 4056 (21%) were already taking statins when they presented to participating hospitals. Among the patients already receiving statin therapy, 428 (11%) did not receive statins during the acute hospitalization. Initiation of statin therapy early during hospitalization varied greatly by hospital and according to whether patients were previously taking statins. Hospital use of early statin therapy varied from 40% to 100% (median, 92%) for patients previously taking statins and from 6% to 91% (median, 42%) for statin-naïve patients.

Effect of Previous Statin Therapy on Hospital Presentation

Patients who were previously taking statins were similar in age to those who were not but were more likely to have a history of hypertension, hyperlipidemia, diabetes, or vascular disease (Table 1). Patients previously taking statins were slightly less ill at presentation; fewer presented with a rapid heart rate or hypotension or while in Killip class IV. They were more likely to already be taking aspirin, β -blockers, or ACE inhibitors and to be treated with β -blockers, statins, or glycoprotein IIb/IIIa inhibitors during hospitalization; however, they were slightly less likely to be treated with aspirin or ACE inhibitors. They were also more likely to undergo cardiac catheterization, percutaneous coronary intervention, or coronary artery bypass graft surgery than those not previously taking statins.

Patients receiving previous statin therapy were much less likely to present with or have a final hospital diagnosis of ST-segment elevation MI. Similarly, they were less likely to develop peak creatine phosphokinase levels of more than 2 times the upper limit of each hospital's normal range. These patients were also less likely to die during hospitalization or develop selected clinical complications (Figure, Table 2).

After we controlled for previously described demographic and medical history variables, patients previously taking statins were less likely to present with ST-segment elevation on their initial or qualifying electrocardiogram (OR, 0.79 [95% CI, 0.71 to 0.88]) or develop creatine phosphokinase levels more than 2 times the upper limit of normal (OR, 0.78 [CI, 0.70 to 0.86]) than patients not previously receiving statin therapy. All models had acceptable goodness of fit ($P > 0.05$) by the Hosmer–Lemeshow test.

Adjustment for hospital random effects did not significantly change the ORs for these outcomes or the interpretation of these results. We also found no significant interaction between hyperlipidemia and statin use, and inclusion of this interaction term in the multivariate models did not appreciably change our point estimates or interpretation of the results.

Predictors of Continuation or Discontinuation of In-Hospital Statin Therapy and Effect on Subsequent Outcomes

Patients who were previously taking statins and received them early during their hospitalization were

Table 1. Characteristics of Patients according to Previous Statin Use*

Characteristic	Long-Term Statin Use (n = 4056)	No Long-Term Statin Use (n = 15 481)	P Value
Demographic			
Median age, y	66.7	66.9	>0.2
Women, %	33.2	34	>0.2
Medical history, %			
Smoking	59.7	56.9	<0.001
Myocardial infarction	53.7	24.9	<0.001
Transient ischemic attack or stroke	11.9	7.9	<0.001
Diabetes	31.6	22.3	<0.001
Positive angiogram	61.5	18.3	<0.001
Peripheral vascular disease	15.3	9.0	<0.001
Hypertension	68.9	56.2	<0.001
Hyperlipidemia	88.5	32.0	<0.001
Percutaneous coronary intervention	35.6	9.0	<0.001
Coronary artery bypass graft surgery	28.9	8.3	<0.001
Presenting characteristic, %			
Killip class			
I	81.5	80.4	<0.001
II	14.0	14.2	
III	4.1	4.2	
IV	0.4	1.2	
Heart rate \geq 100 beats/min	12.3	17.3	<0.001
Systolic blood pressure <90 mm Hg	1.6	2.6	<0.001
ST-segment elevation	22.2	41.4	<0.001
Long-term medications, %			
Aspirin	72.8	32.6	<0.001
ACE inhibitors	41.5	21.9	<0.001
β -Blockers	58.4	21.6	<0.001
Other lipid-lowering agents	2.8	2.5	>0.2
Hospital medications, %			
Aspirin	92.0	93.1	0.016
Unfractionated heparin	52.8	51.3	0.088
Enoxaparin	43.7	42.3	0.108
Other LMWH	8.2	10.8	<0.001
ACE inhibitor	57.4	59.8	0.014
β -Blockers	80.7	77.0	<0.001
Statins	89.5	38.5	<0.001
Other lipid-lowering agents	3.4	3.6	>0.2
Glycoprotein IIb/IIIa (at any time)	21.7	18.5	<0.001
Interventions, %			
Cardiac catheterization	55.8	48.7	<0.001
Percutaneous coronary intervention	32.0	29.8	0.007
Coronary artery bypass graft surgery	7.4	5.3	<0.001

* ACE = angiotensin-converting enzyme; LMWH = low-molecular-weight heparin.

younger, more often men, and more likely to smoke but less likely to have diabetes or hypertension than those who discontinued statin therapy. The former group was also more likely to have been previously treated with aspirin (Table 3) and less likely to be hypotensive at hospital presentation. Patients who continued to receive statin therapy were much more likely to receive other effective cardiac therapies in the hospital (aspirin, other antiplatelet agents, enoxaparin, ACE inhibitors, β -blockers, or glycoprotein IIb/IIIa inhibitors) or undergo percutaneous coronary intervention. Patients previously receiving statin therapy who had statin therapy continued were much less likely to die in the hospital, to have certain hospital complications, or to die or have in-hospital MI or stroke (the composite end point) (Table 4).

After we controlled for previously described demographic and clinical variables, patients who were taking statins at presentation and continued taking them during hospitalization were significantly less likely to die in the hospital (OR, 0.38 [CI, 0.28 to 0.52]) or experience the composite end point (OR, 0.66 [CI, 0.56 to 0.77]) than patients who never received statins (Table 5). In contrast, patients previously taking statins who did not have statin therapy continued were no less likely to die during hospitalization (OR, 1.39 [CI, 0.91 to 2.14]) than those never receiving statin therapy. All models had acceptable goodness of fit ($P > 0.05$) by the Hosmer–Lemeshow test.

Adjustment for hospital random effects did not significantly change the previously observed ORs for in-hospital death, recurrent MI or MI after 24 hours, stroke, or the

primary composite study end point. We also found no statistically significant interaction between a history of hyperlipidemia and subsequent statin use. In addition, inclusion of this interaction term in the multivariate models did not appreciably change our point estimates or interpretation of the results (statistically significant findings remained significant).

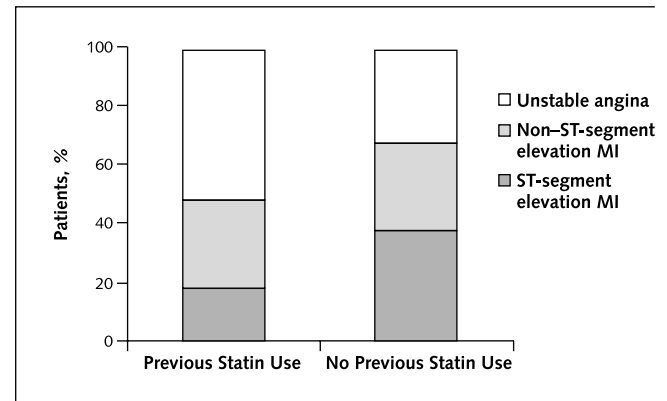
Effect of Initiation of In-Hospital Statin Therapy on Statin-Naive Patients

Of 15 481 patients not previously taking statins, 5959 (38%) began receiving statin therapy in the hospital. These patients were younger, more likely to be men, and less likely to have any of the comorbid conditions examined (with the exception of smoking and hyperlipidemia) than patients who never received statins (Table 3). They were also less likely to be taking aspirin, β -blockers, or ACE inhibitors before hospital presentation. These patients were less ill on presentation, as reflected by a heart rate of less than 100 beats/min, systolic blood pressure greater than 90 mm Hg, or absence of advanced Killip class, but were more likely to present with ST-segment elevations on their initial electrocardiogram.

Patients who began receiving statins in the hospital were much more likely to also be treated with other effective cardiac medications or undergo cardiac catheterization or percutaneous coronary intervention than patients who never received statins. With the exception of in-hospital infarction, these patients were less likely to develop important in-hospital complications and were much less likely to die in the hospital or experience the composite study end point (Table 4).

After we controlled for previously mentioned factors, patients who were not previously taking statin therapy but began taking statins during hospitalization were less likely to die in the hospital (OR, 0.38 [CI, 0.30 to 0.48]) or experience the primary composite end point (OR, 0.87 [CI, 0.78 to 0.97]) than patients who never received statins

Figure. Final diagnosis of acute coronary syndromes according to previous treatment with statins.



MI = myocardial infarction.

(Table 5). All regression models had acceptable goodness of fit ($P > 0.05$) by the Hosmer–Lemeshow test.

Adjustment for hospital random effects did not significantly change the ORs for in-hospital death, infarction, or stroke. However, adjustment for hospital of admission resulted in attenuation of the statistical significance for the association between initiation of statin therapy and the previously observed decrease in the composite end point (OR, 0.84 [CI, 0.65 to 1.10]). We also found no significant interaction between hyperlipidemia and subsequent statin therapy. In addition, inclusion of this interaction term in the multivariate models did not appreciably change our point estimates or interpretation of the results (statistically significant findings remained significant).

DISCUSSION

The results of this contemporary multinational registry of more than 19 000 patients with acute coronary syndromes suggest that previous statin therapy significantly

Table 2. Incidence of Hospital Outcomes according to Previous Statin Therapy*

Outcome	Long-Term Statin Use (n = 4056), %	No Long-Term Statin Use (n = 15 481), %	P Value
In-hospital events			
Creatine phosphokinase level >2 times the upper limit of normal	24.7	45.0	<0.001
MI after 24 h or recurrent MI	6.9	10.1	<0.001
Congestive heart failure	12.4	15.6	<0.001
Cardiogenic shock	2.3	5.0	<0.001
Pulmonary edema	5.2	6.8	<0.001
Cardiac arrest	2.6	5.9	<0.001
Sustained ventricular tachycardia or ventricular fibrillation	3.1	4.7	<0.001
Stroke	0.8	1.1	0.078
Death	3.1	6.9	<0.001
Final diagnosis			
ST-segment elevation MI	18.4	37.6	<0.001
Non-ST-segment elevation MI	29.7	29.8	<0.001
Unstable angina	51.9	32.6	<0.001

* MI = myocardial infarction.

Table 3. Characteristics of Patients with Acute Coronary Syndromes according to Statin Therapy Group*

Characteristic	Long-Term and In-Hospital Statin Use (n = 3628)	Long-Term Statin Use Only (n = 428)	P Value	No Statin Use (n = 9522)	In-Hospital Statin Use Only (n = 5959)	P Value
Demographic						
Median age, y	66.4	68.5	0.004	69.8	62.7	<0.001
Women, %	32.6	37.8	0.032	36.7	29.6	<0.001
Medical history, %						
Smoking	60.8	50.0	<0.001	52.6	63.7	<0.001
Myocardial infarction	54	50.9	>0.2	28.2	19.6	<0.001
Transient ischemic attack or stroke	11.7	13.5	>0.2	9.4	5.6	<0.001
Diabetes	31.1	35.8	0.048	23.7	20.1	<0.001
Positive angiogram	61.8	58.1	0.15	20.2	15.5	<0.001
Peripheral vascular disease	15.4	14.5	>0.2	9.9	7.5	<0.001
Hypertension	68.3	74.1	0.016	58.7	52.1	<0.001
Hyperlipidemia	88.8	86.2	0.111	25.0	43.0	<0.001
Percutaneous coronary intervention	36.1	31.9	0.091	9.6	8.0	<0.001
Coronary artery bypass graft surgery	28.8	30	>0.2	9.5	6.4	<0.001
Presenting characteristics, %						
Killip class						
I	81.6	80.3	0.081	76.7	86.2	<0.001
II	14.0	14.2		16.3	10.8	
III	4.0	4.3		5.3	2.5	
IV	0.3	1.2		1.7	0.5	
Heart rate \geq 100 beats/min	12.1	14.2	>0.2	19.5	13.8	<0.001
Systolic blood pressure <90 mm Hg	1.2	4.7	<0.001	3.2	1.6	<0.001
ST-segment elevation	22	24.3	>0.2	36.7	49	<0.001
Other long-term medications, %						
Aspirin	73.4	67.7	0.012	36.2	26.9	<0.001
ACE inhibitors	41.9	38.2	0.155	24.9	17	<0.001
β -Blockers	58.7	55.8	>0.2	24.1	17.5	<0.001
Other lipid-lowering agents	2.8	3.0	>0.2	2.6	2.4	>0.2
Other in-hospital medications, %						
Aspirin	93.2	81.7	<0.001	90.9	96.6	<0.001
Ticlopidine or clopidogrel	42.7	31.4	<0.001	25.9	46.9	<0.001
Unfractionated heparin	52.9	52.0	>0.2	49.9	53.5	<0.001
Enoxaparin	44.4	37.1	0.004	38.5	48.3	<0.001
Other LMWH	8.2	8.1	>0.2	9.6	12.9	<0.001
ACE inhibitor	58.6	47.3	<0.001	56.7	64.8	<0.001
β -Blockers	82.4	66.6	<0.001	71.4	85.9	<0.001
Other lipid-lowering agent	3.5	2.5	>0.2	4.6	2.1	<0.001
Glycoprotein IIb/IIIa inhibitors	22.2	17.1	0.017	13.2	27.1	<0.001
Interventions, %						
Cardiac catheterization	56.1	52.8	0.198	41.7	59.9	<0.001
Percutaneous coronary intervention	32.6	26.9	0.018	22.8	40.9	<0.001
Coronary artery bypass graft surgery	7.2	9.0	0.182	5.3	5.4	>0.2

* ACE = angiotensin-converting enzyme; LMWH = low-molecular-weight heparin.

affects the severity of hospital presentation and that previous or early statin therapy favorably affects clinically relevant hospital outcomes. Patients who presented with an acute coronary syndrome and were previously taking statins generally had more comorbid conditions but were less likely to present with ST-segment elevation MI, experience a large infarct, have important clinical complications, or die during the index hospitalization. Of interest, much of the observed effect associated with statin pretreatment was lost if statin therapy was not continued during hospitalization for an acute coronary syndrome. Despite having less severe hospital presentation, such patients had

hospital death rates similar to those of patients who had never received statins.

A similar effect of pretreatment with statins, and a corresponding loss of any observed reduction in outcome events with subsequent statin withdrawal, was previously demonstrated in a subgroup analysis of the PRISM database (6). In this analysis of patients receiving either tirofiban or placebo for an acute coronary syndrome, patients presenting while taking statins had significantly lower rates of nonfatal MI and all-cause mortality at 30 days than statin-naive patients. However, if statin therapy was discontinued, these patients experienced an almost 3-fold

Table 4. Hospital Outcomes of Patients with Acute Coronary Syndromes according to Statin Group*

In-Hospital Events	Long-Term and In-Hospital Statin Use	Long-Term Statin Use Only	P Value	No Statin Use	In-Hospital Statin Use Only	P Value
	%			%		
MI after 24 h or recurrent MI	7	6.1	>0.2	9.3	11.5	<0.001
Congestive heart failure	12.3	13.3	>0.2	19	10.1	<0.001
Pulmonary edema	4.9	8.0	0.007	8.5	4.0	<0.001
Cardiogenic shock	1.6	8.7	<0.001	6.5	2.5	<0.001
Cardiac arrest	1.9	8.2	<0.001	7.5	3.4	<0.001
Sustained ventricular tachycardia or ventricular fibrillation	2.8	6.2	<0.001	5	4.1	0.006
Stroke	0.7	1.4	0.142	1.3	0.9	0.043
Death	2.1	11.6	<0.001	9.9	2.1	<0.001
Death, stroke, or in-hospital MI	9.2	17.3	<0.001	17.9	13.5	<0.001

* MI = myocardial infarction.

higher event rate than those who continued therapy. This study was limited by a small sample size and few fatal or nonfatal coronary events.

Our study, using a large, more generalizable database, confirms and extends the PRISM findings. Unlike the PRISM researchers, we were able to further explore the effect of pretreatment with statins on the severity of presentation of acute coronary syndromes. Our data suggest that previous statin therapy may be protective in that patients previously taking statins are less likely to present with ST-segment elevation or have a large infarct. This decrease in acute disease severity would be expected to translate to improved hospital outcomes, which we observed in both univariate and multivariable adjusted analyses for patients continuing statin therapy. These findings

are similar to the results of previous studies that have examined the effect of previous aspirin therapy on acute coronary syndrome presentation. These studies documented an association between previous use of aspirin and less severe presentation of patients hospitalized with acute MI (10–12).

Statins probably attenuate the severity of acute coronary syndromes through numerous pathophysiologic mechanisms that involve more than lipid-lowering capabilities. Emerging clinical and basic science data suggest that statins have numerous pleiotropic actions, including inhibition of inflammation, antithrombotic and antiplatelet effects, and modulation of endothelial function (13–16). Any of these functions might be expected to attenuate the consequences of an acute plaque rupture and hinder devel-

Table 5. Hospital Outcomes of Patients with Acute Coronary Syndrome Stratified according to Statin Use Pattern and Compared with Outcomes in Patients Never Receiving Statins*

Outcome	OR for Long-Term Statin Use Only (95% CI)	OR for Long-Term and In-Hospital Statin Use (95% CI)	OR for In-Hospital Statin Use Only (95% CI)
Death			
Crude	1.19 (0.88–1.62)	0.20 (0.16–0.25)	0.19 (0.16–0.23)
Multivariate adjusted†	1.39 (0.91–2.14)	0.38 (0.28–0.52)	0.38 (0.30–0.48)
MI after 24 h or recurrent MI			
Crude	0.64 (0.43–0.95)	0.74 (0.64–0.85)	1.27 (1.14–1.41)
Multivariate adjusted‡	0.69 (0.43–1.11)	0.90 (0.75–1.07)	1.22 (1.08–1.37)
Stroke			
Crude	1.14 (0.50–2.59)	0.58 (0.38–0.88)	0.72 (0.52–0.99)
Multivariate adjusted§	1.08 (0.43–2.73)	0.68 (0.42–1.12)	0.80 (0.57–1.14)
Composite end point (death, MI, or stroke)			
Crude	0.95 (0.74–1.23)	0.46 (0.41–0.52)	0.71 (0.65–0.78)
Multivariate adjusted	1.02 (0.74–1.41)	0.66 (0.56–0.77)	0.87 (0.78–0.97)

* $P > 0.05$ for the Hosmer–Lemeshow goodness-of-fit test for all multivariate analyses. MI = myocardial infarction; OR = odds ratio.

† Adjusted for age, sex, history of hyperlipidemia, history of hypertension, history of diabetes, presenting heart rate >100 beats/min, presenting systolic blood pressure >90 mm Hg, presenting Killip class >1 , ST-segment elevation or left bundle-branch block pattern on presentation, positive cardiac enzymes, long-term aspirin use, in-hospital aspirin use, in-hospital thienopyridine use, in-hospital low-molecular-weight heparin use, in-hospital angiotensin-converting enzyme inhibitor use, in-hospital β -blocker use, in-hospital glycoprotein IIb/IIIa inhibitor use, cardiac catheterization, and coronary artery bypass graft surgery.

‡ Adjusted for age, sex, history of hyperlipidemia, presenting heart rate >100 beats/min, ST-segment elevation or left bundle-branch block pattern on presentation, long-term angiotensin-converting enzyme inhibitor use, long-term use of other lipid-lowering agents, in-hospital aspirin use, in-hospital heparin use, in-hospital angiotensin-converting enzyme inhibitor use, in-hospital glycoprotein IIb/IIIa inhibitor use, and coronary artery bypass graft surgery.

§ Adjusted for age, sex, history of hyperlipidemia, history of hypertension, positive cardiac enzymes, and coronary artery bypass graft surgery.

|| Adjusted for age, sex, history of hyperlipidemia, presenting heart rate >100 beats/min, presenting systolic blood pressure >90 mm Hg, presenting Killip class >1 , ST-segment elevation or left bundle-branch block pattern on presentation, long-term aspirin use, long-term use of other lipid-lowering agents, in-hospital aspirin use, in-hospital heparin use, in-hospital β -blocker use, in-hospital glycoprotein IIb/IIIa inhibitor use, cardiac catheterization, and coronary artery bypass graft surgery.

opment of a fully occlusive platelet-rich thrombus. In addition, increasing data from *in vitro* studies suggest that statins may modulate physiologic processes occurring after an acute infarct. Pretreatment with statins has been shown to minimize ischemic injury in normocholesterolemic mouse models of MI and stroke (17, 18). In these studies, the investigators suggested that the beneficial effects of statin therapy were mediated by an increase in the endothelial release of nitrous oxide that appeared to be unrelated to any inhibitory effect on cholesterol biosynthesis. Possible protective mechanisms of enhanced nitrous oxide production include augmentation of endothelial-dependent blood flow, inhibition of platelet aggregation, and suppression of leukocyte–endothelial interactions. In another mouse model of MI, mice treated early and for 4 subsequent weeks with statin therapy displayed attenuated left ventricular dilatation, decreased left ventricular filling pressures, and improved survival compared with those receiving placebo (19). These effects were associated with and may have been mediated by attenuation of cardiac matrix metalloproteinases.

Unlike previous studies demonstrating the benefit of pretreatment with aspirin in patients with acute MI (who usually continued taking aspirin in the hospital), we were also able to explore the effect of discontinuation of therapy with a beneficial therapeutic agent on many important hospital outcomes. Although it must be acknowledged that patients who stopped taking statins in the hospital may have had worse outcomes because of differences in measured (or unmeasured) baseline characteristics, clinical presentation, and use of concomitant therapies, regression analyses controlling for these and several additional variables did not significantly attenuate our findings.

Our data suggest that withdrawal of statins abrogates the protective effect of statin pretreatment and perhaps results in a “rebound” in previously described pathophysiologic mechanisms. This rebound phenomenon may contribute to destabilization of recently ruptured atherosclerotic plaque. Indeed, in the PRISM study, event rates in patients who had received but then discontinued statin therapy were increased during the first 7 days after discontinuation (6). The actual mechanisms by which a rebound effect may occur remain to be delineated. In a study of 8 healthy patients, treatment with atorvastatin resulted in early (<48 hours) decreases in high-sensitivity C-reactive protein level and significant augmentation of endothelium-dependent blood flow (20). After discontinuation of therapy, endothelium-dependent blood flow diminished to below baseline within 24 hours, suggesting a paradoxical increase in endothelial dysfunction. Of note, C-reactive protein level remained suppressed for 3 days after discontinuation of atorvastatin therapy, thereby providing little evidence for a concomitant rebound in inflammation. In a subsequent series of experiments involving a mouse model, the same investigators demonstrated that withdrawal of statins can result in marked suppression of endothelial ni-

tric oxide production within 2 days (21). This effect was subsequently shown to be mediated through negative-feedback regulation of gene transcription of the guanosine triphosphate–binding protein rho. Since this protein is instrumental in the endothelial release of nitrous oxide, release of tissue plasminogen activator, adhesion of monocytes to endothelium, and migration of vascular smooth-muscle cells, the effect of statin withdrawal on guanosine triphosphate may substantially alter the physiologic characteristics of the healing atherosclerotic plaque.

We were also able to assess the effect of early statin therapy on outcomes in statin-naïve patients presenting with acute coronary syndromes. The demonstrated ability of statins to affect numerous pathophysiologic processes independent of their lipid-lowering capacity has generated considerable interest in their efficacy as an early treatment for patients with acute coronary syndromes. The MIRACL trial demonstrated a modest reduction in a composite end point of death, MI, or recurrent ischemia in patients with an acute coronary syndrome treated with early high-dose atorvastatin (5). This reduction was primarily driven by a reduction in the “softer” trial end point of recurrent ischemia. Therefore, the clinical impact of early statin therapy for patients with an acute coronary syndrome remains controversial. Our study suggests that early treatment with statin therapy in patients with acute coronary syndromes may be associated with decreased hospital mortality. However, we could not demonstrate any concomitant association with a reduced risk for stroke or infarction or reinfarction. Accordingly, these findings should be interpreted with the appropriate caution. Patients treated with statins were significantly younger, had fewer comorbid conditions, and were more likely to receive effective cardiac therapies than any of the other respective comparison groups. These and possible differences in other unmeasured factors make our findings susceptible to several possible biases that may attenuate or exaggerate any observed associations.

These caveats notwithstanding, some data suggest that initiation of lipid-lowering therapy during hospitalization in patients with acute MI is associated with enhanced long-term adherence and postdischarge outcomes. The Cardiac Hospitalization Atherosclerosis Management Program was an algorithm-driven treatment-management program that increased the use of lipid-lowering agents before hospital discharge in patients with MI from 6% to 86% (22). At 1-year follow-up, use of lipid-lowering therapy had increased markedly from before the intervention (10%) to after it (91%). The increased use of statins and other cardioprotective therapies (aspirin, β -blockers, and ACE inhibitors) was associated with a significant reduction in the rate of death and nonfatal MI at 1 year. Similarly, patients enrolled in the Swedish Register of Cardiac Intensive Care who received statins at or before hospital discharge experienced a 25% reduction in 1-year mortality compared with patients who were not receiving statins when discharged (23). These data suggest that, barring substantial contra-

indications, early statin therapy should at least be considered in all patients admitted with acute MI to enhance long-term use and adherence rates.

The strengths of our investigation include its large sample size, the extent of data collected, and the ability to contrast the use and effect of statin therapy in a broad spectrum of patients with acute coronary syndromes before and after hospital presentation. However, our work has several limitations. Since our study was not a randomized trial of statin therapy or therapy discontinuation, no firm conclusions can be made about a causal relationship between early statin treatment or withdrawal and hospital outcomes. We could not examine the effect of specific types of statins, dosages, or previous duration of therapy on observed outcomes. Finally, we could not document reasons for use or nonuse of statin therapy by the different treating physicians. Specifically, we could not document the reasons for discontinuation of statin therapy during hospitalization. This represents a potential source of confounding by indication, since our regression analyses could not control for all clinical variables that may have prompted statin withdrawal and may have been associated with worse hospital outcomes. It is also possible that other unmeasured variables influenced the effect of previous or early statin therapy on acute coronary syndrome presentation and hospital outcomes.

In summary, the results of this large observational study suggest that patients who present with an acute coronary syndrome despite taking statins have less severe presentation, fewer in-hospital complications, and lower hospital death rates. The observed beneficial effect on hospital outcomes is less apparent in patients who do not continue taking statins during hospitalization. In statin-naïve patients with acute coronary syndromes, early statin therapy was associated with an improvement in hospital outcomes. These data support the hypothesis that statin therapy can modulate pathophysiologic processes in patients with acute coronary syndromes. Future randomized trials evaluating the effect of early statin therapy on clinical outcomes in patients with acute coronary syndromes are needed to more systematically address this question. In addition, researchers should consider including patients previously taking statin therapy in these trials. This could provide otherwise unobtainable data on the impact of early statin withdrawal in patients with acute coronary syndromes.

From University of Massachusetts Medical School, Worcester, Massachusetts; The University and The Royal Infirmary of Edinburgh, Edinburgh, Scotland, United Kingdom; Duke University Medical Center, Durham, North Carolina; University of Michigan, Ann Arbor, Michigan; and Concord Hospital, Sydney, Australia.

Grant Support: GRACE is supported by an unrestricted educational grant from Aventis Pharma, Bridgewater, New Jersey.

Potential Financial Conflicts of Interest: *Honoraria:* K.A.A. Fox (Aventis, Bristol-Myers Squibb/Sanofi); *Grants received:* K.A.A. Fox

(Aventis, Bristol-Myers Squibb/Sanofi), C.B. Granger (Aventis, Bristol-Myers Squibb/Sanofi, Organon, Novartis, AstraZeneca).

Requests for Single Reprints: Frederick A. Spencer, MD, Department of Medicine/Division of Cardiovascular Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655; e-mail, spencerf@ummc.org.

Current author addresses and author contributions are available at www.annals.org.

References

1. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001-9. [PMID: 8801446]
2. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med*. 1998;339:1349-57. [PMID: 9841303]
3. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-9. [PMID: 7968073]
4. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. *JAMA*. 1998;279:1643-50. [PMID: 9613915]
5. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711-8. [PMID: 11277825]
6. Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD, et al. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation*. 2002;105:1446-52. [PMID: 11914253]
7. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J*. 2001;141:190-9. [PMID: 11174331]
8. Fox KA, Goodman SG, Klein W, Brieger D, Steg PG, Dabbous O, et al. Management of acute coronary syndromes. Variations in practice and outcome; findings from the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2002;23:1177-89. [PMID: 12127920]
9. Steg PG, Goldberg RJ, Gore JM, Fox KA, Eagle KA, Flather MD, et al. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol*. 2002;90:358-63. [PMID: 12161222]
10. Spencer FA, Santopinto JJ, Gore JM, Goldberg RJ, Fox KA, Moscucci M, et al. Impact of aspirin on presentation and hospital outcomes in patients with acute coronary syndromes (The Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol*. 2002;90:1056-61. [PMID: 12423703]
11. Col NF, Yarzbski J, Gore JM, Alpert JS, Goldberg RJ. Does aspirin consumption affect the presentation or severity of acute myocardial infarction? *Arch Intern Med*. 1995;155:1386-9. [PMID: 7794087]
12. Borzak S, Cannon CP, Kraft PL, Douthat L, Becker RC, Palmeri ST, et al. Effects of prior aspirin and anti-ischemic therapy on outcome of patients with unstable angina. TIMI 7 Investigators. Thrombin Inhibition in Myocardial Ischemia. *Am J Cardiol*. 1998;81:678-81. [PMID: 9527073]
13. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation*. 2001;103:926-33. [PMID: 11181465]
14. Notarbartolo A, Davi G, Averna M, Barbagallo CM, Ganci A, Giammarresi C, et al. Inhibition of thromboxane biosynthesis and platelet function by simvastatin in type IIa hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 1995;15:247-51. [PMID: 7749833]
15. Hernandez-Perera O, Perez-Sala D, Navarro-Antolin J, Sanchez-Pascuala

- R, Hernandez G, Diaz C, et al. Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. *J Clin Invest* 1998;101:2711-9. [PMID: 9637705]
16. Fukumoto Y, Libby P, Rabkin E, Hill CC, Enomoto M, Hirouchi Y, et al. Statins alter smooth muscle cell accumulation and collagen content in established atheroma of watanabe heritable hyperlipidemic rabbits. *Circulation*. 2001;103:993-9. [PMID: 11181475]
17. Lefer AM, Campbell B, Shin YK, Scalia R, Hayward R, Lefer DJ. Simvastatin preserves the ischemic-reperfused myocardium in normocholesterolemic rat hearts. *Circulation*. 1999;100:178-84. [PMID: 10402448]
18. Endres M, Laufs U, Huang Z, Nakamura T, Huang P, Moskowitz MA, et al. Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci U S A*. 1998;95:8880-5. [PMID: 9671773]
19. Hayashidani S, Tsutsui H, Shiomu T, Suematsu N, Kinugawa S, Ide T, et al. Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. *Circulation*. 2002;105:868-73. [PMID: 11854129]
20. Laufs U, Wassmann S, Hilgers S, Ribaudo N, Bohm M, Nickenig G. Rapid effects on vascular function after initiation and withdrawal of atorvastatin in healthy, normocholesterolemic men. *Am J Cardiol*. 2001;88:1306-7. [PMID: 11728362]
21. Laufs U, Endres M, Custodis F, Gertz K, Nickenig G, Liao JK, et al. Suppression of endothelial nitric oxide production after withdrawal of statin treatment is mediated by negative feedback regulation of rho GTPase gene transcription. *Circulation*. 2000;102:3104-10. [PMID: 11120702]
22. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol*. 2001;87:819-22. [PMID: 11274933]
23. Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA*. 2001;285:430-6. [PMID: 11242427]

APPENDIX: GRACE SCIENTIFIC ADVISORY COMMITTEE

Keith A.A. Fox, United Kingdom, and Joel M. Gore, United States (*Co-Chairs*); Kim A. Eagle, United States, and Philippe Gabriel Steg, France (*Publication Committee Co-Chairs*); Giancarlo Agnelli, Italy; Frederick A. Anderson, United States; Álvaro Avezum, Brazil; David Brieger, Australia; Andrzej Budaj, Poland; Marcus D. Flather, United Kingdom; Robert J. Goldberg, United States; Shaun G. Goodman, Canada; Christopher B. Granger, United States; Dietrich C. Gulba, Germany; Enrique P. Gurfinkel, Argentina; Brian M. Kennelly, United States; Werner Klein, Austria; José López-Sendón, Spain; Gilles Montalescot, France; and Frans Van de Werf, Belgium.

Current Author Addresses: Drs. Spencer, Goldberg, and Gore and Ms. Allegrone: Department of Medicine/Division of Cardiovascular Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655.
Dr. Fox: The Royal Infirmary of Edinburgh, Department of Cardiology, Edinburgh, Scotland EH3 9WY, United Kingdom.

Dr. Granger: Duke University Medical Center, 2400 Pratt Street, Room 0311, Terrace Level, Box 3409, Durham, NC 27705.

Dr. Mehta: University of Michigan Health System, Division of Cardiology, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0366.

Dr. Brieger: Concord Repatriation Hospital, Coronary Care Unit, Level 3, Multi Building, Hospital Road, Concord NSW 2139, Australia.

Author Contributions: Conception and design: F.A. Spencer, J.M. Gore, C.B. Granger.

Analysis and interpretation of the data: F.A. Spencer, J. Allegrone, R.J. Goldberg, J.M. Gore, K.A.A. Fox.

Drafting of the article: F.A. Spencer, R.J. Goldberg.

Critical revision of the article for important intellectual content: F.A. Spencer, R.J. Goldberg, J.M. Gore, K.A.A. Fox, C.B. Granger, R.H. Mehta, D. Brieger.

Final approval of the article: F.A. Spencer, J. Allegrone, R.J. Goldberg, J.M. Gore, K.A.A. Fox, C.B. Granger, R.H. Mehta, D. Brieger.

Provision of study materials or patients: R.H. Mehta, D. Brieger.

Statistical expertise: J. Allegrone.

Obtaining of funding: J.M. Gore.

Administrative, technical, or logistic support: J.M. Gore.