

# Withdrawal of Statins Increases Event Rates in Patients With Acute Coronary Syndromes

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**Background**—HMG-CoA Reductase Inhibitors (statins) reduce cardiac event rates in patients with stable coronary heart disease. Withdrawal of chronic statin treatment during acute coronary syndromes may impair vascular function independent of lipid-lowering effects and thus increase cardiac event rate.

**Methods and Results**—We investigated the effects of statins on the cardiac event rate in 1616 patients of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study who had coronary artery disease and chest pain in the previous 24 hours. We recorded death and nonfatal myocardial infarction during the 30-day follow-up. Baseline clinical characteristics did not differ among 1249 patients without statin therapy, 379 patients with continued statin therapy, and 86 patients with discontinued statin therapy after hospitalization. Statin therapy was associated with a reduced event rate at 30-day follow-up compared with patients without statins (adjusted hazard ratio, 0.49 [95% CI, 0.21 to 0.86];  $P=0.004$ ). If the statin therapy was withdrawn after admission, cardiac risk increased compared with patients who continued to receive statins (2.93 [95% CI, 1.64 to 6.27];  $P=0.005$ ) and tended to be higher compared with patients who never received statins (1.69 [95% CI, 0.92 to 3.56];  $P=0.15$ ). This was related to an increased event rate during the first week after onset of symptoms and was independent of cholesterol levels. In a multivariate model, troponin T elevation ( $P=0.005$ ), ST changes ( $P=0.02$ ), and continuation of statin therapy ( $P=0.008$ ) were the only independent predictors of patient outcome.

**Conclusions**—Statin pretreatment in patients with acute coronary syndromes is associated with improved clinical outcome. However, discontinuation of statins after onset of symptoms completely abrogates this beneficial effect. (*Circulation*. 2002;105:1446-1452.)

**Key Words:** angina ■ coronary disease ■ statins ■ ischemia ■ prognosis

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) block mevalonate synthesis, resulting in positive effects on lipid parameters, particularly LDL cholesterol. Landmark trials have demonstrated a marked reduction in the risk for coronary events in patients with stable coronary heart disease.<sup>1-6</sup> These compelling data constitute the evidence for the widespread use of statins to improve coronary risk profiles in the settings of primary and secondary prevention. However, this reduction in cardiovascular events is incompletely explained by the achieved reduction in LDL cholesterol level.<sup>7-9</sup> There is growing evidence that local and systemic inflammation play key roles in the progression of atherosclerosis; eg, higher plasma levels of C-reactive protein were found in patients with unstable angina compared with patients with stable angina.<sup>10-12</sup> Such

inflammatory reactions may promote plaque fissuring or erosion and may be involved in the onset as well as promotion of acute coronary syndromes.<sup>13,14</sup>

In this respect, recent studies indicated that statins increase the release of endothelial nitric oxide (NO) independent of cholesterol levels.<sup>15,16</sup> Apart from its vasodilator activity, endothelium-derived NO also modifies inflammatory responses,<sup>17,18</sup> platelet aggregation,<sup>19</sup> and smooth muscle cell proliferation.<sup>20</sup> Animal studies have demonstrated that the short-term withdrawal of statin therapy leads to a profound rebound phenomenon with impaired NO bioavailability.<sup>21</sup> Consistently, a recent study in patients with stable coronary heart disease showed a 3-fold increase in thrombotic vascular events after simvastatin treatment was stopped and continued with relatively lower doses of fluvastatin.<sup>22</sup>

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To test the hypothesis that the discontinuation of statin therapy has an adverse impact on patients with acute coronary syndromes, we performed the present subgroup analysis by using the data set of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial.<sup>23</sup>

## Methods

### Patients

The study population of the PRISM trial was composed of 3232 patients with chest pain at rest or accelerating chest pain within the last 24 hours. For all patients, coronary artery disease had to be manifested by one of the following criteria: ECG evidence of myocardial ischemia (new ST-segment changes or T-wave inversion), elevation of creatine kinase (CK) enzyme activity above twice the upper limit of normal, or history of coronary heart disease (myocardial infarction [MI] or coronary revascularization, a positive exercise or dipyridamole nuclear stress test, or narrowing of at least 50% of the luminal diameter of a major coronary artery on a previous angiogram).<sup>23</sup>

All patients received aspirin before random assignment to treatment with either tirofiban or heparin. Angiography and revascularization during 48-hour infusion therapy were discouraged. The primary end point was a composite of death, MI, or recurrent ischemia at the end of the 48-hour infusion period. The secondary end point was death, MI, or recurrent ischemia at 7-day and 30-day follow-up. Recurrent ischemia was defined as recurrent chest pain with ischemic ST-T-segment changes despite full anti-anginal therapy. MI was defined as typical chest pain with new ST-T-segment changes, new pathological Q waves, or both, accompanied by an increase in CK level to more than twice the upper limit of normal.<sup>23</sup>

Plasma samples for the determination of the cardiac marker troponin T and total cholesterol levels were collected at baseline and at 24, 48, and 72 hours. Troponin T was quantified with the use of a one-step enzyme immunoassay based on electrochemiluminescence technology (Elecys 2010, Roche Diagnostics).<sup>24</sup>

### Statistical Analysis

Thirty-day event rates (death, MI) were estimated with the use of Kaplan-Meier techniques, and the impact of statin therapy as a time-dependent covariate on patient outcome was evaluated with a Cox proportional hazards regression model, adjusting for baseline prognostic factors (eg, troponin T, ECG changes, cardiac risk factors, age, sex) and randomized treatment.<sup>25</sup>

Cox proportional hazards regression models with time-dependent covariates were fitted to obtain the hazard ratios (including 95% CI) for the measures of the efficacy of treatment with statins; the analysis was adjusted for the confounding effects of relevant prognostic indicators (troponin T, ECG changes, cardiac risk factors, age, sex) and randomized treatment.<sup>25</sup> Homogeneity of the odds ratios across the different statins and statin dosages was examined with the Breslow-Day statistic. If the resulting *P* value was nonsignificant, individual event rates were weighted and pooled.

All results for continuous variables are expressed as medians with 95% CI. Comparisons between groups were analyzed by *t* test (2-sided) or ANOVA for experiments with more than 2 subgroups. Post hoc range tests and pairwise multiple comparisons were performed with the *t* test (2-sided) with Bonferroni adjustment. Comparison of categorical variables was generated by the Pearson  $\chi^2$  test. All analyses were performed with SPSS 10.0 (SPSS Inc). Probability values <0.05 were considered statistically significant.

## Results

Of 3232 PRISM patients, complete medical records including statin therapy were available for 1616 patients (n=808 heparin, n=808 tirofiban, 50.0%). Absolutely no differences were observed between this substudy population and the excluded patients regarding the baseline characteristics of

age, sex, cardiovascular risk profile, concomitant treatment before and after random assignment, and randomized treatment. For the substudy population, a total of 47 deaths and 65 nonfatal MIs (49% of the patients had a CK rise >5 times the upper limit of normal) were recorded during the 30-day follow-up period (event rate, 6.9%).

### Pretreatment With Statins

The majority of the baseline clinical characteristics did not differ between 379 patients with statin therapy and 1151 patients without statins (Table 1). However, more patients who received statins before onset of symptoms had a history of coronary heart disease. The majority of patients in the statin group received simvastatin with 50.0% followed by lovastatin (24.1%) and pravastatin (20.4%). Most of the patients received an intermediate statin dose. For simvastatin, 85.2% of the patients received an intermediate dose of 10 to 20 mg per day. Fewer than 10% of the patients were treated with a low or a high statin dose, respectively. Median cholesterol level in the statin group was 10.1% lower compared with patients who did not receive statins (*P*=0.041). A total cholesterol level >200 mg/dL was observed in 43% for the statin group and in 58% for the patients who did not receive statins (*P*<0.001).

At 30-day follow-up, statin therapy was associated with a significantly reduced incidence of death and nonfatal MI compared with patients who did not receive statins throughout the study period (adjusted hazard ratio, 0.49 [95% CI, 0.21 to 0.86]; *P*=0.004) (Figure 1). Recurrent ischemia was significantly lower in the statin group at 48-hour follow-up (adjusted hazard ratio, 0.35 [95% CI, 0.16 to 0.89]; *P*<0.01), but this difference lost statistical significance at 30-day follow-up (adjusted hazard ratio, 0.79 [95% CI, 0.41 to 1.56]; *P*=0.21) (Table 2). Revascularization procedures were also significantly lower in patients treated with statins (adjusted hazard ratio, 0.60 [95% CI, 0.35 to 0.97]; *P*=0.042). The duration of hospitalization was shorter for patients who received statin therapy (11.5 versus 9.2 days; *P*=0.02). There was a consistent trend toward a reduced event rate for patients receiving different types of statins, as indicated by the *P* value of 0.59 with the Breslow-Day test for odds ratio heterogeneity. All statins appeared to provide a similar protective effect when patients were pretreated for at least 6 months. Because most of the patients received an intermediate statin dose, we cannot provide a ranking of the statins with respect to the dosing.

Regression analysis, including a term of interaction, indicated no significant correlation between statin therapy and benefit of treatment with tirofiban. The treatment benefit of tirofiban was consistent throughout all subgroups and for all three investigated time points. At 30-day follow-up, benefit of treatment with tirofiban was similar in patients receiving statins (adjusted hazard ratio, 0.80 [95% CI, 0.56 to 1.23]; *P*=0.18) and those patients who did not receive statins (adjusted hazard ratio, 0.72 [95% CI, 0.58 to 1.05]; *P*=0.08) (Figure 2).

### Discontinuation of Statin Therapy After Admission

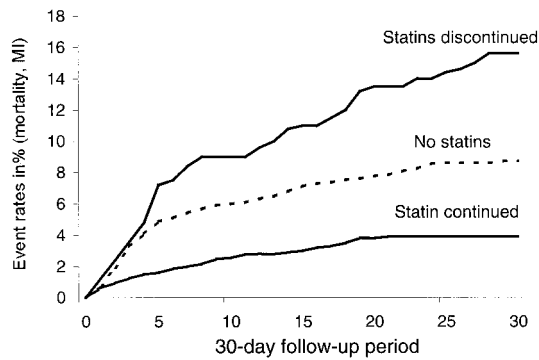
Of 465 patients who were pretreated with statins before onset of symptoms, statin therapy was withdrawn in 18.5% of patients (n=86). Baseline characteristics did not differ from

**TABLE 1. Patients' Baseline Characteristics According to Statin Therapy**

	No Statins	Statins Continued	Statins Discontinued	<i>P</i>
No. of patients	1151	369	86	
Male sex, %	68.5	67.5	65.1	0.55
Age, y	62.2±10.6	62.7±11.1	61.4±10.8	0.69
Baseline troponin T level, μg/L	0.17±0.09	0.15±0.06	0.14±0.06	0.26
Time after onset of symptoms, wk	7.9±2.8	8.3±3.1	7.8±4.7	0.72
Killip class ≥II, %	11.5	12.4	10.9	0.59
Systolic BP, mm Hg	132±27	135±28	133±25	0.81
Heart rate, bpm	79±22	83±21	81±20	0.62
Qualified by unstable angina, %	52.3	51.3	52.2	0.89
Qualified by non-Q-wave MI, %	47.7	48.7	47.8	0.90
Anterior MI location, %	44.8	46.4	41.0	0.62
Peak CK, IU	137±42	135±28	128±51	0.39
Baseline ECG characteristics, %				
ST elevation	7.6	7.0	4.5	0.92
ST depression	31.6	28.4	34.3	0.61
T-wave inversion	51.2	36.1	47.3	0.59
History of				
Congestive heart failure, %	12.5	12.7	9.3	0.38
Myocardial infarction, %	44	59.8	60.5	0.05
PTCA, %	12.3	31.2	25.6	0.03
CABG, %	15.2	30.2	30.5	0.012
Risk factors, %				
Diabetes	20.9	21.6	22.1	0.51
Hypercholesterolemia	38.9	97.6	100.0	0.002
Hypertension	53.8	58.4	55.9	0.38
Current smokers	68.9	72.5	70.2	0.72
Medication before enrollment, %				
Aspirin	94.8	96.1	96.8	0.91
Heparin	35.6	33.5	33.1	0.62
Nitrates	83.4	82.5	85.6	0.71
β-Blockers	53.2	60.2	60.9	0.26
ACE inhibitors	35.5	37.2	36.8	0.31
Medication after enrollment, %				
Aspirin	96.8	98.4	95.1	0.89
Heparin	32.8	33.7	36.7	0.45
Nitrates	90.0	88.5	88.1	0.65
β-Blockers	73.9	71.3	72.2	0.94
ACE inhibitors	46.2	48.5	47.3	0.46

patients who continued to receive statin therapy or did not receive statin therapy throughout the study period. There was no evidence that the discontinuation of the statins was related to the risk profile of the patients (Table 1). Risk factors including baseline cholesterol levels (Figure 3) and troponin T levels (Figure 4) were similar in patients who continued to receive statins and those who no longer received statins after admission. The type and dose of the statins that patients received was not different between the two groups (Table 3). Furthermore, at baseline the percentage of patients that required treatment in the intensive or coronary care unit and the duration of symptoms were similar for both groups.

If statin therapy was withdrawn during or after admission, the incidence of death and nonfatal MI significantly increased compared with patients who continued to receive statins (2.93 [95% CI, 1.64 to 6.27];  $P=0.005$ ) and tended to be higher compared with patients who did not receive statins during the entire study period (1.69 [95% CI, 0.92 to 3.56];  $P=0.15$ ) (Table 2). Coronary revascularizations were discouraged during the initial 48 hours and subsequently revascularization rate was low, with no differences between the subgroups (Table 2). At 7-day follow-up, revascularization rate was significantly higher in patients who did not continue to receive statins as compared with patients who continued



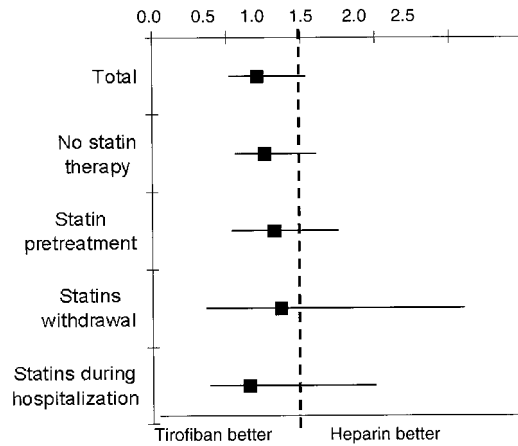
**Figure 1.** Event rate curves (death, nonfatal MI) during 30-day follow-up period for patients with continued statin therapy, withdrawn statin therapy, and without statin therapy.

statin therapy. The benefit of treatment with tirofiban did not differ between patients who continued to receive statins and those patients with discontinued statin therapy ( $P=0.72$ ).

Cholesterol levels during subsequent measurements did not change (Figure 3), whereas the troponin levels, despite similar baseline levels, increased as the result of the patients' adverse clinical course (Figure 4).

**Initiation of Statin Therapy During Hospitalization**

Baseline clinical characteristics did not differ between 165 patients with statin therapy initiated during hospitalization and patients without statin therapy. If statin therapy was initiated after onset of the acute coronary syndrome, a trend to a reduced incidence of death and nonfatal MI was observed compared with patients who did not receive statins (0.76



**Figure 2.** Adjusted hazard ratios (including 95% CI) for treatment with tirofiban according to statin therapy. Benefit of treatment is defined as reduction of death or nonfatal MI at 30-day follow-up. Hazard ratios <1.0 indicate benefit for treatment with tirofiban compared with heparin.

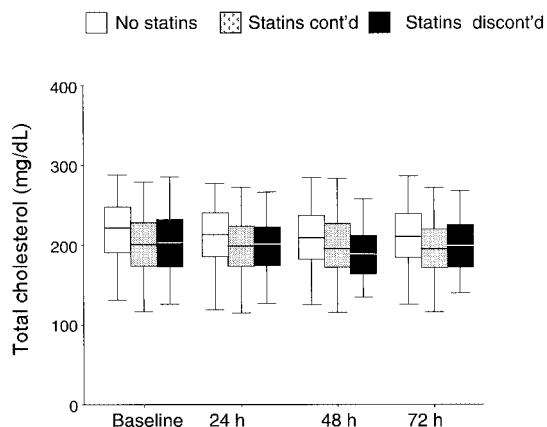
[95% CI, 0.51 to 1.35];  $P=0.22$ ). Event rate curves did not diverge before day 14 between patients who were given statins during hospitalization and those patients who did not receive statin therapy.

A multivariate analysis was performed for patients who were pretreated with statins for at least 6 months ( $n=455$ ). For the end points of death and nonfatal MI during the 30-day follow-up period, none of the established risk factors were independent predictors after the troponin status at baseline

**TABLE 2. Event Rates for 3 Periods of Time According to Statin Therapy**

	No Statins	Statins Continued	Statins Discontinued	P
<b>48 Hours</b>				
Combined end point	68 (5.9)	10 (2.6)	9 (10.5)	0.009
Refractory ischemia	51 (4.4)	12 (3.2)	7 (8.1)	0.032
Death, MI	19 (1.7)	2 (0.5)	4 (4.7)	0.21
Death	3 (0.3)	0	0	0.97
MI	16 (1.4)	2 (0.5)	4 (4.7)	0.06
Revascularizations	6 (0.5)	3 (0.8)	1 (1.1)	0.90
<b>7 Days</b>				
Combined end point	139 (12.1)	36 (8.5)	13 (15.1)	0.25
Refractory ischemia	122 (10.6)	26 (6.9)	12 (13.9)	0.16
Death, MI	61 (5.3)	7 (1.9)	8 (9.3)	0.006
Death	25 (2.2)	2 (0.5)	1 (1.2)	0.58
MI	36 (3.1)	5 (1.6)	7 (8.1)	0.010
Revascularizations	235 (20.4)	64 (17.3)	22 (25.6)	0.002
<b>30 Days</b>				
Combined end point	165 (14.3)	38 (10.0)	15 (17.4)	0.07
Refractory ischemia	125 (10.9)	30 (7.9)	13 (15.1)	0.22
Death, MI	86 (7.5)	14 (3.7)	12 (14.0)	0.004
Death	40 (3.5)	6 (1.6)	1 (1.2)	0.31
MI	46 (4.0)	8 (2.1)	11 (12.8)	0.012

Values are n (%).



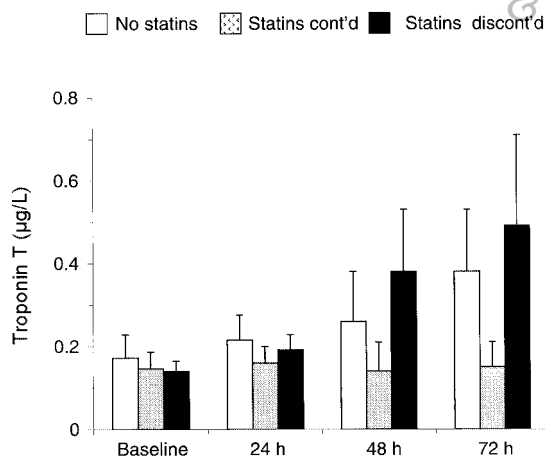
**Figure 3.** Total cholesterol levels at baseline and at 24, 48, and 72 hours according to statin therapy.

and ST-segment changes were introduced into the model (Table 4). Regarding medical therapy, discontinuation of statin therapy was the only independent predictor of patient outcome.

### Discussion

The present substudy of the PRISM trial provides evidence that pretreatment with statins in patients with acute coronary syndromes significantly reduces cardiac risk during the first 30 days after onset of symptoms. Early withdrawal of statin therapy after onset of symptoms completely abrogated this protective effect of statins. In contrast, initiation of statin therapy during the index hospital stay showed a less robust effect on patient outcome and did not reach the level of statistical significance in our study population.

The most striking finding of the present study is that withdrawal of statin therapy shortly after onset of symptoms in patients with acute coronary syndromes abrogated the beneficial effect of the statins. This was observed despite a lack of change in the cholesterol levels during the initial 72 hours (Figure 3). However, it was exactly in this early time period after onset of symptoms that the event rate curves for the two groups diverged.



**Figure 4.** Baseline troponin levels at baseline and at 24, 48, and 72 hours according to statin therapy.

**TABLE 3. Type of Statin (Average Dose) Used in Patients Who Continued and Discontinued Statin Therapy, Respectively**

	Statin Continued	Statin Discontinued
Simvastatin	50.0% (19.5mg/d)	51.8% (20.9mg/d)
Lovastatin	24.1% (44.4mg/d)	23.5% (51.2mg/d)
Pravastatin	20.4% (22.8mg/d)	20.0% (20.5mg/d)
Fluvastatin	5.6% (21.4mg/d)	4.7% (19.8mg/d)

These findings are consistent with the hypothesis that statins have significant effects on vascular function independent of their lipid-lowering effects. Recent experimental studies demonstrate that statins control important factors involved in the pathology of acute coronary syndromes. This includes endothelial NO, endothelin, metalloproteinases, plasminogen activator inhibitor, tissue-type plasminogen activator, and free radical production.<sup>6,26</sup> The molecular mechanism of these noncholesterol effects of statins is the inhibition of the isoprenoid intermediates of the cholesterol pathway. Isoprenoids are essential for the function of signal transduction molecules of the *Rho* family. Regulation of *Rho* activity by statins may be much more rapid compared with the effects of statins on lipids. Indeed, withdrawal of statin therapy in mice resulted in a marked reduction of endothelial NO production below baseline levels mediated by regulation of *Rho*, whereas lipid levels remained unchanged during this early period.<sup>21</sup> Therefore, the discontinuation of statin therapy in our patients with acute coronary syndromes might have not only reversed the upregulation of endothelial NO synthase by statins rather than suppressed NO production and potentially other *Rho*-dependent pathways. The majority of PRISM patients (~90%) received nitrates before and after enrollment, and one might wonder whether exogenous administration of NO might at least in part compensate for the suppressed NO production after statin withdrawal. Nitrates induce an intermittent vasodilation in resistant vessels through a direct cGMP effect on smooth muscle cells. In contrast, the upregulation of constitutive endothelial NO

**TABLE 4. Multivariate Analysis for Predicting 30-Day Outcome (Death, MI) in Patients Who Were Pretreated With Statins (n=455)**

Variable	OR	95% CI	P
Sex	0.91	0.65–1.49	0.59
Age >65 y	1.24	1.12–4.26	0.26
Diabetes mellitus	1.15	0.84–1.46	0.64
Hypercholesterolemia	0.89	0.71–1.16	0.65
Hypertension	0.99	0.85–1.06	0.99
History of MI	0.89	0.72–1.25	0.66
History of PCI	0.73	0.58–1.13	0.53
History of CABG	1.16	0.91–1.24	0.65
ST changes	1.21	0.86–1.98	0.02
T-wave inversion	0.84	0.65–1.05	0.14
Troponin T elevation	2.68	1.54–5.89	0.005
Tirofiban	0.82	0.45–1.08	0.15
Statins discontinued	2.93	1.64–6.27	0.008

bioavailability results in a persistent improvement of endothelial function. This includes among others the inhibition of leukocyte adhesion, platelet activation, and LDL oxidation.<sup>17–20</sup> Consequently, improvement of endothelial function has prognostic impact, whereas nitrate therapy does not improve patient outcome. The above experimental study demonstrated that statin withdrawal reduces endothelial NO synthase activity,<sup>21</sup> but other statin effects might have been at least as important for patients with acute coronary syndromes. Because the effect was seen very early after withdrawal of statins, the anti-inflammatory effects of statins are very likely to play a significant role. Statins have also been demonstrated to increase number and migratory capacity of endothelial progenitor cells.<sup>27</sup> These cells appear to play an important role in angiogenesis and thus might also contribute to stabilization of patients with acute coronary syndromes.<sup>28</sup>

It appears possible that the withdrawal of statin therapy was related to the worse clinical course of these patients who might not have allowed continuing statin therapy. However, in a multivariate analysis including patients who were pretreated with statins and adjusting for all baseline characteristics (Table 1), the difference in cardiovascular outcome between patients who continued to receive statins and those with discontinued statin therapy remained robust (2.93 [95% CI, 1.51 to 5.92];  $P=0.008$ ) (Table 4). Because medical therapy was left to the discretion of the responsible physician, we conclude that physicians either assumed that statin therapy may not be beneficial in the current setting of an acute coronary syndrome or simply forgot to continue statin therapy.

It is important to recognize that the trials, which established the benefit of lipid lowering with statins in both primary and secondary prevention of cardiovascular disease, excluded patients who had had an acute coronary syndrome within the preceding 3 to 6 months.<sup>1,4</sup> However, it is precisely in this early period after onset of symptoms that recurrent ischemic events occur most frequently. To date, the MIRACL (Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes) Trial and FLORIDA (Effects of Fluvastatin Administered Immediately After an Acute MI on Myocardial Ischemia) Trial prospectively investigated the effects of an early initiation of statin therapy directly after an acute coronary syndrome.<sup>29</sup> The MIRACL trial showed a significant reduction in early recurrent ischemic events (relative risk, 0.84 [95% CI, 0.70 to 0.99],  $P=0.048$ ), a difference that was mainly driven by a reduction in recurrent ischemia.<sup>29</sup> These findings are consistent with our present observation from the PRISM trial: Initiation of statin therapy after onset of acute coronary syndromes appears to be less effective (14% relative risk reduction for death and nonfatal MI) compared with pretreatment with statins before the onset of symptoms (51% relative risk reduction). The pretreatment with statins resulted in an early divergence of the event rate curve, whereas the curve for the patients who received statins during the index hospital stay showed a later benefit starting not before 14 days after onset of symptoms. These results are consistent with those from MIRACL, in which before day 30, no benefit of atorvastatin was observed.<sup>29</sup>

In conclusion, statin therapy in patients with acute coronary syndromes is associated with an improved clinical outcome. Pretreatment with statins before onset of symptoms significantly reduced cardiac events during the first days after onset of symptoms. Discontinuation of this statin therapy after onset of symptoms completely abrogated its beneficial effect. Thus, withdrawal of statin therapy in unstable patients should be avoided. Unconscious patients who were pretreated with statins may also benefit from continuation of statin therapy. In contrast, initiation of statin therapy during hospitalization failed to reduce early cardiac events but reduced later cardiac events. Of course, the conclusions of this retrospective analysis are inherently more “hypothesis generating” rather than “hypothesis proving.” The data were drawn from a substudy of a randomized trial and the analysis of effect of statin pretreatment was performed retrospectively.

## References

- SSSS Investigators. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
- Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301–1307.
- Sacks FM, Pfeffer MA, Moye LA, 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;335:1001–1009.
- LIPID Investigators. 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;339:1349–1357.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
- Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation*. 2000;101:207–213.
- Massy ZA, Keane WF, Kasiske BL. Inhibition of the mevalonate pathway: benefits beyond cholesterol reduction? *Lancet*. 1996;347:102–103.
- Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. *Lancet*. 1996;348:1079–1082.
- Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. *JAMA*. 1998;279:1643–1650.
- Haverkate F, Thompson SG, Pyke SD, et al. Production of C-reactive protein and risk of coronary events in stable and unstable angina: European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet*. 1997;349:462–466.
- Heeschen C, Hamm CW, Bruemmer J, et al. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis: CAPTURE Investigators: Chimeric c7E3 Anti-Platelet Therapy in Unstable angina REfractory to standard treatment trial. *J Am Coll Cardiol*. 2000;35:1535–1542.
- Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med*. 1994;331:417–424.
- Maseri A. Inflammation, atherosclerosis, and ischemic events: exploring the hidden side of the moon. *N Engl J Med*. 1997;336:1014–1016.
- Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med*. 1999;340:115–126.
- Kaesemeyer WH, Caldwell RB, Huang J, et al. Pravastatin sodium activates endothelial nitric oxide synthase independent of its cholesterol-lowering actions. *J Am Coll Cardiol*. 1999;33:234–242.
- Laufs U, La Fata V, Plutzky J, et al. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation*. 1998;97:1129–1135.

17. Hansen PR. Inflammatory alterations in the myocardial microcirculation. *J Mol Cell Cardiol.* 1998;30:2555–2559.
18. Fleming I, Busse R. NO: the primary EDRF. *J Mol Cell Cardiol.* 1999; 31:5–14.
19. Kibbe M, Billiar T, Tzeng E. Inducible nitric oxide synthase and vascular injury. *Cardiovasc Res.* 1999;43:650–657.
20. Jeremy JY, Rowe D, Emsley AM, et al. Nitric oxide and the proliferation of vascular smooth muscle cells. *Cardiovasc Res.* 1999;43:580–594.
21. Laufs U, Endres M, Custodis F, 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;102:3104–3110.
22. Thomas M, Mann J. Increased thrombotic vascular events after change of statin. *Lancet.* 1998;352:1830–1831. Letter.
23. PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina: Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med.* 1998;338:1498–1505.
24. Muller-Bardorff M, Hallermayer K, Schroder A, et al. Improved troponin T ELISA specific for cardiac troponin T isoform: assay development and analytical and clinical validation. *Clin Chem.* 1997;43:458–466.
25. Harrell FE Jr, Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst.* 1988;80:1198–1202.
26. Kwak B, Mulhaupt F, Myit S, et al. Statins as a newly recognized type of immunomodulator. *Nat Med.* 2000;6:1399–1402.
27. Dimmeler S, Aicher A, Vasa M, et al. HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. *J Clin Invest.* 2001;108:391–397.
28. Asahara T, Masuda H, Takahashi T, et al. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. *Circ Res.* 1999;85: 221–228.
29. 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.



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