Absence of Interaction Between Atorvastatin or Other Statins and Clopidogrel

Results From the Interaction Study

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Background: Some, but not all, post hoc analyses have suggested that the antiplatelet effects of clopidogrel are inhibited by atorvastatin. We sought to address this issue prospectively by performing serial measurements of 19 platelet characteristics using conventional aggregometry, rapid analyzers, and flow cytometry.

Methods: The Interaction of Atorvastatin and Clopidogrel Study (Interaction Study) was designed for patients undergoing coronary stenting. All patients (n=75) received 325 mg of aspirin daily for at least 1 week and 300 mg of clopidogrel immediately prior to stent implantation. They had been taking atorvastatin (n=25), any other statin (n=25), or no statin (n=25) for at least 30 days prior to stenting. The main outcome measure was comparison of platelet biomarkers 4 and 24 hours after clopidogrel intake, with the exception of a lower collagen-induced aggregation at 24 hours and a constantly diminished expression of PAR-1 in patients treated with any statin.

Results: At baseline, patients from both statin groups exhibited diminished platelet aggregation and reduced platelet expression of G–protein-coupled protease-activated thrombin receptor (PAR)-1. There were no significant differences in measured platelet characteristics among the study groups 4 and 24 hours after clopidogrel intake, with the exception of a lower collagen-induced aggregation at 24 hours and a constantly diminished expression of PAR-1 in patients treated with any statin.

Conclusions: Statins in general, and atorvastatin in particular, do not affect the ability of clopidogrel to inhibit platelet function in patients undergoing coronary stenting. These prospective data also suggest that statins may inhibit platelets directly via yet unknown mechanism(s) possibly related to the regulation of the PAR-1 thrombin receptors.

Arch Intern Med. 2004;164:2051-2057
Clopidogrel for Reduction of Events During Observation (CREDO)\textsuperscript{13} show no clinically meaningful adverse interactions between atorvastatin and clopidogrel.

Further studies, especially prospectively designed, are necessary to test this potentially deleterious interaction.\textsuperscript{14} Our prospective Interaction Study was designed to address this issue by serial measurements of platelet characteristics using conventional aggregometry, rapid platelet function analyzers, and whole blood flow cytometry.

### METHODS

#### PATIENTS

The study was approved by the Western Investigational Review Board, Olympia, Wash (protocol 20020908). Written informed consent was obtained from all patients. The study population consisted of 3 equal cohorts totaling 75 willing and eligible patients undergoing coronary artery stenting who had been treated for at least 30 days with atorvastatin, other statins, or medications other than statins. All patients received 325 mg of aspirin daily for at least 1 week; 300 mg of clopidogrel (loading dose) immediately prior to the intervention; and 75 mg of clopidogrel the next day, before the discharge blood sample was obtained. All but 2 patients received heparin intravenously prior to stent implantation to achieve an activated clotting time greater than 300 seconds. Antiocoagulation in 2 patients was achieved with hirudin, and controlled by keeping the activated clotting time above 320 seconds. No other antiplatelet agents were used. At enrollment, participants had been receiving daily 10 to 80 mg of atorvastatin (n = 25), 20 to 40 mg of simvastatin (n = 10), 10 to 40 mg of pravastatin (n = 8), 20 mg of lovastatin (n = 2), 20 to 80 mg of fluvastatin (n = 5), or no statin treatment for 30 days. Patients were excluded for a history of bleeding diathesis (n = 0), a stroke in the past 3 months (n = 2), drug or alcohol abuse (n = 4), prothrombin time greater than 1.5 times control (n = 2), platelet count of 100,000/µL or less (n = 0), hemoglobin of 0.25 g/dL or less (n = 0), or a creatinine level of 4.0 mg/dL (353.6 mmol/L) or less (n = 2). Patients who had completed participation in other investigational drug trials less than 1 month before study initiation were also excluded (n = 3). No patient had previously received thienopyridines or intravenous platelet glycoprotein (GP) IIb/IIIa inhibitors. Finally, 7 patients did not sign the informed consent and refused to participate in the study. The Interaction Study algorithm is presented in the Figure.

#### SAMPLES

Blood samples were obtained with a 19-gauge needle by direct venipuncture and drawn into two 7-mL Vacutainer tubes (Becton, Dickinson and Co, Franklin Lakes, NJ) at room temperature, each containing a 3.8% trisodium citrate solution. The tubes were filled to capacity and gently inverted 3 to 5 times to ensure complete mixing of the anticoagulant. The first 4 to 5 mL of blood was used for lipid analysis or discarded. All samples were labeled with coded numbers and analyzed by blinded technicians. Research coordinators were not aware of the platelet data, and laboratory personnel did not know the treatment allocation. Platelet studies were performed at baseline as well as 4 and 24 hours after stent implantation.

#### PLATELET AGGREGATION

The blood-citrate mixture was centrifuged at 1200g for 2.5 minutes. The resulting platelet-rich plasma was kept at room temperature for use within 1 hour. The platelet count was determined in the platelet-rich plasma sample and adjusted to 3.5 × 10\(^{10}\)/µL with homologous platelet-poor plasma. Platelets were stimulated with 5-µmol ADP or 1-µg/mL collagen (Chrono-Log Corp, Havertown, Pa) and aggregation was assessed as previously described, using a Lumi-Aggregometer 560-Ca with the Aggrolink software package (Chrono-Log Corp). Aggregation was expressed as the maximal percentage change in light transmittance from baseline, using platelet-poor plasma as reference.\textsuperscript{15}

#### Cartridge-Based Platelet Analyzers

We used the platelet function analyzer PFA-100 (Dade Behring, Miami, Fla). In this instrument the blood-citrate mixture is aspirated under a constant negative pressure, contacts an ADP- and collagen-coated membrane, and passes through an aperture that induces high shear stress and simulates primary hemostasis after injury to a small blood vessel under flow conditions. The time to aperture occlusion (the closure time) is recorded in seconds and is inversely related to the degree of shear-induced platelet activation.\textsuperscript{16} We also used the rapid platelet function assay device Ultraegra (Accumetrics, San Diego, Calif), with ADP as agonist. This device is also a turbidimetric-based optical detection system, but it measures platelet-induced aggregation as an increase in light transmittance. This test cartridge has been designed to monitor antplatelet effects of ADP-receptor antagonists. When the activated platelets are exposed to the fibrinogen-coated microparticles, agglutination occurs in proportion to the number of available platelet receptors. The whole blood–citrate mixture is added to the cartridge, and agglutination between platelets and coated beads is recorded.\textsuperscript{17} Assay results are reported as platelet activation units. The values reflect both turbidimetric platelet aggregate formation and the degree of platelet ADP blockade. Platelet function and rapid platelet function assays were performed in duplicate. An electronic quality control test was performed for each instrument each day prior to analyzing patient samples.

#### Whole Blood Flow Cytometry

The surface expression of platelet receptors was determined by flow cytometry using the following monoclonal antibodies: CD41 antigen (integrin \(\alpha\)\(_{IIb}\), or platelet GPIIb); CD42b (GPIIb); CD62p (P-selectin; Dako Corp, Carpinteria, Calif); PAC-1 (integrin \(\alpha\)\(_{IIb}\), or active GPIIb/IIIa); CD31 (plateletendothelial cell adhesion molecule [PECAM-1]); CD51/CD61 (integrin \(\alpha\)\(_{Ib}\), or vitronectin receptor); CD63 (lysosome-associated membrane glycoprotein [LAMP]-3);

![Interaction Study algorithm.](https://example.com/algorithm.png)
CD107a (LAMP-1); CD151 (platelet-endothelial tetraspan antigen [PETA]-3); CD154 (CD40 ligand); CD163 (GP37; PharMingen, San Diego, Calif); CD36 (thrombospondin, GIV). The protease-activated G-protein-coupled thrombin receptors (PAR)-1 and PAR-4 were measured using SPAN12 and WEDE15 antibodies (Beckman Coulter, Brea, Calif) (SPAN12 recognizes an epitope that is lost when thrombin cleaves the receptor; WEDE15 is topical for epitopes that are retained following receptor cleavage, allowing these antibodies to bind to both intact and cleaved receptors). Formation of platelet-leukocyte aggregates was assessed by dual labeling with pan-platelet marker (CD151) and CD14, the macrophage receptor for endotoxin lipopolysaccharides. The blood-citrate mixture (50 µL) was diluted with 450 µL of Tris-buffered saline (10-mmol/L Tris with 0.15-mol/L sodium chloride) and mixed by gently inverting an Eppendorf Tube twice. The appropriate primary antibody was then added (5 µL) and incubated at 37°C for 30 minutes; then, a secondary antibody was applied if needed. After incubation, 400 µL of 2% buffered paraformaldehyde was added for fixation. The samples were analyzed on a Becton Dickinson flow cytometer (FACScan; San Diego, Calif) set up to measure fluorescent light scatter, as previously described. All parameters were collected using 4-decade logarithmic amplification. The data were collected in list-mode files and analyzed. P-selectin was expressed as percentage of positive cells, as previously described. Other antigens were expressed as log mean fluorescence intensity.

STATISTICAL ANALYSIS

Categorical data for baseline patient characteristics are given as frequencies and percentages; the χ² test or the Fisher exact test were used for comparisons, as appropriate. Continuous data are presented as means±SDs and were compared using 1-way analysis of variance.

To examine between treatments the effects of clopidogrel on platelet characteristics, repeated measures were performed and 1-way analysis of variance was used, selecting the most appropriate covariance structure for each platelet characteristic.

Statistical analyses were performed using the software packages SPSS/E11.5 (SPSS Inc, Chicago, Ill) or SAS 8.02 (SAS Inc, Cary, NC). Differences between individual flow cytometric histograms were assessed using the Kolmogorov-Smirnov test incorporated in the CELLQuest software, version 3.2.1 (Becton, Dickinson, and Co).

RESULTS

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Seventy-eight patients with angina pectoris or acute myocardial infarction were screened for the study and underwent baseline platelet function assessment. All patients completed the 24-hour study, but 3 were excluded from the final analyses because they received an epifibatide infusion during stent implantation. There were no deaths or serious adverse events. Demographic and clinical characteristics are shown in Table 1.

Age, sex, and race were similar among groups. Unstable angina was the most common admission diagnosis in all groups, with a nonstatistically significant prevalence of chest pain of unknown etiology among patients treated with a statin other than atorvastatin. Risk factor distribution was also similar, although there was a higher prevalence of myocardial infarction in the group receiving no statin treatment. There were more prior coro-

### Table 1. Baseline Characteristics of Interaction Study Participants*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Statins (n = 25)</th>
<th>Atorvastatin (n = 25)</th>
<th>Other Statins (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>65.1 ± 11.0</td>
<td>62.2 ± 9.8</td>
<td>65.5 ± 6.62</td>
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<tr>
<td><strong>Male sex</strong></td>
<td>17 (68)</td>
<td>15 (60)</td>
<td>16 (64)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>21 (84)</td>
<td>22 (88)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>African American</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Asians</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Admission diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>16 (64)</td>
<td>17 (68)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (28)</td>
<td>7 (28)</td>
<td>10 (40)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>200.0 ± 27.9</td>
<td>170.3 ± 28.2†</td>
<td>171.0 ± 28.4‡</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>147 ± 72.6</td>
<td>161.6 ± 90.2</td>
<td>147.7 ± 71.6</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>37.9 ± 13.4</td>
<td>40.0 ± 9.27</td>
<td>36.2 ± 6.3</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>121.9 ± 44.1</td>
<td>98.5 ± 33.4</td>
<td>116.0 ± 33</td>
</tr>
<tr>
<td><strong>Tobacco use</strong></td>
<td>14 (56)</td>
<td>13 (52)</td>
<td>16 (64)</td>
</tr>
<tr>
<td><strong>Arterial hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>121.9 ± 44.1</td>
<td>98.5 ± 33.4</td>
<td>116.0 ± 33</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>7 (28)</td>
<td>6 (24)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2 (8)</td>
<td>4 (16)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td>2 (8)</td>
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<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart surgery</td>
<td>2 (8)</td>
<td>5 (20)</td>
<td>2 (8)</td>
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<tr>
<td><strong>Medications</strong></td>
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<tr>
<td>β-Blockers</td>
<td>16 (64)</td>
<td>16 (64)</td>
<td>14 (56)</td>
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<tr>
<td>ACE inhibitors</td>
<td>9 (36)</td>
<td>7 (28)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>6 (24)</td>
<td>8 (32)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>AT receptor antagonists</td>
<td>4 (16)</td>
<td>4 (16)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>8 (32)</td>
<td>10 (40)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Glycosides</td>
<td>4 (16)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>7 (28)</td>
<td>4 (16)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>3 (12)</td>
<td>7 (28)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1 (4)</td>
<td>NA</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Heparin</td>
<td>24 (96)</td>
<td>25 (100)</td>
<td>24 (96)</td>
</tr>
<tr>
<td>Hirudin</td>
<td>1 (4)</td>
<td>NA</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Stents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length, mm</td>
<td>18.5 ± 6.5</td>
<td>18.54 ± 8.32</td>
<td>17.6 ± 6.2</td>
</tr>
<tr>
<td>Diameter, mm</td>
<td>3.03 ± 0.38</td>
<td>3.05 ± 0.39</td>
<td>3.09 ± 0.57</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; AT, angiotensin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NA, not applicable.

SI conversion factors: To convert total cholesterol, HDL cholesterol, and LDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*Values are given as number (percentage) or mean ± SD.
†P values of .03 for both statin-treated groups vs the no-statin group were calculated using individual pairwise comparisons, not by comparing both statin groups with the no-statin group.
‡Arterial hypertension was defined by a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg.
nary artery bypass graft in the group treated with atorvastatin. The 25 patients in the atorvastatin group were taking a mean±SD medication dose of 27.9±15.5 mg/d (range, 10-40 mg/d); the 10 patients in the simvastatin group were taking 33.8±8.2 mg/d (range, 20-40 mg/d); the 8 patients in the pravastatin group were taking 29.3±12.1 mg/d (range, 10-40 mg/d); the 5 patients in the lovastatin group all received 20 mg/d; and of the 2 patients in the fluvastatin group, one received 20 mg/d and the other 80 mg/d. As expected, total cholesterol levels were lower in patients treated with a statin than in those receiving no statin treatment. The stent characteristics and the characteristics of concomitant medications were similar among groups.

### PLATELET FINDINGS

Findings regarding platelet data are presented in Table 2. They were dependent on treatment assignments, and were adjusted for the differences at baseline.

At baseline, compared with the “no statins group,” platelets were significantly inhibited in the “atorvastatin” and the “other statins” groups, as reflected by ADP- and collagen-induced conventional aggregometry as well as SPAN12 receptor expression. Despite changes in platelet characteristics before administration of clopidogrel, there were no significant differences between groups in platelet characteristics 4 and 24 hours after loading with clopidogrel, with 2 exceptions: a lower collagen-induced ag-
gregability at 24 hours and, in the 2 groups treated with statins, the constantly diminished expression of PAR-1 measured by SPAN12 antibody.

**COMMENT**

**STUDY RESULTS**

The Interaction Study is the first prospective study to show no differences in the platelet-related effects of clopidogrel among patients undergoing coronary stenting while taking atorvastatin, other statins, or no statins. In fact, the pattern of platelet inhibition by clopidogrel was nearly identical among these 3 groups of patients.

Although these were beyond the scope of the primary objective of the Interaction Study, and independent of the effects of clopidogrel, we observed 2 interesting phenomena related to the effects of statins on platelet function. First, at baseline, conventional aggregometry revealed that patients from both statin groups exhibited decreased platelet activity compared with patients not treated with statins. Second, the expression of thrombin receptor PAR-1 was consistently diminished in the 2 groups receiving statin treatment. This inhibition of platelet expression of PAR-1 was not affected by clopidogrel therapy, and was significant at all time points for both statin groups when compared with the group taking no statins.

**STATINS AND PLATELETS**

The hypothesis that statins may affect platelet function is not new. Therapy with statins has clinical benefits extending beyond simply lowering the blood cholesterol level.
These properties include protecting the vascular endothelium, decreasing low-density lipoprotein oxidation and ensuing inflammation, stabilizing atherosclerotic plaques and perhaps promoting their regression, modulating smooth muscle growth, stimulating fibrinolysis, and improving blood viscosity and flow. Surprisingly, there are only a few reports describing the effect of statins on platelet function, and most of their findings are from in vitro tests, animal experiments, uncontrolled human studies in healthy volunteers, and hypercholesterolemic subjects. It has been reported that hypercholesterolemia is directly related to enhanced cell superoxide anion production, including oxygen radicals released from human platelets. The oxidation burden can be reversed by low-dose atorvastatin in vitro. Low-dose statin therapy has also been associated with a 38% reduction in brain infarct size in a mouse model, presumably by upregulating endothelial (type 3) nitric oxide synthase. Surprisingly, plasma levels of established platelet biomarkers such as β-thromboglobulin and platelet factor 4 were not affected by statin therapy, suggesting an alternative mechanism of platelet inhibition independent of α-granule release. The contribution of the nitric oxide metabolism to the antiplatelet properties of statins has been suggested by a study of hypercholesterolemic patients treated with atorvastatin. Another recent report suggests that statins may decrease platelet activation by directly influencing platelet membrane lipid content.

On the other hand, statins, even in high doses, do not diminish prothrombinase activity, as serially measured by the plasma levels of prothrombin fragment 1 + 2 in patients with acute coronary syndromes. Obviously, large randomized studies are needed to determine the clinical importance, validity, and meaningfulness of the proposed beneficial pleiotropic effects of statins.

**METABOLISM OF CLOPIDOGREL AND STATINS**

Clopidogrel is extensively metabolized by the liver, and an active thiol metabolite binds rapidly and irreversibly to platelet ADP receptors, thus inhibiting platelet aggregation. The main circulating clopidogrel metabolite is a carboxylic acid derivative with no apparent effects on platelet function. The active metabolite is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. Results of in vitro studies in human liver microsomes with recombinant cytochromes P-450 have shown that several cytochromes are involved in the oxidative metabolism of clopidogrel. Cytochrome P-4503A4 (of the CYP enzyme system) plays an important part in the metabolism of statins, leading to clinically relevant interactions with other agents that are also metabolized by this enzyme pathway, particularly cyclosporin, erythromycin, itraconazole, ketoconazole, and human immunodeficiency virus protease inhibitors. An additional complicating feature is that individual statins are metabolized to different degrees, in some cases producing active metabolites. The CYP3A family metabolizes lovastatin, simvastatin, atorvastatin, and cerivastatin, whereas CYP2C9 metabolizes fluvastatin. Pravastatin is not significantly metabolized by the CYP system. In addition, statins are substrates for P-glycoprotein, a drug transporter present in the small intestine that may influence their oral bioavailability. In clinical practice, statins may therefore alter the concentrations of fibrates, nicotinic acid derivatives, or other drugs requiring monitoring such as warfarin or digoxin.

**PRIOR RETROSPECTIVE FINDINGS AND INTERACTION**

Two recent reports, one from a post hoc analysis of a small sample size data set and the other from an in vitro study from the same group, raised the possibility that the ability of clopidogrel to affect platelets is inhibited by atorvastatin. However, several methodologic limitations affect their interpretability. The sample size was small (n=44), patient selection was poorly defined, no control for the presence of medications affecting cytochrome P-4503A4 was performed prior to initiation, treatment with platelet GPIIb/IIIa inhibitors was allowed, and the evaluation of concomitant statin and clopidogrel use was retrospective. Finally, a single, nonconventional method was used to assess platelet function.

Because of growing concerns among treating physicians, 2 additional large-scale retrospective analyses were recently carried out. The retrospective data analyses of the MITRA PLUS registry involved 883 patients receiving atorvastatin and 1,203 receiving another statin, who were all concomitantly treated with clopidogrel after an acute coronary event. There were no differences in all-cause mortality or in combined end point of mortality and stroke between the 2 groups.

Finally, the retrospective data from the CREDO database demonstrated the clinical benefits of clopidogrel irrespective of treatment with a statin metabolized by CYP3A4 (n=1,001), or a statin not metabolized metabolized by CYP3A4 (n=158), with regard to a composite of deaths, myocardial infarction, and stroke at 1 year. Moreover, when outcomes were reanalyzed based on the type of statin taken at the time of discharge or 28 days after loading with clopidogrel, no difference in results was found.

**PAR-1 AND STATINS**

Proteinase-activated receptor 1, a member of a novel gene family of G-protein-coupled receptors, is expressed by human platelets and responsible for attracting α-thrombin to the platelet surface. We found a consistent and significant reduction of PAR-1 platelet expression in patients treated with statins independent of the type of statin used, and this effect was not modified by clopidogrel intake. This finding is presently of uncertain importance, but it may represent a mechanism of antiplatelet activity by statins. Our results are consistent with those of a previous report demonstrating that statins, but not diet, are able to diminish excessive platelet-derived thrombin generation in patients with type II-a hyperlipoproteinemia. The Interaction Study, however, was neither designed nor powered to prove this association.

**STUDY LIMITATIONS**

The overall sample size of 25 patients per arm is small, and the Interaction Study did not have adequate statis-
tical power to test all statins individually. Pravastatin and fluvastatin are not metabolized by CYP3A4, and grouping these statins with simvastatin and lovastatin, which are metabolized by CYP3A4, may bias our results in fa-
vor of the statins metabolized by CYP3A4 in the “any other statin” group. Although the expression of multiple acti-
vation-dependent receptors was studied, their indi-
vidual roles in patients with acute coronary syndromes are unknown. Similarly, the relation of platelet receptor
expression to established platelet function measure-
ments is currently under investigation.

CONCLUSIONS

Statins in general, and atorvastatin in particular do not inhibit the antiplatelet effects of clopidogrel in patients undergoing coronary stenting. The pattern of platelet in-
hibition by clopidogrel was almost identical among the “atorvastatin,” “any other statin,” and “no statin” groups. These prospective findings also suggest that statins may inhibit platelets directly via as yet unknown mecha-
nism(s) presumably related to the cleavage of PAR-1 by α-thrombin.

Accepted for publication April 26, 2004.
From the HeartDrug Research, LLC, Baltimore, Md
(Drs Serebruany and Malinin and Mr Oshrine), Midatlant-
ic Cardiovascular Associates (Drs Midei and Lowry);
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Montreal Heart Institute, Montreal, Quebec (Dr Tan-
guy); University of North Carolina at Chapel Hill (Dr
Steinbugl); Duke Clinical Research Institute, Durham, NC
(Drs Berger and O’Connor), and the University of Miami,
Miami, Fla (Dr Hennekens). Dr Hennekens is now also
with the Agatston Research Institute.

Dr Serebruany has filed US patent application 10,811563 (“Treating vascular events with statins by in-
hibiting platelet PAR-1 and PAR-4”).

We thank all the nurses and laboratory personnel for
their technical excellence and outstanding effort during this
study.

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