Treatment With Ezetimibe Plus Low-Dose Atorvastatin Compared With Higher-Dose Atorvastatin Alone
Is Sufficient Cholesterol-Lowering Enough to Inhibit Platelets?

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Objectives
We sought to test the platelet inhibitory and anti-inflammatory effects of a higher statin dosage compared with combined treatment with ezetimibe plus a low statin dose.

Background
Reducing the level of low-density lipoprotein cholesterol (LDL-C) with statins induces important pleiotropic effects such as platelet inhibition. An insufficient LDL-C reduction often is treated with ezetimibe, an intestinal cholesterol absorption inhibitor, in combination with a low statin dose. It is not known whether this combination therapy has the same pleiotropic effects as a statin monotherapy.

Methods
Fifty-six patients with coronary artery disease were assigned randomly to receive either 40 mg/day of atorvastatin or 10 mg/day of ezetimibe plus 10 mg/day of atorvastatin for 4 weeks. The levels of LDL-C, platelet activation markers after stimulation, platelet aggregation, and plasma chemokine levels (i.e., regulated on activation normally T-cell expressed and secreted [RANTES]) were measured before and after changing lipid-lowering medication.

Results
Platelet activation markers (P-selectin) after stimulation (adenosine diphosphate) were reduced by 40 mg/day of atorvastatin (\(5.2 \pm 1.6\) arbitrary units) but not by ezetimibe plus low-dose atorvastatin (\(2.1 \pm 1.8\) arbitrary units; \(p = 0.005\)) despite a similar reduction of LDL-C (atorvastatin \(-1.01 \pm 0.18\) mmol/l vs. ezetimibe plus atorvastatin \(-1.36 \pm 0.22\) mmol/l, \(p = \text{NS}\)). Thrombin receptor-activating peptide-induced platelet aggregation as well as plasma RANTES levels were reduced by 40 mg/day of atorvastatin but not by ezetimibe plus low-dose atorvastatin.

Conclusions
Platelet reactivity and a proinflammatory chemokine were reduced more by the higher atorvastatin dose than by ezetimibe plus low-dose atorvastatin. In patients with coronary artery disease, it might be important to combine ezetimibe with higher statin dosages to benefit from cholesterol-independent pleiotropic effects.

The relationship between coronary artery disease (CAD) and elevated low-density lipoprotein cholesterol (LDL-C) levels is well established (1,2). The lowering of LDL-C using HMG-CoA reductase inhibitors (statins) has been found to substantially reduce cardiovascular mortality (3). The reduced mortality is attributed not only to the lowering of LDL-C but also to the numerous pleiotropic effects of statins (3–6). The inhibition of platelets by statins is well documented in patients with hypercholesterolemia and CAD as well as in healthy individuals (7–10).

Despite the established efficacy of statins, the number of patients who achieve and maintain a LDL-C level as recommended by the U.S. National Cholesterol Education Program and the Joint Task Force of European Societies is suboptimal (11–14). Titration to higher statin dosages is limited because of increasing adverse side effects, such as myopathy and hepatotoxicity (15,16).

Ezetimibe, an intestinal cholesterol absorption inhibitor, can be used as an additional therapy if statin therapy fails to reduce a patient’s levels of LDL-C (17,18). The complementary actions of statins and ezetimibe offer a potent treatment option via dual inhibition of 2 sources of cholesterol (19). Moreover, combining the 2 substances eliminates side effects such as statin-associated myopathy and hepatotoxicity and ezetimibe-induced compensatory-elevated
hepatic cholesterol synthesis (18,20). Although the combination of ezetimibe with a low atorvastatin dosage provides a very potent tool for reducing LDL-C, it is not known whether the combined treatment strategy achieves the same platelet inhibitory and anti-inflammatory effects as therapy with higher atorvastatin dosages (21–23). We therefore investigated patients with CAD to determine whether combined treatment with ezetimibe plus low-dose atorvastatin had different effects on platelet function and plasma chemokine levels than higher-dose therapy with atorvastatin alone.

Methods

Study design. The study included 56 patients with clinically stable CAD and LDL-C >2.5 mmol/l despite ongoing atorvastatin therapy with 10 or 20 mg/day. The patients met the following inclusion criteria: angiographically documented CAD, concurrent medication with aspirin and clopidogrel, and age between 18 and 80 years. Antiplatelet therapy with aspirin and clopidogrel had to be maintained throughout the entire study period. Exclusion criteria were a history of myocardial infarction or creatine kinase elevation within the last 4 weeks, recent warfarin treatment, tumors, severe renal insufficiency, active liver disease or known liver cirrhosis, unclarified transaminase increase, recent antibiotic therapy, and known alcohol abuse.

Patients were assigned randomly (28:28) to receive either 40 mg/day of atorvastatin (group A) or a combination of 10 mg/day of atorvastatin plus 10 mg/day of ezetimibe (group B). The experimental regimen was initiated without a washout period. Before and 4 weeks after changing the LDL-C-lowering medication, blood was drawn for ex vivo platelet stimulation, platelet aggregation, plasma chemokine levels (i.e., regulated on activation normally T-cell expressed and secreted [RANTES]), and lipid levels (LDL-C, high-density lipoprotein cholesterol [HDL-C], triglycerides [TG]). At the end of the study, 2 patients dropped out after the general practitioner changed their lipid-lowering medication, and 3 patients did not present again. Therefore, 51 patients (25:26) remained for statistical analysis.

The institutional review board of the hospital approved the study protocol, and written informed consent was obtained from each subject. All procedures were performed in accordance with the Declaration of Helsinki.

Ex vivo platelet stimulation. Platelet reactivity during LDL-C lowering was evaluated by ex vivo platelet stimulation with adenosine diphosphate (ADP) as previously described (9). The protocol was tested in advance for artificial platelet activation (9). In brief, whole blood was collected in acidic citrate dextrose. Platelets were pelleted by centrifugation. The resuspended platelets were stimulated for 30 min with 20 μmol/l ADP (Sigma Chemical Co., St. Louis, Missouri), 10 μmol/l of thrombin receptor-activating peptide (TRAP; Calbiochem, San Diego, California) or were left unstimulated. The density of P-selectin and CD 63 (lyosomal glycoprotein 53) was measured by flow cytometry using monoclonal antibodies as previously described (9,24,25). Data are given as the median immunofluorescence intensity (MFI) in arbitrary units (AU) after subtraction of the unspecific mouse IgG binding.

Platelet aggregation. Ex vivo platelet aggregation was evaluated by optical aggregometry in citrated plasma samples at 37°C using the PAP 4 platelet aggregation profiler (Biodata Corporation, Horsham, Pennsylvania). Platelet-rich plasma was prepared from citrated whole blood by centrifugation (1,315 g for 75 s). The final platelet count was adjusted to 300 nl with autologous plasma. A total of 50 μl of ADP (final concentration of 20 μmol/l) or TRAP (final concentration of 10 μmol/l) were added to induce platelet aggregation. Platelet aggregation was measured and assessed in 38 of the 51 patients (n = 17 in the atorvastatin group and n = 21 in the ezetimibe plus atorvastatin group). Curves were characterized by the maximum aggregation (MA) in % and the maximum slope (SL) in%/s.

Measurements of plasma chemokine levels. The plasma RANTES levels were determined by an enzyme-linked immunosorbent assay (ELISA). The ELISA-developing kits were purchased from Bender MedSystems, and measurements conforming to the manufacturer’s recommendations were performed with a VersaMax microplate ELISA reader. Plasma RANTES levels were calculated using a polynomial standard curve with SoftMax Pro 4.6 software and given in nanograms per milliliter.

Statistics. Data from all numeric variables were tested for normal distribution using the Kolmogoroff-Smirnov test. Thus, continuous data were presented as the mean ± the standard error of the mean. The t test for dependent samples was used to analyze the expressions of platelet activation markers, platelet aggregation, plasma chemokine levels, and plasma lipid levels before and after changing treatment. Differences in platelet activation markers (ΔMFI), platelet aggregation (ΔMA, ΔSL), plasma chemokine levels (Δc), and plasma lipid levels (ΔLDL-C, ΔHDL-C, ΔTG) were calculated as the values after minus before changing treatment. ΔMFI, ΔMA, ΔSL, Δc, ΔLDL-C, ΔHDL-C, and ΔTG were compared between groups using the t test for independent samples. Demographic and clinical data were compared between groups using the t test for independent samples or the chi-square test for nominal values. Values of p ≤ 0.05 (2-sided) were
considered significant. All analyses were performed using SPSS for Windows, Release 11.0.1 (SPSS Institute, Chicago, Illinois).

**Results**

Both groups of patients had a typical cardiovascular risk profile. They did not differ significantly with regard to age, gender, body mass index, cardiovascular risk factors, cardiac characteristics and medication before changing lipid-lowering therapy (Tables 1 and 2). The study included patients who had been receiving either 10 or 20 mg/day of atorvastatin. Ten of 25 patients in the atorvastatin group and 12 of 26 patients in the combination group (p = NS) had an intake of 10 mg/day of atorvastatin before changing to study medication. With regard to the initial atorvastatin dose, there were no differences in platelet inhibitory and lipid-lowering effects obtained by the study medication (data not shown).

**Change in serum lipid levels.** Low-density lipoprotein cholesterol levels were reduced in both groups 4 weeks after changing the lipid-lowering therapy (Table 2). The extent of LDL-C reduction (ΔLDL-C) did not differ significantly between the groups (atorvastatin, −1.01 ± 0.18 mmol/l vs. ezetimibe plus atorvastatin, −1.36 ± 0.22 mmol/l) (Fig. 1). Accordingly, 16 of 25 (64%) patients in the atorvastatin group and 20 of 26 (77%) in the combination group achieved the LDL-C treatment goal of ≤2.5 mmol/l (p = NS atorvastatin vs. ezetimibe plus atorvastatin). The HDL-C level did not change in either group during the observation period (Table 2). Reduced TG levels were observed in both the atorvastatin and the combination group (Table 2). The ΔTG did not differ significantly between the groups (data not shown).

**Platelet reactivity after ex vivo platelet stimulation.** Although the two treatment groups showed a similar LDL-C reduction, they differed in their agonist-induced platelet reactivity. The ADP-induced platelet P-selectin expression

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical Characteristics and Medication of the Study Population</th>
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<tbody>
<tr>
<td></td>
<td>Atorvastatin (n = 25)</td>
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<tr>
<td>Age (yrs)</td>
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<tr>
<td>Gender (male/female)</td>
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<tr>
<td>Weight (kg)</td>
<td>83.0 ± 2.6</td>
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<tr>
<td>Height (cm)</td>
<td>174.6 ± 1.9</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<tr>
<td>Ejection fraction (%)</td>
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<tr>
<td>Cardiovascular risk factors (n)</td>
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<td>Hypercholesterolemia</td>
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<td>Systemic hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Adipositas</td>
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<tr>
<td>Tobacco use</td>
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<tr>
<td>Medication (n)</td>
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<td>Aspirin and clopidogrel</td>
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<tr>
<td>Beta-blocker</td>
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<td>Angiotensin-converting enzyme-inhibitor/AT-1 blocker</td>
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<td>Diuretics</td>
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<tr>
<td>Proton-pump inhibitor</td>
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<tr>
<td>Insulin/oral antidiabetics/diet</td>
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</tr>
</tbody>
</table>

No differences were observed between the groups.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Alteration of Laboratory and Lipid Parameters by the Study Medication</th>
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<tbody>
<tr>
<td></td>
<td>Atorvastatin (n = 25)</td>
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<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>ASAT (IU/ml)</td>
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<tr>
<td>ALAT (IU/ml)</td>
<td>26.9 ± 1.8</td>
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<tr>
<td>Creatinine (mM/ml)</td>
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<tr>
<td>Creatinine (mM/ml)</td>
<td>86.6 ± 3.3</td>
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<tr>
<td>LDL-C (mmol/l)</td>
<td>3.49 ± 0.18</td>
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<tr>
<td>HDL-C (mmol/l)</td>
<td>1.31 ± 0.07</td>
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<tr>
<td>TG (mmol/l)</td>
<td>1.81 ± 0.15</td>
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</table>

* p < 0.05, † p < 0.005, before versus after changing lipid-lowering medication.

ALAT = alanine transaminase; ASAT = aspartate transaminase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.
was reduced 4 weeks after atorvastatin treatment with 40 mg/day (from 18.2 ± 1.7 AU to 12.9 ± 1.0 AU; p < 0.005) (Fig. 2A). In addition, TRAP-induced P-selectin exposure also was diminished 4 weeks after higher-dose atorvastatin treatment (from 29.2 ± 2.1 AU to 23.0 ± 2.0 AU; p < 0.01) (Fig. 3A). The administration of ezetimibe plus low-dose atorvastatin for 4 weeks did not reduce P-selectin expression after stimulation with ADP (16.4 ± 1.4 AU vs. 18.5 ± 2.0 AU; p = NS) (Fig. 2A) or TRAP (32.1 ± 2.8 AU vs. 31.8 ± 3.1 AU; p = NS) (Fig. 3A). Furthermore, a significant difference in ΔMFI was found between the 2 treatment groups. Higher-dose atorvastatin led to a larger reduction of ADP-induced P-selectin expression than ezetimibe combined with low-dose atorvastatin (ΔMFI −5.2 ± 1.6 AU vs. 2.1 ± 1.8 AU; atorvastatin vs. ezetimibe plus atorvastatin; p < 0.005; Fig. 2B). The 2 study groups showed no significant differences in ΔMFI after stimulation with TRAP (−6.2 ± 2.2 AU vs. −0.2 ± 3.1 AU; atorvastatin vs. ezetimibe plus atorvastatin; p = 0.1) (Fig. 3B).

Comparable results were obtained when analyzing CD 63 expression on the surface of stimulated platelets. High-dose statin therapy reduced CD 63 expression on platelets stimulated with ADP and TRAP (Table 3). However, CD 63 expression was not reduced on stimulated platelets after combination therapy with ezetimibe plus statin (Table 3). There was a significant difference in ΔMFI between the 2 groups. Thus, therapy with 40 mg/day of atorvastatin resulted in a larger reduction of CD 63 expression than combination treatment with ezetimibe plus 10 mg/day of atorvastatin (Table 3).

Figure 2 Differences in ADP-Induced P-Selectin Expression on Platelets

(A) Platelet P-selectin expression after adenosine diphosphate (ADP) stimulation at baseline and after 4 weeks of lipid-lowering therapy with atorvastatin (open bars, n = 25) or a combination of ezetimibe plus atorvastatin (solid bars, n = 26). (B) Differences in median immunofluorescence intensity (ΔMFI) in P-selectin expression (level after 4 weeks of lipid-lowering therapy minus level before changing treatment). AU = arbitrary units.

Figure 3 Differences in TRAP-Induced P-Selectin Expression on Platelets

(A) Platelet P-selectin expression after stimulation with thrombin receptor-activating peptide (TRAP) at baseline and after 4 weeks of lipid-lowering therapy with atorvastatin (open bars, n = 25) or a combination of ezetimibe plus atorvastatin (solid bars, n = 26). (B) Differences in median immunofluorescence intensity in P-selectin expression (level after 4 weeks of lipid-lowering therapy minus level before changing treatment). Abbreviations as in Figure 2.
Platelet aggregation. Platelet aggregation measurements also reflected the different effects of the lipid-lowering medication in patients with CAD. We discovered that ADP-induced platelet aggregation was not altered by both therapies (Tables 4 and 5). However, the TRAP-induced maximum platelet aggregation, as well as the maximum slope of the aggregation curves, was reduced by 40 mg/day atorvastatin but not by the combination of ezetimibe plus low-dose atorvastatin (Tables 4 and 5). Neither ΔMA nor ΔSL differed significantly between the 2 study groups (Tables 4 and 5).

Plasma chemokine levels. The plasma RANTES concentrations were reduced from 0.81 ± 0.04 ng/ml to 0.70 ± 0.05 ng/ml by higher-dose atorvastatin (p < 0.05) (Fig. 4A) but were not significantly lowered by the combination of ezetimibe plus 10 mg/day of atorvastatin (0.81 ± 0.04 ng/ml vs. 0.75 ± 0.04 ng/ml, before vs. after p = NS) (Fig. 4A). No significant difference was found when comparing RANTES Δc between the 2 groups (−0.10 ± 0.04 ng/ml vs. −0.06 ± 0.04 ng/ml; atorvastatin vs. ezetimibe + atorvastatin, p = NS) (Fig. 4B).

Discussion

In this study, three major findings were observed: 1) during a 4-week treatment period, the degree of LDL-C reduction achieved by 40 mg/day of atorvastatin was comparable with that obtained by 10 mg/day of ezetimibe in combination with 10 mg/day of atorvastatin; 2) platelet reactivity was reduced by lipid-lowering treatment with 40 mg/day of atorvastatin but not by combination therapy with ezetimibe plus atorvastatin; and 3) the plasma RANTES concentration was reduced by 40 mg/day of atorvastatin but not by ezetimibe combined with 10 mg/day of atorvastatin.

Changes in serum lipid levels by lipid-lowering treatment. The extent of LDL-C reduction and the number of patients achieving the LDL-C goal of ≤2.5 mmol/l by the ezetimibe-atorvastatin combination in this study were comparable with data from previous studies evaluating the safety and tolerability of ezetimibe and atorvastatin coadministration (21,23). Although ΔLDL-C did not differ significantly between the 2 groups, LDL-C tended to be more reduced by the combined treatment than by the 40 mg/day of atorvastatin. In a double-blind trial, Ballantyne et al. (21) reported that 10 mg/day of ezetimibe combined with 10 mg/day of atorvastatin had the same LDL-C reducing effect as 80 mg/day of atorvastatin. This report indicates that the combination of ezetimibe plus low-dose atorvastatin is very potent in reducing LDL-C levels. However, combining ezetimibe with higher statin dosages provided only small additional LDL-C reductions (21). Thus, higher-dose statin therapy may not be necessary in combination with ezetimibe, considering the efficacy and safety of the low-dose combinations (21).

Platelet inhibition and anti-inflammatory effects. Inhibition of platelets by statin therapy is a well-documented dose-dependent effect (3–10). Cholesterol-dependent and -independent mechanisms may contribute to it. Impaired platelet aggregation in vivo and in vitro was shown as a result of a decreased platelet stimulation by low-density lipoproteins and their oxidation products, a cholesterol depletion in the platelet plasma membrane, an impaired signal transduction because of a lack of intracellular isoprenoids, a decreased thromboxane A2 synthesis, and an improved nitric oxide bioavailability (3–7,26,27). However, it has not yet been clarified whether platelet inhibition by statin therapy depends on the reduction of LDL-C or on the inhibition of intracellular signal pathways accompanied by disaggregating effects. In the present study, ADP- and TRAP-induced platelet degranulation as well as TRAP-induced platelet aggregation was reduced by 40 mg/day of atorvastatin but not by ezetimibe plus low-dose atorvastatin despite a comparable LDL-C reduction. The platelet inhibitory effects observed here were achieved by increasing the atorvastatin dosage. A comparable reduction of the LDL-C level by ezetimibe plus low-dose atorvastatin did not result in similar platelet inhibitory effects. Therefore, we assume that the observed platelet inhibition by higher atorvastatin dose was mainly related to mechanisms independent of the LDL-C-lowering.

Despite the reduction of agonist-induced platelet degranulation and TRAP-induced platelet aggregation, 40 mg/day of atorvastatin had no influence on ADP-induced platelet aggregation. One explanation might be a previously described minor effect of atorvastatin on ADP-induced platelet aggregation.
let aggregation (28). A more important reason is the coadministration of clopidogrel in our study. Because clopidogrel inhibits ADP-induced platelet aggregation, an influence of atorvastatin is underestimated. This observation is consistent with findings in several studies evaluating possible drug-drug interactions between atorvastatin and clopidogrel (29–32).

The chemokine RANTES is produced by a variety of leukocytes and platelets’ (33). It is expressed on the platelets’ surface after platelet α-granule degranulation (34). It mediates platelet activation, platelet-leukocyte interaction, as well as attraction and homing of leukocytes (monocytes, lymphocytes, natural killer cells, mast cells) at sites of vascular injury and platelet deposition (33,34). It also is thought to play a key role in the progression of atherosclerosis by promoting monocyte MCP-1 production, macrophage accumulation, and neointimal growth (34,35). Thus, plasma RANTES not only serves as a marker of platelet activation in vivo but also reflects inflammatory processes at sites of vascular injury and platelet deposition (33,34). In the present study, the plasma RANTES concentration was decreased by 40 mg/day of atorvastatin but not by ezetimibe plus low-dose atorvastatin despite the similar LDL-C reduction. Although the comparison of the reduction in the RANTES concentration between the 2 groups showed no significant difference, it demonstrates that in vivo platelet activation and an inflammatory chemokine tend to be more reduced by higher-dose atorvastatin therapy. These results here are in agreement with findings indicating that the anti-inflammatory effects of atorvastatin are independent of the degree of LDL-C reduction (6). In addition, pleiotropic effects for simvastatin but not for ezetimibe have been described by Landmesser et al. (39). The authors demonstrated that, independent of their LDL-C-reducing capacity, simvastatin, but not ezetimibe, improved endothelial function in chronic heart failure patients.

Clinical trials have shown that a statin-associated reduction of CAD-related events correlates with the LDL-C level achieved (3,40). Recommended LDL-C levels of 1.8 mmol/l (70 mg/dl) or 2.5 mmol/l (100 mg/dl) were only obtained by high-dose statin treatment. Thus, the dose-dependent reduction of CAD-related events has been attributed to the LDL-C–lowering properties of statins. Moreover, many of the pleiotropic effects of statins were also shown to be dose-dependent (6). We demonstrated here that atorvastatin has dose-dependent platelet inhibitory effects independent of its LDL-C–lowering capacity. Because platelet hyperreactivity is a strong predictor of cardio-

### Table 5: Maximal Slope of Aggregation After ADP and TRAP Stimulation

<table>
<thead>
<tr>
<th>SL (%/s)</th>
<th>ADP</th>
<th>TRAP</th>
<th>ADP</th>
<th>TRAP</th>
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<tbody>
<tr>
<td>SL before changing treatment</td>
<td>0.85 ± 0.05</td>
<td>0.72 ± 0.05</td>
<td>0.84 ± 0.05</td>
<td>0.72 ± 0.06</td>
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<tr>
<td>SL after changing treatment</td>
<td>0.82 ± 0.06</td>
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<tr>
<td>∆SL</td>
<td>−0.04 ± 0.05</td>
<td>−0.17 ± 0.06</td>
<td>0.04 ± 0.04</td>
<td>0.01 ± 0.07</td>
</tr>
</tbody>
</table>

*p < 0.05, before versus after changing lipid-lowering medication.

SL = maximum slope of aggregation; other abbreviations as in Table 3.

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**Figure 4** RANTES Levels in Blood Pre- and Post-Lipid-Lowering Therapy

(A) Plasma regulated on activation normally T-cell expressed and secreted (RANTES) concentration at baseline and after 4 weeks of lipid-lowering therapy with atorvastatin (open bars, n = 25) or a combination of ezetimibe plus atorvastatin (solid bars, n = 26). (B) Differences (Δc) in plasma RANTES concentration (level after 4 weeks of lipid-lowering therapy minus level before changing treatment). c = concentration.
vascular events in patients with CAD, platelet inhibition by statins may well influence their clinical outcome (2).

In this study, we only tested platelet inhibitory effects of atorvastatin at 10 and 40 mg/day. Conclusions regarding the platelet inhibitory effect of atorvastatin at dosages different from the study medication have to be drawn carefully. However, the existence of a threshold dose below which no additional pleiotropic effects are observed cannot be definitely excluded.

It should be noted that the reduction of platelet reactivity by higher-dose atorvastatin dose was observed under full antiplatelet therapy with aspirin and clopidogrel. This supports results demonstrating platelet inhibition when 20 mg/day of atorvastatin were coadministered with clopidogrel (9). These observations are in contrast with previous findings suggesting that atorvastatin dose-dependently limits clopidogrel efficacy (41).

Conclusions

The present study provides evidence that the therapy with 40 mg/day of atorvastatin has beneficial cholesterol-independent effects on platelets and plasma RANTES levels in patients with CAD. The administration of ezetimibe plus 10 mg of atorvastatin did not have these effects, although it achieved an excellent reduction of LDL-C. These findings might be relevant in patients with atherosclerotic cardiovascular disease where LDL-C reduction cannot be sufficiently reduced under standard statin therapy. In these patients, it might not be sufficient to lower the LDL-C level to ≤2.5 mmol/l by using a combination of ezetimibe plus low-dose statin. Considering the pleiotropic effects of statins, we hypothesize that it might be better to adjust the lipid-lowering medication by combining ezetimibe with a higher statin dose. Further clinical and experimental studies are required to test this hypothesis.

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REFERENCES