

Atorvastatin Reduces the Ability of Clopidogrel to Inhibit Platelet Aggregation

A New Drug–Drug Interaction

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Background—We observed that the prodrug clopidogrel was less effective in inhibiting platelet aggregation with coadministration of atorvastatin during point-of-care platelet function testing. Because atorvastatin is metabolized by cytochrome P450 (CYP) 3A4, we hypothesized that clopidogrel might be activated by CYP3A4.

Methods and Results—Platelet aggregation was measured in 44 patients undergoing coronary artery stent implantation treated with clopidogrel or clopidogrel plus pravastatin or atorvastatin, and in 27 volunteers treated with clopidogrel and either erythromycin or troleandomycin, CYP3A4 inhibitors, or rifampin, a CYP3A4 inducer. Atorvastatin, but not pravastatin, attenuated the antiplatelet activity of clopidogrel in a dose-dependent manner. Percent platelet aggregation was 34 ± 23 , 58 ± 15 ($P=0.027$), 74 ± 10 ($P=0.002$), and 89 ± 7 ($P=0.001$) in the presence of clopidogrel and 0, 10, 20, and 40 mg of atorvastatin, respectively. Erythromycin attenuated platelet aggregation inhibition (55 ± 12 versus $42 \pm 12\%$ platelet aggregation; $P=0.002$), as did troleandomycin (78 ± 18 versus $45 \pm 18\%$ platelet aggregation; $P<0.0003$), whereas rifampin enhanced platelet aggregation inhibition (33 ± 18 versus $56 \pm 20\%$ platelet aggregation, $P=0.001$).

Conclusions—CYP3A4 activates clopidogrel. Atorvastatin, another CYP3A4 substrate, competitively inhibits this activation. Use of a statin not metabolized by CYP3A4 and point-of-care platelet function testing may be warranted in patients treated with clopidogrel. (*Circulation*. 2003;107:32-37.)

Key Words: drugs ■ pharmacology ■ platelets ■ statins

Clopidogrel inhibits platelet aggregation.¹ It decreases the incidence of coronary artery stent thrombosis and is approved for reduction of myocardial infarction, stroke, and vascular death in patients with atherosclerotic vascular disease.^{2–4} Clopidogrel is an inactive thienopyridine prodrug that requires in vivo conversion in the liver to an active metabolite that exerts its antiplatelet effect by forming an inactivating disulfide bond with the platelet P2Y₁₂ (P2Y₁₂) adenosine diphosphate (ADP) receptor.^{5–8} The P2Y₁₂ ADP receptor is a guanosine triphosphate (GTP)-coupled 7 trans-membrane protein that mediates platelet aggregation by inhibiting adenyl cyclase.⁸ In rats, it has been suggested that clopidogrel is activated by cytochrome P450 1A2,⁶ whereas an analogue of clopidogrel, CS-747, is speculated to be activated by human cytochrome P450 3A4 (CYP3A4).⁹ In humans, it is not known how clopidogrel is activated.

Atorvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor widely used to treat hypercho-

lesteremia. It is metabolized by CYP3A4,¹⁰ the most abundant cytochrome P450 in human liver. Patients with atherosclerotic disease are frequently treated for hypercholesterolemia with both clopidogrel and atorvastatin or another statin.

During the course of evaluating the effect of clopidogrel on platelet function using a novel bedside platelet aggregometer, it was noted that the antiplatelet activity of clopidogrel was diminished significantly when patients were also taking atorvastatin. This prompted prospective studies to test the hypothesis that atorvastatin was inhibiting clopidogrel activation by CYP3A4.

Methods

Patients and Study Protocols

The institutional review board approved the study protocols and written informed consent was obtained from each subject before enrollment. In the initial study, 44 patients undergoing successful elective coronary artery stent implantation received an oral loading dose of 300 mg of clopidogrel followed by 75 mg/d for 28 days.

Before stent placement, the patients also received a loading dose of eptifibatide 180 $\mu\text{g/kg}$ followed by a continuous infusion of 2.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for <12 hours. Sixteen patients were not on statin therapy, 9 were taking 40 mg of pravastatin a day, and 19 were taking either 10 mg ($n=7$), 20 mg ($n=7$), or 40 mg ($n=5$) of atorvastatin a day. Platelet aggregation was measured^{11,12} before clopidogrel administration and 24 hours later, hours after the eptifibatide effect was finished.¹³ Platelet aggregation measurements were repeated in 13 patients on clopidogrel and in 13 patients on clopidogrel plus atorvastatin 6 to 8 days after successful stent implantation.

In the second study, 19 volunteers aged 18 to 40 years were enrolled in a randomized 30-day protocol to examine the effects of erythromycin (a CYP3A4 inhibitor) and rifampin (a CYP3A4 inducer) on platelet aggregation in the presence of clopidogrel. Volunteers were excluded from the study if they had a history of thrombocytopenia or bleeding disorder or if they were taking any medications, alcohol, caffeine, tobacco, herbal remedies such as St John's wort, grapefruit juice, birth control pills, or charcoal broiled food. Group 1 ($n=9$) received a maintenance dose of 75 mg/d of clopidogrel for 6 days, followed by a washout period of 14 days, followed by 4 days of erythromycin stearate 250 mg 4 times a day, followed by 6 days of both clopidogrel and erythromycin. Group 2 ($n=10$) was treated similarly, except they received rifampin 300 mg twice a day instead of erythromycin. Platelet aggregation was determined on days 0, 6, 20, 24, and 30.

In the third study, the effect of troleandomycin (a CYP3A4 inhibitor) on CYP3A4 activity and platelet aggregation was examined in 8 volunteers. The exclusion criteria were the same as in the second study. An erythromycin breath test was performed¹⁴ and platelet aggregation was measured before and 2 hours after ingesting clopidogrel 450 mg. After a 14-day washout period, the erythromycin breath test and measurement of platelet aggregation were repeated. Troleandomycin 500 mg was administered, and 1 hour later 450 mg of clopidogrel was ingested. Two hours after clopidogrel, the erythromycin breath test and platelet aggregation measurements were repeated.

Platelet Aggregation Measurement

Platelet aggregation was measured with the point-of-care MICROS cell counter (ABX Diagnostics) and the Plateletworks test platform (Helena Laboratories). The cell counter uses traditional electronic impedance cell counting principles.^{11,12} In brief, a reference platelet count is performed on 1 mL of fresh whole blood in a Plateletworks tube containing $\text{K}_3\text{-EDTA}$ as the anticoagulant. The sample is then passed through the cell counter and the platelet count is determined. This process is repeated with a second 1 mL sample of fresh whole blood in a Plateletworks tube containing both citrate and 20 $\mu\text{mol/L}$ ADP. In the presence of ADP, platelets associate and aggregate. As the aggregated platelets exceed the threshold limitations for platelet size, they are no longer counted as individual platelets. The ratio of the platelet count between the agonist and reference tubes is calculated as percent platelet aggregation. The results are available within 4 minutes. A previous study comparing this device to light transmission aggregometry using platelet-rich plasma demonstrated a correlation coefficient of 0.83 in 225 paired samples.¹²

Erythromycin Breath Test

The erythromycin breath test (Metabolic Solutions, Inc) was used to measure hepatic CYP3A4 activity *in vivo*.¹⁴ A preinjection breath sample was obtained. An intravenous dose of [¹⁴C-N-methyl]-erythromycin (3 μCi , 0.01 mmol of erythromycin) was then administered. Subsequently, a single breath sample was collected after 20 minutes. Quantitation of exhaled ¹⁴CO₂ provides a selective measure of the "instantaneous" hepatic CYP3A4 activity.¹⁵ Inhibitors, such as erythromycin and troleandomycin, and inducers, such as rifampin, will respectively decrease and increase the percentage of the administered dose excreted as ¹⁴CO₂. Troleandomycin was used because it is a more effective inhibitor of CYP3A4 activity than erythromycin.

Statistics

In patients undergoing stent implantation, unpaired 2-sample *t* tests were used to compare platelet aggregation in controls and those taking atorvastatin. In normal volunteers taking either erythromycin or rifampin, paired 2-sample *t* tests with Bonferroni's correction were used to compare platelet aggregation between 0, 6, 20, 24, and 30 days within each group. In volunteers undergoing the erythromycin breath test, a paired 2-sample *t* test was used to compare platelet aggregation at 0 and 2 hours. Nonparametric data that did not conform to a normal distribution were analyzed using Mann-Whitney *U* tests for unpaired data and Wilcoxon tests for paired data. All values were expressed as mean \pm SD. A probability value of <0.05 was considered significant.

Results

Patients

There were no differences in age, sex, atherosclerotic risk factors, or other medications that might promote or inhibit CYP3A4 in the 3 groups of patients undergoing stent implantation. Other CYP3A4 co-medications (number of patients on clopidogrel alone/pravastatin/atorvastatin) included diltiazam (3/1/3), dexamethasone (0/0/1), and phenytoin (0/0/1). Clopidogrel alone inhibited platelet aggregation (Figure 1A). Coadministration with pravastatin did not influence platelet aggregation. In the presence of clopidogrel and 10 to 40 mg of atorvastatin, however, platelet aggregation inhibition was attenuated. Figure 1B illustrates that atorvastatin produced a dose-dependent, statistically significant attenuation of the antiplatelet activity of clopidogrel. Moreover, atorvastatin administered in a dose of 40 mg/d completely inhibited the antiplatelet activity of clopidogrel. Inhibition of platelet aggregation continued to be significantly attenuated 6 to 8 days after stent implantation in patients receiving both clopidogrel and atorvastatin compared with clopidogrel alone ($74 \pm 13\%$ platelet aggregation versus $41 \pm 19\%$ platelet aggregation; $P < 0.0001$).

CYP3A4 Inhibition and Induction

Clopidogrel inhibited platelet aggregation in normal volunteers (Figure 2). Platelet aggregation returned to baseline after the 14-day washout period. Neither erythromycin nor rifampin altered platelet aggregation. Clopidogrel was significantly less active when coadministered with erythromycin, a CYP3A inhibitor (Figure 2A). Conversely, the antiplatelet activity of clopidogrel was significantly enhanced by rifampin (Figure 2B).

Erythromycin Breath Test

The *in vivo* CYP3A4 activity was unambiguously inhibited by troleandomycin, as measured by the erythromycin breath test (Figure 3A). Clopidogrel alone inhibited platelet aggregation (Figure 3B). When clopidogrel was administered during the time CYP3A4 was known to be dysfunctional, platelet aggregation was not inhibited (Figure 3A and 3B).

Discussion

The overall goal of drug-metabolizing CYP enzymes is the conversion of lipophilic drugs into more hydrophilic compounds to facilitate elimination by the kidney. This study showed that clopidogrel is less effective in inhibiting platelet aggregation when coadministered with atorvastatin, a

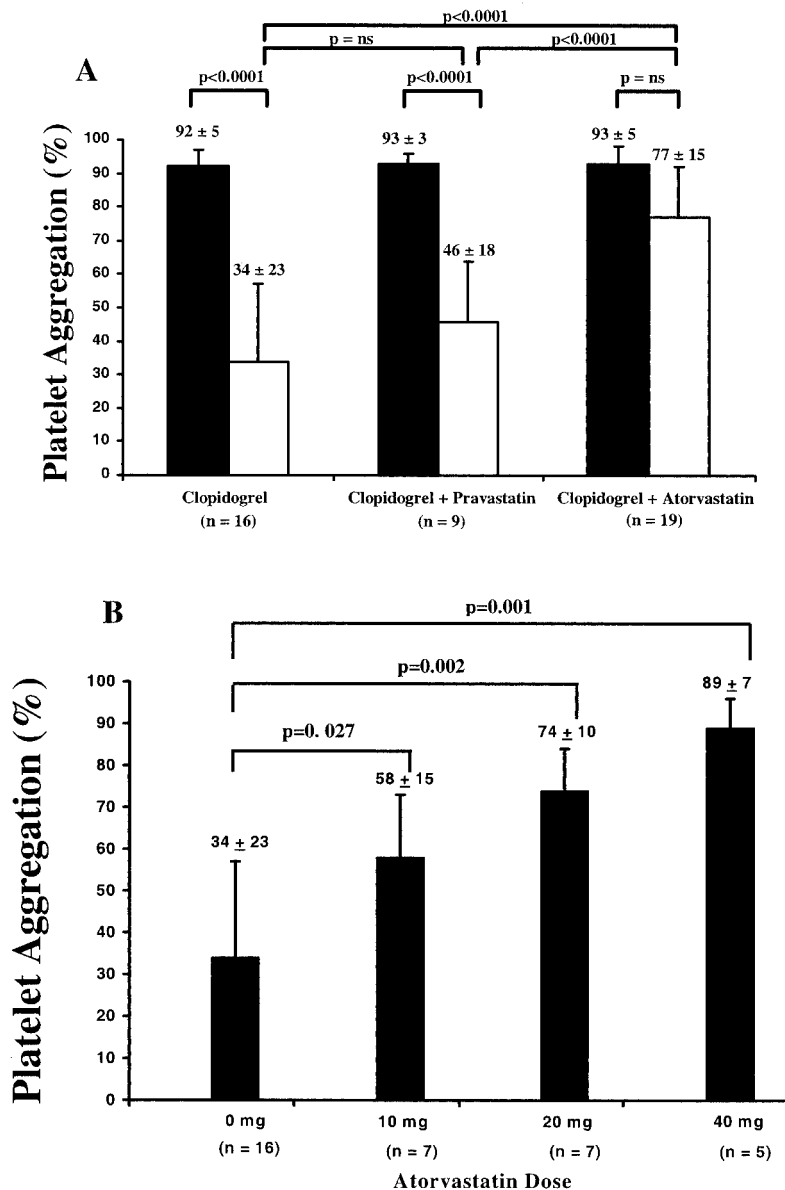


Figure 1. The in vivo effect of pravastatin and atorvastatin on the antiplatelet activity of clopidogrel. A, Platelet aggregation before (black columns) and 24 hours after (white columns) clopidogrel administration in patients treated without or with pravastatin (40 mg) and without or with atorvastatin (10 to 40 mg). B, The antiplatelet activity of clopidogrel as a function of the dose of atorvastatin.

CYP3A4 substrate. In contrast, when clopidogrel was administered with pravastatin, a hydrophilic drug not metabolized by the CYP system, platelet aggregation inhibition was not altered. Furthermore, in vivo studies demonstrated that clopidogrel is metabolized by CYP3A4, the most prominently expressed CYP in the human liver. We conclude that atorvastatin, at doses routinely administered to patients, inhibits CYP3A4 activity in a dose-dependent manner, and thereby decreases the metabolic conversion of clopidogrel to its pharmacologically active form.

Clopidogrel is a methyl ester, which is hydrolyzed in vivo by esterases to an inactive carboxylic acid derivative, which achieves a peak plasma concentration of $\approx 9 \mu\text{mol/L}$ after a 75 mg oral dose. The acid represents more than 85% of the circulating drug-related compounds in plasma. As a result, only a small unknown portion of clopidogrel is available for metabolism to the active metabolite after oral administration.¹⁶ Thus, it is likely that the intrahepatocyte level of

clopidogrel is at least 10-fold lower than the plasma level of the inactive carboxylic acid form. Atorvastatin is an hydroxy acid which is reversibly converted to its lactone form in vivo with approximately equal amounts of lactone and acid in the serum.¹⁷ Atorvastatin acid, but not the lactone, competitively and selectively inhibits HMG-CoA reductase in the liver, whereas the more lipophilic atorvastatin lactone is a better CYP3A4 substrate than atorvastatin acid.¹⁰ Approximately 70% of the circulating inhibitory activity for HMG-CoA reductase has been attributed to atorvastatin acid,¹⁸ whereas atorvastatin lactone rather than the acid form is the relevant pathway for atorvastatin elimination and drug interactions because atorvastatin lactone binds more tightly to CYP3A4 than the majority of its other substrates.^{10,19}

Because the degree of competitive inhibition between 2 substrates depends on the relative affinity of the substrates for the binding site of CYP3A4 and their relative concentrations, atorvastatin is expected to be a potent inhibitor of many

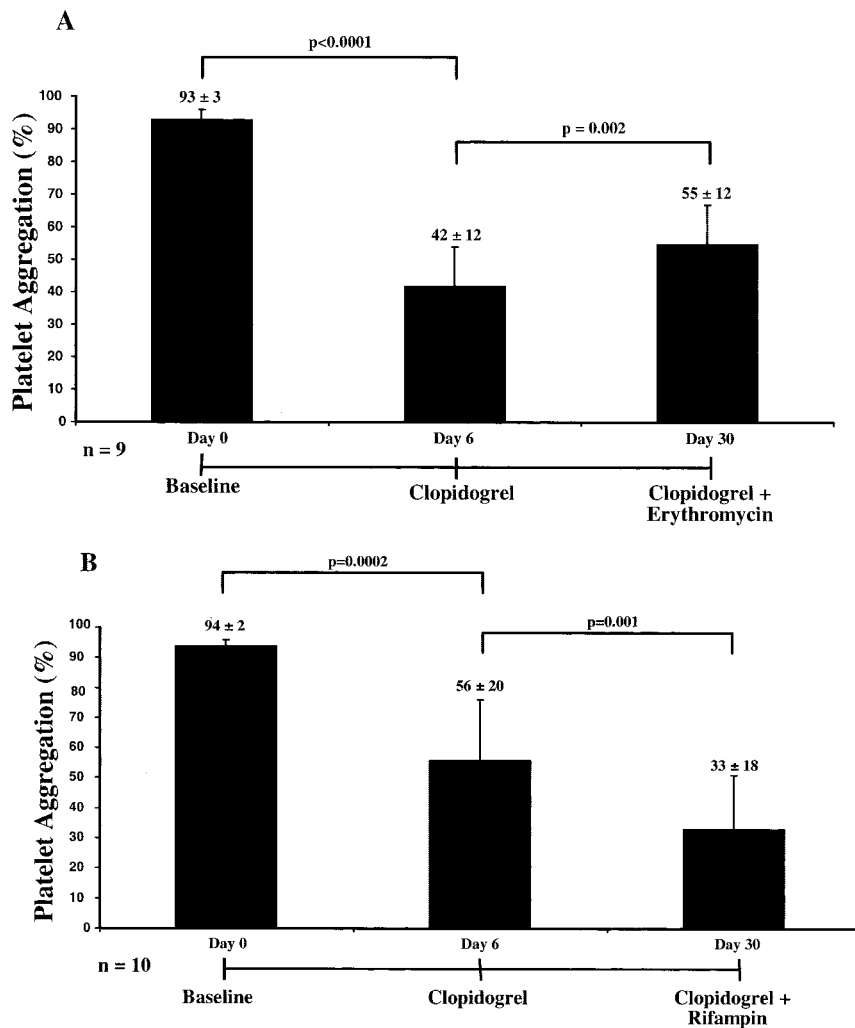


Figure 2. Cytochrome P450 3A4 inhibition and induction. A, The effect of erythromycin on the antiplatelet activity of clopidogrel. B, The effect of rifampin on the antiplatelet activity of clopidogrel.

CYP3A4 substrates if both substrates are present at the same concentration.¹⁹ However, atorvastatin lactone exists at a low concentration in vivo because its parent compound is so potent.¹⁷ Atorvastatin has previously been shown to inhibit the metabolism of only a few substrates, such as ethinyl estradiol,¹⁹ which binds CYP3A4 ≈ 30 -fold less tightly than atorvastatin lactone and is also present in vivo at low concentrations. Clopidogrel metabolism is inhibited by atorvastatin in vivo presumably because clopidogrel occurs at a low concentration and binds CYP3A4 less tightly than atorvastatin lactone.

The azole antifungals like itraconazole,²⁰ selected immunosuppressants like cyclosporin, protease inhibitors, macrolide antibiotics like erythromycin, and dihydropyridine calcium channel blockers are all potent inhibitors of CYP3A4. These drugs either bind more tightly to CYP3A4 and/or are present at significantly higher concentrations than atorvastatin. As a result of their ability to competitively inhibit the metabolism of atorvastatin, these drugs raise the plasma concentration of the atorvastatin acid and increase the risk of myositis and rhabdomyolysis.²¹ Drugs that inhibit atorvastatin metabolism would, therefore, also be expected to inhibit clopidogrel metabolism. Other inducers (St John's wort) and inhibitors (grapefruit juice) of CYP3A4 should also increase

and decrease, respectively, the activation of clopidogrel. Lovastatin and simvastatin are metabolized by CYP3A4 and are predicted to exhibit pharmacological properties similar to those of atorvastatin.²¹ In contrast, pravastatin, fluvastatin, and rosuvastatin are not metabolized by CYP3A4 and would not be expected to alter clopidogrel activation.^{21,22}

Traditional turbidimetric platelet aggregometry is labor intensive, is subject to operator variables, and provides indirect measurements because it uses citrated platelet-rich plasma devoid of other blood elements. In response to these limitations, 2 automated point-of-care devices have been developed that provide rapid and reproducible results using a small sample of whole blood. One is based on the ability of platelets to agglutinate fibrinogen-coated beads when activated by thrombin receptor activating peptide.²³ To date, this device has only been able to measure platelet glycoprotein IIb/IIIa receptor blockade. The other device, which was used in this study, uses ADP to promote platelet aggregation and allowed us the unique opportunity to measure the activity of clopidogrel, an ADP receptor antagonist.^{11,12}

Drug interactions with other antiplatelet agents have recently been reported. Post-hoc analyses²⁴ have suggested that aspirin may reduce the benefit of angiotensin-converting enzyme inhibitors by interfering with their prostaglandin-

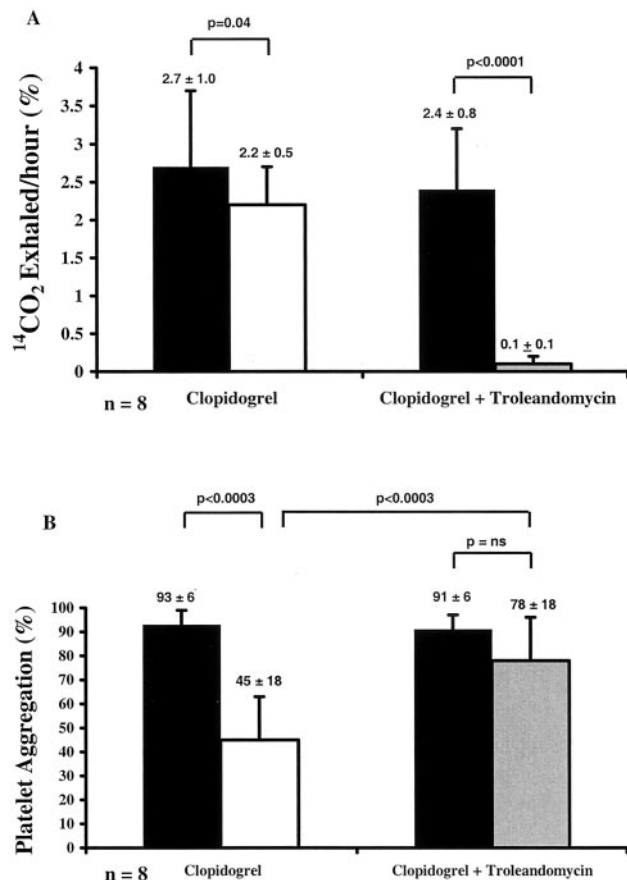


Figure 3. Erythromycin breath test. A, The effect of troleandomycin on CYP 3A4 activity as measured by the erythromycin breath test (black column, control on day 1 and day 14; white column, 2 hours after clopidogrel; gray column, 3 hours after troleandomycin but only 2 hours after clopidogrel). B, The effect of troleandomycin on the antiplatelet activity of clopidogrel in the same subjects as in A (black column, control on day 1 and day 14; white column, 2 hours after clopidogrel; gray column, 3 hours after troleandomycin but only 2 hours after clopidogrel).

mediated actions on vasodilation, renal perfusion, and vascular remodeling, although other studies²⁵ dispute this observation. More recently, it has been reported that ibuprofen antagonizes the irreversible platelet inhibition induced by aspirin.²⁶ This study suggests that atorvastatin, but not pravastatin, decreases or prevents clopidogrel from inhibiting platelet aggregation.

Other investigators have confirmed our preliminary observations. Clarke and Waskell,²⁷ using genetically engineered human microsomes, have demonstrated that clopidogrel is metabolized by human CYP3A4 and that its metabolism is strongly inhibited by atorvastatin lactone.

It is not known whether the inhibition of clopidogrel activation by atorvastatin or other drugs increases the risk of subacute stent thrombosis. First, some of the reduction in this complication achieved a few years ago was due to technical improvements in stent expansion rather than to dual antiplatelet therapy.²⁸ Second, with an incidence of only 1 percent,³ it would be difficult to recognize the potential impact of drug interactions on event rates. Third, only a minority of patients undergoing stent implantation is treated with lipid-lowering

therapy, and most patients on statin drugs are taking low doses, which have a smaller inhibitory effect on clopidogrel activation. Finally, statin therapy quickly decreases thrombosis risk and inflammation, and these effects may balance the loss of clopidogrel efficacy.^{29–31}

Most recently, institution of statin therapy with atorvastatin 80 mg/d before hospital discharge has been encouraged.^{32,33} If clopidogrel therapy is being instituted, however, it may be prudent to either initially use a low dose of atorvastatin (or presumably another lipophilic statin) until the clopidogrel therapy has ended, or to treat with pravastatin, with the option of switching to a lipophilic statin at a later date if necessary to achieve target lipid levels. Two other options, withholding statin therapy until clopidogrel therapy is completed or substituting ticlopidine for clopidogrel, are not clinically attractive. First, aggressive treatment of dyslipidemia to target goals is strongly recommended for all patients with coronary artery disease and should not be delayed. Second, clopidogrel has almost completely replaced ticlopidine therapy because of its favorable side effect profile and once daily dosing.³

Potential drug interactions with clopidogrel may be particularly important to recognize in patients diagnosed with acute coronary syndromes^{4,34} or treated with coronary brachytherapy for in-stent restenosis,³⁵ where clopidogrel may be prescribed for 6 to 12 months. It has already been suggested that point-of-care platelet function testing may be necessary to identify patients who are aspirin resistant.³⁶ Because many drugs are metabolized by CYP3A4, it is likely that other drugs may affect the efficacy of clopidogrel, making it even more important to determine whether platelet aggregation inhibition targets are being met in individual patients by point-of-care platelet function testing.

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