

Clinical Significance of the Atorvastatin–Clopidogrel Drug–Drug Interaction

To the Editor:

The recent study by Mitsios et al¹ in patients with acute coronary syndromes concluded that the coadministration of atorvastatin and clopidogrel “does not have an adverse interaction in platelet function and does not affect the clinical outcome” (p 1337). We would suggest that these conclusions are premature because: (1) other reports using platelet aggregometry² and flow cytometry³ have demonstrated that there is an adverse interaction in platelet function; (2) comparing 13 patients on atorvastatin and clopidogrel with 8 patients on clopidogrel is an inadequate sample size on which to make such sweeping conclusions; and (3) the 10-mg dose of atorvastatin used in this study does not reflect the importance of the dose-response relationship described for this interaction² or the concern that recent recommendations to routinely use 40 mg or 80 mg atorvastatin doses might accentuate the interaction.

There is a real possibility that this drug-drug interaction may be associated with increased adverse cardiac events. Although not statistically significant because of sample size, Wienbergen et al⁴ reported a 26% increased odds ratio for mortality in patients on clopidogrel for an acute coronary syndrome prescribed atorvastatin versus other statin therapies. A recent preliminary report by Brophy et al⁵ describes a significant 2-fold increased relative risk for the combined end point of death, hospitalization for myocardial infarction or unstable angina, repeat revascularization, or stroke in patients after percutaneous coronary intervention treated with coadministration of atorvastatin and clopidogrel versus clopidogrel without atorvastatin. Moreover, other reports are appearing that show increased cardiac events in patients who are resistant to aspirin or clopidogrel or who are taking aspirin and ibuprofen or aspirin and an angiotensin-converting enzyme inhibitor. Therefore, it is likely that drug resistance or drug-drug interactions with antiplatelet agents are clinically important.

The pharmacological demonstration of the atorvastatin-clopidogrel drug-drug interaction because of competition for the hepatic cytochrome P450 3A4 metabolic pathway is well established and only one of many drug-drug interactions involving the pathway responsible for metabolizing as many as half of the drugs physicians prescribe. Although mechanistic and observational studies are valuable for generating hypotheses, they should not be used to determine whether coadministration of 2 drugs may have a clinically important interaction. Only an adequately designed, prospective, randomized clinical trial can prove whether coadministration with atorvastatin inhibits the therapeutic benefit expected with clopidogrel therapy.

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1. Mitsios JV, Papanthanasios AI, Rodis FI, et al. Atorvastatin does not affect the antiplatelet potency of clopidogrel when it is administered concomitantly for 5 weeks in patients with acute coronary syndromes. *Circulation*. 2004;109:1335–1338.
2. Lau WC, Waskell LA, Watkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug–drug interaction. *Circulation*. 2003;107:32–37.
3. Neubauer H, Gunesdogan B, Hanefeld C, et al. Lipophilic statins interfere with the inhibitory effects of clopidogrel on platelet function: a flow cytometry study. *Eur Heart J*. 2003;24:1744–1749.
4. Wienbergen H, Gitt AK, Schiele R, et al. Comparison of clinical benefits of clopidogrel therapy in patients with acute coronary syndromes taking atorvastatin versus other statin therapies. *Am J Cardiol*. 2003;92:285–288.
5. Brophy J, Costa V, Babapulle M. A pharmaco-epidemiological study of the interaction between atorvastatin and clopidogrel following percutaneous coronary interventions. *J Am Coll Cardiol*. 2004;43(suppl A):50A. Abstract.

Response

We appreciate the comments by Lau and colleagues regarding our recently published work.¹ Our study included patients with a first episode of an acute coronary syndrome and mild dyslipidemia. They were treated with atorvastatin (10 mg/d) or an equally efficient lipid-lowering dose of pravastatin (40 mg/d), as well as with clopidogrel (loading dose 375 mg followed by 75 mg/d). After 5 weeks of treatment (maintenance phase), both hypolipidemic drugs significantly improved the patients' lipidemic profiles, whereas they did not affect clopidogrel's antiplatelet efficacy. Contrasting results have been published on whether atorvastatin diminishes the antiplatelet potency of clopidogrel during the loading phase (within 24 hours of drug administration). In this context, Müller et al² suggested that atorvastatin, at a dose of 20 mg/d (a 2-fold higher dose compared with that given in our study) did not influence platelet inhibition induced by a high loading dose of clopidogrel. By contrast, Lau et al³ found a dose-dependent attenuation of clopidogrel's antiplatelet activity 24 hours after drug administration. Accordingly, Neubauer et al⁴ showed that atorvastatin reduced clopidogrel's antiplatelet potency during the loading phase. However, during the maintenance phase (at 48 hours), this reduction was not as pronounced as that observed in the loading phase. Furthermore, a post hoc analysis of the Clopidogrel for Reduction of Events During Observation (CREDO) trial data showed that there is no adverse effect on the 28-day or 1-year composite clinical end points with clopidogrel and atorvastatin coadministration.⁵ Thus, we suggest that although there are contrasting results on whether atorvastatin inhibits clopidogrel's activation during the loading phase, no adverse interaction between these drugs occurs during the maintenance phase of therapy.^{1,5}

The interaction between CYP3A4-metabolized statins and clopidogrel should be further elucidated during the loading and the maintenance phase of therapy in prospective randomized clinical trials, at both the platelet and the clinical level.

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