Potential Statin–Clopidogrel Interaction Requires More Study

To the Editor:

The recent article by Mitsios et al. suggests that atorvastatin does not affect the antiplatelet potency of clopidogrel after coadministration for 5 weeks in patients who have suffered from acute coronary syndromes. However, we believe that uncertainty persists regarding a possible interaction. Firstly, the dose of atorvastatin in this study may have been too low to cause a significant drug interaction. Secondly, the anti-aggregatory effects of clopidogrel were attenuated in a dose-dependent manner. Neubauer et al. found a non-significant trend of increasing attenuation of the effect of clopidogrel with increasing dose of coadministered cytochrome P450 3A4-metabolized statins (simvastatin and atorvastatin). Furthermore, the greatest effect was seen in the initial loading period with clopidogrel and had diminished within 48 hours. These results suggest that any potential interaction may be dose-dependent and that some form of adaptation of platelet function may occur.

The use of 2 methods to detect platelet activation-aggregation and flow cytometric measurement of P-selectin expression would be expected to increase the chance of detecting a potential interaction. However, we wonder why the P-selectin results were reported in the article by Mitsios et al. as changes in mean fluorescence intensity and not as the percentage of activated platelets, which would provide a better indication of the magnitude of platelet inhibition by clopidogrel.

Although it is reassuring to find no effect of atorvastatin on antiplatelet activity after 5 weeks of coadministration with clopidogrel, we would suggest that further work is required using higher doses of statins in both the acute and chronic phase of statin-clopidogrel use.

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Response

We appreciate the comments by Williams and colleagues regarding our recently published work. These comments are in agreement with our suggestion that no adverse interaction between atorvastatin-clopidogrel occurs during the maintenance phase of therapy (ie, after 5 weeks of coadministration). However, there are contrasting results on whether atorvastatin inhibits clopidogrel’s activation during the loading phase (within 24 hours of drug administration). The above hypothesis is supported by studies focusing on platelet activation as well as on the clinical outcome, suggesting that an adaptation of platelet function or even the liver metabolic capability may occur during the maintenance phase of treatment.

Our study included patients with a first episode of an acute coronary syndrome and mild dyslipidemia. Thus, in addition to clopidogrel (75 mg/d), they were treated with a low dose of atorvastatin (10 mg/d) or an equally efficient lipid-lowering dose of pravastatin (40 mg/d). Both statins significantly improved the lipidemic profile of our patients, but they did not affect the platelet responsiveness to clopidogrel. In addition to the reduction in mean fluorescence intensity found in all studied groups, there was a similar decrease in the percentage of activated platelets expressing P-selectin (50% reduction). However, we cannot exclude the possibility that atorvastatin at 10 mg/d may influence clopidogrel’s antiplatelet efficacy during the loading phase of treatment. In accordance with our results are those reported recently by Smith et al. who suggest that there is no significant effect of statin type or dose on platelet responsiveness to clopidogrel’s metabolite levels, measured after 10 or 28 days of statin-clopidogrel coadministration.

We agree that further prospective randomized clinical trials are necessary before any conclusions can be drawn on whether CYP3A4-metabolized statins could influence clopidogrel’s antiplatelet efficacy during the loading and the maintenance phase of therapy.

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