Editorial

Are Antiplatelet Effects of Clopidogrel Inhibited by Atorvastatin?
A Research Question Formulated but Not Yet Adequately Tested

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With respect to antiplatelet therapy, randomized trials and their meta-analyses indicate benefits of clopidogrel either as an alternative or an adjunct to aspirin in some high-risk patients. Regarding the metabolic pathways of clopidogrel, the active thiol metabolite binds rapidly and irreversibly to platelet adenosine diphosphate (ADP) receptors, thus inhibiting platelet aggregation. Clopidogrel, a thienopyridine, is a platelet ADP-receptor blocker that is known to be beneficial during and after coronary stenting. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, which has no effect on platelet aggregation. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. Results of in vitro studies in human liver microsomes and recombinant cytochromes P450 have shown that several cytochromes are involved in the oxidative metabolism of clopidogrel.

In randomized trials of secondary and primary prevention of cardiovascular disease and their meta-analyses, statins reduce risks of myocardial infarction, stroke, and cardiovascular death. Recently, in a randomized trial in patients undergoing percutaneous coronary intervention, statins have shown to be reduced the incidence of major adverse coronary events, especially among the subgroups of diabetics and those with multivessel disease. In these high-risk patients, the National Cholesterol Education Program III guidelines recommend statin therapy to achieve low-density lipoprotein (LDL) goals of less than 100 mg/dL. Of the 5 marketed statins (atorvastatin, fluvasatin, lovastatin, pravastatin, and simvastatin), four (atorvastatin, fluvastatin, lovastatin, and simvastatin) are also metabolized by the cytochrome P450 pathway.

Thus, in patients receiving coronary stents, both clopidogrel and statin therapy are likely to contribute to beneficial effects on subsequent cardiovascular disease. A recent report has raised the possibility that the ability of clopidogrel to affect platelets is inhibited by atorvastatin. We have a number of concerns about the validity of these findings and therefore believe the totality of evidence to be far from complete and not consistent. In that study, the sample size was small (n=44), patient selection was poorly defined, no control for the presence of medications affecting CYP 450 3A4 pathway was performed before initiation, and the data were retrospective and non-randomized. Using a single method to assess platelet function was also unconventional. Furthermore, data from the larger retrospective Plavix Reduction Of New Thrombus Occurrence (PRONTO) trial compared platelet inhibition with clopidogrel in 100 patients undergoing coronary intervention who also received statins.

In PRONTO, there was no evidence of any specific deleterious interaction between clopidogrel and atorvastatin in terms of platelet activity. The analysis showed that only 4 of 25 patients in the atorvastatin treated group did not exhibit sustained platelet inhibition on days 2 and 5 after treatment with clopidogrel and aspirin. A similar pattern was observed in 2 of 9 patients treated with fluvasatin and 1 of 6 patients treated with pravastatin, neither of which is metabolized by the cytochrome P450 3A4 pathway. Finally, of perhaps even greater relevance to this hypothesis, a similar pattern was observed in 12 of 75 patients who did not receive any statin. In total, about 20% of patients did not achieve profound platelet inhibition with clopidogrel, but this seemed unrelated to treatment with any statins. It is tempting to speculate that in certain patients, the burden of platelet activation is so excessive that usual treatment regimens are not sufficient to achieve even moderate platelet inhibition. Retrospective data from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) and Clopidogrel Unstable angina to prevent Recurrent Events (CURE) trials among subgroups of patients concurrently administered clopidogrel and statins indicated no clinically significant adverse interactions.

Further data, especially from prospective studies, are necessary to test the hypothesis of potential interactions between clopidogrel and statins. One such study, INTERACTIONs of atorvastatin and clopidogrel therapy (INTERACT), has been designed to address this issue by serial measurements of various platelet characteristics by conventional as well as whole blood aggregometry, by point of care tests with 2 rapid analyzers, and by assessment of 14 receptors on the platelet surface by whole blood flow cytometry.

At present, therefore, the suggested inhibition of antiplatelet effects of clopidogrel by atorvastatin represents a formulated but untested hypothesis awaiting further data, including those from prospective studies such as the ongoing INTERACTIONs.
ACTION trial. Thus, the hypothesis should remain a research challenge but not a clinical one.\textsuperscript{13} In the meantime, clinicians should continue using these drugs when indicated, alone and in combination, until a sufficient totality of evidence emerges to support any change in clinical practice.

References

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