Clopidogrel-Atorvastatin Interaction

To the Editor:
Clopidogrel is a pro-drug, which must be converted to its active form to exert its antiplatelet effect. This conversion appears to occur via the cytochrome P4503A4 isoenzyme. Several statins are substrates for CYP3A4, whereas others are not.

As a result, some investigators have proposed that the coadministration of statins that are CYP3A4 substrates with clopidogrel may competitively inhibit the metabolic activation of clopidogrel in the liver in a dose-related manner.\(^1\)

We read with interest the paper by Saw et al\(^2\) evaluating the interaction between statins and clopidogrel from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Although similar event rates at 1 year comparing atorvastatin and pravastatin were reported, there appears to be a trend toward improved outcomes with pravastatin. In addition, event rates from day 29 to 1 year appear to be significantly higher with atorvastatin compared with pravastatin. This post hoc evaluation unfortunately was not adequately powered to assess event rates in the pravastatin group. Given these data and the in vivo data published by Lau et al\(^2\) and more recently by Neubauer et al,\(^3\) the potential for a significant interaction between clopidogrel and statins that are CYP3A4 substrates cannot be discounted. Because of limitations with post hoc and observational study evaluations of drug interactions, well-designed clinical trials are needed to specifically evaluate this interaction.

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Response
A recent ex vivo study suggesting attenuation of clopidogrel’s antiplatelet effectiveness by atorvastatin roused widespread concerns in the medical community.\(^1\) Our post-hoc analysis of the Clopidogrel for the Reduction of Events During Observation (CREDO) trial specifically addressed whether this potential adverse laboratory interaction translates to adverse clinical effects after percutaneous coronary interventions (PCI) with concomitant clopidogrel and statin administration.\(^2\) Hobbs et al\(^2\) raised an important limitation of our study. Because our analysis was retrospective, it was limited by the intended enrollment numbers to address the primary CREDO analysis comparing bolus/long-term clopidogrel to placebo. Thus, our analysis was underpowered for the groups of patients who received a non-CYP3A4-metabolized statin (n = 158) or pravastatin (n = 142). The 1-year death, myocardial infarction, or stroke event rate was 6.5% with atorvastatin and 4.6% with pravastatin (P = 0.62). The relative risk reduction of 1-year events for clopidogrel compared with placebo was 49.8% when atorvastatin was coadministered and 63.3% when pravastatin was coadministered. The Breslow-Day test was performed to compare the odds ratio (OR) of 1-year event rates in the atorvastatin (OR = 0.49) and pravastatin (OR = 0.34) arms, which showed no difference (P = 0.634). Despite these comparisons, we could not exclude that the lack of difference was due to a beta error; in short, our study could not exclude a small benefit with the use of pravastatin compared with atorvastatin. However, we think that more importantly, our analysis reassures clinicians because there was no demonstrable adverse clinical interaction between clopidogrel and atorvastatin or other predominantly CYP3A4-metabolized statin with regard to 1-year event rates. In fact, the relative risk reduction of 1-year events appeared greater with atorvastatin (49.8%) than the overall cohort (26.9%), patients on any statin (38.6%), or no statin at all (12.4%).

Our findings are concordant with Wienbergen et al, who retrospectively evaluated acute coronary syndrome patients receiving both clopidogrel and statins.\(^3\) They found no significant difference in mortality and stroke incidence among patients receiving atorvastatin compared with other statins. However, this study was limited as a nonrandomized, retrospective, observational study, and the comparison of atorvastatin to “other statins” was irrespective of CYP3A4-metabolism. In the recently presented INTERACTION (Interaction of Atorvastatin and Clopidogrel) study, Serebruany et al prospectively assessed platelet function in 75 patients undergoing PCI (pretreated with aspirin and clopidogrel) to atorvastatin, other statins, or no statins.\(^4\) They found similar platelet inhibition assessed by conventional aggregometry, 2 point-of-care platelet-function analyzers, and flow cytometry (eg, measurement of PECAM-1, p-selectin, CD40 ligand), irrespective of atorvastatin or other statin administration. To definitively address this clinical dilemma, a rigorous randomized study evaluating both platelet activation and long-term clinical ischemic events will be necessary.

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