Should Proton Pump Inhibitors Be Withheld From Patients Taking Clopidogrel?

The Issue That Has Been Giving Me Heartburn!

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Both the Food and Drug Administration in the USA and the European Medicines Agency, have published warnings against the coadministration of clopidogrel with proton pump inhibitors (PPIs). Accordingly, many patients attempting to fill prescriptions for a PPI and clopidogrel (or even worse, a PPI with clopidogrel and aspirin, or with clopidogrel, aspirin, and an anticoagulant) are warned by pharmacists and often by providers not to take them together. Accordingly, some patients have delayed initiating the PPI and others the clopidogrel until they spoke with their physician and have experienced stent thrombosis and worse as a result. It is timely, therefore, that a talented group of investigators from Duke would study the quality of the evidence supporting the existence of a clinically relevant interaction between PPIs and clopidogrel, reported in this issue of Circulation: Cardiovascular Quality and Outcomes. Briefly, the investigators found that all randomized trials (they included 4 in their analysis) examining the issue suggest that no clinically detectable interaction exists, but that most of the 36 observational studies they analyzed suggest that an interaction does exist that patients on clopidogrel and a PPI have more thrombotic events that those taking clopidogrel without a PPI. The authors conclude that unmeasured confounders in the observational studies are the likely explanation of the discordant findings between randomized control trials and observational studies, and call for more studies examining the issue.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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clopidogrel, aspirin and clopidogrel, or triple therapy (aspirin, clopidogrel, and an anticoagulant), rather than administered too frequently or administered at all.

Finally, closely examine the event curves in the randomized trials included in the analysis by Melloni et al. These trials do not simply fail to confirm that a negative interaction might exist. The virtually superimposable strongly curved would seem to strongly refute that a clinically significant interaction exists at all. Yet somewhat surprisingly, the authors of those studies, and Melloni et al, call for more studies of the issue, rather than calling for acceptance the randomized data and rejection of the hopelessly cofounded observational studies.

How can it be, then, that certain PPIs (and statins and calcium channel blockers) inhibit the ex vivo inhibition of aggregation (they do), and reduce the level of clopidogrel’s active metabolite (they do), but do not reduce the efficacy of clopidogrel?\(^2\)\(^3\)\(^4\) The answer is not entirely clear. Possible explanations include that the reduction in inhibition of aggregation (and levels of active metabolite) are too small to be clinically significant and that perhaps the relationship between ex vivo aggregability (and metabolite levels) and risk of thrombosis is curvilinear rather than linear. Another possible explanation is that some of the beneficial effects of clopidogrel, such as inhibition of platelet activation, are not measured by ex vivo aggregometers account for some or much of the benefit of clopidogrel. One line of evidence possibly in support of this explanation is that 75 mg of clopidogrel without a loading dose produced a significant reduction in mortality in the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), even within even 24 hours, far too low a dose to produce any measurable inhibition of aggregation in that time frame.\(^5\)\(^6\) A third possible explanation is that ex vivo aggregometers are measuring a nonmodifiable risk factor, and that altering what is measured does not truly influence platelet function or clinical outcome.\(^7\)\(^8\) Whether any of these actually explain the lack of clinical significance between clopidogrel and PPIs is not clear. What does seem clear, however, is that warnings about the coadministration of PPIs with clopidogrel ought be removed, and that more patients have experienced as a result of the warnings by not filling of their prescriptions of clopidogrel and a PPI that have been benefited from them.

Disclosures
Dr Berger would like to declare that he has potential conflicts of interest related to this editorial in that his institution has received research grants for which he was the PI from Lilly, Sanofi, and BMS in the past 3 years.

References

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