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.

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Because of the design of their analysis, the investigators did not include several other lines of evidence indirectly and directly indicating that no such clinically relevant interaction exists.

First, a similar interaction was described previously between clopidogrel and statins, particularly atorvastatin, which like omeprazole and other PPIs are also metabolized by CYP 2C19, the enzyme responsible for conversion of the prodrug clopidogrel into its active metabolite. As is the case with the observational and randomized studies of clopidogrel and PPIs reviewed by Melloni et al, analyses of randomized trials failed to suggest any apparent clinically significant interaction between clopidogrel and statins, whereas observation studies (which were undoubtedly confounded like those of clopidogrel and PPIs) did generally suggest that a negative interaction exists. Later, the same phenomenon was reported with clopidogrel and calcium channel blockers: uniformly negative randomized trials and generally positive observation studies examining an interaction between those drugs. It has now been accepted widely that no such clinically significant interactions exist between clopidogrel and either statins or calcium channel blockers.

Second, the magnitude of the purported negative interaction between clopidogrel and PPIs exceeds the magnitude of the benefit from clopidogrel. Even if PPIs suppress 100% of the beneficial effects of clopidogrel, it could not explain the results of many of the observational studies. In randomized placebo-controlled trials of clopidogrel such as Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), Clopidogrel for the Reduction of Events During Observation (CREDOS), and the >8000 patient subgroup of patients with vascular disease in Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA), the relative reduction in risk of thrombotic events from clopidogrel ranged as high as 26.9%. However, in the observational studies purporting to show a negative interaction between clopidogrel and PPIs, the relative risk of harm often exceeded 30% and incredibly have ranged as high as 50% to 150%. Therefore, if confounding is not the explanation, one would have to conclude the PPIs do not only eliminate all of the potential efficacy of clopidogrel but that they actually directly increase thrombotic events, which was not found in randomized trials comparing PPIs with placebo. Therefore, this provides strong evidence that the observational studies are severely confounded.

Third, there have been several randomized trials indicating that several medications that increase inhibition of platelet aggregation measured with ex vivo aggregometers did not reduce thrombotic events. These should serve to at least partially alleviate concern raised by a reduction in inhibition of aggregation from clopidogrel from the concomitant administration of certain PPIs (and statins and calcium channel blockers).

And partially lost in the hubbub has been that there are several randomized trials of PPIs with aspirin or aspirin and clopidogrel, all of which revealed less gastrointestinal adverse effects, and less cessation of antiplatelet therapy, in the PPI arms of the studies. So the more appropriate concern would seem to be that PPIs are too infrequently administered with...
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 curves 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? 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 load dose acetylsalicylic acid: a randomised, controlled trial (OBERON).

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Should Proton Pump Inhibitors Be Withheld From Patients Taking Clopidogrel?: The Issue That Has Been Giving Me Heartburn!

Peter B. Berger

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