The debate continues regarding the existence of an adverse interaction between proton pump inhibitors (PPIs) and clopidogrel. Concerns for a drug-drug interaction first emerged when experimental pharmacodynamic data indicated that omeprazole might diminish the in vitro antiplatelet effects of clopidogrel.1,2 These concerns were escalated when retrospective data from 2 large observational studies demonstrated that use of a PPI was associated with an increased risk of cardiovascular events for patients treated with clopidogrel.3,4 In response to these findings, the US Food and Drug Administration updated the drug’s label to warn that the effectiveness of clopidogrel is reduced when administered in combination with omeprazole.5 However, these findings have since been disputed by a growing number of analyses from clinical trial populations that have failed to show an increased risk of adverse outcomes when PPIs are administered in combination with clopidogrel.6–8 Furthermore, the results of the only randomized clinical trial to address this issue demonstrated similar cardiovascular risk regardless of whether subjects were assigned to clopidogrel alone or in combination with omeprazole.9

In light of the accumulating evidence that suggests that PPIs can be administered safely in combination with clopidogrel, one may wonder why this continues to be a topic of heated debate. There are several valid reasons that support these theoretical concerns. Clopidogrel is a prodrug that requires hepatic biotransformation that involves 2 CYP2C19-dependent steps to form its active metabolite.10 In turn, PPIs variably inhibit CYP2C19 enzyme activity.11 As well, genetic polymorphisms that naturally confer reduced CYP2C19 enzyme activity are associated with an increased risk of cardiovascular events in clopidogrel-treated patients,12 thereby supporting the concept that the isoenzyme is an integral step in the metabolism of clopidogrel. Finally, studies have consistently demonstrated that some PPIs, in particular omeprazole, diminish the pharmacodynamic effects of clopidogrel.12,13 However, the evidence to suggest that changes in this pharmacodynamic response to clopidogrel has been observed when coadministered with lipophilic statins and calcium channel blockers.15–17 However, concerns about a clinical drug-drug interaction with statins largely have been dismissed because subsequent outcome studies failed to demonstrate increased cardiovascular risk.18,19 These findings highlight the fact that observational analyses are subject to confounding and also raise concern about the use of in vitro platelet reactivity as a surrogate end point.

To that end, there is still much we need to learn to better understand the relationship between in vitro platelet activity and adverse clinical outcomes. It is plausible that the pharmacodynamic interaction between clopidogrel, PPIs, calcium channel blockers, or lipophilic statins is too weak to translate into cardiovascular harm. Another consideration is that the shape of the relationship between platelet reactivity and clinical outcomes is not linear; rather, there might exist a threshold effect such that platelet reactivity must be raised above a certain threshold before a patient is placed at

CYP2C19 Genotype and Proton Pump Inhibitors in Clopidogrel-Treated Patients
Does It Take Two to Tango?

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

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The debate continues regarding the existence of an adverse interaction between proton pump inhibitors (PPIs) and clopidogrel. Concerns for a drug-drug interaction first emerged when experimental pharmacodynamic data indicated that omeprazole might diminish the in vitro antiplatelet effects of clopidogrel. These concerns were escalated when retrospective data from 2 large observational studies demonstrated that use of a PPI was associated with an increased risk of cardiovascular events for patients treated with clopidogrel. In response to these findings, the US Food and Drug Administration updated the drug’s label to warn that the effectiveness of clopidogrel is reduced when administered in combination with omeprazole. However, these findings have since been disputed by a growing number of analyses from clinical trial populations that have failed to show an increased risk of adverse outcomes when PPIs are administered in combination with clopidogrel. Furthermore, the results of the only randomized clinical trial to address this issue demonstrated similar cardiovascular risk regardless of whether subjects were assigned to clopidogrel alone or in combination with omeprazole.

In light of the accumulating evidence that suggests that PPIs can be administered safely in combination with clopidogrel, one may wonder why this continues to be a topic of heated debate. There are several valid reasons that support these theoretical concerns. Clopidogrel is a prodrug that requires hepatic biotransformation that involves 2 CYP2C19-dependent steps to form its active metabolite. In turn, PPIs variably inhibit CYP2C19 enzyme activity. As well, genetic polymorphisms that naturally confer reduced CYP2C19 enzyme activity are associated with an increased risk of cardiovascular events in clopidogrel-treated patients, thereby supporting the concept that the isoenzyme is an integral step in the metabolism of clopidogrel. Finally, studies have consistently demonstrated that some PPIs, in particular omeprazole, diminish the pharmacodynamic effects of clopidogrel. However, the evidence to suggest that changes in this pharmacodynamic response to clopidogrel has been observed when coadministered with lipophilic statins and calcium channel blockers. However, concerns about a clinical drug-drug interaction with statins largely have been dismissed because subsequent outcome studies failed to demonstrate increased cardiovascular risk. These findings highlight the fact that observational analyses are subject to confounding and also raise concern about the use of in vitro platelet reactivity as a surrogate end point.

To that end, there is still much we need to learn to better understand the relationship between in vitro platelet activity and adverse clinical outcomes. It is plausible that the pharmacodynamic interaction between clopidogrel, PPIs, calcium channel blockers, or lipophilic statins is too weak to translate into cardiovascular harm. Another consideration is that the shape of the relationship between platelet reactivity and clinical outcomes is not linear; rather, there might exist a threshold effect such that platelet reactivity must be raised above a certain threshold before a patient is placed at...
increased risk. In support of this hypothesis, it has been reported that ischemic events appear to be more clustered above a particular cut point in the upper tertile or quartile of on-treatment platelet reactivity.20

Perhaps the most intriguing question to be addressed in the present analysis is whether the pharmacodynamic interaction between PPIs and clopidogrel might be clinically relevant only to those individuals who carry a loss-of-function CYP2C19 allele. To date, it remains unknown whether CYP2C19 genotype and PPI use might have an additive effect toward diminishing the antiplatelet effects of clopidogrel. In the present analysis, a DNA sample was available in 1579 subjects (67%), and 446 (28%) of those subjects carried at least 1 loss-of-function CYP2C19 allele. In propensity-matched cohorts, PPI use was not associated with an increased risk of either in-hospital (odds ratio 0.29, 95% confidence interval 0.06 to 1.44) or 1-year cardiovascular events (odds ratio 0.68, 95% confidence interval 0.26 to 1.79) in carriers of a single loss-of-function CYP2C19 allele, although the confidence intervals were relatively wide.14 These new data support our previously published findings from the TRITON-TIMI 38 study (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibi-
tioN with prasugrel-Thrombolysis In Myocardial Infarction 38), which similarly demonstrated that PPI use was not associated with an increased risk of adverse outcomes in either wild-type carriers or carriers of a loss-of-function CYP2C19 allele.7

Although the present study was underpowered to examine whether a drug-drug interaction might exist in carriers of 2 loss-of-function CYP2C19 alleles, such an interaction is unlikely to be clinically meaningful. Because the most common loss-of-function alleles (*2 and *3) code for an inactive form of the CYP2C19 isoenzyme, carriers of 2 loss-of-function alleles would be expected to have little or no CYP2C19 enzyme activity at baseline. As such, it is unlikely that PPI use could lead to further inhibition of the CYP2C19 enzyme to an extent that would be clinically meaningful.

A possible limitation to the present analysis is whether the FAST-MI registry is an appropriate study population in whom to examine outcomes for carriers of a single loss-of-function CYP2C19 allele. Although several studies have shown that carriers of a single loss-of-function CYP2C19 allele are at increased risk of adverse outcomes on clopi-
dogrel,12 these findings were not replicated in the present study population. Rather, in FAST-MI, carriers of a single loss-of-function allele had a trend toward a lower risk of cardiovascular events than wild-type carriers, whereas those who carried 2 copies of a loss-of-function allele had excess risk.21 These findings are perhaps explained by a lower incidence of percutaneous coronary intervention in the study population, because the relative benefit of clopidogrel ap-
pears to be greater in patients in whom a coronary stent has been implanted.22 Unfortunately, pharmacodynamic data are not available to help us better understand whether carriers of a single loss-of-function allele had higher or lower on-
treatment platelet reactivity than wild-type carriers.

Additional limitations to the present study merit consideration. In particular, in the present study, use of a PPI was only captured during the index hospitalization. Because patients may have started or stopped a PPI during the year after hospital discharge, the results could be biased toward the null. Finally, as with all observational studies, there exists the risk of residual confounding, because it is nearly impossible to identify all variables that may influence the decision to treat a patient with a PPI.

Nevertheless, the present findings provide further support-
ive evidence to indicate that PPIs can be used safely in patients taking clopidogrel. Although omeprazole might at-
tenuate some of the in vitro antiplatelet effects of clopidogrel, convincing evidence is currently lacking to indicate that this combination places patients at increased risk of harm. Fur-
thermore, PPIs have been shown to decrease the risk of gastrointestinal complications, including bleeding, for pa-
tients taking dual-antiplatelet therapy,9 and in turn, gastroin-
testinal bleeding is associated with an increased risk of cardiovascular events.23 Until the relationship between plate-
let function assays and clinical outcomes is better delineated, the weight of the evidence suggests that clopidogrel can be administered safely in combination with a PPI for patients at risk of gastrointestinal complications.2

Disclosures

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References


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