

## Letter by Pacheco et al Regarding Article, “Proton Pump Inhibitors, Platelet Reactivity, and Cardiovascular Outcomes After Drug-Eluting Stents in Clopidogrel-Treated Patients: The ADAPT-DES Study”

To the Editor:

In a predefined subanalysis of the Assessment of Dual Antiplatelet Therapy With Drug Eluting Stents (ADAPT-DES) study, Weisz et al<sup>1</sup> found an association between co-prescription of clopidogrel and proton pump inhibitors (PPIs) and higher rates of major adverse cardiac events. Similar to prior studies,<sup>2</sup> increased platelet reactivity on PPI therapy was demonstrated.<sup>1</sup> However, although increased platelet reactivity was associated with a higher incidence of stent thrombosis (ST),<sup>3</sup> PPI use was not associated with a statistically significant increase in either ST or myocardial infarction after adjustment.<sup>1</sup>

Rather, the difference in major adverse cardiac event observed in ADAPT-DES seems to have been primarily driven by revascularization, which includes a broad spectrum of clinical syndromes not necessarily related to increased platelet reactivity. With the inherent risks of bias and confounding in a study of this kind, it is paramount to ensure that a plausible pathophysiologic mechanism can be proposed to explain the findings. We are unaware of a mechanism by which inadequate platelet inhibition would result in increased revascularization without increasing ST or myocardial infarction. As such, the findings of this study should be interpreted with caution.

As the analysis stands, ADAPT-DES raises 3 troublesome possibilities in addition to a simple lack of statistical power for the ST outcome: First and not surprisingly, that of residual confounding; second, that high platelet reactivity on PPI therapy might not have the same prognostic implications as high platelet reactivity in the absence of PPIs, which seems unlikely; and, third, that of a flaw in the multivariable adjustment leading to erasure of the effect of concomitant PPI use on the ST outcome.

In the first scenario, it is possible that the majority of adverse events in patients prescribed PPIs are not related to platelet reactivity at all.<sup>4</sup> Although multivariate analyses were performed, additional confounding variables such as the complexity and diffuseness of coronary artery disease, residual ischemia post percutaneous coronary intervention, left ventricular ejection fraction, and previous gastrointestinal bleeding were not included in the Cox model. (It is unclear whether they were used in the propensity model.) As such, one might reasonably conclude that there is sufficient evidence to suggest that patients taking PPIs are at greater risk of major adverse cardiac event. However, evidence is equally lacking to suggest that this increased risk is either because of the use of PPIs per se or any interaction with clopidogrel.

With regards to the third scenario, we invite the authors to comment on the decision to include high platelet reactivity as a variable in

the Cox model. As high platelet reactivity because of PPI–clopidogrel interaction is ostensibly part of the presumed causal pathway between PPI co-prescription and major adverse cardiac event, it would seem, on the surface at least, to be a debatable choice. Moreover, it is unclear whether platelet reactivity variables were part of the propensity scoring method. Although more concerning for the Cox model, inclusion of platelet reactivity variables in either model could in essence suppress any signal of a clopidogrel–PPI interaction.

## Disclosures

None.

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*Circ Cardiovasc Interv.* 2016;9:e003499

doi: 10.1161/CIRCINTERVENTIONS.115.003499

*Circulation: Cardiovascular Interventions* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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