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Proton Pump Inhibitors and Cardiovascular Risk

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To the Editor,

We thank the authors for their positive comments and amplifying remarks [1-3] in response to our paper in *Circulation* [4]. We agree with the authors that the proton pump inhibitors (PPIs) may adversely influence cardiovascular physiology in multiple ways. We found that PPIs reduce the enzymatic activity of dimethylarginine dimethylaminohydrolase (DDAH). In this way, PPIs increase plasma levels of asymmetric dimethylarginine (ADMA) [4]. Because it inhibits the generation of vascular nitric oxide, ADMA would be expected to increase platelet interaction with the vessel wall. Chyrchel and colleagues [1] correctly point out that our findings may explain why PPIs attenuate the benefit of clopidogrel as well as other $P2Y_{12}$ anti-platelet agents not dependent upon CYP2C19 for their activity.

We thank Montenegro and Lunberg [2] for pointing out that NO may be generated in the stomach by the reduction of ingested nitrite, an effect that is dependent upon low gastric pH. Dietary nitrate (NO_3^-) and nitrite (NO_2^-) are absorbed in the gastrointestinal tract, concentrated in the saliva as NO_2^- by the action of oral bacteria and then converted to nitrous acid (HNO_2) in the stomach. The spontaneous decomposition of HNO_2 generates NO. Gastric NO is known to increase blood flow, protect the gastric mucosa and provide defense against pathogenic microorganisms. Accordingly, Montenegro and Lunberg raise the concern that PPIs could impair this exogenous nitrate/nitrite/NO cycle. Pinheiro and co-workers [3] echo this concern and point out that the PPI esomeprazole has been observed to reduce the anti-hypertensive benefit of oral nitrates. The adverse effect of PPIs on this pathway may be of equal or greater importance to that which we described. The ingestion of

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Disclosures:
YTG and JPC are inventors on patents owned by Stanford University that protect the use of agents that modulate the NOS/DDAH pathway therapeutically. They are also co-founders of Altitude Pharma; a biotechnology company that is developing a product to therapeutically regulate the NOS/DDAH pathway. LePendu P, Lee JC, Erlanson DA, Slaviero A, Shah NH and Leiper JM have no disclosures to declare.

nitrate and nitrite may be critical to the cardiovascular benefits of diets rich in leafy greens and root vegetables as in the Dietary Approaches to Stop Hypertension (DASH) study [5].

In addition, PPIs could influence circulating ADMA through their interference with the absorption of vitamin B12 [6]. This vitamin is required for the conversion of homocysteine to cysteine. Elevated plasma homocysteine levels increase plasma levels of ADMA, and may increase the susceptibility to coronary artery disease [7]. We have previously observed that acute increase in homocysteine level acutely increases plasma ADMA and impairs endothelium dependent vasodilation [7].

To conclude, we and the other respondents agree that the PPIs may dysregulate interdependent pathways that regulate vascular NO generation. As a result, chronic exposure to PPIs might be expected to impair vascular homeostasis, and potentially expose consumers to an increased risk of major adverse cardiovascular events. We will soon publish pharmacovigilance data regarding this question. The accumulating data raises a concern for the medical community and regulatory bodies regarding the cardiovascular safety of these agents.

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