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Mechanisms involved in proton pump inhibitors-induced increases in ischemic events

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To the Editor,

Casula et al. carried out an interesting nested case-control study aiming to estimate the risk of hospitalization for cardio/cerebrovascular (CV) events in a cohort of incident proton pump inhibitors (PPIs) users [1]. In their study, they found a significantly increased risk of hospitalization for CV events in current and recent PPIs users compared to past users, regardless of the type of PPIs. As discussed by Casula et al., PPIs, as a class, reduce the enzymatic activity of dimethylarginine dimethylaminohydrolase (DDAH), the enzyme that metabolizes asymmetric dimethylarginine (ADMA), an endogenous and competitive inhibitor of nitric oxide synthase (NOS). By inhibiting endothelial NOS, ADMA disrupts the production of vascular nitric oxide (NO) leading to vascular inflammation and increased risk of cardiovascular events [2]. However, there is now recent evidence strongly suggesting interference with new biologic mechanisms involving the potent vasodilator NO, which may contribute to disruption of NO vascular homeostasis in patients taking PPIs, thus promoting the pathogenesis of cardiovascular diseases [3]. This mechanism involves NO generation in the nitrate-nitrite-NO pathway, which is now accepted as a major alternative source of NO to the classical L-arginine-NO synthase pathway. This mechanism involves the bioconversion of nitrate to nitrite in the entero-salivary circulation, followed by nitrite reduction to NO by enzymatic and non-enzymatic pathways in blood and tissues. Inorganic nitrate is commonly present in our diet and is rapidly absorbed in the small intestine, increasing levels of plasma nitrate, which is then taken up by the salivary glands and is concentrated up to 20-fold in saliva [3]. In the oral cavity, commensal bacteria reduce nitrate to nitrite by the action of nitrate reductase enzymes and once saliva enters the acidic stomach, a non-enzymatic reduction of nitrite to NO and other bioactive NO-related species occurs. Among these bioactive compounds, S-nitrosothiols act as a relatively stable NO donor and are associated with beneficial cardiovascular effects [4].

Interestingly, orally administered nitrate caused dose-dependent decreases in blood pressure and vasoprotection in humans while nitrite lowered blood pressure in hypertensive rats [5,6]. Moreover, the use of PPIs was shown to attenuate the nitrite-induced decrease in blood pressure by reducing the excess of protons in the gastric juice, which is necessary for the conversion of nitrite to NO, consequently impairing the nitrate-nitrite-NO pathway [7]. These findings show that PPIs may also prevent the protective effects of a nitrate-nitrite-rich diet, and may have major clinical implications, especially in patients taking PPIs. The increase in gastric pH induced by PPIs may impair the beneficial effects of dietary nitrites and nitrates present in leafy greens and root vegetables. In conclusion, these results further support the suggestion by Casula et al. and provide another mechanism for impaired vascular homeostasis in users of PPIs.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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