

# Increased Proton Pump Inhibitors – Induced Mortality Risk in Hemodialysis Patients



**To the Editor:** de Francisco *et al.* carried out an interesting study showing an association between the use of proton pump inhibitors (PPIs) by hemodialysis patients and increased risk of all-cause and cardiovascular mortality.<sup>1</sup> In addition to mechanisms that may explain the relationship between the use of PPIs and the increased risk of cardiovascular mortality discussed in their article, there is now compelling evidence for an additional mechanism that should be taken into account. The chronic use of PPIs may impair vascular function and increase the risk of adverse cardiovascular events by interfering with the nitrate–nitrite–nitric oxide (NO) pathway, which is accepted as a major alternative source of NO to the classical L-arginine–NO synthase pathway.<sup>2</sup> First, this mechanism involves the bioconversion of nitrate to nitrite in the entero-salivary circulation by the action of nitrate reductase enzymes from commensal bacteria in the oral cavity. Once saliva containing nitrite enters the acidic gastric lumen, nitrite is converted by nonenzymatic reduction to NO and other bioactive NO-related species, including S-nitrosothiols, which act as relatively stable NO donors and may promote cardiovascular protection.<sup>3</sup> Proton pump inhibitors reduce the excess of protons in the gastric juice, which are necessary for the conversion of nitrite to NO, consequently disrupting the nitrate–nitrite–NO pathway. In addition, PPIs promote oxidative stress mediated by increased xanthine oxidase formation of superoxide, thus impairing endothelium-dependent vasodilation.<sup>4</sup> These results reported by de Francisco *et al.* may critically involve mechanisms associated with impaired nitrate–nitrite–NO pathway in patients taking PPIs, which add to the mechanisms mentioned in their article.

## DISCLOSURE

All the authors declared no competing interests.

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The scope of the use of proton pump inhibitors (PPIs) in hemodialysis patients is really worrying because of its widespread use, often in the absence of medical supervision and its implications have potential adverse effects.

First, the use of PPIs has risen more than 500% between 2000 and 2012, and Spain has notably increased the rate of consumption in recent years, even in hemodialysis patients, that is especially high compared with other countries of the European Union.<sup>2</sup> In addition, a significant percentage of prescriptions, estimated at 25% in the European Union and 70% in the United States, is not based on the approved indications.<sup>3,4</sup>

Second, several observational studies suggest that PPI use is associated with an increased risk of adverse health outcomes and cardiovascular (CV) events in particular.<sup>5</sup> There would be different interpretations to explain the association between PPIs and CV events in a patient with acute myocardial ischemia. An important opinion is based on the PPI’s reduction of the capacity