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.[1] 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.[2] 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.[3] 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.[4] 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.[2] 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.[3,4]

Second, several observational studies suggest that PPI use is associated with an increased risk of adverse health outcomes and cardiovascular (CV) events in particular.[5] 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

of clopidogrel to prevent clot formation in subjects at risk for coronary thrombosis and myocardial infarction.[6] Although this effect has been associated with clopidogrel-activating hepatic isoenzyme CYP2C19, PPIs also may diminish the cardioprotective effects of drugs that do not depend on CYP2C19 activation, such as ticagrelor.[7] Moreover, PPIs may be associated with CV risk in the general population,[8] and may represent a marker of CV risk rather than the cause of reduced efficacy of antithrombotic drugs.[9] Thus, it would be interesting to further investigate more precise mechanisms of the effect of PPIs on CV mortality in hemodialysis patients.

As Sertorio and Tanus-Santos pointed out, NO (nitric oxide) is a key regulator of vascular homeostasis, and NO deficiency seems to be a major factor in the initiation and progression of vascular diseases. In line with this, they describe a rational approach about the chronic use of PPIs on vascular function with increase in the risk of adverse CV events by interfering with the gastric pH and the nitrate-nitrite-NO pathway, which is accepted as a major alternative source of NO.[10] Some other studies also showed that PPIs inhibit the enzymatic activity of dimethylarginine dimethylaminohydrolase,[11] which is responsible for 80% of the clearance of asymmetric dimethylarginine, and thus PPIs may reduce NO synthesis. However, further prospective studies should be carried out to confirm the possibility that PPIs may impair vascular function and increase the risk of adverse CV events by interfering with the nitrate-nitrite-NO pathway.

In conclusion, because PPIs are among the most prescribed medicines and the long-term effects of their use are still not well described, the balance between positive and possible negative effects should be carefully considered before their prescription, notably in special populations such as hemodialysis patients.

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