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Editorial commentary: Pathophysiological effects of proton pump inhibitors in cardiac patients: Time for a critical reappraisal

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Since the late 1980s, evidence-based guidelines support proton pump inhibitors (PPI) as the best treatment of gastroesophageal reflux disease, esophagitis, and peptic ulcer disease. However, apart from treating frank diseases where their use is at present irrevocable, this class of drugs has been increasingly prescribed as "prophylactic" in patients on chronic non steroidal anti inflammatory drugs, corticosteroids, single and double antiplatelet therapies, or just as protection in patients with different risk profiles. In the cardiovascular context this issue is of primary interest, especially in view of the average advanced age of cardiac patients, the high prevalence of patients on antiplatelet therapy and on poly-therapy, all conditions considered as at high risk for the potential occurrence of gastric bleeding. This attitude translates in the concept that "most, if not all, cardiac patients are on PPI therapy". However, in the recent years several epidemiological studies, mainly based on health insurance databases, have reported an increased risk of complications associated to PPI use and a possible dose-response relationship. PPI have been associated to the occurrence of enteric infections, community-acquired pneumonia, nephrotoxicity, bone fractures, antiplatelet drugs interactions, nutritional deficiencies, cognitive impairment and dementia. Endothelial dysfunction and hypomagnesemia have been shown to be the main factors leading to PPI induced impairment of vascular homeostasis, paving the way to these complications. Despite the mounting evidence that these agents may be associated to increased morbidity and mortality, these drugs continue to be definitely overprescribed [1]. In the present issue of TCM, a timely review by Lattanzio and Corsonello [2] underlines the mounting epidemiological evidence of the relation between PPI use and adverse effects. They review the main pathophysiological pathways involved in PPI-induced endothelial dysfunction and atherosclerosis, hypomagnesemia, drug interactions, reduced absorption of selected nutrients, increased gastric microbiota and small intestine bacterial overgrowth, reduced immune response, tubular-interstitial inflammation, increased bone turnover, accumulation of amyloid in the brain.

Among the potential mechanisms related to PPI induced adverse effects, the massive increase of chromogranin induced by these drugs is grossly underscored. PPI administration induce a marked increase in chromogranin-A (CGA) release [3]. CGA is a member of the granin family of neuroendocrine secretory proteins, located in secretory vesicles of neurons and endocrine cells. The principal cells producing CGA are chromaffin cells of the adrenal medulla, paraganglia, enterochromaffin-like cells and beta cells of the pancreas. PPI raise CgA levels by inducing gastric enterochromaffin cell hyperplasia as a consequence of hypochlorhydria. Circulating CGA and its fragments, exert a broad spectrum of regulatory influences on the cardiovascular system [4,5]. In fact, plasma CGA concentrations have been shown to be increased in patients with essential hypertension [6], myocardial infarction [7], chronic heart failure [8], decompensated heart failure [9], acute coronary syndromes [10] hypertrophic cardiomyopathy [11]. In particular, Ceconi et al. [8], demonstrated that circulating CGA levels are significantly related to prognosis severity in patients with chronic heart failure, representing an independent predictor for mortality. However, whether the role of CGA is beneficial for the diseased heart or it may concur to aggravate its pathology, is not yet clear. For example, in acute coronary syndromes the vasodilatory, negative inotropic and lusitropic properties and the anti-adrenergic effect elicited by CGA, might be either detrimental, thus contributing to HF development, or compensatory, at least at the beginning of pathological process. We could surmise that CGA may be adaptative in the short and maladaptative in the long term. The pathophysiological and clinical significance of the observed gross PPI-induced increase of CGA warrant further studies.

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The reported evidence of PPI-induced untoward and unexpected effects is not an isolated case in clinical pharmacology. Many drugs utilized in the daily clinical practice, with massive evidence of their effectiveness to treat the specific disease they are being used for, with time could reveal unexplored effects. To remain in the cardiovascular setting, most commonly utilized drugs can induce additional effects, either beneficial or detrimental, usually not taken into consideration by the prescriber [12]. These ancillary effects are very difficult to be standardized by the results of clinical trials. In fact, evidence-based medicine takes into account the beneficial effects of drugs on hard end-points, obtained by clinical trials of relatively short duration and it cannot be excluded that over longer time periods these beneficial effects of drugs could be either eliminated or reinforced due to their ancillary effects. As daily prescribers of tens of different compounds, we have to cope with this. However, the very critical point is that regulatory agencies and prescribing doctors are either not aware or think that a specific drug unwanted effect could definitely be less insidious than the disease we could induce by stopping the drug in question. For these reasons, future trials employing PPI should take into account the evaluation of specific action on cardiovascular physiology, in order to better define their long term indication in cardiac patients with different gastric bleeding risk profiles.

In conclusion, the information provided by the well-timed review by Lattanzio and Corsonello [2] should be considered as a further warning for cardiologists and physicians prescribing long term PPI to their patients. Drug regulatory agencies and medical professional associations should officially warn prescribers to limit PPI use to instances and durations where they are medically indicated. In patients with gastro-oesophageal reflux and ulcer disease the benefits of PPI likely outweigh their potential harm. However, for less serious symptoms and for prevention of gastric bleeding in patients at low risk, potential harm may outweigh the benefit [13]. These concepts should be further validated by “ad hoc” studies. In the meantime, those thousands and thousands patients who are on chronic PPI therapy for no clear reason, often remote symptoms of “gastric discomfort” that have since resolved, should withdraw PPIs and determine if symptomatic treatment is needed.

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