



EDITORIAL

Do proton pump inhibitors increase the risk of myocardial infarction?☆



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¿Aumentan los inhibidores de la bomba de protones el riesgo de infarto?

Proton pump inhibitors (PPI) are one of the most widely used pharmacological groups in the world. They are generally considered safe, although their safety profile has been called into question on numerous occasions.¹

Reported side effects of PPI include: vitamin and mineral deficiency (hypomagnesaemia, vitamin B₁₂ deficiency),² osteoporosis-related pathological fractures,^{3–5} *Clostridium difficile* infection,^{6–8} community-acquired pneumonia^{9–12} and ischaemic heart disease due to inhibition of the anti-platelet effect of clopidogrel.^{13–26} However, most of these associations were established from non-randomised retrospective observational studies, and many were later questioned on the basis of findings from prospective, randomised trials or other epidemiological studies.¹

A recent study published in *Plos One* by Shah et al. associated the use of PPIs with acute myocardial infarction (AMI).¹⁶ In this study, patients with gastro-oesophageal reflux disease (GERD) were selected from 2 databases (*Stanford Translational Research Integrated Database Environment* [STRIDE]) and (*Practice Fusion, Inc.* [PF]), which include hundreds of thousands of patient records.

A complex software data-mining tool, widely used in computer science and economics, was employed. This method was used to extract information from a set of unstructured clinical notes (written up by doctors, nurses and healthcare workers, and including information on drugs, disease, devices, etc.) to form a matrix, with patient characteristics described according to standard medical terminology and ordered by date and time.^{17,18}

The authors explained clearly that this was not an epidemiological analysis. The method behaved, for all intents and purposes, like a cohort study, and in fact enabled a relationship to be established between the use of PPI and AMI, which was expressed in a final odds ratio (OR). It also adjusted for a series of possible confounding variables using another statistical technique known as *propensity score matching* (PSM). This estimates the probability of a certain drug being used in a particular subject, based on their characteristics. The effect of treatment is then compared among patients with a similar propensity score. PSM—more complex than multivariate analysis—is used in observational studies to reduce the confounding bias secondary to selection by treatment indication.¹⁹

The authors “confirmed” the findings by performing a survival analysis—unadjusted and, later, only partially adjusted for confounding factors (age, sex, race, total and high density lipoprotein [HDL] cholesterol levels, systolic arterial pressure, use of antihypertensive drugs and total pack-years)—in the prospective *Genetic Determinants of Peripheral Arterial Disease* (GenePAD) cohort, where the primary outcome measure was to evaluate cardiovascular mortality according to genetic determinants over a mean follow-up of 5.2 years.

PPIs were associated with a mild to moderately increased risk of presenting an AMI, with OR of 1.16 (95% CI 1.09–1.24) and 1.19 (95% CI 1.09–1.24) in the STRIDE and PF databases, respectively. However, no association was found with H₂ receptor antagonists (anti-H₂), which are also used in the treatment of GERD (OR 0.93 [95% CI 0.86–1.02]). The authors examined whether this could be due to an interaction between PPI and clopidogrel, but ruled this out, since the analysis showed similar results even when these patients were excluded: STRIDE (OR 1.14 [95% CI 1.06–1.24]) and PF (OR 1.19 [95% CI 1.09–1.30]).

Finally, in the survival analysis, they observed that the cardiovascular mortality risk was twice as high in patients

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who took PPI compared to controls (hazard ratio [HR] 2.22 [95% CI 1.07–3.78]) in an unadjusted analysis. This association persisted in an analysis adjusted for the previously mentioned risk factors (HR 2.00 [95% CI 1.07–3.78]).

In view of these findings, we need to ask ourselves whether we should amend our policy for prescribing PPIs.

The study methodology seems sound: the authors used a computer-based data screening method—a *data mining pipeline*—that had been previously validated in pharmacovigilance studies by the same group.¹⁷ The studies reported 97.5% specificity and 39% sensitivity in detecting associations, with false positive and negative rates of 3.5% and 61%, respectively; the overall accuracy was 89% and the positive predictive value was 81%. This means that the technique was designed to be restrictive and only detects just over half the associations. However, the probability that the association detected is true is very high. The main limitation of this method is that it is a new technique that has not been validated by other groups, so the results should be considered with caution.

Additionally, the programme uses an observational database and is therefore not exempt from bias and confounding factors. For this reason, the authors used a system to correct for confounding factors, the PSM, adjusted for age, gender, race, length of observation, number of drugs and number of diseases diagnosed, first with 1:5 matching, and then with 1:3 or 1:1 matching when the former was not possible. However, other potentially important confounding factors such as insulin resistance, obesity, smoking or family history of AMI, among others, were not taken into consideration.

Furthermore, as with any observational study, the fact that an association is observed does not necessarily imply causality. In this sense, one might ask if the association observed between PPIs and AMI meets the criteria for causality (the study does not prove this) in observational studies. To that end, each of these criteria must be analysed individually, namely: the temporal sequence, strength of association, consistency, coherence, biological gradient (or dose-response relationship), specificity, analogical reasoning, biological plausibility and experimental evidence.

First of all, the association appears to respect the temporal sequence, i.e. exposure (taking PPI) precedes the event (cardiovascular events).

In contrast, the strength of association is low in each database (STRIDE: OR of 1.16 and PF: OR of 1.19). Low strength associations generally have a high risk of being due to confounding factors. For example, in the case of the recent controversy surrounding the effect of PPIs on the anti-platelet activity of clopidogrel, the latest meta-analysis²⁰ analysed 39 studies, with a total of 214 851 patients, observing an OR of 1.41 (95% CI 1.20–1.65). However, when 23 552 patients from 8 randomised, controlled studies were analysed, no increase in cardiovascular events was observed in patients on clopidogrel treatment who received a PPI. Current studies thus strongly suggest that the pharmacological interaction between PPI and clopidogrel has no significant clinical consequences. In the case of the study by Shah et al., the strength of association is weak and does not therefore support a causal association.

Secondly, to assess the consistency of the association (whether this is reproduced in different studies and in different populations), we must explore whether the effect has been observed in other studies. In this respect, the study is consistent with other previous epidemiological studies that analysed the same topic. However, the ORs in all of them were low: OR 1.66 (95% CI 1.00–2.76)²¹, OR 1.58 (95% CI 1.11–2.25)²² and OR 1.29 (95% CI 1.21–1.37).²³ Furthermore, the previous observational studies present multiple limitations with a high risk of indication bias,^{21–23} inadequate correction of confounding factors²² or small sample size.²¹ Findings in the literature are therefore still inconsistent.

With respect to the biological gradient, given the study characteristics, the authors were unable to evaluate the PPI doses employed, or take into account self-medication. Additionally, the association of PPIs and the risk of AMI are not specific. The use of these drugs has been associated with other uncorrelated side effects (community-acquired pneumonia, osteoporosis, vitamin deficiency, *C. difficile*, etc.).

It is also important to consider that the use of PPI is a clear marker of comorbidity: the more seriously ill the patient, the more medical visits and admissions and, consequently, the more drugs they require. All these factors are related with a higher probability of receiving PPIs to prevent bleeding or to treat dyspeptic symptoms. This is the main basis for the argument that many of the associations observed with PPIs are due to the difficulty in adjusting for the confounding factors inherent to observational studies, and are therefore probably baseless.

As far as analogical relationships are concerned, there are no data to evaluate this possible association. Although one might think that other drugs that inhibit gastric acid secretion, such as H₂ antagonists, could also be associated with an increased cardiovascular risk, this association has not been observed by either Shah et al. or other authors.^{24,25} Nevertheless, given that the potential pathophysiological mechanism proposed by the authors (see below) does not involve inhibition of acid secretion, this argument is not applicable.

Various mechanisms by which PPI might increase cardiovascular risk have been proposed. The working group responsible for Shah's paper observed in previous in vitro studies that PPIs inhibit the enzyme activity of dimethylarginine dimethylaminohydrolase (DDAH), an enzyme that metabolises asymmetric dimethylarginine (ADMA), which in turn inhibits nitric oxide synthetase (NOS), increasing the risk of cardiovascular events.^{26–28} The same group reported that PPIs increased ADMA levels in mice and human endothelial cells by 20% to 30%.²⁹ This is a plausible but weak biological mechanism, firstly because the findings are limited to cell culture and an animal model and, secondly, because it does not explain why there are differences of association between the different types of PPI (pantoprazole: OR 1.34 [95% CI 1.16–1.55] versus esomeprazole: OR 1.08 [95% CI 0.88–1.31]).

In short, the article by Shah et al. detects a possible increased risk of AMI in patients treated with PPI. However, the increase in risk is very small (OR 1.16) and the study is far from firmly showing a causal relationship.

This epidemiological signal should be investigated. In this respect, multiple randomised studies have been published in recent years comparing PPI with placebo or anti-H₂ in different indications. The findings from these studies can be used to evaluate whether the association between PPI and AML is real or, again, is due to the limitations inherent to observational studies, as has been done in the case of the possible interaction with clopidogrel.

Meanwhile, the findings of this observational study do not appear to have sufficient strength to convince us to amend current practice relating to the use of PPI. Nevertheless, although the likelihood of a real association may be low, the results of this study provide an additional reason for limiting the use of these drugs to patients in whom they are clearly indicated.

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Diana Horta^{a,c}, Pilar García-Iglesias^{a,c}, Xavier Calvet^{a,b,c,*}

^a *Unidad de Gastroenterología, Servicio de Digestivo, Corporació Sanitària Parc Taulí, Sabadell, Barcelona, Spain*

^b *Departament de Medicina, Universitat Autònoma de Barcelona, Sabadell, Barcelona, Spain*

^c *Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto Carlos III, Madrid, Spain*

* Corresponding author.

E-mail address: xcalvet@tauli.cat (X. Calvet).