THERAPY

Risks associated with chronic PPI use — signal or noise?

Leila Kia and Peter J. Kahrilas

Chronic kidney disease has joined the growing list (pneumonia, myocardial infarction, hip fracture, *Clostridium difficile* infections, acute interstitial nephritis, hypomagnesaemia) of putative risks associated with chronic PPI use based on results from an observational epidemiological study. However, the low hazard ratio (<1.5) makes it doubtful that this association is a causal relationship.

Refers to Lazarus, B. *et al.* Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern. Med.* **176**, 238–246 (2016)

Since their introduction in 1988, PPIs have revolutionized the management of reflux disease and peptic ulcer disease with substantial reduction in the morbidity and mortality associated with these conditions. As such, PPIs are now among the most commonly prescribed medications worldwide. However, perhaps because of their laudable benefits, PPIs have also been prescribed for a myriad of gastrointestinal complaints or suspected reflux syndromes without clear need or benefit, resulting in substantial overutilization[1]. The over-the-counter availability of PPIs has probably accelerated this trend. To complicate matters, several epidemiological studies in recent years have identified possible adverse outcomes associated with long-term PPI use. Each of these publications has been widely reported in the media, prompting both physicians and patients to question the safety of long-term PPI use. The recent article by Lazarus *et al.*[1] published in *JAMA Internal Medicine* is part of this growing literature reporting potential risks of PPIs use.

The study by Lazarus *et al.*[1]aimed to quantify the association between PPIuse and incident chronic kidney disease (CKD) in two population-based cohorts,the Atherosclerosis Risk in Communities (ARIC) study and the Geisinger Health System replication cohort in the USA. H_2 receptor antagonist use was considered a negative control and active comparator. Using statistical modelling tools and controlling for several potential confounding variables, the authors reported that PPI use was associated with the development of incident CKD with an adjusted hazard ratio (HR) of 1.5 (95% CI 1.14–1.96) in the ARIC studyand 1.24 (95% CI 1.20–1.28) in the Geisinger cohort. In the Geisinger cohort, twice-daily PPI dosing was associated with a higher risk (adjusted HR 1.46; 95% CI 1.28–1.67) than once-daily dosing (adjusted HR 1.15; 95% CI 1.09–1.21). From this finding, they concluded that PPI use is associated with an increased risk of incident CKD. Within days, *The New York Times* ran a health column entitled, "Study Finds Growing Reason to Be Wary of Some Reflux Drugs". But was this research really a positive study giventhat it was an uncontrolled observational epidemiological study reporting a HR of <1.5?

Observational studies often demonstrate weak associations, defined by epidemiologists as a relative risk or odds ratio between 1 and 4 but, by their nature, they cannot assess the validity of those observations[2]. Although statistically significant and quite 'precise', as reflected by the small confidence intervals and *P* values <0.05, precision does not equate with validity. In other words, they can be precisely wrong[2]. There are just too many potential confounding variables and sources of bias in observational studies. Increasing the sample size increases the precision of the estimate, but does not circumvent the problem of selection bias and confounding variables. Furthermore, simply identifying potential confounding variables as the authors have endeavoured to do does not eliminate them; beyond being unrecognized, confounding variables can be unmeasured or poorly measured, causing bias. In reviewing the data presented, one has to agree that there was an association between CKD and incident PPI use in these cohorts. However, this association does not establish causality. Large sample sizes, small *P* values and narrow confidence intervals in the context of a small effect size do not prove the validity of those small effects. Furthermore, the validity of any small effects in observational studies such as this one is doubtful, with numerous epidemiologists suggesting that effect sizes <3 are usually wrong and more appropriately classified as 'noise, not signal' (REF. 2). One has to accept the inherent selection, surveillance and confounding biases associated with large observational studies

Table 1 | **Reported associations with PPI use and adverse events**

Adverse event	Odds or hazard ratio	95% CI
Hip fracture with PPI use >1 year[4]	OR 1.44	1.30–1.59
Hip fracture with long-term PPI use	OR 2.65	1.80–3.90
Community-acquired pneumonia[5]	OR 1.49	1.16–1.92
Clostridium difficile infection[6]	OR 2.10	1.20–3.50
Acute interstitial nephritis[7]	OR 5.16	2.21–12.05
Acute kidney injury in patients >18 years[8]	OR 1.72	1.27–2.32
Hypomagnesaemia[3]	OR 1.78	1.01–2.92
Myocardial infarction[9]	HR 1.16	1.09–1.24
Dementia[10]	HR 1.44	1.36–1.52

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of this kind, any of which can easily account for the reported outcome. Although Lazarus *et al.*[1] used elegant statistical modelling and present statistically significant findings, the fact remains that the effect size was very small, much less than the threshold value of 2–3 usually deemed necessary to make the finding worthy of consideration for possible causality[2].

Regardless of these arguments, the alarm has been sounded with the new findings reported on network TV news as a "PPI risk" and patients already clamouring for advice. So, like it or not, CKD has been added to the list of potential adverse events associated with PPI use. How do Lazarus *et al.*[1] findings compare with previous reports of PPI risks? Although the information in TABLE 1 is not comprehensive, it includes the major relevant studies. In reviewing these data, the majority of effect sizes are small or very small, similar to values reported by the Lazarus *et al.*[1] study. Acute interstitial nephritis is the exception with an odds ratio >5, suggesting probable signal as opposed to noise. As for the remainder, it is unclear whether or not any of them have clinical relevance. They might, but this evidence does not warrant changing practice patterns, particularly when a PPI is appropriately clinically indicated. A case in point would be that of hypomagnesaemia. Although initially reported as a potential PPI risk with a (low) HR of 1.78, a critical re-examination of possible cases of PPI-related hypomagnesaemia in a large health maintenance organization database published in 2016 concluded: "in the absence of known precipitating factors, chronic PPI use does not appear to be associated with hypomagnesemia" (REF. 3).

So faced with the patient or physician contemplating discontinuation of PPI therapy due to concern over long-term risks, how to respond? First, the indication for PPI use should be reviewed. If the PPI was initiated for a dubious syndrome for which it proved to be ineffective, it should be discontinued. That is an easy one. No matter how miniscule the risk, there is no benefit. Secondly, if the PPI was started at a higher than standard dose, or if the dosage was increased without clear reason or clinical benefit, the dosage should be decreased to the standard dose. More is not necessarily better. In fact, higher doses are more likely to lead to adverse effects and events. Finally, one needs to have a frank discussion with patients and providers about the lack of meaningful data on PPI risk to warrant changing practice. Remember, PPIs revolutionized the management of acid-related disorders. Yes, they have been severely over-used, but used appropriately they have proven to be extremely safe drugs and have helped innumerable patients.

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