



Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Gastrointestinal disease: observational study and randomised trial give conflicting evidence on association between long-term PPI use and increased risk of death

A large US cohort study has suggested that long-term proton pump inhibitor (PPI) use is associated with an increased risk of all-cause mortality, in particular death from cardiovascular disease or chronic kidney disease. However, a later randomised controlled trial found no increased risk of death from any cause, or cardiovascular adverse events. The NICE guideline on [gastro-oesophageal reflux disease and dyspepsia in adults](#) recommends offering people who need long-term management of dyspepsia symptoms an annual review of their condition, encouraging them to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment).

Overview and current advice

Proton pump inhibitors (PPIs) are effective in treating peptic ulcers (including *Helicobacter pylori* eradication), gastro-oesophageal reflux disease (GORD) and dyspepsia, and are recommended for these indications in the NICE guideline on [GORD and dyspepsia in adults](#). They are also effective in providing protection against gastrointestinal damage from non-steroidal anti-inflammatory drugs (NSAIDs), and NICE guidelines on [osteoarthritis](#) and [rheumatoid arthritis](#) recommend gastroprotection with PPIs when oral NSAIDs are used.

Long term use of PPIs is not without risks. The MHRA has warned of an increased risk of [fractures](#), [hypomagnesaemia](#) and, infrequently, [subacute cutaneous lupus erythematosus](#). NICE guidance on [GORD and dyspepsia in adults](#) recommends offering people who need long-term management of dyspepsia symptoms an annual review of their condition, encouraging them to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment).

New evidence

A large cohort study has estimated all-cause mortality and cause-specific mortality associated with taking PPIs ([Xie et al 2019](#)). The study included US veterans who started taking PPIs (n=157,625) or H2 blockers (n=56,842) between July 2002 and June 2004 and followed them for 10 years. Participants, who were mainly male (96%), white (87%) and older (mean age 65 years) had no acid suppression drug prescribed for at least 2.75 years before study entry. They all had more than 90 days of medication prescribed in the first 180 days after first prescription. None of the PPI cohort had a prescription or H2 blocker in this time, and vice versa.

After adjusting for numerous possible [confounding factors](#), the authors estimate that over the 10 years of follow-up there was an excess 45 deaths (95 % [confidence interval](#) [CI] 28 to 61) per 1000 PPI users.

The longer the duration of exposure to PPI the greater the risk of death. For example, among PPI users and compared with 0–120 days exposure, the [hazard ratio](#) (HR) for 241–360 days exposure was 1.47 (95% CI 1.34 to 1.60), and for 481–600 days exposure it was 1.71 (95% CI 1.56 to 1.87). Analysis of cause of death suggested that cardiovascular disease and chronic kidney disease were the major contributors the excess death rates: 15 (95% CI 5 to 25) and 4 (95% CI 2 to 7) excess deaths per 1000 over 10 years, respectively.

The authors note several possible limitations to their work. Firstly, the predominantly white, older, male population may limit generalisability to other populations. Secondly, people can buy PPIs over the counter, and also may not adhere to the prescribed regimen; thus the prescription data may not truly reflect PPI consumption. Finally, as is inevitable in [observational studies](#), and despite careful efforts, some unknown residual confounders may not have been accounted for.

Commentary

Commentary provided by Professor Janusz Jankowski, Consultant Gastroenterologist, Sherwood Forest Hospitals NHS Foundation Trust and Professor Paul Moayyedi, Assistant Dean of Research, McMaster University, Canada

The use of PPIs is widespread and many millions of people take them for reflux and dyspepsia symptoms. Many people who take PPIs also have comorbidities, including ischaemic heart disease, chronic kidney disease, pneumonia and obesity. This new study found an association between PPIs and an increased mortality rate. Although there were attempts made to correct for confounding factors, the authors recognise the possibility that this association may be subject to this bias as patients who are more ill tend to be prescribed PPI therapy.

In contrast to this observational study, a large RCT published a few months later ([Moayyedi et al 2019](#)) found no statistically significant increase in mortality from PPIs compared with placebo (HR 1.03; 95% CI 0.92 to 1.15). This study was a pre-specified analysis within the COMPASS study of rivaroxaban alone or with aspirin compared with aspirin alone in people with stable atherosclerotic vascular disease ([Eikelboom 2017](#)). In addition to the antithrombotic medication, all study participants who were not already taking a PPI at baseline and who did not have a clinical need for a PPI were randomised to receive either pantoprazole 40 mg or matching placebo once daily (n=17598). Median follow up was 3 years. The study also found no statistically significant difference in any of the cardiovascular outcomes from PPIs compared with placebo.

Although an RCT study design avoids issues of residual confounding, the [MHRA recognises that safety issues](#) may require data from clinical practice or observational studies together with RCTs to best inform practice regarding side effects of medicines. Some side effects only become apparent when medicines are used in the community:

- by many people (because of the rarity of some side effects)
- for a long time (because of the slow onset of some side effects)
- when high doses are used more frequently than in clinical trials
- by people who are not typically included in clinical trials because they have multiple medical conditions, use other medicines, have differences in genetic make-up or lifestyle, or are younger or older than those included in trials (all these factors might affect the risk of side effects).

Data from clinical practice can help identify side effects occurring in these situations. However, clinical practice data are subject to other limitations, including the stimulated reporting of side effects (for example due to media interest); under-reporting of side effects; and possible contribution of concomitant medications, the underlying disease, and patient characteristics and lifestyle.

This new observational study, together with the data from other clinical trials is important. Nevertheless, we should continue to follow current [NICE guidance for PPIs](#) and use them for recommended indications at the lowest dose and the shortest time period possible that is needed to improve symptoms. Higher doses of PPIs might be required for Barrett's oesophagus irrespective of symptoms.

Declaration of interests:

Professor Janusz Jankowski and Professor Paul Moayyedi were both involved in PPI clinical trials including those quoted in this commentary.

Study sponsorship

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