Proton pump inhibitors: observational study suggests increased risk of death with long-term use

A large observational study in US veterans found an increased risk of death among users of PPIs, compared with non-users or those who took H₂ receptor antagonists. Median follow up was for around 6 years and found that the risk appeared to be greater with prolonged duration of use. While the results were supported by extensive sensitivity analyses and adjustment for confounding, the cohort included mostly older, white male US veterans, which might limit the generalisability of the findings to other populations. Nevertheless, this study is consistent with NICE guidance on gastro-oesophageal reflux disease (GORD) and dyspepsia in adults, which recommends that people who need long-term management of dyspepsia symptoms are offered an annual review of their condition, and encouraged to try stepping down or stopping treatment if appropriate.

Overview and current advice

Proton pump inhibitors (PPIs) are widely prescribed and are also available to purchase over-the-counter without a prescription in the UK. For people with uninvestigated dyspepsia, the NICE guideline on gastro-oesophageal reflux disease (GORD) and dyspepsia in adults recommends offering empirical full-dose PPI therapy for 4 weeks, as well as testing and treatment of Helicobacter pylori. If symptoms return after initial care strategies, it recommends stepping down PPI therapy to the lowest dose needed to control symptoms, and discussing ‘as needed’ use of PPI therapy with the person, so that they can manage their own symptoms. People who need long-term management of dyspepsia symptoms should be offered an annual review of their condition, and encouraged to try stepping down or stopping treatment (unless there is an underlying condition or co-medication that needs continuing treatment). For other clinical situations, please consult the relevant NICE guideline for recommendations on the dose and duration of PPI treatment.

Over recent years several safety concerns relating to PPIs have been raised, mainly with long-term use. In particular, the MHRA has advised of an increased risk of hip fracture, reports of hypomagnesaemia and a very low risk of subacute cutaneous lupus erythematosus with these drugs. Other concerns that have been highlighted by observational studies have included a risk of chronic kidney disease, acute interstitial nephritis, dementia and recurrent Clostridium difficile infections (Xie et al. 2017). However, studies have often been inconsistent for some safety concerns. Until recently, large epidemiological studies looking at the risk of PPIs on long-term mortality over a sufficient duration have been lacking.
The NICE interactive flowcharts on GORD and dyspepsia, acute gastrointestinal bleeding, rheumatoid arthritis and osteoarthritis bring together all related NICE guidance and associated products on these topics where PPIs might be indicated, in a set of interactive topic-based diagrams.

New evidence

A longitudinal observational cohort study examined the association between PPI use and risk of all-cause mortality and also whether the risk of death is increased with prolonged duration of use (Xie et al. 2017). Using administrative data from the US Department of Veterans Affairs, the authors identified people who received an outpatient prescription for a PPI or H₂ receptor antagonist between October 2006 and September 2008 but had not received acid suppression treatment in the previous 8 years. People who did not have a serum creatinine value were excluded to try to minimise any effect that poor kidney function might have on the results. The primary outcome in the survival analyses was time to death. All cohorts were followed until 30 September 2013 or until the person died.

The primary analysis compared the rate of death among people prescribed a PPI (n=275,977) with the rate among those prescribed an H₂ receptor antagonist (n=73,335). Within the H₂ receptor antagonist group, 33,136 people were switched to a PPI later and were then considered to be in the PPI group from the date of their first PPI prescription. At baseline, people treated with PPIs tended to be older, more likely to have co-morbid conditions including diabetes, hypertension, cardiovascular disease, hyperlipidaemia and certain gastrointestinal (GI) diseases such as upper GI tract bleeding, peptic ulcer and oesophageal adenocarcinoma. Over a median follow-up of 5.71 years, and after adjusting for these and other variables, use of a PPI was associated with a statistically significant increased risk of death compared with new use of a H₂ receptor antagonist (hazard ratio [HR] 1.25, 95% confidence interval [CI] 1.23 to 1.28). The authors used several other techniques based on propensity score matching to adjust for other confounding factors that might also affect participants' risks using several different methods, and again found a statistically significant increased risk of death.

Larger, secondary cohorts included people who took a PPI compared with those who did not have a prescription for a PPI (n=3,288,092); and people who took a PPI compared with people who did not take either a PPI or a H₂ receptor antagonist (n=2,887,030). In both cohorts, PPI use was also associated with an increased risk of death (HR 1.15, 95% CI 1.14 to 1.15 and 1.23, 95% CI 1.22 to 1.24, respectively). When people were excluded who did not have GI conditions generally considered as indications for a PPI (such as GORD and peptic ulcer disease), PPIs still increased the risk of death for each comparison. Among new users of PPIs (n=166,098), a graded association between duration of exposure and risk of death was found. For example, compared with up to 30 days' exposure, for 31 to 90 days' PPI exposure the HR was 1.05, but this increased to 1.51 for 361 to 720 days' (approximately 1 to 2 years') exposure. Extensive sensitivity analyses and other analyses attempted to account for confounding, but results remained consistent with the rest of the study.

The authors concluded that the results suggest there is an excess risk of death among people who take PPIs and that this risk is also increased with prolonged duration of use and among people without GI conditions. They suggest that limiting PPI use and duration to instances where it is medically indicated may be warranted.

Commentary

Commentary provided by NICE

This large cohort study found an association between use of PPIs and an increased risk of death compared with people who were taking an H₂ antagonist and compared with those who took neither treatment. This risk appeared to be greater with prolonged duration of use.
The strengths of this study are that it was based on large-scale data from a network of integrated US health systems and that several different analytical approaches to the data consistently found a statistically significant association between PPI exposure and risk of death.

However, it is important to consider these findings in the context of the study's limitations. The causes of death are unknown and the cohort included mostly older, white male US veterans, which might limit the generalisability of the findings to other populations. In addition, it did not consider purchase of PPIs or H\textsubscript{2} receptor antagonists over the counter. A weakness of this study, compared with a randomised controlled trial, is that it is observational and subject to many confounding factors. Despite attempts to minimise bias, it is possible that the authors did not fully account for the imbalances, and also that other confounders existed which were not known and, therefore, not adjusted for. The authors did not adjust for 3 potential confounders: obesity, smoking and use of anticoagulants, antiplatelet medicines and non-steroidal anti-inflammatory drugs. However, they estimate that these would not explain the magnitude of the observed increase in risk of death.

Despite the limitations of this study its findings are concerning, especially as there is evidence that PPIs are often prescribed or continued inappropriately (Hamzat et al. 2012), particularly without an appropriate indication (Xie et al. 2017). It is worth noting that this study still found an increase in mortality with PPIs in people who did not have GI conditions. In view of this and the fact that the MHRA has also raised several concerns about the use of PPIs, mainly with long-term use (see Overview and current advice), it is reasonable to review regularly people who are taking PPIs to ensure that treatment is not continued for longer than is clinically indicated.

This study is consistent with NICE guidance on gastro-oesophageal reflux disease (GORD) and dyspepsia in adults, which recommends that people who need long-term management of dyspepsia symptoms are offered an annual review of their condition, and encouraged to try stepping down or stopping treatment (unless there is an underlying condition or co-medication that necessitates continuing treatment). The NICE guideline also highlights the importance of offering simple lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation. People should be advised to avoid known precipitants they associate with their dyspepsia where possible (such as smoking, alcohol, coffee, chocolate and fatty foods) and avoid being overweight. Raising the head of the bed and having a main meal well before going to bed may help some people.

**Study sponsorship**

No source of funding is reported for this study.

**References**


---

**About this Medicines Evidence Commentary**

Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

Visit Evidence Search