Chronic kidney disease: increased risk with proton pump inhibitors

An observational study found the use of proton pump inhibitors (PPIs) was associated with a 20% to 50% increased relative risk of chronic kidney disease (CKD). The increase in absolute risk was 1.7% to 3.3% over 10 years. PPIs are widely prescribed for the management of dyspepsia and gastro-oesophageal reflux disease (GORD), and to reduce the gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs). However, the NICE guideline on GORD and dyspepsia recommends that reviewing the need for long-term use of PPIs is important for the management of these conditions, as are more general discussions with patients about the safe and effective use of medicines (see the NICE guideline on medicines optimisation).

Overview and current advice

Proton pump inhibitors (PPIs) are widely prescribed for the management of dyspepsia and gastro-oesophageal reflux disease (GORD), and to reduce the gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs). NICE guidelines on osteoarthritis, rheumatoid arthritis and low back pain (which is being updated; publication expected September 2016) include recommendations to co-prescribe a PPI with NSAIDs for people who have osteoarthritis, rheumatoid arthritis or for people over 45 years who have low back pain.

The NICE guideline on GORD and dyspepsia recommends PPIs in various clinical situations including for people with uninvestigated reflux-like symptoms or dyspepsia, GORD, severe oesophagitis, peptic ulcer disease or symptomatic functional dyspepsia (see the guideline for details). However, the guideline also places emphasis on reviewing patient care and 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, where appropriate. This may involve returning to self-treatment with antacids or alginites, or using PPIs at the lowest dose possible to control symptoms on an ‘as-needed’ basis.

In recent years the use of PPIs has been associated with several potential safety concerns. In 2012, the MHRA reported that prolonged use of PPIs had been associated with case reports of hypomagnesaemia, and epidemiological studies had suggested an association between long-term PPI use and an increased risk of fracture. There is also increasing evidence that acid-suppressing medications, in particular PPIs may be a risk factor for Clostridium difficile infection (Public Health England guidance on the management and treatment of Clostridium difficile infection). More recently,
in 2015, the MHRA reported that PPIs had been associated with very infrequent cases of subacute cutaneous lupus erythematosus.

This medicines evidence commentary considers a recently published cohort study, which suggests that PPI use may also be associated with an increased risk of chronic kidney disease (CKD). The NICE guideline on CKD states that CKD is common, usually asymptomatic (but it is detectable), frequently unrecognised and often exists together with other conditions (such as cardiovascular disease and diabetes). Moderate to severe CKD is associated with an increased risk of other significant adverse outcomes such as acute kidney injury, falls, frailty and mortality. The risk of developing CKD increases with age and it can progress to end-stage kidney disease in a small but significant percentage of people.

New evidence

An observational study aimed to quantify the association between PPI use and incident kidney disease in the general population (Lazarus et al. 2016). Incident CKD was the primary outcome. H₂-receptor antagonist use was considered as an active comparator and a negative control. Analyses were performed in the Atherosclerosis Risk in Communities (ARIC) study, a long-running US population-based cohort study, and were replicated in people receiving care in the Geisinger Health System, an integrated health system in the USA.

The population for this study included 10,482 adults (mean age 63 years; 44% male) with an estimated glomerular filtration rate (eGFR) of at least 60 ml/min/1.73 m² at baseline who were followed up for a median of 13.9 years (1996 to 1999) from the ARIC study, and 248,751 adults (mean age 50 years; 43% male) with an eGFR of at least 60 ml/min/1.73 m² followed up for a median of 6.2 years in the replication cohort. At baseline in both cohorts, people taking PPIs were more likely than those not taking PPIs to have a higher body mass index and take antihypertensives, aspirin or statins. The characteristics of people taking H₂-receptor antagonists were similar to those taking PPIs. The prevalence of ever use of PPIs increased substantially over time, from about 3% of the ARIC population at baseline (1996) to over 25% in 2011. In the ARIC study, all medication use was measured at baseline through direct visual inspection, with subsequent exposure obtained during annual telephone follow-up with questions about medication use. In the replication cohort, it was through prescription data. Incident CKD was defined using diagnostic codes at hospital discharge or death in the ARIC study and by a sustained eGFR of less than 60 ml/min/1.73 m² in the replication cohort.

In the ARIC study there were 56 incident CKD events among 322 people who were taking PPIs at baseline (14.2 per 1000 person-years) and 1382 events among 10,160 people not taking PPIs at baseline (10.7 per 1000 person-years). This gave an unadjusted hazard ratio (HR) of 1.45 (95% confidence interval [CI] 1.11 to 1.90; p=0.006) for the risk of CKD with use of PPIs compared with no use. After adjusting for potential confounding factors including demographics, socioeconomic status, comorbidities and concomitant use of medications, the HR was 1.50 (95% CI 1.14 to 1.96; p=0.003). The 10-year estimated absolute risk of CKD among people taking PPIs at baseline was 11.8% compared with 8.5% in people who were not taking PPIs at baseline; an absolute risk increase of 3.3% (or a number needed to harm of 30 over 10 years). When PPI use over time was considered, the HR for the risk of CKD with ever use compared with never use of PPIs was 1.35 (95% CI 1.17 to 1.55; p<0.001). Compared with people taking H₂-receptor antagonists at baseline, the HR for the risk of CKD among people taking PPIs at baseline was 1.39 (95% CI 1.01 to 1.91; p=0.05). Similarly, increased risks of acute kidney injury (AKI; a secondary outcome) were seen with PPI use; with an adjusted HR of 1.64 (95% CI 1.22 to 2.21; p<0.001) for the risk of AKI with PPI use at baseline compared with no use at baseline.
In the replication cohort, there were 1921 incident CKD events among 16,900 people who were taking PPIs at baseline (20.1 per 1000 person-years) and 28,226 events among 231,851 people not taking PPIs at baseline (18.3 per 1000 person-years). The adjusted HR was 1.17 (95% CI 1.12 to 1.23; \( p < 0.001 \)) for the risk of CKD with use of PPIs compared with no use. The 10-year estimated absolute risk of CKD among people taking PPIs at baseline was 15.6% compared with 13.9% in people who were not taking PPIs at baseline; an absolute risk increase of 1.7% (or a number needed to harm of 58 over 10 years). Ever use of PPIs was associated with a HR of 1.22 (95% CI 1.19 to 1.25; \( p < 0.001 \)) compared with never use; and use of PPIs compared with use of \( \mathrm{H}_2 \)-receptor antagonists at baseline, a HR of 1.29 (95% CI 1.19 to 1.40; \( p < 0.001 \)). Twice-daily dosing of PPIs was associated with a higher risk of CKD than once-daily dosing (adjusted HR 1.22; 95% CI 1.28 to 1.67; \( p < 0.001 \)). Again, similar associations were seen with incident AKI.

The use of \( \mathrm{H}_2 \)-receptor antagonists at baseline compared with no use was not associated with a statistically significantly increased risk of incident CKD (or AKI) in either the ARIC study (HR 1.15; 95% CI 0.98 to 1.36; \( p = 0.01 \)) or the replication cohort (HR 0.93; 95% CI 0.88 to 0.99; \( p = 0.03 \)).

**Commentary**

**Commentary provided by NICE**

This observational study found the use of PPIs was associated with an increased risk of CKD. However, observational data can only show an association, not causality. There are a number of limitations inherent in the observational design, such as the possibility that observed differences in outcomes may be due to differences among the participants, not only among the treatments. At baseline in both cohorts, people taking PPIs were more likely to be obese, have hypertension and be taking cardiovascular medications. The investigators adjusted for these and other confounding factors and conducted propensity score-matched analyses, each of which showed a consistent association between PPI use and a higher risk of CKD. However, it is possible that residual confounding remained. Other limitations include surveillance bias, where outcomes could have been more frequently assessed in people using PPIs because of more frequent medical contact and hospital discharge codes not accurately reporting a diagnosis of CKD. There is also a risk that patient self-reporting or prescription usage did not accurately reflect actual PPI use, which could also have been bought over the counter.

In this study, PPI use was associated with a 20% to 50% increased relative risk of CKD, or an absolute increase of 1.7% to 3.3% over 10 years. The observational nature of the study and its limitations mean the findings are not definitive. However, even a modest increase in associated risk equates to potential patient harm at a population level when the amount of PPI use is considered. In 2015, nearly 56 million prescription items for PPIs were dispensed in the community in England at a cost of over £121 million (Health & Social Care Information Centre, Prescription Cost Analysis, England 2015).

As discussed above, PPIs have been associated with several adverse effects recently, including hypomagnesaemia, fractures, \( \textit{C. difficile} \) infection, subacute cutaneous lupus erythematosus, and now possibly kidney disease. These risks are discussed in more detail in an accompanying editorial (Schoenfeld and Grady 2016). The evidence suggests that long-term PPI use in particular is not without a risk of harm, therefore people should have clear indications for using PPIs. The NICE guideline on GORD and dyspepsia recommends that people who need long-term management of symptoms should have an annual review of their condition. Where appropriate, this could result in stopping PPIs and returning to self-treatment with antacids or alginates, or using PPIs at the lowest dose possible to control symptoms on an 'as-needed' basis.
Using PPIs appropriately is important in relation to medicines optimisation, to ensure people obtain the best possible outcomes from their medicines. The NICE guideline on medicines optimisation discusses the importance of shared decision-making and an individualised approach to treatment choices including how safe the medicines are, how well they work for the person and how appropriate they are. Previously, the focus was on ensuring efficient use of PPIs to maximise productivity opportunities. The ‘better care, better value’ indicator focused on the percentage of low cost PPI prescribing, and there is still a volume comparator relating to PPIs on the NHS Business Services Authority website. With the emerging potential safety concerns, localities may wish to re-examine their prescribing of PPIs to make sure it is in line with NICE guidance, and that clear indications for treatment are given.

Study sponsorship

The authors of this observational study were funded by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, USA. The ARIC study is supported by the National Heart, Lung and Blood Institute, USA.

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.