267 | August 2020 | 2.0

PrescQIPP Community Interest Company

Proton Pump Inhibitors (PPIs): Long term safety and gastroprotection

Nationally £128 million is spent annually on proton pump inhibitors (PPIs) (NHSBSA Feb-Apr 2020). Medicines optimisation projects in this area focus on reducing prescribing of PPIs for safety and cost reasons by reviewing the continued need, and stepping-down therapy or deprescribing where appropriate in line with current guidance. This bulletin offers guidance and support materials for organisations considering reviewing gastroprotection with PPIs as a medicines optimisation project.

Recommendations

- Offer lifestyle advice to all people to manage dyspepsia, including advice on healthy eating, weight reduction, smoking cessation, and avoiding factors associated with dyspepsia.
- Review medications for possible causes of dyspepsia. These include calcium antagonists, nitrates, theophyllines, bisphosphonates, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs).
- PPIs should only be prescribed when needed for a recognised indication and for an appropriate duration at the lowest effective dose, taking into account the person's preference and clinical circumstances and the acquisition cost of the PPI. Histamine H2-receptor antagonist (H_2RA) therapy should be offered instead of a PPI if there is an inadequate response to the PPI.
- The use of short courses, as-needed doses and self-treatment with antacid and/or alginate therapy should be first line unless there is a recognised indication for long-term PPI treatment e.g. in Barrett's oesophagus, prevention of NSAID-associated ulcers, chronic NSAID users with bleeding risk, history of bleeding GI ulcers or severe oesophagitis complicated by past strictures, ulcers, or haemorrhage.
- All PPIs should be reviewed between four and eight weeks after starting treatment.
- When defined short-term courses are prescribed, the person's symptoms should be reviewed on course completion and the PPI discontinued/reduced if symptoms have resolved.
- Due to adverse effects people who need long-term PPI therapy should be offered an annual review and encouraged to try stepping down PPI therapy to the lowest dose needed to control symptoms, treatment on an 'as needed' basis, self-treatment with antacid and/or alginate therapy either prescribed or purchased over-the-counter.
- Prescribers should consider reviewing the need for and stopping PPIs in people with *Clostridium difficile* infection (CDI), or those at high risk of CDI.
- Due to an increased risk of fracture with long-term PPI use, ensure people at risk of osteoporosis maintain an adequate intake of calcium and vitamin D, and if necessary, receive other preventative therapy.
- Severe hypomagnesaemia has been infrequently reported with PPIs. Consider the measurement of magnesium levels before starting PPI treatment and periodically during prolonged treatment, especially in those who take a PPI concomitantly with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics).

Recommendations

- If a person treated with a PPI develops lesions, especially in sun-exposed areas of the skin and it is accompanied by arthralgia, although a very low risk, consider a diagnosis of subacute cutaneous lupus erythematosus (SCLE) and advise avoiding exposure to sunlight and discontinuing PPI treatment unless it is imperative.
- People presenting with 'alarm features' including significant acute GI bleeding, or in those aged 55 years and over with unexplained weight loss and symptoms of upper abdominal pain, reflux or dyspepsia should be referred for urgent endoscopic investigation.
- Consider PPIs other than omeprazole or esomeprazole in patients taking clopidogrel or if other gastrointestinal therapy such as H_2RAs (except cimetidine) or antacids may be more suitable.
- If a person is prescribed an NSAID, anticoagulant, antiplatelet, corticosteroid or SSRI and considered at high risk of GI adverse effects due to the risk factors, consider prescribing an appropriate PPI or alternative gastroprotection agent if the benefits outweigh the risks of adverse effects.
- Medication that requires gastroprotection should be reviewed regularly. If that medication is stopped then the PPI should be deprescribed too if this is the only indication for prescribing.

Background

PPIs inhibit gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') of the gastric parietal cell. They have a number of indications including:

- Effective short-term treatment for gastric and duodenal ulcers.
- Combination therapy with antibacterials for the eradication of *Helicobacter pylori (H. pylori)*.
- Following endoscopic treatment of severe peptic ulcer bleeding, an intravenous, high-dose PPI reduces the risk of rebleeding and the need for surgery.
- Treatment of dyspepsia.
- Treatment of gastro-oesophageal reflux disease.
- Prevention and treatment of NSAID-associated ulcers.
- Maintenance therapy in patients who need to continue NSAID treatment after an ulcer has healed.
- To reduce the degradation of pancreatic enzyme supplements in patients with cystic fibrosis.
- To control excessive secretion of gastric acid in Zollinger–Ellison syndrome.[1]

There are five PPIs available in the UK, omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. Esomeprazole is also available in combination with the NSAID naproxen in Vimovo® (naproxen 500mg/esomeprazole 20mg) modified-release tablets. This is indicated for patients requiring naproxen for osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, who are at risk of NSAID-associated duodenal or gastric ulcer and when treatment with lower doses of naproxen or other NSAIDs is ineffective.[1]

Differences between the PPIs in terms of clinical efficacy and safety are minimal. No PPI is more effective than another at equivalent doses, and so the National Institute for Health and Care Excellence (NICE) recommends using the least expensive PPI.[2] Branded preparations and alternative formulations, such as dispersible tablets or oral suspensions are less cost effective than standard generic formulations. If treatment with one PPI is ineffective, switching to an alternative PPI is a cost-effective therapeutic strategy.[3] See chart 1 under costs and savings for a cost comparison for prescribing PPIs.

PPIs are among the most frequently prescribed drugs globally. Although they are cost effective when used appropriately, studies show they are prescribed without a clear indication in up to 70% of cases.[4] Although the absolute risk of harm to individuals from PPIs is low, their widespread, long-term use can

cause adverse effects that contribute to significant negative impact at a population level. Over the past decade, many adverse effects of PPI therapy have been identified. The most widely studied of these is *Clostridium difficile* infection.[4] Other adverse effects include a higher risk of mortality, an increased fracture risk, pneumonia, acute interstitial nephritis, chronic kidney disease, hypomagnesaemia, vitamin B12 deficiency, cardiovascular events, subacute cutaneous lupus erythematosus and gastric cancer.[3]

National guidance

Dyspepsia and gastro-oesophageal reflux disease

Dyspepsia has no universally accepted definition. The British Society of Gastroenterology (BSG) defines dyspepsia as a group of symptoms arising from the upper gastrointestinal (GI) tract, which typically are present for four weeks or more. Symptoms include upper abdominal pain or discomfort, heartburn, gastric reflux, nausea or vomiting.[2] Gastro-oesophageal reflux disease (GORD) is a chronic condition where there is reflux of gastric contents (particularly acid, bile, and pepsin) back into the oesophagus, causing predominant symptoms of heartburn and acid regurgitation. GORD may also be associated with atypical symptoms affecting the oropharynx and/or respiratory tract, such as hoarseness, cough, asthma, and dental erosions in some people. Complications of GORD include oesophageal ulcers, haemorrhage and stricture (usually secondary to severe oesophagitis, where fibrosis leads to narrowing of the oesophageal lumen), anaemia due to chronic blood loss (usually secondary to severe oesophagitis), aspiration pneumonia, Barrett's oesophagus which has malignant potential and an increased risk of developing oesophageal adenocarcinoma.[5]

NICE clinical guidance 184 looks at the investigation and management of GORD and dyspepsia in adults. It recommends all people should be offered simple lifestyle advice, including advice on healthy eating, weight reduction, smoking cessation and avoiding factors associated with dyspepsia such as alcohol, coffee, chocolate and fatty food. Having the main meal well before bedtime (3-4 hours beforehand) and raising the head of the bed may help some people. People should be provided with educational materials to support their care, or access to them. Psychological therapies, such as cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people.[1,2] Medications should be reviewed for possible causes of dyspepsia, e.g. calcium antagonists, nitrates, theophyllines, bisphosphonates, corticosteroids, and NSAIDs.[1,6]

People presenting with 'alarm features' including significant acute GI bleeding, or in those aged 55 years and over with unexplained weight loss and symptoms of upper abdominal pain, reflux or dyspepsia should be referred for urgent (to be performed within two weeks) endoscopic investigation.[2,7] Suspend use of NSAIDs in people needing referral.[2] Urgent investigation should also be considered for patients aged over 55 years, with unexplained, recent-onset dyspepsia that has not responded to treatment.[1] If endoscopy is planned, rather than urgent, any acid suppression therapy should be stopped for at least two weeks before the procedure date. This is recommended as it may mask or delay the detection of gastric and oesophageal cancer. Self-treatment with antacid and/or alginate therapy is recommended if needed.[6] H. pylori 'test and treat' should be offered to people with dyspepsia and there should be a two week washout period after the PPI is stopped before testing for H. pylori with a breath test or a stool antigen test.[2]

NICE clinical guidance 184 - Management of GORD and Dyspepsia in Adults recommends:

- Offering full-dose PPI for four weeks to people with dyspepsia.
  - » If symptoms return after initial care strategies, step down PPI therapy to the lowest dose needed to control symptoms.
  - » Discuss using the treatment on an 'as-needed' basis with people to manage their own symptoms.
  - » Offer H_2RA therapy as an alternative if there is an inadequate response to a PPI.

  - Offer people who need long-term management of dyspepsia symptoms an annual review of their condition.
  - Encourage them to try stepping down or stopping treatment (unless there is an underlying condition or co-medication that needs continuing treatment).
  - Advise people that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the-counter and taken as needed).
- Offering full-dose PPI for four or eight weeks in people with GORD.
  - If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms.
  - Discuss with people how they can manage their own symptoms by using the treatment when they need it.
  - Offer H_2RA therapy as an alternative if there is an inadequate response to a PPI.
  - People who have had dilatation of an oesophageal stricture should remain on long-term full-dose PPI therapy.
- To heal severe oesophagitis offer a full-dose PPI for eight weeks. See guidance for definition of dosing schedules - table 2 appendix A
  - If initial treatment fails, consider a high dose of the initial PPI, switching to another full-dose PPI or switching to another high-dose PPI.
  - Offer a full-dose PPI long-term as maintenance treatment.
  - If maintenance treatment fails, carry out a clinical review. Consider switching to another PPI at full dose or high dose.[2]

NICE clinical guidelines on osteoarthritis, rheumatoid arthritis, low back pain and sciatica, and spondyloarthritis all include recommendations to consider using gastroprotective treatment with NSAIDs. The gastroprotective treatment recommended is a PPI of the lowest acquisition cost.[8-12]

NICE clinical guideline 141 - Acute upper gastrointestinal bleeding in over 16s: management recommends:

- Acid-suppression drugs (PPIs or H_2RAs) should not be offered before endoscopy to patients with suspected non-variceal upper GI bleeding.
- PPIs should be offered to patients with non-variceal upper GI bleeding and stigmata of recent haemorrhage shown at endoscopy.
- Offer PPIs or H_2RAs for primary prevention of upper GI bleeding in acutely ill patients admitted to critical care. If possible, use the oral form of the drug.
- Review the ongoing need for acid-suppression drugs for primary prevention of upper GI bleeding in acutely ill patients when they recover or are discharged from critical care.
- The PPIs omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole are not licensed for prophylaxis of GI bleeding in acutely ill patients. The use of PPIs and H_2RAs other than ranitidine and cimetidine for this indication would be off label.[13]

Clinical effectiveness

Differences between PPIs in terms of clinical efficacy and safety are minimal. No PPI is more effective than another at equivalent doses, and therefore NICE recommends using the least expensive PPI.[3]

Safety

Adverse effects of PPIs are usually mild and reversible and include the following very common (greater than 1 in 10 people) and common (1 in 100 to 1 in 10 people) side effects such as abdominal pain, constipation, diarrhoea, dizziness, dry mouth, gastrointestinal disorders, headache, insomnia, nausea,

skin reactions and vomiting.[1] There is increasing evidence that long-term PPI use is associated with an increased risk of adverse effects listed below. Some of these adverse effects, such as fractures and *Clostridium difficile* infection, are themselves associated with considerable morbidity and mortality, as well as high treatment costs.[3]

Clostridium difficile infection (CDI)

The weight of evidence appears to support an association between PPI use and an increased risk of CDI. A MeReC Rapid Review highlighted two US studies investigating PPI use and CDI. A large observational study showed that hospital inpatients taking daily PPIs were over 70% more likely to develop CDI than those not taking PPIs. A second study in the US found that people who already had CDI and were treated with PPIs had a greater than 40% increased relative risk of infection recurrence.[3,14]

Although a causal link has not yet been proven, because gastric acid is thought to play a principal role in sterilising the stomach contents entering the digestive tract, it is plausible that raising the pH of the stomach with a PPI may increase the load of pathogenic microbes. However, it is possible that these associations are confounded by other CDI risk factors including:

- Older age
- Antibiotic treatment
- Underlying morbidity
- Hospitalisation
- History of CDI.[3]

Prescribers should consider reviewing the need for, and stopping, PPIs in people with CDI or at high risk of CDI, for example, hospitalised patients receiving antibiotics. Given the extent of PPI prescribing, the number of potentially avoidable CDI cases could be significant. The challenge presented by CDI, the evidence of an association with PPI use, and current concerns about overuse of PPIs, provide good reasons to critically review PPI prescribing.[15]

Increased risk of bone fractures

The Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Update advised of an increased risk of fracture with long-term use of PPIs. This was based on observational studies which suggested there may be a modest increase in the risk of hip, wrist, or spine fracture, especially if PPIs are used in high doses and over long durations (>1 year). The increased risk was observed mainly in elderly patients, and it is possible that other risk factors contributed to this increase in risk.[16]

Two meta-analyses of published pharmacoepidemiology studies suggest the risk of fracture is increased by 10–40% above baseline. The primary studies in these analyses have varied in the extent to which they have adjusted for other potential risk factors for fracture, and use of calcium or vitamin D.[16]

A meta-analysis of 18 observational studies involving a total of 244,109 fracture cases concluded that PPI use modestly increased the risk of any-site fracture (relative risk [RR] 1.33, 95% confidence interval [CI] 1.15 to 1.54). However, there was no determinable difference between short- or long-term use of PPIs.[3,17] A more recent systematic review and meta-analysis evaluated the association between PPI use and bone fracture incidence and bone mineral density (BMD). It looked at thirty-three studies which provided data from 2,714,502 individuals found that PPI use might increase fracture risk, however, there was no effect of PPI use on BMD.[18]

The mechanism for PPI-induced increased fracture risk remains largely unexplained; one proposed theory is the decreased absorption of calcium due to increased pH in the small intestine. However, a causal relationship is yet to be established so other factors could be contributing to the increased risk.[3]

No association between PPI use and osteoporosis has been demonstrated; the MHRA recommends patients at risk of osteoporosis should be treated according to current clinical guidelines and ensure they have an adequate intake of vitamin D and calcium. If necessary, they should also receive other preventative therapy, such as bisphosphonates.[3,16]

Allergic Interstitial Nephritis (AIN)

AIN is often caused by exposure to a drug and associated with an acute decline in renal function which may result in permanent renal insufficiency. The most common class of medications causing AIN are antibiotics such as penicillins, cefalosporins, rifampicin, sulfonamides, and ciprofloxacin which accounts for approximately 30% to 49% of drug-induced cases. Other commonly implicated drugs include NSAIDS, indinavir, PPIs, allopurinol, 5-aminosalicylates, diuretics, and cimetidine.[19] AIN due to PPIs is considered rare, but wide prescribing and greater over-the-counter availability may increase incidence.[20] Although lansoprazole and omeprazole are most commonly implicated, all PPIs are associated with AIN.[19,20] Case reports associating PPI use with the development of AIN suggest these are humoral and cell-mediated hypersensitivity reactions that can occur within days of therapy initiation and for as long as 18 months thereafter.[21]

Patients should be educated about the symptoms of AIN, including nausea, vomiting, fatigue, fever, and haematuria as the prognosis is usually good if the PPI is stopped promptly, and spontaneous recovery occurs after withdrawal in most cases.[3,20,21] A delay in diagnosis could result in chronic kidney disease.[20] Immunosuppressive therapy has been used to treat AIN, but the paucity of randomised controlled trials has limited the evidence for this approach. Several small, uncontrolled studies have suggested improvement with the use of steroids, with the most improvement noted in patients receiving steroids within seven days of drug withdrawal.[19] PPIs can often be replaced with lifestyle measures, an antacid and/or alginate treatment, and/or ranitidine (which is very rarely associated with acute interstitial nephritis).[3]

Kidney injury

An observational study investigated the risk of developing acute kidney injury (primary outcome) and AIN (secondary outcome) in older people taking PPIs. A total of 290,592 individuals taking PPIs were matched with an equal number of controls. In those taking PPIs, there was a higher rate of acute kidney injury (13.5 vs. 5.5 per 1,000 person-years; HR 2.52, 95% CI 2.27 to 2.79) and acute interstitial nephritis (0.3 vs. 0.1 per 1,000 person-years; HR 3.00, 95% CI 1.47 to 6.14). However, the risks may be overstated, as only a small proportion of patients who subsequently received another PPI were subsequently re-admitted with acute kidney injury. Some recent reports have also suggested that PPIs may be responsible for increased incidence of chronic kidney disease (CKD).[22]

In 2017 the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency concluded there was insufficient evidence for a causal relationship between PPIs and incident CKD and progression to end-stage renal disease to warrant an update of the product information or any additional risk minimisation measure.[23]

The possible mechanisms of PPI-related renal injury are poorly evidenced at present and there is a need for a greater understanding of the effects of PPIs on the kidney before any definite recommendations can be made. Prescribers should be vigilant to these adverse effects and periodically monitor renal function in people taking PPIs long-term.[24]

Higher mortality in older patients

A recent observational study of people taking PPIs showed that their all-cause mortality increased the longer they took them. People who received PPIs for between one and two years had a 50% increased risk of death compared with those who took them for less than a month. An increased risk of death was also associated with the lack of a documented gastrointestinal indication for PPI use.

The higher risk of death with PPI use is likely to be mediated by the occurrence of one or more of the adverse events associated with PPI use, for example, osteoporotic fracture, chronic kidney disease, hypomagnesaemia, and *Clostridium difficile* infection. Long-term PPI use should be limited to people who have a clear medical indication and in whom the benefits will outweigh any potential risks.[25]

Community Acquired Pneumonia (CAP)

There is conflicting evidence from observational studies on an association between PPI use and an increased risk of CAP.[3] A meta-analysis from 2010 of six observational studies found an association between PPI use and CAP. The risk of CAP was two times higher in newly prescribed PPI users than in non-users, whereas there was no difference in risk of pneumonia in chronic users.[26] A separate study found that PPI therapy is associated with an approximately two-fold increased risk of develop CAP and that this association was particularly strong during the first seven days of PPI treatment.[3,27] A more recent study concluded that the association between the use of PPIs and risk of community acquired pneumonia is likely to be due entirely to confounding factors.[28] Further research is needed into a link between PPI and CAP before the impact on clinical practice can be determined. However, it seems that caution is warranted when prescribing PPIs for older people who are at increased risk of infection and for whom pneumonia may be an important cause of morbidity and mortality, and for people with asthma or chronic obstructive pulmonary disease.[29,30]

Hypomagnesaemia

In 2012 the MHRA warned that severe hypomagnesaemia had been reported infrequently in patients treated with PPIs. Although the exact incidence is unknown, a review of case reports suggested that PPIs may cause hypomagnesaemia. Some cases occurred after three months of PPI therapy, but most occurred after one year of treatment. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia can occur, but they may begin insidiously and be overlooked. In most case reports, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. The Drug Safety Update recommends healthcare professionals consider measuring magnesium levels before starting PPI treatment and periodically during prolonged treatment, especially in those who will take a PPI concomitantly with digoxin or drugs that may also cause hypomagnesaemia (e.g. diuretics).[31]

Vitamin B_{12} deficiency

Gastric acid is needed to cleave vitamin B_{12} from ingested dietary proteins and enable it to be absorbed from the small bowel. Therefore, PPIs, which suppress gastric acid production, may lead to malabsorption of vitamin B_{12}.[32] A large case-control study of more than 200,000 people found a significantly (65%) increased risk of vitamin B_{12} deficiency associated with taking PPIs for two or more years. The same study found a 25% increased risk with the use of H_2RA.[33] Further studies are needed to clarify the clinical significance of these associations.[34]

However, people at particular risk of vitamin B_{12} deficiency include, older or malnourished people taking PPIs for more than one year and people taking other medicines that can affect vitamin B_{12} levels, such as metformin. Routinely monitoring vitamin B_{12} in all people taking a PPI is not recommended.[33]

Subacute cutaneous lupus erythematosus (SCLE)

The MHRA issued a Drug Safety Update in 2015 advising that PPIs are associated with very infrequent cases of SCLE, a non-scarring dermatosis that can develop in sun-exposed areas. They advised that if a patient treated with a PPI develops lesions, especially in sun-exposed areas of the skin and it is accompanied by arthralgia they should consider SCLE as a possible diagnosis. The patient should be advised to avoid further exposure of skin to sunlight and consider stopping the PPI unless it is imperative for a serious acid-related condition. A patient who develops SCLE with a particular PPI may be at risk of the same reaction with another PPI. In most cases, symptoms resolve on PPI withdrawal, topical or systemic steroids might be necessary for treatment of SCLE only if there are no signs of remission after a few weeks or months.[35]

Cardiovascular events

A large US study used multiple data sources to assess whether there was any association between use of PPIs and cardiovascular risk in the general population. They queried more than 16 million clinical documents, including patients' clinical notes, providing information on a total of 2.9 million people. The results reported that, among patients with GORD, taking a PPI was associated with a 16% increased risk of myocardial infarction (adjusted odds ratio 1.16 (95% confidence interval 1.09 to 1.24)). There was no association with myocardial infarction for H_2RAs (adjusted odds ratio 0.93 (0.86 to 1.02)).[36] This association does not in itself provide proof of causation, and further studies are needed. However, if appropriate, prescribers should consider reducing PPI doses, or stopping PPI treatment, in people with existing cardiovascular disease and no strong indication for PPI therapy.[34]

Cancer

PPI use is associated with increased serum gastrin levels and bacterial overgrowth, resulting in an increased formation of toxic bile salts.[37] Concerns that this may increase the risk of developing gastric cancer have been raised.[32] A population-based study in Hong Kong considered the risk of developing gastric cancer with long-term PPI use after *H. pylori* eradication treatment. It reported that among the 63,397 eligible subjects, 153 (0.24%) developed gastric cancer during a median follow-up of 7.6 years. PPI use was associated with an increased gastric cancer risk (HR 2.44, 95% CI 1.42 to 4.20), while H_2RA use was not (HR 0.72, 95% CI 0.48 to 1.07). The risk increased with duration of PPIs use even after *H. pylori* eradication treatment.[32,38]

Dementia

There is conflicting evidence on the risk of dementia associated with PPI use.[32] A cohort study used a German healthcare insurance database to compare no PPI use (70,729 patients) with regular PPI use (2,950 patients) and calculated a hazard ratio of 1.4 (95% CI 1.4 to 1.5, $p<0.001$) for developing dementia. Adjustments were made for age, sex, co-morbidity and polypharmacy as confounding factors.[39] A study in the USA using the National Alzheimer's Coordinating Center database recorded PPI use in those attending with suspected cognition problems. Out of a total of 10,486 patients, those taking PPI (continuously [884] or intermittently [1,925]) were compared with patients who never took PPIs (7,677). After adjusting for confounding factors, there was a lower risk of decline in cognitive function and a lower risk of conversion to Alzheimer's disease in those who took PPIs continuously.[40]

Interaction with clopidogrel

In May 2009, the EU Committee for Medicinal products for Human Use (CHMP) concluded that concomitant use of any PPIs with clopidogrel should be avoided unless considered essential. Omeprazole competitively inhibits the CYP2C19 isoenzyme which metabolises clopidogrel to its active metabolite. This reduces the ability of clopidogrel to inhibit platelet aggregation and reduces the beneficial effect. Although evidence for a similar effect on clopidogrel metabolism with the other PPIs was relatively sparse, a precautionary approach was applied to the whole class. In light of the most recent evidence, this previous advice (to avoid all PPIs unless absolutely necessary for patients taking clopidogrel) is no longer considered necessary. However, concomitant use of clopidogrel with omeprazole or esomeprazole should be discouraged and healthcare professionals should check whether patients who are taking clopidogrel are also buying over-the-counter omeprazole or esomeprazole. Consider PPIs other than omeprazole or esomeprazole in patients who are taking clopidogrel. Other gastrointestinal therapy such as H_2RAs (except cimetidine) or antacids may be more suitable in some patients.[41]

PPIs as gastroprotection

NSAIDs, anticoagulants and antiplatelets cause over a third of hospital admissions due to avoidable adverse drug reactions (ADRs). GI bleeds are implicated in half of the deaths from primary care ADRs.[42]

NSAIDs

NSAIDs inhibit cyclo-oxygenase-1 which is thought to be responsible for GI toxicity. Risk factors for NSAID–induced GI adverse effects include:[43]

- Aged over 65 years.
- A high dose of an NSAID.
- A history of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation.
- Concomitant use of medications that are known to increase the likelihood of upper GI adverse effects (for example, anticoagulants, corticosteroids, selective serotonin reuptake inhibitors SSRIs).
- A serious comorbidity, such as cardiovascular disease, hepatic or renal impairment (including dehydration), diabetes, or hypertension.
- Heavy smoking.
- Excessive alcohol consumption.
- Previous adverse reaction to NSAIDs.
- Prolonged requirement for NSAIDs.

The risk of serious GI side effects varies between individual NSAIDs: piroxicam, ketoprofen and ketorolac are associated with the highest risk, and ibuprofen (up to 1.2 g daily) is associated with the lowest risk.[1] To prevent GI adverse effects associated with the use of NSAIDs:

- Avoid prescribing more than one NSAID at a time.
- Avoid concomitant use of an NSAID with low-dose aspirin (if possible) — if this is essential, monitor closely.
- Prescribe the lowest dose of NSAID for the shortest period of time.
- Use a short-acting NSAID (such as ibuprofen) in preference to a long-acting NSAID (such as naproxen).
- Consider an alternative analgesic if appropriate.[43]

Not all people who are prescribed an NSAID will need gastroprotection to prevent adverse effects. A PPI should be co-prescribed for:

- People with osteoarthritis and rheumatoid arthritis.
- People who are elderly aged 65 and over.
- People with low back pain, axial spondyloarthritis, psoriatic arthritis and other peripheral spondyloarthritides.
- People at moderate risk (1–2 risk factors) of NSAID–induced GI adverse effects.
- People at high risk (history of previously complicated ulcer, or >2 risk factors) of NSAID–induced GI adverse effects.[43]

Antiplatelets

Antiplatelet drugs increase the risk of major bleeding, particularly upper GI bleeds, but this risk is reduced by 70–90% by PPIs. However, co-prescription of PPIs with antiplatelets is not routine, possibly due to concerns about adverse effects and because upper GI bleeds had a low case fatality in trials of aspirin and are not generally thought to cause permanent disability. Clinical guidelines on secondary prevention of vascular events make no recommendations on PPI use, although some consensus statements advocate use in high-risk patients, however definitions of high risk vary and uptake in practice remains low.[44]

A large prospective population-based study of long-term antiplatelet treatment in secondary prevention of vascular disease showed that the severity, case fatality, and poor functional outcome of bleeds increase with age. In patients aged 75 years or older, most major upper GI bleeds were disabling or fatal, substantially outnumbering disabling or fatal intracerebral haemorrhage. Given that half of the major bleeds in patients aged 75 years or older were upper GI, the estimated Number-Needed-to-

Treat (NNT) for routine PPI use to prevent one major upper GI bleed over five years is low (25) and the authors concluded that co-prescription should be considered in future secondary prevention guidelines. However, more research is still required into how best to identify patients at high risk of bleeding, how to reduce the risk of non-upper GI bleeds, and into the overall balance of risks and benefits of long-term antiplatelet treatment at older ages in both primary and secondary prevention.[44]

The NICE Clinical Knowledge Summary (CKS) on antiplatelet treatment advises that if the person has a high risk of GI adverse effects and is taking low-dose aspirin alone, or in combination with ticagrelor or prasugrel, a PPI should be co-prescribed for gastroprotection. If a person is taking clopidogrel alone, or in combination with low-dose aspirin, a PPI, except omeprazole or esomeprazole, should be co-prescribed. NICE CKS considers a person is at high risk of GI adverse effects with antiplatelet treatment if the following risk factors are present:

- High dose of aspirin
- Older age, especially aged over 70 years
- History of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation
- Helicobacter pylori infection
- Concomitant use of medicines that are known to increase the risk of GI bleeds.[45]

PPIs are the preferred option to reduce GI adverse effects in people taking antiplatelets as they are more effective than H_2RAs. They are also the preferred option for people taking low dose aspirin as H_2RAs do not provide the level of suppression required to prevent NSAID related ulcers. Clopidogrel should not be used alone as an alternative to low dose aspirin, or low dose aspirin plus PPI in people with high risk of GI adverse effects risk.[45]

Anticoagulants

A recent study looked at the association of oral anticoagulants (with or without PPI co-therapy) with hospitalisation for upper GI tract bleeding. The study estimated that 1% to 1.5% of patients on oral anticoagulants will experience upper GI bleeds every year. For all anticoagulants, the incidence of hospitalisation for upper gastrointestinal tract bleeding was lower among patients who were receiving PPI co-therapy.[46,47] For patients starting on oral anticoagulant treatment, anticoagulant choice and PPI co-therapy can materially affect the risk of upper GI bleeding hospitalisation. These factors are particularly important for patients at high GI risk and so a GI risk assessment is suggested before initiating oral anticoagulant treatment.[46] In some patients, PPIs may be considered to reduce the risk of GI bleeding, especially in those with a history of such bleeding or ulcer.[48]

Corticosteroids

People receiving long-term oral corticosteroids (more than three weeks duration) and those needing frequent courses (three or four per year) are at risk of systemic adverse effects, which includes peptic ulceration with perforation and haemorrhage, dyspepsia, abdominal distension, and oesophageal ulceration; especially in high-risk people. The NICE CKS on oral corticosteroids says consider prescribing a PPI for gastrointestinal protection in people at high risk of gastrointestinal bleeding or dyspepsia, although PPIs are not routinely indicated for prophylaxis of peptic ulceration in people using oral corticosteroids. The risk factors for GI adverse effects with oral corticosteroids include:

- History of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation.
- Older age.
- Concomitant use of drugs that are known to increase the risk of GI bleeding, such as nonsteroidal anti-inflammatory drugs (for example aspirin and ibuprofen) and anticoagulants.
- Serious comorbidity, such as advanced cancer.[49]

Selective Serotonin Reuptake Inhibitors (SSRIs)

An association between SSRI use and upper GI bleeding was reported in 1999 following analysis of data from a UK general practice research database. In several studies in which an increased risk has been noted with SSRIs alone, the risk has been found to be elevated further by the concomitant use of SSRIs and NSAIDs. Being over the age of 80 or having a previous history of GI bleeding may also add to the risk of upper GI bleeding with SSRIs.[39]

If an SSRI is required in a patient at high risk of an upper GI bleed, consider the use of a gastro-protective agent. Studies have shown the use of PPIs, to be protective against upper GI bleeds in patients receiving single-therapy SSRI or combined NSAID and SSRI treatment. NICE guidance for depression in adults (CG90) recommends considering a gastroprotective drug in older people on SSRIs who are also taking NSAIDs or aspirin.[39,51]

Reviewing PPI therapy and deprescribing

NICE recommends that people treated with PPIs receive regular reviews and should be encouraged to reduce their use of these medicines where possible (unless there is an underlying condition or co-medication that needs continuing treatment). Reviews should be conducted after the initial 4-8 week course of PPI treatment, and at least annually for patients taking PPIs longer-term. During the review the need for ongoing therapy (particularly at full treatment doses) should be assessed, if symptoms are well controlled by the initial PPI treatment course, and if there is no strong indication for long-term therapy, a step-down in treatment can be considered.[2] A deprescribing algorithm for adults taking PPIs is set out in attachment 5. It has been estimated that up to 30% of patients may be able to stop a PPI immediately after the initial course of therapy without experiencing symptoms.[52] For adults over 18 with upper GI symptoms, who have completed a minimum 4 week course of PPI treatment, which has resulted in the resolution of upper GI symptoms, it is recommended that the daily dose is decreased, or stopped and changed to an 'as needed'/ 'on demand'' use. A H2Ra can be considered as an alternative.[53]

However, rebound hypersecretion (a rise in acid secretion after discontinuing PPI treatment) can occur after courses as short as eight weeks' duration.[54] This can often lead to an increase in GI symptoms, which may be mistaken for disease relapse.[3] Patients should be warned about the possibility of rebound hypersecretion when PPIs are deprescribed. The duration of rebound hypersecretion is unknown, but some studies show reflux-like symptoms within two weeks, and for at least four weeks after withdrawal from PPI therapy. To help limit the occurrence of rebound hypersecretion, the dose of PPI could be reduced and an antacid and/or alginate could be prescribed for at least two weeks.[3] If a step-down approach does not adequately control symptoms, treatment could be resumed with the lowest effective dose of PPI, with consideration to future step-down when appropriate. Prescribers should talk with the patient about the options available for stepping down therapy, considering their preferences in developing the step-down plan.[55] Also see attachment 5: Proton Pump Inhibitor (PPI): Deprescribing algorithm (adults).

Stopping or reducing therapy may not be appropriate for some people, for example:

- People with Barrett's oesophagus.
- People with a documented history of bleeding GI ulcers.
- People with severe oesophagitis complicated by past strictures, ulcers, or haemorrhage.[53]
- People co-prescribed a PPI for NSAID gastroprotection:
  - With osteoarthritis and rheumatoid arthritis.
  - Who are elderly.
  - With low back pain, axial spondyloarthritis, psoriatic arthritis and other peripheral spondyloarthritides.
  - Who are at high or moderate risk of GI adverse events.[43]

If long term treatment is necessary, ensure the dose of PPI does not exceed usual maintenance doses and use the minimum dose required to treat symptoms.[56]

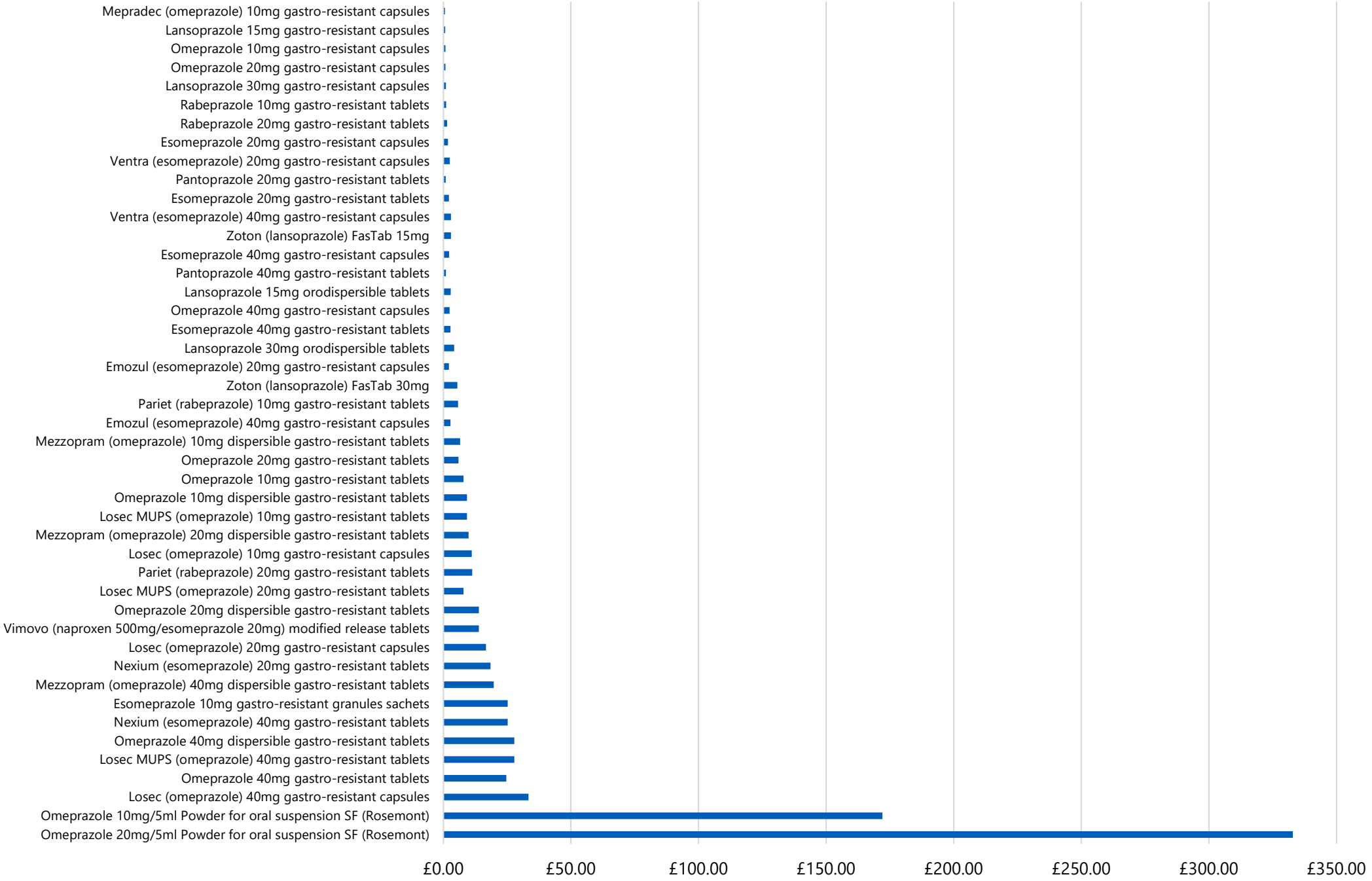
Patients suitable for 'as needed'/'on demand' PPI use may prefer to self care and purchase their PPI over the counter (OTC). Esomeprazole and pantoprazole are available for adults to purchase OTC for self care as either pharmacy only medicines (P) and as general sales list (GSL) medicines. The following preparations are available OTC:

Esomeprazole 20mg	Guardium acid reflux control 20mg gastro-resistant tablets (GSL) £6.99 for 7 tablets or £11.99 for 14 tablets
	Nexium Control® 20mg gastro-resistant hard capsules (GSL) £12.99 for 14 capsules)
Omeprazole 20mg	Pyrocalm Control 20mg gastro-resistant tablets (GSL) £6.99 for 7 tablets or £10.99 for 14 tablets.
Pantoprazole 20mg	Pantoloc Control® 20mg gastro-resistant tablets (P) £7.76 for 7 tablets or £13.37 for 14 tablets.
Ranitidine 75mg	Gavilast 75mg Tablets (GSL) £4.32 for 12 tablets.
	Ranicalm Tablets (GSL) £3.00 for 12 tablets.[57]

Costs and savings

There is a significant difference in cost between the different PPIs and the different formulations available. Chart 1 on the next page illustrates the cost differences for 28 days treatment (one daily dose) for generic and brand versions of PPIs.

Chart 1. 28 day cost for prescribing once daily generic and brand PPIs[1,58,59]



Generic omeprazole capsules and generic lansoprazole capsules are the preferred PPI options as they cost approximately £1.00 per month at a once daily dose. Generic esomeprazole 20mg capsules and pantoprazole 20mg tablets are under £3.00 per month at a once daily dose and are alternatives if omeprazole or lansoprazole are unsuitable. The brands, Nexium® (esomeprazole), Losec® capsules (omeprazole) and Losec® MUPS (omeprazole) are the non-preferred options, due to their comparatively high cost.

A licensed omeprazole powder for oral suspension has recently become available in two strengths, 2mg/ml and 4mg/ml, but it is costly compared to other formulations. A 20mg daily dose costs £332.92 for 28 days treatment using the 4mg/ml oral suspension.[1,60]

If prescribing of PPIs reduced by 30% through deprescribing or an appropriate switch to self care, this **could save £38.4 million in England and Wales over 12 months (NHSBSA Feb-April 2020). This equates to £61,933 per 100,000 patients.**

Prescribing the least costly PPIs in preference to the more costly brands, Nexium® (esomeprazole), Losec® capsules (omeprazole) and Losec® MUPS (omeprazole) **could save £17.3 million in England and Wales over 12 months (NHSBSA Feb-April 2020). This equates to £27,804 per 100,000 patients.**

Summary

- PPIs should only be prescribed when needed for a recognised indication and for an appropriate duration at the lowest effective dose.[2,3] The use of short courses, as-needed doses and self-treatment with antacid and/or alginate therapy should be first line unless there is a recognised indication for long-term PPI treatment.[3]
- All people prescribed PPIs should be reviewed between four and eight weeks after starting treatment. If they are prescribed for a defined short-term course, the person's symptoms should be reviewed when the course is completed, and the PPI discontinued if appropriate.[3] People prescribed long-term PPI therapy should be offered an annual review due to the adverse effects of PPIs. During the review people should be encouraged to try stepping down PPI therapy to the lowest dose needed to control symptoms.[2,3]
- There is increasing evidence that long-term PPI use is associated with an increased risk of adverse effects. Some of these adverse effects, such as fractures and *Clostridium difficile* infection, are themselves associated with considerable morbidity and mortality, as well as high treatment costs. Older people may be more susceptible to the adverse effects of long-term PPI use.[3] Caution is required in the elderly and in patients with other risk factors for *C. difficile* infection or bone fractures.[14]
- PPIs other than omeprazole or esomeprazole should be considered in patients who are taking clopidogrel. Other gastrointestinal therapy such as H_2RAs (except cimetidine) or antacids may be more suitable.[41]
- If a person is prescribed an NSAID, anticoagulant, antiplatelet, corticosteroid or SSRI and is considered at high risk of GI adverse effects due to the risk factors, consider prescribing an appropriate PPI as gastroprotection if the benefits outweigh the risks.[43,45,48,49,51] If the medication that requires gastroprotection is stopped, then the PPI should be stopped too if this was the only indication for prescribing.

References

1. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. Available at bnf.nice.org.uk/ Accessed 08/04/19.
2. NICE. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Clinical Guideline [CG184]. Published September 2014, last updated 18 October 2019. https://www.nice.org.uk/guidance/cg184
3. All Wales Medicines Strategy Group. Safe Use of Proton Pump Inhibitors. February 2018. www.awmsg.org/docs/awmsg/medman/Safe%20Use%20of%20Proton%20Pump%20Inhibitors.pdf

4. Marks DJB. Time to halt the overprescribing of proton pump inhibitors. Clinical Pharmacist 2016; 8(8) online | DOI: 10.1211/CP.2016.20201548. https://www.pharmaceutical-journal.com/opinion/insight/time-to-halt-the-overprescribing-of-proton-pump-inhibitors/20201548.article?firstPass=false
5. Clinical Knowledge Summaries. Dyspepsia - proven GORD. Last revised in April 2017. https://cks.nice.org.uk/dyspepsia-proven-gord
6. Clinical Knowledge Summaries. Dyspepsia - unidentified cause. Last revised in October 2018. https://cks.nice.org.uk/dyspepsia-unidentified-cause
7. NICE guideline on Suspected cancer: recognition and referral [NG12] (Published 23 June 2015, last updated 26 July 2017) https://www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer#upper-gastrointestinal-tract-cancers
8. NICE. Osteoarthritis: care and management. Clinical guideline [CG177]. Published February 2014. https://www.nice.org.uk/guidance/cg177
9. NICE. Rheumatoid arthritis in adults: management. Clinical guideline [CG100]. Published July 2018. https://www.nice.org.uk/guidance/ng100
10. NICE. Low back pain and sciatica in over 16s: assessment and management. Clinical guideline [CG59]. Published November 2016. https://www.nice.org.uk/guidance/ng59
11. NICE. Spondyloarthritis in over 16s: diagnosis and management. Clinical guideline [CG65]. Published June 2017. https://www.nice.org.uk/guidance/ng65
12. NICE. Non-steroidal anti-inflammatory drugs. Key therapeutic topic [KTT13]. Published June 2015. https://www.nice.org.uk/advice/ktt13/resources/nonsteroidal-antiinflammatory-drugs-pdf-58757951055301
13. NICE. Acute upper gastrointestinal bleeding in over 16s: management. Clinical guideline [CG141]. Published June 2012. https://www.nice.org.uk/guidance/cg141
14. Centre for Medicines Optimisation. NPC Archive Item: Increased risk of C difficile infections and of fractures: two more good reasons to review PPI prescribing. June 2010. https://www.centreformedicinesoptimisation.co.uk/increased-risk-of-c-difficile-infections-and-of-fractures-two-more-good-reasons-to-review-ppi-prescribing/
15. UK Medicines Information (UKMi). Clostridium difficile infection – is use of proton pump inhibitors a risk factor? Q&A 244.3. November 2015. https://www.sps.nhs.uk/articles/clostridium-difficile-infection-is-use-of-proton-pump-inhibitors-a-risk-factor-2/
16. Proton pump inhibitors in long-term use: increased risk of fracture. Drug Safety Update 2012; 5(9): A2. https://www.gov.uk/drug-safety-update/proton-pump-inhibitors-in-long-term-use-increased-risk-of-fracture
17. Zhou B, Huang Y, Li H, et al. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016; 27(1): 339-47. https://www.ncbi.nlm.nih.gov/pubmed/26462494
18. Nassar Y, Richter, S. Proton-pump Inhibitor Use and Fracture Risk: An Updated Systematic Review and Meta-analysis. J Bone Metab 2018; 25(3): 141–15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6135649/
19. Finnigan NA, Bashir K. Allergic Interstitial Nephritis (AIN). Updated 18 March 2020. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. https://www.ncbi.nlm.nih.gov/books/NBK482323/
20. Woods D, Fonteles MM. Interstitial nephritis caused by PPIs. The Pharmaceutical Journal 2013; 290 | DOI: 10.1211/PJ.2013.11117189 https://www.pharmaceutical-journal.com/learning/learning-article/interstitial-nephritis-caused-by-ppis/11117189.article?firstPass=false
21. Ambizas EM, Etzel JV. Proton Pump Inhibitors: Considerations with Long-Term Use. US Pharm 2017; 42(7): 4-7. https://www.uspharmacist.com/article/proton-pump-inhibitors-considerations-with-longterm-use

22. Lazarus B et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med 2016; 176: 238–46 https://pubmed.ncbi.nlm.nih.gov/26752337/
23. European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC): minutes of the meeting 9-12 January 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2017/04/WC500225782.pdf
24. Xie Y, Bowe B, Li TT et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney International 2017. http://www.sciencedirect.com/science/article/pii/S0085253817300054
25. Xie Y, Bowe B, Li T, et al. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017; 7: e015735. doi:10.1136/bmjopen-2016-015735.
26. Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. Alimentary Pharmacology and Therapeutics 2010; 31(11): 1165-1177. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2036.2010.04284.x
27. de Jager CPC, Wever PC, Gemen EFA, et al. Proton pump inhibitor therapy predisposes to community-acquired Streptococcus pneumoniae pneumonia. Alimentary Pharmacology and Therapeutics 2012; 36(10): 941-949. https://onlinelibrary.wiley.com/doi/full/10.1111/apt.12069
28. Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. British Medical Journal 2016; 355: i5813. https://www.bmj.com/content/bmj/355/bmj.i5813.full.pdf
29. Masclee GMC, Sturkenboom MCJM, Kuipers EJ. A benefit-risk assessment of the use of proton pump inhibitors in the elderly. Drugs Aging 2014;31(4):263- 282. http://link.springer.com/article/10.1007/s40266-014-0166-4
30. Fine MJ, Smith MA, Carson CA et al. Review: prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. Journal of the American Medical Association 1996;275(2):134-141. https://www.ncbi.nlm.nih.gov/pubmed/8531309
31. Proton pump inhibitors in long-term use: reports of hypomagnesaemia. Drug Safety Update 2012; 5(9): A1. https://www.gov.uk/drug-safety-update/proton-pump-inhibitors-in-long-term-use-reports-of-hypomagnesaemia
32. Prescribing PPIs. Drug and Therapeutics Bulletin 2017; 55 (10): 117-120. https://bmjopen.bmj.com/content/7/6/e015735
33. Lam JR, Schneider JL, Zhao W et al. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. Journal of the American Medical Association 2013;310(22):2435-2442. http://jamanetwork.com/journals/jama/fullarticle/1788456
34. Welsh Medicines Resource Centre. Bulletin: Proton pump inhibitors. 2015. https://www.wemerec.org/Documents/Bulletins/PPIBulletinOnline.pdf
35. Proton pump inhibitors: very low risk of subacute cutaneous lupus erythematosus. Drug Safety Update 2015; 9(2): 1. https://www.gov.uk/drug-safety-update/proton-pump-inhibitors-very-low-risk-of-subacute-cutaneous-lupus-erythematosus
36. Mayor S. People taking proton pump inhibitors may have increased risk of myocardial infarction, study shows. BMJ 2015; 350: h3220. https://www.bmj.com/content/350/bmj.h3220
37. Van Soest EM, Van Rossum LGM, Dieleman JP et al. Proton pump inhibitors and the risk of colorectal cancer. American Journal of Gastroenterology 2008;103(4):966-973. http://search.proquest.com/openview/69a8c9fc1aebf7fc7652100107545335/1.pdf?pq-origsite=gscholar
38. Cheung KS, Chan EW, Wong AY, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2018; 67: 28-35.2017. https://gut.bmj.com/content/67/1/28
39. Gomm W et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol 2016; 73: 410–6.

40. Goldstein FC et al. Proton pump inhibitors and risk of mild cognitive impairment and dementia. J Am Geriatr Soc 2017; DOI:10.1111/jgs.14956
41. Clopidogrel and proton pump inhibitors: interaction—updated advice. Drug Safety Update 2010; 3(9): 4. https://www.gov.uk/drug-safety-update/clopidogrel-and-proton-pump-inhibitors-interaction-updated-advice
42. Elliott R CE, Campbell F, Jankovic D, et al. Prevalence and economic burden of medication errors in the NHS in England. Economic Evaluation of Health & Care Interventions (EEPRU). 2018. http://www.eepru.org.uk/wpcontent/uploads/2018/02/medication-error-report-revised-final.2-22022018.pdf
43. Clinical Knowledge Summaries. NSAIDs - prescribing issues. Last revised August 2019. https://cks.nice.org.uk/nsaids-prescribing-issues
44. Li L, Geraghty OC, Mehta Z, et al. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017; 390(10093): 490-499. https://www.ncbi.nlm.nih.gov/pubmed/28622955
45. Clinical Knowledge Summaries. Antiplatelet treatment. Last revised September 2018. https://cks.nice.org.uk/antiplatelet-treatment
46. Swift D. PPIs Cut Upper GI Bleeds From Anticoagulants. MedPage Today. December 2018. https://www.medpagetoday.com/cardiology/prevention/76810
47. Ray WA, Chung CP, Murray KT et al. Association of Oral Anticoagulants and Proton Pump Inhibitor Co-therapy With Hospitalization for Upper Gastrointestinal Tract Bleeding. JAMA 2018; 320(21): 2221-2230. https://jamanetwork.com/journals/jama/article-abstract/2717474
48. Heidbuchel, H, Verhamme P, Alings, M et al. (2015) Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 17(10), 1467-1507 https://academic.oup.com/europace/article/17/10/1467/2467018
49. Clinical Knowledge Summaries. Corticosteroids – oral. Last revised March 2020. https://cks.nice.org.uk/corticosteroids-oral
50. UK Medicines Information (UKMi). What is the risk of gastrointestinal bleeding associated with selective serotonin reuptake inhibitors (SSRIs)? Published 18 March 2015, last updated 17 October 2019. https://www.sps.nhs.uk/articles/what-is-the-risk-of-gastrointestinal-bleeding-associated-with-selective-serotonin-reuptake-inhibitors-ssris/
51. NICE. Depression in adults: recognition and management. Clinical Guideline [CG90]. Published October 2009. https://www.nice.org.uk/guidance/cg90
52. Digestive Health Foundation. Clinical update: Gastrooesophageal reflux disease in adults. Sydney: Gastroenterological Society of Australia, 2011. [Online] https://www.gesa.org.au/resources/clinical-guidelines-and-updates/gastro-oesophageal-reflux-disease/
53. Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. Canadian Family Physician 2017; 63(5): 354-364. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5429051/
54. Reiner C, Søndergaard B, Hilsted L et al. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. Gastroenterology 2009;137(1):80-87. DOI:https://doi.org/10.1053/j.gastro.2009.03.058
55. MedicinesWise News. 2015. https://www.nps.org.au/news/proton-pump-inhibitors-too-much-of-a-good-thing
56. Scottish Government Polypharmacy Model of Care Group. Polypharmacy Guidance, Realistic Prescribing 3rd Edition, 2018. Scottish Government. https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/09/Polypharmacy-Guidance-2018.pdf
57. PAGB. OTC Directory online. https://www.otcdirectory.co.uk/pagb Accessed 01/06/2020.

58. NHS Business Services Authority. Drug Tariff. July 2020. www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
59. C+D Data. Accessed 03/07/20. http://www.cddata.co.uk/homesearch
60. Summaries of Product Characteristics - Omeprazole 2mg/ml and 4mg/ml, Powder for Oral Suspension. Rosemont Pharmaceuticals Limited. Date of revision of the text 1 October 2019. www.medicines.org.uk

Additional PrescQIPP resources

 Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-267-ppis-long-term-safety-and-gastroprotection/
 Implementation tools	
 Data pack	https://pdata.uk/#/views/B267_PPIslongtermsafetyandgastroprotection/FrontPage?:iid=1

Information compiled by Sarah Clarke, PrescQIPP CIC, July 2020 and reviewed by Katie Smith and Sajida Khatri, PrescQIPP CIC August 2020. Non-subscriber publication August 2021.

This document represents the view of PrescQIPP CIC at the time of publication, which was arrived at after careful consideration of the referenced evidence, and in accordance with PrescQIPP's quality assurance framework.

The use and application of this guidance does not override the individual responsibility of health and social care professionals to make decisions appropriate to local need and the circumstances of individual patients (in consultation with the patient and/or guardian or carer). Terms and conditions