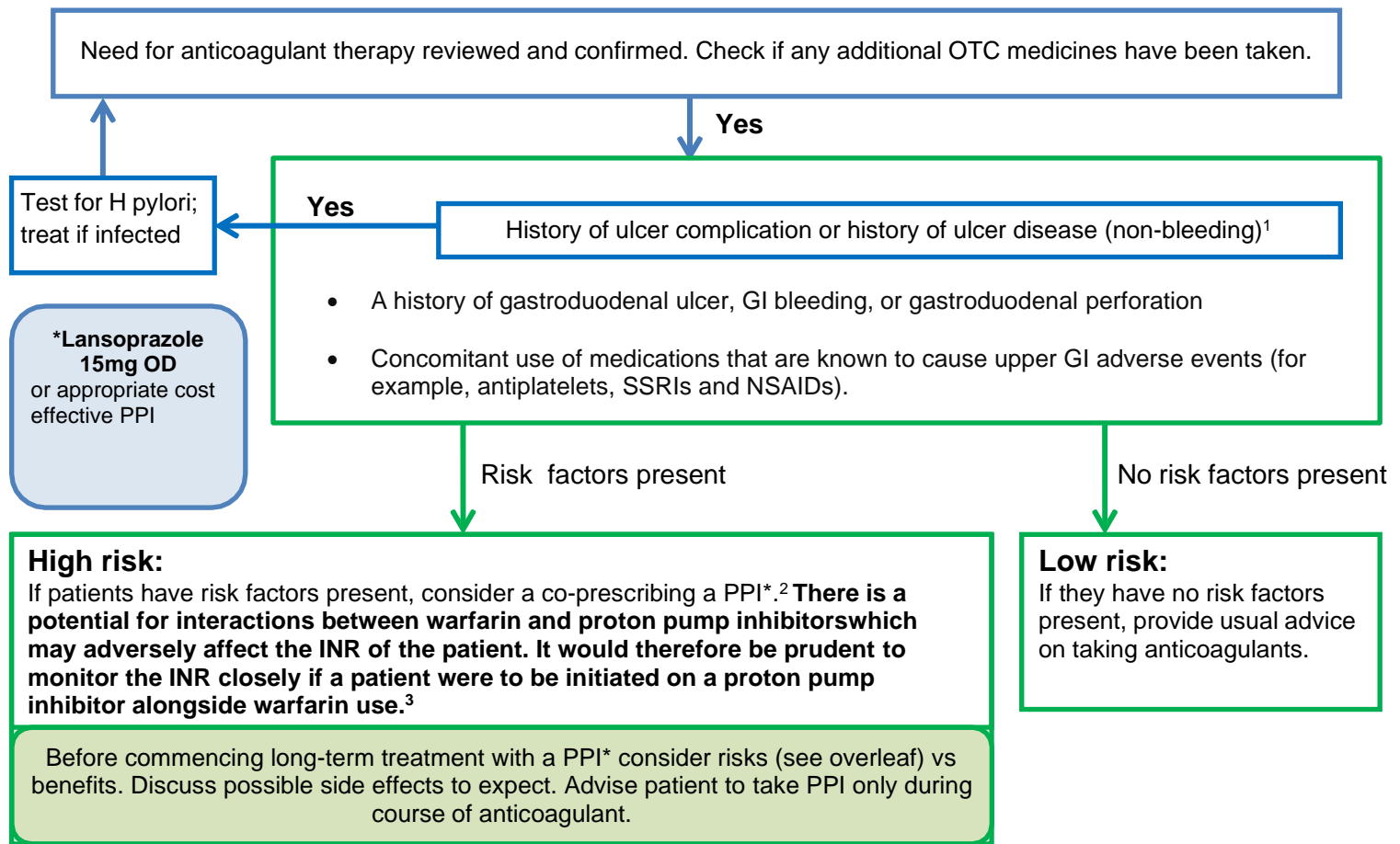


Proton Pump Inhibitors (PPIs) and anticoagulants

Advisory guidance on when to initiate a PPI for gastro-protection

This document is intended as advisory it does not replace clinical judgement which is assessed on a case-by-case basis. As PPIs have become widely used, evidence has started to emerge regarding their long-term safety and potential for adverse effects. Clinicians when considering prescribing long-term PPIs should consider if the risks (seeoverleaf) outweigh the benefits.

Particular concerns have been raised regarding the association between direct-acting oral anticoagulants (DOACs) and the risk of gastrointestinal bleeding (GIB); however, current findings are still inconclusive. Similar to DOACs patients who have started on warfarin should be assessed for their bleeding risk with regards to their past medical history and concomitant medications such as antiplatelets, SSRIs and NSAIDs which increase the risk of gastro-intestinal bleeding.



Monitoring and Review

Review long term PPI prescribing to reduce the potential risk of Clostridium difficile, bone fractures and to a lesser extent the risk of higher mortality in older patients, acute interstitial nephritis, community acquired pneumonia, hypomagnesaemia, vitamin B12 deficiency and rebound acid hypersecretion. There may be indications where the benefits of long-term PPI use outweigh the risks (e.g. Barrett's Oesophagus, oesophageal stricture) Assess on an individual basis and review regularly.

^{4,5} Use an H2 antagonist if a PPI is not appropriate.¹⁰

Key Points

- Ensure that appropriate patients are regularly reviewed and monitored for side effects during treatment.
- PPI should be stopped when the anticoagulant is stopped. For other indications of PPI usages ensure there is a set duration / review date.
- Avoid concomitant use of an NSAID/ antiplatelet/SSRI (if possible) – if this is essential, monitor closely.
- Before commencing treatment risks need to be discussed and explained as below and documented in the patient's notes.
- Monitor the INR closely when a proton pump inhibitor is either initiated or stopped alongside warfarin use.³

Known risks associated with long term PPI use

Adverse effects of PPIs are usually mild and reversible and include headache, diarrhoea, nausea, abdominal pain, constipation, dizziness and skin rashes.⁴ However long-term PPI treatment may be associated with uncommon, serious adverse effects such as:

Clostridium difficile infection (CDI)

As per NICE guidance [NG199](#), it is good prescribing practice to review the continuing need for existing proton pump inhibitor (PPI) treatment in people with suspected or confirmed *C. difficile* infection. Although some associations have been made between PPI use and the risk of *C. difficile* infection or recurrence, there is no definitive evidence of a causal or exacerbator effect. Also, no evidence from systematic reviews or randomised controlled trials was found to support stopping current PPI treatment. It was therefore concluded that suddenly stopping a PPI during an acute episode of infection may cause additional gastric symptoms. Additionally, some people will need ongoing gastroprotection for a clinical indication. However, they were aware that many people may be taking a PPI without a clear indication, so concluded that the use and need for a PPI should be reviewed.⁵

Osteoporotic fractures

As per [MHRA drug safety update](#) - observational studies suggest there may be a modest increase in the risk of hip, wrist or spine fracture associated with high dose and long term (>1 year) PPIs. Risk increases with a longer duration of PPI use in post-menopausal women with a history of smoking, which is known to inhibit calcium absorption. Smoking and PPI use may have a synergistic effect on fracture risk mediated by impaired calcium absorption. The Medicines and Healthcare products Regulatory Agency (MHRA) advice issued in April 2012 stated “There is recent epidemiological evidence of an increased risk of fracture with long-term use of PPIs. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium”.⁷

Hypomagnesaemia

The [MHRA](#) have warned of the risk of hypomagnesaemia following prolonged use of PPIs (>1 year). Serious manifestations of hypomagnesaemia include fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia. For patients expected to be on prolonged treatment, and especially for those who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during treatment.⁸

Community acquired Pneumonia

There is a small but significant increase in hospitalisation from pneumonia due to PPI exposure. It has been suggested that the greatest risk of pneumonia is within 48 hours of starting PPI therapy. This is inconsistent with bacterial overgrowth as a mechanism of colonisation. PPIs take 5 days to reach steady state but bacterial overgrowth due to PPI use would require substantially longer periods of exposure. GORD may itself be a risk factor for pneumonia (from stomach content aspiration) and is a confounding factor. No specific interventions are recommended in clinical practice.⁴

Rebound hypersecretion

PPI withdrawal may induce rebound acid hypersecretion. This could present as a worsening of symptoms that could be mistaken for disease relapse. However, due to weaknesses in the studies it cannot be concluded if symptoms are clinically important in patients or lead to reuptake of acid-suppressive medication.⁴

Acute interstitial nephritis (AIN):

A rare association has been reported between acute interstitial nephritis and PPIs. It can occur between several hours and four months following treatment with a PPI. The standard treatment involves early diagnosis, withdrawing the causative drug, administering steroids and clinical assessment.⁴

Very low risk of subacute cutaneous lupus erythematosus:

PPIs are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE), a non-scarring dermatosis that can develop in sun-exposed areas as per a [MHRA drug safety update](#). Consider stopping use of 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.⁹

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