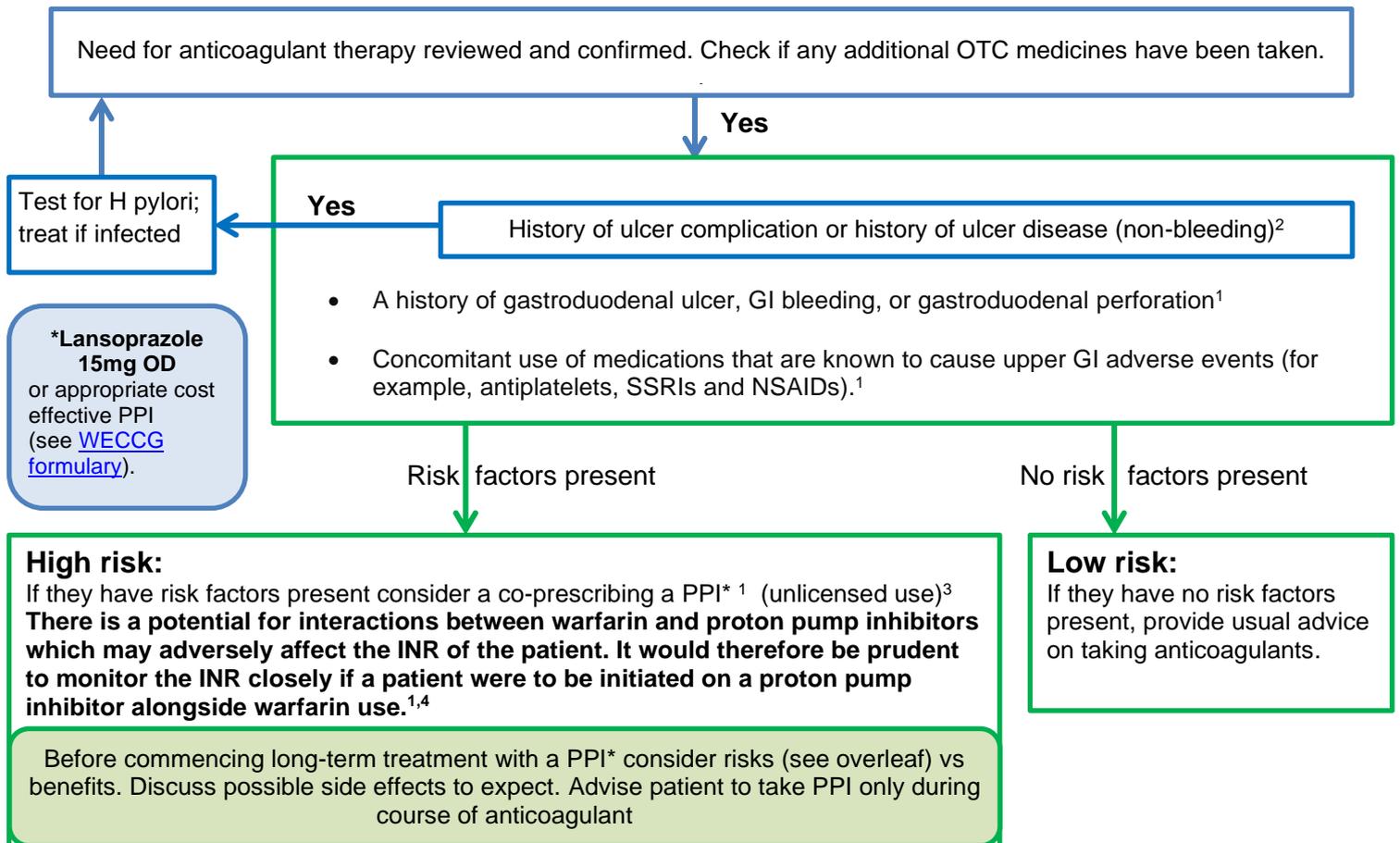


Proton Pump Inhibitors (PPIs) and anticoagulants

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 (see overleaf) outweigh the benefits.

Particular concerns have been raised regarding the association between non-vitamin K antagonist oral anticoagulants (NOACs) and the risk of gastrointestinal bleeding (GIB); however, current findings are still inconclusive. Similar to NOACs patient 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.¹



Test for H pylori; treat if infected

***Lansoprazole 15mg OD**
 or appropriate cost effective PPI (see [WECCG formulary](#)).

Need for anticoagulant therapy reviewed and confirmed. Check if any additional OTC medicines have been taken.

History of ulcer complication or history of ulcer disease (non-bleeding)²

Yes

- A history of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation¹
- Concomitant use of medications that are known to cause upper GI adverse events (for example, antiplatelets, SSRIs and NSAIDs).¹

↓ Risk factors present

↓ No risk factors present

High risk:
If they have risk factors present consider a co-prescribing a PPI*¹ (unlicensed use)³
There is a potential for interactions between warfarin and proton pump inhibitors which may adversely affect the INR of the patient. It would therefore be prudent to monitor the INR closely if a patient were to be initiated on a proton pump inhibitor alongside warfarin use.^{1,4}

Before commencing long-term treatment with a PPI* consider risks (see overleaf) vs benefits. Discuss possible side effects to expect. Advise patient to take PPI only during course of anticoagulant

Low risk:
If they have no risk factors present, provide usual advice on taking anticoagulants.

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.⁵ Offer Nizatidine if a PPI is not appropriate, at a dose of 150mg BD or 300mg OD^{10, 11} If Nizatidine unavailable use an alternative H2 antagonist

- 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 closely¹.
 - Before commencing treatment risks need to be discussed and explained as below and documented in the patient's notes.
 - Monitor the INR closely if a patient were to be initiated on a proton pump inhibitor alongside warfarin use^{1,4}

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.⁵ However long term PPI treatment may be associated with uncommon, serious adverse effects such as:

Clostridium difficile infection (CDI)

A study published in 2005 based on the UK General Practice Research Database (GPRD), found that people with CDI were about three times more likely to have been prescribed a PPI in the previous 3 months than people without CDI. Other studies found that hospital inpatients taking daily PPIs were over 70% more likely to develop CDI than non-users. Patients who received more frequent PPIs had more than a doubling of this risk.⁵ Public Health England guidance recommends that consideration be given to stopping or reviewing the need for PPIs in patients with or at high risk of CDI⁶ (antibiotic use, hospitalisation, advanced age & underlying morbidity and inflammatory bowel disease).

Osteoporotic fractures

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) PPIs⁷. 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 absorption⁵. 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.⁷

Community acquired Pneumonia

A small but significant increase in hospitalisation from pneumonia due to PPI exposure has been found. 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.⁵

Rebound hypersecretion

PPI withdrawal may induce rebound acid hypersecretion, which 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.⁵

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.⁵

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. 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.⁸

References

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Document history

Date	Guidance checked	information
07/01/2022	Medicine supply information	Ranitidine has been discontinued, Nizatidine is recommended as an alternative
07/01/2022	CG184 Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management	No new clinical update