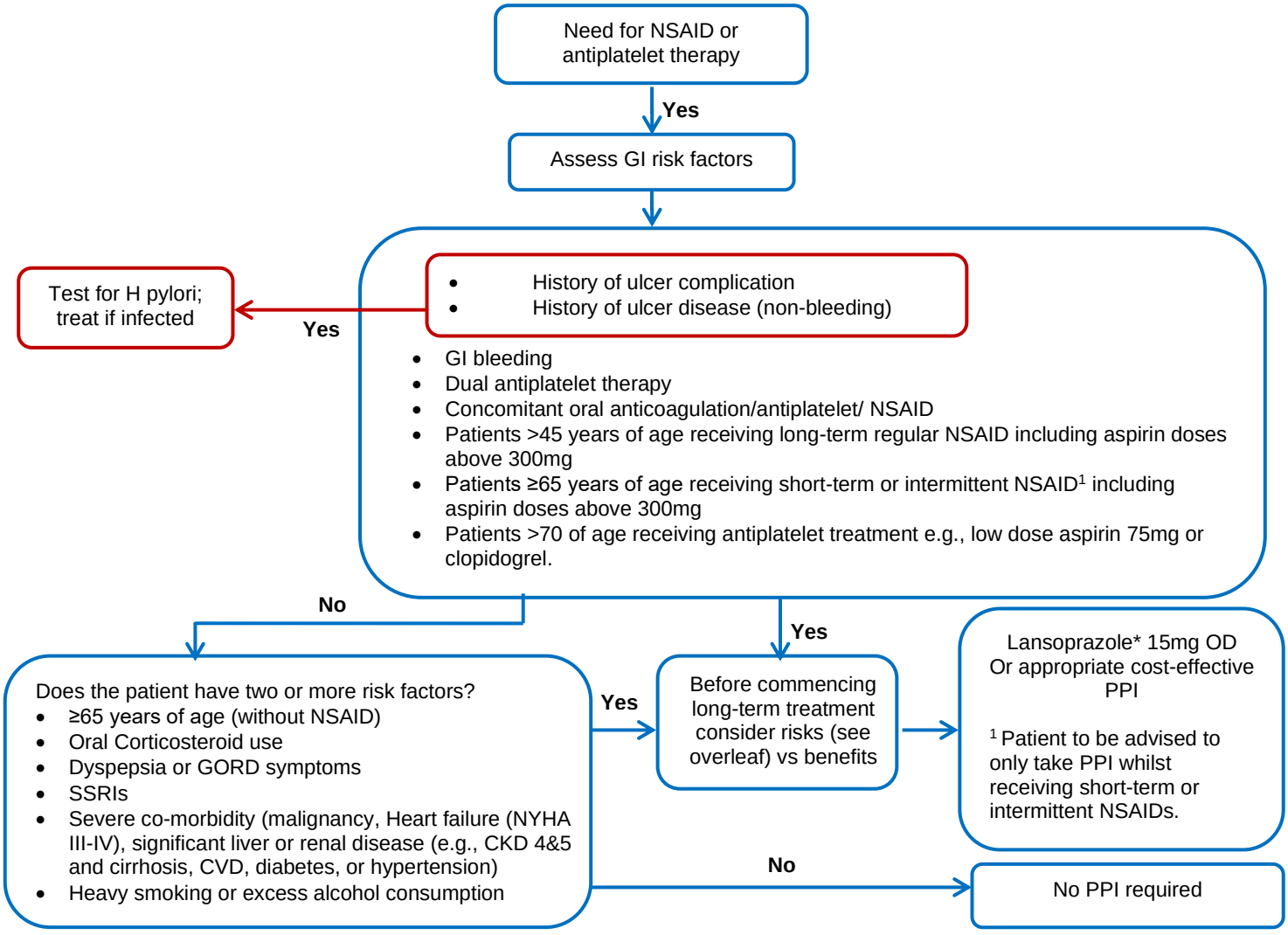
DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

Proton Pump Inhibitors
Advisory guidance on when to initiate a PPI with a NSAID (or antiplatelet) for gastro-protection

Where a NSAID is indicated and to reduce the risk of gastrointestinal adverse effects the **lowest effective dose for the shortest duration** of treatment should be used. 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 below) outweigh the benefits.



***To aid bioavailability of lansoprazole it should be taken at least 30 minutes before food. If this is difficult pantoprazole 20mg taken 1 hour before food is an alternative.

Key points

- Ensure that appropriate patients are monitored for side effects during treatment.
- PPI should be stopped when the NSAID/antiplatelet is stopped. For other indications of PPI usages ensure there is a set duration/ review date. Long term PPI use should be reviewed at least annually.
- Exercise caution in the elderly and in patients with other risk factors for *Clostridium difficile* infection or bone fractures.

Known risks associated with long term PPI use

Clostridium difficile infection (CDI)

Observational studies have found the risk of acquiring CDI is 2-3 times higher in PPI users than in non-users. PPI use during CDI treatment was associated with a 40% increased risk of recurrence. Public Health England guideline recommends that consideration be given to stopping or reviewing the need for PPIs in patients with or at high risk of CDI (antibiotic use, hospitalisation, older 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) PPIs. Risk increases with a longer duration of PPI use in elderly patients and 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."

Other adverse effects associated with PPI

Adverse effects of PPIs are usually mild and reversible; however, through case reports and observational studies (subject to bias and causation difficult to prove) long term PPI treatment *may* be associated with uncommon, serious adverse effects such as:

- **Hypomagnesaemia:** MHRA, 2012 have warned of the risk of hypomagnesaemia following long-term use of PPIs, which occurs most commonly after one year of PPI treatment. Serious manifestations- fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia- can occur, but may begin insidiously and may be overlooked. Routinely monitoring serum magnesium levels is not recommended but should be considered before prescribing long-term PPI to people concomitantly treated with drugs associated with hypomagnesaemia e.g., digoxin, diuretics.

- **Pneumonia**: There is conflicting evidence on an association between PPI use and an increased risk of pneumonia. Although there appears to be an increase in risk of developing community acquired pneumonia in patients who have recently started PPI therapy, there is a lack of evidence to show that this applies to patients on long-term treatment.

- **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.

- **Tubulo-interstitial nephritis (TIN):** A rare association has been reported between acute tubule-interstitial nephritis (TIN) and PPIs. It can occur between several hours and four months following treatment with a PPI. Patients should be educated about the symptoms of TIN, including nausea, vomiting, fatigue, fever, and haematuria. The standard treatment involves early diagnosis, withdrawing the causative drug, administering steroids and clinical assessment.

- **Very low risk of subacute cutaneous lupus erythematosus (Drug Safety Update – September 2015)**: PPIs are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE), a non-scarring dermatosis that can develop in sun-exposed areas.

References

1. NICE, Clinical Knowledge Summaries. Antiplatelet treatment: Scenario: Antiplatelet treatment for secondary prevention of cardiovascular disease (CVD). Last revised November 2022. Available at: https://cks.nice.org.uk/topics/antiplatelet-treatment/management/secondary-prevention-of-cvd/ (Accessed 09.02.23)
2. NICE, Clinical Knowledge Summaries. Dyspepsia - proven GORD. Last revised December 2022. Available at: https://cks.nice.org.uk/topics/dyspepsia-proven-gord/prescribing-information/proton-pump-inhibitors/ (Accessed 08.02.23)
3. NICE, Clinical Knowledge Summaries. NSAID – prescribing issues. Last revised April 2020. Available at: https://cks.nice.org.uk/topics/nsaids-prescribing-issues/ (Accessed 08.02.23)
4. MHRA. Proton pump inhibitors in long-term use: increased risk of fractures. Drug Safety Update 2012; 5 (9): A2. Available at: https://www.gov.uk/drug-safety-update/proton-pump-inhibitors-in-long-term-use-increased-risk-of-fracture (Accessed 08.02.23)
5. MHRA. Clopidogrel and proton pump inhibitors: interaction – updated advice. Drug Safety Update 2010; 3 (9): 4. (Accessed 08.02.23)
6. Abraham NS, Hlatky MA, Antman EM et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: A focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *J Am Coll Cardiol.* 2010, 122:2619–2633. Available at: https://www.ahajournals.org/doi/10.1161/CIR.0b013e318202f701 (Accessed 08.02.23)
7. All Wales Medicines Strategy Group, Safe Use of Proton Pump Inhibitors. February 2018. Available at: https://awttc.nhs.wales/files/guidelines-and-pils/safe-use-of-proton-pump-inhibitors-pdf/ (Accessed 08.02.23)
8. Revised PINCER Query Library 2015, Evidence-based summaries. PRIMIS and The University of Nottingham. Available at: https://www.nottingham.ac.uk/primis/documents/audit-docs/evidence-based-summaries-for-health-foundation-pincer-12-07-2018.pdf (Accessed 08.02.23)
9. Proton Pump Inhibitors (PPIs): Long term safety and gastroprotection. PrescQIPP Bulletin 267 (2). Last revised August 2020. Available at: https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f5085%2f267-ppis-long-term-safety-and-gastroprotection-20.pdf (Accessed 08.02.23)
10. Non-steroidal anti-inflammatory drugs (NSAIDs). PrescQIPP Bulletin 265 (2). Last revised July 2020. Available at: ttps://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f5055%2f265-nsaids-20.pdf (Accessed 08.02.23)
11. Prescribing PPIs DTB 2017; 55:117-120. Available at: https://dtb.bmj.com/content/55/10/117 (Accessed 08.02.23)

Further reading

WHO third Global Patient Safety Challenge: *Medication Without Harm*. Medication safety in High-risk Situations. https://www.who.int/initiatives/medication-without-harm

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