NICE National Institute for Health and Care Excellence

Surveillance proposal consultation document

2018 surveillance of gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (NICE guideline CG184)

Proposed surveillance decision

We propose to not update the NICE guideline on gastro-oesophageal reflux disease (GORD) and dyspepsia in adults.

We considered this guideline alongside the following related guidelines:

- Gastro-oesophageal reflux disease in children and young people: diagnosis and management (NICE guideline NG1)
- Acute upper gastrointestinal bleeding in over 16s: management (NICE guideline CG141)
- Barrett's oesophagus: ablative therapy (NICE guideline CG106)

Separate consultations on the surveillance decisions for the guidelines on acute upper gastrointestinal bleeding and GORD in children and young people are underway. See the webpages for each guideline to participate in consultation on these guidelines.

We propose to fully update the guideline on Barrett's oesophagus so we are not conducting public consultation on the surveillance decision for that guideline.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Overview of 2018 surveillance methods

NICE's surveillance team checked whether recommendations in GORD and dyspepsia in adults (NICE guideline CG184) remain up to date.

The surveillance process consisted of:

- Initial feedback from topic experts via a questionnaire.
- Input from stakeholders on known variations in practice and policy priorities.
- Literature searches to identify relevant evidence.

- Assessing the new evidence against current recommendations and deciding whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the decision with stakeholders (this document)
- Consideration of comments received during consultation and making any necessary changes to the decision.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

When considering the options for surveillance of this guideline, we noted that the existing evidence base showing the effectiveness of PPIs and H_2RAs was robust.

Additionally, in our initial evidence-gathering processes, we did not identify any new interventions for dyspepsia or GORD that were likely to impact on current recommendations.

Two areas appeared to need further investigation:

- Long-term safety of proton pump inhibitors (PPIs)
  - We searched for new evidence related to the long-term safety of PPIs. We found 43 studies in a search for systematic reviews published before 22 August 2018.
- *H pylori* eradication regimens.
  - For *H pylori* eradication regimens we checked a total of 3 yearly reports by the English surveillance programme for antimicrobial utilisation and resistance.

We also included 5 Cochrane reviews (one of which was included in the search for systematic reviews noted above) and 1 other study identified in this surveillance review. Overall we included 48 studies from all sources.

The focus on PPI safety data and *H pylori* resistance patterns means that full literature searching was not conducted for sections of the guideline including: the community pharmacist, common elements of care, referral guidance for endoscopy, reviewing patient care, laparoscopic fundoplication, referral to a specialist service, and surveillance for people with Barrett's oesophagus.

See appendix A: data summary tables below for details of all evidence considered, and references.

Effectiveness of PPIs and H_2RAs

The findings of two systematic reviews supported the view that evidence of effectiveness for these drugs is robust.

A recent systematic review (Scally 2018) assessed PPIs, histamine 2 receptor antagonists (H_2RAs), and prostaglandins in a range of indications. These drug classes were considered together as 'gastroprotectant drugs'. Overall, 849 trials were included, 580 of which assessed prevention of ulcers; 233 assessed healing; and 36 assessed treatment of acute upper gastrointestinal bleeding. The median duration of treatment was 1.4 months. In prevention trials, gastroprotectants reduced development of endoscopic and symptomatic ulcers and upper gastrointestinal bleeding. There was no significant reduction in mortality. Reductions in upper gastrointestinal bleeding had a larger effect size with PPIs than prostaglandin analogues or H_2RAs. Prevention of gastrointestinal bleeding was not affected by use of non-steroidal anti-inflammatory drugs. In healing trials, gastroprotectants increased endoscopic ulcer healing and PPIs were more effective than prostaglandin analogues or H_2RAs. The authors noted that the results may have overestimated the size of the effect because of small study bias (median n=78). This study shows that PPIs and H_2RAs are effective for a range of indications.

A Cochrane review (Pinto-Sanchez 2017), concluded that PPIs are effective for the treatment of functional dyspepsia, independent of the dose and duration of treatment compared with placebo. Additionally, PPIs may be slightly more effective than prokinetics. There appeared to be no benefit of adding prokinetics to proton pump inhibitor treatment. The findings support current guidance on PPI use for functional dyspepsia. If symptoms continue or recur after initial treatment, a PPI or H_2RA should be taken at the lowest dose possible to control symptoms.

Long-term safety of PPIs

The MHRA has issued several drug safety updates covering the following risks:

- interaction of omeprazole or esomeprazole with clopidogrel (April 2010)
- hypomagnesaemia (April 2012)
- fracture (April 2012) and
- subacute cutaneous lupus erythematosus (September 2015).

Topic expert feedback indicated ongoing concerns about the long-term safety of PPIs.

We searched for new evidence in this area. We restricted the search to systematic reviews to improve the robustness of the data and to obtain a manageable set of highly relevant search results. We discussed this approach with the MHRA, and shared our findings for its consideration.

The summary of products characteristics (SPC) was checked for each proton pump inhibitor to determine whether the identified adverse events were already recognised. Appendix A below summarises the findings.

Overall, we identified 43 systematic reviews of adverse events with use of PPIs or H_2RAs. Studies identified in searches were summarised from the information presented in their abstracts. This approach allowed consideration of the overall direction of effect observed in studies, and whether the effect was consistent across studies.

Cardiovascular adverse events

Several of the SPCs for PPIs licensed in the UK (esomeprazole, lansoprazole and omeprazole) recognise an interaction with clopidogrel whereas the SPCs for pantoprazole and rabeprazole do not. None of the SPCs recognises a risk of cardiovascular events in people not on clopidogrel. We identified 14 systematic reviews reporting on cardiovascular outcomes in people taking PPIs. Evidence consistently supporting an association between taking the combination of clopidogrel plus a PPI and adverse cardiovascular events. Evidence of a possible association between PPIs and cardiovascular events in people who are not taking clopidogrel was also identified. A somewhat smaller body of evidence suggests there may be no adverse cardiovascular risk associated with taking PPIs plus aspirin.

Infection

The SPCs recognise an increased risk of gastrointestinal infections with PPIs. We found 12 systematic reviews addressing infection. The evidence consistently suggests increased occurrence of community-acquired pneumonia and infection with *Clostridium difficile* in people taking PPIs. PPIs may also increase the occurrence of spontaneous bacterial peritonitis in people with cirrhosis. One study suggested an association with H_2RAs and spontaneous bacterial peritonitis in people with cirrhosis. One study suggested an association between PPI use and small intestinal bacterial overgrowth.

Kidney disease

Kidney disease, particularly interstitial nephritis is recognised in all SPCs as a very rare adverse event. We found 7 systematic reviews that consistently suggested that PPIs are associated with adverse effects on the kidney. Studies reporting on H_2RAs suggested that there may be no association with adverse effects on the kidney.

Cancer and precancerous conditions

All SPCs for PPIs recognise a risk of benign fundic gland polyps. We found 5 systematic reviews in this area. The evidence suggests there may be an association between taking PPIs and fundic gland polyps, enterochromaffin-like hyperplasia and gastric cancer. However, *H pylori* infection may have a role, which may be a confounding factor. No association was seen between PPIs and colorectal cancer or corporal atrophy or metaplasia.

Fracture

Fracture risks are recognised in SPCs for all PPIs. Four systematic reviews consistently found an association between PPIs and fractures, including spine and hip fractures.

Other adverse effects

Gastric atrophy was identified as an adverse event in one systematic review. The SPC for rabeprazole notes no increase in atrophic gastritis with up to 8 weeks of treatment. However, the SPC for omeprazole notes that atrophic gastritis is associated with *H pylori* infection. This may be an important confounding factor to consider against the finding of increased gastric atrophy, particularly if *H pylori* status was unknown for the populations informing the systematic review.

All SPCs recognise that dose adjustment is necessary for people with severe liver disease, which is consistent with the finding in one systematic review of hepatic encephalopathy in people with liver dysfunction who were taking a PPI. SPCs for PPIs also already recognise the risk of hypomagnesaemia, which was seen in 2 systematic reviews.

Impact on the guideline

The guideline recommends PPIs in several sections of the guideline:

- Interventions for uninvestigated dyspepsia
- Interventions for gastro-oesophageal reflux disease
- Interventions for peptic ulcer disease
- Interventions for functional dyspepsia
- *H pylori* testing and eradication.

The guideline additionally recommends an annual review for people who need long-term management of dyspepsia symptoms, and encouraging them to try stepping down or stopping treatment (unless there is an underlying condition or co-medication that needs continuing treatment).

The data on PPI safety are from retrospective observational studies and so the observed effects may be influenced by both recognised and unrecognised confounding factors that are often not completely accounted for in analyses. Recognised confounding factors include adherence to the drug being studied, concomitant use of other drugs, smoking status, and presence of obesity or diabetes. These studies may also be affected by indication bias, in which the adverse event may be associated with the underlying condition, and by protopathic bias, in which treatments are taken for an early manifestation of an undiagnosed condition. Overall, the evidence was considered to be insufficient to affect current recommendations to use proton pump inhibitors, which are an effective treatment for conditions needing gastric acid suppression.

We have shared these findings with the MHRA, which will consider this evidence in their ongoing monitoring of the safety of medicines, alongside data from other sources such as case reports, non-clinical studies, data from clinical trials, and other published and unpublished data. If any SPCs are updated based on the new evidence, we will again consider the impact on the guideline.

H pylori eradication

The guideline currently recommends first-and second-line regimens for *H pylori* eradication. To reduce the development of antibiotic resistance, different regimens are recommended depending on the person's previous exposure to antibiotics. Changes in resistance patterns have an important role in determining whether these antimicrobial agents remain appropriate. However, we found no information on *H pylori* resistance patterns in the UK.

We checked reports from the English surveillance programme for antimicrobial utilisation and resistance for any information that could impact on the currently recommended antimicrobial regimens for *H pylori* eradication. The 2017 report covered data for the years 2012 to 2016, but did not mention treatment of *H pylori*.

The 2016 report had no information on *H pylori* resistance; however, it highlighted a UK-based study that surveyed clinical pathology accreditation laboratories in England. This indicated that few laboratories routinely perform culture and antibiotic sensitivity testing for *H pylori*. The 2015 report, which covered 2010 to 2014 also had no information on *H pylori* resistance.

Public Health England (PHE) has indicated that there is increasing anecdotal evidence of difficult-to-treat *H pylori* infections. However, without laboratory evidence of emerging resistance patterns, it is not possible to update the guideline in this area at this time.

We are also aware that a preparation of tri-potassium di-citrato bismuth suitable for use in the *H pylori* eradication regimen recommended in the guideline is no longer available in the UK. Several preparations of bismuth subsalicylate remain available for treating symptoms of dyspepsia, although none are specifically licensed for *H pylori* eradication.

Impact on the guideline

Overall, we identified no need to update current recommendations on *H pylori* eradication.

Cochrane reviews

We searched for new Cochrane reviews related to the whole guideline. We found 5 relevant Cochrane reviews published before 2 May 2018.

One Cochrane review (Pinto-Sanchez 2017) was considered alongside the evidence on PPI effectiveness above. One Cochrane review (Song 2014) was considered alongside the evidence on PPI safety (see Appendix A).

Lan (2014) assessed acupuncture in dyspepsia, concluding 'The body of evidence identified cannot yet permit a robust conclusion regarding the efficacy and safety of acupuncture for functional dyspepsia'. The guideline does not cover acupuncture for treating dyspepsia, and evidence is currently insufficient to support recommendation development in this area.

One Cochrane review (Boghossian 2017) concluded that in people with mild GORD, on-demand deprescribing may lead to an increase in symptoms such as dyspepsia or regurgitation as well as a reduction in pill burden. Participant satisfaction was lower with on-demand PPIs. This study highlights the difficulties that may be faced when following recommendations to encourage patients on long-term treatment to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment). However, the guideline committee noted that periodic medication review is an important component of good patient care. Additionally, dyspepsia was considered to have a relapsing and remitting nature, so taking medication would not be necessary during periods of relapse. Thus, the current recommendations remain valid despite the apparently conflicting evidence from this Cochrane review.

The final identified Cochrane review (Garg 2015) found 'considerable uncertainty' in the balance of benefits versus harms of laparoscopic fundoplication compared with long-term treatment with PPIs. Because of a lack of alternative options, this finding is unlikely to impact on current guidance to offer fundoplication to people with confirmed reflux who do not want or cannot tolerate long-term treatment with PPIs.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 1 study was assessed as having the potential to change recommendations; therefore we plan to check the publication status regularly, and evaluate the impact of the results on current recommendations as quickly as possible. This study is:

- *Helicobacter* eradication to prevent ulcer bleeding in aspirin users: a large simple randomised controlled trial (HEAT).

Intelligence gathered during surveillance

Views of topic experts

Topic expert feedback indicated ongoing concerns about the long-term safety of PPIs.

Related NICE guidance

The issue of proton pump inhibitor safety is also relevant to the other guidelines undergoing surveillance alongside this guideline. However, there is no immediate impact on these other guidelines.

Gastro-oesophageal reflux disease in children and young people: diagnosis and management (NICE NG1).

Acute upper gastrointestinal bleeding in over 16s: management (NICE CG141)

Barrett's oesophagus: ablative therapy (NICE CG106)

Other sources of information

We considered all other correspondence received since the guideline was published. We received notification that a preparation of bismuth used for *H pylori* eradication was no longer available in the UK, as noted in the section on *H pylori* eradication above.

Views of stakeholders

We are consulting on this surveillance decision because we propose to not update this guideline.

In this consultation, in addition to expressing views on the proposal we request that stakeholders highlight:

- any large observational studies of PPI safety that would be missed by the searches, for example:
  - studies published after the search dates for the included systematic reviews
  - studies addressing adverse events that were not the focus of existing systematic reviews
- any information on *H pylori* resistance patterns in the UK
- any information suggesting a need to update a section of the guideline that was not a focus of this surveillance.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all evidence and other intelligence and the impact on current recommendations, we propose that no update is necessary.

Appendix A: data summary tables

2018 surveillance of Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (2014) NICE guideline CG184

The following tables summarise the outcomes and direction of effect in systematic reviews reporting adverse effects of proton pump inhibitors (PPIs).

Table 1 Cardiovascular adverse events

Study	Included data	Outcome	Result
Hu 2018 (1)	12 studies; n=33,492	Major cardiovascular events Stent thrombosis Revascularisation	More common with PPI use in people taking clopidogrel plus aspirin
Hu 2018 (1)	12 studies; n=33,492	Myocardial infarction Cardiogenic death All-cause mortality	No significant association with PPI use in people taking clopidogrel plus aspirin
Malhotra 2018 (2)	22 studies; 131,714	Ischaemic stroke Stroke or myocardial infarction or cardiovasacular death Myocardial infarction	More common with PPI use in people on thienopyridines Similar results seen in adjusted analyses for all outcomes except for myocardial infarction, which showed no significant association with PPI use
Shiraev 2018 (3)	5 studies; n= 376,873	All-cause mortality Major cardiovascular events	More common with PPI use
Al-Shammari 2017 (4)	5 studies; n=743,427	Cardiovascular events	More common with PPI use
Bundhun 2017 (5)	11 studies; n=55,494	Short-term mortality and target vessel revascularisation	More common with PPI use in people taking clopidogrel
Bundhun 2017 (5)	11 studies; n=55,494	Long-term major adverse cardiac events, myocardial infarction, stent thrombosis, and target vessel revascularisation	More common with PPI use in people taking clopidogrel
Bundhun 2017 (5)	11 studies; n=55,494	Long-term mortality	No significant association with PPI use in people taking clopidogrel †
Dahal 2017 (6)	9 studies; n=6,382	All-cause mortality Cardiovascular mortality Non-fatal myocardial infarction or ischemia Ischaemic stroke or transient ischaemic attack	No significant association with PPI use in people taking aspirin

Sun 2017 (7)	17 studies; n=7,540	Cardiovascular events	More common with PPI use Similar results seen for subgroups of people taking omeprazole and for long-term treatment
Zuhri 2017 (8)	3 studies‡; n=3,847	Mortality Cardiovascular events Cerebrovascular events Non-fatal serious adverse events Drug-related adverse events	No significant association with esomeprazole use in people taking aspirin
Niu 2016 (9)	–†	Major adverse cardiovascular events	More common with PPI use in people taking clopidogrel Similar results seen in subgroup analysis of CYP2C19 'rapid metabolisers', but no significant association was seen in 'decreased metabolisers'. Similar results seen for individual PPIs, except for rabeprazole, which showed no significant association
Serbin 2016 (10)	12 studies; n=50,277	Major adverse cardiovascular event Myocardial infarction Stroke	More common with PPI use in people taking clopidogrel
Serbin 2016 (10)	12 studies; n=50,277	Stent thrombosis Cardiovascular death Major bleeding Major bleeding	No significant association with PPI use in people taking clopidogrel
Singh 2016 (11)	9 studies‡; n=6,382	All-cause mortality Cardiovascular mortality Non-fatal myocardial infarction or ischaemia Ischaemia stroke or transient ischaemic attack	No significant association with PPI use in people taking aspirin
Sherwood 2015 (12)	6 studies*	Adverse cardiovascular events	More common with pantoprazole use More common with lanzoprazole use More common with esomeprazole use
Sherwood 2015 (12)	6 studies*	Adverse cardiovascular events	No significant association with omeprazole use
Han 2013 (13)	14 studies; n=34,967	Restenosis Recurrent acute coronary syndrome All-cause mortality	More common with PPI use in people taking clopidogrel
Han 2013 (13)	14 studies; n=34,967	Revascularisation Cardiovascular death Stent thrombosis	No significant association with PPI use in people taking clopidogrel
Kwok 2013 (14)	23 studies; n=222,311	Cardiovascular events	More common with PPI use in people taking clopidogrel†
Kwok 2013 (14)	23 studies; n=222,311	Cardiovascular events	More common with PPI use

PPI = proton pump inhibitor. H_2RA = histamine 2 receptor antagonist.

* Number of participants not reported in the abstract. † Data not reported in the abstract. ‡ Included randomised controlled trials only – not all abstracts specified the type of included studies, so some other studies may also have included this study type only.

Table 2 Infections

Study	Included data	Outcome	Result
Cao 2018 (15)	50 studies*	Hospital-acquired Clostridium difficile infection Hospital-acquired Clostridium difficile infection in general wards	More common with PPI use
Cao 2018 (15)	50 studies*	Hospital-acquired Clostridium difficile infection in intensive care units Community-acquired Clostridium difficile infection	No significant association with PPI use
Islam 2018 (16)	28 studies*	Community-acquired pneumonia	More common with PPI use
Oshima 2018 (17)	67 studies*	Clostridium difficile infection	More common with PPI use
Oshima 2018 (17)	67 studies*	Recurrent clostridium difficile infection	More common with PPI use
Su 2018 (18)	19 studies; n=7,055	Small intestine bacterial overgrowth	More common with PPI use
Tariq 2017 (19)	16 studies; n=1525	Recurrent Clostridium difficile infection	More common with PPI use Similar results were seen studies that adjusted for age and other potential confounders
Trifan 2017 (19)	56 studies; n=356,683	Clostridium difficile infection	More common with PPI use The association remained in sensitivity analyses (type of study, adjustment, single centre or multicentre study, and age group of 65 years and older or younger than 65).
Abramowitz 2016 (20)	33 studies*	Community-acquired pneumonia	More common with PPI use, with greater association with short duration of PPI use and higher doses
Abramowitz 2016 (20)	33 studies*	Clostridium difficile infection	More common with PPI use
Arriola 2016 (21)	23 studies; n=186,033	Hospital-acquired Clostridium difficile infection	More common with PPI use
Yu 2016 (22)	10 studies; n=8,145	Spontaneous bacterial peritonitis	More common with PPI use in people with cirrhosis In sensitivity analysis, the association remained in case-control studies but not in cohort studies
Yu 2016 (22)	10 studies; n=8,145	In-hospital or 30-day mortality	No significant association with PPI use in people with cirrhosis

Khan 2015 (23)	14 studies*	Spontaneous bacterial peritonitis	More common with PPI use Similar results were seen in sensitivity analysis of only case-control or only cohort studies, only peer-reviewed publications, and only high-quality studies
Khan 2015 (23)	14 studies*	Spontaneous bacterial peritonitis	More common with H_2RA use
Lambert 2015 (24)	33 studies; n=6,351,656	Community-acquired pneumonia	More common with PPI use More common in the first month of PPI use irrespective of dosage or patient's age.
Lambert 2015 (24)	33 studies; n=6,351,656	Admission to hospital with community-acquired pneumonia	More common with PPI use
Xu 2015 (25)	17 studies*	Spontaneous bacterial peritonitis	More common with PPI use in people with cirrhosis and ascites
Xu 2015 (25)	17 studies*	Bacterial infection	More common with PPI use in people with cirrhosis and ascites
PPI = proton pump inhibitor. H_2RA = histamine 2 receptor antagonist. * Number of participants not reported in the abstract.			

Table 3 Kidney disease

Hussain 2018 (26)	6 studies; n=804,836	Chronic kidney disease End-stage renal disease	More common with PPI use
Nochaiwong 2018 (27)	9 studies; n=2.6 million	Acute kidney injury Chronic kidney disease Acute interstitial nephritis End-stage renal disease	More common with PPI use
Qiu 2018 (28)	10 studies; n=128,020	Acute interstitial nephritis	More common with PPI use
Qiu 2018 (28)	10 studies; n=128,020	Acute kidney injury Chronic kidney disease End stage renal disease	More common with PPI use More common with PPI use compared with H_2RA use
Sun 2018 (29)	5 studies; n=662,624	Chronic kidney disease End-stage renal disease Reduction in glomerular filtration rate	More common with PPI use In subgroup analysis, age and dosage did not affect risk of chronic kidney disease. Duration of PPI exposure in days 31–720 was significantly associated with progression to end-stage renal disease.
Sun 2018 (29)	5 studies; n=662,624	Chronic kidney disease	No significant association with H_2RA use

Wu 2018 (30)	10 studies; n=2,484,924	Acute interstitial nephritis Acute kidney injury Chronic kidney disease End stage renal disease	More common with PPI use
Wijarnpreecha 2017 (31)	5 studies; n=536,902	Chronic kidney disease End-stage renal disease	More common with PPI use
Wijarnpreecha 2017 (31)	5 studies; n=536,902		No association with H_2RA use
Yang 2017 (32)	7 studies; n=513,696	Acute kidney injury	More common with PPI use
PPI = proton pump inhibitor. H_2RA = histamine 2 receptor antagonist.			

Table 4 Cancer and pre-cancerous conditions

Study	Included data	Outcome	Result
Islam 2018 (16)	28 studies*	Colorectal cancer	No significant association with PPI use
Martin 2016 (33)	20 studies; 40,218	Fundic gland polyps	More common with PPI use Odds of fundic gland polyps were larger with PPI use longer than 12 months and were larger again with PPI use of more than 1 year.
Tran-Duy 2016 (34)	12 studies; n=87,324	Fundic gland polyps	More common with PPI use
Tran-Duy 2016 (34)	12 studies; n=87,324	Gastric cancer	More common with PPI use
Lundell 2015 (35)	16 studies; n=1,920	Enterochromaffin-like hyperplasia Corpus atrophy	More common with PPI use in people with *H pylori* infection
Lundell 2015 (35)	16 studies; n=1,920	Enterochromaffin-like hyperplasia Corpus atrophy	No significant association with PPI use in people without *H pylori* infection
Song 2014 (36)	7 studies; n=1,789	Diffuse enterochromaffin-like hyperplasia Linear or micronudular enterochromaffin-like hyperplasia	More common with PPI use
Song 2014 (36)	7 studies; n=1,789	Corporal atrophy Corporal intestinal metaplasia	No significant association with PPI use
PPI = proton pump inhibitor. H_2RA = histamine 2 receptor antagonist. * Number of participants not reported in the abstract.			

Table 5 Fracture

Study	Included data	Outcome	Result
Islam 2018 (16)	28 studies*	Hip fracture	More common with PPI use
Abramowitz 2016 (20)	33 studies*	Hip fracture	More common with PPI use, particularly with long-term use
Zhou 2016 (37)	18 studies; n=244,109	Hip fracture Spine fracture Any fracture	More common with PPI use The association with hip fracture remained after sensitivity analysis of only cohort studies or duration of PPI use (up to a year or more than a year)
Yang 2015 (38)	4 studies; n=57,259	Fracture Spine fracture	More common with PPI use in people on bisphosphonates

PPI = proton pump inhibitor. H_2RA = histamine 2 receptor antagonist.

* Number of participants not reported in the abstract.

Table 6 Other adverse effects

Study	Included data	Outcome	Result
Bian 2017 (39)	3 studies*	Hepatic encephalopathy	More common with PPI use in people with liver dysfunction No significant association with PPI use in sensitivity analysis using the 'trim and fill' method
Li 2017 (40)	13 studies; n=1,465	Gastric atrophy	More common with PPI use
Wijarnpreecha 2016 (41)	4 studies*	Dementia	No significant association with PPI use – except in sensitivity analysis of only cohort studies (dementia more common with PPI use).
Cheungpasitporn 2015 (42)	9 studies; n=109,798	Hypomagnesaemia	More common with PPI use Similar results seen in sensitivity analysis of studies with high quality score only
Park 2014 (43)	9 studies; n=115,455	Hypomagnesaemia	More common with PPI use

PPI = proton pump inhibitor. H_2RA = histamine 2 receptor antagonist.

* Number of participants not reported in the abstract.

Table 7 Recognition of adverse effects in the summary of product characteristics of each proton pump inhibitor

	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Cardiovascular	Interaction with clopidogrel	Interaction with clopidogrel	Interaction with clopidogrel	No recognised risk	No recognised risk
Infection	Gastrointestinal infections	Gastrointestinal infections	Gastrointestinal infections	Gastrointestinal infections	Infection
Kidney disease	Recognised as very rare adverse event	Recognised as very rare adverse event	Recognised as very rare adverse event	Recognised as very rare adverse event	Recognised as very rare adverse event
Cancer and precancerous conditions	Recognised risk of benign fundic gland polyps	Recognised risk of benign fundic gland polyps	Recognised risk of benign fundic gland polyps	Recognised risk of benign fundic gland polyps	Recognised risk of benign fundic gland polyps
Fracture	Recognised risk	Recognised risk	Recognised risk	Recognised risk	Recognised risk
Liver disease	Dose adjustment in severe liver disease	Dose adjustment in moderate and severe liver disease	Dose adjustment in impaired hepatic function	Dose adjustment in severe liver disease	Use caution on starting treatment in severe hepatic impairment
Hypomagnesaemia	Recognised risk	Recognised risk	Recognised risk	Recognised risk	Recognised risk

All PPIs available in the UK are available from several manufacturers. For each proton pump inhibitor, one SPC was checked. The original branded product was chosen where possible. An oral capsule or tablet formulation was chosen as follows:

esomeprazole magnesium trihydrate 20 mg tablets

lansoprazole 15 mg tablets

omeprazole 10 mg capsules

pantoprazole sodium sesquihydrate 20 mg tablets

rabeprazole sodium 10 mg tablets

References

1. Hu W, Tong J, Kuang X, Chen W, Liu Z (2018) Influence of proton pump inhibitors on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: A meta-analysis. Medicine 97(3):e9638
2. Malhotra K, Katsanos AH, Bilal M, Ishfaq MF, Goyal N, Tsivgoulis G (2018) Cerebrovascular Outcomes With Proton Pump Inhibitors and Thienopyridines: A Systematic Review and Meta-Analysis. Stroke 49(2):312–8
3. Shiraev TP, Bullen A (2018) Proton Pump Inhibitors and Cardiovascular Events: A Systematic Review. Heart, Lung & Circulation 27(4):443–50
4. Al-Shammari M, Shah S, Maklad M, Yoo JW, Makar RS (2017) Do proton pump inhibitors really increase cardiovascular risk? A systematic review and meta-analyses of existing literature. American Journal of Gastroenterology 112(Supplement 1):S666–7
5. Bundhun PK, Teeluck AR, Bhurtu A, Huang WQ (2017) Is the concomitant use of

clopidogrel and Proton Pump Inhibitors still associated with increased adverse cardiovascular outcomes following coronary angioplasty?: a systematic review and meta-analysis of recently published studies (2012 - 2016). BMC Cardiovascular Disorders 17(1):3

6. Dahal K, Sharma SP, Kaur J, Anderson BJ, Singh G (2017) Efficacy and Safety of Proton Pump Inhibitors in the Long-Term Aspirin Users: A Meta-Analysis of Randomized Controlled Trials. American Journal of Therapeutics 24(5):e559–69

7. Sun S, Cui Z, Zhou M, Li R, Li H, Zhang S, et al. (2017) Proton pump inhibitor monotherapy and the risk of cardiovascular events in patients with gastro-esophageal reflux disease: a meta-analysis. Neurogastroenterology & Motility 29(2)

8. Zuhri E, Abidin R (2017) Efficacy and safety of esomeprazole in the prevention of recurrent peptic ulcer in patients receiving low-dose acetyl salicylic acid for cardiovascular protection: A meta-analysis of multicenter double-blind randomised controlled trial. Clinical Gastroenterology and Hepatology 15(1):e26

9. Niu Q, Wang Z, Zhang Y, Wang J, Zhang P, Wang C, et al. (2016) Combination Use of Clopidogrel and Proton Pump Inhibitors Increases Major Adverse Cardiovascular Events in Patients With Coronary Artery Disease: A Meta-Analysis. Journal of Cardiovascular Pharmacology & Therapeutics 10:10

10. Serbin MA, Guzauskas GF, Veenstra DL (2016) Clopidogrel-Proton Pump Inhibitor Drug-Drug Interaction and Risk of Adverse Clinical Outcomes Among PCI-Treated ACS Patients: A Meta-analysis. Journal of Managed Care & Specialty Pharmacy 22(8):939–47

11. Singh G, Sharma S, Kaur J, Dahal K (2016) Efficacy and tolerability of proton pump inhibitors in the long-term aspirin users: Meta-analysis of randomized controlled trials. American Journal of Gastroenterology 111(Supplement 1):444

12. Sherwood MW, Melloni C, Jones WS, Washam JB, Hasselblad V, Dolor RJ (2015) Individual Proton Pump Inhibitors and Outcomes in Patients With Coronary Artery Disease on Dual Antiplatelet Therapy: A Systematic Review. Journal of the American Heart Association 4(11):29

13. Han S, Jin Y (2013) Safety of clopidogrel and proton pump inhibitors in patients undergoing percutaneous coronary intervention; a meta-analysis. Heart 3:a246

14. Kwok CS, Jeevanantham V, Dawn B, Loke YK (2013) No consistent evidence of differential cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: meta-analysis. International Journal of Cardiology 167(3):965–74

15. Cao F, Chen CX, Wang M, Liao HR, Wang MX, Hua SZ, et al. (2018) Updated meta-analysis of controlled observational studies: proton-pump inhibitors and risk of Clostridium difficile infection. Journal of Hospital Infection 98(1):4–13

16. Islam MM, Poly TN, Walther BA, Dubey NK, Anggraini NDN, Shabbir SA, et al. (2018) Adverse outcomes of long-term use of proton pump inhibitors: a systematic review and meta-analysis. European Journal of Gastroenterology & Hepatology 19:19

17. Oshima T, Wu L, Li M, Fukui H, Watari J, Miwa H (2018) Magnitude and direction of the association between Clostridium difficile infection and proton pump inhibitors in adults and pediatric patients: a systematic review and meta-analysis. Journal of Gastroenterology 53(1):84–94

18. Su T, Lai S, Lee A, He X, Chen S (2018) Meta-analysis: proton pump inhibitors moderately increase the risk of small intestinal bacterial overgrowth. Journal of Gastroenterology 53(1):27–36

19. Tariq R, Singh S, Gupta A, Pardi DS, Khanna S (2017) Association of Gastric Acid Suppression With Recurrent Clostridium difficile Infection: A Systematic Review and Meta-analysis. JAMA Internal Medicine 177(6):784–91

20. Abramowitz J, Thakkar P, Isa A, Truong A, Park C, Rosenfeld RM (2016) Adverse Event Reporting for Proton Pump Inhibitor Therapy: An Overview of Systematic Reviews. Otolaryngology - Head & Neck Surgery 155(4):547–54

21. Arriola V, Tischendorf J, Musuuza J, Barker A, Rozelle JW, Safdar N (2016) Assessing the Risk of Hospital-Acquired Clostridium Difficile Infection With Proton Pump Inhibitor Use: A Meta-Analysis. Infection Control & Hospital Epidemiology 37(12):1408–17

22. Yu T, Tang Y, Jiang L, Zheng Y, Xiong W, Lin L (2016) Proton pump inhibitor therapy and its association with spontaneous bacterial peritonitis incidence and mortality: A meta-analysis. Digestive & Liver Disease 48(4):353–9

23. Khan MA, Kamal S, Khan S, Lee WM, Howden CW (2015) Systematic review and meta-analysis of the possible association between pharmacological gastric acid suppression and spontaneous bacterial peritonitis. European Journal of Gastroenterology & Hepatology 27(11):1327–36

24. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA (2015) Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS ONE [Electronic Resource] 10(6):e0128004

25. Xu HB, Wang HD, Li CH, Ye S, Dong MS, Xia QJ, et al. (2015) Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: a systematic review and meta-analysis. Genetics & Molecular Research 14(3):7490–501

26. Hussain S, Singh A, Habib A, Najmi AK (2018) Proton pump inhibitors use and risk of chronic kidney disease: Evidence-based meta-analysis of observational studies. Clinical Epidemiology and Global Health.

27. Nochaiwong S, Ruengorn C, Awiphan R, Koyratkoson K, Chaisai C, Noppakun K, et al. (2018) The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. Nephrology Dialysis Transplantation 33(2):331–42

28. Qiu T, Zhou J, Zhang C (2018) Acid-suppressive drugs and risk of kidney disease: A systematic review and meta-analysis. Journal of Gastroenterology and Hepatology (Australia) 33(9):1566–73

29. Sun J, Sun H, Cui M, Sun Z, Li W, Wei J, et al. (2018) The use of anti-ulcer agents and the risk of chronic kidney disease: a meta-analysis. International Urology & Nephrology 13:13

30. Wu B, Shang W, Li Y, Ren Y, Liu Z, Wei H, et al. (2018) Association between proton pump inhibitors use and kidney diseases: A meta-analysis. International Journal of Clinical and Experimental Medicine 11(7):6465–73

31. Wijarnpreecha K, Thongprayoon C, Chesdachai S, Panjawatanana P, Ungprasert P, Cheungpasitporn W (2017) Associations of Proton-Pump Inhibitors and H2 Receptor

Antagonists with Chronic Kidney Disease: A Meta-Analysis. Digestive Diseases & Sciences 62(10):2821–7

32. Yang Y, George KC, Shang WF, Zeng R, Ge SW, Xu G (2017) Proton-pump inhibitors use, and risk of acute kidney injury: a meta-analysis of observational studies. Drug design, development & therapy 11:1291–9

33. Martin FC, Chenevix-Trench G, Yeomans ND (2016) Systematic review with meta-analysis: fundic gland polyps and proton pump inhibitors. Alimentary Pharmacology & Therapeutics 44(9):915–25

34. Tran-Duy A, Spaetgens B, Hoes AW, de WNJ, Stehouwer CD (2016) Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis. Clinical Gastroenterology & Hepatology 14(12):1706–1719.e5

35. Lundell L, Vieth M, Gibson F, Nagy P, Kahrilas PJ (2015) Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. Alimentary Pharmacology & Therapeutics 42(6):649–63

36. Song H, Zhu J, Lu D (2014) Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions. Cochrane Database of Systematic Reviews (12):cd010623

37. Zhou B, Huang Y, Li H, Sun W, Liu J (2016) Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporosis International 27(1):339–47

38. Yang SD, Chen Q, Wei HK, Zhang F, Yang DL, Shen Y, et al. (2015) Bone fracture and the interaction between bisphosphonates and proton pump inhibitors: a meta-analysis. International journal of clinical and experimental medicine 8(4):4899–910

39. Bian J, Wang A, Lin J, Wu L, Huang H, Wang S, et al. (2017) Association between proton pump inhibitors and hepatic encephalopathy: A meta-analysis. Medicine 96(17):e6723

40. Li Z, Wu C, Li L, Wang Z, Xie H, He X, et al. (2017) Effect of long-term proton pump inhibitor administration on gastric mucosal atrophy: A meta-analysis. Saudi Journal of Gastroenterology 23(4):222–8

41. Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Ungprasert P (2016) Proton pump inhibitors and risk of dementia. Annals of Translational Medicine 4(12):1–6

42. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert P, et al. (2015) Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Renal Failure 37(7):1237–41

43. Park CH, Kim EH, Roh YH, Kim HY, Lee SK (2014) The association between the use of proton pump inhibitors and the risk of hypomagnesemia: a systematic review and meta-analysis. PLoS ONE [Electronic Resource] 9(11):e112558