NICE National Institute for Health and Care Excellence

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 et al. 2018 (1)	12 studies; n=33,492	Major cardiovascular events Stent thrombosis Revascularisation	More common with PPI use in people taking clopidogrel plus aspirin
		Myocardial infarction Cardiogenic death All-cause mortality	No significant association with PPI use in people taking clopidogrel plus aspirin
Malhotra et al. 2018 (2)	22 studies; 131,714	Ischaemic stroke Stroke or myocardial infarction or cardiovascular 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 and Bullen 2018 (3)	5 studies; n= 376,873	All-cause mortality Major cardiovascular events	More common with PPI use
Al-Shammari et al. 2017 (4)	5 studies; n=743,427	Cardiovascular events	More common with PPI use
Bundhun et al. 2017 (5)	11 studies; n=55,494	Short-term mortality and target vessel revascularisation	More common with PPI use in people taking clopidogrel
		Long-term major adverse cardiac events, myocardial infarction, stent thrombosis, and target vessel revascularisation	More common with PPI use in people taking clopidogrel
		Long-term mortality	No significant association with PPI use in people taking clopidogrel †

Dahal et al. 2017 (6)	9 studies; n=6,382	All-cause mortality Cardiovascular mortality Non-fatal myocardial infarction or ischaemia Ischaemic stroke or transient ischaemic attack	No significant association with PPI use in people taking aspirin
Sun et al. 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 and Abidin 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 et al. 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 et al. 2016 (10)	12 studies; n=50,277	Major adverse cardiovascular event Myocardial infarction Stroke	More common with PPI use in people taking clopidogrel
		Stent thrombosis Cardiovascular death Major bleeding Major bleeding	No significant association with PPI use in people taking clopidogrel
Singh et al. 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 et al. 2015 (12)	6 studies*	Adverse cardiovascular events	More common with pantoprazole use More common with lanzoprazole use More common with esomeprazole use
		Adverse cardiovascular events	No significant association with omeprazole use
Han and Jin 2013 (13)	14 studies; n=34,967	Restenosis Recurrent acute coronary syndrome All-cause mortality	More common with PPI use in people taking clopidogrel
		Revascularisation Cardiovascular death Stent thrombosis	No significant association with PPI use in people taking clopidogrel

Kwok et al. 2013 (14)	23 studies; n=222,311	Cardiovascular events	More common with PPI use in people taking clopidogrel†
		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 et al. 2018 (15)	50 studies*	Hospital-acquired *Clostridium difficile* infection Hospital-acquired *Clostridium difficile* infection in general wards	More common with PPI use
		Hospital-acquired *Clostridium difficile* infection in intensive care units Community-acquired *Clostridium difficile* infection	No significant association with PPI use
Islam et al. 2018 (16)	28 studies*	Community-acquired pneumonia	More common with PPI use
Oshima et al. 2018 (17)	67 studies*	*Clostridium difficile* infection	More common with PPI use
		Recurrent *Clostridium difficile* infection	More common with PPI use
Su et al. 2018 (18)	19 studies; n=7,055	Small intestine bacterial overgrowth	More common with PPI use
Tariq et al. 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 et al. 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 et al. 2016 (20)	33 studies*	Community-acquired pneumonia	More common with PPI use, with greater association with short duration of PPI use and higher doses
		Clostridium difficile infection	More common with PPI use
Arriola et al. 2016 (21)	23 studies; n=186,033	Hospital-acquired *Clostridium difficile* infection	More common with PPI use
Yu et al. 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
		In-hospital or 30-day mortality	No significant association with PPI use in people with cirrhosis

Khan et al. 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
		Spontaneous bacterial peritonitis	More common with H_2RA use
Lambert et al. 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
		Admission to hospital with community-acquired pneumonia	More common with PPI use
Xu et al. 2015 (25)	17 studies*	Spontaneous bacterial peritonitis	More common with PPI use in people with cirrhosis and ascites
		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 et al. 2018 (26)	6 studies; n=804,836	Chronic kidney disease End-stage renal disease	More common with PPI use
Nochaiwong et al. 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 et al. 2018 (28)	10 studies; n=128,020	Acute interstitial nephritis	More common with PPI use
		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 et al. 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
		Chronic kidney disease	No significant association with H_2RA use

Wu et al. 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 et al. 2017 (31)	5 studies; n=536,902	Chronic kidney disease	More common with PPI use No association with H_2RA use
		End-stage renal disease	More common with PPI use
Yang et al. 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 et al. 2018 (16)	28 studies*	Colorectal cancer	No significant association with PPI use
Martin et al. 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 et al. 2016 (34)	12 studies; n=87,324	Fundic gland polyps	More common with PPI use
		Gastric cancer	More common with PPI use
Lundell et al. 2015 (35)	16 studies; n=1,920	Enterochromaffin-like hyperplasia Corpus atrophy	More common with PPI use in people with *H pylori* infection
		Enterochromaffin-like hyperplasia Corpus atrophy	No significant association with PPI use in people without *H pylori* infection
Song et al. 2014 (36)	7 studies; n=1,789	Diffuse enterochromaffin-like hyperplasia Linear or micronodular enterochromaffin-like hyperplasia	More common with PPI use
		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 et al. 2018 (16)	28 studies*	Hip fracture	More common with PPI use
Abramowitz et al. 2016 (20)	33 studies*	Hip fracture	More common with PPI use, particularly with long-term use
Zhou et al. 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 et al. 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 et al. 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 et al. 2017 (40)	13 studies; n=1,465	Gastric atrophy	More common with PPI use
Wijarnpreecha et al. 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 et al. 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 et al. 2014 (43)	9 studies; n=115,455	Hypomagnesaemia	More common with PPI use
Samji et al. 2014 (44)	Seven studies; n=968,571	Congenital malformation	More common with PPI use in the first trimester
		Low birth weight	More common with PPI use
		Preterm delivery, stillbirth	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 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 pre-cancerous 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
Prenatal effects	No recognised risk, but exercise caution in prescribing during pregnancy	No recognised risk, but use during pregnancy is 'not recommended'	Omeprazole can be used during pregnancy	It is preferable to avoid the use of pantoprazole during pregnancy	Contraindicated in pregnancy

All PPIs available in the UK are available from several manufacturers. For each proton pump inhibitor, one summary of product characteristics (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

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