INSTITUT NATIONAL D'ASSURANCE MALADIE-INVALIDITÉ
SERVICE DES SOINS DE SANTÉ
Comité d'évaluation des pratiques médicales en matière de médicaments

RIJKSINSTITUUT VOOR ZIEKTE- EN INVALIDITEITSVERZEKERING
DIENST GENEESKUNDIGE VERZORGING
Comité voor de evalutie van de medische praktijk inzake geneesmiddelen

The rational use of proton pump inhibitors (PPIs) in gastro-oesophageal diseases (with the exclusion of gastroduodenal ulcer disease)

Systematic literature review: full report

Consensus conference
May 31st 2018
Auditorium Lippens (Royal Library)
Brussels

This literature review was performed by BCFI/CBIP and was supervised by a reading committee.

Researchers
Main researcher:
Natasja Mortier MD*, BCFI/CBIP*

Co-researchers:
Abdelbari Baitar, MSc. *, BCFI/CBIP*
Bérengère Couneson*, PharmD, BCFI/CBIP*

Reading committee

Alain Van Meerhaeghe MD, PHD, Prof (Umons)
Louis Ferrant MD (UA)
Gilles Henrard MD (Ulg)
Michel Vanhaeverbeek MD, Em. Prof (ULB)
Tim Vanuytsel MD, PHD, Prof (KUL)

Administrative and IT support
Stijn Dumon, *BCFI/CBIP*

Translation
BCFI/CBIP

Table of contents

1 Abbreviations

AR	Absolute risk
ARD	Absolute risk difference
ARR	Absolute risk reduction
ASA	Acetylsalicylic acid
AKI	Acute kidney injury
AIN	Acute interstitial nephritis
CKD	Chronic kidney disease
AE	Adverse events
BE	Barrett's oesophagus
CV	Cardiovascular
ESRD	End-stage renal disease
CI	Confidence interval
CO	Cross-over
DB	Double blind
ENRD	Endoscopy-negative reflux disease
OTC	Over the counter
eGFR	Estimated glomerular filtration rate
FD	Functional dyspepsia
GORD, GERD	Gastro-(o)esophageal reflux disease
GI	Gastro-intestinal
H2RA	H2 receptor antagonist
HR	Hazard ratio
ITT	Intention to treat analysis
LS MD	Least-squares mean difference
MD	Mean difference
MA	Meta-analysis
MCID	Minimal clinically important difference
mITT	Modified intention to treat
NT	No statistical test
NERD	Non-erosive reflux disease
NSAID	Non-steroidal anti-inflammatory drug
NA	Not applicable
NR	Not reported
NS	Not statistically significant
n	Number of patients
N	Number of studies
OR	Odds ratio
OL	Open label
QoL	Quality of life
PG	Parallel group
PO	Primary outcome
PPI	Proton pump inhibitor
RCT	Randomized controlled trial
RDQ	Reflux Disease Questionnaire
RR	Relative risk
SB	Single blind
SMD	Standardized mean difference
SS	Statistically significant
TIF	Transoral incisionless fundoplication

Table 1

2 Methodology

2.1 Introduction

This systematic literature review was conducted in preparation of the consensus conference "**The rational use of proton pump inhibitors (PPIs) in gastro-oesophageal diseases (with the exclusion of gastroduodenal ulcer disease)",** which will take place on the 31st of May 2018.

2.2 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are:

*1. Chez un adulte, en cas de dyspepsie **sans** reflux cliniquement typique, quelle est la balance bénéfices/risques d'un traitement par IPP (bénéfice clinique potentiel versus autres traitements médicamenteux (anti H_2, antiacides) et/ou mesures d'hygiène de vie ?*
*2. Chez un adulte, en cas de dyspepsie **avec** reflux cliniquement typique (pyrosis et/ou régurgitation), quelle est la balance bénéfices/risques d'un traitement par IPP (bénéfice clinique potentiel) versus autres traitements médicamenteux (anti H_2, antiacides) et/ou mesures d'hygiène de vie ?*
*3. Chez un adulte, en cas de dyspepsie **avec** reflux cliniquement typique et **œsophagite documentée** (et stadifiée), quelle est la balance bénéfices/risques d'un traitement par IPP (bénéfice clinique potentiel) versus autres traitements médicamenteux (anti H_2, antiacides) et/ou mesures d'hygiène de vie ?*
4. En cas d'œsophage de Barrett, quelle est la balance bénéfices/risques des IPP (bénéfice clinique potentiel) versus absence de traitement médicamenteux, autres traitements médicamenteux (anti H_2, antiacides), traitement endoscopique ou chirurgical et/ou mesures d'hygiène de vie, en fonction des caractéristiques endoscopiques/histologiques ?
5. Parmi les effets indésirables recensés pour les différents IPP, quels sont ceux qui sont certains ou incertains ? Quelle est leur fréquence ? Existe-t-il des groupes plus à risque ? *Note : un expert documentera la relation possible entre le mécanisme d'action des IPP et les effets indésirables observés.*
6. Quelles sont les interactions médicamenteuses cliniquement significatives avec les différents IPP ? (clopidogrel, aspirine, etc..).
7. Faut-il prescrire un IPP en cas de prise d'AINS (y compris aspirine) : *- de manière systématique (pour tout type de patient)* *- en fonction des caractéristiques du patient* *- pour toute durée et/ou dose de prise (aiguë, intermittente, chronique) ?*
8. Comment réduire et stopper un traitement (déprescription) d'IPP ?
9. Existe-t-il des différences cliniquement pertinentes entre les différents IPP à dose équivalente à préciser) ?

Table 2

The answers to these questions can be found in the following chapters of this document:

Question	Chapters
question 1	chapter 5 (for details: chapter 14)
question 2	chapter 6 (for details: chapter 15)
question 3	chapter 6 and 7 (for details: chapters 15 and 16)
question 4	chapter 8 (for details: chapter 17)
question 5	chapter 11 (for details: chapter 20)
question 6	chapter 12
question 7	chapter 10 (for details: chapter 19)
question 8	chapter 9 (for details: chapter 18)
question 9	chapter 6, 7, and 10 (for details: chapters 15, 16 and 19)

Table 3

2.3 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

2.3.1 Populations

The following populations are to be evaluated:

- Adult patients with
  - dyspepsia, without typical reflux symptoms (including functional dyspepsia and uninvestigated dyspepsia)
  - reflux symptoms (including GORD and uninvestigated reflux symptoms)
  - documented oesophagitis
  - Barrett oesophagus

Children and pregnant women will be excluded.

2.3.2 Interventions

The following medications, available in Belgium, are to be studied:

Proton pump inhibitors (PPI)
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole

Table 4: PPIs available in Belgium

They will be compared to (where appropriate):

- Placebo
- Lifestyle changes
- Antacids
- H2 receptor antagonists (H2RA)
- Prokinetics
- Endoscopic treatment
- Surgery

H2RA	Prokinetics
Cimetidine Ranitidine	Alizapride Domperidone Metoclopramide

Table 5: H2Ras and prokinetics available in Belgium

2.3.3 Endpoints

The following endpoints are to be reported:

Efficacy
Validated symptom scores Quality of life (QoL) Gastric pH Endoscopic healing (for oesophagitis and Barrett) Histological evolution (for Barrett)
Safety
Total adverse events Selected adverse events (see 1.3.4.1)

Table 6

2.3.4 Specific research questions

The organising committee has asked that the literature review also focuses on the following research questions.

2.3.4.1 *Adverse events*

Information from RCTs, meta-analyses of RCT's and observational studies, and large observational (cohort) studies.

Focusing on the following adverse events:

- Cardiovascular events
- Gastro-intestinal infections (Clostridium, Campylobacter and Salmonella infections)
- Community-acquired pneumonia
- Fractures
- Acute and chronic kidney disease
- Dementia
- Gastric cancer

2.3.4.2 *Medication interactions*

Information from guidelines, BCFI/CBIP, and La Revue Prescrire "Guide des interactions".

Subject:

- Clinically significant interactions with PPI's
- specific focus on efficacy of clopidogrel and/or ASA in combination with a PPI

2.3.4.3 *Gastroprotection with PPI*

Information from guidelines and RCT's.

Subject:

- Is gastroprotection needed when prescribing an NSAID (including COXIBs and high-dose ASA)?
- Is gastroprotection needed when prescribing clopidogrel and/or low-dose ASA?

Outcome: gastric bleeding, gastric complications

2.3.4.4 *Deprescribing*

Information from guidelines and RCT's.
Subject:

- How to deprescribe a PPI?

Outcome: % of participants with successful discontinuation or decrease in the use of PPI, gastric complications

2.3.5 Study types

We will look at meta-analyses, systematic reviews, RCTs and observational (cohort) studies.
To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases
- Systematic reporting of results
- Inclusion of randomised controlled trials (or observational studies for certain research questions)
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

RCT's

- Blinding: unblinded (open-label) studies will not be included
- Duration: Minimum duration of 1 month
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)
- Post hoc (subgroup) analyses are excluded, except for comparisons between different PPI's.

Observational (cohort) studies

- Prospective or retrospective **cohort** studies
- Minimum follow-up of 1000 person-years

Other sources for safety, dosing and interactions

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI), *Folia Pharmacotherapeutica*
- Guidelines
- La Revue Prescrire: *Guide des interactions*

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

2.3.6 Guidelines

Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2013 onwards are to be selected.
- Quality assessment: Only guidelines that report levels of evidence/recommendation are to be selected.
- Systematic review: the guideline needs to be based on a good systematic search and review of the literature.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain "Rigour of development". More information can be found on http://www.agreetrust.org/. [1]

This table gives an overview of the items assessed in this domain according to the Agree II score.[1]

No.	**Description of the item**
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table 7: Items assessed by the domain "Rigour of development" in AgreeII score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.

In the section about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

Similarities and discrepancies between guidelines are to be reported.

2.4 Search strategy

2.4.1 Principles of systematic search

*Relevant RCTs, meta-analyses and systematic review*s were searched in a stepwise approach.

- As a start we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library, TRIPP database) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.
- In a second step, we conducted a systematic search in the Medline (PubMed) electronic database for randomised controlled trials (RCTs), meta-analyses, systematic reviews (and sometimes observational studies) that were published after the search date of our selected systematic reviews **up until January 1st 2018.**

Guidelines were searched through the link "evidence-based guidelines" on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to 'guideline search engines', like National Guideline Clearinghouse and G-I-N.

2.4.2 Source documents

Useful source documents for the topics **GORD** and **oesophagitis** were not identified in our initial search. Therefore we searched without a starting date. Because of great overlap of search results for **dyspepsia** and **Barrett oesophagus**, all four topics were included in this search (see appendix 1 for the full search strategy).

The following systematic reviews were selected as source documents and starting points to find relevant publications for the other topics:

For deprescribing

Boghossian TA, Rashid FJ, Thompson W, Welch V, Moayyedi P, Rojas-Fernandez C, et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. The Cochrane database of systematic reviews 2017;3: Cd011969.

For gastroprotection

Tran-Duy A, Vanmolkot FH, Joore MA, Hoes AW, Stehouwer CD. Should patients prescribed long-term low-dose aspirin receive proton pump inhibitors? A systematic review and meta-analysis. International journal of clinical practice 2015;69: 1088-111.

For adverse events: Dementia

Batchelor R, Gilmartin JF, Kemp W, Hopper I, Liew D. Dementia, cognitive impairment and proton pump inhibitor therapy: A systematic review. Journal of gastroenterology and hepatology 2017;32: 1426-35.

For adverse events: Fractures

Zhou B, Huang Y, Li H, Sun W, Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2016;27: 339-47.

For adverse events: Community-acquired pneumonia

Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PloS one 2015;10: e0128004.

For adverse events: Clostridium infection

Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, et al. Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis. World journal of gastroenterology 2017;23: 6500-15.

For adverse events: Salmonella and Campylobacter infection

Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Alimentary pharmacology & therapeutics 2011;34: 1269-81.

For adverse events: Acute and chronic kidney disease

Nochaiwong S, Ruengorn C, Awiphan R, Koyratkoson K, Chaisai C, Noppakun K, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2017.

For adverse events: Gastric cancer

Tran-Duy A, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD. Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2016;14: 1706-19.e5.

For all these research questions, a search string was developed to search Medline via Pubmed from the research date of the selected source document up until 1st January 2018. If no source document could be found, a search of Medline without a starting date was performed.

2.4.3 Search strategy details

The full search strategies can be found in appendix 1.

2.5 Selection procedure

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

In– and exclusion criteria of the different types of studies are found in chapter 1.1.2 with relevant populations, interventions, endpoints and study criteria.
The list of articles excluded after reading of the full text can be found in Appendix 2.

2.6 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.

The GRADE system assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table 8. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.
In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:
Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.
For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.5 to ≥1.5).

Additional considerations for observational studies

For observational studies, when no points are deducted for risk of bias in one of the above categories, a point can be added if there is a large magnitude of effect (high odds ratio), if there is evidence of a dose-response gradient or (very rarely) when all plausible confounders or other biases increase our confidence in the estimated effect.

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

2.7 Synopsis of the study results

The complete report contains per research question:

- (Comprehensive) summary of selected guidelines.
- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English).

The synopsis report contains per research question:

- (Brief) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

3 Critical reflections of the reading committee and the literature group

3.1 General remarks

3.1.1 Definitions

The first two questions to the jury make a distinction between dyspepsia without typical reflux symptoms, and dyspepsia with typical reflux symptoms such as heartburn and regurgitation.

In trials, and also in practice, this distinction is not as straightforward to make, as symptoms often overlap, and patients are classified in a myriad of ways.

3.1.2 Dyspepsia

The definition of dyspepsia is not universal and has shifted over time. Dyspepsia was originally defined as any symptom referable to the upper gastrointestinal tract, but the definition has become more specific in recent years in order to exclude typical reflux symptoms(1). However, the trials we have included in this document use many different definitions of dyspepsia, sometimes including patients with heartburn. It was not possible to separately analyze dyspepsia patients without any typical reflux symptoms.

For the purpose of this document, the chapter “Dyspepsia” encompasses trials that included dyspepsia patients of any definition.

It is also important to note the distinction between *dyspepsia* as a symptom, and *functional dyspepsia* (FD). Functional dyspepsia is a diagnosis of exclusion, in which the symptom dyspepsia has been thoroughly investigated and no evidence of organic disease that can explain the symptom is found.

3.1.3 Reflux, GORD and oesophagitis

Not only dyspepsia is challenging to diagnose and categorize accurately. In the chapters “Reflux” and “Oesophagitis”, many distinct patient groups are studied, and they are grouped differently in each trial.

The chapter “GORD” encompasses patients with uninvestigated typical reflux symptoms, and patients with reflux symptoms who have had a formal diagnosis, mostly via upper gastrointestinal endoscopy. The latter group can be divided into patients with normal endoscopic findings (non-erosive reflux disease, NERD) and patients with erosive lesions (erosive reflux oesophagitis). All fall under the umbrella of gastro-oesophageal reflux disease (GORD).

The chapter “Oesophagitis” contains only trials that have focused specifically on patients with erosive reflux oesophagitis.

3.1.4 Population

Some trials employed run-in periods of weeks to months, so patients who were not or partially responding to a PPI could be excluded from the trial before randomization. The patient groups in the

trials were therefore highly selected to have a maximum response to PPIs. This may decrease the applicability of the results to a real-life population.

In the trials, serious comorbidities and previous gastrointestinal problems are generally a cause for exclusion. The patients in the trials are, in general, healthier than patients with the same symptoms in a real-life population.

Many elderly patients take PPIs chronically. In the trials of functional dyspepsia and GORD, elderly people are usually excluded. Most trials include patients between the ages of 18 to 70 years old, with a mean age of 45 to 50. In contrast, in the trials for gastroprotection, and in the cohort studies focusing on safety endpoints, the elderly are well represented.

3.1.5 Comparisons

A question to the jury was whether there are important differences between PPIs at an equivalent dose. What these equivalent doses are, is not readily answered.

The doses recommended in guidelines, the doses used in trials comparing two PPIs, and the relative potencies to increase gastric pH, as assessed by Kirchheiner 2009(2), do not wholly coincide.

PPI	**Relative potency** (compared to omeprazole)	**Standard dose**
Pantoprazole	0.23	40 mg once daily
Lansoprazole	0.90	30 mg once daily
Omeprazole	1.00	20 mg once daily
Esomeprazole	1.60	20 mg once daily
Rabeprazole	1.82	20 mg once daily

Table 9: Relative potencies of different PPIs for lowering gastric pH, according to Kirchheiner 2009 and recommended standard doses of different PPIs for GORD, according to the NICE 2014 guideline

For example, esomeprazole has a relative potency of 1.6 compared to omeprazole for increasing gastric pH. One would expect esomeprazole, in a lower dose, to be as potent as omeprazole. Yet in the NICE 2014(3) guideline, 20 mg esomeprazole is considered an equivalent dose to 20 mg omeprazole. And in some studies, esomeprazole 40 mg/day is compared to omeprazole 20 mg/day. This presumably gives esomeprazole an advantage over omeprazole in the trial.

3.1.6 Outcomes

Many RCTs reported only a p-value, without point estimates or confidence intervals, which makes it difficult to appreciate the clinical relevance of a statistically significant outcome.

Dyspepsia and reflux symptoms are complaints that cannot be objectively measured. There are many ways to record and report the presence and severity of symptoms, and these are not easily compared. Many validated symptom scores are available, but it is not clear how these compare to each other. Sometimes subscales of these scores are reported. It is not clear if these subscales are validated.

It is also unclear how meta-analyses handled the pooling of these outcomes.

Many studies did not report adverse events, or did not report them adequately.

3.1.7 Problems with the trial design

Almost all studies were industry-sponsored. Especially in the head-to-head comparison trials, this could lead to bias.

Trial duration is often relatively short, with common durations being 4 to 8 weeks. This is not necessarily a flaw of the trial, as many of the interventions are meant to be limited in duration. However, many real-life patients take PPIs for a far longer period. It is not clear whether the benefit of PPIs for symptom relief also extends to these longer durations.

3.2 Remarks on specific chapters

3.2.1 Guidelines

The guidelines on dyspepsia and functional dyspepsia recommend to test for H. pylori and, if positive, offer eradication therapy as a first measure after lifestyle advice. As it was not a question to the jury, we did not perform a search for studies evaluating the place of H. pylori eradication in (functional) dyspepsia. As the detection and eradication of H. pylori for dyspepsia is a mainstay in the guidelines, as well as in the clinical practice of physicians, this omission is a limitation of this report.

In case of dyspepsia symptoms resistant to PPI treatment, the ACG/CAG DYSPEPSIA 2017 guideline recommends trying (among other treatments) a tricyclic antidepressant, or if medical treatment fails, psychological treatment. We did not perform a search for studies to evaluate the place of tricyclic antidepressants or psychological treatment in (functional) dyspepsia.

3.2.2 Dyspepsia

The Cochrane meta-analysis of Pinto-Sanchez 2017(4), which compared PPIs to placebo, H2RA and prokinetics, included trials in patients with functional dyspepsia only.

In the RCT Van Marrewijk 2009(5), where step-up treatment was compared to step-down treatment, the participants are patients presenting to primary care with new-onset symptoms of dyspepsia. None of them had been formally diagnosed via endoscopy.

As explained above, these are two distinctly different patient groups.

The Reading Committee has expressed concern with the overconsumption of PPIs, particularly in dyspepsia and functional dyspepsia. In light of a large observed placebo effect and doubt whether excessive acid production is the cause of dyspeptic symptoms, the role of PPIs in (functional) dyspepsia needs close scrutiny.

3.2.3 Reflux

In this chapter, meta-analyses pool a mixed group of patients. Some trials included patients with uninvestigated reflux symptoms, some included patients with non-erosive GORD, and others included patients with erosive oesophagitis.

3.2.4 Oesophagitis

In reflux oesophagitis, it is important to make the distinction between therapy for oesophagitis healing (usually 8 weeks) and maintenance therapy (trials with a duration up to 12 months).

3.2.5 Barrett

We did not find RCTs comparing PPIs to placebo in Barrett. This makes it more difficult to assess the role of PPIs in preventing progression to oesophageal cancer.

3.2.6 Deprescribing

No trials investigating tapering before stopping PPIs, that met our inclusion criteria, have been found.

3.2.7 Gastroprotection

In the meta-analysis evaluating non-selective NSAID, aspirin (ASA) is also included in this category. Thus there is some overlap of studies with the meta-analysis evaluating aspirin.

Some of the included studies were done in patients that took the combination of ASA with clopidogrel. The risk of a gastrointestinal complication and the protective effect of the PPI could be modified by one or both medications.

Many of the RCTs, and all of the trials in patients taking COX2-inhibitors, included patients at high risk of gastric complications (patients with a previous peptic ulcer). It is not possible to extrapolate the results to all people taking NSAID, ASA or clopidogrel.

As many of the trials about gastroprotection involved patients taking medication for secondary cardiovascular prevention, the mean and upper limit of ages of the participants is higher compared to the trials concerning dyspepsia/GORD.

3.2.8 Adverse events

For this report, a selection of possible adverse events to evaluate was made. Suspicions remain that PPIs could play a role in causing many other adverse events, such as micronutrient deficiencies (iron, vitamin B12, possibly leading to anaemia), spontaneous bacterial peritonitis, rhabdomyolysis, etc.(6) However, for many of these outcomes there is no sufficient evidence base at present.

It is difficult to draw conclusions from adverse events reported in RCTs, since they are usually set up in a way to minimize adverse events.

Also, some adverse events are rare occurrences. The less common they are, the longer and/or larger the studies need to be to identify a difference between active and control group.

To assess rare adverse events, we included observational studies (cohort studies). An observational study cannot prove a causal link, it can merely establish an association between the treatment and a specific outcome. The quality of evidence in the GRADE approach for observational studies is LOW by default, although upgrading or downgrading according to certain rules is possible.

Results from observational studies are very sensitive to hidden bias. Results are generally statistically adjusted to correct for confounders, but not all possible confounders are known or measured.

The Bradford-Hill criteria(7) can be used to assess the likelihood that a given association is causal. However, for many of these criteria, incomplete or no data is available from studies. Furthermore, the validity and feasiblity some of the Hill criteria themselves have been debated(8).

1. Strength of association 2. Consistency 3. Specificity 4. Temporality 5. Biological gradient 6. Plausibility 7. Coherence 8. Experiment 9. Analogy

Table 10: Bradford-Hill criteria for causation

3.3 Some methodological issues explained

3.3.1 Statistically significant versus clinically relevant

A study may show non-inferiority of a certain drug, or superiority, when compared to another treatment. A point estimate and a confidence interval around this estimate are usually provided. The confidence interval gives us an idea of the (im)precision of the estimate and of the range in which the true effect plausibly lies(9). It is important to realize that the true effect can be anywhere within this confidence interval.

The GRADE score reflects how certain we are that this estimate is close to the true effect.

This is how the results in this document are reported.

Whether a difference found in a study is also clinically relevant (i.e. will make a noticeable difference to the patient), is another matter. Some authors have tried to propose thresholds for clinical relevance. The point estimate, as well as the upper and lower boundary of the confidence interval is then examined in relation to this threshold. For hard endpoints, usually a relative risk reduction of 25% is proposed.

It will be up to the jury to consider the results of the trials in this report in the light of clinical relevance.

3.3.2 Meta-analyses

We reported many **meta-analyses.** Although a meta-analysis allows for a more robust point estimate than an individual RCT, one should be cautious when interpreting the results. Results from clinically heterogenous studies are often combined. RCTs employing different diagnostic criteria (e.g. endoscopically confirmed reflux disease versus uninvestigated reflux symptoms), different definitions of outcomes (e.g. “Improvement of symptoms”), including different populations (e.g. patients with uninvestigated reflux symptoms and endoscopically confirmed oesophagitis), as well as RCTs of differing methodological quality, are sometimes pooled. It can be misleading to generalize these pooled results to the entire population.

4 Guidelines. Summaries and conclusions.

4.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in the table below.

Abbreviation	Guideline
NICE GORD 2014(3)	NICE. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. NICE Clinical guideline. 2014
ACG/CAG Dyspepsia 2017(1)	Moayyedi, P. ACG and CAG clinical guideline: management of dyspepsia. The American Journal of gastroenterology. 2017
GORD 2013(10)	Katz, P. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. The American Journal of Gastroenterology. 2013
ACG Barrett 2016(11)	Shaheen, N. ACG clinical guideline: diagnosis and management of Barrett's Esophagus. The American Journal of Gastroenterology. 2016
Australia Barrett 2015(12)	Whiteman, D. Australian clinical practice guidelines for the diagnosis and management of Barrett's esophagus and early esophageal adenocarcinoma. Journal of Gastroenterology and Hepatology. 2015
British society Barrett 2014(13)	Fitzgerald, R. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. BMJ. 2014
Deprescribing 2017(14)	Farrell, B. Deprescribing proton pump inhibitors. Canadian Family Physician. 2017
Long-term PPI 2017(15)	Freedberg, D. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology. 2017
NICE NSAID 2015(16)*	NICE. Non-steroidal anti-inflammatory drugs. Key therapeutic topic. 2015
NICE rheumatoid arthritis 2009(17)*	NICE. Rheumatoid arthritis in adults: management. Clinical guideline. 2009
NICE osteoarthritis 2014(18)*	NICE. Osteoarthritis: care and management. Clinical guideline. 2014

Table 11: Selected guidelines and their abbreviations as used in this report.

* These guidelines were discussed, at the request of the Organising Committee, only for their recommendations concerning PPIs for gastroprotection in long-term NSAID use. As none of these guidelines performed a search to answer this particular question, and no evidence or rationale is provided for these recommendations, we did not perform a review of the methodology of these guidelines. Recommendations taken from these guidelines can be regarded as expert opinion.

4.2 Recommendations from guidelines

4.3 Interventions for dyspepsia

Two guidelines make recommendations about the management of dyspepsia (NICE GORD 2014 and ACG/CAG DYSPEPSIA 2017).

Both guidelines differentiate between uninvestigated dyspepsia and functional dyspepsia.

Uninvestigated dyspepsia:

NICE GORD 2014 recommends to offer lifestyle advice, including advice on:

- healthy eating
- weight reduction
- smoking cessation
- avoiding known triggers
- raising the head of the bed
- having the main meal well before going to bed

Both guidelines recommend to offer "test and treat" for H. pylori.

Both guidelines recommend to offer empirical treatment with a PPI:

- ACG/CAG: if H. pylori tests negative or if eradication does not alleviate symptoms;
- NICE recommends an empirical full-dose PPI for 4 weeks, with or without H. pylori testing.

If symptoms are recurring, NICE GORD 2014 recommends stepping down the PPI to the lowest effective dose or to an "as needed" strategy.

If symptoms are resistant to PPI treatment, both guidelines recommend different strategies:

- NICE GORD 2014 recommends to try treatment with an H2RA.
- ACG/CAG DYSPEPSIA 2017 recommends to try either a tricyclic antidepressant or prokinetics, or, if medical treatment fails, to offer psychological treatment.

Functional dyspepsia:

NICE GORD 2014 recommends to offer lifestyle advice, including advice on:

- healthy eating

- weight reduction
- smoking cessation
- avoiding known triggers
- raising the head of the bed
- having the main meal well before going to bed

Both guidelines recommend to offer H. pylori testing, and eradication if H. pylori is present.

If H. pylori eradication was not successful, or H.pylori was not present:

- NICE GORD 2014 recommends to offer either a low-dose PPI or an H2RA for 4 weeks;
- ACG/CAG recommends PPI therapy.

If symptoms continue or recur:

- NICE GORD 2014 recommends PPI or H2RA at the lowest possible dose or taken on demand. NICE GORD 2014 also advises to suggest it may be appropriate to return to self-treatment with antacids or alginate therapy.

If symptoms do not get better with PPI therapy:

- ACG/CAG DYSPEPSIA 2017 recommends to offer tricyclic antidepressants. If this does not help, prokinetics can be offered. If no medical therapy helps, ACG/CAG recommends offering psychological therapy.

ACG/CAG DYSPEPSIA 2017 did not mention duration of treatments.

4.4 Interventions for GORD

Three guidelines make recommendations about interventions for GORD and reflux symptoms (NICE GORD 2014, GORD 2013, Long-term PPI 2017).

Two guidelines recommend advising lifestyle changes (NICE GORD 2014 , GORD 2013)
Both recommend:

- weight reduction
- raising the head of the bed
- having the main meal well before going to bed

NICE GORD 2014 additionally recommends:

- healthy eating
- smoking cessation
- avoiding known triggers; while GORD 2013 advises against routinely avoiding (general) triggers.

A PPI is recommended for 4-8 weeks in one guideline (NICE GORD 2014), for 8 weeks in another (GORD 2013)

If symptoms recur after the PPI therapy:

- three guidelines (NICE GORD 2014 , GORD 2013, Long-term PPI 2017) recommend a maintenance therapy of PPI at the lowest dose possible or as needed.
- One guideline (Long-term 2017) recommends to refer the patient to exclude a functional problem before committing to lifelong PPI therapy.

If the response to PPIs is partial, one guideline (GORD 2013) recommends:

- taking PPIs twice a day instead of once a day;
- to switch PPIs;
- or to switch to or add an H2RA.

If there is no response to PPIs;

- NICE recommends to try H2RA;
- GORD 2013 recommends to refer the patient to exclude other causes.

If PPI are effective but not tolerated, or if the patient does not wish to take continuous PPI:

- reflux surgery is recommended by two guidelines (NICE GORD 2014, GORD 2013)

4.5 Interventions for oesophagitis

Three guidelines make recommendations about interventions for oesophagitis (NICE GORD 2014, GORD 2013, Long-term PPI 2017).

Two guidelines recommend advising lifestyle changes (NICE GORD 2014 , GORD 2013)

Both recommend:

- weight reduction
- raising the head of the bed
- having the main meal well before going to bed

NICE GORD 2014 additionally recommends:

- healthy eating
- smoking cessation
- avoiding known triggers; while GORD 2013 advises against routinely avoiding (general) triggers.

A PPI, for healing, is recommended for 8 weeks in two guidelines (NICE GORD 2014, GORD 2013).

If the response to PPIs is partial:

- GORD 2013 recommends taking PPIs twice a day instead of once a day, or to switch PPIs.

If there is no response to PPIs:

- NICE recommends to either continue the same PPI in a double dose, or to switch to another PPI (either standard dose or double dose).
- GORD 2013 recommends to refer the patient to exclude other causes.

A long-term PPI maintenance therapy is recommended by three guidelines (NICE GORD 2014 , GORD 2013, Long-term 2017).

4.6 Interventions for Barrett's oesophagus

Note: we sought recommendations specifying the role of PPIs in the management of Barrett's oesophagus, and information comparing PPIs to other treatments. We did not seek further

recommendations regarding surveillance or specialised treatment (e.g. endoscopic therapy, surgery). For more information on these treatments, please refer to the full guidelines.

Four guidelines mentioned the use of PPI's in the management of Barrett's oesophagus (Australia Barrett 2015, British Society Barrett 2014, Long-term PPI 2017, ACG BARRETT 2016).

Three guidelines recommend PPI's for the symptomatic management of reflux symptoms (Australia Barrett 2015, British Society Barrett 2014, Long-term PPI 2017).

Two guidelines recommend long-term PPIs as a preventive measure against malignant progression (ACG BARRETT 2016, Long-term PPI 2017).

Two guidelines specifically mention that there is insufficient evidence to recommend the use of a PPI as a chemopreventive agent (Australia Barrett 2015, British Society Barrett 2014).

4.7 Gastroprotection

Four guidelines recommend prescribing a PPI for people taking NSAID, for as long as the NSAID is taken (Long-term PPI 2017, NICE Rheumatoid arthritis 2009, NICE Osteoarthritis 2014, NICE NSAID 2015).

One guideline recommends this for patients at high risk for ulcer-related bleeding from NSAIDs, but does not specify how to determine a patient is at high risk (Long-term PPI 2017).

The NICE guidelines recommend to:

- co-prescribe a PPI in patients with rheumatoid arthritis or osteoarthritis taking NSAID;
- consider co-prescribing a PPI in patients taking NSAID for low back pain.

We did not find recommendations regarding the use of PPI when taking low-dose aspirin or clopidogrel in the selected guidelines.

4.8 Deprescribing PPIs

Three guidelines mention deprescribing PPIs (NICE GORD 2014, Deprescribing 2017, Long-term PPI 2017)

Two of these guidelines mention this deprescribing is meant for patients with dyspepsia (NICE GORD 2014, Deprescribing 2017), mild to moderate GORD or healed oesophagitis (Deprescribing 2017).

Three guidelines recommend lowering the PPI dose when prescribing PPIs long-term (NICE GORD 2014 , Deprescribing 2017, Long-term PPI 2017).

One guideline (NICE GORD 2014) recommends encouraging step-wise reduction:

- Using the lowest effective dose;
- then an as needed-use;
- then returning to self-treatment with an antacid or alginate therapy.

One guideline recommends either lowering the dose or using an as-needed approach (Deprescribing 2017).

H2RAs are suggested as an alternative to PPIs in one guideline (Deprescribing 2017).

4.9 Recommendations regarding adverse events

Two guidelines make recommendations concerning adverse events associated with PPIs (GORD 2013 and Long term PPI 2017).

One guideline recommends switching PPIs in the setting of adverse events (GORD 2013), the other guideline does not (Long-term PPI 2017).

One guideline (GORD 2013) suggests care with PPI use in:

- people at risk for Clostridium difficile infection;
- patients with known osteoporosis and additional risk factors for hip fracture .

One guideline(GORD 2013) recommends against altering PPI therapy in:

- patients with osteoporosis (without additional risk factors for hip fracture);
- clopidogrel users.

One guideline recommends against routinely taking probiotics, additional calcium, vitamin B12 or magnesium to avoid risks associated with long-term PPI use (Long-term 2017).

One guideline recommends against routinely screening or monitoring bone mineral density, serum creatinine, magnesium, or vitamin B12 in PPI users (Long-term 2017).

5 Dyspepsia. Summaries and conclusions

5.1.1 PPI vs placebo

PPI vs placebo in dyspepsia			
Bibliography: Cochrane Pinto-Sanchez 2017(4), including Blum 2000(19), Bolling-Sternevald 2002(20), Catapani 2015(21), Farup 1999(22), Fletcher 2011(23), Gerson 2005(24), Hengels 1998(25), Iwakiri 2013(26), Majewski 2016(27), Peura 2004(28), Suzuki 2013(29), Talley 1998a(30), Talley 1998b(30), Talley 2007(31), Tominaga 2010(32), Tominaga 2010(32), Van Zanten 2006(33), Wong 2002(34)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Global symptoms of dyspepsia Using the most stringent definition of "not symptom-free"	6172 (18 studies) 2 weeks-6 months	PPI: 2811/ 4079 Placebo: 1552/2093 **RR 0.88 (95%CI 0.82 to 0.94)** **SS in favour of PPI**	⊕⊕⊖⊖ **LOW** Study quality: -1 (8 studies did not meet our inclusion criteria for duration or sample size; risk of incomplete outcome data in 6 studies) Consistency: -1 (inconsistency between studies) Directness: ok Imprecision: ok
Quality of Life	1177 (2 studies) 4 weeks 453 (1 study) 4 weeks	Psychological General Well-being Index MD 0.54 (95%CI -1.55 to 2.63) NS 36-Item Short Form MD -1.11 (95%CI -5.32 to 3.10) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1 (95%CI includes both appreciable harm and benefit)
Adverse events	2693 (6 studies) 2 weeks-8 weeks	PPI: 264/1909 Placebo: 133/784 RR 0.99 (0.73 to 1.33) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (3 studies did not meet our inclusion criteria for duration or sample size; risk of incomplete outcome data in two studies) Consistency: ok Directness: ok Imprecision: ok

Table 12

In this systematic review and meta-analysis, RCTs were sought that compared PPI to placebo in patients with a diagnosis of functional dyspepsia.

18 RCTs were found. The duration of the RCTs varied from 2 weeks to 6 months.

Eight of the studies did not meet our inclusion criteria for duration or sample size. One RCT had unclear blinding. In six studies there was an unclear to high risk of incomplete outcome data. These problems could lead to bias and limit our confidence in the results.

PPI treatment resulted in **fewer global symptoms of dyspepsia** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **quality of life** between PPI and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **adverse events** between PPI and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

5.1.2 PPI vs lifestyle

No RCTs that compared PPIs with lifestyle, and that met our inclusion criteria, were found.

5.1.3 PPI vs antacids

No RCTs that compared PPIs with antacids, and that met our inclusion criteria, were found.

5.1.4 PPI vs H2RA

PPI vs H2RA in dyspepsia			
Bibliography: Cochrane Pinto-Sanchez 2017(4), including Blum 2000(19), Dillon 2004(35)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Global symptoms of dyspepsia Using the most stringent definition of "not symptom-free"	740 (2 studies) 2 weeks-8 weeks	PPI: 314/468 H2RA: 201/272 RR 0.88 (95%CI 0.74 to 1.04) NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (one study very short duration, one study with very limited information and unclear to high risk of bias) Consistency: ok Directness: ok Imprecision: ok
Adverse events	589 (1 study) 2 weeks	PPI: 57/395 H2RA: 29/194 RR 0.97 (95%CI 0.64 to 1.46) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (study did not meet our inclusion criteria for duration) Consistency: NA Directness: ok Imprecision: -1 (95%CI includes both appreciable benefit and harm)

Table 13

In this systematic review and meta-analysis, RCTs were sought that compared PPI to H2RA in patients with a diagnosis of functional dyspepsia.

2 RCTs were found. The duration of the RCTs varied from 2 weeks to 8 weeks.

One study had a very short duration (2 weeks). There was very limited information about the other study, as only an abstract was available. This could lead to bias and limits our confidence in the results.

There was **no statistically significant difference** in **global symptoms of dyspepsia** between PPI and H2RA.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **adverse events** between PPI and H2RA.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

5.1.5 PPI vs prokinetics

PPI vs prokinetics in dyspepsia			
Bibliography: Cochrane Pinto-Sanchez 2017(4), including Hsu 2011(36), Jiang 2011(37), Jung 2016(38), Kamiya 2017(39), Li 2003(40)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Global symptoms of dyspepsia Using the most stringent definition of "not symptom-free"	1033 (5 studies) 2 weeks -4 weeks	PPI: 272/520 Prokinetics: 298/513 **RR 0.89 (0.81 to 0.99)** **SS in favour of PPI**	⨁⨁⨀⨀ **LOW** Study quality: -2 (3 very short studies, one open label) Consistency: ok Directness: ok Imprecision: ok
Quality of Life Nepean Dyspepsia index MCID: 10 points	262 (1 study) 4 weeks	MD -0.50 (-4.42 to 3.42) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Adverse events	1033 (5 studies) 2 weeks -4 weeks	PPI: 64/520 Prokinetics: 58/513 RR 1.09 (0.79 to 1.49)	⨁⨁⨀⨀ **LOW** Study quality: -2 (3 very short studies, one open label) Consistency: ok Directness: ok

		NS	Imprecision: -1 (95%CI includes both appreciable benefit and harm)

Table 14

In this systematic review and meta-analysis, RCTs were sought that compared PPI to prokinetics in patients with a diagnosis of functional dyspepsia.

5 RCTs were found. The duration of the RCTs varied from 2 weeks to 4 weeks.

Three of the studies had a very short duration (2 weeks). One RCT had an open-label design. These problems could lead to bias and limit our confidence in the results.

PPI treatment resulted in **fewer global symptoms of dyspepsia** compared to prokinetics treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **quality of life** between PPI and prokinetics.
GRADE: HIGH quality of evidence
We have high confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **adverse events** between PPI and prokinetics.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

5.1.6 PPI step-up vs step-down treatment

Step up versus step-down in dyspepsia			
Bibliography: van Marrewijk 2009 DIAMOND(5)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Treatment success Defined as adequate symptom relief at 6 months, indicated by a "yes" or "no" answer.	645 (1 study) 6 months	Step-up : 238/332 Step-down : 219/313 OR 0.92 (95%CI 0.7 to 1.3) p=0.63 NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (modified ITT) Consistency: NA Directness: ok Imprecision: ok
Quality of Life (Worsened) (EuroQoL-5D)	545 (1 study) 6 months	Step-up : 36/325 Step-down : 41/220 p=0.53	⊕⊕⊖⊖ **LOW** Study quality: -1 (large proportion of participants did not complete QoL questionnaire and were not analysed – large imbalance

		NS	between groups) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)
Adverse events	664 (1 study) 6 months	Step-up : 94/341 Step-down : 93/323 p=0.73 NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: -1 (unable to assess)

Table 15

In this double blind RCT, a step-up treatment (stepwise treatment with an antacid, then an H2RA if the antacid was insufficient to control symptoms, and a PPI next if the H2RA was insufficient) was compared to a step-down treatment (reverse order: PPI, H2RA, antacid)in 664 patients with new-onset symptoms of dyspepsia.

The mean age of participants was 55y, 35% of the patients were H. pylori positive. The patients underwent no endoscopic diagnosis before trial initiation. The duration of follow-up was 6 months.

The interpretation of these results is somewhat limited because only patients with data for the outcome at 6 months were analysed.

There was **no statistically significant difference** in **treatment success** between step-up and step-down treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **quality of life** between step-up and step-down treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **adverse events** between step-up and step-down treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

6 GORD. Summaries and conclusions

6.1.1 PPI vs placebo

PPi vs placebo in non-erosive reflux disease			
Bibliography: Zhang 2013(41), including Bytzer 2004(42), Fass 2009(43), Kahrilas 2005(44), Kinoshita 2011(45), Lind 1997(46), Lind 1999(47), Miner 2002(48), Richter 2000(49), Talley 2001(50), Talley 2002(51), Uemura 2008(52)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of symptomatic relief	5416 (11 studies) 4 weeks- 6 months	PPI: 1546/3287 placebo: 573/2129 **RR 1.90 (1.57 to 2.30)** **SS in favour of PPI**	⨁⨁⨀⨀ **LOW** Study quality: -1 (inadequate reporting of allocation concealment in 11 and unclear randomisation method in 10 studies) Consistency: -1 (high heterogeneity I^2=84%) Directness: ok Imprecision: ok
Adverse events	4150 (8 studies) 4 weeks- 6 months	PPI: 530/2494 placebo: 404/1656 RR 1.00 (0.90 to 1.12) NS	⨁⨁⨁⨀ **MODERATE** Study quality: -1 (inadequate reporting of allocation concealment in 8 and unclear randomisation method in 7 studies) Consistency: ok Directness: ok Imprecision: ok

Table 16

In this systematic review and meta-analysis, RCTs were sought that compared proton pump inhibitors to placebo in patients with non-erosive reflux disease.

11 RCTs were found. The duration of the RCTs varied from 4 weeks to 6 months.

None of the 11 RCTs adequately reported allocation concealment and 10 had an unclear reporting of randomization method. This could lead to bias and limits our confidence in the results.

PPI treatment resulted in **a higher rate of symptomatic relief** compared to placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **adverse events** between PPIs and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

6.1.2 PPI vs lifestyle

No RCTs that compared PPIs with lifestyle, and that met our inclusion criteria, were found.

6.1.3 PPI vs antacids

Alginates versus PPI in non-erosive GORD			
Bibliography: Chiu 2013(53)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Percentage of patients achieving adequate heartburn or regurgitation relief* *defined as no more than 1 day of mild heartburn or regurgitation episodes in the last 7 days	195 (1 study) 4 weeks	Sodium alginate: 49/92 Omeprazole: 46/91 MD 2.7% (95%CI -11.9% to 17.4%) p=0.175 NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: -1 (wide confidence interval)
Change from baseline of the Reflux Disease Questionnaire total score	195 (1 study) 4 weeks	Sodium alginate: -12.4 SD 8.4 Omeprazole: -11.4 SD 9.8 p= 0.487 NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: -1 (unable to assess)
Adverse events	195 (1 study) 4 weeks	Sodium alginate: 5.4% Omeprazole: 5.5% No severe adverse events reported NT	Not applicable

Table 17

In this double blind RCT, an oral suspension of sodium alginate (3x/day) was compared to omeprazole 20 mg 1x/day in 195 patients with non-erosive GORD.

The mean age was 47 y, 20.5% of the patients were H. pylori positive. The patients underwent endoscopic diagnosis before trial initiation. The duration of follow-up was 4 weeks.

There were no major methodological remarks for this RCT.

There was **no statistically significant difference** in **percentage of patients achieving adequate heartburn or regurgitation relief** between sodium alginate and omeprazole.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **change from baseline of the Reflux Disease Questionnaire** between sodium alginate and omeprazole.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

6.1.4 PPI vs H2RA

PPi vs H2RA in non-erosive reflux disease			
Bibliography: Zhang 2013(41), including Armstrong 2001(54), Fujiwara 2005(55), Juul-Hansen 2009(56), Kobeissy 2012(57), Nakamura 2010(58), Richter 2000(49), Talley 2002(59)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of symptomatic relief	1678 (6 studies) 4 weeks - 6months	PPI: 350/834 H2RA: 219/844 **RR 1.63 (1.42 to 1.87)** **SS in favour of PPI**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (2 RCTs too small; 3 with inadequate allocation concealment; 2 with unclear randomisation and blinding) Consistency: ok Directness: ok Imprecision: ok
Adverse events	565 (3 studies) 4 weeks- 6 months	PPI: 120/287 H2RA: 126/278 RR 0.93 (0.87 to 1.11) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (1 RCT too small; 2 with inadequate allocation concealment) Consistency: ok Directness: ok Imprecision: ok

Table 18

In this systematic review and meta-analysis, RCTs were sought that compared PPI to H2RA in patients with non-erosive reflux disease.

7 RCTs were found. The duration of the RCTs varied from 4 weeks to 6 months.

3 RCTs did not meet our inclusion criteria for sample size. None of the study adequately reported allocation concealment, and most did not clearly report the method of randomization. These problems could lead to bias and limit our confidence in the results.

Treatment with PPIs resulted in **a higher rate of symptomatic relief** compared to treatment with H2RAs.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **adverse events** between PPIs and H2RAs.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

6.1.5 PPI vs prokinetics

PPI vs prokinetic in reflux symptoms or in endoscopy-negative reflux disease			
Bibliography: Cochrane Sigterman 2013(60), including Galmiche 1997(61), Hatlebakk 1999(62)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Heartburn remission **(empirical treatment)**	747 (2 studies) 4 to 8 weeks	PPI: 151/446 (33.9%) Prokinetic: 179/301 (59.5%) **RR 0.53 (0.32 to 0.87)** **SS in favour of PPI**	⨁⨁⨀⨀ **LOW** Study quality: -1 (insufficient information about allocation concealment, and unclear risk of selective reporting in 2 RCTs) Consistency: -1 (high heterogeneity I^2=87%) Directness: ok Imprecision: ok
Heartburn remission **(endoscopy negative reflux disease)**	302 (1 study) 4 weeks	PPI: 80/206 Prokinetic: 52/96 **RR 0.72 (0.56 to 0.92)** **SS in favour of PPI**	⨁⨁⨁⨀ **MODERATE** Study quality: -1 (insufficient information about allocation concealment, unclear risk of selective reporting) Consistency: NA Directness: ok Imprecision: ok

Table 19

In this systematic review and meta-analysis, RCTs were sought that compared PPIs to H2RAs in patients with reflux symptoms or with endoscopy-negative reflux disease. Participants had to be either from an empirical treatment group (no endoscopy used in treatment allocation) or from an endoscopy negative reflux disease group (no signs of erosive oesophagitis).

2 RCTs were found. The duration of the RCTs varied from 4 to 8 weeks.

Both RCTs had insufficient information about allocation concealment and an unclear risk of selective reporting. This could lead to bias and limits our confidence in the results.

Empirical treatment with PPIs resulted in **more heartburn remission** compared to empirical treatment with a prokinetic in patients with reflux symptoms.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Treatment with PPIs resulted in **more heartburn remission** compared to treatment with a prokinetic in patients with endoscopy-negative reflux disease.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

6.1.6 PPI vs surgery

6.1.6.1 *laparoscopic fundoplication surgery vs PPI*

Laparascopic fundoplication surgery versus medical management for GORD			
Bibliography: Garg 2015(63), including Anvari 2011(64), Grant 2008(65), Lundell 2008(66), Mahon 2005(67). RCT Galmiche 2011(68)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Estimated remission rates(PO) (5 years) defined for surgery group as need for additional medical treatment; for PPI group as insufficient symptom control even after 2 dose escalations	554 (1 study) 5 years	surgery: 85% PPI: 92% **p=0.048** **SS in favour of PPI**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (>20% drop-out, open label) Consistency: ok Directness: -1 (3 month run-in; only responders to esomeprazole were randomized) Imprecision: ok
Health-related QoL (<1 year)	605 (3 studies) 1 to 3 years	SMD 0.14 (-0.02 to 0.30) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (>20% drop-out in 2 RCTs, open label) Consistency: ok Directness: ok Imprecision: ok
Health-related QoL (1-5 years)	323 (2 studies) 1 to 3 years	SMD 0.03 (-0.19 to 0.24) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (>20% drop-out in 1 RCT, open label) Consistency: ok Directness: ok Imprecision: ok
GORD-specific QoL (< 1 year)	1160 (4 studies) 1 to 3 years	**SMD 0.58 (0.46 to 0.70)** **SS in favour of surgery**	⊕⊕⊖⊖ **LOW** Study quality: -2(>20% drop-out in 2 RCTs, unclear allocation concealment/randomization in 2 RCTs, open label) Consistency: ok Directness: ok Imprecision:ok
GORD-specific QoL (1-5 years)	994 (3 studies) 1 to 3 years	SMD 0.28 (-0.27 to 0.84) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 (>20% drop-out in 1 RCT, unclear allocation concealment/randomization in 1

			RCT, open label) Consistency: -1 (high heterogeneity: I^2=94%) Directness: ok Imprecision: ok
Serious adverse events	637 (2 studies) 3 years	Laparoscopic fundoplication: 60/331 Medical management: 38/306 **RR 1.46 (1.01 to 2.11)** **SS in favour of medical management**	⨁⨁⨀⨀ **LOW** Study quality: -2 (>20% drop-out in 1 RCT, unclear allocation concealment/randomization in 1 RCT, open label) Consistency: ok Directness: ok Imprecision: ok
Adverse events	83 (1 study) 3 years	Laparoscopic fundoplication: 7/43 Medical management: 0/40 RR 13.98 (0.82 to 237.07) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -2 (>20% drop-out in small study, open label) Consistency: NA Directness: ok Imprecision: -1 (very large CI)

Table 20

In this systematic review and meta-analysis, RCTs were sought that compared laparoscopic fundoplication with medical treatment with people with GORD.

4 RCTs were found. The duration of the RCTs varied from 1 year to 3 years.

Additionally, we separately reported the primary outcome at 5 years' follow-up of RCT Galmiche 2011(68) (LOTUS trial). A different publication of this trial was included in the systematic review, but at the 3-year timepoint.

All RCTs were open-label. We included these studies despite them being open-label, as one intervention arm concerned surgery and blinding is difficult in this situation. However, as the possibility to blind an RCT with a surgical arm does exist (by using sham surgery), we rated down the score. Three of the RCTs had more than 20% drop-out by the end of the trial. There was an unclear reporting of allocation concealment and randomization method in two RCTs. These problems could lead to bias and limit our confidence in the results.

PPI treatment resulted in **higher estimated remission rates** compared to laparoscopic antireflux surgery.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **Health-related QoL (at <1 year)** between PPI treatment and laparoscopic fundoplication surgery.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **Health-related QoL (at 1-5 years)** between PPI treatment and laparoscopic fundoplication surgery.
GRADE: LOW quality of evidence

We have low confidence that the results of the study reflect the true effect.

PPI treatment resulted in **lower GORD-specific QoL (< 1 year)** compared to laparoscopic antireflux surgery.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect

There was **no statistically significant difference** in **GORD-specific QoL (at 1-5 years)** between PPI treatment and laparoscopic fundoplication surgery.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

PPI treatment resulted in **fewer serious adverse events** compared to laparoscopic antireflux surgery.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect

There was **no statistically significant difference** in **adverse events** between PPI treatment and laparoscopic fundoplication surgery.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

6.1.7 PPI vs endoscopic procedures

6.1.7.1 *Transoral incisionless fundoplication vs PPI*

Transoral incisionless fundoplication versus PPI in GORD			
Bibliography: Hunter 2015(Hunter, Kahrilas et al. 2015)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Elimination of troublesome regurgitation (RDQ)	129 (1 study) 6 months	TIF/placebo: 58/87 Sham/PPI: 19/42 **p=0.023** **SS in favour of transoral incisionless fundoplication**	⊕⊕⊖⊖ **LOW** Study quality: -2 (severely unbalanced drop-out) Consistency: NA Directness: ok Imprecision: ok
Percent total time pH<4 intraoesophageal acid exposure	129 (1 study) 6 months	TIF/placebo: -2.9% Sham/PPI: +0.3% **p=0.003** **SS in favour of transoral incisionless fundoplication**	⊕⊕⊖⊖ **LOW** Study quality: -2 (severely unbalanced drop-out) Consistency: NA Directness: ok Imprecision: ok
Significant adverse events	129 (1 study)	TIF/placebo: 7/87 (8%) Sham/PPI: 1/42 (2.4%)	Not applicable

	6 months NT

Table 21

In this double blind RCT, transoral incisionless fundoplication (plus placebo) was compared to omeprazole 40 mg/day (plus sham surgery) in 129 patients with GORD and troublesome regurgitation, despite PPI treatment.

The median age was 52 y to 55y. The patients underwent endoscopic diagnosis of GORD before trial initiation. It is unknown what proportion of patients were H. pylori positive. The duration of follow-up was 6 months.

The interpretation of these results is limited by the severe imbalance of drop-out in both groups. The Transoral fundoplication group had 11.5% drop-out, while the PPI group had 31% drop-out.

Transoral incisionless fundoplication resulted in **more elimination of troublesome regurgitation** compared to PPI treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Transoral incisionless fundoplication resulted in **a lower proportion of time with an intra-oesophageal pH<4** compared to PPI treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

6.1.7.2 *Stretta procedure vs PPI*

No RCTs that compared PPIs with Stretta procedure, and that met our inclusion criteria, were found.

6.1.8 continuous PPI vs on demand PPI

Continuous PPI vs on demand PPI in GORD			
Bibliography: Ip(69), including Szucs 2009(70), Sjosted 2005(71), Morgan 2007(72), Bour 2005(73), Pace 2005(74)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
% of patients without symptoms **(heartburn and regurgitation)**	1935 (1 study) 6 months	Esomeprazole 20 mg 1x/day: 86% Esomeprazole 20 mg on demand: 80% **p<0.01** **SS in favour of once daily PPI**	⊕⊕⊖⊖ **LOW** Study quality: -2 (open label) Consistency: NA Directness: ok Imprecision: ok
Overall symptomatic relapse	477 (1 study) 6 months	Esomeprazole 20 mg 1x/day: 5.0% Esomeprazole 20 mg on demand: 5.7% p=0.77 NS	⊕⊖⊖ ⊖**VERY LOW** Study quality: -2 (open label) Consistency: NA Directness: ok; reflux oesophagitis Imprecision: -1; unable to assess
% of heartburn-free days	268 (1 study) 6 months	Rabeprazole 20 mg 1x/day: 90.3% Rabeprazole 20 mg on demand: 64.6% **p<0.0001** **SS in favour of once daily PPI**	⊕⊕⊖⊖ **LOW** Study quality: -2 (open label) Consistency: NA Directness: ok Imprecision: ok
% of patients with symptom relief	152 (1 study) 6 months	Rabeprazole 10 mg 1x/day: 86.4% Rabeprazole 10 mg on demand: 74.6% p=0.065 NS	⊕⊖⊖ ⊖**VERY LOW** Study quality: -2 (open label) Consistency: NA Directness: ok Imprecision: -1; unable to assess
QoLRAD Quality of Life in Reflux and Dyspepsia (QOLRAD) 25 items questionnaire of five dimensions with each item scored on a 7-grade Likert scale; lower values indicate more severe impact on daily functioning.	6017 (1 study) 6 months	Esomeprazole 20 mg 1x/day Esomeprazole 20 mg on demand **p<0.0001** **SS in favour of once daily PPI**	⊕⊕⊖⊖ **LOW** Study quality: -2 (open label) Consistency: NA Directness: ok Imprecision: ok

QoL Patient assessment of upper gastrointestinal disorders – quality of life questionnaire (PAGIQOL): 30-item questionnaire about the quality of life. The range for total PAGI-QOL is 0-5, with lower scores indicating better health.	268 (1 study) 6 months	Rabeprazole 20 mg 1x/day Rabeprazole 20 mg on demand **p<0.05** **SS in favour of once daily PPI**	⊕⊕⊖⊖ **LOW** Study quality: -2 (open label) Consistency: NA Directness: ok Imprecision: ok
% of patients in endoscopic remission	477 (1 study) 6 months	Esomeprazole 20 mg 1x/day: 81% Esomeprazole 20 mg on demand: 58% **p<0.0001** **SS in favour of once daily PPI**	⊕⊕⊖⊖ **LOW** Study quality: Consistency: NA Directness: reflux oesophagitis Imprecision: ok

Table 22

In this systematic review without meta-analysis, RCTs were sought that compared the effectiveness of different management options of adults with GORD.

5 RCTs were found that compared continuous (daily) PPI use to on-demand use of PPI for GORD. The duration of all the RCTs was 6 months.

All RCTs were open-label and sponsored by the industry. This could lead to bias and limits our confidence in the results.

One study concerned endoscopically confirmed reflux oesphagitis. The other four studies were done in patients with GORD or symptoms of GORD.

Continuous PPI use resulted in **a higher proportion of patients without symptoms** compared to on-demand use.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **overall symptomatic relapse** between continuous PPI use and on demand use.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

Continuous PPI use resulted in **a higher proportion of heartburn-free days** compared to on demand use.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **proportion of patients with symptom relief** between continuous PPI use and on demand use.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Continuous PPI use resulted in **a higher Quality of Life in Reflux and Dyspepsia (QoLRAD) score** compared to on demand use.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Continuous PPI use resulted in **a higher quality of life** compared to on demand use.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Continuous PPI use resulted in **a higher proportion of patients in endoscopic remission** compared to on demand use.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

6.1.9 PPI vs PPI

6.1.9.1 *Pantoprazole vs esomeprazole*

Pantoprazole vs esomeprazole in GORD			
Bibliography: Ip(69), including Goh 2007(75), Labenz 2009a(76), Labenz 2009b(77), Glatzel 2007(78), Bardhan 2007(79), Vcec 2006(80)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mean sum score of GI symptoms Symptoms included	1316 (1 study) 6 months	Pantoprazole 20 mg: 0.1 Esomeprazole 20 mg: 0.1 NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (unclear randomization and allocation concealment, industry sponsor) Consistency: NA Directness: ok Imprecision: ok

heartburn, acid regurgitation, dysphagia, epigastric pain/discomfort, retrosternal tightness, burping/ belching, nausea/vomiting, fullness, lower abdominal pain, and flatulence. The intensity of symptoms was scored as none (0), mild (1), moderate (2), and severe (3) by investigators.			
Heartburn resolution	3151 (1 study) 4 weeks	Pantoprazole 40 mg: 66.9% Esomeprazole 40 mg: 72.5% **OR 1.31 (1.12 to 1.54)** **p=0.0008** **SS in favour of esomeprazole**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (unclear randomization and allocation concealment, industry sponsor) Consistency: NA Directness: ok Imprecision: ok
Heartburn relapse	2766 (1 study) 4 weeks	Pantoprazole 20 mg: 17.4% Esomeprazole 20 mg: 9.8% More relapse in pantoprazole NT	Not applicable
Median 3-day mean ReQuest GI score ReQuest-GI comprises 4 dimensions of acid complaints, upper abdominal stomach complaints, lower abdominal/digestive complaints and nausea. Each dimension's score is a product of its intensity and frequency. The ReQuest-GI score is sum of the weighted scores of its four dimensions.	585 (1 study) 4 weeks	Pantoprazole 40 mg: 0.24 Esomeprazole 40 mg: 0.31 Pantoprazole non-inferior to esomeprazole	⨁⨁⨁⊖ **MODERATE** Study quality:-1 (industry sponsor) Consistency: NA Directness: ok Imprecision: ok
Rate of symptom relief	582 (1 study) 12 weeks	Pantoprazole 40 mg: 79% Esomeprazole 40 mg: 77% TD 2% (-4.7 to 8.8) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (industry sponsor) Consistency: NA Directness: ok

			Imprecision: ok
Heartburn-free days	180 (1 study) 8 weeks	Pantoprazole 40 mg: 69.8% Esomeprazole 40 mg: 70.2% NT "Similar"	Not applicable
Endoscopic healing	582 (1 study) 12 weeks	Pantoprazole 40 mg: 91% Esomeprazole 40 mg: 88% TD 2% (-1.75, 8.27) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (industry sponsor) Consistency: NA Directness: ok Imprecision: ok
Endoscopic healing	180 (1 study) 8 weeks	Pantoprazole 40 mg: 91.1% Esomeprazole 40 mg: 92.2% NT "Similar"	Not applicable

Table 23

In this systematic review without meta-analysis, RCTs were sought that compared the effectiveness of different management options of adults with GORD.

6 RCTs were found that compared pantoprazole to esomeprazole. The duration of the RCTs varied from 4 weeks to 6 months.

All RCTs concern endoscopically proven reflux oesophagitis, LA grade A to D.

In 5 RCTs, esomeprazole 40 mg 1x/day was compared to pantoprazole 40 mg 1x/day. In one RCT, esomeprazole 20 mg1x/day was compared to pantoprazole 20 mg 1x/day.

5 RCTs were industry-sponsored. The allocation concealment and method of randomization were unclear in 4 RCTs. These problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **mean sum score of GI symptoms** between esomeprazole and pantoprazole.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Esomeprazole resulted in **more heartburn resolution** compared to pantoprazole treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Pantoprazole was **non-inferior** to esomeprazole when assessed with the **median 3-day mean ReQuest GI score**.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **rate of symptom relief** between esomeprazole and pantoprazole.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **endoscopic healing** between esomeprazole and pantoprazole.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

6.1.9.2 *Rabeprazole vs esomeprazole*

Rabeprazole vs esomeprazole in GORD			
Bibliography: Ip(69), including Eggleston 2009(81), Fock 2005(82)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Complete resolution of heartburn	1392 (1 study) 4 weeks	Rabeprazole: 58.4% Esomeprazole: 20 mg 60.6% Esomeprazole 40 mg: 64.4% p=0.184 NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear alloc concealment, sponsored by industry) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)
Complete resolution of regurgitation	1392 (1 study) 4 weeks	Rabeprazole: 60.6% Esomeprazole: 20 mg 60.1% Esomeprazole 40 mg: 60.3% p=0.363 NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear alloc concealment, sponsored by industry) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)
Time to first 24-hour heartburn and regurgitation-free interval	134 (1 study) 4 weeks	Rabeprazole 10 mg Esomeprazole 20 mg NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear alloc concealment, sponsored by industry) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)
Resolution of heartburn	134 (1 study) 4 weeks	Rabeprazole: 8.5 days Esomeprazole: 9 days p=0.265 NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear alloc concealment, sponsored by industry) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)
Resolution of acid regurgitation	134 (1 study) 4 weeks	Rabeprazole: 6 days Esomeprazole: 7.5 days p=0.405	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear alloc concealment, sponsored by industry) Consistency: NA

		NS	Directness: ok Imprecision: -1 (unable to assess)
QoL (SF-36) SF-36 contains 8 scales and 2 summary scores with a range of scores from 0 -100; higher scores indicate better functioning and well-being.	1392 (1 study) 4 weeks	Rabeprazole 20 mg Esomeprazole 20 mg Esomeprazole 40 mg NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear alloc concealment, sponsored by industry) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)

Table 24

In this systematic review without meta-analysis, RCTs were sought that compared the effectiveness of different management options of adults with GORD.

2 RCTs were found that compared rabeprazole to esomeprazole. The duration of these RCTs was 4 weeks.

One RCT was performed in patients presenting to their general practitioner with symptoms of GORD, while the other RCT included patients who had endoscopically confirmed non-erosive reflux disease (LA classification grade 0).

Both RCTs compared rabeprazole 20 mg 1x/day to esomeprazole 20 mg 1x/day.

Both RCTs were sponsored by the industry, and had unclear allocation concealment. This could lead to bias and limits our confidence in the results.

There was **no statistically significant difference** in **complete resolution of heartburn** between rabeprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **complete resolution of regurgitation** between rabeprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **time to first 24-hour heartburn and regurgitation-free interval** between rabeprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **resolution of heartburn** between rabeprazole and esomeprazole.
GRADE: LOW quality of evidence

We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **resolution of acid regurgitation** between rabeprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **quality of life** between rabeprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

6.1.9.3 *Lansoprazole vs esomeprazole*

Lansoprazole vs esomeprazole in GORD			
Bibliography: Ip(69), including Fass 2006(83)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
% of heartburn-free days	328 (1 study) 8 weeks	Lansoprazole: 57.5% Esomeprazole: 54.4% LS MD -3.1 (-9.02 to 2.87) esomeprazole is non-inferior to lansoprazole	⊕⊕⊖⊖ **LOW** Study quality: -1 (industry-sponsored) Consistency: NA Directness: -1 (persistent symptoms on lansoprazole) Imprecision: ok
% of epigastric pain free days	328 (1 study) 8 weeks	Lansoprazole: 66.9% Esomeprazole: 65% LS MD -1.9 (-7.27 to 3.41) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (industry-sponsored) Consistency: NA Directness: -1 (persistent symptoms on lansoprazole) Imprecision: ok
% of acid regurgitation-free days	328 (1 study) 8 weeks	Lansoprazole: 65.3 % Esomeprazole: 60.3% LS MD -5 (-10.41 to 10.40) NS	⊕⊖⊖ ⊖**VERY LOW** Study quality: -1 (industry-sponsored) Consistency: NA Directness: -1 (persistent symptoms on lansoprazole) Imprecision: -1 (wide confidence interval)

Table 25

In this systematic review without meta-analysis, RCTs were sought that compared the effectiveness of different management options of adults with GORD.

One RCT was found that compared lansoprazole to esomeprazole. The duration of this RCT was 8 weeks.

This RCT was performed in patients with persistent heartburn symptoms, while receiving lansoprazole 30 mg once daily.

It compared lansoprazole 30 mg 2x/day to esomeprazole 40 mg 1x/day.

It was sponsored by the industry. This could lead to bias and limits our confidence in the results.

Esomeprazole was **non-inferior** to lansoprazole for **% of heartburn-free days**.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **% of epigastric pain free days** between esomeprazole and lansoprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **% of acid regurgitation-free days** between esomeprazole and lansoprazole.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

6.1.9.4 *Esomeprazole vs omeprazole*

Omeprazole vs esomeprazole in GORD			
Bibliography: Teng 2015(84), including Armstrong 2004(85)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Resolution of heartburn *defined as no days with heartburn episodes during the last 7 days before day 28	2645 (3 studies) 4 weeks	<u>Study A</u> Esomeprazole 40mg: 56.7 % Esomeprazole 20mg: 60.5 % Omeprazole 20mg: 58.1 % NS <u>Study B</u> Esomeprazole 40mg: 70.3 % Omeprazole: 20mg: 67.9 % NS <u>Study C</u> Esomeprazole 20mg: 61.9 % Omeprazole 20mg: 59.6 %	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear allocation concealment and randomization, industry-sponsored) Consistency: ok Directness: ok Imprecision: -1 (unable to assess)

	NS

Table 26

In this systematic review and meta-analysis, RCTs were sought that esomeprazole to omeprazole in adults with GORD.

One publication was found; it reported on 3 RCTs with an identical design. The duration of the RCTs was 4 weeks.

These RCTs were performed in patients with endoscopy-negative reflux disease.

In one study, esomeprazole 20 mg 1x/day was compared to omeprazole 20 mg 1x/day. In one study, esomeprazole 40 mg 1x/day was compared to omeprazole 20 mg 1x/day. In one study, esomeprazole 40 mg 1x/day and esomeprazole 20 mg 1x/day were compared to omeprazole 20 mg 1x/day.

These RCTs had unclear reporting of allocation concealment and randomization method. They were all industry-sponsored. These problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **the resolution of heartburn** between esomeprazole and omeprazole.
GRADE: LOW of evidence
We have low confidence that the results of the study reflect the true effect.

7 Reflux oesophagitis. Summaries and conclusions

7.1.1 PPI vs placebo

7.1.1.1 *pantoprazole vs placebo*

Pantoprazole vs placebo in severe reflux oesophagitis			
Bibliography: NICE 2014(3), including Richter 2000(86)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Endoscopy-confirmed healing	153 (1 study) 8 weeks	Pantoprazole 20 mg: 45/65 (69%) Pantoprazole 40 mg: 51/60 (85.7%) Placebo: 2/28 (5.9%) **pantoprazole 20 mg or 40 mg vs placebo** **p<0.001** **SS in favour of pantoprazole**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (unclear allocation concealment, randomization, industry-sponsored) Consistency: NA Directness: ok Imprecision: ok

Table 27

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

1 RCT was found that compared pantoprazole to placebo for the healing of severe oesophagitis. The RCT had a follow-up of 8 weeks.

Pantoprazole 20 or 40 mg once daily was compared to placebo.

This RCT had unclear reporting of allocation concealment and randomization method, and was industry-sponsored. This could lead to bias and limits our confidence in the results.

Pantoprazole treatment resulted in **more endoscopy-confirmed healing** compared to placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

7.1.1.2 *lansoprazole vs placebo*

Lansoprazole vs placebo in severe reflux oesophagitis

Bibliography: NICE 2014(3), including Robinson 1996(87)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Patients remaining in remission after 12 months' treatment	98 (1 study) 12 months	patients with grade 3 erosive oesophagitis: Lansoprazole: 43/55 (78.8%) Placebo: 8/31 (26.5%) NT patients with grade 4 erosive oesophagitis: Lansoprazole: 9/12 (76.5%) placebo: 0 NT	Not applicable

Table 28

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

1 RCT was found that compared lansoprazole to placebo for the maintenance therapy of severe reflux oesophagitis. The RCT had a follow-up of 12 months.

Lansoprazole 15 or 30 mg once daily was compared to placebo.

Only the patients with oesophagitis grade C or D were evaluated in this meta-analysis. As a result, the sample size used for the meta-analysis was very small.

There was a higher proportion of patients remaining in remission after 12 months' treatment with lansoprazole in patients with grade 3 and grade 4 erosive oesophagitis, but no statistical testing was performed.

For this reason, GRADE could not be assessed.

7.1.2 PPI vs lifestyle

No RCTs that compared PPIs with lifestyle, and that met our inclusion criteria, were found.

7.1.3 PPI vs antacids

No RCTs that compared PPIs with antacids, and that met our inclusion criteria, were found.

7.1.4 PPI vs H2RA

7.1.4.1 *Lansoprazole vs ranitidine*

Lansoprazole vs H2RA in severe reflux oesophagitis			
Bibliography: NICE 2014(3); including Jansen 1999(88), Robinson 1995(89)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Endoscopy confirmed healing rates	161 (2 studies) 8 weeks	Jansen 1999 lansoprazole: 10/11 (91%) ranitidine: 7/16 (44%) NT Robinson 1995 lansoprazole: 48/63 (76.8%) ranitidine: 46/71 (64.2%) NT	Not applicable

Table 29

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

2 RCTs were found that compared lansoprazole to ranitidine for the healing of severe oesophagitis. The RCTs had a follow-up of 8 weeks.

Lansoprazole 30 mg once daily was compared to ranitidine 150 mg twice daily in one RCT, and to ranitidine 300 mg twice daily.

Only the patients with oesophagitis grade C or D were evaluated in this meta-analysis. As a result, the sample size used for the meta-analysis was very small.

There was a higher proportion of patients with endoscopy-confirmed healing with lansoprazole, compared to ranitidine, in patients with grade 3 and grade 4 erosive oesophagitis, but no statistical testing was performed.

For this reason, GRADE could not be assessed.

7.1.4.2 *Pantoprazole vs ranitidine*

Pantoprazole vs H2RA in severe reflux oesophagitis			
Bibliography: NICE 2014(3), including Koop 1995(90), Meneghelli 2002(91), Metz 2003(92), Richter 2004(93)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Endoscopy-confirmed healing rates **after 4 weeks' treatment**	92 (2 studies) 8 weeks	<u>Koop 1995</u> pantoprazole: 17/30 (56%) ranitidine: 9/14 (63%) <u>Meneghelli 2002</u> pantoprazole: 20/24 (82%) ranitidine: 10/24 (43%)	Not applicable
% of patients remaining in remission **after 12 months' treatment**	83 (1 study) 12 months	Pantoprazole 20 mg: 15/23 (64.3%) Pantoprazole 40 mg: 16/26 (62.1%) ranitidine: 3/34 (9.3%) **pantoprazole (20 or 40 mg) versus ranitidine:** **p<0.001** **SS in favour of pantoprazole**	⊕⊕⊖⊖ **LOW** Study quality: -2 (very small sample size, unclear allocation concealment, unclear randomization, industry-sponsored) Consistency: NA Directness: ok Imprecision: ok
Endoscopy-confirmed maintenance of healing (no relapse of erosive oesophagitis) **within 12 months of start of maintenance therapy**	76 (1 study) 12 months	Pantoprazole 20 mg: 17/31 (53.6%) Pantoprazole 40 mg: 14/19 (71.1%) ranitidine: 5/26 (19.6%) **pantoprazole 20 mg versus ranitidine:** **p<0.05** **SS in favour of pantoprazole 20 mg** **pantoprazole 40 mg versus ranitidine:** **p<0.01** **SS in favour of pantoprazole 40 mg**	⊕⊕⊖⊖ **LOW** Study quality: -2 (very small sample size, industry-sponsored) Consistency: NA Directness: ok Imprecision: ok

Table 30

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

4 RCTs were found that compared pantoprazole to ranitidine. The duration of the RCTs varied from 8 weeks to 12 months.

Two RCTs evaluated the healing of reflux oesophagitis and compared pantoprazole 40 mg once daily to ranitidine 150 mg twice daily. Two RCTs evaluated the maintenance therapy of reflux oesophagitis and compared pantoprazole 20 or 40 mg once daily to ranitidine 150 mg twice daily.

This systematic review only evaluated patients with grade 3 or 4 erosive oesophagitis, which resulted in a very small sample size for the meta-analyses. Furthermore, one RCT had unclear allocation concealment and randomization methods, and all RCTs were industry-sponsored. These problems could lead to bias and limit our confidence in the results.

Pantoprazole resulted in **a higher proportion of patients remaining in remission** compared to ranitidine.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Pantoprazole resulted in **more endoscopy-confirmed maintenance of healing** compared to ranitidine.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

7.1.5 PPI vs PPI

7.1.5.1 *Esomeprazole vs lansoprazole*

Esomeprazole vs lansoprazole in severe reflux oesophagitis			
Bibliography: NICE 2014(3), including Fennerty 2005(94), Castell 2002(95), DeVault 2006(96), Lauritsen 2003(97)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Endoscopy-confirmed healing	6240 (2 studies) 8 weeks	After 8 weeks Fennerty 2005 Esomeprazole : 77.5% Lansoprazole: 73.3% P=0.099 NS Castell 2002 Esomeprazole : 552/640 (86%) Lansoprazole: 477/646 (74%)	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: -1 Directness: ok Imprecision: -1 (unable to assess)

		NT	
% of patients remaining in remission **After 6 months treatment**	468 (2 studies) 6 months	<u>DeVault 2006</u> Esomeprazole : 96/121 (79.3%) Lansoprazole: 91/131 (69.5%) P not reported NT <u>Lauritsen 2003</u> Esomeprazole : 87/114 (76%) Lansoprazole: 60/102 (59%) **P<0.01** **SS in favour of esomeprazole**	⊕⊕⊖⊖ **LOW** Study quality: -1 (1 RCT with unbalanced and large drop-out, both industry-sponsored) Consistency: ok Directness: ok Imprecision: -1 (unable to assess)

Table 31

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

4 RCTs were found that compared esomeprazole to lansoprazole. The duration of the RCTs varied from 8 weeks to 6 months.

Two RCTs evaluated the healing of reflux oesophagitis and compared esomeprazole 40 mg once daily to lansoprazole 30 mg once daily. Two RCTs evaluated the maintenance therapy of reflux oesophagitis and compared esomeprazole 20 mg once daily to lansoprazole 15 mg once daily.

One RCT had a drop-out of 18%, which was also unbalanced: more participants in the lansoprazole group dropped out. All 4 RCTs were sponsored, and by the same firm. This could lead to bias and limits our confidence in the results.

There was **no statistically significant difference** in **endoscopy-confirmed healing** between esomeprazole and lansoprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Esomeprazole resulted in **a higher proportion of patients remaining in remission** compared to lansoprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

7.1.5.2 *Rabeprazole vs esomeprazole*

Rabeprazole vs esomeprazole in severe reflux oesophagitis			
Bibliography: NICE 2014(3), including Laine 2011(98)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Endoscopy-confirmed healing	2120 (2 studies) 8 weeks	After 8 weeks Laine 2001a Rabeprazole: 80.0% Esomeprazole: 75.0% 95% CI for the difference between treatment groups: 0 to 10.0% Rabeprazole is non-inferior to esomeprazole Laine 2001b Rabeprazole: 77.5% Esomeprazole: 78.4% 95% CI for the difference between treatment groups: -5.9 to 4.0% Rabeprazole is non-inferior to esomeprazole	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

Table 32

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

2 RCTs (with identical study design, reported in one publication) were found that compared esomeprazole to rabeprazole. The duration of the RCTs was 8 weeks.

The RCTs compared esomeprazole 40 mg once daily to rabeprazole extended release 50 mg once daily.

Rabeprazole was **non-inferior** to esomeprazole for **endoscopy-confirmed healing.**
GRADE: HIGH quality of evidence
We have high confidence that the results of the study reflect the true effect.

7.1.5.3 *Omeprazole vs pantoprazole*

Omeprazole vs pantoprazole in severe reflux oesophagitis			
Bibliography: NICE 2014(3), including Mossner 1995(99)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Proportion of patients with endoscopy-confirmed healing **At 4 weeks**	58 (1 study) 4 weeks	Pantoprazole: 21/36 (59%) Omeprazole: 12/22 (53%) P>0.05 NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (very small sample size, unclear allocation concealment) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)

Table 33

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

1 RCT was found that compared omeprazole to pantoprazole. The duration of the RCT was 4 weeks.

Pantoprazole 40 mg once daily was compared to omeprazole 20 mg once daily.

This systematic review only evaluated patients with grade 3 or 4 erosive oesophagitis, which resulted in a very small sample size for the meta-analysis. Furthermore, this RCT had unclear allocation concealment. This could lead to bias and limits our confidence in the results.

There was **no statistically significant difference** in **proportion of patients with endoscopy-confirmed healing** between omeprazole and pantoprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

7.1.5.4 *Pantoprazole vs esomeprazole*

Pantoprazole vs esomeprazole in reflux oesophagitis
Bibliography: NICE 2014(3), including Gillessen 2004(100)

and Moraes-Filho 2014 (101)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Proportion of patients with endoscopy-confirmed healing **at 4 weeks**	593 (1 study) 8 weeks	<u>at 4 weeks</u> pantoprazole: 208/284 (73.2%) esomeprazole: 211/279 (75.6%) NS non-inferior	⊕⊕⊖⊖ **LOW** Study quality: -1 (industry-sponsored) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)
Proportion of patients with endoscopy-confirmed healing **at 8 weeks**	593 (1 study) 8 weeks	<u>at 8 weeks</u> pantoprazole: 246/284 (86.6%) esomeprazole: 253/279 (90.7%) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (industry-sponsored) Consistency:NA Directness: ok Imprecision: -1 (unable to assess)
Proportion of patients with endoscopy-confirmed healing **at 10 weeks**	37 (1 study) 10 weeks	<u>at 10 weeks</u> Pantoprazole: 12/18 (67%) Esomeprazole: 9/19 (45%) NT	not applicable
% patients in complete remission* at 4 weeks *defined as endoscopic healing AND symptom relief	593 (1 study) 8 weeks	<u>at 4 weeks</u> pantoprazole: 170/278 (61.2%) esomeprazole: 165/270 (61.1%) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (industry-sponsored Consistency: NA Directness: ok Imprecision: 1 (unable to assess)
% patients in complete remission* at 8 weeks *defined as endoscopic healing AND symptom relief	593 (1 study) 8 weeks	<u>at 8 weeks</u> pantoprazole: 224/276 (81.2%) esomeprazole: 210/267 (78.7%) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (industry-sponsored Consistency: NA Directness: ok Imprecision: 1 (unable to assess)
Symptom relief* **at 4 weeks** *defined as ReQuest-GI score <1.73 on the	593 (1 study) 8 weeks	<u>at 4 weeks</u> pantoprazole: 230/273 (84.2%) esomeprazole: 211/263 (80.2%)	⊕⊕⊖⊖ **LOW** Study quality: -1 (industry-sponsored) Consistency: NA Directness: ok Imprecision: 1 (unable to assess)

last 3 days		NS	
Symptom relief* **at 8 weeks** *defined as ReQuest-GI score <1.73 on the last 3 days	593 (1 study) 8 weeks	**<u>at 8 weeks</u>** **pantoprazole: 252/275 (91.6%)** **esomeprazole: 227/264 (86.0%)** **SS** **p=0.0370**	⊕⊕⊖⊖ **MODERATE** Study quality: -1 (industry-sponsored) Consistency: NA Directness: ok Imprecision: ok
Adverse events	593 (1 study) 8 weeks	pantoprazole: 95/290 (32.8%) esomeprazole: 104/288 (36.1%) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (industry-sponsored) Consistency: NA Directness: ok Imprecision: -1 (unable to assess)

Table 34

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

1 RCT was found that compared esomeprazole to pantoprazole. The duration of the RCT was 10 weeks.

Pantoprazole 40 mg once daily was compared to esomeprazole 40 mg once daily.

This systematic review only evaluated patients with grade 3 or 4 erosive oesophagitis, which resulted in a very small sample size for the meta-analysis. Furthermore, this RCT had unbalanced drop-out and was industry-sponsored. This could lead to bias and limits our confidence in the results.

Pantoprazole resulted in a greater proportion of patients with endoscopy-confirmed healing after 10 weeks, in patients with grade 3 and grade 4 erosive oesophagitis, but no statistical testing was performed.

For this reason, GRADE could not be assessed for this outcome.

We found an additional RCT, published after the final search date of the systematic review.

In this double blind RCT, pantoprazole 40 mg once daily was compared to esomeprazole 40 mg once daily in 593 patients with endoscopically confirmed erosive oesophagitis (LA grade A to D). The mean age was 43 y. The duration of follow-up was 4 weeks and an additional 4 weeks in nonresponding patients.

The interpretation of these results is somewhat limited by the lack of outcome measures with a confidence interval, and because it was an industry-sponsored trial.

Pantoprazole was **non-inferior** to esomeprazole for the **proportion of patients with endoscopy-confirmed healing at 4 weeks.**
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **proportion of patients with endoscopy-confirmed healing at 8 weeks** between pantoprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **proportion of patients in complete remission at 4 weeks** between pantoprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **proportion of patients in complete remission at 8 weeks** between pantoprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **symptom relief at 4 weeks** between pantoprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Pantoprazole resulted in **more symptom relief at 8 weeks** compared to esomeprazole.
GRADE: MODERATE HIGH quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **adverse events** between pantoprazole and esomeprazole.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

7.1.5.5 *Esomeprazole vs omeprazole*

Esomeprazole versus omeprazole in reflux oesophagitis			
Bibliography: Teng 2015(84), including Chen 2005(102), Kahrilas 2000(103), Lightdale 2006(104), Richter 2001(105), Schmitt 2006(106), Zheng 2009(107) H.pylori studies: Anagnostopoulos 2004(108), Choi 2007(109), Sheu 2005(110), Miehlke 2003(111), Subei 2007(112), Tulassay 2000(113), Veldhuyzen 2000(114), Veldhuyzen 2003(115)			
Outcomes	**N° of participants (studies)**	**Results**	**Quality of the evidence (GRADE)**

	Follow up		
Oesophagitis healing rates at week 8	6892 (6 studies) 8 weeks	Esomeprazole 40 or 20mg Omeprazole 20 mg **RR 1.06 (1.03 to 1.10)** **SS in favour of esomeprazole**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (one study small sample size, 4 sponsored by same firm, 5 unclear risk incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
Oesophagitis healing rates at week 4	5533 (3 studies) 8 weeks	Esomeprazole 40 or 20mg Omeprazole 20 mg **RR 1.12 (1.05 to 1.19)** **SS in favour of esomeprazole**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (all sponsored by same firm, unclear risk incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
Adverse effects	9200 (14 studies) 1 to 8 weeks	Esomeprazole vs omeprazole NS	⊕⊖⊖ ⊖**VERY LOW** Study quality: -1 (several studies did not meet our inclusion criteria) Consistency: ok Directness: -1 (mix of patients with reflux oesophagitis with 8-week therapy and H. pylori infection patients with 1-week PPI therapy) Imprecision: -1 unable to assess

Table 35

In this systematic review and meta-analysis, RCTs were sought that compared esomeprazole to omeprazole in adults with reflux oesophagitis.

6 RCTs were found. All of the RCTs had a follow-up of 8 weeks.

Esomeprazole 40 mg once daily was compared to omeprazole 20 mg once daily in 4 RCTs. Esomeprazole 20 mg once daily was compared to omeprazole 20 mg once daily in 1 RCT. Both doses of esomeprazole were compared to omeprazole 20 mg in 1 RCT.

One RCT had a very small sample size and did not meet our inclusion criteria. Four of the RCTs were sponsored by the industry and by the same firm. In 5 RCTs the risk of incomplete outcome data was unclear. These problems could lead to bias and limit our confidence in the results.

For the outcome “adverse effects”, 14 RCTs were analysed. 8 of these RCTs concerned patients undergoing eradication therapy for H. pylori infection.

Esomeprazole resulted in **more oesophagitis healing at week 8** compared to omeprazole.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Esomeprazole resulted in **more oesophagitis healing at week 4** compared to omeprazole.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **adverse effects** between esomeprazole and omeprazole.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

7.1.5.6 *Lansoprazole vs omeprazole*

Lansoprazole vs omeprazole in severe reflux oesophagitis			
Bibliography: NICE 2014(3)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Endoscopy-confirmed healing	82 (1 study) 8 weeks	Lansoprazole: 26/37 (70%) Omeprazole 27/38 (71%) NT	Not applicable

Table 36

In this systematic review and meta-analysis, RCTs were sought that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4).

1 RCT was found that compared omeprazole to lansoprazole. The duration of the RCT was 8 weeks.

Lansoprazole 30 mg once daily was compared to omeprazole 20 mg once daily.

This systematic review only evaluated patients with grade 3 or 4 erosive oesophagitis, which resulted in a very small sample size for the meta-analysis. This could lead to bias and limits our confidence in the results.

The proportion of endoscopy-confirmed healing was similar with lansoprazole and omeprazole, but no statistical testing was performed.

For this reason, GRADE could not be assessed.

7.1.5.7 *Rabeprazole vs omeprazole*

Rabeprazole vs omeprazole in reflux oesophagitis

Bibliography: Xia 2013(116), including Dekkers 1999(117), Delchier 2000(118), Adachi 2003(119), Pace 2005(120), Bytzer 2006(121), Pilotto 2007(122)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Endoscopic relief rates	1178 (5 studies) 8 weeks	Rabeprazole vs omeprazole RR 1.02 (0.99 to 1.05) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (1 RCT small sample size, 1 open label) Consistency: ok Directness: ok Imprecision: ok
Heartburn relief rates	1628 (4 studies) 1 to 8 weeks	Rabeprazole vs omeprazole RR 1.13 (1.03 to 1.25) **SS in favour of rabeprazole p= 0.012**	⊕⊖⊖ ⊖**VERY LOW** Study quality: -2 (1 RCT short duration, 1 open label, 1 with unclear allocation conc and randomization method) Consistency: -1 (heterogeneity I^2 >70%) Directness: ok Imprecision: ok
Adverse events	1126 (3 studies) 1 to 8 weeks	Rabeprazole vs omeprazole RR 1.06 (0.83 to 1.34) NS	⊕⊕⊖⊖ **LOW** Study quality: -2(1 RCT short duration, 1 with unclear allocation conc and randomization method) Consistency: ok Directness: ok Imprecision: ok

Table 37

In this systematic review and meta-analysis, RCTs were sought that compared rabeprazole to omeprazole in adults with erosive GORD.

6 RCTs were found. The duration of the RCTs varied from 1 to 8 weeks.

In all RCTs, rabeprazole 20 mg was compared to omeprazole 20 mg.

3 RCTs did not meet our inclusion criteria: one had a very small sample size, one a very short duration, and one was open label. One remaining RCT had unclear reporting of allocation concealment and randomization method. These problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **endoscopic relief rates** between rabeprazole and omeprazole.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Rabeprazole resulted in **more heartburn relief** compared to omeprazole.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.
There was **no statistically significant difference** in **adverse events** between rabeprazole and omeprazole.

GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

8 Barrett's oesophagus. Summaries and conclusions

8.1.1 PPI vs placebo

No RCTs that compared PPIs with placebo, and that met our inclusion criteria, were found.

8.1.2 PPI vs lifestyle

No RCTs that compared PPIs with lifestyle, and that met our inclusion criteria, were found.

8.1.3 PPI vs antacida

No RCTs that compared PPIs with antacids, and that met our inclusion criteria, were found.

8.1.4 PPI vs H2RA

PPI vs H2RA in Barrett's oesophagus			
Bibliography: Rees 2010(123), including Caldwell 1996(124), Weinstein 1996(125), Peters 1999(126)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Reduction in length (cm) of Barrett's oesophagus	163 (3 studies) 12 months	Mean Difference -0.42 (-1.65, 0.82) NS	⨁⊖⊖ ⊖**VERY LOW** Study quality: -2 (2 from 3 studies published as abstract only) Consistency: -1 Directness: ok Imprecision: -1 (sparse data)
Reduction in area (%) of Barrett's oesophagus	143 (2 studies) 12 months	**Mean Difference 4.06 (0.08, 8.04)** **SS**, favours omeprazole	⨁⊖⊖ ⊖**VERY LOW** Study quality: -2 (1 from 2 studies published as abstract only) Consistency: ok Directness: ok Imprecision: -1 (sparse data)

Table 38

In this systematic review and meta-analysis, RCTs were sought that compared PPI (omeprazole) to H2RA (cimetidine or ranitidine) in patients with Barrett's oesophagus.

3 RCTs were found that evaluated a reduction in length of Barrett's oesophagus at 12 months. There were no RCTs that evaluated the risk for oesophageal adenocarcinoma or high-grade dysplasia.

2 RCTs were published as abstract only. This could lead to bias and limits our confidence in the results.

There was **no statistically significant difference** in **the reduction in length of Barrett's oesophagus** between PPI and H2RA.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

PPI resulted in **a higher reduction in area of Barrett's mucosa** compared to H2RA.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

8.1.5 Endoscopic treatment vs PPI

No RCTs that compared PPIs with endoscopic treatment, and that met our inclusion criteria, were found.

8.1.6 PPI vs surgery

Antireflux surgery vs PPI in Barrett's oesophagus			
Bibliography: Rees 2010(123) discusses Parrilla P et al. 2003(127)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Any reduction/reversal of Barrett's oesophagus/dysplasia	101 (1 study) 12 months	2/53 vs 2/40 OR 0.75 (0.10-5.53) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (incomplete outcome data: unclear) Consistency: NA Directness: ok Imprecision: -1 (wide CI)
Progression to cancer	101 (1 study) 5 years or latest possible time point	2/53 vs 2/40 OR 0.75 (0.10-5.53) NS (as reported by cochrane) Correction: 1/203 patient years (0.5% per year) vs 1/129 patient years (0.8% years); NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (incomplete outcome data: unclear) Consistency: NA Directness: ok Imprecision:-1 (sparse data)
Any complication	101 (1 study)	1/58 vs 0/43 OR 2.27 (0.09-57.07) NS	⨁⨀⨀ ⨀**VERY LOW** Study quality: -1 (incomplete outcome data: unclear) Consistency: NA Directness: ok Imprecision: -2 (low number of events, wide CI)
Complete eradication of Barrett's oesophagus at 12 months	101 (1 study)	0/53 vs 0/40	NA
Developing de novo dysplasia	101 (1 study)	3/58 vs 8/43 **OR 0.22 (0.05-0.88)** **SS;** favours surgery	⨁⨁⨀⨀ **LOW** Study quality: -2 (incomplete outcome data: unclear, inconsistent reporting) Consistency: NA

			Directness: ok Imprecision: ok
Complete eradication of dysplasia	101 (1 study) 5 years	5/58 vs 3/43 OR 1.26 (0.28-5.58) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (incomplete outcome data: unclear) Consistency: NA Directness: ok Imprecision: -1 (wide CI)

Table 39

In this systematic review and meta-analysis, RCTs were sought that compared antireflux surgery (Nissen fundoplication) to PPI (H2RA/PPI) in patients with Barrett's oesophagus.

1 RCT was found with a median follow up of 6 years (range: 1-18) and 5 years (range: 1-18) for patients who received surgery and H2RA/PPI, respectively.

The interpretation of the results is complicated because patients in the acid suppression group received ranitidine from 1982 which was converted to omeprazole from 1992. Furthermore, prior to 1997, only patients with a Barrett's segment > 3 cm were included. Nine out of the 56 (16%) surgical patients with recurrent reflux as measured by pH monitoring were excluded since their surgery was unsuccessful. Finally, there seems to be some inconsistency in the reporting in the MA (Rees 2010) and the original paper (Parrilla 2003).

There was **no statistically significant difference** in **reduction/ reversal of Barrett's oesophagus/ dysplasia at 12 months** between surgery and H2RA/PPI.

GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **progression to cancer** between surgery and H2RA/PPI.

GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **complications** between surgery and H2RA/PPI.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflect the true effect.

Surgery resulted **in fewer patients progressing to de novo dysplasia** compared to H2RA/PPI.

GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **complete eradication of dysplasia (at 5-year follow up)** between surgery and H2RA/PPI.

GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

8.1.7 PPI vs PPI

No RCTs that compared PPIs head-to-head, and that met our inclusion criteria, were found.

9 Deprescribing. Summaries and conclusions.

9.1.1 On-demand vs continued use of PPI

Deprescribing PPI : on-demand use vs continued use			
Bibliography: Boghossian et al. 2017, including Bour 2005(73), Janssen 2005(128), Morgan 2007(72), Van der Velden 2010(129), Bayerdörffer 2016(130)			
Outcomes	**N° of participants (studies) Follow up (FU)**	**Results**	**Quality of the evidence (GRADE)** (as judged by Cochrane authors)
Lack of symptom control	1653 (4 studies) FU: 6 months (in one study 13 weeks)	16.3% vs 9.2% **RR 1.71 (95%CI 1.31 to 2.21);** **SS in favour of continued dose**	⨁⨁⊖⊖ **LOW** Study quality: -1 (high risk of detection bias and attrition bias) Consistency: ok Directness: ok Imprecision: -1 (wide confidence intervals and summary statistic close to the line of no effect)
Pill use (pills/ week)	1152 (3 studies) FU: 6 months	**Mean difference : -3.79 (-4.73, -2.84);** **SS in favour of deprescribing**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (high risk of detection bias and attrition bias) Consistency: ok Directness: ok Imprecision: ok
Adverse drug withdrawal events – oesophagitis (endoscopic findings)	598 (1 study) FU: 6 months	5.0% vs 0.0% **RR 30.59 (95%CI 1.84 to 508.91);** **SS in favour of continued use**	⨁⨁⊖⊖ **LOW** Study quality: -1 (high risk of detection bias and attrition bias) Consistency: ok Directness: ok Imprecision: -1 (wide confidence intervals and summary statistic close to the line of no effect)
Participant satisfaction (unwillingness to continue or inadequate symptom relief)	1653 (5 studies) FU: 6 months (in one study 13 weeks)	15.8% vs 8.8% **RR 1.82 (95%CI 1.26 to 2.65);** **SS in favour of continued use**	⨁⊖⊖ ⊖**VERY LOW** Study quality: -1 (high risk of detection and attrition bias) Consistency: ok Directness: -1 (poor methods of satisfaction used (willingness to continue or ‘‘inadequate relief ’’)). Imprecision: -1 (wide confidence intervals and summary statistic close to the line of no effect)

Table 40

In this systematic review and meta-analysis, RCTs were sought that compared deprescribing PPI use (on-demand use) to continuation of PPI use in patients on PPI.

5 RCTs were found, including a total of 1653 patients. The duration of the RCTs varied from 13 weeks to 6 months.

Several methodological issues were present concerning the study quality, the directness of the evidence and the precision of the results of the included RCTs. This could lead to bias and limits our confidence in the results.

Deprescribing PPI (on-demand) resulted in **more patients with a lack of symptom control** compared to continued use of PPI.
GRADE: LOW quality of evidence
We have a low confidence that the results of the study reflect the true effect.

Deprescribing PPI (on-demand) resulted in **less pill use** compared to continued use of PPI.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Deprescribing PPI (on-demand) resulted in **an increased risk of developing oesophagitis** compared to continued use of PPI.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

Deprescribing PPI (on-demand) resulted in **a lower participant satisfaction** compared to continued use of PPI.
GRADE: VERY LOW quality of evidence
We have a very low confidence that the results of the study reflect the true effect.

9.1.2 Abrupt stop vs continued use of PPI

Deprescribing PPI : abrupt stop vs continued use			
Bibliography: Boghossian et al. 2017, including Pilotto 2003(131)			
Outcomes	**N° of participants (studies) Follow up (FU)**	**Results**	**Quality of the evidence (GRADE)** (as judged by Cochrane authors)
Lack of symptom control	105 (1 study) FU: 6 months	67.9% vs 22.4% **RR 3.02 (95%CI 1.74 to 5.24);** **SS in favour of continued use**	⨁⊖⊖ ⊖**VERY LOW** Study quality: -2 (high risk of detection and attrition bias) Consistency: ok Directness: ok Imprecision: -1 (wide confidence intervals, small number of participants and events)
Adverse drug withdrawal events – esophagitis (endoscopic findings)	105 (1 study) FU: 6 months	69.6% vs 6.09% **RR 3.41 (95%CI 1.91 to 6.09);** **SS in favour of continued use**	⨁⊖⊖ ⊖**VERY LOW** Study quality: -2 (high risk of detection and attrition bias) Consistency: ok Directness: ok Imprecision: -1 (wide confidence intervals, small number of participants and events)

Table 41

In this systematic review and meta-analysis, RCTs were sought that compared deprescribing PPI use (on-demand use) to continuation of PPI use in patients on PPI.

1 RCT was found that included a total of 105 patients. The duration of the RCT was 6 months.

Several methodological issues were present concerning the study quality, the directness of the evidence and the precision of the results. This could lead to bias and limits our confidence in the results.

Deprescribing PPI (on-demand) resulted in **more patients with a lack of symptom control** compared to continued use of PPI.
GRADE: VERY LOW quality of evidence
We have a very low confidence that the results of the study reflect the true effect.

Deprescribing PPI (on-demand) resulted in **an increased risk of developing oesophagitis** compared to continued use of PPI.
GRADE: VERY LOW quality of evidence
We have a very low confidence that the results of the study reflect the true effect.

10 Gastroprotection. Summaries and conclusions.

10.1.1 Nonselective NSAID (including aspirin) vs Nonselective NSAID (including aspirin) + PPI

Nonselective NSAID (including aspirin) + PPI vs nonselective NSAID (including aspirin)			
Bibliography: Yuan 2016 (132), including Cullen 1998(133), Ekstrom 1996(134), Goldstein 2010a(135), Goldstein 2010b(135), Graham 2002(136), Hawkey 1998(137), Lai 2002(138), Lai 2003(139), Li 2009(140), Scheiman 2011(141), Sugano 2012(142), Xie 2013(143), Yeomans 2008(144), Yuan 2010(145)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Ulcer complications bleeding, perforation and obstruction	5695 (12 studies) 4 to 26 weeks	NSAID + PPI: 10/3418 NSAID: 36/2277 **RR 0.23 (0.12 to 0.44)** **SS in favour of NSAID+ PPI**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (3 RCTs too small, unclear allocation and/or randomisation methods in 5 RCTs, most studies sponsored by industry) Consistency: ok Directness: ok, but mix of NSAID use for muscuoloskeletal conditions and aspirin for cardiovascular prevention (presumably low dose) Imprecision: ok
Symptomatic ulcers	852 (5 studies) 8 to 52 weeks	NSAID + PPI: 6/427 NSAID: 60/425 **RR 0.11 (0.05 to 0.24)** **SS in favour of NSAID+ PPI**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (1 RCT too small, 3 RCTs with unclear allocation and/or randomisation methods, most studies sponsored by industry) Consistency: ok Directness:ok, but mix of NSAID use for muscuoloskeletal conditions and aspirin for cardiovascular prevention (presumably low dose) Imprecision: ok

Table 42

In this systematic review and meta-analysis, RCTs were sought that compared the risk of gastrointestinal adverse events in patients taking nonselective NSAIDs (including aspirin), selective COX2-inhibitors, or nonselective NSAIDs/COX2-inhibitors plus gastroprotective agents (PPIs, H2RAs, misoprostol).

14 RCTs were found that compared nonselective NSAIDs to nonselective NSAIDs plus PPI. The duration of the RCTs varied from 4 weeks to 52 weeks.

3 RCTs had a very small sample size (<40 participants per study arm). Most studies were industry-sponsored. 6 studies had unclear randomisation and/or allocation concealment. This could lead to bias and limits our confidence in the results.

It is important to note that the authors of this systematic review included RCTs in patients taking aspirin for cardiovascular prevention (presumably in a low dose) in this evaluation.

Treatment with a nonselective NSAID + PPI resulted in **fewer ulcer complications** compared to treatment with a nonselective NSAID alone.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Treatment with a nonselective NSAID + PPI resulted in **fewer symptomatic ulcers** compared to treatment with a nonselective NSAID alone.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

10.1.2 Selective COX2-inhibitor + PPI vs selective COX2-inhibitor

Selective COX2-inhibitor + PPI vs selective COX2-inhibitor			
Bibliography: Yuan 2016 (132), including Chan 2007(146), Scheiman 2006(147)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Ulcer complications bleeding, perforation and obstruction	673 (2 studies) 26 to 52 weeks	Selective COX-2 inhibitor + PPI: 0/403 Selective COX-2 inhibitor: 14/270 **RR 0.06 (0.01 to 0.48)** **SS in favour of Selective COX-2 inhibitor + PPI**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (industry-sponsored, allocation concealment unclear in both studies) Consistency: ok Directness: ok (NB: specific population: 100% history of peptic ulcer) Imprecision: ok

Table 43

In this systematic review and meta-analysis, RCTs were sought that compared the risk of gastrointestinal adverse events in patients taking nonselective NSAIDs (including aspirin), selective COX2-inhibitors, or nonselective NSAIDs/COX2-inhibitors plus gastroprotective agents (PPIs, H2RAs, misoprostol).

2 RCTs were found that compared selective COX2-inhibitors to selective COX2-inhibitors plus PPI. The duration of the RCTs varied from 26 weeks to 52 weeks.

Both studies were industry-sponsored. Both studies had unclear allocation concealment. This could lead to bias and limits our confidence in the results.

It is important to note that all participants of these studies were patients with a previous peptic ulcer, and that these results cannot be extrapolated to all patients taking selective COX2-inhibitors.

Treatment with a selective COX2-inhibitor+ PPI resulted in **fewer ulcer complications** compared to treatment with a selective COX2-inhibitor alone.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

10.1.3 Aspirin + PPI vs aspirin

Low-dose aspirin vs low-dose aspirin + PPI			
Bibliography: Mo 2013(148), including Bhatt 2010(149, Lai 2002{Lai, 2002 #2293), Ren 2011(150), Scheiman 2011(141), Yeomans 2008(144)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Upper gastrointestinal ulcer	7302 (4 studies) 180 days – 12 months	Low-dose aspirin + PPI: 30/4054 Low-dose aspirin + placebo: 95/3248 **RR 0.20 (0.13 to 0.30)** **SS in favour of Low-dose aspirin + PPI**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 but combined with clopidogrel in 1 study Imprecision: ok
GI Bleeding	7474 (5 studies) 30 days- 12 months	Low-dose aspirin + PPI: 11/4140 Low-dose aspirin + placebo: 43/3334 **RR 0.26 (0.14 to 0.49)** **SS in favour of Low-dose aspirin + PPI**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 but combined with clopidogrel in 2 studies Imprecision: ok

Table 44

In this systematic review and meta-analysis, RCTs were sought that investigated the effect of PPIs, in comparison with a control group (placebo, cytoprotective agents, or H2RA) in reducing adverse GI events (hemorrhage, ulcer, perforation, or obstruction) in adult patients taking low-dose aspirin.

5 RCTs were found. The duration of the RCTs varied from 30 days to 12 months.

There were no major methodological remarks on these RCTs. It is, however, important to note that 2 of the included studies were done in patients that took aspirin in combination with clopidogrel. It is possible that the risk of a gastrointestinal complication and/or the protective effect of the PPI was modified by the addition of clopidogrel.

Treatment with low-dose aspirin + PPI resulted in **fewer upper gastrointestinal ulcers** compared to low-dose aspirin alone.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Treatment with low-dose aspirin + PPI resulted in **less GI bleeding** compared to low-dose aspirin alone.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Low-dose aspirin vs low-dose aspirin + PPI			
Bibliography: Sugano 2014(151)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Time to ulcer recurrence	430 (1 study) 48 weeks	**HR 0.09 (0.02 to 0.41)** **p<0.001** **SS in favour of esomeprazole**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (>20% dropout, unbalanced between groups (more dropout in placebo group)) Consistency: NA Directness: ok (NB all patients had a history of peptic ulcer) Imprecision: ok
Adverse events	427 (1 study) 48 weeks	Esomeprazole: 155/214 (72.4%) placebo: 139/213 (65.3%) NT	Not applicable
Severe adverse events	427 (1 study) 48 weeks	Esomeprazole: 7/214 (3.3%) placebo: 10/213 (4.7%) NT	Not applicable

Table 45

In this double blind RCT, esomeprazole 20 mg/day was compared to placebo in 430 patients receiving a low-dose aspirin (81-314 mg/day) and a history of peptic ulcer.

The mean age was 67 y, 44.8% of the patients were H. pylori positive. The patients underwent diagnostic endoscopic of before trial initiation, and patients with an active ulcer or oesophagitis were

excluded. The duration of follow-up was 72 weeks, however, the primary outcome was recorded at 48 weeks.

The interpretation of these results is somewhat limited by the high and unbalanced drop-out rate.

Esomeprazole treatment resulted in **a lower rate of ulcer recurrence** compared to placebo, in patients receiving low-dose aspirin.
GRADE: MODERATEquality of evidence
We have moderate confidence that the results of the study reflect the true effect.

10.1.4 PPI vs no PPI for the prevention of gastrointestinal bleeding in patients receiving clopidogrel

PPI vs no PPI for the prevention of gastrointestinal bleeding in patients receiving clopidogrel			
Bibliography: Cardoso 2015(152), including Aihara 2012(153), Bhatt 2010(149),Hsu 2012(154)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Gastro-intestinal bleeding	5079 (3 studies) 180 days-1 year	PPI: 5/2533 (0.2%) no PPI: 22/2546 (0.9%) **OR 0.24 (0.09 to 0.62)** **SS in favour of clopidogrel + PPI**	⨁⨁⨀⨀ **LOW** Study quality: -2 (1 cohort study, 1 abstract) Consistency: ok Directness: ok Imprecision: ok

Table 46

In this systematic review and meta-analysis, RCTs and obervational studies were sought that compared PPI to no PPI in patients receiving clopidogrel, and that had a follow-up of at least 6 months.

2 RCTs and 1 cohort study were found. The duration of the follow-up varied from 180 days to 1 year.

One cohort study was included in the analysis. We had an abstract only for one RCT. This could lead to bias and limits our confidence in the results.

It is important to note that most included patients were receiving dual antiplatelet therapy, and that it is possible that the addition of aspirin modified the risk of gastrointestinal complications and/or the preventive effect of PPIs.

Treatment with a PPI resulted in **less gastrointestinal bleeding** compared to no PPI, in patients receiving clopidogrel.
GRADE: LOW quality of evidence

We have low confidence that the results of the study reflect the true effect.

11 Adverse events. Summaries and conclusions.

11.1.1 Cardiovascular adverse events

This chapter looks at the link between PPI's and cardiovascular adverse events. We address two questions: do PPI on their own heighten the risk of cardiovascular adverse events; and does the combination of PPI with antiplatelet therapy heighten cardiovascular adverse events?

11.1.1.1 *PPI vs no PPI*

We identified systematic reviews and meta-analyses looking at the risk of cardiovascular adverse events and PPI's. We chose the recent systematic review by Shiraev as source document and found additional observational studies.

Risk for cardiovascular adverse events with PPI use – meta-analysis and observational studies				
Bibliography: (155),(156), (157), (158)				
Study	**Type**	**Population**	**Outcomes**	**Results**
Shiraev 2017	MA of obs studies n = 7	354 446 Some post MI, some on aspirin, some post PCI, some CAD	Mortality	Odds ratio: 1.68 (95% CI: 1.53 – 1.84) **SS more mortality with PPI**
			Cardiovascular events	Odds ratio: 1.54 (95% CI: 1.11 – 2.13) **SS more CV events with PPI**
Sehested 2018	Prospective cohort 6 months follow up	214 998 No prior coronary heart disease	Fatal or non-fatal ischemic stroke	adjusted HR: 1.13 (95% CI: 1.08 – 1.19) **SS more stroke with PPI**
			Fatal or non-fatal MI	adj HR: 1.31 (95% CI: 1.23 – 1.39) **SS more MI with PPI**
Wang 2017	Retrospective cohort 4 months follow up	198 146 Stroke naive	Hospitalization due to ischemic stroke	HR: 1.36 (1.14 – 1.62) **SS more hospitalization due to stroke with PPI**

Yoshihisa 2017	Prospective cohort PSM Follow up mean 995 days (33 months)	1191 78.0% on antiplatelets and / or anticoagulants	Cardiac Mortality	Prematched cohort: HR: 0.488 (95% CI: 0.310 – 0.768) **SS less cardiac mortality with PPI** Postmatched cohort: HR: 0.528 (95% CI: 0.298 – 0.933) **SS less cardiac mortality with PPIs**

Table 47

In the systematic review and meta-analysis by Shiraev, obervational studies were sought that evaluated the risk of **cardiovascular adverse events** in patients treated with PPIs, compared to no PPI's.

7 cohort studies were found. The duration of the studies varied from 14 days to 3 years.

None of the included observational studies used the same inclusion criteria. In some studies patients on clopidogrel and antiplatelets were excluded, in others they weren't. Some of the included observational studies reported composite endpoint while others didn't. Some of the studies reported that patients in groups prescribed PPIs were different from the patients not prescribed PPIs. This lowers our confidence in the results.

We found 3 additional observational studies comparing the risk of cardiovascular adverse events in patients with PPI compared to no PPI. None of the studies reported the same outcomes. The inclusion criteria were different. This lowers our confidence in the results.

GRADE: LOW to VERY LOW quality of evidence

11.1.1.2 *Acetylsalicylic acid + PPI vs acetylsalicylic acid*

Risk for cardiovascular adverse events with PPI + ASA use				
Bibliography:				
Study	**Type**	**Population**	**Outcomes**	**Results**
Fortuna 2016 (159)	Retrospective cohort Mean follow-up 3.1 years	2011 Diagnosis of CAD On ASA On clopidogrel: excluded	MACE (major adverse cardiovascular events)	HR: 1.32 (95% CI: 0.8 – 2.4) NS
			Mortality	HR: 1.33 (0.9 – 1.9) NS

Charlot 2011(160)	Retrospective propensity score matched cohort Follow-up: 1 year	Denmark aspirin treated patients surviving 30 days after a first myocardial infarction clopidogrel excluded	Combined endpoint of CV death, myocardial infarction or stroke	time dependent Cox proportional hazar model: **HR: 1.46 (95%CI 1.33 to 1.61; p< 0.001)** **SS more adverse CV events with PPI** propensity score matched model: **HR: 1.61 (95%CI 1.45 to 1.79; p<0.001)** **SS more adverse CV events with PPI**

Table 48

Fortuna 2016 (159) is an observational study ,included in the meta-analysis by Shiraev et al. It looks at the risk of **MACE** and **mortality** in patients taking ASA, with or without a PPI. There is no statistically significant difference.

Charlot 2011(160) is a retrospective, propensity score matched cohort study, that found an **increased risk** of adverse cardiovascular events (**CV death, myocardial infarction or stroke**) of PPI treatment in patients taking aspirin after a first time myocardial infarction.

GRADE: LOW to VERY LOW quality of evidence

11.1.1.3 *Clopidogrel/Dual Antiplatelet therapy & PPI vs clopidogrel/DAPT*

Clopidogrel is an antiplatelet used in the treatment of patients with coronary heart disease. It is metabolized by CYP450 enzyme (CYP2C19) to aquire its anti-aggregant properties. PPI's are also metabolized by CYP enzymes, leading to a potential interaction where the CYP2C19 enzyme is competitively inhibited by the PPI and thus reduces the activation of clopidogrel.

Risk for cardiovascular adverse events with PPI use – meta-analysis				
Bibliography: Cardoso 2015 (152)				
Study	**Type**	**Population**	**Outcomes**	**Results**
Cardoso 2015	SR+MA of observational studies and RCTs	**N = 39** **Patients: 214 851**	**All cause mortality**	Odds Ratio 1.39 (95% CI 1.19 to 1.61) **SS more with PPI**
			Myocardial Infarction	Odds Ratio : 1.41 (95% CI 1.20 to 1.65) **SS more with PPI**
			Acute Coronary Syndrome	Odds Ratio : 1.92 (1.23 – 3.00) **SS more with PPI**
			Cerebrovascular accidents	Odds Ratio: 1.66 (1.40 – 1.97)

				SS more with PPI
	SR+MA of propensity score matched observational studies and RCT's	**N = 7** **n = 64 494**	**Overall Mortality**	Odds Ratio: 0.91 (0.58 – 1.40) NS
			Myocardial Infarction	Odds Ratio: 1.05 (0.86 – 1.28) NS
			Acute Coronary Syndrome	Odds Ratio: 0.96 (0.88 – 1.05) NS
			Cerebrovascular accidents	Odds Ratio: 1.47 (0.66 – 3.25) NS

Table 49

Risk for cardiovascular adverse events with PPI + clopidogrel – observational studies

Bibliography: Ayub 2016 (161), Chandrasekhar 2017 (162), Hsieh 2015 (163), Jackson 2016 (164), Leonard 2015 (165), Zhu 2017 (166)

Study	Type	Population	Outcomes	Results
Ayub 2016	Retrospective cohort study 720 days mean follow up	n = 740 Post - PCI + DAPT	Adverse CV events	**HR: 0.58 (95 % CI 0.39 to 0.88)** **SS less adverse CV events with PPI**
Chandrasekhar 2017	Prospective cohort study 2 year follow up	n = 19 925 DAPT 24% with prior MI	MACE	Adj HR: 1.28 (1.05 – 1.56) NS
			Death	Adj HR: 1.16 (0.86 – 1.58) NS
			MI	Adj HR: 1.19 (0.83 – 1.71) NS
Hsieh 2015	Prospective Propensity score adjusted 1 year follow up	n = 6603 Diabetic patients DAPT + PPI vs DAPT	ACS (after LES)	3 months : Adj HR: 1.45 (0.99 – 2.11) NS 6 months : Adj HR: 1.45 (0.99 – 2.11) NS **12 months**: **Adj HR 1.37 (1.09 – 1.71)** **SS more with PPI**
			ACS (after PES)	**3 months : Adj HR : 1.72 (1.02 – 2.89)** **SS more with PPI** 6 months: Adj HR: 1.35 (0.89 – 2.04) NS

				12 months: Adj HR: 1.33 (0.95 – 1.87) NS
Jackson 2016	Prospective cohort 1 year follow up	n = 11 955 MI patients DAPT	MACE	**Adj. HR: 1.38 (1.21 – 1.58)** **SS more with PPI**
Leonard 2015	Prospective cohort Propensity score matched 6 months follow up	n = 325 559 medicaid patients	Hospitalization for ischemic stroke	Esomeprazole vs pantoprazole Adj HR: 0.99 (0.83 – 1.18) NS Lansoprazole vs pantoprazole Adj. HR : 1.05 (0.91 – 1.20) NS Omeprazole vs pantoprazole Adj. HR : 0.98 (0.84 – 1.15) NS Rabeprazole vs pantoprazole Adj. HR : 0.85 (0.63 – 1.13) NS
Zhu 2017	Prospective cohort PSM Follow up: 2 years	7868 Patients post DCI on DAPT	MACE	HR: 0.970 (0.808–1.165) NS
			All cause death	HR: 0.935 (0.534–1.634) NS
			MI	HR: 0.904 (0.597–1.368) NS

Table 50

A number of reviews have been published on this subject. We chose the review by Cardoso et al. due to the search date, included articles and separate analysis using data from RCTs or PSM observational studies, as well as the non-composite endpoints.

An important methodological remark is that the I^2 scores were given by Cardoso et al., reflecting the heterogeneity of the pooled studies. This heterogeneity was high for pooling of all observational studies (77%, 79%, 98% and 0% for the outcomes shown above respectively), but was low for the RCT's and PSM cohort studies (0% for all outcomes). This has an impact on our interpretation, as it seems to suggest that the type of study and the randomization (and eventual blinding) has an effect on the results.

6 additional cohort studies were found, published after the search date of Cardoso et al. The duration of the studies varied from 6 months to 2 years. There was a large variety in the reported outcomes. Some results are statistically significant, some aren't. The varied outcomes and the lack of clear effect makes it difficult to come to a conclusion about an influence of PPI's on cardiovascular outcomes.

GRADE: LOW to VERY LOW quality of evidence

11.1.2 Dementia

The studies evaluating the association between PPI and dementia show conflicting data.

The systematic review of 11 studies from Batchelor R et al. 2017(167) showed that the majority of studies reported **an increased risk** of dementia and acute cognitive impairment with PPI use. However, the authors concluded that the reported association between PPI use and dementia is limited by methodological issues and conflicting results. All studies were observational, with the exception of one RCT.

The population-based cohort study from Tai SY et al. 2017 found **an increased risk** for dementia in Asian patients receiving PPI therapy. The mean age of this population was 55 years and the average follow-up was about 8-9 years. In the discussion of the limitations of this retrospective study, the authors mention the lack of detailed information on potential confounders such as smoking habits, educational level, and socioeconomic status.

The prospective population-based cohort study from Gray SL et al. 2017(168) found **no significant association** between PPI use and dementia or Alzheimer's disease. The mean age of this population was 74 years and the mean follow-up was 7.5 years.

The longitudinal observational study from Goldstein FC et al. 2017(169) found a **lower risk** of mild cognitive impairment or dementia with continuous and intermittent PPI use. This study was not conducted in the primary care setting but in a tertiary academic Alzheimer's Disease Center setting. The mean age of this population was about 74 years and based on the number of annual visits, we estimate a median follow-up time of 3, 5 and 4 years for always PPI users, intermittent PPI users, and never PPI users, respectively.

GRADE: LOW to VERY LOW quality of evidence

11.1.3 Community-acquired pneumonia

The systematic review and meta-analysis of Lambert 2015(170) sought observational studies that evaluated the association between PPI use and community-acquired pneumonia (CAP).

It found 32 studies, of which 10 were cohort studies, 17 were case-control studies, and 1 was a case-crossover study. The cohort studies were performed in different populations: some in (relatively) healthy adults, others in people with specific comorbidities or risk factors like asthma or COPD, or elderly people admitted at internal medicine wards.

It found **more CAP diagnoses** and **more hospitalization for CAP** in PPI users compared to non-PPI users. However, there was very high statistical heterogeneity (I^2= 99.2%), which raises the question whether pooling the results of these studies was appropriate.

In subgroup analyses, the association of PPI use with more CAP diagnosis was consistent across different ages of the patient (>65 or <65y) and doses of PPI (low or high dose). However, when analysing the different durations of PPI therapy, only the **short duration** (<1 month) was statistically significantly associated with CAP diagnosis.

Lambert 2015 also evaluated the association between H2RA use and CAP, and found no statistically significant association.

Estborn 2015(171), a meta-analysis of individual patient data from 24 RCTs (both published and unpublished), sourced from the AstraZeneca safety database, found no higher risk of pneumonia between esomeprazole and placebo use. It did find a statistically higher risk in the subgroup of people over 65, but this was not clearly reported.

Six additional cohort studies, published after the final search date of Lambert 2015, were found. These studies concerned very different populations. Five of the cohort studies used a Taiwanese healthcare database and evaluated pneumonia risk in populations with specific comorbidities:

- Ho 2014 (172) found **more pneumonia** in PPI users versus PPI non-users in adults with *non-traumatic intracranial haemorrhage*.
- Lee 2015(173) found **more pneumonia** in PPI users versus PPI non-users in patients with *newly-diagnosed COPD*.
- Chen 2015(174) found **more pneumonia** in PPI users versus PPI non-users in patients with *chronic kidney disease*.
- Ho 2017(175) found **more pneumonia** in new PPI users versus PPI non-users in *dementia* patients.
- Hsu 2017(176) found **more pneumonia** in PPI users *newly diagnosed with GORD* versus PPI non-users in the general population.

One cohort study from the UK (Othman 2016(177)) compared adult patients with a new prescription for a PPI with individually-matched controls and found **more pneumonia** in PPI users. In addition, this study used two different analytical methods to minimize the effect of confounders, and concluded that the increased risk could be entirely explained by an underlying increased risk of pneumonia in the period *before* a PPI prescription.

GRADE: LOW to VERY LOW quality of evidence

11.1.4 Renal adverse events

The systematic review and meta-analysis of Nochaiwong 2017(178) sought observational studies that evaluated the association between PPI use and adverse kidney outcomes, both acute and chronic.

It found 9 cohort studies, involving 11 unique cohorts.

Most cohort studies were performed in adults with no specific comorbidities or risk factors, with the exception of one which was done in critically ill patients.

It found **more acute interstitial nephritis (AIN)** and **more acute kidney injury (AKI),** as well as **more chronic kidney disease (CKD)** and **more end-stage renal disease (ESRD)** in PPI users compared to non-PPI users.

It also found **more AKI, more CKD** and **more ESRD** in PPI users compared to H2RA users.

Two additional cohort studies, published after the final search date of Nochaiwong 2017, were found. Both studies compared PPI users to H2RA users.

- As AKI is a risk factor for CKD, Xie 2017(179) evaluated whether PPI use was also associated with CKD in patients without evidence of an intervening acute kidney injury. They saw **more CKD**, as well as **more ESRD**, in PPI users, compared to H2RA users.
- Klatte 2017(180) saw **more progression CKD** (defined as doubling of creatinine) and **more AKI** in PPI users versus H2RA users, but **no difference in ESRD**.

GRADE: LOW to VERY LOW quality of evidence

11.1.5 Gastro-intestinal infections

11.1.5.1 *Clostridium difficile infections*

The systematic review and meta-analysis from Trifan et al. 2017(181) found 40 case control and 16 cohort studies. The authors concluded that there was **an increased risk** for Clostridium Difficile infection in patients receiving PPI therapy. There was substantial statistical heterogeneity among the studies and evidence of publication bias. Other limitations that were reported included the lack of adjustment for important confounding factors (e.g. comorbidity) and the lack of information regarding dose and duration of PPI use.

The population-based cohort study from Wei L et al. 2017(182) found that acid-suppression medicines were associated with **an increased risk** of Clostridium Difficile infection both in the community and hospital setting. Separate results for PPI and H2RA were not reported. Only in their analysis to evaluate a dose responses relationship, results were reported separately. In this analysis, no dose-response relationship was observed.

In their discussion of the limitations of the study, the authors mentioned possible sources of confounding including the lack of adjustment for OTC PPI, NSAID use, information on smoking, alcohol, and other unrecorded confounding factors.

GRADE: LOW to VERY LOW quality of evidence

11.1.5.2 *Other gastro-intestinal infections*

Based on case-control evaluations, the systematic review by Bavishi C et al. 2011(183) concluded that PPI use is associated with **an increased susceptibility** to infections with Campylobacter and Salmonella. Some of the studies reported results for bacterial gastroenteritis in general and not per specific pathogen.
As mentioned by other authors(184), these case-control studies might have suffered from a 'healthy control bias'. Non-healthy controls showed similar infection rates as to those taking PPI.

The cohort study from Brophy S et al. 2013(185) concluded that there is **no evidence** that the increased infection rate is **attributable to PPI**. Patients prescribed a PPI had a higher rate of Salmonella and Campylobacter infection before receiving their PPI prescription compared with those who did not receive a PPI prescription during the study period. Both those prescribed a PPI and those who were not prescribed a PPI had an increase in the rate of Salmonella and Campylobacter infection with time.

The prospective study from Hassing RJ et al. 2016(184) supported an association between PPI and **an increased risk** of bacterial gastroenteritis. However, by reducing the risk of selection and information bias in their study design, the authors demonstrated that **the increased risk is lower** than previously assumed. The authors mention some possible sources of confounding to consider involving the dietary pattern, the lack of information on travelling, diagnostic accuracy, and the older population in this study.

The study from Wei L et al. 2017(182) found that acid-suppression medicines were associated with **an increased risk** of bacterial gastroenteritis both in the community and hospital setting. Separate results for PPI and H2RA were not reported. Only in their analysis to evaluate a dose responses relationship, results were reported separately.
Both Brophy S et al. 2013(185) and Wei L et al. 2017(182) attempted to address risk changes over time, especially for PPI exposure. However, inconsistent results are reported. Both studies are difficult to compare due to differences in analysis technique, follow-up time, and the method of defining PPI exposure.

GRADE: LOW to VERY LOW quality of evidence

11.1.6 Gastric cancer

The systematic review and meta-analysis from Tran-Duy et al. 2016(186) identified 3 retrospective studies that evaluated the risk of gastric cancer with PPI use. This study found **an increased risk** for gastric cancer. However, the authors conclude that this association might be biased because of the limited number of studies and possible confounding factors. For example, the studies did not control for H pylori status. Furthermore, protopathic bias was not taken into account.

The nationwide population-based study from Brusselaers et al. 2017(187) found **an increased risk** of gastric cancer among maintenance PPI users. Despite the lack of information on some potential confounders, this study attempted to take confounding by indication and protopathic bias into account. An analysis in patients on H2RA found no significant association with gastric cancer. The mean follow-up of the PPI cohort was 4.9 years.

The population-based study form Cheung et al. 2018(188) found **an increased risk** of gastric cancer with PPI use in H pylori infected patients who received eradication treatment. Furthermore, this increased risk was dose-dependent and time-dependent. No significant association was observed among H2RA users. The analysis was adjusted to avoid protopathic bias. However, several other potential confounders were not taken into account. The median follow-up of the PPI cohort was 7.4 years.

The retrospective sub-group analysis from Niikura et al. 2018(189) found **an increased risk** for gastric cancer with PPI use in patients who received H Pylori eradication. No association was found for H2RA. The mean follow-up was 6.9 years.

GRADE: LOW to VERY LOW quality of evidence

11.1.7 Fractures

The systematic review and meta-analysis of Zhou 2016(190) sought observational studies that evaluated the association between PPI use and fracture risk.

It found 18 studies, of which 9 were cohort studies and 9 were case-control studies.

Most of the cohort studies were performed in postmenopausal women without specific comorbidities or risk factors.

It found **more hip, any-site and spine fractures** in PPI users compared to non-PPI users. Both long (>1 year) and shorter durations (<1 year) of PPI use were associated with more fractures.

Three additional cohort studies, published after the final search date of the systematic review, were found. These studies concerned three very different populations:

- One cohort study (van der Hoorn 2015(191)) that evaluated fracture risk in *elderly women*, saw a statistically significant **increase of fractures** in PPI users compared to PPI non-users.
- One cohort study (Chen 2016(192)) evaluated *GORD patients* with PPI use, and a matched cohort from the general population. It saw **no significant difference** between PPI users and non-users for hip fracture.
- One cohort study (Lin 2018(193)) evaluated fracture risk in *patients newly diagnosed with stroke*. In this cohort, PPI use was associated with a statistically significant **increase of risk of hip fracture and vertebral fracture**, compared to PPI non-users.

GRADE: LOW to VERY LOW quality of evidence

12 Interactions

Interactions between PPI's and other medications can be subdivided in three categories: changes to the intestinal absorption of medication, effects from PPI, and additive effects.

12.1 Changes to intestinal absorption

PPIs raise stomach pH and can change the absorption of certain medications. Most of the available information is on omeprazole(194).

Medication class	Molecules	Effect
Antifungal azole derivatives	*Ketoconazole, posaconazole, itraconazole, variconazole*	↓Decreased absorption of the azole derivatives
Vitamines and minerals	*Vitamin B12, Iron*	↓ Decreased absorption of B12 and iron
Protein kinase inhibitors	*Dasatinib, gefitinib, erlotinib, lapatinib, bosutinib, ponatinib, dabrafenib, ibrutinib*	↓ Decreased absorption of the protein kinases
Others	*Dipyramidole, mycophenolic acid, rilpivirine, ledipasvir, ulipristal, riociguat*	↓ Decreased absorption of mentioned molecules
Protease inhibitors	Saquinavir	↑ Heightened intestinal absorption
Integrase inhibitors	Raltegravir	

Table 51

12.2 Effects of PPI on metabolization and excretion

PPI's are metabolized by the CYP450 enzymes, mostly CYP2C19. How much of this enzyme is present in the cytochrome P450 varies from one person to the other. On top of that omeprazole (molecule with the most available evidence) is only a weak inhibitor of the CYP2C19.

Medication class	Molecules	Effect
Antiretrovirals	Atazanavir, fosamprenavir, indinavir, tipranavir,	↓ Less bioavailability (up to 75% for atazanavir)
Anti-aggregants	Clopidogrel, prasugrel	See below
Anti-psychotics	Clozapine	↓ Lower concentrations of clozapine
Antimetabolites	Methotrexate	↑ Higher methothrexate plasma levels due to competition for renal excretion

Table 52

The interaction between **clopidogrel** and PPI's is the one drawing the most attention. A multitude of studies have been published on the subject (see also part 11.1.1 of this document). Some guidelines mention this interaction but are dismissive of this effect (GORD 2013(10)). One guideline even states that an RCT "*provided reassurance that PPIs do not meaningfully interact with clopidogrel*" (Freedberg 2017 long term PPI guideline(15)).

Our own research for this review of the literature was not able to find strong evidence for an effect of PPI's on clopidogrel.

13 Guidelines - details

13.1 General information on selected guidelines

13.1.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in the table below.

Abbreviation	Guideline
NICE GORD 2014(3)	NICE. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. NICE Clinical guideline. 2014
ACG/CAG Dyspepsia 2017(1)	Moayyedi, P. ACG and CAG clinical guideline: management of dyspepsia. The American Journal of gastroenterology. 2017
GORD 2013(10)	Katz, P. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. The American Journal of Gastroenterology. 2013
ACG Barrett 2016(11)	Shaheen, N. ACG clinical guideline: diagnosis and management of Barrett's Esophagus. The American Journal of Gastroenterology. 2016
Australia Barrett 2015(12)	Whiteman, D. Australian clinical practice guidelines for the diagnosis and management of Barrett's esophagus and early esophageal adenocarcinoma. Journal of Gastroenterology and Hepatology. 2015
British society Barrett 2014(13)	Fitzgerald, R. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. BMJ. 2014
Deprescribing 2017(14)	Farrell, B. Deprescribing proton pump inhibitors. Canadian Family Physician. 2017
Long-term PPI 2017(15)	Freedberg, D. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology. 2017
NICE NSAID 2015(16)*	NICE. Non-steroidal anti-inflammatory drugs. Key therapeutic topic. 2015
NICE rheumatoid arthritis 2009(17)*	NICE. Rheumatoid arthritis in adults: management. Clinical guideline. 2009
NICE osteoarthritis 2014(18)*	NICE. Osteoarthritis: care and management. Clinical guideline. 2014

Table 53: Selected guidelines and their abbreviations as used in this report.

* These guidelines were selected only for their recommendations concerning PPIs for gastroprotection in long-term NSAID use. As none of these guidelines performed a search to answer this particular question, and no evidence or rationale is provided for these recommendations, we did

not perform a review of the methodology of these guidelines. Recommendations taken from these guidelines can be regarded as expert opinion.

13.1.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in the tables below.
The NICE GORD 2014 guideline did not explicitly attribute grades of recommendation or levels of evidence to their recommendations. They did perform a modified GRADE- evaluation of the included evidence on which the recommendations are based. They also express the grade of recommendation in the wording of the recommendation itself (i.e. using words as "offer" or "advise" in strong recommendations and "consider" in weaker recommendations).

ACG/CAG Dyspepsia 2017		
Grades of recommendation:	Strong	"Most patients should receive the recommended course of action."
	conditional	"Many patients will have this recommended course of action but different choices may be appropriate for some patients and a greater discussion is warranted so each patient can arrive at a decision based on their values and preferences."
Levels of evidence	High	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate	
	Low	
	Very Low	

Table 54: Grades of recommendation and Level of evidence of the ACG/CAG Dyspepsia 2017 guideline.

GORD 2013		
Grades of recommendation:	Strong	"when the desirable effects of an intervention clearly outweigh the undesirable effects"
	conditional	"when there is uncertainty about the trade-offs"
Levels of evidence	High	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate	
	Low	
	Very Low	

Table 55: Grades of recommendation and Level of evidence of the GORD 2013 guideline.

Australia Barrett 2015		
Grades of recommendation: According to GRADE (assessment of risk of bias, directness, consistency, and precision of the estimates)	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	Practice point	Where no good-quality evidence is available but there is consensus among expert working group

		members, so-called Practice points are given
Levels of evidence	I	A systematic review of level II studies
	II	A randomized controlled trial (intervention) or a prospective cohort study (etiology)
	III-1	A pseudo-randomized controlled trial (intervention) or all or none design (etiology)
	III-2	A comparative study with concurrent controls (intervention) or a retrospective cohort study (etiology)
	III-3	A comparative study without concurrent controls (intervention) or a case–control study (etiology)
	IV	Case series with either post-test or pre-test/post-test outcomes or a cross-sectional study

Table 56: Grades of recommendation and Level of evidence of the Australia Barrett 2015 guideline.

ACG Barrett 2016		
Grades of recommendation:	Strong	"when the desirable effects of an intervention clearly outweigh the undesirable effects"
	conditional	"when there is uncertainty about the trade-offs"
Levels of evidence	High	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate	
	Low	
	Very Low	

Table 57: Grades of recommendation and Level of evidence of the ACG Barrett 2016 guideline

British society Barrett 2014		
Grades of recommendation:	A	requires at least one RCT of good quality addressing the topic of recommendation.
	B	requires the availability of clinical studies without randomisation on the topic of recommendation.
	C	requires evidence from category IV in the absence of directly applicable clinical studies.
Levels of evidence (According to the North of England evidence-based guidelines**)**	Ia	Evidence obtained from meta-analysis of RCTs.
	Ib	Evidence obtained from at least one RCT.
	IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
	IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
	III	Evidence obtained from well-designed descriptive studies such as comparative studies, correlative studies and case studies.
	IV	Evidence obtained from expert committee reports, or opinions or clinical experience of respected authorities.

Table 58: Grades of recommendation and Level of evidence of the British society Barrett 2014 guideline.

Deprescribing PPI 2017		
Grades of recommendation:	Strong	"when the desirable effects of an intervention clearly outweigh the undesirable effects"
	conditional	"when there is uncertainty about the trade-offs"
Levels of evidence	High	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate	
	Low	
	Very Low	

Table 59: Grades of recommendation and Level of evidence of the Deprescribing PPI 2017 guideline.

Long-term PPI 2017		
Grades of recommendation:	Advices on best practices are given including a rationale for each advice: expert opinion. "There is no evidence for or against"; "there is no high quality evidence on which to base this recommendation"; "this is a weak recommendation".	
Levels of evidence	High	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate	
	Low	
	Very Low	

Table 60: Grades of recommendation and Level of evidence of the Long-term PPI 2017 guideline.

13.1.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in **Fout! Verwijzingsbron niet gevonden.**the table below. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
NICE GORD 2014	5	6	7	6	6	6	4	7	**47**	**84%**
ACG/ CAG Dyspepsia 2017	7	4	7	7	5	7	4	1	**42**	**75%**
GORD 2013	5	3	5	3	6	5	3	1	**31**	**55%**
Australia Barrett 2015	7	7	7	7	6	7	7	6	**54**	**96%**
ACG Barrett 2016	7	6	4	3	5	7	3	3	**38**	**68%**
British society Barrett 2014	7	6	7	7	6	6	5	4	**48**	**86%**
Deprescribing PPI 2017	3	4	7	7	7	7	6	5	**46**	**82%**
Long-term PPI 2017	2	2	5	4	7	4	3	1	**28**	**50%**

Table 61: AGREE score of selected guidelines on item "Rigour of development", see methodology for a description of the items.

13.1.4 Included populations – interventions – main outcomes

In the tables below, the populations, interventions and main outcomes considered in the selected guidelines are represented.

NICE GORD 2014	
Population	Adults (18 years and older) with symptoms of dyspepsia or symptoms suggestive of GORD, or both. Adults with a diagnosis of Barrett's oesophagus.
Interventions	Interventions for: • uninvestigated dyspepsia • gastro-oesophageal reflux disease • peptic ulcer disease • functional dyspepsia • Helicobacter pylori
Outcomes	**General** • Reduction in symptoms (severity/frequency). • Biopsy findings (pathology). • Endoscopic appearance of oesophagus. • Health-related quality of life (measured using EQ-5D and/or disease-specific tools, if available). • Reduction in medication requirement (frequency and dose). • Adverse effects of interventions (diagnostic or treatment). • Resource use and costs. **GORD-specific** • Occurrence of Barrett's oesophagus and progression to adenocarcinoma.

Table 62: Included population, intervention and main outcomes of the NICE GORD 2014 guideline.

ACG/CAG Dyspepsia 2017	
Population	Adults with • Uninvestigated dyspepsia • Dyspepsia + normal upper GI endoscopy + H. pylori positive • Dyspepsia + normal upper GI endoscopy
Interventions	Interventions: • Endoscopy • H.pylori test and treatment • PPI therapy • Antidepressant therapy • Prokinetic therapy

	• Psychological therapy
Outcomes	• Detection upper GI cancer • Dyspepsia resolution or improvement • Quality of life • Health-related dyspepsia costs • Adverse events

Table 63: Included population, intervention and main outcomes of the ACG/CAG Dyspepsia 2017 guideline.

GORD 2013	
Population	Adults with • GORD • Extra-oesophageal presentation of GORD • GORD refractory to treatment with PPI's
Interventions	Interventions: • Diagnostic procedures • Life style • PPI therapy; H_2RA; Prokinetics; combinations • Intermittant vs continuous PPI therapy • baclofen • Surgery
Outcomes	• Symptom control (e.g. heartburn relief) • Quality of life • Relapse • Adverse events

Table 64: Included population, intervention and main outcomes of the GORD 2013 guideline.

Australia Barrett 2015	
Population	Patients with • Barrett without dysplasia • Barrett with dysplasia or early cancer
Interventions	Interventions: • Screening, endoscopic surveillance • PPI • Endoscopic techniques (ablative therapy) • Surgery
Outcomes	• Symptom control • Regression/ complete eradication of Barrett • Progression to cancer

	• Accuracy of diagnosis

Table 65: Included population, intervention and main outcomes of the Australia Barrett 2015 guideline.

ACG Barrett 2016	
Population	Patients with • Barrett
Interventions	Interventions: • Screening, endoscopic surveillance • PPI • Acetylsalicyclic acid (ASA) • Endoscopic techniques (ablative therapy) • Surgery
Outcomes	• Symptom control • Regression/ complete eradication of Barrett • Progression to cancer • Accuracy of diagnosis

Table 66: Included population, intervention and main outcomes of the ACG Barrett 2016 guideline.

British society Barrett 2014	
Population	Patients with • Barrett's oesophagus • Early oesophageal adenocarcinoma
Interventions	Interventions: • PPI • NSAID • Antireflux surgery
Outcomes	• Progression to cancer • Symptom control

Table 67: Included population, intervention and main outcomes of the British society Barrett 2014 guideline.

Deprescribing PPI 2017	
Population	Patients with • GORD or oesophagitis • Continuous PPI usage ≥ 28 days

Interventions	Interventions: • Deprescribing: stopping, stepping down, reducing
Outcomes	• Change in upper GI symptoms • Pill burden • Cost • Patient satisfaction • Positive drug withdrawal events (e.g. Resolution of side effects) • Adverse drug withdrawal events (e.g. recurrence of oesophagitis on endoscopy)

Table 68: Included population, intervention and main outcomes of the Deprescribing PPI 2017 guideline.

Long-term PPI 2017	
Population	Patients with • GORD • Barrett's oesophagus • NSAID bleeding prophylaxis
Interventions	The aim of this expert review is to review the risks associated with long-term use of PPIs.
Outcomes	The aim is to help practitioners weigh the risks and benefits of PPIs.

Table 69: Included population, intervention and main outcomes of the Long-term PPI 2017 guideline.

13.1.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the tables below.

NICE GORD 2014	
Development group	patients, gastroenterologists, general practitioners, gastrointestinal surgeon, consultant paediatric intensive care; information specialists, health economists
Target audience	The primary care team, including general practitioners, nurses, community pharmacists and other primary care professionals who have direct contact with patients.

Table 70: Members of the development group and target audience of the NICE GORD 2014 guideline.

ACG/CAG Dyspepsia 2017	
Development group	The group was chosen to represent a US and Canadian secondary and tertiary care perspective on managing dyspepsia with experience in guideline methodology, motility, endoscopy, and pharmacological therapies.

Target audience	US and Canada

Table 71: Members of the development group and target audience of the ACG/CAG Dyspepsia 2017 guideline.

GORD 2013	
Development group	Not described. All authors are affiliated to a department of gastroenterology of different centers in the USA.
Target audience	Not specified in the text.

Table 72: Members of the development group and target audience of the GORD 2013 guideline.

Australia Barrett 2015	
Development group	A multidisciplinary working group
Target audience	Gastroenterologists, pathologists, surgeons and physicians, and other members of multidisciplinary teams to which patients with Barrett's oesophagus and oesophageal adenocarcinoma are referred. The guidelines will also be relevant to primary care practitioners and patients diagnosed with this condition.

Table 73: Members of the development group and target audience of the Australia Barrett 2015 guideline.

ACG Barrett 2015	
Development group	Not described. All authors are affiliated to a department of gastroenterology of different centers in the USA.
Target audience	Not specified in the text.

Table 74: Members of the development group and target audience of the ACG Barrett 2015 guideline.

British society Barrett 2014	
Development group	The authors comprised gastroenterologists, endoscopists, surgeons, pathologists, economists, public health physicians and patient representatives.
Target audience	Gastroenterologists, physicians and nurse practitioners, as well as members of multidisciplinary teams (MDTs; surgeons, radiologists, pathologists), who take decisions on the management of such patients.

Table 75: Members of the development group and target audience of the British society Barrett 2014 guideline.

Deprescribing PPI 2017	
Development group	The Guideline Development Team comprised 5 clinicians—a family physician, a gastroenterologist, and 3 pharmacists —and 5 nonvoting members—a methodologist, 2 pharmacy residents, and 2 project coordinators. Additional support was provided by a librarian and a master's student
Target audience	The target audience includes primary care physicians, pharmacists, nurse practitioners, and specialists who care for patients who might use PPIs.

Table 76: Members of the development group and target audience of the Deprescribing PPI 2017 guideline.

Long-term PPI 2017	
Development group	Experts linked to the American gastroenterological association.

Target audience	Not specified in the text.

Table 77: Members of the development group and target audience of the Long-term PPI 2017 guideline.

13.2 Recommendations from guidelines

13.2.1 Interventions for dyspepsia

13.2.1.1 *NICE GORD 2014*

Lifestyle

- **Offer simple lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation. [2004]**
- **Advise people to avoid known precipitants they associate with their dyspepsia where possible. These include smoking, alcohol, coffee, chocolate, fatty foods and being overweight. Raising the head of the bed and having a main meal well before going to bed may help some people. [2004]**

General advice

- **Provide people with access to educational materials to support the care they receive. [2004]**
- **Recognise that psychological therapies, such as cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people. [2004, amended 2014]**

Uninvestigated dyspepsia: diagnosis

- **Be aware that dyspepsia in unselected people in primary care is defined broadly to include people with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting. [2004, amended 2014]**
- **Leave a 2-week washout period after proton pump inhibitor (PPI) use before testing for Helicobacter pylori (hereafter referred to as H pylori) with a breath test or a stool antigen test. [2004, amended 2014]**

Interventions for uninvestigated dyspepsia

- **Offer empirical full-dose PPI therapy (see table 1) for 4 weeks to people with dyspepsia. [2004]**

Table 1 PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17; 2004)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg[1] once a day	Not available	40 mg[3] once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg[2] twice a day
Omeprazole	20 mg once a day	10 mg[2] once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg[2] twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg[2] twice a day

[1] Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg.

[2] Off-label dose for GORD.

[3] 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

- **Offer H pylori 'test and treat' to people with dyspepsia. [2004]**
- **If symptoms return after initial care strategies, step down PPI therapy to the lowest dose needed to control symptoms. Discuss using the treatment on an 'as needed' basis with people to manage their own symptoms. [2004]**
- **Offer H2 receptor antagonist (H2RA) therapy if there is an inadequate response to a PPI. [2004, amended 2014]**

Interventions for functional dyspepsia

- **Manage endoscopically determined functional dyspepsia using initial treatment for H pylori if present, followed by symptomatic management and periodic monitoring. [2004]**
- **Offer eradication therapy to people testing positive for H pylori. [2004]**
- **Do not routinely offer re-testing after eradication, although the information it provides may be valued by individual people. [2004]**
- **If H pylori has been excluded and symptoms persist, offer either a low-dose PPI (see table 1) or an H2RA for 4 weeks. [2004, amended 2014]**
- **If symptoms continue or recur after initial treatment, offer a PPI or H2RA to be taken at the lowest dose possible to control symptoms. [2004, amended 2014]**
- **Discuss using PPI treatment on an 'as-needed' basis with people to manage their own symptoms. [2004]**
- **Avoid long-term, frequent dose, continuous antacid therapy (it only relieves symptoms in the short term rather than preventing them). [2004, amended 2014]**
- **Offer people who need long-term management of dyspepsia symptoms an annual review of their condition, and encourage them to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment). [2004, amended 2014]**

- **Advise people that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the counter and taken as needed). [2004, amended 2014]**

13.2.1.2 *ACG/CAG Dyspepsia 2017*

*We have used a clinically relevant definition of **dyspepsia** as predominant epigastric pain lasting at least 1 month. This can be associated with any other upper gastro intestinal symptom such as epigastric fullness, nausea, vomiting, or heartburn, provided epigastric pain is the patient's primary concern.*
Functional dyspepsia (FD)*refers to patients with dyspepsia where endoscopy (and other tests where relevant) has ruled out organic pathology that explains the patient's symptoms.*

- **We recommend dyspepsia patients under the age of 60 should have empirical PPI therapy if they are H. pylori -negative or who remain symptomatic after H. pylori eradication therapy. Strong recommendation, high quality evidence.**
- **We suggest dyspepsia patients under the age of 60 not responding to PPI or H. pylori eradication therapy should be offered prokinetic therapy. Conditional recommendation very low quality evidence.**
- **We suggest dyspepsia patients under the age of 60 not responding to PPI or H. pylori eradication therapy should be offered TCA therapy. Conditional recommendation low quality evidence.**
- **We recommend FD patients that are H. pylori positive should be prescribed therapy to treat the infection. Strong recommendation, high quality evidence.**
- **We recommend FD patients who are H. pylori -negative or who remain symptomatic despite eradication of the infection should be treated with PPI therapy. Strong recommendation, moderate quality evidence.**
- **We recommend FD patients not responding to PPI or H. pylori eradication therapy (if appropriate) should be offered TCA therapy. Conditional recommendation, moderate quality evidence.**
- **We suggest FD patients not responding to PPI, H. pylori eradication therapy or tricyclic antidepressant therapy should be offered prokinetic therapy. Conditional recommendation, very low quality evidence.**
- **We suggest FD patients not responding to drug therapy should be offered psychological therapies. Conditional recommendation, very low quality evidence.**
- **We do not recommend the routine use of complementary and alternative medicines for FD. Conditional Recommendation, very low quality evidence.**

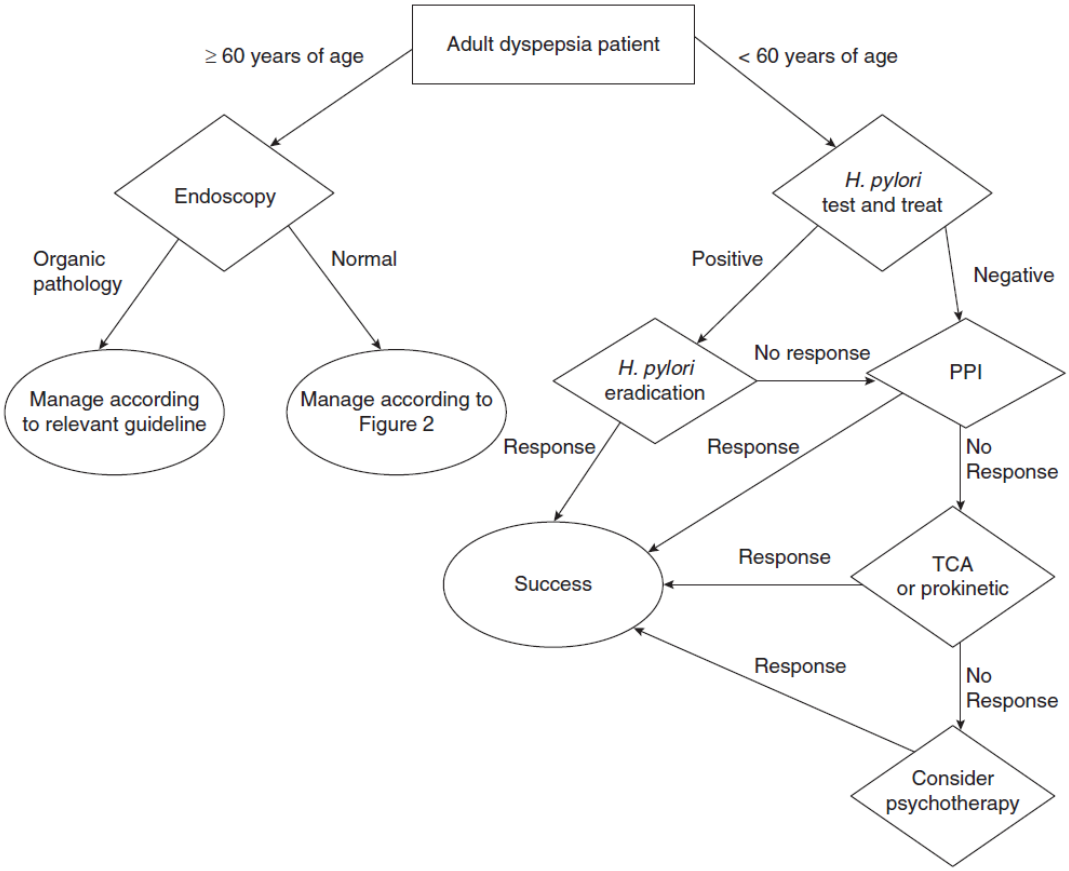

Figure 1: ACG/CAG's algorithm for the management of uninvestigated dyspepsia

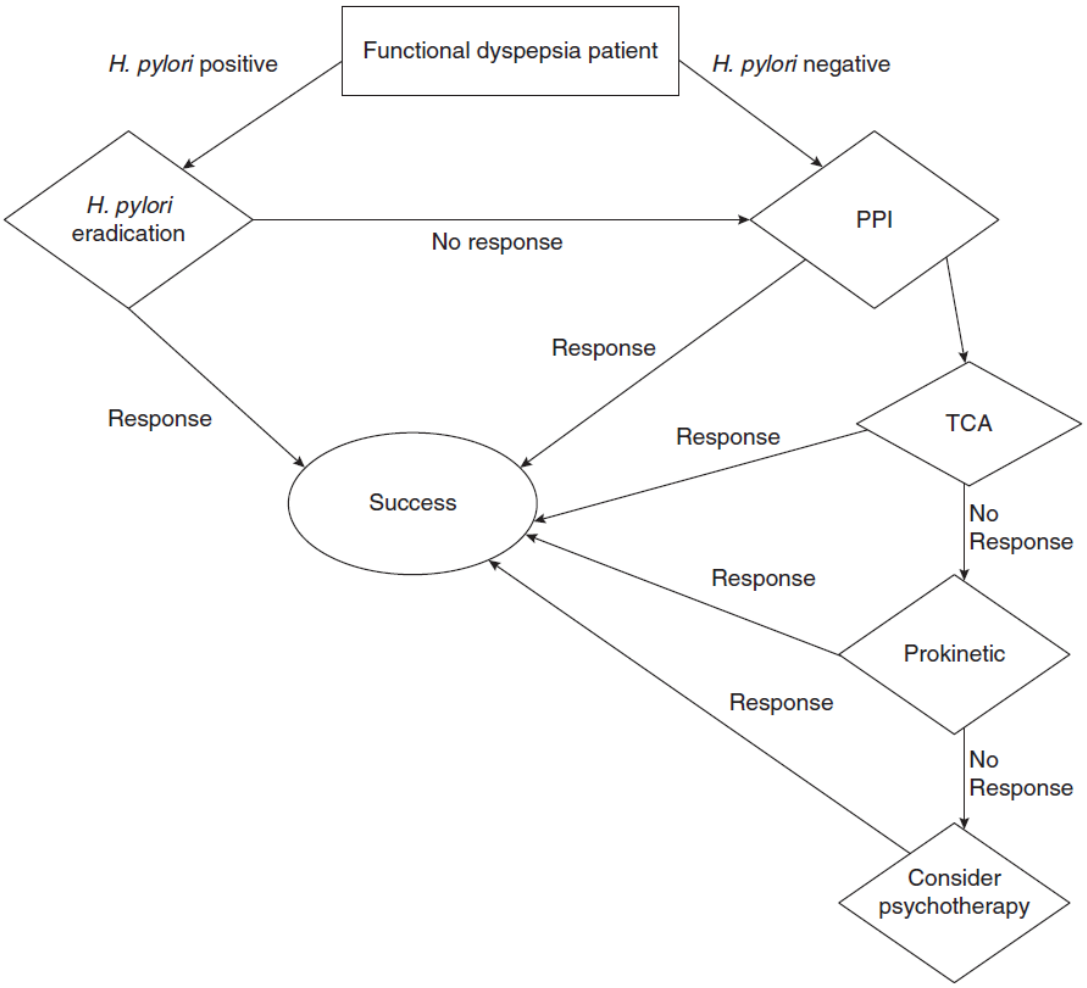

Figure 2: ACG/CAG's algorithm for the treatment of functional dyspepsia

13.2.2 Interventions for GORD

13.2.2.1 *NICE GORD 2014*

In this guideline, GORD refers to endoscopically determined oesophagitis or endoscopy-negative reflux disease.

Recommendations are marked as [new 2014], [2014], [2004] or [2004, amended 2014]:

- ***[new 2014]*** *indicates that the evidence has been reviewed and the recommendation has been added or updated*
- ***[2014]*** *indicates that the evidence has been reviewed but no change has been made to the recommended action*
- ***[2004]*** *indicates that the evidence has not been reviewed since 2004*
- ***[2004, amended2014]*** *indicates that the evidence has not been reviewed since 2004, but changes have been made to the recommendation wording that change the meaning.*

Common elements of care

- **Offer simple lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation. [2004]**
- **Advise people to avoid known precipitants they associate with their dyspepsia where possible. These include smoking, alcohol, coffee, chocolate, fatty foods and being overweight. Raising the head of the bed and having a main meal well before going to bed may help some people. [2004]**
- **Provide people with access to educational materials to support the care they receive. [2004]**
- **Recognise that psychological therapies, such as cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people. [2004, amended 2014]**

Interventions for GORD

- **Manage uninvestigated 'reflux-like' symptoms as uninvestigated dyspepsia. [2004, amended 2014]**
- **Offer people with GORD a full-dose PPI (see table 1) for 4 or 8 weeks. [2004]**

Table 1 PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17; 2004)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg[1] once a day	Not available	40 mg[3] once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg[2] twice a day
Omeprazole	20 mg once a day	10 mg[2] once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg[2] twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg[2] twice a day

[1] Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg.

[2] Off-label dose for GORD.

[3] 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

- **If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms. [2004, amended 2014]**
- **Discuss with people how they can manage their own symptoms by using the treatment when they need it. [2004]**
- **Offer H2RA therapy if there is an inadequate response to a PPI. [2004, amended 2014]**
- **Consider laparoscopic fundoplication for people who have: a confirmed diagnosis of acid reflux and adequate symptom control with acid suppression therapy, but who do not wish to continue with this therapy long term a confirmed diagnosis of acid reflux and symptoms that are responding to a PPI, but who cannot tolerate acid suppression therapy. [new 2014]**

13.2.2.2 *GORD 2013*

The authors have used the following working definition to define the disease: GERD should be defined as symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung. GERD can be further classified as the presence of symptoms without erosions on endoscopic examination (nonerosive disease or NERD) or GERD symptoms with erosions present (ERD).

Management of GERD

- **Weight loss is recommended for GERD patients who are overweight or have had recent weight gain. (Conditional recommendation, moderate level of evidence)**
- **Head of bed elevation and avoidance of meals 2 – 3 h before bedtime should be recommended for patients with nocturnal GERD. (Conditional recommendation, low level of evidence)**

- **Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and / or spicy foods) is not recommended in the treatment of GERD. (Conditional recommendation, low level of evidence)**
- **An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis. There are no major differences in efficacy between the different PPIs. (Strong recommendation, high level of evidence)**
- **Traditional delayed release PPIs should be administered 30 – 60 min before meal for maximal pH control. (Strong recommendation, moderate level of evidence). Newer PPIs may offer dosing flexibility relative to meal timing. (Conditional recommendation, moderate level of evidence)**
- **PPI therapy should be initiated at once a day dosing, before the first meal of the day. (Strong recommendation, moderate level of evidence). For patients with partial response to once daily therapy, tailored therapy with adjustment of dose timing and / or twice daily dosing should be considered in patients with night-time symptoms, variable schedules, and / or sleep disturbance. (Strong recommendation, low level of evidence).**
- **Non-responders to PPI should be referred for evaluation. (Conditional recommendation, low level of evidence, see refractory GERD section).**
- **In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. (Conditional recommendation, low level evidence).**
- **Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued, and in patients with complications including erosive esophagitis and Barrett's esophagus. (Strong recommendation, moderate level of evidence). For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy. (Conditional recommendation, low level of evidence)**
- **H 2 -receptor antagonist (H 2 RA) therapy can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. (Conditional recommendation, moderate level of evidence). Bedtime H 2 RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but may be associated with the development of tachyphylaxis after several weeks of use. (Conditional recommendation, low level of evidence)**
- **Therapy for GERD other than acid suppression, including prokinetic therapy and / or baclofen, should not be used in GERD patients without diagnostic evaluation. (Conditional recommendation, moderate level of evidence)**
- **There is no role for sucralfate in the non-pregnant GERD patient. (Conditional recommendation, moderate level of evidence)**

<u>Surgical options for GERD</u>

- **Surgical therapy is a treatment option for long-term therapy in GERD patients. (Strong recommendation, high level of evidence)**
- **Surgical therapy is generally not recommended in patients who do not respond to PPI therapy. (Strong recommendation, high level of evidence)**
- **Preoperative ambulatory pH monitoring is mandatory in patients without evidence of erosive esophagitis. All patients should undergo preoperative manometry to rule out**

achalasia or scleroderma-like esophagus. (Strong recommendation, moderate level of evidence)

- **Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon. (Strong recommendation, high level of evidence)**
- **Obese patients contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation in these patients. (Conditional recommendation, moderate level of evidence)**
- **The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy. (Strong recommendation, moderate level of evidence)**

<u>GERD refractory to treatment with PPI s</u>

- **The first step in management of refractory GERD is optimization of PPI therapy. (Strong recommendation, low level of evidence)**
- **Upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologies. (Conditional recommendation, low level of evidence)**
- **In patients in whom extraesophageal symptoms of GERD persist despite PPI optimization, assessment for other etiologies should be pursued through concomitant evaluation by ENT, pulmonary, and allergy specialists. (Strong recommendation, low level of evidence)**
- **Patients with refractory GERD and negative evaluation by endoscopy (typical symptoms) or evaluation by ENT, pulmonary, and allergy specialists (extraesophageal symptoms), should undergo ambulatory reflux monitoring. (Strong recommendation, low level of evidence)**
- **Reflux monitoring off medication can be performed by any available modality (pH or impedance-pH). (Conditional recommendation, moderate level evidence). Testing on medication should be performed with impedance-pH monitoring in order to enable measurement of nonacid reflux. (Strong recommendation, moderate level of evidence).**
- **Refractory patients with objective evidence of ongoing reflux as the cause of symptoms should be considered for additional antireflux therapies, which may include surgery or TLESR inhibitors. (Conditional recommendation, low level of evidence). Patients with negative testing are unlikely to have GERD and PPI therapy should be discontinued. (Strong recommendation, low level of evidence)**

13.2.2.3 *Long-term PPI 2017*

Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia).

Rationale: Short-term PPIs are highly effective for uncomplicated GERD. Most patients with uncomplicated GERD respond to short-term PPIs and are subsequently able to reduce PPIs to less than

daily dosing. Because patients who cannot reduce PPIs face lifelong therapy, we would consider testing for an acid-related disorder in this situation. However, there is no high-quality evidence on which to base this recommendation.

13.2.3 Interventions for oesophagitis

13.2.3.1 *NICE GORD 2014*

In this guideline, GORD refers to endoscopically determined oesophagitis or endoscopy-negative reflux disease.

Recommendations are marked as [new 2014], [2014], [2004] or [2004, amended 2014]:

- ***[new 2014]*** *indicates that the evidence has been reviewed and the recommendation has been added or updated*
- ***[2014]*** *indicates that the evidence has been reviewed but no change has been made to the recommended action*
- ***[2004]*** *indicates that the evidence has not been reviewed since 2004*
- ***[2004, amended2014]*** *indicates that the evidence has not been reviewed since 2004, but changes have been made to the recommendation wording that change the meaning.*

Common elements of care

- **Offer simple lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation. [2004]**
- **Advise people to avoid known precipitants they associate with their dyspepsia where possible. These include smoking, alcohol, coffee, chocolate, fatty foods and being overweight. Raising the head of the bed and having a main meal well before going to bed may help some people. [2004]**
- **Provide people with access to educational materials to support the care they receive. [2004]**
- **Recognise that psychological therapies, such as cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people. [2004, amended 2014]**

Interventions for severe oesophagitis

- **People who have had dilatation of an oesophageal stricture should remain on long-term full-dose PPI therapy (see table 1). [2004] Offer people a full-dose PPI (see table 2) for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, underlying health conditions and possible interactions with other drugs). [new 2014]**

Table 1 PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17; 2004)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg[1] once a day	Not available	40 mg[3] once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg[2] twice a day
Omeprazole	20 mg once a day	10 mg[2] once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg[2] twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg[2] twice a day

[1] Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg.

[2] Off-label dose for GORD.

[3] 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

Table 2 PPI doses for severe oesophagitis in this guideline update (2014)

PPI	Full/standard dose	Low dose (on-demand dose)	High/double dose
Esomeprazole	40 mg[1] once a day	20 mg[1] once a day	40 mg[1] twice a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg[2] twice a day
Omeprazole	40 mg[1] once a day)	20 mg[1] once a day)	40 mg[1] twice a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg[2] twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg[2] twice a day

[1] Change from the 2004 dose, specifically for severe oesophagitis, agreed by the GDG during the update of CG17.

[2] Off-label dose for GORD.

- **If initial treatment for healing severe oesophagitis fails, consider a high dose of the initial PPI, switching to another full-dose PPI (see table 2) or switching to another high-dose PPI (see table 2 in appendix A), taking into account the person's preference and clinical circumstances (for example, tolerability of the initial PPI, underlying health conditions and possible interactions with other drugs). [new 2014]**
- **Offer a full-dose PPI (see table 2 in appendix A) long-term as maintenance treatment for people with severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, tolerability of the PPI, underlying health conditions and possible interactions with other drugs), and the acquisition cost of the PPI. [new 2014]**

- **If the person's severe oesophagitis fails to respond to maintenance treatment, carry out a clinical review. Consider switching to another PPI at full dose or high dose (see table 2 in appendix A), taking into account the person's preference and clinical circumstances, and/or seeking specialist advice. [new 2014]**
- **Do not routinely offer endoscopy to diagnose Barrett's oesophagus, but consider it if the person has GORD. Discuss the person's preferences and their individual risk factors (for example, long duration of symptoms, increased frequency of symptoms, previous oesophagitis, previous hiatus hernia, oesophageal stricture or oesophageal ulcers, or male gender). [new 2014]**
- **Consider laparoscopic fundoplication for people who have:**
    - **a confirmed diagnosis of acid reflux and adequate symptom control with acid suppression therapy, but who do not wish to continue with this therapy long term;**
    - **a confirmed diagnosis of acid reflux and symptoms that are responding to a PPI, but who cannot tolerate acid suppression therapy. [new 2014]**

13.2.3.2 *GORD 2013*

The authors have used the following working definition to define the disease: GERD should be defined as symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung. GERD can be further classified as the presence of symptoms without erosions on endoscopic examination (nonerosive disease or NERD) or GERD symptoms with erosions present (ERD).

Management of GERD

- **Weight loss is recommended for GERD patients who are overweight or have had recent weight gain. (Conditional recommendation, moderate level of evidence)**
- **Head of bed elevation and avoidance of meals 2 – 3 h before bedtime should be recommended for patients with nocturnal GERD. (Conditional recommendation, low level of evidence)**
- **Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and / or spicy foods) is not recommended in the treatment of GERD. (Conditional recommendation, low level of evidence)**
- **An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis. There are no major differences in efficacy between the different PPIs. (Strong recommendation, high level of evidence)**
- **Traditional delayed release PPIs should be administered 30 – 60 min before meal for maximal pH control. (Strong recommendation, moderate level of evidence). Newer PPIs may offer dosing flexibility relative to meal timing. (Conditional recommendation, moderate level of evidence)**
- **PPI therapy should be initiated at once a day dosing, before the first meal of the day. (Strong recommendation, moderate level of evidence). For patients with partial response to once daily therapy, tailored therapy with adjustment of dose timing and / or twice daily**

dosing should be considered in patients with night-time symptoms, variable schedules, and / or sleep disturbance. (Strong recommendation, low level of evidence).

- **Non-responders to PPI should be referred for evaluation. (Conditional recommendation, low level of evidence, see refractory GERD section).**
- **In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. (Conditional recommendation, low level evidence).**
- **Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued, and in patients with complications including erosive esophagitis and Barrett's esophagus. (Strong recommendation, moderate level of evidence). For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy. (Conditional recommendation, low level of evidence)**
- **Therapy for GERD other than acid suppression, including prokinetic therapy and / or baclofen, should not be used in GERD patients without diagnostic evaluation. (Conditional recommendation, moderate level of evidence)**
- **There is no role for sucralfate in the non-pregnant GERD patient. (Conditional recommendation, moderate level of evidence)**

<u>Surgical options for GERD</u>

- **Surgical therapy is a treatment option for long-term therapy in GERD patients. (Strong recommendation, high level of evidence)**
- **Surgical therapy is generally not recommended in patients who do not respond to PPI therapy. (Strong recommendation, high level of evidence)**
- **Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon. (Strong recommendation, high level of evidence)**
- **The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy. (Strong recommendation, moderate level of evidence)**

<u>GERD refractory to treatment with PPI s</u>

- **The first step in management of refractory GERD is optimization of PPI therapy. (Strong recommendation, low level of evidence)**
- **Upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologies. (Conditional recommendation, low level of evidence)**
- **In patients in whom extraesophageal symptoms of GERD persist despite PPI optimization, assessment for other etiologies should be pursued through concomitant evaluation by ENT, pulmonary, and allergy specialists. (Strong recommendation, low level of evidence)**
- **Patients with refractory GERD and negative evaluation by endoscopy (typical symptoms) or evaluation by ENT, pulmonary, and allergy specialists (extraesophageal symptoms), should undergo ambulatory reflux monitoring. (Strong recommendation, low level of evidence)**
- **Reflux monitoring off medication can be performed by any available modality (pH or impedance-pH). (Conditional recommendation, moderate level evidence). Testing on**

medication should be performed with impedance-pH monitoring in order to enable measurement of nonacid reflux. (Strong recommendation, moderate level of evidence).

- **Refractory patients with objective evidence of ongoing reflux as the cause of symptoms should be considered for additional antireflux therapies, which may include surgery or TLESR inhibitors. (Conditional recommendation, low level of evidence). Patients with negative testing are unlikely to have GERD and PPI therapy should be discontinued. (Strong recommendation, low level of evidence)**

13.2.3.3 *Long-term PPI 2017*

Patients with GERD and acid-related complications (i.e., erosive esophagitis or peptic stricture) should take a PPI for short-term healing and for long-term symptom control.

Rationale: PPIs are highly effective in healing esophagitis and for GERD symptom control, and this benefit is likely to outweigh PPI-related risks. There is no evidence for or against PPIs in asymptomatic patients with healed esophagitis or for PPIs beyond 12 months.

13.2.4 Interventions for Barrett's oesophagus

13.2.4.1 *ACG Barrett 2016*

Chemoprevention

Patients with BE should receive once-daily PPI therapy. Routine use of twice-daily dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis (strong recommendation, moderate level of evidence).

Aspirin or NSAIDs should not be routinely prescribed to patients with BE as an antineoplastic strategy. Similarly, other putative chemopreventive agents currently lack sufficient evidence and should not be administered routinely (conditional recommendation, high level of evidence).

Surgical therapy

Antireflux surgery should not be pursued in patients with BE as an antineoplastic measure. However, this surgery should be considered in those with incomplete control of reflux symptoms on optimized medical therapy (strong recommendation, high level of evidence).

13.2.4.2 *Australia Barrett 2015*

What is appropriate medical systemic therapy for symptoms associated with BE?

Medical systemic therapy for patients with BE aims to control symptoms and reduce the risk of complications. Uncomplicated BE is not a cause of symptoms (indeed patients with BE may have reduced sensitivity to esophageal acidification); rather these are due to the symptoms of gastro-esophageal reflux. Acid suppression with PPI is the most effective systemic therapy for reflux symptoms in patients with BE and will control symptoms in most patients with a durable effect over years (level of evidence II, IV) Higher than standard doses of PPI may be required to control symptoms in a proportion of patients (level of evidence IV).

Recommendation. Symptomatic patients with BE should be treated with PPI therapy, with the dose titrated to control symptoms (grade C).

Are there any medical or surgical interventions that cause regression of BE?

Regression of BE is defined by a reduction in the length or area of metaplastic columnar epithelium; however, the significance of regression in BE is unclear. There are insufficient data to indicate that regression leads to reduced incidence of EAC. The degree of Barrett's regression appears largest among patients undergoing anti-reflux surgery although a randomized trial comparing surgical and medical therapy found no significant differences. Combined analysis of randomized trials has not demonstrated BE regression with medical therapy (level of evidence I).

Recommendation. There is insufficient evidence to recommend the use of acid suppressive therapy for the regression of BE (grade B).

There is insufficient evidence to recommend anti-reflux surgery for the regression of BE (grade C).

Practice point. Acid suppressive therapy and anti-reflux surgery can be used to control symptoms and heal reflux esophagitis in patients with BE. There is insufficient evidence to recommend high-dose (twice daily) acid suppressive therapy when symptom control or mucosal healing is achieved with standard dosing.

13.2.4.3 *British society Barrett 2014*

Strategies for chemoprevention and symptom control

- **There is not yet sufficient evidence to advocate acid suppression drugs as chemopreventive agents (Recommendation grade C).**
- **Use of medication to suppress gastric acid production is recommended for symptom control (Recommendation grade A).**
- **Proton pump inhibitors (PPIs) have the best clinical profile for symptomatic management (Recommendation grade A).**
- **Antireflux surgery is not superior to pharmacological acid suppression for the prevention of neoplastic progression of Barrett's oesophagus (Recommendation grade C).**
- **Antireflux surgery should be considered in patients with poor or partial symptomatic response to PPIs (Recommendation grade A).**
- **There is currently insufficient evidence to support the use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or other chemopreventive agents in patients with Barrett's oesophagus (Recommendation grade C).**

13.2.4.4 ***Long-term PPI 2017***

Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI.

Rationale: PPIs have a clear symptomatic benefit and a possible benefit in slowing progression of Barrett's. There is likely to be a net benefit for long-term PPIs in these patients.

Asymptomatic patients with Barrett's esophagus should consider a long-term PPI.

Rationale: The evidence that PPIs slow progression of Barrett's is low in quality but the evidence of PPI adverse effects is also low in quality. Because there is no high quality evidence on either side of this question, this is a weak recommendation and this decision should be individualized with patients.

13.2.5 Gastroprotection

13.2.5.1 *Long-term PPI 2017*

Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs.

Rationale: PPIs are highly effective in preventing ulcer-related bleeding in appropriately selected patients who take NSAIDs, and this benefit is likely to outweigh PPI-related risks.

13.2.5.2 *NICE rheumatoid arthritis 2009*

When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either case, these should be co-prescribed with a proton pump inhibitor (PPI), choosing the one with the lowest acquisition cost. [2009]

13.2.5.3 *NICE Osteoarthritis 2014*

When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor (other than etoricoxib 60 mg). In either case, co-prescribe with a proton pump inhibitor (PPI), choosing the one with the lowest acquisition cost. [2008]

13.2.5.4 *NICE NSAID 2015*

Co-prescribe a proton pump inhibitor with NSAIDs for people who have osteoarthritis or rheumatoid arthritis, and think about the use of gastroprotective treatment when prescribing NSAIDs for low back pain.

13.2.6 Deprescribing PPIs

13.2.6.1 *NICE GORD 2014*

Encourage people who need long-term management of dyspepsia symptoms to reduce their use of prescribed medication stepwise: by using the effective lowest dose, by trying 'as-needed' use when appropriate, and by returning to self-treatment with antacid and/or alginate therapy (unless there is an underlying condition or comedication that needs continuing treatment). [2004, amended 2014]

13.2.6.2 *Deprescribing PPI 2017*

This guideline recommends deprescribing PPIs (reducing dose, stopping, or using "on-demand" dosing) in adults who have completed a minimum of 4 weeks of PPI treatment for heartburn or mild to moderate gastroesophageal reflux disease or esophagitis, and whose symptoms are resolved.

The recommendations do not apply to those who have or have had Barrett esophagus, severe esophagitis grade C or D, or documented history of bleeding gastrointestinal ulcers.

For adults (>18 y) with upper GI symptoms, who have completed a minimum 4-wk course of PPI treatment, resulting in resolution of upper GI symptoms, we recommend the following:

- **Decrease the daily dose or stop and change to on-demand (as needed) use (strong recommendation, low-quality evidence)**

Alternatively, we suggest the following:

- **Consider an H2RA as an alternative to PPIs (weak recommendation, moderate-quality evidence)**

How should tapering be approached? Our systematic search did not identify trials that adequately addressed optimal tapering approaches to minimize symptom recurrence. There is very low-quality evidence that abrupt discontinuation (without tapering or using on-demand strategies) does increase symptom relapse. Therefore, it might be prudent to reduce the PPI to the lowest effective dose before discontinuation and to provide patients with a symptom management strategy that might include on-demand PPIs. Anecdotally, clinicians seem to prefer gradual dose reduction (eg, from twice daily to once daily, from high dose to low dose, from daily to every other day) and any of these approaches can be used, taking into consideration the patient's current medication supply, as well as the convenience of the approach.

Explaining the rationale for deprescribing PPIs, and the option of beginning with lowering the dose or using on-demand therapy, will facilitate patient and family acceptance.

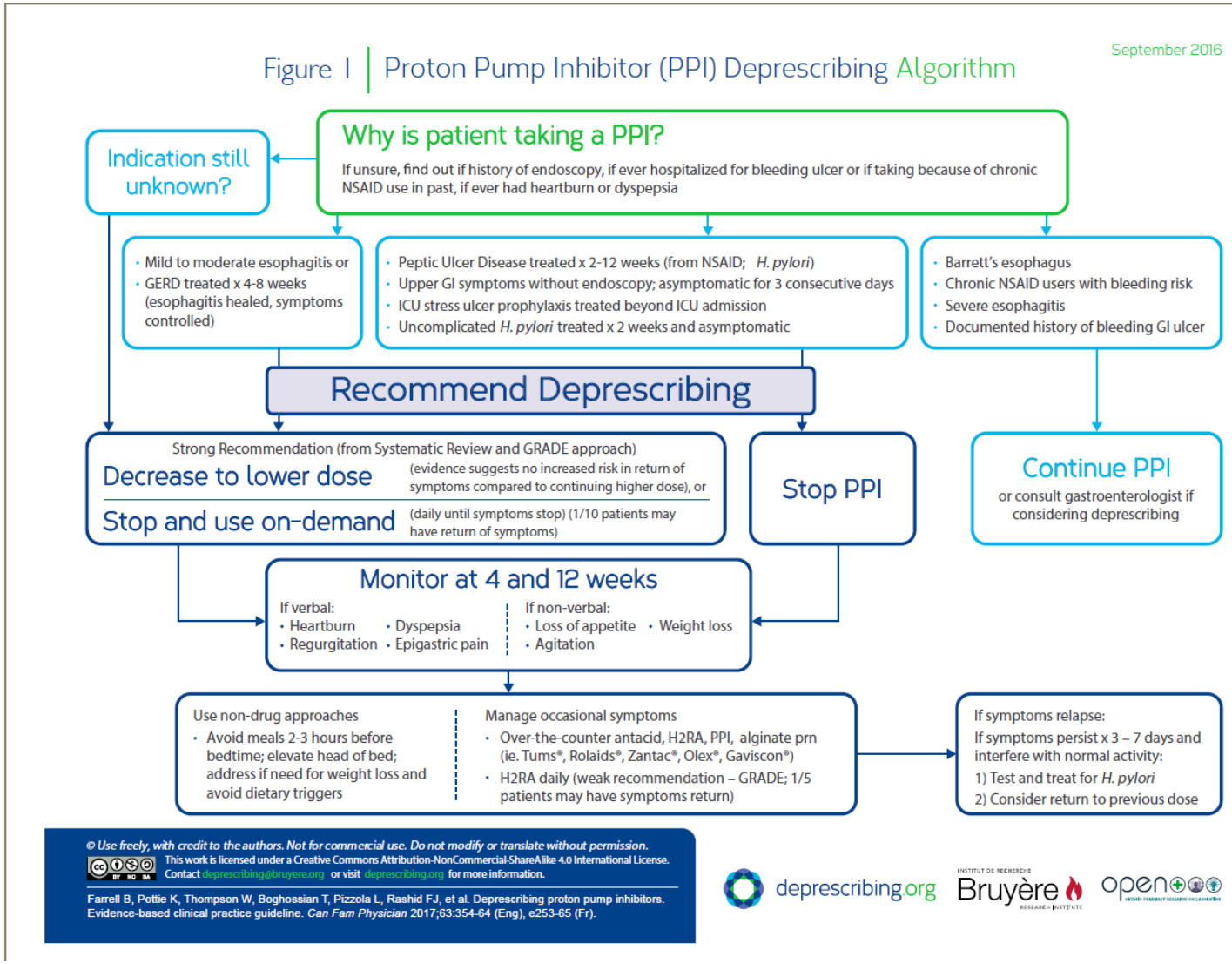
Figure 1 | Proton Pump Inhibitor (PPI) Deprescribing Algorithm
September 2016
Why is patient taking a PPI?
If unsure, find out if history of endoscopy, if ever hospitalized for bleeding ulcer or if taking because of chronic NSAID use in past, if ever had heartburn or dyspepsia
Indication still unknown?
• Mild to moderate esophagitis or
• GERD treated x 4-8 weeks (esophagitis healed, symptoms controlled)
• Peptic Ulcer Disease treated x 2-12 weeks (from NSAID; H. pylori)
• Upper GI symptoms without endoscopy; asymptomatic for 3 consecutive days
• ICU stress ulcer prophylaxis treated beyond ICU admission
• Uncomplicated H. pylori treated x 2 weeks and asymptomatic
• Barrett's esophagus
• Chronic NSAID users with bleeding risk
• Severe esophagitis
• Documented history of bleeding GI ulcer
Recommend Deprescribing
Strong Recommendation (from Systematic Review and GRADE approach)
Decrease to lower dose (evidence suggests no increased risk in return of symptoms compared to continuing higher dose), or
Stop and use on-demand (daily until symptoms stop) (1/10 patients may have return of symptoms)
Stop PPI
Continue PPI
or consult gastroenterologist if considering deprescribing
Monitor at 4 and 12 weeks
If verbal:
• Heartburn • Dyspepsia
• Regurgitation • Epigastric pain
If non-verbal:
• Loss of appetite • Weight loss
• Agitation
Use non-drug approaches
• Avoid meals 2-3 hours before bedtime; elevate head of bed; address if need for weight loss and avoid dietary triggers
Manage occasional symptoms
• Over-the-counter antacid, H2RA, PPI, alginate prn (ie. Tums®, Rolaids®, Zantac®, Olex®, Gaviscon®)
• H2RA daily (weak recommendation – GRADE; 1/5 patients may have symptoms return)
If symptoms relapse:
If symptoms persist x 3 – 7 days and interfere with normal activity:
1) Test and treat for H. pylori
2) Consider return to previous dose
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This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.
Contact deprescribing@bruyere.org or visit deprescribing.org for more information.
Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors. Evidence-based clinical practice guideline. Can Fam Physician 2017;63:354-64 (Eng), e253-65 (Fr).
deprescribing.org
Bruyère
open

deprescribing.org | Proton Pump Inhibitor (PPI) Deprescribing Notes

September 2016

PPI Availability

PPI	Standard dose (healing) (once daily)*	Low dose (maintenance) (once daily)
Omeprazole (Losec*) - Capsule	20 mg+	10 mg+
Esomeprazole (Nexium*) - Tablet	20[a] or 40[b] mg	20 mg
Lansoprazole (Prevacid*) - Capsule	30 mg+	15 mg+
Dexlansoprazole (Dexilant*) - Tablet	30[c] or 60[d] mg	30 mg
Pantoprazole (Tecta* , Pantoloc*) - Tablet	40 mg	20 mg
Rabeprazole (Pariet*) - Tablet	20 mg	10 mg

Legend

a Non-erosive reflux disease

b Reflux esophagitis

c Symptomatic non-erosive gastroesophageal reflux disease

d Healing of erosive esophagitis

\+ Can be sprinkled on food

* Standard dose PPI taken BID only indicated in treatment of peptic ulcer caused by *H. pylori*; PPI should generally be stopped once eradication therapy is complete unless risk factors warrant continuing PPI (see guideline for details)

Key

GERD = gastroesophageal reflux disease

NSAID = nonsteroidal anti-inflammatory drugs

H2RA = H2 receptor antagonist

SR = systematic review

GRADE = Grading of Recommendations Assessment, Development and Evaluation

Engaging patients and caregivers

Patients and/or caregivers may be more likely to engage if they understand the rationale for deprescribing (risks of continued PPI use; long-term therapy may not be necessary), and the deprescribing process

PPI side effects

- When an ongoing indication is unclear, the risk of side effects may outweigh the chance of benefit
- PPIs are associated with higher risk of fractures, *C. difficile* infections and diarrhea, community-acquired pneumonia, vitamin B12 deficiency and hypomagnesemia
- Common side effects include headache, nausea, diarrhea and rash

Tapering doses

- No evidence that one tapering approach is better than another
- Lowering the PPI dose (for example, from twice daily to once daily, or halving the dose, or taking every second day) OR stopping the PPI and using it on-demand are equally recommended strong options
- Choose what is most convenient and acceptable to the patient

On-demand definition

Daily intake of a PPI for a period sufficient to achieve resolution of the individual's reflux-related symptoms; following symptom resolution, the medication is discontinued until the individual's symptoms recur, at which point, medication is again taken daily until the symptoms resolve

Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors. Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354-64 (Eng), e253-65 (Fr).

deprescribing.org | Bruyère Research Institute | OPEN

13.2.6.3 *Long-term PPI 2017*

The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition.

Rationale: Long-term PPI users often receive PPIs at doses higher than necessary to manage their condition. Since PPI reduction is often successful, it is logical to periodically reevaluate PPI dosing so that the minimum necessary dose is prescribed.

13.2.7 Recommendations regarding adverse events

13.2.7.1 *GORD 2013*

Potential risks associated with PPIs

- **Switching PPIs can be considered in the setting of side-effects. (Conditional recommendation, low level of evidence)**
- **Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture. (Conditional recommendation, moderate level of evidence)**
- **PPI therapy can be a risk factor for Clostridium difficile infection, and should be used with care in patients at risk. (Moderate recommendation, moderate level of evidence)**
- **Short-term PPI usage may increase the risk of community-acquired pneumonia. The risk does not appear elevated in long-term users. (Conditional recommendation, moderate level of evidence)**
- **PPI therapy does not need to be altered in concomitant clopidogrel users as there does not appear to be an increased risk for adverse cardiovascular events. (Strong recommendation, high level of evidence)**

13.2.7.2 *Long-term PPI 2017*

Long-term PPI users should not routinely use probiotics to prevent infection.

Rationale: There is no evidence for or against probiotics to prevent infections in long-term users of PPIs.

Long-term PPI users should not routinely raise their intake of calcium, vitamin B12 or magnesium beyond the Recommended Dietary Allowance (RDA).

Rationale: There is no evidence for or against use of vitamins or supplements beyond the RDA in long-term users of PPIs. Many adults fall below the RDA in several vitamins or minerals and, in these adults, it is reasonable to raise intake to meet the RDA regardless of PPI use.

Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12.

Rationale: There is no evidence for or against dedicated testing for patients taking long-term PPIs. Such screening (eg, for iron or vitamin B12 deficiency) can be offered but is of no proven benefit.

Specific PPI formulations should not be selected based on potential risks.

Rationale: There is no convincing evidence to rank PPI formulations by risk.

14 Evidence tables. Dyspepsia.

14.1.1 PPI vs placebo

Meta-analysis: Cochrane Pinto-Sanchez 2017(4) "Proton pump inhibitors for functional dyspepsia" Inclusion criteria: RCTs comparing any PPI with placebo, H2RAs or prokinetics for the treatment of (adequately diagnosed) functional dyspepsia of at least two weeks' duration. Adults (16 years or greater). Search strategy: the Cochrane Library, MEDLINE, Embase , and SIGLE grey literature, clinical trial registries; abstracts from conferences up were searched to May 2017. Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result (95%CI)
ref* Cochrane Pinto-Sanchez 2017(4) Design: SR + MA Search date: (May 2017)	PPI vs placebo	N= 18 n= 6172 (Blum 2000, Bolling-Sternevald 2002, Catapani 2015, Farup 1999, Fletcher 2011, Gerson 2005, Hengels 1998, Iwakiri 2013, Majewski 2016, Peura 2004, Suzuki 2013, Talley	Global symptoms of dyspepsia using the most stringent definition of "not symptom-free"	PPI: 2811/ 4079 Placebo: 1552/2093 **RR 0.88 (0.82 to 0.94)** **SS in favour of PPI**

		1998a, Talley 1998b, Talley 2007, Tominaga 2010, Van Rensburg 2008, Van Zanten 2006, Wong 2002)		
		N= 2 n= 1177 (Talley 1998a, Talley 1998b)	Quality of life (Psychological General Well-being Index)	MD 0.54 (-1.55 to 2.63) NS
		N= 1 n= 453 (Wong 2002)	Quality of life (36-item Short Form)	MD -1.11 (-5.32 to 3.10) NS
		N= 6 n= 2693 (Blum 2000, Fletcher 2011, Hengels 1998, Iwakiri 2013, Talley 2007, Van Rensburg 2008)	Adverse events	PPI: 264/1909 Placebo: 133/784 RR 0.99 (0.73 to 1.33) NS

Table 78

* Characteristics of included studies: see below

Ref + design	n (randomized)	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)

Blum 2000(19)	792		2 weeks		*RCT did not meet our inclusion criteria*
Bolling-Sternevald 2002(20)	197		2 weeks		*RCT did not meet our inclusion criteria*
Catapani 2015(21)	131	Participants with functional dyspepsia who met Rome II criteria	6 months	• Group A1: traditional medical therapy + omeprazole (dose unknown) • Group A2: traditional medical therapy + placebo. • Group B1: therapeutic encounter + omeprazole. • Group B2: therapeutic encounter + placebo. Data from A1 + B1 were combined as PPI arm, data from A2 + B2 were combined as control arm in this systematic review	RANDO: Adequate ALLOCATION CONC: unclear (no data provided) BLINDING : Participants: unclear personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: high risk (per protocol included 65% of PPI users and 33% of placebo users). Reasons not provided. SELECTIVE REPORTING: conference abstract – unclear OTHER BIAS: unclear
Farup 1999(22)	24				*RCT did not meet our inclusion criteria*
Fletcher 2011(23)	105		2 weeks		*RCT did not meet our inclusion criteria*
Gerson 2005(24)	40				*RCT did not meet our inclusion criteria*
Hengels 1998(25)	269		2 weeks		*RCT did not meet our inclusion criteria*
Iwakiri 2013(26)	338	Functional dyspepsia (Rome III) Normal endoscopy Did not respond to 1 week of single-blind	8 weeks	PPI: rabeprazole 10 mg/day. PPI: rabeprazole 20 mg/day. PPI: rabeprazole 40 mg/day.	RANDO: Adequate ALLOCATION CONC:

		placebo treatment in a run-in period		Placebo.	Adequate BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Majewski 2016(27)	73				*RCT did not meet our inclusion criteria*
Peura 2004(28)	921	Functional dyspepsia (Rome II) Normal endoscopy Exclusion: IBS NSAID users	8 weeks	PPI: lansoprazole 15 mg/day. PPI: lansoprazole 30 mg/day. Placebo.	RANDO: Adequate ALLOCATION CONC: unclear (no data provided) BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: unclear risk (no information on lost to follow-up) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Suzuki 2013(29)	54				*RCT did not meet our inclusion criteria*
Talley 1998a(30)	642	Functional dyspepsia: “persistent or recurrent epigastric pain or discomfort, or both, in participants with normal findings at upper gastrointestinal	4 weeks	PPI: omeprazole 10 mg. PPI: omeprazole 20 mg. Placebo.	RANDO: Adequate ALLOCATION CONC: Adequate

		endoscopy. Symptoms at least 1 month of duration, 25% of days during month and least 3 days during the last week before enrolment" Normal endoscopy			BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Talley 1998b(30)	606	Functional dyspepsia: "persistent or recurrent epigastric pain or discomfort, or both, in participants with normal findings at upper gastrointestinal endoscopy. Symptoms at least 1 month of duration, 25% of days during month and least 3 days during the last week before enrolment" Normal endoscopy	4 weeks	PPI: omeprazole 10 mg. PPI: omeprazole 20 mg. Placebo.	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Talley 2007(31)	1589	intermittent or continuous epigastric pain or burning for at least 3 months Normal endoscopy <u>Exclusions:</u> people with predominant GORD symptoms HP eradication NSAID use	1 week run-in + 7 weeks	PPI: esomeprazole 40 mg/day. Placebo.	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: high risk (imbalanced discontinuation between

					groups) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Tominaga 2010(32)	115	Functional dyspepsia (Rome III) Normal endoscopy	4 weeks	PPI: rabeprazole 10 mg/day. Placebo.	RANDO: Unclear (no information) ALLOCATION CONC: unclear (no information) BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: unclear risk (imbalanced lost to follow-up; unclear impact on effect estimates) SELECTIVE REPORTING: unclear (no adverse events data reported) OTHER BIAS: unclear (conference proceedings, no information)
Van Rensburg 2008(195)	419	Functional dyspepsia: “intermittent episodes of epigastric pain for at least the 3 months prior to screening” Normal endoscopy and ultrasound	4 weeks	PPI: pantoprazole 20 mg/day. Placebo.	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: unclear risk (balanced

					drop-out but nearly 20%) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Van Zanten 2006(33)	224	Functional dyspepsia (Rome II) Normal endoscopy <u>Exclusion</u>: people with IBS people with GORD predominant symptoms	8 weeks	PPI: esomeprazole 40 mg/day. Placebo.	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: unclear risk (imbalanced lost to follow-up; unclear impact on effect estimates) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Wong 2002(34)	453	Functional dyspepsia (Rome II) Predominant epigastric pain/discomfort Normal endoscopy	4 weeks	PPI: lansoprazole 15 mg once daily. PPI: lansoprazole 30 mg once daily. Placebo.	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: unclear risk (imbalanced lost to follow-up; unclear impact on effect estimates)

					SELECTIVE REPORTING: low risk OTHER BIAS: low risk

Table 79

14.1.2 PPI vs lifestyle

No RCTs that compared PPIs with lifestyle, and that met our inclusion criteria, were found.

14.1.3 PPI vs antacids

Meta-analysis: Cochrane Moayyedi 2006(196) "Pharmacological interventions for non-ulcer dyspepsia ";

Inclusion criteria: All RCTs comparing drugs of any of the six groups (antacids, H2RAs, PPIs, prokinetics, mucosal protection agents, antimuscarinics) with each other or with placebo for non-ulcer dyspepsia.
Search strategy: CENTRAL, MEDLINE, EMBASE, CINAHL, SIGLE and reference lists of articles were searched up until January 2006.
Assessment of quality of included trials: yes

This systematic review sought RCTs that compared any of the following treatments to each other (or placebo): antacids, H2RAs, PPIs, prokinetics, mucosal protection agents, antimuscarinics.

No RCTs that compared PPIs with lifestyle were found.

14.1.4 PPI vs H2RA

Meta-analysis: Cochrane Pinto-Sanchez 2017(4) "Proton pump inhibitors for functional dyspepsia"

Inclusion criteria: RCTs comparing any PPI with placebo, H2RAs or prokinetics for the treatment of (adequately diagnosed) functional dyspepsia of at least two weeks' duration. Adults (16 years or greater).
Search strategy: the Cochrane Library, MEDLINE, Embase , and SIGLE grey literature, clinical trial registries; abstracts from conferences up were searched to

May 2017. Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
ref* Cochrane Pinto-Sanchez 2017(4) Design: SR + MA Search date: (May 2017)	PPI vs H2RA	N= 2 n= 740 (Dillon 2004, Blum 2000)	Global symptoms of dyspepsia using the most stringent definition of "not symptom-free"	PPI: 314/468 H2RA: 201/272 RR 0.88 (0.74 to 1.04) NS
		N= 1 n= 589 (Blum 2000)	Adverse events	PPI: 57/395 H2RA: 29/194 RR 0.97 (0.64 to 1.46) NS

Table 80

* Characteristics of included studies: see below

Ref + design	n (randomized)	Population	Duration	Comparison	Methodology
Blum 2000(19)	792		2 weeks		*RCT did not meet our inclusion criteria*
Dillon 2004(35)	152	Participants with dyspepsia (Rome II)	8 weeks	PPI: lansoprazole 30 mg/day. H2RA: ranitidine 150 mg 2	RANDO: Unclear risk(no details) ALLOCATION CONC: Unclear risk(single blinded)

				times/day.	BLINDING : Participants: adequate personnel: single blinded; high risk assessors: unclear risk (not described) INCOMPLETE OUTCOME DATA: unclear risk (conference abstract) SELECTIVE REPORTING: unclear risk (conference abstract) OTHER BIAS: unclear risk (conference abstract)

Table 81

14.1.5 PPI vs prokinetics

Meta-analysis: Cochrane Pinto-Sanchez 2017(4) "Proton pump inhibitors for functional dyspepsia"

Inclusion criteria: RCTs comparing any PPI with placebo, H2RAs or prokinetics for the treatment of (adequately diagnosed) functional dyspepsia of at least two weeks' duration. Adults (16 years or greater).
Search strategy: the Cochrane Library, MEDLINE, Embase , and SIGLE grey literature, clinical trial registries; abstracts from conferences up were searched to May 2017.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
ref* Cochrane Pinto-Sanchez 2017(4)	PPI vs prokinetics	N= 5 n= 1033 (Hsu 2011, Jiang 2011, Jung 2016,	Global symptoms of dyspepsia using the most stringent definition of "not symptom-free"	PPI: 272/520 Prokinetics: 298/513 **RR 0.89 (0.81 to 0.99)** **SS in favour of PPI**

Design: SR + MA Search date: (May 2017)		Kamiya 2017, Li 2003)		
		N= 1 n= 262 (Jung 2016)	Quality of life (Korean version of Nepean Dyspepsia index)	MD -0.50 (-4.42 to 3.42) NS
		N= 5 n= 1033 (Hsu 2011, Jiang 2011, Jung 2016, Kamiya 2017, Li 2003)	Adverse events	PPI: 64/520 Prokinetics: 58/513 RR 1.09 (0.79 to 1.49) NS

Table 82

* Characteristics of included studies: see below

Ref + design	n (randomized)	Population	Duration	Comparison	Methodology
Hsu 2011(36)	329		2 weeks		*RCT did not meet our inclusion criteria*
Jiang 2011(37)	148		2 weeks		*RCT did not meet our inclusion criteria*
Jung 2016(38)	389	Functional dyspepsia (Rome III) HP tested	4 weeks	PPI: pantoprazole 40 mg/day. Prokinetic: DA 9701 30 mg 3 times/day. PPI + prokinetic: pantoprazole + DA 9701.	RANDO: adequate ALLOCATION CONC: adequate BLINDING : Participants: adequate personnel: adequate assessors: adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk

					OTHER BIAS: low risk
Kamiya 2017(39)	134	Functional dyspepsia (Rome III)	4 weeks	PPI: rabeprazole 10 mg/day. Prokinetic: itopride.	RANDO: adequate ALLOCATION CONC: unclear (no information provided) BLINDING : inadequate Participants: no blinding personnel: no blinding assessors: no blinding INCOMPLETE OUTCOME DATA: unclear risk (enrollment not balanced) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Li 2003(40)	160		2 weeks		*RCT did not meet our inclusion criteria*

Table 83

14.1.6 PPI step-up vs step-down treatment

Study details	n/Population	Comparison	Outcomes		Methodological
Ref van Marrewijk 2009 DIAMOND(5) Design: RCT DB PG Duration of follow-up: 6 months	n= 664 Age: 32% ≥55 years H. pylori status: 35% positive H. pylori eradication: no diagnostic endoscopy : n <u>Inclusion:</u> >18y New-onset dyspepsia (Dyspepsia defined as pain or discomfort centered in the upper abdomen, judged by the physician to originate in the upper gastrointestinal tract, which might be accompanied with symptoms such as regurgitation,	Step-up treatment (stepwise treatment with antacid, H2RA, PPI*) vs Step-down treatment (reverse order: PPI, H2RA, antacid*) * **<u>Antacid</u>**: aluminium oxide 200 mg/ magnesium hydroxide 400 mg 4x/day **<u>H2RA</u>**: ranitidine 150 mg 2x/day	Efficacy		RANDO: Adequate (computer generated sequence) ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 3% Drop-out and Exclusions: 0% • Described: yes • Balanced across groups: yes ITT: modified ITT (“all patients with data for the primary outcome at 6 months”) SELECTIVE REPORTING: no
			Treatment success (PO) defined as adequate symptom relief at 6 months, indicated by a “yes” or “no” answer.	Step-up : 238/332 Step-down : 219/313 OR 0.92 (95%CI 0.7 to 1.3) p=0.63 NS	
			Symptom: Regurgitation	Step-up : 70/256 Step-down : 77/224 p=0.30 NS	
			Symptom: Heartburn	Step-up : 90/253 Step-down : 86/240 p=0.95 NS	
			Symptom: Epigastric pain	Step-up : 54/246 Step-down : 60/237 p=0.38 NS	

	heartburn, nausea, or bloating.) <u>Exclusion</u> • Previous gastroscopy within the previous year • Use of prescribed acid-suppressive medication in previous 3 months • Alarm symptoms (dysphagia, unintended weight loss, anaemia, haematomesis) • pregnancy • insufficient knowledge of the Dutch language	**<u>PPI</u>**: pantoprazole 40 mg 1x/day <u>remarks</u> each step lasted 4 weeks and treatment only continued with the next step if symptoms persisted or relapsed within 4 weeks			Sponsor: The Netherlands Organisation for Health Research and Development (ZonMw)
			Symptom: Nausea	Step-up : 39/256 Step-down : 40/245 p=0.74 NS	
			Symptom: Bloating	Step-up : 93/257 Step-down : 92/245 p=0.75 NS	
			Quality of Life (Worsened) (EuroQoL-5D)	Step-up : 36/325 Step-down : 41/220 p=0.53 NS	
			Safety		
			Adverse events	Step-up : 94/341 Step-down : 93/323 p=0.73 NS	

Table 84

15 Evidence tables. GORD.

15.1.1 PPI vs placebo

Meta-analysis: Zhang 2013(41): "Proton pump inhibitor for non-erosive reflux disease: A meta-analysis"

Inclusion criteria: RCTs that evaluated efficacy, safety and influential factors of PPI treatment for non-erosive reflux disease
Search strategy: Pubmed, MEDLINE, EMBASE and the Cochrane Library were searched up to April 2013. The medical subject headings which were used in retrieving citation were: non-erosive reflux disease or NERD, proton pump inhibitors or PPI or esomeprazole or pantoprazole or omeprazole or rabeprazole or lansoprazole.
Assessment of quality of included trials: yes
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Zhang 2013(41) Design: SR Search date: (April 2013)	PPI vs placebo	N= 11 n= 5416 (Lind 1997, Lind 1999, Richter 2000, Talley 2001, Talley 2002, Miner 2002, Bytzer 2004, Uemura 2008, Fass 2009, Kahrilas 2005,	Rate of symptomatic relief	PPI: 1546/3287 placebo: 573/2129 **RR 1.90 (1.57 to 2.30)** **SS in favour of PPI** High heterogeneity I^2=84.3%

		Kinoshita 2011)		
		N= 8 n= 4150 (Lind 1997, Talley 2001, Talley 2002, Miner 2002, Bytzer 2004, Uemura 2008, Fass 2009, Kinoshita 2011)	Adverse events	PPI: 530/2494 placebo: 404/1656 RR 1.00 (0.90 to 1.12) NS

Table 85

* Characteristics of included studies: see below

Meta-analysis: Zhang 2013(41): "Proton pump inhibitor for non-erosive reflux disease: A meta-analysis"

Inclusion criteria: RCTs that evaluated efficacy, safety and influential factors of PPI treatment for non-erosive reflux disease
Search strategy: Pubmed, MEDLINE, EMBASE and the Cochrane Library were searched up to April 2013. The medical subject headings which were used in retrieving citation were: non-erosive reflux disease or NERD, proton pump inhibitors or PPI or esomeprazole or pantoprazole or omeprazole or rabeprazole or lansoprazole.
Assessment of quality of included trials: yes
Other methodological remarks:

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Bytzer 2004(42)	418	Denmark mean age 47 y	6 months	Rabeprazole 10 mg Placebo	ALLOCATION CONC: inadequate

					RANDO: Unclear BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Fass 2009(43)	947	US mean age 48 y	4 weeks	Dexlansoprazole 30 mg Dexlansoprazole 60 mg Placebo	ALLOCATION CONC: inadequate RANDO: Adequate BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Kahrilas 2005(44)	261	US mean age 44 y	4 weeks	Rabeprazole 20 mg Placebo	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Kinoshita 2011(45)	285	Japan mean age 48 y	4 weeks	Rabeprazole 5 mg Rabeprazole 10 mg	ALLOCATION CONC: inadequate

				Placebo	RANDO: Unclear BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Lind 1997(46)	509	Sweden mean age 50 y	4 weeks	Omeprazole 10 mg Omeprazole 20 mg Placebo	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel/assessors unclear INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Lind 1999(47)	424	Sweden mean age 50 y	4 weeks	Omeprazole 10 mg Omeprazole 20 mg Placebo	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Miner 2002(48)	203	US mean age 45 y	4 weeks	Rabeprazole 10 mg Rabeprazole 20 mg	ALLOCATION CONC: inadequate

				Placebo	RANDO: Unclear BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Richter 2000(49)	898	US mean age 45 y	8 weeks	Lansoprazole 15 mg Lansoprazole 30 mg Ranitidine 150 mg Placebo	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel/assessors unclear INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Talley 2001(50)	342	Australia mean age 49y	6 months	Esomeprazole 20 mg Placebo	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Talley 2002(51)	721	UK mean age 48y	6 months	esomeprazole 20mg esomeprazole 40mg	ALLOCATION CONC: inadequate

				Placebo	RANDO: Unclear BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Uemura 2008(52)	281	Japan mean age 44y	4 weeks	Omeprazole 10 mg Omeprazole 20 mg Placebo	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel/assessors unclear INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk

Table 86

15.1.2 PPI vs lifestyle

15.1.3 PPI vs antacids

Alginates versus PPI

Meta-analysis: Leiman 2017(197): "Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis"

Inclusion criteria: RCTs of alginates in adult patients with GORD and written in English. Exclusion of patients with erosive oesophagitis
Search strategy: Pubmed/MEDLINE, Embase, and the Cochrane databases were searched up until October 2015.
Assessment of quality of included trials: yes

This SR found 14 RCTs, of which three compared alginates to PPI. Of these three RCTs, only one met our inclusion criteria. Because of this reason, we will report the individual RCT (Chiu 2013(53)), and not the meta-analysis results, below.

Study details	n/Population	Comparison	Outcomes		Methodological
Chiu 2013(53) Design: non-inferiority RCT DB PG Duration of follow-up: 4 weeks	n= 195 randomised Mean age: 47y H. pylori status: 20.5% positive urea breath test H. pylori eradication: unknown diagnostic endoscopy y Inclusion:	Sodium alginate oral suspension 50 mg/mL 20 mL 3x/day vs omeprazole 20 mg 1x/day remarks			RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 3.6 % Drop-out and Exclusions: 2.6% • Described: yes
			percentage of patients achieving adequate heartburn or regurgitation relief* (PO) *defined as no more than 1 day of mild heartburn or regurgitation episodes in the last 7 days	Sodium alginate: 49/92 Omeprazole: 46/91 MD 2.7% (95%CI -11.9% to 17.4%) p=0.175 NS	
			Change from baseline of the Reflux Disease Questionnaire total score	Sodium alginate: -12.4 SD 8.4 Omeprazole: -11.4 SD 9.8 p= 0.487 NS	

	• 20-75 y old • Endoscopic diagnosis of non-erosive GORD • Heartburn or regurgitation (either one) as main symptom at least 2 days a week and had been present for ≥1 month before screening. • Heartburn or regurgitation (either one) during the 7 days screening period, either with frequency for ≥4 days of mild symptom or ≥2 days of moderate to severe symptom . • Agreement to sign the informed consent form. <u>Exclusion</u> • Erosive GORD	Sodium alginate suspension also contained sodium bicarbonate (26.7 mg/mL) and calcium carbonate (16 mg/mL) Patients were allowed to receive antacid as rescue medication if necessary in an open-label fashion up to a maximum of six tablets per day. Each tablet contains aluminium hydroxide 200 mg, magnesium hydroxide 200 mg and simethicone 25 mg.	Patients' overall satisfaction	Sodium alginate: • Poor: 0% • Unsatisfactory: 3.6% • Satisfactory: 9.5% • Good: 48.8% • Very good: 38.1% Omeprazole: • Poor: 1.1% • Unsatisfactory: 4.5% • Satisfactory: 7.7% • Good: 48.3% • Very good: 38.2% Difference: p= 0.778 NS	• Balanced across groups: yes ITT: modified ITT ("All randomised subjects who administered at least one dose of study medication.") SELECTIVE REPORTING: yes, not all safety data reported Other important methodological remarks: • 1 week run-in period before randomisation Sponsor: TTY Biopharm Co., Ltd. Taipei Branch
			Safety		
			Adverse events	Sodium alginate: 5.4% Omeprazole: 5.5% No severe adverse events reported	

	• Barrett's oesophagus • Oesophageal stricture • Gastroduodenal ulcer • History of gastric, duodenal or oesophageal surgery • Malignant disease of any kind • Intrahepatic stone, gallstone, gall-bladder sludge, hepatic or pancreatic carcinoma; • ischaemic heart disease; • Pregnant or nursing mother; • History of allergy to any of the study drugs or their related compounds; • History of alcohol or drug abuse; • Liver disease (AST/ SGOT, ALT/SGPT >2 9 upper limits				

	of normal); • Renal disease (serum creatinine >1.5 mg/dL); • Using a proton pump inhibitor (PPI) within 14 days before screening, or a H2-blocker, prokinetic agent or antacid within 7 days before screening; • Participating in any investigational drug trial within 4 weeks before screening; • Any other conditions or diseases that an investigator considered not appropriate study.				

Table 87

15.1.4 PPI vs H2RA

Meta-analysis: Zhang 2013(41): "Proton pump inhibitor for non-erosive reflux disease: A meta-analysis"

Inclusion criteria: RCTs that evaluated efficacy, safety and influential factors of PPI treatment for non-erosive reflux disease
Search strategy: Pubmed, MEDLINE, EMBASE and the Cochrane Library were searched up to April 2013. The medical subject headings which were used in retrieving citation were: non-erosive reflux disease or NERD, proton pump inhibitors or PPI or esomeprazole or pantoprazole or omeprazole or rabeprazole or lansoprazole.
Assessment of quality of included trials: yes
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Zhang 2013(41) Design: SR Search date: (April 2013)	PPI vs H2RA	N= 6 n= 1678 (Richter 2000, Talley 2002, Fujiwara 2005, Juul-Hansen 2009, Nakamura 2010, Kobeissy 2012)	Rate of symptomatic relief	PPI: 350/834 H2RA: 219/844 **RR 1.63 (1.42 to 1.87)** **SS in favour of PPI**
		N= 3 n= 565 (Armstrong 2001, Talley 2002, Juul-Hansen 2009)	Adverse events	PPI: 120/287 H2RA: 126/278 RR 0.93 (0.87 to 1.11) NS

Table 88

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Armstrong 2001(54)	208	Canada mean age 47y	4 weeks	Pantoprazole 40 mg Nizatide 150 mg	ALLOCATION CONC: inadequate RANDO:

					Adequate BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Fujiwara 2005(55)	98	Japan mean age 55y	4 weeks	Omeprazole 20 mg Famotidine 20 mg	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel/assessors unclear INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Juul-Hansen 2009(56)	63				*RCT did not meet our inclusion criteria*
Kobeissy 2012(57)	83				*RCT did not meet our inclusion criteria*
Nakamura 2010(58)	33				*RCT did not meet our inclusion criteria*
Richter 2000(49)	898	US mean age 45 y	8 weeks	Lansoprazole 15 mg Lansoprazole 30 mg Ranitidine 150 mg Placebo	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel/assessors unclear INCOMPLETE OUTCOME DATA: low

					risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Talley 2002(59)	307	Australia mean age 53 y	6 months	Pantoprazole 20 mg Ranitidine 150 mg	ALLOCATION CONC: inadequate RANDO: Unclear BLINDING : Participants/personnel Adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk

Table 89

15.1.5 PPI vs prokinetics

Meta-analysis: Cochrane Sigterman 2013(60): "Short-termtreatment with proton pump inhibitors, H2- receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease."
Inclusion criteria: RCTs reporting symptomatic outcome after short-term treatment for GORD using proton pump inhibitors, H2-receptor antagonists or prokinetic agents. Participants had to be either from an empirical treatment group (no endoscopy used in treatment allocation) or from an endoscopy negative reflux disease group (no signs of erosive oesophagitis).
Search strategy: MEDLINE, EMBASE, EBMR were searched up until November 2011.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result (95%CI)

Cochrane Sigterman 2013(60) Design: SR Search date: (November 2011)	PPI vs prokinetic	N= 2 n= 747 (Galmiche 1997, Hatlebakk 1999)	Heartburn remission (empirical treatment)	PPI: 151/446 Prokinetic: 179/301 **RR 0.53 (0.32 to 0.87)** **SS in favour of PPI**
		N= 1 n= 302 (Galmiche 1997)	Heartburn remission (endoscopy negative reflux disease)	PPI: 80/206 Prokinetic: 52/96 **RR 0.72 (0.56 to 0.92)** **SS in favour of PPI**

Table 90

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Galmiche 1997(61)	423	Heartburn No circumferential oesophagitis	4 weeks	Omeprazole 20 mg Omeprazole 10 mg Cisapride 10 mg 4x/day	ALLOCATION CONC: unclear (not described) RANDO: unclear (insufficient information) BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: low risk SELECTIVE REPORTING: Unclear risk (insufficient information) OTHER BIAS: high risk (inadequate dose of omeprazole in one treatment arm)
Hatlebakk 1999(62)	483	Heartburn No grade C or D oesophagitis	8 weeks	Omeprazole 20 mg Cisapride 20 mg 2x/day	ALLOCATION CONC: unclear (insufficient information)

				Placebo	RANDO: adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: low risk SELECTIVE REPORTING: Unclear risk (insufficient information) OTHER BIAS: Unclear risk (insufficient information)

Table 91

15.1.6 PPI vs surgery

15.1.6.1 *laparoscopic fundoplication surgery vs PPI*

Meta-analysis: Garg 2015(63): "Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults"

Inclusion criteria: RCTs comparing laparoscopic fundoplication with medical treatment with people with GORD.
Search strategy: The Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trial Register, Cochrane Central Register of Controlled Trials, Ovid MEDLINE and EMBASE were searched up until June 2015.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Garg 2015(63) Design: SR+ MA	Laparoscopic fundoplication vs medical management	N= 3 n= 605 (Anvari 2011, Grant 2008, Mahon 2005)	Health-related QoL (<1 year)	SMD 0.14 (-0.02 to 0.30) NS
		N= 2	Health-related QoL (1-5 years)	SMD 0.03 (-0.19 to 0.24)

Search date: (June 2015)		n= 323 (Anvari 2011, Grant 2008)		NS
		N= 4 n= 1160 (Anvari 2011, Grant 2008, Lundell 2008, Mahon 2005)	GORD-specific QoL (< 1 year)	**SMD 0.58 (0.46 to 0.70)** **SS in favour of surgery**
		N= 3 n= 994 (Anvari 2011, Grant 2008, Lundell 2008)	GORD-specific QoL (1-5 years)	SMD 0.28 (-0.27 to 0.84) NS
		N= 2 n= 637 (Anvari 2011, Lundell 2008)	Serious adverse events	Laparoscopic fundoplication: 60/331 Medical management: 38/306 **RR 1.46 (1.01 to 2.11)** **SS in favour of medical management**
		N= 1 n= 83 (Anvari 2011)	Adverse events	Laparoscopic fundoplication: 7/43 Medical management: 0/40 RR 13.98 (0.82 to 237.07) NS

Table 92

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Anvari 2011(64)	104	Mean age 43y Inclusion:	3 years	Laparoscopic Nissen fundoplication	RANDO: Adequate

		• 18-70y • chronic reflux symptoms requiring long-term therapy • prior long-term treatment with PPI (minimum 1 year) • symptoms controlled before study		vs PPI (same dose as previous treatment)	ALLOCATION CONC: Adequate BLINDING : Participants/personnel/assessors Inadequate (no blinding) INCOMPLETE OUTCOME DATA: high risk (drop-out >20%) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Grant 2008(65)	357	Mean age 46y <u>Inclusion</u>: • >12 months symptoms requiring PPI for control • endoscopic or 24h pH monitoring evidence of GORD	12 months	Laparoscopic fundoplication vs Medical treatment as per local protocol	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants/personnel/assessors Inadequate (no blinding) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: high risk (adverse events not adequately reported) OTHER BIAS: low risk
Lundell 2008(66) (LOTUS)	554	Mean age 45y <u>Inclusion</u>: • Adults 18-70y • Confirmed GORD with requirement for long-term acid suppressive therapy	3 years	Laparoscopic Nissen fundoplication vs Esomeprazole 20 mg -40 mg/day	RANDO: Unclear (no information) ALLOCATION CONC: Unclear (no information) BLINDING : Participants/personnel/assessors Inadequate (no blinding) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: high risk (Sponsored by

					AstraZeneca)
Mahon 2005(67)	271	Mean age 48y Inclusion: • 16-70 y • ≥6 months GORD symptoms • ≥ 3 months PPI maintenance therapy • Proven reflux	12 months	Laparoscopic Nissen fundoplication vs PPI adjusted to symptom control	RANDO: Unclear (no information) ALLOCATION CONC: Unclear (no information) BLINDING : Participants/personnel/assessors Inadequate (no blinding) INCOMPLETE OUTCOME DATA: high risk (>20% drop-out) SELECTIVE REPORTING: high risk (adverse events not adequately reported) OTHER BIAS: high risk (Sponsored by Janssen Pharmaceuticals)

Table 93

Study details	n/Population	Comparison	Outcomes		Methodological
Galmiche 2011(68)(LOTUS) Design: RCT open-label PG	n= 554; 372 completed 5-year follow-up Mean age: 45y h pylori status: 12.3% positive h pylori eradication: unknown	Laparoscopic antireflux surgery (surgery) vs esomeprazole 20mg or 40 mg/day	Estimated remission rates(PO) after 5 years defined for surgery group as need for additional medical treatment;	surgery: 85% PPI: 92% **p=0.048** **SS in favour of PPI**	RANDO: Adequate ALLOCATION CONC: Unclear (not described) BLINDING : Participants: no Personnel: no Assessors: no POWER CALCULATION: Unclear, not described

Duration of follow-up: 5 years	diagnostic endoscopy: y oesophagitis grade: A: 24.4% B: 24.4% C: 3.6% D: 0.2% No oesophagitis: 47.5% <u>Inclusion:</u> 18-70 y Patients with chronic GORD Suitable and willing to accept both treatments Only esomeprazole responders (run-in period) <u>Exclusion</u> • Previous upper gastrointestinal surgery • Zollinger-Ellison syndrome • primary oesophageal disorders	<u>remarks</u> esomeprazole was initiated at 20 mg once daily and increased stepwise to 40 mg once daily, then to 20 mg twice daily in case of incomplete control	for PPI group as insufficient symptom control even after 2 dose escalations Safety Serious adverse events	surgery: 71/288 (25%) PPI: 64/266 (24%) NT	FOLLOW-UP: Lost-to follow-up: Surgery: 8% PPI: 3% Drop-out and Exclusions: Surgery: 30% PPI: 25% • Described: yes • Balanced across groups: no; sensitivity analyses were performed (best and worst case scenarios) to evaluate impact ITT: Yes: all randomized patients were analysed SELECTIVE REPORTING: no Other important methodological remarks: • 3-month run-in period was used to assess the clinical response to esomeprazole 40 mg/day; responders were randomized • Study was not designed as an

	• major comorbidities				equivalence or superiority study • Patients were not permitted to switch treatment groups if they requested the alternative treatment; patients had to leave the study to receive the alternative treatment Sponsor: AstraZeneca

Table 94

Remarks: This trial is also described and analysed in the Cochrane systematic review and meta-analysis of Garg 2015(63). In Garg 2015, the interim 3-year outcomes are used (publication of Lundell 2008(66)).

15.1.7 PPI vs endoscopic procedures

15.1.7.1 *Transoral incisionless fundoplication vs PPI*

Meta-analysis:Huang 2017(198): "Efficacy of transoral incisionless fundoplication for the treatment of GERD: a systematic review with meta-analysis"
Inclusion criteria: RCTs or prospective observational studies. Study subjects are patients with GORD requiring PPIs and TIF with/without PPIs. Average follow-up duration more than 90 days.
Search strategy: EMBASE, SCOPUS, PubMed, and the Cochrane Library Central were searched up until February 2016.
Assessment of quality of included trials: yes/no

This SR found 5 RCTs, of which four compared transoral incisionless fundoplication to PPI. Of these four RCTs, only one met our inclusion criteria. Because of this reason, we will report the individual RCT (Hunter 2015), and not the meta-analysis results, below.

Study details	n/Population	Comparison	Outcomes	Methodological

Hunter 2015(199) Design: RCT DB PG Duration of follow-up: 6 months	n= 129 Median age: TF/placebo: 52 y sham/PPI:55 y h pylori status: % not tested h pylori eradication n diagnostic endoscopy: yes Oesophagitis Grade A: 10% Grade B: 8% Grade C and D excluded <u>Inclusion:</u> 18-80 years old >6 months of GORD symptoms and troublesome regurgitation, despite a minimum 40 mg omeprazole or equivalent	Transoral incisionless fundoplication (TF) + placebo vs Sham surgery + omeprazole 40 mg/day <u>remarks</u> All patients were given omeprazole 40 mg for 14 days for healing. Thereafter, TF patients were switched to placebo and sham patients were continued on omeprazole.			RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes (sham-controlled) Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 1.6% Drop-out and Exclusions: TF/placebo 11.5% Sham/PPI 31% • Described: yes • Balanced across groups: no ITT: Yes (All randomized patients were analysed) SELECTIVE REPORTING: yes; limited reporting of outcomes (no comparative outcome measures
			Elimination of troublesome regurgitation (RDQ) (PO)	TF/placebo: 58/87 Sham/PPI: 19/42 **p=0.023** **SS in favour of TF**	
			Percent total time pH<4 Intra-oesophageal acid exposure	TF/placebo: -2.9% Sham/PPI: +0.3% **p=0.003** **SS in favour of TF**	
			Safety		
			Significant adverse events	TF/placebo: 7/87 Sham/PPI: 1/42 no statistical analysis	

	Exclusion • included systemic disease not well controlled • BMI>35 • oesophageal ulcer or stricture • Barrett's oesophagus >2 cm in length • hiatal hernia >2 cm in length • Los Angeles grade C or D oesophagitis • oesophageal dysmotility • previous oesophageal or gastric surgery • peptic ulcer disease • gastric outlet obstruction • gastroparesis • pregnancy or plans for pregnancy in the next 12 months • immunosuppression • portal hypertension • coagulopathy	If troublesome symptoms of GORD recurred after 2 weeks, the medication dose was doubled (omeprazole 40 mg bid or placebo bid). If troublesome symptoms persisted at 3 months, despite bid medication use, the patient was declared a failure and the blind was broken. Once the blind was broken, failed TF patients were given PPI and sham patients were offered TF			with confidence interval) Other important methodological remarks: At 3 months follow-up, 15 of 42 patients (36%) in the sham group met criteria for early failure, and 12 of 15 patients (80%) underwent crossover to TF. In the TF/placebo group 10 of 87 patients (11%) met the criteria for early failure and all 10 returned to PPI treatment. Sponsor: EndoGastric Solutions, Redmond, WA.

Table 95

15.1.7.2 *Stretta procedure vs PPI*

Meta-analysis: Das 2016 (200): "Is the Stretta procedure as effective as the best medical and surgical treatments for gastro-oesophageal reflux disease? A best evidence topic"

Inclusion criteria: Studies (interventional or observational) that compared Stretta procedure to other surgical and medical treatments in patients with GORD.
Search strategy: MEDLINE via Pubmed was search up until February 2016.
Assessment of quality of included trials: yes

This SR found 5 RCTs, of which only one (Coron 2008) compared the Stretta procedure to PPI. This RCT had a very small sample size and was underpowered for its primary outcome, and thus did not meet our inclusion criteria.

15.1.8 Continuous PPI vs on demand PPI

Systematic review: Ip 2011(69): "Comparative effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Updat."

Inclusion criteria: Studies of various designs, comparing effectiveness of different management options of adults with GORD

Search strategy: MEDLINE, Cochrane Central Register of Controlled Trials were searched up until August 2010.
MEDLINE, The Cochrane Database of Systematic Reviews, The American College of Physicians Journal Club, the Database of Abstracts of Reviews of Effects, and the Centre for Reviews and Dissemination's Health Technology Assessments were searched up until October 2009 for published MAs and SRs.

Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Ip 2011(69): Design: SR Search date: (August 2010)	Continuous PPI vs on demand PPI	N= 1 n= 1935 (Szucs 2009)	% of patients without symptoms (heartburn and regurgitation)	Esomeprazole 20 mg 1x/day: 86% Esomeprazole 20 mg on demand: 80% **p<0.01** **SS in favour of once daily PPI**
		N= 1 n= 477 (Sjosted 2005)	Overall symptomatic relapse	Esomeprazole 20 mg 1x/day: 5.0% Esomeprazole 20 mg on demand: 5.7% p=0.77 NS
		N= 1 n= 268 (Morgan 2007)	% of heartburn-free days	Rabeprazole 20 mg 1x/day: 90.3% Rabeprazole 20 mg on demand: 64.6% **p<0.0001** **SS in favour of once daily PPI**
		N= 1 n= 152 (Bour 2005)	% of patients with symptom relief	Rabeprazole 10 mg 1x/day: 86.4% Rabeprazole 10 mg on demand: 74.6% p=0.065 NS
		N= 1 n= 6017 (Pace 2005)	QoLRAD Quality of Life in Reflux and Dyspepsia (QOLRAD) 25 items questionnaire of five dimensions with each item scored on a 7-grade Likert scale; lower values indicate more severe impact on daily functioning.	Esomeprazole 20 mg 1x/day Esomeprazole 20 mg on demand **p<0.0001** **SS in favour of once daily PPI**
		N= 1	QoL	Rabeprazole 20 mg 1x/day

		n= 268 (Morgan 2007)	Patient assessment of upper gastrointestinal disorders – quality of life questionnaire (PAGIQOL): 30-item questionnaire about the quality of life. The range for total PAGI-QOL is 0-5, with lower scores indicating better health.	Rabeprazole 20 mg on demand **p<0.05** **SS in favour of once daily PPI**
		N= 1 n= 477 (Sjosted 2005)	% of patients in endoscopic remission	Esomeprazole 20 mg 1x/day: 81% Esomeprazole 20 mg on demand: 58% **p<0.0001** **SS in favour of once daily PPI**

Table 96

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Szucs 2009(70)	1935	endoscopically uninvestigated patients seeking primary care for symptoms suggestive of GORD	6 months	Esomeprazole 20 mg 1x/day vs Esomeprazole 20 mg on demand	ALLOCATION CONC: low risk RANDO: low risk BLINDING : high risk (open label) FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear (sponsor AstraZeneca)
Sjosted 2005(71)	477	Endoscopy- verified erosive reflux oesophagitis (LA grades A–D)	6 months	Esomeprazole 20 mg 1x/day vs Esomeprazole 20 mg on demand	ALLOCATION CONC: unclear (no info) RANDO: low risk BLINDING : high risk (open label) FOLLOW-UP: low risk SELECTIVE REPORTING: low risk

					OTHER BIAS: unclear (involvement of AstraZeneca)
Morgan 2007(72)	268	GORD, heartburn predominant	6 months	Rabeprazole 20 mg 1x/day vs Rabeprazole 20 mg on demand	ALLOCATION CONC: unclear (no info) RANDO: unclear (method not described) BLINDING : high risk (open label) FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor Janssen-Ortho)
Bour 2005(73)	152	Patients presenting with a relapse of GORD symptoms non-erosive reflux; SM grade 1-2	6 months	Rabeprazole 10 mg 1x/day vs Rabeprazole 10 mg on demand	ALLOCATION CONC: unclear (no info) RANDO: unclear (method not described) BLINDING : high risk (open label) FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor Janssen-Cilag)
Pace 2005(74)	6017	GORD Exclusion of esopghagitis SM grade 2-4 Mean age 47y	6 months	Esomeprazole 20 mg 1x/day vs Esomeprazole 20 mg on demand	ALLOCATION CONC: unclear RANDO: low risk BLINDING : high risk (open label) FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor AstraZeneca)

Table 97

15.1.9 PPI vs PPI

15.1.9.1 *Pantoprazole vs esomeprazole*

Systematic review: Ip 2011(69): "Comparative effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Updat."

Inclusion criteria: Studies of various designs, comparing effectiveness of different management options ofr adults with GORD

Search strategy: MEDLINE, Cochrane Central Register of Controlled Trials were searched up until August 2010.
MEDLINE, The Cochrane Database of Systematic Reviews, The American College of Physicians Journal Club, the Database of Abstracts of Reviews of Effects, and the Centre for Reviews and Dissemination's Health Technology Assessments were searched up until October 2009 for published MAs and SRs.

Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Ip 2011(69): Design: SR Search date: (August 2010)	Pantoprazole vs esomeprazole	N= 1 n= 1316 (Goh 2007)	Symptoms Mean sum score of GI symptoms Symptoms included heartburn, acid regurgitation, dysphagia, epigastric pain/discomfort, retrosternal tightness, burping/ belching, nausea/vomiting, fullness, lower abdominal pain, and flatulence. The intensity of symptoms was scored as none (0), mild (1), moderate (2), and severe (3) by investigators.	Pantoprazole 20 mg: 0.1 Esomeprazole 20 mg: 0.1 NS
		N= 1 n= 3151 (Labenz 2009a)	Symptoms Heartburn resolution	Pantoprazole 40 mg: 66.9% Esomeprazole 40 mg: 72.5% **OR 1.31 (1.12 to 1.54)**

				p=0.0008 **SS in favour of esomeprazole**
		N= 1 n= 2766 (Labenz 2009b)	Symptoms Heartburn relapse	Pantoprazole 20 mg: 17.4% Esomeprazole 20 mg: 9.8% More relapse in pantoprazole NT
		N= 1 n= 585 (Glatzel 2007)	Symptoms Median 3-day mean ReQuest GI score ReQuest-GI comprises 4 dimensions of acid complaints, upper abdominal stomach complaints, lower abdominal/digestive complaints and nausea. Each dimension's score is a product of its intensity and frequency. The ReQuest-GI score is sum of the weighted scores of its four dimensions.	Pantoprazole 40 mg: 0.24 Esomeprazole 40 mg: 0.31 Pantoprazole non-inferior to esomeprazole
		N= 1 n= 582 (Bardhan 2007)	Symptoms Rate of symptom relief	Pantoprazole 40 mg: 79% Esomeprazole 40 mg: 77% TD 2% (-4.7 to 8.8) NS
		N= 1 n= 180 (Vcev 2006)	Symptoms Heartburn-free days	Pantoprazole 40 mg: 69.8% Esomeprazole 40 mg: 70.2% NT "Similar"
		N= 1 n= 582 (Bardhan 2007)	Endoscopic healing	Pantoprazole 40 mg: 91% Esomeprazole 40 mg: 88% TD 2% (-1.75, 8.27)

				NS
		N= 1 n= 180 (Vcev 2006)	Endoscopic healing	Pantoprazole 40 mg: 91.1% Esomeprazole 40 mg: 92.2% NT “Similar”

Table 98

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Goh 2007(75)	1316	endoscopically confirmed gastro-oesophageal reflux disease (Los Angeles grades A-D)	6 months	pantoprazole 20 mg 1x/day vs esomeprazole 20 mg 1x/day	ALLOCATION CONC: unclear (no info) RANDO: unclear (method not described) BLINDING : low risk FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor ALTANA Pharma AG)
Labenz 2009a(76)	3151	Reflux oesophagitis [Los Angeles (LA) grade A–D, as documented by endoscopy	4 weeks	pantoprazole 40 mg 1x/day vs esomeprazole 40 mg 1x/day	ALLOCATION CONC: unclear (no info) RANDO: unclear (no method described) BLINDING : low risk FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor AstraZeneca)
Labenz 2009b(77)	2766	Healed reflux oesophagitis [Los Angeles	6 months	pantoprazole 40 mg 1x/day	ALLOCATION CONC: unclear (no

		(LA) grade A–D, as documented by endoscopy		vs esomeprazole 40 mg 1x/day	info) RANDO: unclear (no method described) BLINDING : low risk FOLLOW-UP: low risk SELECTIVE REPORTING: high risk (post hoc analysis) OTHER BIAS: unclear risk (sponsor AstraZeneca)
Glatzel 2007(78)	585	Endoscopically confirmed GORD grades A–D	4 weeks	pantoprazole 40 mg 1x/day vs esomeprazole 40 mg 1x/day	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor ALTANA Pharma AG)
Bardhan 2007(79)	582	Endoscopically confirmed erosive oesophagitis [Los Angeles (LA) classification A-D]	12 weeks	pantoprazole 40 mg 1x/day vs esomeprazole 40 mg 1x/day	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor ALTANA Pharma AG)
Vcec 2006(80)	180	Endoscopically proven GORD grade A,B,C	8 weeks	pantoprazole 40 mg 1x/day vs esomeprazole 40 mg 1x/day	ALLOCATION CONC: unclear risk (no info) RANDO: unclear risk (no info about randomization method) BLINDING : unclear risk (single blind) FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (no info)

Table 99

15.1.9.2 *Rabeprazole vs esomeprazole*

Systematic review: Ip 2011(69): "Comparative effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Updat."

Inclusion criteria: Studies of various designs, comparing effectiveness of different management options ofr adults with GORD

Search strategy: MEDLINE, Cochrane Central Register of Controlled Trials were searched up until August 2010.
MEDLINE, The Cochrane Database of Systematic Reviews, The American College of Physicians Journal Club, the Database of Abstracts of Reviews of Effects, and the Centre for Reviews and Dissemination's Health Technology Assessments were searched up until October 2009 for published MAs and SRs.

Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Ip 2011(69): Design: SR Search date: (August 2010)	Rabeprazole vs esomprazole	N= 1 n= 1392 (Eggleston 2009)	Complete resolution of heartburn	Rabeprazole: 58.4% Esomeprazole: 20 mg 60.6% Esomeprazole 40 mg: 64.4% p=0.184 NS
		N= 1 n= 1392 (Eggleston 2009)	Complete resolution of regurgitation	Rabeprazole: 60.6% Esomeprazole: 20 mg 60.1% Esomeprazole 40 mg: 60.3% p=0.363 NS
		N= 1 n= 134 (Fock 2005)	Time to first 24-hour heartburn and regurgitation-free interval	Rabeprazole 10 mg Esomeprazole 20 mg NS

		N= 1 n= 134 (Fock 2005)	Time to first 48-hour heartburn-free interval	Rabeprazole 10 mg Esomeprazole 20 mg NS
		N= 1 n= 134 (Fock 2005)	Time to first 48-hour regurgitation-free interval	Rabeprazole 10 mg Esomeprazole 20 mg NS
		N= 1 n= 134 (Fock 2005)	Resolution of heartburn	Rabeprazole: 8.5 days Esomeprazole: 9 days p=0.265 NS
		N= 1 n= 134 (Fock 2005)	Resolution of acid regurgitation	Rabeprazole: 6 days Esomeprazole: 7.5 days p=0.405 NS
		N= 1 n= 1392 (Eggleston 2009)	QoL (SF-36) SF-36 contains 8 scales and 2 summary scores with a range of scores from 0 -100; higher scores indicate better functioning and well-being.	Rabeprazole 20 mg Esomeprazole 20 mg Esomeprazole 40 mg NS

Table 100

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Eggleston 2009(81)	1392	Patients presenting to their general practitioner with symptoms of GORD	4 weeks	Rabeprazole 20 mg 1x/day vs	ALLOCATION CONC: unclear (no info) RANDO: low risk

				Esomeprazole 20 mg 1x/day vs Esomeprazole 40 mg 1x/day	BLINDING : low risk FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor Janssen-Cilag)
Fock 2005(82)	134	non-erosive reflux disease (grade 0 according to the LA Classification)	4 weeks	Rabeprazole 20 mg 1x/day vs Esomeprazole 20 mg 1x/day	ALLOCATION CONC: unclear (no info) RANDO: low risk BLINDING : low risk FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor Eisai Co.)

Table 101

15.1.9.3 *Lansoprazole vs esomeprazole*

Systematic review: Ip 2011(69): "Comparative effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Updat."

Inclusion criteria: Studies of various designs, comparing effectiveness of different management options ofr adults with GORD

Search strategy: MEDLINE, Cochrane Central Register of Controlled Trials were searched up until August 2010.
MEDLINE, The Cochrane Database of Systematic Reviews, The American College of Physicians Journal Club, the Database of Abstracts of Reviews of Effects, and the Centre for Reviews and Dissemination's Health Technology Assessments were searched up until October 2009 for published MAs and SRs.

Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result (95%CI)

Ip 2011(69): Design: SR Search date: (August 2010)	Lansoprazole vs esomprazole	N= 1 n= 328 (Fass 2006)	% of heartburn-free days	Lansoprazole: 57.5% Esomeprazole: 54.4% LS MD -3.1 (-9.02 to 2.87) esomeprazole is non-inferior to lansoprazole
		N= 1 n= 328 (Fass 2006)	% of epigastric pain free days	Lansoprazole: 66.9% Esomeprazole: 65% LS MD -1.9 (-7.27 to 3.41) NS
		N= 1 n= 328 (Fass 2006)	% of acid regurgitation-free days	Lansoprazole: 65.3 % Esomeprazole: 60.3% LS MD -5 (-10.41 to 10.40) NS

Table 102

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Fass 2006(83)	328	Patients with persistent heartburn symptoms while receiving therapy with lansoprazole 30 mg once daily	8 weeks	Lansoprazole 30 mg 2x/day vs Esomeprazole 40 mg 1x/day	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk FOLLOW-UP: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (sponsor AstraZeneca.)

Table 103

15.1.9.4 *Esomeprazole vs omeprazole*

Meta-analysis: Teng 2015(84) Inclusion criteria: adults who had GORD, peptic ulcer disease or H. pylori infection. Exclusion of studies in specific patient groups (e.g. elderly) or studies that only reported pH measurement. For this literature review, we only reported the findings in patients with GORD. Search strategy: PubMed and the Cochrane Library were searched for RCTs comparing esomeprazole to omeprazole up to February 2015 Assessment of quality of included trials: yes Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Teng 2015(84) Design: SR+MA Search date: (February 2015)	esomeprazole vs omeprazole	N= 1 n= 2645 (Armstrong 2004)	Resolution of heartburn day 28* in patients with **endoscopy-negative reflux disease** *defined as no days with heartburn episodes during the last 7 days before day 28	Study A Esomeprazole 40mg: 56.7 % Esomeprazole 20mg: 60.5 % Omeprazole ME 20mg: 58.1 % NS Study B Esomeprazole 40mg: 70.3 % Omeprazole ME: 20mg: 67.9 % NS Study C Esomeprazole 20mg: 61.9 % Omeprazole 20mg: 59.6 % NS

Table 104

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Armstrong 2004(85)	Study A 1282 Study B 693 Study C 670	Patients with **endoscopy-negative reflux disease**	4 weeks	Esomeprazole 40 mg 1x/day vs Esomeprazole 20 mg 1x/day vs Omeprazole 20 mg 1x/day	ALLOCATION CONC: Unclear RANDO: Unclear BLINDING : Participants/personnel/assessors Low risk Incomplete outcome data: Unclear Selective reporting: Low risk FUNDING: AstraZeneca: High risk

Table 105

16 Evidence tables. Reflux oesophagitis.

16.1.1 PPI vs placebo

16.1.1.1 *pantoprazole vs placebo*

Systematic review: NICE 2014 (3) "Dyspepsia and gastro-oesophageal reflux disease: investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both" Inclusion criteria: SRs and RCTs that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed **severe erosive reflux** (LA classification grade C or D or Savary-Miller grade 3 or 4). Exclusion of studies that did not report outcome data by grade of erosive oesophagitis. Search strategy: EMBASE, MEDLINE (Ovid), CDSR, CENTRAL, DARE, and the Health Technology Database were searched up until December 2013) Assessment of quality of included trials: yes Other methodological remarks:/

Ref	Comparison	N/n	Outcomes	Result (95%CI)
NICE 2014 (3) Design: SR Search date: (December 2013)	pantoprazole vs placebo	N= 1 n= 153 (Richter 2000)	Endoscopy-confirmed healing	pantoprazole 20 mg: 45/65 (69%) pantoprazole 40 mg: 51/60 (85.7%) placebo: 2/28 (5.9%) **pantoprazole 20 mg or 40 mg vs placebo** **p<0.001** **SS in favour of pantoprazole**

Table 106

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Richter 2000(86)	603	Erosive oesophagitis at least grade 2 Mean age 48-49y	8 weeks	pantoprazole 20 mg 1x/day OR pantoprazole 40 mg 1x/day vs placebo	ALLOCATION CONC: unclear (not described) RANDO: unclear (not described) BLINDING : Participants/personnel: Adequate Assessors: Unclear if outcome assessment blinded FOLLOW-UP: Adequate ITT: unclear FUNDING: Wyeth-Ayerst research

Table 107

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

16.1.1.2 *lansoprazole vs placebo*

Ref	Comparison	N/n	Outcomes	Result (95%CI)
NICE 2014 (3) Design: SR Search date: (December 2013)	lansoprazole vs placebo	N= 1 n= 98 (Robinson 1996)	Patients remaining in remission after 12 months' treatment	<u>patients with grade 3 erosive oesophagitis:</u> lansoprazole: 43/55 (78.8%) placebo: 8/31 (26.5%) <u>patients with grade 4 erosive oesophagitis:</u> lansoprazole: 9/12 (76.5%) placebo: 0

Table 108

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Robinson 1996(87)	170	patients with endoscopy-confirmed Savary-Miller grade 2 erosive oesophagitis or higher Mean age 43-47y	12 months	lansoprazole 15 mg 1x/day OR lansoprazole 30 mg 1x/day vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: Adequate ITT: no FUNDING: TAP Holdings Inc

Table 109

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

16.1.2 PPI vs lifestyle

16.1.3 PPI vs antacids

16.1.4 PPI vs H2RA

16.1.4.1 *lansoprazole vs ranitidine*

Systematic review: NICE 2014 (3) "Dyspepsia and gastro-oesophageal reflux disease: investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both"

Inclusion criteria: SRs and RCTs that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4). Exclusion of studies that did not report outcome data by grade of erosive oesophagitis.
Search strategy: EMBASE, MEDLINE (Ovid), CDSR, CENTRAL, DARE, and the Health Technology Database were searched up until December 2013)
Assessment of quality of included trials: yes

Other methodological remarks:/

Ref	Comparison	N/n	Outcomes	Result (95%CI)
NICE 2014 (3) Design: SR Search date: (December 2013)	lansoprazole vs ranitidine	N= 2 n= 161 (Jansen 1999, Robinson 1995)	Endoscopy confirmed healing rates	at 8 weeks Jansen 1999 lansoprazole: 10/11 (91%) ranitidine: 7/16 (44%) Robinson 1995 lansoprazole: 48/63 (76.8%) ranitidine: 46/71 (64.2%)

Table 110

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Jansen 1999(88)	133	endoscopy-confirmed reflux oesophagitis grade 2 or 3b mean age 54 y	8 weeks	lansoprazole 30 mg 1x/day vs ranitidine 300 mg 2x/day	ALLOCATION CONC: unclear (not described) RANDO: unclear (SS more smokers randomized to ranitidine) BLINDING : Participants/personnel: adequate Assessors: unclear if outcome assessment was blinded

					FOLLOW-UP: adequate ITT: unclear FUNDING: Janssen Cilag
Robinson 1995(89)	242	patients with erosive oesophagitis of at least grade 2a age not reported	8 weeks	lansoprazole 30 mg 1x/day vs ranitidine 150 mg 2x/day	ALLOCATION CONC: unclear (not described) RANDO: unclear (not described) BLINDING : Participants/personnel: adequate Assessors: unclear if outcome assessment was blinded FOLLOW-UP: adequate ITT: no FUNDING: Unclear (unstated)

Table 111

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

16.1.4.2 *pantoprazole vs ranitidine*

Ref	Comparison	N/n	Outcomes	Result (95%CI)
NICE 2014 (3) Design: SR Search date: (December 2013)	pantoprazole vs ranitidine	N= 2 n= 92 (Koop 1995, Meneghelli 2002)	Endoscopy-confirmed healing rates after 4 weeks' treatment	<u>Koop 1995</u> pantoprazole: 17/30 (56%) ranitidine: 9/14 (63%) <u>Meneghelli 2002</u> pantoprazole: 20/24 (82%) ranitidine: 10/24 (43%)
		N= 1 n= 83	% of patients remaining in remission	Pantoprazole 20 mg: 15/23 (64.3%) Pantoprazole 40 mg: 16/26 (62.1%)

		(Metz 2003)	after 12 months' treatment	ranitidine: 3/34 (9.3%) **pantoprazole (20 or 40 mg) versus ranitidine:** **p<0.001** **SS in favour of pantoprazole**
		N= 1 n= 76 (Richter 2004)	Endoscopy-confirmed maintenance of healing (no relapse of erosive oesophagitis) within 12 months of start of maintenance therapy	Pantoprazole 20 mg: 17/31 (53.6%) Pantoprazole 40 mg: 14/19 (71.1%) ranitidine: 5/26 (19.6%) **pantoprazole 20 mg versus ranitidine:** **p<0.05** **SS in favour of pantoprazole 20 mg** **pantoprazole 40 mg versus ranitidine:** **p<0.01** **SS in favour of pantoprazole 40 mg**

Table 112

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Koop 1995(90)	249	patients with reflux oesophagitis SM grade 2 or 3 and at least one of the following: heartburn, acid eructation, and/or pain on swallowing	8 weeks	pantoprazole 40 mg 1x/day vs ranitidine 150 mg 2x/day	ALLOCATION CONC: unclear (not described) RANDO: unclear (not described) BLINDING : Participants/personnel: adequate Assessors: unclear (blinding of outcome assessment not described) FOLLOW-UP: adequate ITT: no FUNDING: Byk Gulden Pharmaceuticals

Meneghelli 2002(91)	256	patients with reflux oesophagitis and at least one of the following: heartburn, acid eructation, and/or pain on swallowing	8 weeks	pantoprazole 40 mg 1x/day vs ranitidine 150 mg 2x/day	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel: adequate Assessors: adequate FOLLOW-UP: adequate ITT: not adequately reported FUNDING: Byk Gulden Pharmaceuticals,
Metz 2003(92)	371	patients with healed erosive oesophagitis and a history of at least one symptom: heartburn, acid regurgitation or dysphagia Mean age 49y	12 months	pantoprazole 20 mg 1x/day or pantoprazole 40 mg 1x/day vs ranitidine 150 mg 2x/day	ALLOCATION CONC: unclear (not described) RANDO: unclear (not described) BLINDING : Participants/personnel: adequate Assessors: unclear (not described) FOLLOW-UP: high risk (49% drop)out; significantly more ranitidine-treated participants withdrew from trial) ITT: unclear FUNDING: Wyeth
Richter 2004(93)	349	patients with endoscopy confirmed healing of erosive oesophagitis at baseline Known history of heartburn or regurgitation mean age 48-50y	12 months	pantoprazole 20 mg 1x/day or pantoprazole 40 mg 1x/day vs ranitidine 150 mg 2x/day	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/personnel: adequate Assessors: adequate FOLLOW-UP: adequate ITT: adequate FUNDING: Wyeth

Table 113

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

16.1.5 PPI vs PPI

16.1.5.1 *esomeprazole vs lansoprazole*

Systematic review: NICE 2014 (3) "Dyspepsia and gastro-oesophageal reflux disease: investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both"

Inclusion criteria: SRs and RCTs that evaluate clinical effectiveness of PPIs in adults with endoscopically confirmed severe erosive reflux (LA classification grade C or D or Savary-Miller grade 3 or 4). Exclusion of studies that did not report outcome data by grade of erosive oesophagitis.
Search strategy: EMBASE, MEDLINE (Ovid), CDSR, CENTRAL, DARE, and the Health Technology Database were searched up until December 2013)
Assessment of quality of included trials: yes
Other methodological remarks:/

Ref	Comparison	N/n	Outcomes	Result (95%CI)
NICE 2014 (3) Design: SR Search date: (December 2013)	esomeprazole vs lansoprazole	N= 2 n= 6240 (Fennerty 2005, Castell 2002)	Endoscopy-confirmed healing	After 8 weeks Fennerty 2005 Esomeprazole : 77.5% Lansoprazole: 73.3% P=0.099 NS Castell 2002 Esomeprazole : 552/640 (86%) Lansoprazole: 477/646 (74%) NT

		N= 2 n= 468 (DeVault 2006, Lauritsen 2003)	% of patients remaining in remission After 6 months treatment	<u>DeVault 2006</u> Esomeprazole : 96/121 (79.3%) Lansoprazole: 91/131 (69.5%) P not reported <u>Lauritsen 2003</u> Esomeprazole : 87/114 (76%) Lansoprazole: 60/102 (59%) **P<0.01** **SS in favour of esomeprazole**

Table 114

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Fennerty 2005(94)	999	LA Grade C or D erosive oesophagitis and heartburn Mean age 47 y	8 weeks	Esomeprazole 40 mg 1x/day Vs Lansoprazole 30 mg 1x/day	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: adequate ITT: modified ITT FUNDING: AstraZeneca

Castell 2002(95)	5241	Adults with endoscopy-confirmed erosive oesophagitis (LA grades A to D) and heartburn Mean age 47 y	8 weeks	Esomeprazole 40 mg 1x/day Vs Lansoprazole 30 mg 1x/day	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: unclear risk (withdrawals not described by treatment group) ITT: yes FUNDING: AstraZeneca
DeVault 2006(96)	1001	Patients with healed erosive oesophagitis confirmed by endoscopy and no reflux symptoms in the previous 7 days Mean age 47 y	6 months	Esomeprazole 20 mg 1x/day Vs Lansoprazole 15 mg 1x/day	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: adequate ITT: no FUNDING: AstraZeneca
Lauritsen 2003(97)	1224	Patients with a history of heartburn and reflux oesophagitis (LA grade A to D) who had remission of erosive oesophagitis during an open-label uncontrolled healing phase Mean age 49y	6 months	Esomeprazole 20 mg 1x/day Vs Lansoprazole 15 mg 1x/day	ALLOCATION CONC: Unclear (not described) RANDO: Adequate BLINDING : Participants/personnel/assessors Unclear (blinding outcome assessment not described) FOLLOW-UP: Unclear risk (18% drop-out; more in lansoprazole group) ITT: no FUNDING: AstraZeneca

Table 115

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

16.1.5.2 *rabeprazole vs esomeprazole*

Ref	Comparison	N/n	Outcomes	Result (95%CI)
NICE 2014 (3) Design: SR Search date: (December 2013)	rabeprazole vs esomprazole	N= 2 n= 2120 (Laine 2011a, Laine 2011b)	Endoscopy-confirmed healing	<u>After 8 weeks</u> <u>Laine 2001a</u> Rabeprazole: 80.0% Esomeprazole: 75.0% 95% CI for the difference between treatment groups: 0 to 10.0% Rabeprazole is non-inferior to esomeprazole <u>Laine 2001b</u> Rabeprazole: 77.5% Esomeprazole: 78.4% 95% CI for the difference between treatment groups: -5.9 to 4.0% Rabeprazole is non-inferior to esomeprazole

Table 116

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Laine 2011a(98)	1055	Patients with LA grade C or D erosive	8 weeks	Rabeprazole ER 50 mg	ALLOCATION CONC: Adequate

		oesophagitis and heartburn Mean age 48-49y		1x/day Vs Esomeprazole 40 mg 1x/day	RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: Adequate ITT: no FUNDING: Eisai Inc and Pricara, Division of Ortho-McNeil Janssen Pharmaceuticals Inc.
Laine 2011b(98)	1065	Patients with LA grade C or D erosive oesophagitis and heartburn Mean age 48-49y	8 weeks	Rabeprazole ER 50 mg 1x/day Vs Esomeprazole 40 mg 1x/day	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: Adequate ITT: no FUNDING: Eisai Inc and Pricara, Division of Ortho-McNeil Janssen Pharmaceuticals Inc.

Table 117

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

16.1.5.3 *Omeprazole vs pantoprazole*

Ref	Comparison	N/n	Outcomes	Result (95%CI)
NICE 2014 (3) Design:	omeprazole vs pantoprazole	N= 1 n= 58 (Mossner 1995)	Proportion of patients with endoscopy-confirmed healing At 4 weeks	Pantoprazole: 21/36 (59%) Omeprazole: 12/22 (53%) P>0.05

SR Search date: (December 2013)				NS

Table 118

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Mossner 1995(99)	286	Adults with reflux oesophagitis SM grade 2 or 3 and at least one of the following symptoms: acid regurgitation without nausea, heartburn, or pain on swallowing Median age 53-55 y	8 weeks	Pantoprazole 40 mg 1x/day Vs Omeprazole 20 mg 1x/day	ALLOCATION CONC: Unclear (not described) RANDO: Adequate BLINDING : Participants/personnel: Adequate Assessors: unclear (not described) FOLLOW-UP: Adequate ITT: yes FUNDING: Unclear (unstated)

Table 119

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

16.1.5.4 *pantoprazole vs esomeprazole*

Ref	Comparison	N/n	Outcomes	Result (95%CI)

NICE 2014 (3) Design: SR Search date: (December 2013)	pantoprazole vs esomeprazole	N= 1 n= 37 (Gillesen 2004)	Proportion of patients with endoscopy-confirmed healing After 10 weeks' treatment	Pantoprazole: 12/18 (67%) Esomeprazole: 9/19 (45%)

Table 120

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Gillessen 2004(100)	227	Patients with endoscopy-confirmed erosive oesophagitis LA grades B and C Mean age 53-54y	10 weeks	Pantoprazole 40 mg 1x/day Vs Esomeprazole 40 mg 1x/day	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: Unclear (unbalanced drop-out) ITT: yes FUNDING: Altana Pharma AG

Table 121

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

Study details	n/Population	Comparison	Outcomes		Methodological
Moraes-Filho 2014 (101)	n= 593	pantoprazole 40 mg 1x/day	% patients in	at 4 weeks	RANDO: Adequate

Design: non-inferiority RCT DB PG Duration of follow-up: 4 weeks + additional 4 weeks in nonresponding patients	Mean age: 42.7y h pylori status: % : not stated h pylori eradication: not stated diagnostic endoscopy : yes Oesophagitis LA Grade A: 59.9% B: 32.7% C: 6.9% D:0.5% <u>Inclusion:</u> • Adults (18-70y) • Heartburn or regurgitation ≥2x/ week for 4-8 weeks in previous 3 months • endoscopic diagnosis of erosive oesophagitis (LA grade A-D) <u>Exclusion</u>	vs esomeprazole 40 mg 1x/day <u>remarks</u> All patients received 4 weeks treatment. Patients not achieving complete remission at week 4 received a further 4 weeks of treatment.	complete remission* at 4 weeks (PO) or at 8 weeks *defined as endoscopic healing AND symptom relief	pantoprazole: 170/278 (61.2%) esomeprazole: 165/270 (61.1%) NS <u>at 8 weeks</u> pantoprazole: 224/276 (81.2%) esomeprazole: 210/267 (78.7%) NS	ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.7% Drop-out and Exclusions: 1.9% • Described: yes • Balanced across groups: yes ITT: modified ITT: “all randomised patients who received at least one dose of the study medication and had at least one valid post-baseline efficacy evaluation.” Per protocol also calculated. SELECTIVE REPORTING: unclear (no reporting of comparative outcome measures with confidence interval)
			Endoscopic healing	<u>at 4 weeks</u> pantoprazole: 208/284 (73.2%) esomeprazole: 211/279 (75.6%) NS non-inferior <u>at 8 weeks</u> pantoprazole: 246/284 (86.6%) esomeprazole: 253/279 (90.7%) NS	
			Symptom relief* *defined as ReQuest-GI score <1.73 on the last 3 days	<u>at 4 weeks</u> pantoprazole: 230/273 (84.2%) esomeprazole: 211/263 (80.2%) NS **<u>at 8 weeks</u>**	

	• other gastrointestinal disease, including Barrett's oesophagus,peptic ulcer, Zollinger–Ellison syndrome, and pyloricstenosis; • history of surgeries of the upper gastrointestinal tract (except polypectomy and cholecystectomy); • obstructive oesophageal strictures, Schatzki ring, oesophageal diverticulum, oesophageal varices, achalasia or hiatal hernia≥3 cm on endoscopy; or inflammatory bowel disease. • severe neurological or psychiatric disorders, haematological disorders, or any			**pantoprazole: 252/275 (91.6%)** **esomeprazole: 227/264 (86.0%)** **SS** **p=0.0370**	Other important methodological remarks: • run-in period of up to 14 days • Non-inferiority margin of 15% for PO • Missing data: last observation carried forward Sponsor: Takeda Pharma Ltda
			Safety		
			Adverse events	pantoprazole: 95/290 (32.8%) esomeprazole: 104/288 (36.1%) NS	

	other clinically significant medical condition, hepatic or renal dysfunction/disease, • clinically significant changes in laboratory parameter • a history of alcohol or drug abuse within the previous 6 months, Pregnant or breastfeeding women or women of child-bearing age not using effective contraception • use of PPIs within10 days of study commencement; PPI-based triple therapy for eradication of Helicobacter pylori within the previous28 days; H2RAs, sucralfate or prokinetic agents for 7 days prior to starting the study; or systemic glucocorticoidsand/				

	or nonsteroidal anti-inflammatory drugs for more than 3 consecutive days/week within 28 days of the start of the study (except acetylsalicylicacid up to 163 mg/day).				

Table 122

16.1.5.5 *esomeprazole vs omeprazole*

Meta-analysis: Teng 2015(84)

Inclusion criteria: adults who had GORD, peptic ulcer disease or H. pylori infection. Exclusion of studies in specific patient groups (e.g. elderly) or studies that only reported pH measurement. For this literature review, we only reported the findings in patients with GORD.
Search strategy: PubMed and the Cochrane Library were searched for RCTs comparing esomeprazole to omeprazole up to February 2015
Assessment of quality of included trials: yes
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Teng 2015(84) Design: SR+MA	esomeprazole vs omeprazole	N= 6 n= 6892 (Chen 2005, Kahrilas 2000, Richter 2001, Schmitt 2006,	Oesophagitis healing rates at week 8	Esomeprazole 40 or 20mg Omeprazole 20 mg **RR 1.06 (1.03 to 1.10)** **SS in favour of esomeprazole**

Search date: (February 2015)		Zheng 2009, Lightdale 2006)		
		N= 3 n= 5533 (Kahrilas 2000, Richter 2001, Schmitt 2006)	Oesophagitis healing rates at week 4	Esomeprazole 40 or 20mg Omeprazole 20 mg **RR 1.12 (1.05 to 1.19)** **SS in favour of esomeprazole**
		N= 14 n= 9200 (Chen 2005, Kahrilas 2000, Richter 2001, Schmitt 2006, Zheng 2009, Lightdale 2006, Anagnostopoulos 2004, Choi 2007, Sheu 2005, Miehlke 2003, Subei 2007, Tulassay 2000, Veldhuyzen 2000, Veldhuyzen 2003)	Adverse effects	Esomeprazole vs omeprazole NS

Table 123

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Chen 2005(102)	48	patients with endoscopically confirmed reflux oesophagitis	8 weeks	Esomeprazole 40 mg 1x/day vs Omeprazole 20 mg 1x/day	*RCT did not meet our inclusion criteria*
Kahrilas 2000(103)	1960	patients with reflux oesophagitis	8 weeks	Esomeprazole 40 mg 1x/day vs Esomeprazole 20 mg 1x/day vs Omeprazole 20 mg 1x/day	ALLOCATION CONC: Unclear RANDO: Low risk BLINDING : Participants/personnel: Low risk Assessors: unclear Incomplete outcome data: Unclear Selective reporting: Low risk FUNDING: AstraZeneca: High risk
Lightdale 2006(104)	1175	patients with endoscopically confirmed reflux oesophagitis	8 weeks	Esomeprazole 20 mg 1x/day vs Omeprazole 20 mg 1x/day	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/personnel: Low risk Assessors: unclear Incomplete outcome data: Unclear Selective reporting: Unclear FUNDING: AstraZeneca: High risk
Richter 2001(105)	2425	patients with erosive oesophagitis	8 weeks	Esomeprazole 40 mg 1x/day vs	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/personnel: Low risk Assessors: unclear

				Omeprazole 20 mg 1x/day	Incomplete outcome data: Unclear Selective reporting: Low risk FUNDING: AstraZeneca: High risk
Schmitt 2006(106)	1148	patients with erosive oesophagitis	8 weeks	Esomeprazole 40 mg 1x/day vs Omeprazole 20 mg 1x/day	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/personnel: Low risk Assessors: unclear Incomplete outcome data: Unclear Selective reporting: Low risk FUNDING: AstraZeneca: High risk
Zheng 2009(107)	136	patients with endoscopically confirmed reflux oesophagitis	8 weeks	Esomeprazole 40 mg 1x/day vs Omeprazole 20 mg 1x/day	ALLOCATION CONC: Low risk RANDO: Unclear BLINDING : Participants/personnel: Low risk Assessors: Unclear Incomplete outcome data: Unclear Selective reporting: Low risk FUNDING: Low risk
Anagnostopoulos 2004(108), Choi 2007(109), Sheu 2005(110), Miehlke 2003(111), Subei 2007(112), Tulassay 2000(113), Veldhuyzen 2000(114), Veldhuyzen 2003(115)	*studies evaluated Helicobacter pylori infection; did not meet our inclusion criteria*				

Table 124

16.1.5.6 *lansoprazole vs omeprazole*

Ref	Comparison	N/n	Outcomes	Result (95%CI)
NICE 2014 (3) Design: SR Search date: (December 2013)	lansoprazole vs omeprazole	N= 1 n= 82 (Mee 1996)	Endoscopy-confirmed healing	<u>At 4 weeks</u> Lansoprazole: 18/40 (45%) Omeprazole 24/42 (57%) <u>At 8 weeks</u> Lansoprazole: 26/37 (70%) Omeprazole 27/38 (71%)

Table 125

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Mee 1996(201)	537	Patients with endoscopy-proven reflux oesophagitis SM grades 1 to 4 and a recent history of at least mild heartburn Media age: 52-53y	8 weeks	Lansoprazole 30 mg 1x/day Vs Omeprazole 20 mg 1x/day	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: Adequate ITT: no FUNDING: Unclear (not stated)

Table 126

Remarks: Only patients with grade 3 or 4 erosive oesophagitis were analyzed in this SR

16.1.5.7 *rabeprazole vs omeprazole*

Meta-analysis: Xia 2013(116) Inclusion criteria: RCTs that compared rabeprazole 20 mg to omeprazole 20 mg in adults with erosive GORD and that reported endoscopic and symptomatic relief rates. Search strategy: Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched up until December 2012 Assessment of quality of included trials: yes; but not reported in publication Other methodological remarks:/

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Xia 2013(116) Design: SR+ MA Search date: (December 2012)	rabeprazole 20 mg vs omeprazole 20 mg	N= 5 n= 1178 (Dekkers 1999, Delchier 2000, Adachi 2003, Pace 2005, Pilotto 2007)	Endoscopic relief rates *up to 8 weeks of treatment*	Rabeprazole vs omeprazole RR 1.02 (0.99 to 1.05) NS
		N= 4 n= 1628 (Pace 2005 Bytzer 2006, Dekkers 1999, Pilotto 2007)	Heartburn relief rates *up to 8 weeks of treatment*	Rabeprazole vs omeprazole RR 1.13 (1.03 to 1.25) **SS in favour of rabeprazole** **p= 0.012**
		N= 3 n= 1126 (Bytzer 2006, Dekkers 1999,	Adverse events *up to 8 weeks of treatment*	Rabeprazole vs omeprazole RR 1.06 (0.83 to 1.34) NS

		Delchier 2000)		

Table 127

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Dekkers 1999(117)	202	Mean age: 53 y patients with a previous diagnosis of erosive GORD that had been healed within 90 days before study entry	8 weeks	rabeprazole 20 mg vs omeprazole 20 mg	ALLOCATION CONC: Unclear (not described) RANDO: Unclear (method not described) BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Delchier 2000(118)	207	Mean age: 54 y patients with a previous diagnosis of erosive GORD that had been healed within 90 days before study entry	8 weeks	rabeprazole 20 mg vs omeprazole 20 mg	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Adachi 2003(119)	60	Mean age: 66 y patients with a previous diagnosis of	8 weeks	rabeprazole 20 mg	*RCT did not meet our inclusion criteria*

		erosive GORD that had been healed within 90 days before study entry		vs omeprazole 20 mg	
Pace 2005(120)	549	Mean age: 47y patients with a previous diagnosis of erosive GORD that had been healed within 90 days before study entry	8 weeks	rabeprazole 20 mg vs omeprazole 20 mg	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Unclear (drop-out not well described) SELECTIVE REPORTING: Unclear (safety results inadequately reported) OTHER BIAS: low risk
Bytzer 2006(121)	717	Mean age: 51 y patients with a previous diagnosis of erosive GORD that had been healed within 90 days before study entry	1 week	rabeprazole 20 mg vs omeprazole 20 mg	*RCT did not meet our inclusion criteria*
Pilotto 2007(122)	160	Mean age: 77y patients with a previous diagnosis of erosive GORD that had been healed within 90 days before study entry	8 weeks	rabeprazole 20 mg vs omeprazole 20 mg	*RCT did not meet our inclusion criteria* *(open label)*

Table 128

17 Evidence tables. Barrett's oesophagus.

17.1.1 PPI vs placebo

No RCTs that compared PPIs with placebo, and that met our inclusion criteria, were found.

17.1.2 PPI vs lifestyle

No RCTs that compared PPIs with lifestyle, and that met our inclusion criteria, were found.

17.1.3 PPI vs antacida

No RCTs that compared PPIs with antacids, and that met our inclusion criteria, were found.

17.1.4 PPI vs H2RA

Meta-analysis: Rees et al. 2010(123)

Inclusion criteria: Randomised controlled trials (RCTs) comparing medical, endoscopic or non-resectional surgical treatments for Barrett's oesophagus.The primary outcome measures were complete eradication of Barrett's and dysplasia at 12 months, and reduction in the number of patients progressing to cancer at five years or latest time point.
Search strategy: The authors searched CENTRAL (*The Cochrane Library* 2004, issue 4), MEDLINE (1966 to June 2008) and EMBASE (1980 to June 2008).
Assessment of quality of included trials: yes
Other methodological remarks: Caldwell 1996 was only published as abstract; Weinstein 1996 was not published in full form (no external peer review)

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Rees 2010(123) Design: MA Search date: (June-2008)	Omeprazole vs H2RA	N= 3 n= 163 (Caldwell 1996, Weinstein 1996, Peters 1999)	Reduction in length (cm) of Barrett's oesophagus at 12 months	Mean Difference -0.42 (-1.65, 0.82) NS
		N= 2 n= 143 (Weinstein 1996, Peters 1999)	Reduction in area (%) of Barrett's oesophagus at 12 months	**Mean Difference 4.06 (0.08, 8.04)** **SS**, favours omeprazole

Table 129

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Caldwell 1996(124) Prospective randomised controlled trial	28	Patients with Barrett's oesophagus	2 years	Omeprazole 20 mg QD vs Cimetidine 300 mg TID	Risk of bias: ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING (performance bias and detection bias): unclear risk INCOMPLETE OUTCOME DATA (attrition bias): unclear risk SELECTIVE REPORTING: unclear risk OTHER BIAS: high risk: published only in abstract format
Weinstein 1996(125) Controlled, randomised double	106	Patients with Barrett's oesophagus	2 years	omeprazole 40mg BID for one year followed by 40 mg QD vs	Risk of bias: ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING (performance bias and

blind study				ranitidine 150 mg	detection bias): unclear risk INCOMPLETE OUTCOME DATA (attrition bias): unclear risk SELECTIVE REPORTING: unclear risk OTHER BIAS: unclear risk
Peters 1999(126) Prospective randomised double blind study	61	Patients with endoscopically and histologically proven Barrett's oesophagus over a distance of at least 3 cm from the endoscopically determined oesophagogastric junction. Patients had to have documented acid gastro-oesophageal reflux.	2 years	omeprazole 40mg BID vs ranitidine 150 mg BID	Risk of bias: ALLOCATION CONC: unclear risk RANDO: low risk BLINDING (performance bias and detection bias): low risk INCOMPLETE OUTCOME DATA (attrition bias): unclear risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk

Table 130

17.1.5 Endoscopic treatment vs PPI

17.1.5.1 *Nd-YAG laser vs omeprazole*

Nd-YAG photocoagulation versus PPI

Meta-analysis: Rees et al. 2010(123)

Inclusion criteria: Randomised controlled trials (RCTs) comparing medical, endoscopic or non-resectional surgical treatments for Barrett's oesophagus.The primary outcome measures were complete eradication of Barrett's and dysplasia at 12 months, and reduction in the number of patients progressing to cancer at five years or latest time point.
Search strategy: The authors searched CENTRAL (*The Cochrane Library* 2004, issue 4), MEDLINE (1966 to June 2008) and EMBASE (1980 to June 2008).
Assessment of quality of included trials: yes
Other methodological remarks: /

Remarks:

One small study (n=8) compared Nd-YAG photocoagulation combined with PPI with PPI (Luman 1996). However, there were no studies that compared Nd-YAG photocoagulation with PPI.

17.1.5.2 *Photodynamic therapy vs omeprazole*

Photodynamic therapy (PDT) versus PPI

Meta-analysis: Rees et al. 2010(123)

Inclusion criteria: Randomised controlled trials (RCTs) comparing medical, endoscopic or non-resectional surgical treatments for Barrett's oesophagus.The primary outcome measures were complete eradication of Barrett's and dysplasia at 12 months, and reduction in the number of patients progressing to cancer at five years or latest time point.
Search strategy: The authors searched CENTRAL (*The Cochrane Library* 2004, issue 4), MEDLINE (1966 to June 2008) and EMBASE (1980 to June 2008).
Assessment of quality of included trials: yes
Other methodological remarks: /

Remarks:
Two studies compared photodynamic therapy combined with PPI with PPI (Ackroyd 2000, Overholt 2005). However, there were no studies that compared photodynamic therapy with PPI.

17.1.6 PPI vs Surgery

Meta-analysis: Rees et al. 2010(123)

Inclusion criteria: Randomised controlled trials (RCTs) comparing medical, endoscopic or non-resectional surgical treatments for Barrett's oesophagus.The primary outcome measures were complete eradication of Barrett's and dysplasia at 12 months, and reduction in the number of patients progressing to cancer at five years or latest time point.
Search strategy: The authors searched CENTRAL (*The Cochrane Library* 2004, issue 4), MEDLINE (1966 to June 2008) and EMBASE (1980 to June 2008).
Assessment of quality of included trials: yes
Other methodological remarks: Parrilla 2003: Patients were initially treated with ranitidine 150 mg twice daily, which in 1992 was converted to omeprazole

20 mg twice daily. Prior to 1997 only individuals with a segment more than 3 cm were included. It was unclear whether intestinal metaplasia was an inclusion criteria. After 1997, patients with Barrett's oesophagus < 3 cm with intestinal metaplasia were also included. Nine out of the 56 (16%) surgical patients with recurrent reflux as measured by pH monitoring were excluded since their surgery was unsuccessful.

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Rees 2010(123) Design: MA Search date: (June-2008)	Nissen fundoplication vs H2RA/PPI	N= 1 n= 101 (Parrilla 2003)	Any reduction/reversal of Barrett's oesophagus/dysplasia at 12 months	2/53 vs 2/40 OR 0.75 (0.10-5.53) **NS**
		N= 1 n= 101 (Parrilla 2003)	Progression to cancer at latest possible time point	2/53 vs 2/40 OR 0.75 (0.10-5.53) **NS** (as reported by cochrane) Correction: 1/203 patient years (0.5% per year) vs 1/129 patient years (0.8% years); **NS**
		N= 1 n= 101 (Parrilla 2003)	Any complication	1/58 vs 0/43 OR 2.27 (0.09-57.07) **NS**
		N= 1 n= 101 (Parrilla 2003)	Complete eradication of Barrett's oesophagus at 12 months	0/53 vs 0/40 NA
		N= 1 n= 101 (Parrilla 2003)	progressing to de novo dysplasia	3/58 vs 8/43 **OR 0.22 (0.05-0.88)** **SS;** favours surgery
		N= 1 n= 101 (Parrilla 2003)	Complete eradication of dysplasia (at 5-year follow up)	5/58 vs 3/43 OR 1.26 (0.28-5.58) **NS**

Table 131

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Parrilla 2003(127) Prospective, randomised	n= 113 individuals (12 declined surveillance) 101 in study 72 M: 29 F Median age medical 50 years, surgical 43 years	Patients with Barrett's oesophagus Medical treatment at baseline (n=43): no high grade dysplasia; 3 pts low-grade dysplasia; 40 pts no dysplasia Surgical treatment at baseline (n=58): 0 pts high-grade dysplasia; 5 pts low-grade dysplasia; 53 pts no dysplasia	Median FU Surgery: 6 years (range 1–18) H2RA/PPI:: 5 years (range 1–18)	Surgery (Short Nissen 56 pts or Collis Nissen 2 pts); no acid suppression vs Acid suppression (ranitidine 1982 to 1992 omeprazole 20 mg 1992 to 2000)	Risk of bias: ALLOCATION CONC: low risk RANDO: low risk BLINDING (performance bias and detection bias): unclear risk INCOMPLETE OUTCOME DATA (attrition bias): unclear risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk

Table 132

Study details	n/Population	Comparison	Outcomes		Methodological
Attwood et al. 2008 (202) Design: multicenter randomized study Duration of follow-up: 3 years	n= 60 esomeprazole: n=28 LARS: n=32 Pts with confirmed GORD. Mean age: esomeprazole: 50 years LARS: 47 years Esomeprazole:	Laparascopic antireflux surgery (LARS) vs omeprazole <u>remarks</u> This study compared pts			The RCT does not meet our inclusion criteria
			Gastrointestinal symptoms (GSRS)	NS	
			Quality of life (QOLRAD)	NS	
			Treatment failure at 3 years	1/28 vs 3/21 NS	
			% acid exposure time after 6 months (24h pHmetry)	**From 13.2% to 0.4% vs from 7.4% to 4.9%; p=0.002** **SS**, favours LARS	

	oesophagitis grade: A-B: n=5/28 C-D: n=3/28 oesophagitis grade: A-B: n=16/32 C-D: n=2/32	with and without Barrett (n=554). Results are presented here for pts with Barrett only (n=60).			

Table 133

LARS: Laparascopic antireflux surgery; GSRS: gastrointestinal symptom rating scale; QOLRAD: quality of life in reflux and dyspepsia questionnaire

Remark: This RCT does not meet our inclusion criteria due to the small number of patients. However, we decided to include this study since it was the only one that studied laparascopic surgery.

17.1.7 PPI vs PPI

No RCTs that compared PPIs head-to-head, and that met our inclusion criteria, were found.

18 Evidence tables. Deprescribing

18.1.1 On-demand vs continued use of PPI

Meta-analysis: Boghossian 2017(203): "Deprescribing versus continuation of chronic proton pump inhibitor use in adults"

Inclusion criteria: We included randomized controlled trials (RCTs) and quasi-randomized trials comparing at least one deprescribing modality (e.g. stopping PPI or reducing PPI) with a control consisting of no change in continuous daily PPI use in adult chronic users.
Search strategy: The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10), MEDLINE, Embase, clinicaltrials.gov, and theWorldHealthOrganization International Clinical Trials Registry Platform(WHOICTRP).
Assessment of quality of included trials: yes
ITT analysis: yes

Ref	Comparison	N/n	Outcomes	Result
Boghossian 2017(203) Design: Meta-analysis Search date: (Nov-2016)	on-demand vs continued use of PPI	N= 4 n= 1653 (Bour 2005, Janssen 2005, Morgan 2007, Van der Velden 2010, Bayerdörffer 2016)	Lack of symptom control (treatment failure or inadequate symptom relief)	**RR: 1.71 (1.31-2.21)** **SS** (favors continued PPI use) Event rate: 140/859 (16.3%) vs 73/794 (9.2%)
		N= 3 n= 1152 (Bour 2005, Janssen 2005, Bayerdörffer 2016)	Pill use (per week)	**Mean difference: -3.79 (-4.73, -2.84)** **SS** (favors on-demand PPI use)

		N= 1 n= 598 (Bayerdörffer 2016)	Adverse drug withdrawal event (development of oesophagitis)	**RR: 30.59 (1.84-508.91)** **SS** (favors continued PPI use) Event rate: 15/301 (5.0%) vs 0/297 (0,0%)
		N= 5 n= 1653 (Bour 2005, Janssen 2005, Morgan 2007, Van der Velden 2010, Bayerdörffer 2016)	Participant satisfaction (unwillingness to continue or inadequate symptom relief)	**RR 1.82 (1.26 – 2.65)** **SS** (favors continued PPI use) Event rate: 136/859 (15.8%) vs 70/794 (8.8%)

Table 134

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Cochrane authors)
Bour 2005(73) Prospective, multicenter, open-label, randomized trial	152	Mean age 49 years Moderate GORD 1. ~ 36% absence of erosions or grade 1 or 2* 2. ~ 53% grade 1 GORD* 3. ~ 11% grade 2 GORD* History GORD 6.1 years (*Savary-Miller classification)	6 months	**Intervention:** on-demand rabeprazole 10 mg orally x 6 months **Control:** continuous rabeprazole 10 mg orally once daily x 6 months	Risk of bias: ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING PARTICIPANTS/PERSONNEL/ASSESSORS: high risk INCOMPLETE OUTCOME DATA (ATTRITION BIAS): high risk SELECTIVE REPORTING: high risk FUNDING:

					"this study was supported by a grant from Janssen-Cilag."
Janssen 2005(128) Prospective, multicenter, open-label, randomized trial	432	Mean age 51 years ~ 25% grade 0 GORD (normal mucosa) ~ 75% grade I GORD (patchy red lesions without white coating or with central white coating)	6 months	**Intervention:** on-demand pantoprazole 20 mg orally as needed (maximum 1 pill daily) x 6 months **Control:** continuous pantoprazole 20 mg orally daily x 6 months	Risk of bias: ALLOCATION CONC: low risk RANDO: low risk BLINDING PARTICIPANTS/PERSONNEL/ASSESSORS: high risk INCOMPLETE OUTCOME DATA (ATTRITION BIAS): high risk SELECTIVE REPORTING: low risk FUNDING: No sources of funding/conflict of interest stated.
Morgan 2007(72) Prospective, multicenter, open-label, randomized trial	268	Mean age 48 years ~ 58% no heartburn ~ 22% mild heartburn ~ 19% moderate heartburn	6 months	**Intervention:** on-demand rabeprazole 20 mg orally once daily up to 6 months **Control:** continuous rabeprazole 20 mg orally once daily up to 6 months	Risk of bias: ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING PARTICIPANTS/PERSONNEL/ASSESSORS: high risk INCOMPLETE OUTCOME DATA (ATTRITION BIAS): unclear risk SELECTIVE REPORTING: high risk FUNDING: unclear risk "this work was supported by Janssen-Ortho Inc."
Van der Velden 2010(129) Prospective, multicenter, double-blind, randomized trial	203	Mean age 57 years 35% with oesophagitis A* 19% oesophagitis 7% with hiatus hernia 9% with GORD, reflux, or pyrosis (*Los Angeles Classification system of	13 weeks	**Intervention:** placebo daily + on-demand pantoprazole 20 mg orally daily as needed x 13 weeks **Control:** continuous pantoprazole 20 mg orally	Risk of bias: ALLOCATION CONC: low risk RANDO: low risk BLINDING PARTICIPANTS/PERSONNEL: low risk BLINDING OF ASSESSORS: high risk INCOMPLETE OUTCOME DATA

		oesophagitis)		daily + placebo daily as needed x 13 weeks	(ATTRITION BIAS): high risk SELECTIVE REPORTING: high risk FUNDING: "This study was funded by Nycomed BV, The Netherlands.
Bayerdörffer 2016(130) Prospective, multicenter, open-label, randomized trial	598	86% white ethnicity Mean age 48 years All had NERD and moderate-to-severe GORD	6 months	**Intervention:** on-demand esomeprazole 20 mg orally x 6 months **Control:** continuous esomeprazole 20 mg orally once daily x 6 months	Risk of bias: ALLOCATION CONC: unclear risk RANDO: low risk BLINDING PARTICIPANTS/PERSONNEL/ASSESSORS: high risk INCOMPLETE OUTCOME DATA (ATTRITION BIAS): low risk SELECTIVE REPORTING: unclear risk FUNDING: this study was funded by AstraZeneca R&D and many of authors including lead investigators have received financial support or (were) employees of AstraZeneca.

Table 135

18.1.2 Abrupt stop vs continued use of PPI

Meta-analysis: Boghossian 2017(203): "Deprescribing versus continuation of chronic proton pump inhibitor use in adults" Inclusion criteria: We included randomized controlled trials (RCTs) and quasi-randomized trials comparing at least one deprescribing modality (e.g. stopping PPI or reducing PPI) with a control consisting of no change in continuous daily PPI use in adult chronic users. Search strategy: The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10), MEDLINE, Embase, clinicaltrials.gov, and theWorldHealthOrganization International Clinical Trials Registry Platform(WHOICTRP).

Assessment of quality of included trials: yes ITT analysis: yes

Table 136

Ref	Comparison	N/n	Outcomes	Result
Boghossian et al. 2017(203) Design: Meta-analysis Search date: (Nov-2016)	abrupt stop vs continued use of PPI	N= 1 n= 105 (Pilotto 2003)	Lack of symptom control	**RR 3.02 (1.74 – 5.24)** **SS** (favors continued PPI use) Event rate: 38/56 (67.9%) vs 11/49 (22.4%)
		N= 1 n= 105 (Pilotto 2003)	Adverse drug withdrawal events (relapse-endoscopic findings-)	**RR 3.41 (1.91 – 6.09)** **SS** (favors continued PPI use) Event rate: 39/56 (69.6%) vs 10/49 (20.4%)

Table 137

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Cochrane authors)
Pilotto 2003(131) Prospective, multicenter, double-blind, randomized trial	105	Mean age 73 years (range 65 to 93 years) Symptomatic (heartburn, regurgitation, pain) 43% grade I* oesophagitis 52% grade II* oesophagitis 5% grade III* oesophagitis 67% hiatus hernia 62% *Helicobacter pylori*-negative	6 months	**Intervention:** abrupt discontinuation placebo daily x 6 months **Control:** continuous pantoprazole 20 mg orally, daily x 6 months	Risk of bias: ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING PARTICIPANTS/PERSONNEL/ASSESSORS: high risk INCOMPLETE OUTCOME DATA (ATTRITION BIAS): high risk SELECTIVE REPORTING: unclear risk FUNDING:

					“Unsure of source of funding (Pharmacia, Milano, Italy).”

Table 138

19 Evidence tables. Gastroprotection

19.1.1 Nonselective NSAID (including aspirin) + PPI vs Nonselective NSAID (including aspirin)

Meta-analysis: Yuan 2016 (132): "Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity"
Inclusion criteria: RCTs ≥4 weeks' duration; comparing the risk of gastrointestinal adverse events in patients taking nonselective NSAIDs, selective COX2-inhibitors, or nonselective NSAIDs/COX2-inhibitors plus gastroprotective agents (PPIs, H2RAs, misoprostol).
Search strategy: MEDLINE, Embase and the Cochrane Library were searched up until May 2015
Assessment of quality of included trials: yes
Other methodological remarks: This publication also performed a network meta-analysis, which we did not report as only direct comparisons were included in our literature report.

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Yuan 2016 (132) Design: SR+ MA Search date: (May 2015)	NSAID + PPI vs NSAID	N= 12 n= 5695 (Goldstein 2010a, Goldstein 2010b, Yeomans 2008, Li 2009, Yuan 2010, Scheiman 2011, Xie 2013, Ekstrom 1996, Hawkey 1998, Lai 2003, Lai	Ulcer complications bleeding, perforation and obstruction	NSAID + PPI: 10/3418 NSAID: 36/2277 **RR 0.23 (0.12 to 0.44)** **SS in favour of NSAID+ PPI**

		2002, Graham 2002)		
		N= 5 n= 852 (Sugano 2012, Ekstrom 1996, Cullen 1998, Lai 2003, Lai 2002)	Symptomatic ulcers	NSAID + PPI: 6/427 NSAID: 60/425 **RR 0.11 (0.05 to 0.24)** **SS in favour of NSAID+ PPI**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Cullen 1998(133)	168	NSAID users (Naproxen, Diclofenac, others) Average age 56 y 28.5% previous peptic ulcers 31% H.pylori positive	26 weeks	Omeprazole 20 mg vs placebo	RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Low risk assessors: unclear INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: Unclear OTHER BIAS: Unclear
Ekstrom 1996(134)	177	Chronic musculoskeletal conditions Using various NSAID Average age 59 y 28.5% previous peptic ulcers 31% H.pylori positive	12 weeks	Omeprazole 20 mg vs placebo	RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Low risk assessors: unclear INCOMPLETE OUTCOME DATA: Unclear SELECTIVE REPORTING: Unclear

					OTHER BIAS: Unclear
Goldstein 2010a(135)	434	Chronic musculoskeletal conditions Using naproxen Average age 61 y 8.1 % previous peptic ulcers 0% H.pylori positive	26 weeks	Esomeprazole 40 mg vs placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear OTHER BIAS: Unclear
Goldstein 2010b(135)	420	Chronic musculoskeletal conditions Using naproxen Average age 60y 9.7 % previous peptic ulcers 0 % H.pylori positive	26 weeks	Esomeprazole 40 mg vs placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear OTHER BIAS: Unclear
Graham 2002(136)	537	NSAID users (using various NSAID) Average age 60 y 100% previous peptic ulcers 0% H.pylori positive	12 weeks	Lansoprazole 15 mg vs Lansoprazole 30 mg vs Misoprostol 800 mcg vs placebo	RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Low risk assessors: unclear INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: Unclear OTHER BIAS: Unclear
Hawkey 1998(137)	725	Chronic musculoskeletal conditions Using diclofenac, ketoprofen, naproxen Average age 58 100 % previous peptic ulcers	24 weeks	Omeprazole 20 mg vs misoprostol 800 mcg	RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Low risk

		41.5 % H.pylori positive		vs placebo	assessors: unclear INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: Unclear OTHER BIAS: Unclear
Lai 2002(138)	123	Patients requiring aspirin for cardiovascular protection Average age 70 y 100% previous peptic ulcers 0% H.pylori positive	52 weeks	Lansoprazole 30 mg vs placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear OTHER BIAS: High
Lai 2003(139)	43	Chronic musculoskeletal conditions Using naproxen Average age 69 y 100 % previous peptic ulcers 0 % H.pylori positive	8 weeks	Lansoprazole 30 mg vs placebo	*RCT did not meet our inclusion criteria*
Li 2009(140)	52	NSAID users (using aspirin) Average age 72 y NR % previous peptic ulcers NR % H.pylori positive	4 weeks	Esomeprazole 40 mg vs placebo	*RCT did not meet our inclusion criteria*
Scheiman 2011(141)	2426	Patients requiring aspirin for cardiovascular protection Average age 68 y 27.3 % previous peptic ulcers 19.7 % H.pylori positive	26 weeks	Esomeprazole 40 mg vs esomeprazole 20 mg vs placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear

Sugano 2012(142)	343	Chronic musculoskeletal conditions Using loxoprofen, meloxicam, etodolac Average age 63 y 100 % previous peptic ulcers 53.7 % H.pylori positive	24 weeks	Esomeprazole 20 mg vs placebo	RANDO: Low risk ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Low risk assessors: Unclear INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear
Xie 2013(143)	156	Patients requiring aspirin for cardiovascular protection Average age 63 y NR % previous peptic ulcers 0 % H.pylori positive	26 weeks	Esomeprazole 20 mg vs omeprazole 20 mg vs placebo	RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Unclear assessors: Unclear INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear OTHER BIAS: Unclear
Yeomans 2008(144)	991	Patients requiring aspirin for cardiovascular protection Average age 77 y NR % previous peptic ulcers 22.6 % H.pylori positive	26 weeks	Esomeprazole 20 mg vs placebo	RANDO: Low risk ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Low risk assessors: Unclear INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear
Yuan 2010(145)	73	NSAID users (using various NSAID) Average age NR NR % previous peptic ulcers NR % H.pylori positive	26 weeks	Esomeprazole 20 mg vs omeprazole 20 mg vs famotidine 20 mg vs	*RCT did not meet our inclusion criteria*

				placebo	

Remarks: The authors of this systematic review included RCTs in patients taking aspirin for cardiovascular prevention (presumably in a low dose) in this evaluation.

19.1.2 Selective COX2-inhibitor + PPI vs selective COX2-inhibitor

Meta-analysis: Yuan 2016 (132): "Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity"
Inclusion criteria: RCTs comparing the risk of gastrointestinal adverse events in patients taking nonselective NSAIDs, selective COX2-inhibitors, or nonselective NSAIDs/COX2-inhibitors plus gastroprotective agents (PPIs, H2RAs, misoprostol).
Search strategy: MEDLINE, Embase and the Cochrane Library were searched up until May 2015
Assessment of quality of included trials: yes
Other methodological remarks: This publication also performed a network meta-analysis, which we did not report as only direct comparisons were included in our literature report.

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Yuan 2016 (132) Design: SR+ MA Search date: (May 2015)	Selective COX2-inhibitor + PPI vs selective COX2-inhibitor	N= 2 n= 673 (Chan 2007, Scheiman 2006)	Ulcer complications	Selective COX-2 inhibitor + PPI: 0/403 Selective COX-2 inhibitor: 14/270 **RR 0.06 (0.01 to 0.48)** **SS in favour of Selective COX-2 inhibitor + PPI**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Chan 2007(146)	273	Chronic musculoskeletal conditions Using celecoxib Average age 71 y 100 % previous peptic ulcers 47.3 % H.pylori positive	52 weeks	Esomeprazole 40 mg vs placebo	RANDO: Low risk ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Low risk assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear
Scheiman 2006(147)	805	Chronic musculoskeletal conditions Using various COX-2 selective NSAID Average age 66 y 100 % previous peptic ulcers 8.8 % H.pylori positive	26 weeks	Esomeprazole 20 mg vs esomeprazole 40 mg vs placebo	RANDO: Low risk ALLOCATION CONC: Unclear BLINDING : Participants/personnel: Low risk assessors: Unclear INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear OTHER BIAS: High risk

Remarks: All participants of these studies were patients with a previous peptic ulcer.

19.1.3 Aspirin + PPI vs aspirin

Meta-analysis: Mo 2013(148)

Inclusion criteria: RCTs on the effect of PPIs, in comparison with a control group (placebo, cytoprotective agents, or H2RA) in reducing adverse GI events (hemorrhage, ulcer, perforation, or obstruction) in adult patients taking low-dose aspirin.
Search strategy: MEDLINE, Embase, and Cochrane Controlled Trials Register were searched up until December 2013
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Mo 2013(148) Design: SR+ MA Search date: (December 2013)	low-dose aspirin + PPI vs Low-dose aspirin	N= 4 n= 7302 (Bhatt 2010, Lai 2002, Scheiman 2011, Yeomans 2008)	Upper gastrointestinal ulcer	Low-dose aspirin + PPI: 30/4054 Low-dose aspirin + placebo: 95/3248 **RR 0.20 (0.13 to 0.30)** **SS in favour of Low-dose aspirin + PPI**
		N= 5 n= 7474 (Bhatt 2010, Lai 2002, Ren 2011, Scheiman 2011, Yeomans 2008)	Bleeding	Low-dose aspirin + PPI: 11/4140 Low-dose aspirin + placebo: 43/3334 **RR 0.26 (0.14 to 0.49)** **SS in favour of Low-dose aspirin + PPI**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by review authors)
Bhatt 2010(149)	3761	Combined with clopidogrel	180 days	Omeprazole 20 mg/day	RANDO: Low risk

				vs placebo	ALLOCATION CONC: Unclear BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: High risk
Lai 2002(138)	123	low-dose aspirin-induced ulcer H.pylori eradicated	12 months	Lansoprazole 30 mg/day vs placebo	RANDO: Low risk ALLOCATION CONC: Unclear BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk
Ren 2011(150)	172	Combined with clopidogrel	30 days	Omeprazole 20 mg/day vs placebo	RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants/personnel/assessors Unclear INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk
Scheiman 2011(141)	2427	H.pylori-negative High risk	26 weeks	Esomeprazole 20 -40 mg/day vs placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk

					SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk
Yeomans 2008(144)	991	Aged ≥ 60 y without ulcer	26 weeks	Esomeprazole 20 mg/day vs placebo	RANDO: Low risk ALLOCATION CONC: Unclear BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear OTHER BIAS: Unclear

Study details	n/Population	Comparison	Outcomes		Methodological
Sugano 2014(151) LAVENDER Design: / RCT DB PG Duration of follow-up: ≤72 weeks	n= 430 Mean age: 67 y h pylori status: 44.8 % positive h pylori eradication: n diagnostic endoscopy: yes Oesophagitis (LA classification): Grade A-D excluded	Esomeprazole 20 mg/day vs Placebo <u>remarks</u> All patients received			RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: NR Drop-out and Exclusions: 23.7% in esomprazole group
			Time to ulcer recurrence (PO) week 48	**HR 0.09 (0.02 to 0.41)** **p<0.001** **SS in favour of esomeprazole**	
			Safety		
			Adverse events	Esomeprazole: 155/214 (72.4%) placebo: 139/213 (65.3%) NT	
			Severe adverse events	Esomeprazole: 7/214 (3.3%) placebo: 10/213 (4.7%) NT	

	Inclusion: adult patients with a history of peptic ulcer receiving low-dose acetylsalicylic acid (ASA, aspirin, 81-314 mg/day) for cardiovascular protection in East Asia Exclusion • active ulcer • a history of GI surgery (excluding closure) or current or past evidence (within 12 weeks of randomisation) of a GI disorder (eg, Crohn's disease, inflammatory bowel disease, Zollinger–Ellison syndrome, any malabsorption syndrome, reflux oesophagitis (Los Angeles (LA) classification grade A to D) or gastric outlet obstruction; • malignancy;	concomitant mucosal protection (gefarnate 100 mg/day)			36.3% in placebo group • Described: yes • Balanced across groups: no ITT: modified ITT: "all randomised patients who received at least one dose of study medication and had no active ulcer at baseline" SELECTIVE REPORTING: no Sponsor: AstraZeneca

	• severe liver or renal disease; • severe cardiovascular or cerebrovascular disease; • uncontrolled diabetes mellitus; • unstable hypertension; • pancreatitis; • severe pulmonary disease. • Patients with scarring related to other conditions or endoscopic therapy, such as endoscopic mucosal resection or endoscopic submucosal dissection • patients that needed to continue treatment with anticoagulants after randomization				

Table 139

19.1.4 PPI vs no PPI for the prevention of gastrointestinal bleeding in patients receiving clopidogrel

Meta-analysis: Cardoso 2015(152): "Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis"

Inclusion criteria: RCTs or observational studies in patients taking clopidogrel stratified by concomitant PPI use; at least 6 months follow-up
Search strategy: Pubmed, Scopus and the Cochrane Central Register of Controlled trials were searched up until February 2014
Assessment of quality of included trials: yes
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Cardoso 2015(152) Design: SR+ MA Search date: (February 2014	clopidogrel + PPI vs clopidogrel no PPI	N= 3 n= 5079 (Aihara 2012, Bhatt 2010, Hsu 2012)	Gastro-intestinal bleeding	PPI: 5/2533 (0.2%) no PPI: 22/2546 (0.9%) **OR 0.24 (0.09 to 0.62)** **SS in favour of clopidogrel + PPI**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Aihara 2012(153) Cohort study	1887	Patients with PCI with stent on dual platelet therapy	1 year	Esomeprazole or Omeprazole or Lansoprazole	Observational (cohort) study: d*id not meet our inclusion criteria*

				vs no PPI	
Bhatt 2010(149) RCT	3761	Patients with acute coronary syndrome or stent Dual platelet therapy	180 days	Omeprazole 20 mg/day vs placebo	RANDO: Low risk ALLOCATION CONC: Unclear BLINDING : Participants/personnel/assessors Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: High risk
Hsu 2012(154) RCT	318	Patients with a history of GI ulcer Clopidogrel users	6 months	Clopidogrel + esomeprazole 20 mg 1x/day vs Clopidogrel, no PPI	ALLOCATION CONC: unclear (only abstract available) RANDO: unclear (only abstract available) BLINDING : Participants/personnel/assessors unclear (not described) INCOMPLETE OUTCOME DATA: unclear (only abstract available) SELECTIVE REPORTING: unclear (only abstract available) OTHER BIAS: unclear (only abstract available)

20 Evidence tables. Adverse events.

20.1.1 Cardiovascular adverse events

The evidence tables concerning cardiovascular adverse events are described in the section “summaries and conclusions”.

20.1.2 Dementia

SR Batchelor 2017(167) (4 studies)	country population follow-up	n	comparison	Main results **Outcome: Dementia**
Herghelegiu et al. 2016(204) cross-sectional study	Romania Geriatric outpatients Clinic (2014–2015) Age PPI: 76.3 ± 8.7 Age non-PPI: 74.2 ± 10.3	n = 148 PPI: n= 74, non-PPI: n = 74)	Omeprazole, esomeprazole, lansoprazole, pantoprazol vs non-use of PPI	**OR 3.67 (95% CI: 2.23–19.15)** **p = 0.002** **SS more dementia with PPI use** (analysis corrected for diabetes and hypertension)
Booker et al. 2016(205) case–control study (records database)	Germany General practice (January 2010–December 2014) Age PPI: 80.4 ± 5.3	n = 23 912 11 956 cases, 11 956 matched controls	Unspecified PPI Vs Non-use of PPI	**OR 0.94 (95% CI: 0.90–0.97)** **P = 0.0008** **SS less dementia with PPI use** (controls were matched on age, sex, health insurance, physician)

Gomm et al. 2016(206) Cohort study (insurance records)	Germany Older inpatients and outpatients (2004–2011) Age PPI: 83.0 ± 5.6 Age non-PPI: 83.8 ± 5.4,	n = 73 679 PPI: n= 2950, non-PPI: n= 70 729	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole vs Non-use of PPI	Frequent PPI use With potential confounders: **HR 1.44 (95% CI: 1.36–1.52); p < 0.001;** **SS more dementia with PPI use** Without potential confounders: **HR 1.66 (95% CI 1.57–1.76); p < 0.001;** **SS more dementia with PPI use** Occasional PPI use: **HR 1.16 (95% CI: 1.13–1.19); p < 0.001;** **SS more dementia with PPI use** (confounders: age, sex, stroke, depression, ischemic heart disease, diabetes, polypharmacy, anticholinergic use) Subgroup analysis: Omeprazole: HR 1.51 (p<0.001); pantoprazole: HR 1.58 (p<0.001), esomeprazole: HR 2.12 (p<0.001)
Haenisch et al. 2015(207) Cohort study (database)	Germany General practice (6 years) Age PPI: 79.6 ± 3.4, Age non-PPI: 79.7 ± 3.6	n = 3076 PPI: n= 713, non-PPI: n = 2363	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, dexlansoprazole vs Non-use of PPI	Adjusted analysis: **HR 1.38 (95% CI: 1.04–1.83); p = 0.02;** **SS more dementia with PPI use** Crude analysis: **HR 1.44 (95% CI 1.10–1.90); p = 0.008;** **SS more dementia with PPI use** Outcome: Alzheimer's disease Adjusted analysis: **HR 1.44 (95% CI 1.01–2.06); p = 0.04;** **SS more dementia with PPI use**

				Crude analysis: **HR 1.45 (95% 1.03–2.05); p = 0.03;** **SS more dementia with PPI use** (Confounders: age, sex, education, ApoE4 allele status, polypharmacy, depression, ischemic heart disease, stroke)

Table 140

SR Batchelor 2017 (7 studies)	country population follow-up	n	comparison	Main results **Outcome: Acute cognitive impairment**
Bebarta et al. 2008(208) case report	United States Emergency Department (2008)	n = 1; Age: 46	Omeprazole Vs NA	Acute onset of delirium due to hyponatremia possibly induced by omeprazole.
Delgado et al. 2013(209) case report	Spain Emergency Department (2011–2012)	n = 1; Age: 76	Omeprazole, Esomeprazole Vs NA	Three episodes of confusion due to omeprazole induced hypomagnesemia. Esomeprazole used to test induction of hypomagnesemia and then withdrawn to demonstrate resolution.
Heckmann et al. 2000(210) case report	Germany Neurology Inpatients (Not stated)	n = 1; Age: 77	Omeprazole Vs NA	Delirium, suspected to be induced by use of omeprazole
Pasina et al. 2016(211) case series	Italy Internal medicine Inpatients (February 2014–November 2014)	n = 3 (of nine cases presented relevant);	Unspecified PPI(s) Vs NA	One episode of confusion due to hypomagnesemia, probably induced by PPI. One episode of delirium due to hypomagnesemia, probably induced by PPI. One episode of mild cognitive impairment due to hypomagnesemia with possible link to PPI in the absence of alternative cause for symptomology.

		Age: 77, 86, 83		
Fujii et al. 2012(212) Cohort study retrospective	Japan Oncology Outpatients (January 2006–July 2007) Age PPI: 65.2 ± 6.5, Age non-PPI: n= 65.2 ± 8.1	n = 60 PPI: n= 30 H2RA: n= 30	H2RA vs Unspecified PPI(s)	Outcome: delirium **OR 3.82 (95%CI 1.15–12.71), p = 0.047** **SS; increased risk for H2RA**
Otremba et al. 2016(213) Cohort study	Poland Acute geriatric ward inpatients June 2013 – June 2014 Age: 79.2 ± 7.7	n = 675	Unspecified PPI(s) Vs Non-use of PPI	Outcome: delirium **OR 1.67 (95% CI 1.11–2.53), p= 0.014** **SS more delirium with PPI use** (confounder: age, dementia, congestive heart disease, and previous episodes of delirium)
Akter et al. 2015(214) RCT	Bangladesh Healthy non-patients (1 week in 2015) Mean age: 23 for men, 21 for women	n = 60	Omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole vs Placebo	PPIs had a negative impact on cognitive performance. Statistically and clinically significant impairment in visual memory, attention, executive function and working and planning function in PPI groups. Omeprazole showed significant ($P < 0.05$) results in seven subtests, lansoprazole and pantoprazole showed significant results in five tests, rabeprazole showed significant results in four tests and esomeprazole showed significant results in three tests.

Table 141

The following studies were not included in the above SRs/MAs

Ref **Study type**	**Setting** **Population**	**number of participants**	**Comparison**	**Results**
Tai SY 2017(168) National cohort study (health insurance database)	Taiwan Non PPI users, > 40 years old, free of dementia at baseline Average follow-up: PPI: 8.44 years Non PPI: 9.55 years Mean age: PPI: 55.65 (SD 12.37) Non-PPI: 55.33 (SD 12.23)	n= 15726 PPI: 7863 Non-PPI: 7863	PPI vs no PPI	**Outcome: dementia** **HR 1.22 (95% CI: 1.05-1.42); p=0.009,** **SS more dementia with PPI use** 366 dementia events (4.7%) vs 341 dementia events (4.3%) with an average follow-up of 9 years or 5.51 vs 4.54 per 1000 person-years Association cumulative PPI use and all-cause dementia: **p for trend = 0.013, SS** Sub-group analyses: Omeprazole: **HR 1.30 (95%CI: 1.09-1.54), SS more dementia with omeprazole** Pantoprazole: HR 1.36 (95%CI: 0.98-1.89), NS Lansoprazole: HR 1.20 (95%CI: 0.98-1.46), NS (Covariables included: age, gender, urbanization, Charlson's index, and all comorbidities and comedications) An elevated risk for dementia was shown among PPI users compared to non-PPI users for men, ≥ 70 years, comorbidity (hyperlipidemia, hypertension , depression, Ischemic heart disease), concomitant medications (antiplatelet agents and statins).

Gray SL 2017(215) Prospective population-based cohort study.	USA, Washington Age ≥65 years, without dementia at study entry Mean age: 74 year Mean follow-up: 7.5 years	n= 3484	Cumulative dose of PPI over a 10-year period vs no PPI	**Outcome: dementia or Alzheimer's disease (AD)** 827 participants (23.7%) developed dementia (670 with possible or probable AD). PPI exposure was not associated with risk of dementia: p = 0.66: 1 years of daily use: HR 0.87 (95% CI 0.65–1.18), NS 3 years of daily use: HR 0.99 (95%CI 0.75–1.30), NS 5 years of daily use: HR 1.13 (95%CI 0.82–1.56), NS PPI exposure was also not associated with risk of AD: p = 0.77 (The analyses were adjusted for age, study cohort, sex, education, hypertension, diabetes mellitus, smoking, stroke, coronary heart disease, body mass index, exercise, self-rated health, depression, gait speed, difficulties with activities of daily living, hospitalizations, and cumulative exposure to nonsteroidal anti-inflammatory medications and anticholinergic medications.)

Goldstein FC 2017(169) Observational, longitudinal study (The analyses were controlled for demographic variables (age at baseline, race, sex, education), vascular comorbidities (self-reported hypertension, diabetes mellitus, heart disease, stroke or transient ischemic attack), mood (depression), and anticholinergic medications and H2RAs.)	Tertiary academic Alzheimer's Disease Centers ≥ 50 years, normal cognition at baseline Mean age: Always PPI: 73.5 (SD 8.9) Intermittent PPI: 73.7 (SD 8.4) Never PPI: 72.6 (SD 9.4)	n= 10486 Always PPI : n= 884 Intermittent PPI: n= 1925 never PPI: n= 7677	Continuous or intermittent PPI vs no PPI	**Outcome:** cognitive decline to mild cognitive impairment (MCI) or dementia Continuous (always vs never) PPI use: **HR 0.78 (95% CI 0.66–0.93), p = 0.005; SS** Intermittent PPI use (vs never PPI): **HR 0.84 (95% CI 0.76–0.93), p = 0.001; SS** **Outcome:** cognitive decline to mild cognitive impairment (MCI) or Alzheimer's disease (AD) (n=10156) Continuous (always vs never) PPI use: **HR 0.82 (95% CI 0.69–0.98), p = 0.03; SS** Intermittent PPI use (vs never PPI): **HR 0.82 (95% CI 0.74–0.91), p< 0.001; SS** Similar findings were found for H2RA. **Outcome:** conversion from MCI at baseline (n=3082) to dementia Continuous (always vs never) PPI use: HR 0.83 (95% CI 0.67–1.02), p = 0.08; **NS** Intermittent PPI use (vs never PPI): **HR 0.86 (95% CI 0.76–0.98), p = 0.03; SS** **Outcome:** conversion from MCI at baseline to AD Continuous (always vs never) PPI use: HR 0.97 (95% CI 0.79–1.19), p = 0.78; **NS** Intermittent PPI use (vs never PPI): **HR 0.83 (95% CI 0.73–0.94), p= 0.01; SS**

Table 142

20.1.3 Community-acquired pneumonia

Ref Study type	Setting Population	number of studies	Endpoints	Results
Lambert 2015(170) SR + MA of RCTs and observational studies (case-control, case-crossover, and cohort studies) search date: February 2014	**adults ≥18 y outpatients** **PPI exposure** **vs** **no PPI exposure**	**32 studies** 4 RCTs 10 cohort studies 17 case-control 1 case-crossover	**CAP diagnosis** 26 studies (Almirall 2008, Chen 2013, Dublin 2010, Filion 2013, Gau 2010, Hermos 2012, Jena 2013, Juthani-Metha 2013, Laheij 2003, Laheij 2004, Liu 2012, Long 2013, Mastronarde 2009, Meijvis 2011, Morris 2013, Nielsen 2012, Pasina 2011, Quagliarello 2005, Ramsay 2013, Rodriguez 2009, Roughead 2009, Sarkar 2008, Scheiman 2011, Sugano 2011, Sugano 2012, van de Garde 2006)	PPI-users vs non-PPI users **RR 1.49 (95% CI 1.16 to 1.92)** I^2: 99.2% (high heterogeneity) **SS more with PPI users**
			Subgroup age	<65 y **RR 1.34 (1.04 to 1.71)** **SS** >65 y **RR 1.33 (1.13 to 1.58)** **SS**

			Subgroup PPI dose	low dose **RR 1.31 (1.04 to 1.66)** **SS** high dose **RR 1.33 (1.05 to 1.69)** **SS**
			Subgroup PPI duration	<1 month **RR 2.10 (1.39 to 3.16)** **SS** 1-6 months RR 1.51 (0.92 to 2.49) NS >6 months RR 1.37 (0.85 to 2.20) NS
			Hospitalization for CAP 16 studies (Almirall 2008, Chen 2013, Filion 2013, Gau 2010, Juthani-Metha 2013, Liu 2012, Meijvis 2011, Nielsen 2012, Ramsay 2013, Rodriguez 2009, Roughead 2009, Sarkar 2008, Scheiman 2011, Sugano 2011, Sugano 2012, van de Garde 2006)	PPI-users vs non-PPI users **RR 1.61 (95% CI 1.12 to 2.31)** I^2: 99.3% (high heterogeneity) **SS more with PPI users**
	H2RA exposure **vs** **no H2RA exposure**	**8 studies**	**CAP diagnosis** 8 studies (Almirall 2008, Dublin 2010, Filion 2013, Gau 2010, Laheij 2004, Rodriguez 2009, Sarkar 2008, Sugano 2011**)**	H2RA users vs non-H2RA users RR 1.00 (95% CI 0.90 to 1.12) NS

Table 143

references included in the above SR's	country population follow-up	n	Main results
Almirall 2008	*case-control study; did not meet our inclusion criteria*		
Chen 2013 cohort study	**Taiwan** **CKD patients**	8076	**HR 2.28 (1.64 to 3.15)**
Dublin 2010	*case-control study; did not meet our inclusion criteria*		
Ernst 2012	*case-control study; did not meet our inclusion criteria*		
Filion 2013 cohort study	**Canada, UK, USA** **New NSAID users** **>40 years old**	4 238 504	OR 1.05(0.89 to 1.25)
Gau 2010	*case-control study; did not meet our inclusion criteria*		
Gulmez 2007	*case-control study; did not meet our inclusion criteria*		
Hennessey 2007	*case-control study; did not meet our inclusion criteria*		
Hermos 2012	*case-control study; did not meet our inclusion criteria*		
Jena 2013 cohort study	**USA** **adults >30 years old (employer-based insurance plans)**	54 490	**RR 1.80 (1.71 to 1.89)**
Juthani-Metha 2013 cohort study	**USA** **adults 70-79 years old**	1441	HR 0.81 (0.57 to 1.14)
Laheij 2003 cohort study	**Netherlands,** **outpatient endoscopy service and surrounding community**	405	**OR 18.20 (2.00 to 158.00)**
Laheij 2004	*case-control study; did not meet our inclusion criteria*		
Liu 2012 case-crossover	*case-crossover ; did not meet our inclusion criteria*		
Long 2013	*case-control study; did not meet our inclusion criteria*		
Mastronarde 2009 RCT	**Netherlands,** **adults with poorly controlled asthma**	402	OR 7.24 (0.14 to 365.19)
Meijvis 2011	*case-control study; did not meet our inclusion criteria*		
Morris 2013 cohort study	**USA** **COPD patients >45 years old**	8814	OR 1.85 (0.13 to 26.32)

Muellerova 2012	*case-control study; did not meet our inclusion criteria*		
Myles 2009	*case-control study; did not meet our inclusion criteria*		
Nielsen 2012	*case-control study; did not meet our inclusion criteria*		
Pasina 2011 cohort study	**Italy** **patients >65 years old admitted at internal medicine wards**	1332	**OR 2.37 (1.10 to 5.07)**
Quagliarello 2005 cohort study	**USA** **Nursing home residents > 65 years old**	613	HR 0.92 (0.61 to 1.37)
Ramsay 2013 cohort study	**Australia** **adults >65 years old; veterans**	105 467	**RR 1.55 (1.44 to 1.67)**
Rodriguez 2009 cohort study	**UK** **20-79 years old**	17 920	**RR 1.16 (1.03 to 1.31)**
Roughead 2009 cohort study	**Australia** **>65 years old** **veterans**	185 533	**RR 1.16 (1.11 to 1.22)**
Sarkar 2008	*case-control study; did not meet our inclusion criteria*		
Scheiman 2011 RCT	**Europe, Australia, Asia, Africa, Americas** **Aspirin users > 18 years old with history or risk of peptic ulcer**	2426	OR 0.36 (0.09 to 1.46)
Sugano 2011 RCT	**Japan** **Long-term low-dose aspirin users with history of ulcer**	461	OR 1.04 (0.06 to 16.88)
Sugano 2012 RCT	**Japan** **Long-term NSAID users with history of ulcer**	366	**OR 7.51 (1.50 to 37.65)**
van de Garde 2006 (Thorax) cohort study	*case-control study; did not meet our inclusion criteria*		
van de Garde 2006 (ERJ) cohort study	*case-control study; did not meet our inclusion criteria*		
van de Garde 2007	*case-control study; did not meet our inclusion criteria*		

cohort study	

Table 144

Ref Study type	Setting Population	number of studies	Endpoints	Results
Estborn 2015(171) individual patient data MA of RCTs sourced from the AstraZeneca ARIADNE safety database search date: August 2013	**children and adults** **mean age 53** **esomeprazole** **vs** **placebo**	**24 RCTs** both published and unpublished data	**Pneumonia**	Esomeprazole: 23/9602 Placebo: 18/5500 RR 0.66 (95% CI 0.36 to 1.22) NS
			Subgroup age	<u><65 y</u> reported only graphically, without numerical information NS **<u>≥65 y</u>** **reported only graphically, without numerical information** **SS**
			Subgroup PPI dose	<u>low dose (<40 mg)</u> reported only graphically, without numerical information NS <u>high dose (≥ 40 mg)</u> reported only graphically, without numerical information NS

Table 145

The following studies were not included in the above SRs/MAs

Ref Study type	Setting Population	number of participants	Endpoints	Results
Ho 2014 (172) retrospective cohort up to 2 years follow-up (mean 1 year)	**Adults with non-traumatic intracranial haemorrhage** **Taiwan**	**3 982**	**Pneumonia**	PPI users vs non-PPI users **Adj. HR* 1.61 (95% CI 1.32 to 1.97)** **p<0.001** **SS; more pneumonia in PPI users** adjusted for gender, age, income, urbanisation, Charlson Comorbidity Index.

Table 146

Ref Study type	Setting Population	number of participants	Endpoints	Results
Lee 2015(173) prospective cohort follow-up: 10 years	**Patients >30 years old with newly-diagnosed COPD** **Taiwan**	**17 498**	**Pneumonia**	**PPI users vs non-PPI users** **Adj. HR 1.76 (95% CI 1.33 to 2.34)** **SS; more pneumonia in PPI users**

Table 147

Ref Study type	Setting Population	number of participants	Endpoints	Results

Chen 2015(174) retrospective cohort follow-up: 5 years	Patients with chronic kidney disease Taiwan	**8 076**	Pneumonia	**<u>PPI users vs non-PPI users</u>** **Adj. HR 2.28 (95% CI 1.64 to 3.15)** **SS; more pneumonia in PPI users**
Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoints**	**Results**
Othman 2016(177) retrospective cohort follow-up: unclear	Adult patients with a new prescription for a PPI individually matched with controls UK	160 000 (+ 160 000 matched unexposed controls)	Pneumonia	**<u>PPI users vs non-PPI users</u>** **Adj. HR 1.67 (95% CI 1.55to 1.79)** **SS; more pneumonia in PPI users**

Table 148

Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoints**	**Results**
Hsu 2017(176) retrospective cohort follow-up: 6 years	Patients newly diagnosed with GORD and treated with PPis Taiwan	**15 715 (+ 15 715 non-GORD matched controls)**	Pneumonia	**<u>PPI use <4 months vs Non-GORD (without PPI use)</u>** **1.33 (1.17 to 1.52)** **SS more pneumonia in PPI users** **<u>PPI use ≥4 months vs Non-GORD (without PPI use)</u>** **1.93 (1.64 to 2.28)** **SS more pneumonia in PPI users**

Table 149

Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoints**	**Results**

Ho 2017(175) retrospective cohort follow-up: 4 years	Dementia patients with new PPI usage Taiwan	786 dementia patients with new PPI usage + 786 matched dementia patients without PPI usage	Pneumonia	**<u>PPI users vs non-PPI users</u>** **Adj. HR 1.89 (95% CI 1.51 to 2.37)** **SS; more pneumonia in PPI users**

Table 150

20.1.4 Renal adverse events

Ref Study type	Setting Population	number of studies	Endpoints	Results
Nochaiwong 2017(178) SR + MA of observational studies search date: October 2016	**PPI users** **vs** **non-PPI users**	**9 studies (with 11 unique cohorts)**	**Acute interstitial nephritis (AIN)** **3 studies** (Leonard 2012, Blank 2014, Antoniou 2015,)	**PPI users vs non-PPI users** **RR 3.61 (2.37 to 5.51)** **SS** **more AIN in PPI use**
			Acute kidney injury (AKI) **5 studies** (Leonard 2012, Klepser 2013, Antoniou 2015, Lazarus 2016, Lee 2016)	**PPI users vs non-PPI users** **RR 1.44 (1.08 to 1.91)** **SS** **more AKI in PPI use**
			Chronic kidney disease (CKD) **4 studies** (Arora 2016, Lazarus 2016, Peng 2016, Xie 2016)	**PPI users vs non-PPI users** **RR 1.36 (1.07 to 1.72)** **SS** **more CKD in PPI use**
			End-stage renal disease (ESRD) **2 studies** (Peng 2016, Xie 2016)	**PPI users vs non-PPI users** **RR 1.42 (1.28 to 1.58)** **SS** **more ESRD in PPI use**
			AKI **1 study** (Lazarus 2016)	**PPI vs H2RA** **RR 1.32 (1.17 to 1.51)** **SS** **more AKI in PPI use**

			CKD **2 studies** (Lazarus 2016, Xie 2016)	**PPI vs H2RA** **RR 1.28 (1.24 to 1.33)** **SS** **more CKD in PPI use**
			ESRD **1 study** (Xie 2016)	**PPI vs H2RA** **RR 1.32 (1.28 to 1.37)** **SS** **more ESRD in PPI use**

Table 151

references included in the above SR's	country population follow-up	n	Main results
Leonard 2012a	*nested case-control; does not meet our inclusion criteria*		
Leonard 2012b	*nested case-control; does not meet our inclusion criteria*		
Klepser 2013	*nested case-control; does not meet our inclusion criteria*		
Blank 2014	*nested case-control; does not meet our inclusion criteria*		
Antoniou 2015 *retrospective cohort study*	Canada aged >66 y who started PPI therapy health care claims database	581 184	**PPI vs no PPI** **AIN: HR 3.00 (95% CI 1.47 to 6.14) SS** **AKI: HR 2.52 (95% CI 2.27 to 2.79) SS**
Arora 2016	*case-control; does not meet our inclusion criteria*		
Lazarus 2016a *prospective cohort study*	USA eGFR at baseline >60 mL/min/1.73m^2	10 482	**PPI vs no PPI** **AKI: Adj. HR 1.64 (95%CI 1.22 to 2.21) SS** **CKD: Adj. HR 1.50 (95%CI, 1.14 to 1.96) SS** **PPI vs H2RA** **AKI: Adj. HR 1.58 (95%CI 1.05 to 2.40) SS** **CKD: Adj. HR 1.39 (95%CI, 1.01 to 1.91) SS**
Lazarus 2016b *retrospective cohort study*	USA health care claims database; eGFR at baseline >60 mL/min/1.73m^2 mean 50 y	248 751	**PPI vs no PPI** **AKI: Adj. HR 1.31 (95%CI 1.22 to 1.42) SS** **CKD: Adj. HR, 1.17 (95%CI 1.12 to 1.23) SS**

			PPI vs H2RA **AKI: Adj. HR 1.30 (95%CI 1.13 to 1.48) SS** **CKD: Adj. HR 1.29 (95%CI 1.19 to 1.40) SS**
Lee 2016 *retrospective cohort study*	USA Joint venture research database mean 66 y critically ill patients	15 063	PPI vs no PPI **AKI** Adj. OR 1.02 (95% CI 0.91 to 1.13) NS
Peng 2016	*case-control; does not meet our inclusion criteria*		
Xie 2016 *retrospective cohort study*	USA health care claims and prescription database mean 57 y	193 591	**PPI vs H2RA** **CKD HR 1.28 (95%CI 1.23 to 1.34) SS** **ESDR HR 1.96 (95% CI 1.21 to 3.18) SS**

Table 152

The following studies were not included in the above SRs/MAs

Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoints**	**Results**
Xie 2017(179) prospective cohort 5 years follow-up	**USA** **Department of Veterans Affairs national databases** **PPI and H2RA users**	**144 032**	**CKD without intervening acute kidney injury**	PPI users vs H2RA users **HR 1.26 (1.20 to 1.33)** **SS** **more CKD in PPI users**
			ESRD or eGFR decline over 50%	PPI users vs H2RA users **HR 1.30 (1.15 to 1.48)** **SS** **more ESRD in PPI users**

Table 153

Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoints**	**Results**

Klatte 2017(180) retrospective cohort median 2.7 years follow-up	**Sweden** **New users of PPI and new users of H2RA**	**114 883**	**Progression CKD, defined as doubling of creatinine**	PPI users vs H2RA users **HR 1.26 (95% CI 1.05 to 1.51)** **SS** **more progression CKD in PPI users**
			End-stage renal disease	PPI users vs H2RA users HR 2.40 (95% CI 0.76 to 7.58) NS
			Acute kidney injury	PPI users vs H2RA users **HR 1.30 (95% CI 1.00 to 1.69)** **SS** **more acute kidney injury in PPI users**

Table 154

20.1.5 Gastro-intestinal infections

20.1.5.1 *Clostridium difficile infections*

Ref **Study type**	**Setting** **Population**	**number of studies**	**Endpoints**	**Results**
Trifan A 2017(181) SR + MA of observational studies search date: from January 1990 to March 2017	**Adults on PPI therapy** **PPI** **vs** **no PPI**	**N= 56** (40 case control and 16 cohort studies)	**Clostridium difficile infection**	**OR 1.99 95%CI: 1.73-2.30, p < 0.001** **SS** **More C. diff infections with PPI**

Table 155

references included in the above SR's	Country/region population follow-up	n	comparison	Main results **<u>Outcome</u>**: Clostridium difficile infection
Akhtar AJ *et al.*2007(216) Case-control	America Unicenter, inpatient setting	n= 2190	PPI vs NA	**OR 2.1 (95%CI: 1.6-2.7)** **SS** **More C. diff infections with PPI**
Al-Tureihi *et al*. 2005(217) Case-control	America Unicenter, inpatient setting	n= 53	PPI vs NA	OR 3.1 (95%CI: 1.0-9.7) NS
Aseeri *et al.* 2008(218) Case-control	America Unicenter, inpatient setting	n= 188	PPI vs NA	**OR 4.4 (95%CI: 2.3-8.2)** **SS** **More C. diff infections with PPI**
Bajaj *et al.* 2010(219) Case-control	America Multicenter, Mixt setting	n= 162	PPI vs NA	**OR 37.6 (95%CI: 6.2-227.6)** **SS** **More C. diff infections with PPI**
Barletta *et al.* 2014(220) Case-control	Asia Unicenter, inpatient setting	n= 408	PPI vs NA	**OR 2.1 (95%CI: 1.2-3.8)** **SS** **More C. diff infections with PPI**
Baxter *et al*. 2008(221)	America Multicenter, inpatient setting	n= 4493	PPI vs NA	OR 1.2 (95%CI: 1.0-1.4) NS
Beaulieu *et al.* 2007(222) Cohort study	Unicenter, inpatient setting	n= 827	PPI vs NA	OR 1.3 (95%CI: 0.9-2.0) NS
Branch *et al*. 2007(223) Case control	America Unicenter, inpatient setting Mean age: 66.02	n= 787	PPI vs NA	**OR 13.0 (95%CI: 7.5-22.7)** **SS** **More C. diff infections with PPI**

Buendgens *et al*. 2014(224) Case control	Europe Multicenter, inpatient setting	n= 3286	PPI vs no PPI	**OR 3.1 (95%CI: 1.1-8.7)** **SS** **More C. diff infections with PPI**
Campbell *et al*. 2013(225) Case-control	America Unicenter, inpatient setting	n= 96	PPI vs NA	**OR 2.2 (95%CI: 0.6-8.0)** NS
Cunningham *et al*. 2003(226) Case-control	Europe Unicenter, inpatient setting	n= 320	PPI vs NA	**OR 2.5 (95%CI: 1.5-4.1)** **SS** **More C. diff infections with PPI**
Dalton *et al.* 2009(227) Cohort study	America Multicenter, inpatient setting Mean age: 74.7	n= 14719	PPI vs no PPI	**OR 1.9 (95%CI: 1.4-2.7)** **SS** **More C. diff infections with PPI**
Debast *et al*. 2009(228) Case-control	Europe Unicenter, inpatient setting	n= 154	PPI vs NA	OR 1.1 (95%CI: 0.5-2.4) NS
Dial *et al*. 2004(229) Case-control	America Multicenter, inpatient setting	n= 188	PPI vs NA	**OR** 2.6 (95%CI: 1.3-5.0) **SS** **More C. diff infections with PPI**
Dial *et al.* 2004(229) Cohort study	America Multicenter, inpatient setting	n= 1187	PPI vs no PPI	**OR** 2.1 (95%CI: 1.2-3.5) **SS** **More C. diff infections with PPI**
Dial *et al*. 2005(230) Case-control	Europe Multicenter, outpatient setting	n= 13563	PPI vs NA	**OR** 2.9 (95%CI: 2.4-3.5) **SS** **More C. diff infections with PPI**
Dial *et al*. 2006(231) Case-control	Europe Multicenter, outpatient setting	n= 3484	PPI vs NA	**OR 3.5 (95%CI: 2.3-5.3)** **SS** **More C. diff infections with PPI**

Dial *et al*. 2008(232) Case-control	America Multicenter, outpatient setting Mean age: 79.8	n= 9196	PPI vs NA	**OR 1.6 (95%CI: 1.3-1.9)** **SS** **More C. diff infections with PPI**
Dubberke *et al*. 2007(233) Cohort study	America Multicenter, inpatient setting	n= 36086	PPI vs no PPI	**OR 1.6 (95%CI: 1.3-2.1)** **SS** **More C. diff infections with PPI**
Elseviers *et al*. 2015(234) Case-control	Europe Multicenter, inpatient setting Mean age: 71.9	n= 743	PPI vs NA	**OR 1.9 (95%CI: 1.1-3.4)** **SS** **More C. diff infections with PPI**
Faleck *et al*. 2016(235) Cohort study	America Unicenter, inpatient setting Mean age: 66	n= 11230	PPI vs no PPI	**OR 0.6 (95%CI: 0.4-0.8)** **SS** **Fewer C. diff infections with PPI**
Garzotto *et al*. 2015(236) Case-control	Europe Multicenter, inpatient setting	n= 225	PPI vs NA	**OR 0.4 (95%CI: 0.2-0.8)** **SS** **Fewer C. diff infections with PPI**
Hebbard *et al*. 2017(237) Case-control	Asia Unicenter, inpatient setting Mean age: 59.7	n= 200	PPI vs NA	OR 2.4 (95%CI: 1.0-5.7) NS
Hensgens *et al*. 2011(238) Case-control	Europe Unicenter, inpatient setting	n= 169	PPI vs NA	OR 1.1 (95%CI: 0.5-2.5) NS
Howell *et al*. 2010(239) Cohort study	America Unicenter, inpatient setting Mean age: 65.4	n= 101796	PPI vs no PPI	**OR 1.7 (95%CI: 1.3-2.1)** **SS** **More C. diff infections with PPI**
Ingle *et al*. 2011(240)	Asia Unicenter, Mixt	n= 99	PPI vs no PPI	OR 1.8 (95%CI: 0.4-7.4) NS

Cohort study	setting Mean age: 47			
Ingle *et al*. 2013(241) Case-control	Asia Unicenter, community setting Mean age: 45.3	n= 150	PPI vs NA	OR 2.3 (95%CI: 0.6-9.2) NS
Jayatilaka *et al*. 2007(242) Case-control	America Unicenter, inpatient setting	n= 366	PPI vs NA	**OR 2.7 (95%CI: 1.6-4.8)** **SS** **More C. diff infections with PPI**
Kazakova *et al.* 2006(243) Case-control	America Unicenter, Mixt setting	n= 195	PPI vs NA	**OR 5.0 (95%CI: 1.3-19.3)** **SS** **More C. diff infections with PPI**
Khan *et al*. 2012(244) Cohort study	Asia Unicenter, inpatient setting	n= 123	PPI vs no PPI	**OR 3.2 (95%CI: 1.2-8.5)** **SS** **More C. diff infections with PPI**
Khanafer *et al*. 2013(245) Cohort study	Europe Unicenter, inpatient setting	n= 40	PPI vs no PPI	OR 2.5 (95%CI: 0.6-9.6) NS
Kuntz *et al.* 2011(246) Case-control	America Unicenter, Mixt setting	n= 3344	PPI vs NA	**OR 1.6 (95%CI: 1.1-2.2)** **SS** **More C. diff infections with PPI**
Kutty *et al*. 2010(247) Case-control	America Multicenter, outpatient setting Mean age: 62	n= 144	PPI vs NA	OR 1.7 (95%CI: 0.7-4.0) NS
Lewis *et al*. 2016(248) Cohort study	America Unicenter, inpatient setting	n= 41663	PPI vs no PPI	**OR 6.4 (95%CI: 3.6-11.5)** **SS** **More C. diff infections with PPI**
Lin *et al*. 2013(249)	Asia	n= 86	PPI vs NA	**OR 10.1 (95%CI: 1.2-87.4)**

Case-control	Unicenter, inpatient setting Mean age: 59			**SS** **More C. diff infections with PPI**
Linney *et al*. 2010(250) Case-control	America Unicenter, inpatient setting	n= 284	PPI vs NA	**OR 2.4 (95%CI: 1.4-4.3)** **SS** **More C. diff infections with PPI**
Loo *et al*. 2005(251) Case-control	America Unicenter, Inpatient setting	n= 474	PPI vs NA	OR 1.0 (95%CI: 0.7-1.4) NS
Loo *et al*. 2011(252) Cohort study	America Multicenter, Inpatient setting Mean age: 67.4	n= 4143	PPI vs no PPI	**OR 2.6 (95%CI: 1.7-4.0)** **SS** **More C. diff infections with PPI**
Lowe *et al*. 2006(253) Case-control	America Multicenter, Inpatient setting Mean age: 78.7	n= 13692	PPI vs NA	OR 0.9 (95%CI: 0.7-1.0) NS
McFarland *et al*. 2007(254) Case-control	America Multicenter, Mixt setting	n= 368	PPI vs NA	OR 0.8 (95%CI: 0.5-1.4) NS
Mizui *et al*. 2013(255) Case-control	Asia Multicenter, Inpatient setting Mean age: 71.7	n= 2716	PPI vs NA	**OR 3.2 (95%CI: 1.4-7.3)** **SS** **More C. diff infections with PPI**
Modena *et al*. 2005(256) Case-control	America Unicenter, Inpatient setting	n= 250	PPI vs NA	**OR 3.3 (95%CI: 1.6-6.8)** **SS** **More C. diff infections with PPI**
Mori *et al*. 2015(257)	Asia Unicenter,	n= 78	PPI vs NA	OR 0.4 (95%CI: 0.1-2.0) NS

Case-control	outpatient setting Mean age: 58.2			
Muto *et al*. 2005(258) Case-control	America Multicenter, Inpatient setting	n= 406	PPI vs NA	**OR 2.4 (95%CI: 1.3-4.4)** **SS** **More C. diff infections with PPI**
Pakyz *et al*. 2014(259) Case-control	America Multicenter, Inpatient setting	n= 14164	PPI vs NA	**OR 1.4 (95%CI: 1.3-1.5)** **SS** **More C. diff infections with PPI**
Peled *et al*. 2007(260) Cohort study	America Unicenter, Inpatient setting	n= 217	PPI vs no PPI	**OR 3.7 (95%CI: 1.5-9.3)** **SS** **More C. diff infections with PPI**
Pepin *et al*. 2005(261) Cohort study	America Unicenter, Inpatient setting	n= 5619	PPI vs no PPI	OR 1.0 (95%CI: 0.7-1.2) NS
Ro *et al*. 2016(262) Cohort study	Asia Unicenter, Inpatient setting Mean age: 64.8	n= 1005	PPI vs no PPI	**OR 3.3 (95%CI: 1.5-7.2)** **SS** **More C. diff infections with PPI**
Roughead *et al*.(263) 2016 Cohort study	Asia Multicenter, Mixt setting	n= 54957	PPI vs no PPI	**OR 2.4 (95%CI: 1.9-3.1)** **SS** **More C. diff infections with PPI**
Shah *et al*. 2000(264) Case-control	Europe Unicenter, inpatient setting	n= 252	PPI vs NA	OR 0.8 (95%CI: 0.4-1.5) NS
Southern *et al*. 2010(265)	Europe Multicenter,	n= 3904	PPI vs no PPI	**OR 2.3 (95%CI: 1.1-4.5)** **SS**

Cohort study	inpatient setting Mean age: 65.5			**More C. diff infections with PPI**
Vesteinsdottir *et al*. 2012(266) Case-control	Europe Multicenter, Mixt setting	n= 333	PPI vs NA	OR 1.6 (95%CI: 1.0-2.6) NS
Yang *et al*. 2011(267) Case-control	Asia Multicenter, Inpatient setting Mean age: 67.12	n=1420	PPI vs NA	**OR 1.9 (95%CI: 1.3-2.7)** **SS** **More C. diff infections with PPI**
Yearsley *et al.* 2006(268) Case-control	Europe Unicenter, inpatient setting Mean age: 79.1	n= 308	PPI vs NA	**OR 1.9 (95%CI: 1.1-3.2)** **SS** **More C. diff infections with PPI**
Yip *et al*. 2001(269) Case-control	America Unicenter, Inpatient setting	n= 54	PPI vs NA	OR 3.0 (95%CI: 0.8-11.1) NS

Table 156

The following studies were not included in the above SRs/MAs

Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoints**	**Results**

Wei L 2017(182) Cohort study	UK Community setting + hospital setting Persons on **PPI or H2RA** Mean follow-up: 10 years; 5 729 743 person-years follow up time	n= 552 153; 149636 stool tests from which 22 705 were positive. PPI/H2RA: n= 188 323 Control cohort: n=376 646	Clostridium difficile infection (The primary outcome of this study was bacterial gastroenteritis defined as the composite of a positive stool test for C. difficile, Campylobacter, Salmonella, Shigella or E. coli O157. Only results for C. difficile are presented here)	15 273 C. Difficile infections C. difficile accounted for 92% of positive stool cases in hospitals and 27% of tested positive cases in the community. Community samples: **HR 1.70 (95%CI: 1.28-2.25), SS** **More C. diff infections with PPI** Hospital samples: **HR 1.42 (95%CI: 1.17-1.71), SS** **More C. diff infections with PPI** Censored at first admission (sensitivity analysis due to a very large risk associated with hospitalization): **HR 2.00 (95%CI: 1.25-3.19)** **SS More C. diff infections with PPI** **Results separately mentioned for PPI and H2RA:** High dose PPI: HR 0.97 (95%CI: 0.84-1.12), **NS** Low dose PPI: HR 0.94 (95%CI: 0.78-1.14), **NS** High dose H2RA: HR 1.24 (95%CI: 0.92-1.67), **NS** Low dose H2RA: HR 1.32 (95%CI: 0.91-1.93), **NS**

Table 157

20.1.5.2 *Other gastro-intestinal infections*

Bavishi C 2011(181) (4 studies)	country population follow-up	n	comparison	Main results **Outcome: non-typhoid Salmonella gastroenteritis**
Garcia R 1997(270)	NR	374 cases and 2000 controls	PPI Vs	The article established CI for bacterial diarrhoea, not specifically for the subgroup with Salmonella infection.

Nested case–control study			No PPI	A relative risk of 1.6 (95%CI: 1.0–2.4) was reported between PPI use and bacterial gastroenteritis in general. Among the 374 total diarrhoea cases in the study, 136 (36.4%) cases were caused by Salmonella.
Doorduyn Y 2006(271) case–control study	NR	167 S. enteritidis, 193 S. typhimurium cases and 3119 controls	PPI Vs No PPI	S. enteritidis:**OR 4.2 (95%CI: 2.2–7.9); SS more infections in PPI** S. typhimurium: **OR 8.3 (95%CI: 4.3–15.9); SS more infections in PPI** Population attributable risk was also observed to be very high for PPIs.
Garcia R 2007(272) case–control study	NR	6414 cases and 50 000 controls	PPI Vs No PPI	The article established CI for bacterial diarrhoea, not for the subgroup with Salmonella. A relative risk of **2.9 (95%CI: 2.5–3.5)** was reported between PPI use and bacterial gastroenteritis in general. Among the 6414 total diarrhoea cases in the study, 1885 (29.4%) cases were caused by Salmonella.
Doorduyn Y 2008(273) Nested case–control study	NR	573 cases and 3409 controls	PPI Vs No PPI	**OR 4.3 (95%CI 2.9–6.5); SS more infections in PPI** The association was reported for PPI use and recurrent cases of Salmonella gastroenteritis.

Table 158

Bavishi C 2011(181) (4 studies)	country population follow-up	n	comparison	Main results **Outcome: Campylobacter jejuni**
Neal KR et 1996(274) case–control study	NR	211 cases and 422 controls	PPI Vs No PPI	**RR or OR 11.7 (95%CI: 2.5–54.0)** **SS more infections in PPI** Omeprazole use within 1 month before infection showed the strongest association.
Neal KR 1997(275) case–control study	NR	313 cases and 512 controls	PPI Vs No PPI	**3.5 (95%CI: 1.1–12.0)** **SS more infections in PPI** Foreign travel explained 25% of cases of Campylobacter diarrhoea
Garcia R 1997(270)	NR	374 cases and	PPI	The article established CI for bacterial diarrhoea, not for the subgroup with

Nested case–control study		2000 controls	Vs No PPI	Campylobacter. A relative risk of 1.6 (1.0–2.4) was reported between PPI use and bacterial gastroenteritis in general. Among the 374 total diarrhoea cases in the study, 201 (53.7%) cases were caused by Campylobacter.
Garcia R 2007(272) case–control study	NR	6414 cases and 50 000 controls	PPI Vs No PPI	The article established CI for bacterial diarrhoea, not for the subgroup with Campylobacter. A relative risk of **2.9 (95%CI: 2.5–3.5)** was reported between PPI use and bacterial gastroenteritis in general. Among the 6414 total diarrhoea cases in the study, 4124 (64.3%) cases were caused by Campylobacter.
Doorduyn Y 2008(273) case–control study	NR	1446 cases and 3409 controls	PPI Vs No PPI	**OR 4.5 (95%CI: 3.3–6.1)** **SS more infections in PPI** PPI use and recurrent cases of Campylobacter gastroenteritis were Associated.
Doorduyn Y 2010(276) case–control study	NR	1,019 cases and 3119 controls	PPI Vs No PPI	**OR 4.3 (95%CI: 2.9–6.2);** **SS more infections in PPI** For elderly patients, the OR was observed to be **2.9 (95%CI: 1.5–5.7)**. **SS more infections in PPI**

Table 159

The following studies were not included in the above SRs/MAs

Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoint**	**Results**

Brophy S 2013(185) Retrospective cohort study	Patients who visited the general practitioner in Wales between 1990 and 2010. Average age PPI pts: 58.05 (SD 16.7) Average age non-PPI pts: 51.04 (SD 19.6) Mean follow up: 2 years (12-month period before PPI and 12-month period post PPI)	n= 1913925 PPI: n= 358938 Non-PP: n= 1523828	Campylobacter infection following a PPI prescription	PPI patients Exposed (post PPI prescription) vs Non-exposed (before PPI prescription): **HR 1.46 (95%CI: 1.29-1.65); SS** Non-PPI patients Years '90-'91 vs years '91-'92: HR 1.061 (95%CI: 0.73-1.53); **NS** Years '08-'09 vs years '09-'10: **HR 1.58 (95%CI: 1.26-1.97); SS** Patients matched for date Before start PPI: PPI vs no PPI: **HR 6.91 (95%CI: 5.16-9.26); SS** After start PPI: PPI vs no PPI: **HR 9.50 (95%CI: 7.4-12.2); SS** Analysis taking into account unmeasured confounders: PERR*: 1.17 (95%CI: 0.74-1.61); **NS**
*PERR: Prior Event Rate Ratio. This method assumes that the HR of the exposed to unexposed for a specific outcome before the start of the study reflects the combined effect of all confounders (both measured and unmeasured) independent of any influence of the treatment. To apply the PERR adjustment method, the authors divided the unadjusted HR of date-matched exposed group versus date-matched unexposed group after PPI prescription by the unadjusted hazard ratio of exposed versus unexposed ' before ' prescription.				
			Salmonella infection following a PPI prescription	PPI patients Exposed (post PPI prescription) vs Non-exposed (before PPI prescription): HR 1.2 (95%CI: 0.84-1.9); **NS** Non-PPI patients Years '90-'91 vs years '91-'92: HR 0.95 (95%CI: 0.62-1.5); **NS** Years '08-'09 vs years '09-'10: HR 1.04 (95%CI: 0.68-1.59); **NS** Patients matched for date Before start PPI: PPI vs no PPI: **HR 3.1 (95%CI: 1.7-5.7); SS** After start PPI: PPI vs no PPI: **HR 3.1 (95%CI: 1.82-5.3); SS** Analysis taking into account unmeasured confounders: PERR*: 1.00 (95%CI: 0.5-1.5); **NS**

Table 160

Ref Study type	Setting Population	number of participants	Endpoint	Results

Hassing RJ 2016(184) Prospective population-based cohort study	Community-dwelling > 45 years Rotterdam 24 years of follow-up Age pts with positive stool sample: 65.1 (SD 10.3) Age pts with negative stool sample: 68.1 (SD 12.8)	n= 14926 1299 eligible stool samples were available with 125 positive cultures: 105 (84.0 %) Campylobacter, 16 (12.8 %) Salmonella, 3 (2.4 %) Yersinia, 1 (0.8 %) Shigella sonnei	Bacterial gastroenteritis (Campylobacter, Salmonella, Yersinia or Shigella species)	PPI vs no PPI in patients with stool samples: **OR 1.94 (95%CI: 1.15-3.25); p= 0.013; SS** (adjusted for sex, age, cohort, calendar date, past use of PPI, current use of chronic medication, past use of H2RA) Sensitivity analyses included: Campylobacter only: **OR 1.93 (95CI: 1.11-3.36); p=0.019; SS** Campylobacter and Salmonella: **OR 2.05 (1.20-3.49); p=0.008); SS** Additional analysis: Matched case-control analysis, using all participants of the study: **OR 6.14 (95%CI: 3.81-9.91); p<0.001; SS**

Table 161

Ref Study type	Setting Population	number of participants	Endpoint	Results
Wei L 2017(182) Cohort study	UK Community setting + hospital setting Persons on **PPI or H2RA** between 1999 and 2013 5,7 million person-years follow up time	n= 552 153; 149636 stool tests from which 22 705 were positive (6590 Campylobacter, 852 Salmonella) PPI/H2RA: n= 188 323 Control cohort: n=376 646	Campylobacter infection (The primary outcome of this study was bacterial gastroenteritis defined as the composite of a positive stool test for C. difficile, Campylobacter, Salmonella, Shigella or E. coli O157. Only results for Campylobacter are presented here)	Community samples: **HR 3.71 (95%CI: 3.04-4.53); SS** Hospital samples: **HR 4.53 (95%CI: 1.75-11.8); SS** Censored at first admission (sensitivity analysis due to a very large risk associated with hospitalization): **HR 3.76 (95%CI: 3.05-4.64)** **Results separately mentioned for PPI and H2RA:** High dose PPI: HR 1.00 (95%CI: 0.88-1.14), **NS** Low dose PPI: **HR 0.79 (95%CI: 0.66-0.93), SS** High dose H2RA: HR 0.97 (95%CI: 0.51-1.24), **NS** Low dose H2RA: HR 1.01 (95%CI: 0.55-1.86), **NS**
			Salmonella infection (The primary outcome of this study was bacterial gastroenteritis defined as the composite of a positive stool test for C. difficile, Campylobacter, Salmonella, Shigella or E. coli O157. Only results for Salmonella are presented here.)	There were too few cases of Salmonella to allow an individual analysis.

Table 162

20.1.6 Gastric cancer

Ref Study type	Setting Population	number of studies	Endpoints	Results
Tran-Duy et al. 2016(186) Design: SR and meta-analysis Search date: (Jul-2015)	PPI users and PPI nonusers H. pylori infection status was not considered for adjustment in any of the studies	N= 3 n= 20910 (Garcia Rodriguez et al. 2006; Tamim et al. 2008; Poulsen et al. 2009)	**Gastric cancer** Exposure time: PPI use < 12 months PPI use ≥ 12 months PPI use ≥ 36 months:	**RR 1.43 (1.23 - 1.66)** **SS;** more events in PPI users **RR 1.76 (1.24 - 2.52)** **SS;** more events in PPI users RR 1.31 (0.79 - 2.19) **NS** **RR 2.45 (1.41 -4.25)** **SS;** more events in PPI users

Table 163

references included in the above SR's	country population follow-up	n	comparison	Main results
Garcia Rodriguez et al. 2006(277) Nested case-control; retrospective;	United Kingdom For both cases and control subjects: patients aged 40–84 years, enrolled with a general practitioner for at least 2 years, having at least one year of prescription history recorded in the database, and with no history of cancer. Exposure time PPI: 3 groups, <year, 1–3 years, and >3 years	522 cases and 10 000 control subjects	PPI vs no PPI PPI use: < 12 months ≥ 12 months PPI use: < 12 months ≥ 12 months ≥ 36 months	**<u>Gastric cardia adenocarcinoma</u>** OR: 1.06 (0.57-1.99) **NS** OR: 1.42 (0.72-2.81); **NS** OR: 0.72 (0.22-2.39); **NS** **<u>Gastric non-cardia adenocarcinoma</u>** **OR: 1.75 (1.10-2.79)** **SS;** more events in PPI users OR: 1.67 (0.96-2.90); **NS** OR: 1.61 (0.71-3.63); **NS** OR: 2.95 (0.97-7.97); **NS**
Tamim et al. 2008(278) Nested case-control; retrospective;	Canada All people living in Quebec, eligible for outpatient prescription drug benefits for at least 5 years, and with no history of cancer PPI users in cases: 248 PPI users in control subjects: 402	1598 cases and 12991 control subjects	PPI vs no PPI	**<u>Gastric cancer</u>** **OR: 1.46 (1.22-1.74)** **SS;** more events in PPI users

	Exposure time not reported			
Poulsen et al. 2009(279) Population-based cohort; retrospective;	Denmark Mean age: 62. Patients aged 40–84 years without a history of cancer (except nonmelanoma skin cancer); for patients receiving PPIs, only new users were included (ie, all patients prescribed PPIs during 1989 [the year before the index date] or before 40 years old were excluded) Helicobacter pylori infection prevalence: not available; 13% underwent H Pylori eradication therapy Duration of exposure: 4 groups: <1 year, 1 year, 2–4 years and >5 years	PPI: 18790 No PPI: not reported	PPI vs no PPI PPI use: < 12 months 12 months 24-48 months ≥ 60 months	**<u>Gastric cancer</u>** OR: 1.20 (0.76-1.90) **NS** **OR: 2.30 (1.22-2.35); SS** OR: 0.80 (0.23-23.77); **NS** OR: 0.50 (0.19-1.32); **NS** **OR: 2.30 (1.22-4.35); SS**

Table 164

The following studies were not included in the above SRs/Mas

Ref Study type	Setting Population	number of participants	Endpoints	Results
Brusselaers et al. 2017(187) Nationwide population-based cohort study	Sweden Patients with a maintenance treatment: ≥ 6 months PPI or H2RA estimated exposure PPI cohort: 58.5% women; 66.1% < 70 years. Indication for PPI use*: Aspirin: 34.8%; NSAIDs: 30.4%; GORD: 25.3%; gastroduodenitis: 13.2%; peptic ulcer: 10.0%; H. Pylori: 7.3%; dyspepsia: 5.5%; Barrett <1%.	PPI users: 797067 Vs Swedish background population of the same sex, age and calendar period (7.1–7.6 million adults)	**Gastric cancer** Duration of PPI use: < 1.0 year 1.0-2.9 years 3.0-4.9 years ≥ 5.0 years Sensitivity analysis for protopathic bias (reverse causality)	2219 (0.28%) events vs 5821 events (% not reported) **Standardised incidence ratio (SIR)** **SIR 3.38 (3.25-3.53)** **SS;** more events in PPI users **SIR 12.82 (12.19-13.47)** **SS;** more events in PPI users **SIR 2.19 (1.98-2.42)** **SS;** more events in PPI users SIR 1.10 (0.91-1.31) **NS** SIR 0.61 (0.52-0.72) **NS** Excluding cancer cases <1 year after start study: **SIR 1.61 (1.51-1.71); SS**
	FU PPI users: 3 866 836 person-years (mean 4.9 years)		**Gastric adenocarcinoma**	**SIR 3.38 (3.23-3.53)** **SS;** more events in PPI users
			Cardia cancer	**SIR 3.55 (3.27-3.86)** **SS;** more events in PPI users
			Non-cardia gastric cancer	**SIR 3.33 (3.17-3.50)** **SS;** more events in PPI users
		H2RA-only group (n=20210)	**Gastric cancer**	12 (0.06%) events in H2RA cohort SIR 0.57 (0.29-0.99) **SS** fewer events in H2RA-only group
		Patients on H2RA + PPI (n=25726)	**Gastric cancer**	62 (0.24%) events in PPI/H2RA cohort **SIR 2.09 (1.61-2.69)** **SS;** more events in H2RA/PPI users

Standardised incidence ratios (SIRs) and 95% CIs were calculated by dividing the observed number of gastric cancer cases with the expected number, accounting for changes in age and calendar categories.
*Confounding by indication was evaluated with subgroup analyses for each indication. The highest SIRs for gastric cancer were found in patients with H. pylori (SIR 9.76 (8.87-10.71) and peptic ulcer (SIR 8.75 (8.12-9.41). Increased SIRs were also observed for indications not associated with increased gastric cancer risk (indication: aspirin and NSAID). Furthermore, the SIR was higher in younger ages: <40 years: SIR 22.76 (15.94-31.52); >70 years: SIR 2.76 (2.61-2.92)

Table 165

Ref Study type	Setting Population	number of participants	Endpoints	Results
Cheung et al. 2018(188) Study based on a territory-wide health database	Hong Kong Patients who received clarithromycin-based triple therapy for H. Pylori infection in outpatient clinics PPI prescriptions in the 6 m onths preceding gastric cance r diagnosis were excluded to avoid protopathic bias. Median age PPI users: 64.1 Median age non-PPI users: 54.3	**Total: 63397** Median FU: 7.6 years (IQR 5.1-10.3); 483260 person-years **PPI users: 3271** Median FU: 7.4 years (IQR 4.5-10.0) **Non-PPI users: 60126** Median FU: 7.6 years (IQR 5.2-10.2)	**Gastric adenocarcinoma** Frequency PPI use: Non-user (<weekly) Weekly to < daily Daily Duration PPI use: **≥ 1 year** Weekly to < daily PPI use Daily PPI use **≥ 2 years** Weekly to < daily PPI use Daily PPI use **≥ 3 years** Weekly to < daily PPI use Daily PPI use	153 events (0.24%) in PPI cohort **HR 2.44 (1.42-4.20); p= 0.002** **SS;** more events in PPI users Ref **HR 2.43 (1.37-4.31); p=0.002** **HR 4.55 (1.12-18.52); p=0.034** Non-user: reference HR 1.81 (0.90-3.64); p=0.098 **HR 5.04 (1.23-20.61); p=0.024** HR 0.98 (0.31-3.17); p=0.979 **HR 6.65 (1.62-27.26); p=0.009** HR 0.58 (0.08-4.23); p=0.590 **HR 8.34 (2.02-34.41); p=0.004**
			No-cardia gastric cancer	**HR 2.59 (1.42-4.72); p= 0.002** **SS;** more events in PPI users
			Cardia gastric cancer	HR 1.97 (0.57-6.82); p= 0.286 **NS**
		Total: 63397 H2RA users: 21729 Non-H2RA users: 41668	**Gastric cancer**	HR 0.72 (0.48-1.07) **NS**

Table 166

Ref Study type	Setting Population	number of participants	Endpoints	Results
Niikura et al. 2018(189) Retrospective subgroup analysis	Tokyo Patients who received H. Pylori eradication; 51% ≥ 60 years; 56% male	Total: 571 PPI users: 118 Non-PPI users: 415	**Gastric cancer**	13/118 (11.0%) vs 8/415 (1.9%) **HR 3.61 (1.49-8.77); p=0.005** **SS; more events in PPI users**
	Mean FU: 6.9 years Mean PPI use: 1.3 years Mean H2RA use: 2.3 years	H2RA users: 38 Non-H2RA users: 415	**Gastric cancer**	3/35 (8.6%) vs 8/415 (1.9%) HR 2.65 (0.69-10.2); p=0.155 **NS**

Table 167

20.1.7 Fractures

Ref Study type	Setting Population	number of studies	Endpoints	Results
Zhou 2016(190) SR + MA of observational studies (case-control and cohort studies) search date: February 2015	**PPI use** **vs** **no PPI use**	**18 studies** 9 cohort studies 9 case-control	**Hip fracture** stratified analysis including cohort studies only (6 studies) (Yu 2008a, Yu 2008b, Gray 2010, Khalili 2012, Fraser 2013, Ding 2014)	PPI-users vs non-PPI users **RR=1.24 (95 % CI 1.06 to1.45)** **SS more hip fracture in PPI users**

			Spine fracture (4 studies) (Vestergaard 2006, Roux 2009, Gray 2010, Ding 2014)	PPI-users vs non-PPI users **RR 1.58 (95%CI 1.38 to 1.82)** **SS more spine fracture in PPI users**
			Any-site fractures (10 studies) (Vestergaard 2006, Targownik 2008, Yu 2008a, Yu 2008b, Roux 2009, Gray 2010, Fraser 2013, Moberg 2014, Lewis 2014, Ding 2014)	PPI-users vs non-PPI users **RR 1.33 (95%CI 1.15 to 1.54)** **SS more any-site fracture in PPI users** Duration of PPI use **<1 year of PPI use** **1.25 (1.14 to 1.37)** **SS** **>1 year of PPI use** **1.27 (1.16 to 1.38)** **SS**

Table 168

references included in the above SR Zhou 2016(190) (SR)	country population follow-up	n	Main results
Yu 2008a(280) cohort study	USA Community-dwelling women >65 y	5 339	Hip: RR 1.16 (0.80 to 1.67)
Yu 2008b(280) cohort study	USA Men >65 y	5 755	Hip: RR 0.62 (0.26 to 1.44)
Roux 2009(281) cohort study	Europe 55-79y Post-menopausal women	1 211	**Spine: RR 3.10 (1.14 to 8.44)**

Gray 2010(282) cohort study	USA 50-79y Post-menopausal women	130 487	**Any: RR 1.25 (1.15 to 1.36)** Hip: RR 1.00 (0.71 to 1.40) **Spine: RR 1.47 (1.18 to 1.82)**
Khalili 2012(283) cohort study	USA Postmenopausal women registered in the Nurses' Health study Mean age 67 y	79 899	**Hip: RR 1.36 (1.13 to 1.63)**
Fraser 2013(284) cohort study	Canada >25 y (mean 62-68 y) Community-dwelling men and women	9423	**Any: RR 1.40 (1.11 to 1.76)** Hip: RR 1.75 (0.94 to 3.26)
Moberg 2014(285) cohort study	Sweden 60-70y Postmenopausal women	6416	**Any: RR 2.53 (1.28 to 4.99)**
Lewis 2014(286) cohort study	Australia mean 79.9y Elderly (>70y) postmenopausal women	1025	**Any: RR 2.17 (1.25 to 3.77)**
Ding 2014(287) cohort study	USA >65 y Elderly men and women	25 576	**Any: RR 1.27 (1.12 to 1.43)** **Hip: RR 1.32 (1.01 to 1.71)** **Spine: RR 1.69 (1.26 to 2.27)**
Yang 2006(288)	*case-control study; did not meet our inclusion criteria*		
Vestergaard 2006(289)	*case-control study; did not meet our inclusion criteria*		
Targownik 2008(290)	*case-control study; did not meet our inclusion criteria*		

Corley 2010(291)	*case-control study; did not meet our inclusion criteria*
Chiu 2010(292)	*case-control study; did not meet our inclusion criteria*
Pouwels 2011(293)	*case-control study; did not meet our inclusion criteria*
Reyes 2013(294)	*case-control study; did not meet our inclusion criteria*
Soriano 2014(295)	*case-control study; did not meet our inclusion criteria*
Adams 2014(296)	*case-control study; did not meet our inclusion criteria*

Table 169

The following studies were not included in the above SRs/MAs

Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoints**	**Results**
van der Hoorn 2015(191) prospective cohort average follow-up 6.6 years	**Australia** **Elderly women, birth year 1921 to 1926**	**4432**	**Fractures**	PPI users vs non-PPI users **Adj. sub-HR 1.29 (95% CI 1.08 to 1.55)** **SS; more fractures in PPI users**

Table 170

Ref **Study type**	**Setting** **Population**	**number of participants**	**Endpoints**	**Results**
Chen 2016(192) retrospective cohort follow-up: mean 3.45 y	**GORD patients with PPI use; matched with cohort from general population**	**10 620 (+ 20 738 matched)**	**Hip fracture**	PPI users vs non-PPI users Adj. HR 0.79 (95 % CI 0.53 to1.18) NS

Table 171

Ref Study type	Setting Population	number of participants	Endpoints	Results
Lin 2018(193) retrospective cohort follow-up: mean 4.8 years	**Patients diagnosed with a new stroke** **Taiwan**	**10 596**	**Hip fracture**	PPI users vs non-PPI users **Adj. HR 1.18 (95%CI 1.00 to 1.38)** **p<0.001** **SS; more hip fracture in PPI users**
			Vertebral fracture	PPI users vs non-PPI users **Adj. HR 1.33 (95%CI 1.14 to 1.54)** **p<0.001** **SS; more vertebral fracture in PPI users**

Table 172

21 Appendix 1: Search strategy details

21.1 Dyspepsia, GORD, Oesophagitis and Barrett's oesophagus

(pyrosis*[TIAB] OR GORD[TIAB] OR GERD[TIAB] OR NERD[TIAB] OR ENRD[TIAB] OR reflux*[TIAB] OR Heartburn*[TIAB] OR dyspeps*[TIAB] OR "Gastroesophageal Reflux"[Mesh] OR "Heartburn"[Mesh] OR "Dyspepsia"[Mesh] OR esophagitis[TIAB] OR oesophagitis[TIAB] OR "Esophagitis"[Mesh] OR Barrett*[TIAB] OR "Barrett Esophagus"[Mesh])
AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("0000"[Date - Publication] : "2018/01/01"[Date - Publication])

21.2 Deprescribing

("Deprescriptions"[Mesh] OR deprescri*[TIAB] OR de-prescri*[TIAB] OR unprescri*[TIAB] OR cease*[TIAB] OR ceasing*[TIAB] OR cessation*[TIAB] OR withdraw*[TIAB] OR discontinu*[TIAB] OR stop* OR intermittent[TIAB] OR "on demand"[TIAB])
AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2016/10/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.3 Gastroprotection

("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Aspirin"[Mesh] OR aspirin*[TIAB] OR acetylsalicyl*[TIAB] OR Non-steroidal*[TIAB] OR NSAI*[TIAB] OR Aceclofenac OR Diclofenac*[TIAB] OR Ketorolac*[TIAB] OR Dexketoprofen*[TIAB] OR Ibuprofen*[TIAB] OR Ketoprofen*[TIAB] OR Naproxen*[TIAB] OR Oxaprozin*[TIAB] OR Indometacin*[TIAB] OR Proglumetacin*[TIAB] OR Meloxicam*[TIAB] OR Piroxicam*[TIAB] OR Tenoxicam*[TIAB] OR Celecoxib*[TIAB] OR Etoricoxib*[TIAB] OR Parecoxib*[TIAB] OR Nabumeton*[TIAB] OR clopidogrel[TIAB] OR gastroprotect*[TIAB])

AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2013/10/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.4 Adverse events

21.4.1 Cardiovascular events

("Cardiovascular Diseases"[Mesh]OR myocard*[TIAB] OR corona*[TIAB] OR cardi*[TIAB] OR cerebrovasc*[TIAB] OR stroke[TIAB])

AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
("Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2013/11/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.4.2 Fractures

("Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR osteoporo*[TIAB] OR fractu*[TIAB])
AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
("Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2015/01/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.4.3 Dementia

("Dementia"[Mesh] OR dementia*[TIAB])
AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
("Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2016/05/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.4.4 Community-acquired pneumonia

("Pneumonia"[Mesh] OR pneumoni*[TIAB] OR CAP[TIAB])
AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
("Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2014/01/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.4.5 Clostridium infection

("Clostridium Infections"[Mesh] OR clostridium*[TIAB] OR difficile*[TIAB])
AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
("Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2017/02/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.4.6 Salmonella and campylobacter infections

("Campylobacter Infections"[Mesh] OR "Salmonella Infections"[Mesh] OR campylobact*[TIAB] OR salmonell*[TIAB])
AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
("Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2011/04/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.4.7 Acute and chronic kidney disease

("Acute Kidney Injury"[Mesh]) OR "Kidney Failure, Chronic"[Mesh] OR "Renal Insufficiency, Chronic"[Mesh] OR "Nephritis, Interstitial"[Mesh] OR kidney[TIAB] OR renal[TIAB] OR nephr*[TIAB])
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
("Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2016/09/01"[Date - Publication] : "2018/01/01"[Date - Publication])

21.4.8 Gastric cancer

("Neoplasms"[Mesh] OR neoplas*[TIAB] OR cancer*[TIAB] or malign*[TIAB])
AND
(proton pump inhibit*[TIAB] OR omeprazol*[TIAB] OR rabeprazol*[[TIAB] OR lansoprazol*[TIAB] OR esomeprazol*[TIAB] OR pantoprazol*[TIAB] OR "Proton Pump Inhibitors"[Mesh] OR "Omeprazole"[Mesh] OR "Rabeprazole"[Mesh] OR "Lansoprazole"[Mesh] OR "Esomeprazole"[Mesh])
AND
("Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2015/06/01"[Date - Publication] : "2018/01/01"[Date - Publication])

22 Appendix 2: List of excluded publications

The following publications were excluded after reviewing the full text. The reason for exclusion is stated in **bold.**

22.1 Dyspepsia

no exclusions

22.2 GORD

1. Al Talalwah N, Woodward S. Gastro-oesophageal reflux. Part 2: medical treatment. Br J Nurs 2013;22:277-84.**n; other SR selected**
2. Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. Surg Endosc 2011;25:2547-54.**n; older than included SR**
3. Asghar W, Pittman E, Jamali F. Comparative efficacy of esomeprazole and omeprazole: Racemate to single enantiomer switch. Daru 2015;23:50.**n; more up to date SR selected**
4. Bayerdorffer E, Bigard MA, Weiss W, et al. Randomized, multicenter study: on-demand versus continuous maintenance treatment with esomeprazole in patients with non-erosive gastroesophageal reflux disease. BMC Gastroenterol 2016;16:48.**n; open label**
5. Bell RC. Randomized Controlled Trial of Transoral Incisionless Fundoplication Vs. Proton Pump Inhibitors for Treatment of Gastroesophageal Reflux Disease. Am J Gastroenterol 2015;110:1621-3.**n; commentary**
6. Bello B, Herbella FA, Allaix ME, et al. Impact of minimally invasive surgery on the treatment of benign esophageal disorders. World J Gastroenterol 2012;18:6764-70.**n; not an SR**
7. Boardman HF, Delaney BC, Haag S. Partnership in optimizing management of reflux symptoms: a treatment algorithm for over-the-counter proton-pump inhibitors. Curr Med Res Opin 2015;31:1309-18.**n; full text not found**
8. Bytzer P, van Zanten SV, Mattsson H, et al. Partial symptom-response to proton pump inhibitors in patients with non-erosive reflux disease or reflux oesophagitis - a post hoc analysis of 5796 patients. Aliment Pharmacol Ther 2012;36:635-43.**n; post hoc**
9. Casale M, Sabatino L, Moffa A, et al. Breathing training on lower esophageal sphincter as a complementary treatment of gastroesophageal reflux disease (GERD): a systematic review. Eur Rev Med Pharmacol Sci 2016;20:4547-52.**n; comparison**
10. Cohen H, Tomasso G, Luisa Cafferata M, et al. Latin american consensus on gastroesophageal reflux disease: an update on therapy. Gastroenterol Hepatol 2010;33:135-47.**n; publication type**
11. Coyle C, Crawford G, Wilkinson J, et al. Randomised clinical trial: addition of alginate-antacid (Gaviscon Double Action) to proton pump inhibitor therapy in patients with breakthrough symptoms. Aliment Pharmacol Ther 2017;45:1524-33.**n; comparison**
12. Cremonini F, Ziogas DC, Chang HY, et al. Meta-analysis: the effects of placebo treatment on gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2010;32:29-42.**n; comparison**
13. D'Cunha J, Andrade RS, Maddaus MA. Surgical management of gastroesophageal reflux disease/Barrett's esophagus. Minerva Chir 2011;66:7-19.**n; not an SR**
14. Eherer A. Management of gastroesophageal reflux disease: lifestyle modification and alternative approaches. Dig Dis 2014;32:149-51.**n; not an sr**
15. El-Serag H, Becher A, Jones R. Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. Aliment Pharmacol Ther 2010;32:720-37.**n; comparison**
16. Emken BG, Lundell LR, Wallin L, et al. Effects of omeprazole or anti-reflux surgery on lower oesophageal sphincter characteristics and oesophageal acid exposure over 10 years. Scand J Gastroenterol 2017;52:11-7.**n; open surgery only; secondary analysis**
17. Fass R, Cahn F, Scotti DJ, et al. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. Surg Endosc 2017.**n; intervention**
18. Fuchs KH, Babic B, Breithaupt W, et al. EAES recommendations for the management of gastroesophageal reflux disease. Surg Endosc 2014;28:1753-73.**n; publication type**

19. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. Jama 2011;305:1969-77.**n; older than included SR**
20. Grant AM, Boachie C, Cotton SC, et al. Clinical and economic evaluation of laparoscopic surgery compared with medical management for gastro-oesophageal reflux disease: 5-year follow-up of multicentre randomised trial (the REFLUX trial). Health Technol Assess 2013;17:1-167.**n; older than included SR**
21. Hakansson B, Montgomery M, Cadiere GB, et al. Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. Aliment Pharmacol Ther 2015;42:1261-70.**n; comparison**
22. Hatlebakk JG, Zerbib F, Bruley des Varannes S, et al. Gastroesophageal Acid Reflux Control 5 Years After Antireflux Surgery, Compared With Long-term Esomeprazole Therapy. Clin Gastroenterol Hepatol 2016;14:678-85.e3.**n; post hoc**
23. Hein J. Comparison of the efficacy and safety of pantoprazole magnesium and pantoprazole sodium in the treatment of gastro-oesophageal reflux disease: a randomized, double-blind, controlled, multicentre trial. Clin Drug Investig 2011;31:655-64.**n; no pantoprazole magnesium available in BE**
24. Hosseini M, Salari R, Shariatmaghani S, et al. Gastrointestinal symptoms associated with gastroesophageal reflux disease, and their relapses after treatment with proton pump inhibitors: A systematic review. Electron Physician 2017;9:4597-605.**n; comparison**
25. Iwakiri K, Kinoshita Y, Habu Y, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. J Gastroenterol 2016;51:751-67.**n; publication type**
26. Jiang YX, Chen Y, Kong X, et al. Maintenance treatment of mild gastroesophageal reflux disease with proton pump inhibitors taken on-demand: a meta-analysis. Hepatogastroenterology 2013;60:1077-82.**n; full text not found**
27. Kahrilas PJ, Howden CW, Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastroesophageal reflux disease. Am J Gastroenterol 2011;106:1419-25; quiz 26.**n; outcome**
28. Kotby MN, Hassan O, El-Makhzangy AM, et al. Gastroesophageal reflux/laryngopharyngeal reflux disease: a critical analysis of the literature. Eur Arch Otorhinolaryngol 2010;267:171-9.**n; atypical symptoms**
29. Lipka S, Kumar A, Richter JE. No evidence for efficacy of radiofrequency ablation for treatment of gastroesophageal reflux disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2015;13:1058-67.e1.**n; comparison**
30. Lundell L, Hatlebakk J, Galmiche JP, et al. Long-term effect on symptoms and quality of life of maintenance therapy with esomeprazole 20 mg daily: a post hoc analysis of the LOTUS trial. Curr Med Res Opin 2015;31:65-73.**n; post hoc**
31. Maiti R, Jaida J, Israel PL, et al. Rabeprazole and esomeprazole in mild-to-moderate erosive gastroesophageal reflux disease: A comparative study of efficacy and safety. J Pharmacol Pharmacother 2011;2:150-7.**n; sample size**
32. Maret-Ouda J, Brusselaers N, Lagergren J. What is the most effective treatment for severe gastro-oesophageal reflux disease? Bmj 2015;350:h3169.**n; publication type**
33. McRorie JW, Jr., Gibb RD, Miner PB, Jr. Evidence-based treatment of frequent heartburn: the benefits and limitations of over-the-counter medications. J Am Assoc Nurse Pract 2014;26:330-9.**n; not an SR**
34. Mei J, Yu Y, Ma J, et al. Evaluation of the effectiveness of esomeprazole treatment strategies in the management of patients with gastroesophageal reflux disease symptoms: a meta-analysis. Pharmazie 2016;71:285-91.**n; more comprehensive SR chosen**
35. Mizuki A, Tatemichi M, Sakakibara T, et al. A Multicenter, Randomized, Open-Label Trial: Efficacy of Once-Daily Versus Twice-Daily Double-Dose Rabeprazole on Refractory Gastroesophageal Reflux Disease-Related Symptoms and Quality of Life. Curr Ther Res Clin Exp 2016;79:1-7.**n; open-label**
36. Moraes-Filho JP, Navarro-Rodriguez T, Barbuti R, et al. Guidelines for the diagnosis and management of gastroesophageal reflux disease: an evidence-based consensus. Arq Gastroenterol 2010;47:99-115.**n; guideline**
37. Nagahara A, Asaoka D, Hojo M, et al. Difference in efficacy of proton pump inhibitor between new-onset and recurrent gastroesophageal reflux disease: Result from a study of on-demand versus continuous maintenance therapy in Japan. Hippokratia 2015;19:53-6.**n; post hoc analysis**
38. Nagahara A, Hojo M, Asaoka D, et al. A randomized prospective study comparing the efficacy of on-demand therapy versus continuous therapy for 6 months for long-term maintenance with omeprazole 20 mg in patients with gastroesophageal reflux disease in Japan. Scand J Gastroenterol 2014;49:409-17.**n; open-label**

39. Niaz SK, Quraishy MS, Taj MA, et al. Guidelines on gastroesophageal reflux disease. J Pak Med Assoc 2015;65:532-41.**n; publication type**
40. Pandolfino JE, Krishnan K. Do endoscopic antireflux procedures fit in the current treatment paradigm of gastroesophageal reflux disease? Clin Gastroenterol Hepatol 2014;12:544-54.**n; comparison**
41. Park JH, Park H, Lee DH, et al. A randomized, double blinded, clinical trial to assess the efficacy and cost effectiveness of omeprazole compared to rabeprazole in the maintenance therapy of patients with gastroesophageal reflux disease. J Neurogastroenterol Motil 2013;19:219-26.**n; open-label**
42. Patti MG. An Evidence-Based Approach to the Treatment of Gastroesophageal Reflux Disease. JAMA Surg 2016;151:73-8.**n; comparison**
43. Qi Q, Wang R, Liu L, et al. Comparative effectiveness and tolerability of esomeprazole and omeprazole in gastro-esophageal reflux disease: A systematic review and meta-analysis. Int J Clin Pharmacol Ther 2015;53:803-10.**n; more up to date SR selected**
44. Qian B, Ma S, Shang L, et al. Effects of Helicobacter pylori eradication on gastroesophageal reflux disease. Helicobacter 2011;16:255-65.**n; intervention**
45. Regenbogen E, Helkin A, Georgopoulos R, et al. Esophageal reflux disease proton pump inhibitor therapy impact on sleep disturbance: a systematic review. Otolaryngol Head Neck Surg 2012;146:524-32.**n; outcomes**
46. Rickenbacher N, Kotter T, Kochen MM, et al. Fundoplication versus medical management of gastroesophageal reflux disease: systematic review and meta-analysis. Surg Endosc 2014;28:143-55.**n; more up to date SR selected**
47. Rodrigues Jr L, Faria CM, Geocze S, et al. Helicobacter pylori eradication does not influence gastroesophageal reflux disease: a prospective, parallel, randomized, open-label, controlled trial. Arq Gastroenterol 2012;49:56-63.**n; not a research question**
48. Sami Trad K. Transoral incisionless fundoplication: current status. Curr Opin Gastroenterol 2016;32:338-43.**n; not an SR**
49. Schijven MP, Gisbertz SS, van Berge Henegouwen MI. Laparoscopic surgery for gastro-esophageal acid reflux disease. Best Pract Res Clin Gastroenterol 2014;28:97-109.**n; more up to date SR selected**
50. Schwizer W, Menne D, Schutze K, et al. The effect of Helicobacter pylori infection and eradication in patients with gastro-oesophageal reflux disease: A parallel-group, double-blind, placebo-controlled multicentre study. United European Gastroenterol J 2013;1:226-35.**n; not a research question**
51. Spiegel BM. Treatment strategies for acid reflux: EncomPASSing practical solutions for primary care. Am J Gastroenterol 2010;105:2347-9.**n; editorial**
52. Sun J, Yuan YZ, Hou XH, et al. Esomeprazole regimens for reflux symptoms in Chinese patients with chronic gastritis. World J Gastroenterol 2015;21:6965-73.**n; comparison**
53. Takenaka R, Okada H, Kawano S, et al. Randomized study of lafutidine vs lansoprazole in patients with mild gastroesophageal reflux disease. World J Gastroenterol 2016;22:5430-5.**n; intervention not in Be**
54. Talalwah NA, Woodward S. Gastro-oesophageal reflux. Part 3: medical and surgical treatment. Br J Nurs 2013;22:409-15.**n; full text not found**
55. Vaira D, Gatta L, Ricci C, et al. Gastroesophageal reflux disease and Barrett's esophagus. Intern Emerg Med 2011;6:299-306.**n; not an SR**
56. Vakil NB, Halling K, Becher A, et al. Systematic review of patient-reported outcome instruments for gastroesophageal reflux disease symptoms. Eur J Gastroenterol Hepatol 2013;25:2-14.**n; comparison**
57. van Pinxteren B, Sigterman KE, Bonis P, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2010:Cd002095.**n; old version, more recent update available**
58. Vardar R, Keskin M, Valitova E, et al. Effect of alginate in patients with GERD hiatal hernia matters. Dis Esophagus 2017;30:1-7.**n; sample size**
59. von Rahden BH, Scheurlen M, Filser J, et al. [Newly recognized side-effects of proton pump inhibitors. Arguments in favour of fundoplication for GERD?]. Chirurg 2012;83:38-44.**n; not an SR**
60. Watson DI, Immanuel A. Endoscopic and laparoscopic treatment of gastroesophageal reflux. Expert Rev Gastroenterol Hepatol 2010;4:235-43.**n; not an SR**
61. Weijenborg PW, Cremonini F, Smout AJ, et al. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. Neurogastroenterol Motil 2012;24:747-57, e350.**n; comparison**
62. Wojcik P, Chudziak D, Macioch T, et al. Systematic Review of Esomeprazole for The Treatment of Gastroesophageal Reflux Disease. Value Health 2015;18:A622.**n; full text not available**

63. Zhang H, Yang Z, Ni Z, et al. A Meta-Analysis and Systematic Review of the Efficacy of Twice Daily PPIs versus Once Daily for Treatment of Gastroesophageal Reflux Disease. Gastroenterol Res Pract 2017;2017:9865963.**n; comparison**
64. Zhu HD, Wang H, Xia XM, et al. Rabeprazole 10 mg versus 20 mg in preventing relapse of gastroesophageal reflux disease: a meta-analysis. Chin Med J (Engl) 2013;126:3146-50.**n; not a research question**

22.3 Oesophagitis

1. Hsu PI, Lu CL, Wu DC, et al. Eight weeks of esomeprazole therapy reduces symptom relapse, compared with 4 weeks, in patients with Los Angeles grade A or B erosive esophagitis. Clin Gastroenterol Hepatol 2015;13:859-66.e1.**n; comparison**
2. Kinoshita Y, Kato M, Fujishiro M, et al. Efficacy and safety of twice-daily rabeprazole maintenance therapy for patients with reflux esophagitis refractory to standard once-daily proton pump inhibitor: the Japan-based EXTEND study. J Gastroenterol 2017.**n; comparison**
3. Nagahara A, Suzuki T, Nagata N, et al. A multicentre randomised trial to compare the efficacy of omeprazole versus rabeprazole in early symptom relief in patients with reflux esophagitis. J Gastroenterol 2014;49:1536-47.**n; open-label**
4. Storr M. [Prolonged PPI therapy in reflux esophagitis is sustainable]. MMW Fortschr Med 2015;157:35.**n; publication type**
5. Weijenborg PW, Cremonini F, Smout AJ, et al. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. Neurogastroenterol Motil 2012;24:747-57, e350.**n; comparison**

22.4 Barrett oesophagus

1. Abrams JA. Chemoprevention of esophageal adenocarcinoma. Therap Adv Gastroenterol 2008;1:7-18.**n; not an SR**
2. Babic Z, Bogdanovic Z, Dorosulic Z, et al. One year treatment of Barrett's oesophagus with proton pump inhibitors (a multi-center study). Acta Clin Belg 2015;70:408-13.**n; sample size**
3. Bremholm L, Funch-Jensen P, Eriksen J, et al. Barrett's esophagus. Diagnosis, follow-up and treatment. Dan Med J 2012;59:C4499.**n; not an SR**
4. Bronner MP, Overholt BF, Taylor SL, et al. Squamous overgrowth is not a safety concern for photodynamic therapy for Barrett's esophagus with high-grade dysplasia. Gastroenterology 2009;136:56-64; quiz 351-2.**n; outcomes**
5. Centre for Clinical Practice at N. Barrett's Oesophagus: Ablative Therapy for the Treatment of Barrett's Oesophagus. National Institute for Health and Clinical Excellence: Guidance 2010.**n; is guideline**
6. Das D, Chilton AP, Jankowski JA. Chemoprevention of oesophageal cancer and the AspECT trial. Recent Results Cancer Res 2009;181:161-9.**n; comparison**
7. D'Cunha J, Andrade RS, Maddaus MA. Surgical management of gastroesophageal reflux disease/Barrett's esophagus. Minerva Chir 2011;66:7-19.**n; not an SR**
8. de Bortoli N, Martinucci I, Piaggi P, et al. Randomised clinical trial: twice daily esomeprazole 40 mg vs. pantoprazole 40 mg in Barrett's oesophagus for 1 year. Aliment Pharmacol Ther 2011;33:1019-27.**n; sample size**
9. Ertan A, Zaheer I, Correa AM, et al. Photodynamic therapy vs radiofrequency ablation for Barrett's dysplasia: efficacy, safety and cost-comparison. World J Gastroenterol 2013;19:7106-13.**n; comparison**
10. Excellence NIfHaC. Barrett's Oesophagus: Ablative Therapy for the Treatment of Barrett's Oesophagus. National Institute for Health and Clinical Excellence (UK) 2010.**n; more comprehensive SR selected**
11. Fayter D, Corbett M, Heirs M, et al. A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health Technol Assess 2010;14:1-288.**n; more comprehensive SR selected**
12. Gilbert EW, Luna RA, Harrison VL, et al. Barrett's esophagus: a review of the literature. J Gastrointest Surg 2011;15:708-18.**n; not an SR**
13. Hu Q, Sun TT, Hong J, et al. Proton Pump Inhibitors Do Not Reduce the Risk of Esophageal Adenocarcinoma in Patients with Barrett's Esophagus: A Systematic Review and Meta-Analysis. PLoS One 2017;12:e0169691.**n; SR of observational studies**
14. Jankowski JA, Hooper PA. Chemoprevention in Barrett's esophagus: A pill a day? Gastrointest Endosc Clin N Am 2011;21:155-70.**n; not an SR**

15. Labenz J. [Barrett's esophagus]. Internist (Berl) 2016;57:1079-92.**n; not an SR**
16. Leedham S, Jankowski J. The evidence base of proton pump inhibitor chemopreventative agents in Barrett's esophagus--the good, the bad, and the flawed! Am J Gastroenterol 2007;102:21-3.**n; not an SR**
17. Li YM, Li L, Yu CH, et al. A systematic review and meta-analysis of the treatment for Barrett's esophagus. Dig Dis Sci 2008;53:2837-46.**n; more recent SR selected**
18. Lord RV. Does antireflux surgery prevent progression of Barrett's esophagus? Minerva Chir 2011;66:1-6.**n; not an SR**
19. Manner H, Rabenstein T, Pech O, et al. Ablation of residual Barrett's epithelium after endoscopic resection: a randomized long-term follow-up study of argon plasma coagulation vs. surveillance (APE study). Endoscopy 2014;46:6-12.**n; sample size**
20. Martinek J, Akiyama JI, Vackova Z, et al. Current treatment options for esophageal diseases. Ann N Y Acad Sci 2016;1381:139-51.**n; not an SR**
21. Sie C, Bright T, Schoeman M, et al. Argon plasma coagulation ablation versus endoscopic surveillance of Barrett's esophagus: late outcomes from two randomized trials. Endoscopy 2013;45:859-65.**n; comparison**
22. Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut 2014;63:1229-37.**n; other SR was selected**
23. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology 2011;140:e18-52; quiz e13.**n; n; more recent SR selected**
24. Vaira D, Gatta L, Ricci C, et al. Gastroesophageal reflux disease and Barrett's esophagus. Intern Emerg Med 2011;6:299-306.**n; not an SR**
25. Wani S, Rubenstein JH, Vieth M, et al. Diagnosis and Management of Low-Grade Dysplasia in Barrett's Esophagus: Expert Review From the Clinical Practice Updates Committee of the American Gastroenterological Association. Gastroenterology 2016;151:822-35.**n; not an SR**
26. Winberg H, Lindblad M, Lagergren J, et al. Risk factors and chemoprevention in Barrett's esophagus--an update. Scand J Gastroenterol 2012;47:397-406.**n; comparison**

22.5 Deprescribing

1. Wilsdon TD, Hendrix I, Thynne TR, et al. Effectiveness of Interventions to Deprescribe Inappropriate Proton Pump Inhibitors in Older Adults. Drugs Aging 2017;34:265-87.**n; wider strategies (intervention)**

22.6 Gastroprotection

1. Angiolillo DJ, Datto C, Raines S, et al. Impact of concomitant low-dose aspirin on the safety and tolerability of naproxen and esomeprazole magnesium delayed-release tablets in patients requiring chronic nonsteroidal anti-inflammatory drug therapy: an analysis from 5 Phase III studies. J Thromb Thrombolysis 2014;38:11-23.**n; fixed-dose combination; not an SR**

2. Berger PB. Should proton pump inhibitors be withheld from patients taking clopidogrel? The issue that has been giving me heartburn! Circ Cardiovasc Qual Outcomes 2015;8:6-7.**n; not an SR**
3. Bouziana SD, Tziomalos K. Clinical relevance of clopidogrel-proton pump inhibitors interaction. World J Gastrointest Pharmacol Ther 2015;6:17-21.**n; not an SR**
4. Bundhun PK, Teeluck AR, Bhurtu A, et al. 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 Cardiovasc Disord 2017;17:3.**n; not a full SR**
5. Burlacu A, Genovesi S, Goldsmith D, et al. Bleeding in advanced CKD patients on antithrombotic medication - A critical appraisal. Pharmacol Res 2017.**n; not an SR**
6. Chan FK, Kyaw M, Tanigawa T, et al. Similar Efficacy of Proton-Pump Inhibitors vs H2-Receptor Antagonists in Reducing Risk of Upper Gastrointestinal Bleeding or Ulcers in High-Risk Users of Low-Dose Aspirin. Gastroenterology 2017;152:105-10.e1.**n; comparison**
7. Dahal K, Sharma SP, Kaur J, et al. Efficacy and Safety of Proton Pump Inhibitors in the Long-Term Aspirin Users: A Meta-Analysis of Randomized Controlled Trials. Am J Ther 2017;24:e559-e69.**n; no full text found**

8. D'Ugo E, Rossi S, De Caterina R. Proton pump inhibitors and clopidogrel: an association to avoid? Intern Emerg Med 2014;9:11-22.**n; unclear methodology**
9. Fujishiro M, Higuchi K, Kato M, et al. Long-term efficacy and safety of rabeprazole in patients taking low-dose aspirin with a history of peptic ulcers: a phase 2/3, randomized, parallel-group, multicenter, extension clinical trial. J Clin Biochem Nutr 2015;56:228-39.**n; comparison**
10. Furtado RH, Giugliano RP, Strunz CM, et al. Drug Interaction Between Clopidogrel and Ranitidine or Omeprazole in Stable Coronary Artery Disease: A Double-Blind, Double Dummy, Randomized Study. Am J Cardiovasc Drugs 2016;16:275-84.**n; outcomes**
11. Garcia Rodriguez LA, Martin-Perez M, Hennekens CH, et al. Bleeding Risk with Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies. PLoS One 2016;11:e0160046.**n; SR of observational studies**
12. Gargiulo G, Costa F, Ariotti S, et al. Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6- or 24-month dual-antiplatelet therapy duration: Insights from the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY trial. Am Heart J 2016;174:95-102.**n; no gastric complications outcome**
13. Iwakiri R, Higuchi K, Kato M, et al. Randomised clinical trial: prevention of recurrence of peptic ulcers by rabeprazole in patients taking low-dose aspirin. Aliment Pharmacol Ther 2014;40:780-95.**n; comparison rabeprazole vs teprenone**
14. Juel J, Pareek M, Jensen SE. The clopidogrel-PPI interaction: an updated mini-review. Curr Vasc Pharmacol 2014;12:751-7.**n; not an SR**
15. Laursen SB, Jorgensen HS, Schaffalitzky de Muckadell OB. National consensus on management of peptic ulcer bleeding in Denmark 2014. Dan Med J 2014;61:B4969.**n; publication type**
16. Lavie CJ, Howden CW, Scheiman J, et al. Upper Gastrointestinal Toxicity Associated With Long-Term Aspirin Therapy: Consequences and Prevention. Curr Probl Cardiol 2017;42:146-64.**n; not an SR**
17. Medlock S, Eslami S, Askari M, et al. Co-prescription of gastroprotective agents and their efficacy in elderly patients taking nonsteroidal anti-inflammatory drugs: a systematic review of observational studies. Clin Gastroenterol Hepatol 2013;11:1259-69.e10.**n; observational studies**
18. Mo C, Sun G, Wang YZ, et al. PPI versus Histamine H2 Receptor Antagonists for Prevention of Upper Gastrointestinal Injury Associated with Low-Dose Aspirin: Systematic Review and Meta-analysis. PLoS One 2015;10:e0131558.**n; comparison**
19. Moore RA, Derry S, Simon LS, et al. Nonsteroidal anti-inflammatory drugs, gastroprotection, and benefit-risk. Pain Pract 2014;14:378-95.**n; older SR**
20. Mossner J. The Indications, Applications, and Risks of Proton Pump Inhibitors. Dtsch Arztebl Int 2016;113:477-83.**n; not a full SR**
21. Nuki Y, Umeno J, Washio E, et al. The influence of CYP2C19 polymorphisms on exacerbating effect of rabeprazole in celecoxib-induced small bowel injury. Aliment Pharmacol Ther 2017;46:331-6.**n; sample size**
22. Satoh K, Yoshino J, Akamatsu T, et al. Evidence-based clinical practice guidelines for peptic ulcer disease 2015. J Gastroenterol 2016;51:177-94.**n; is guideline**
23. Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med 2016;14:179.**n; methodology of SR unclear**
24. Scarpignato C, Lanas A, Blandizzi C, et al. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis--an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. BMC Med 2015;13:55.**n; not an SR**
25. Schjerning Olsen AM, Lindhardsen J, Gislason GH, et al. Impact of proton pump inhibitor treatment on gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug use among post-myocardial infarction patients taking antithrombotics: nationwide study. Bmj 2015;351:h5096.**n; cohort**
26. Scott SA, Owusu Obeng A, Hulot JS. Antiplatelet drug interactions with proton pump inhibitors. Expert Opin Drug Metab Toxicol 2014;10:175-89.**n; not an SR**
27. Shamliyan TA, Middleton M, Borst C. Patient-centered Outcomes with Concomitant Use of Proton Pump Inhibitors and Other Drugs. Clin Ther 2017;39:404-27.e36.**n; no gastric complication outcomes**
28. Szabo IL, Matics R, Hegyi P, et al. PPIs Prevent Aspirin-Induced Gastrointestinal Bleeding Better than H2RAs. A Systematic Review and Meta-analysis. J Gastrointestin Liver Dis 2017;26:395-402.**n; comparison**
29. Tanguay JF, Bell AD, Ackman ML, et al. Focused 2012 update of the Canadian Cardiovascular Society guidelines for the use of antiplatelet therapy. Can J Cardiol 2013;29:1334-45.**n; is guideline**

30. Tran-Duy A, Vanmolkot FH, Joore MA, et al. Should patients prescribed long-term low-dose aspirin receive proton pump inhibitors? A systematic review and meta-analysis. Int J Clin Pract 2015;69:1088-111.**n; more up to date SR chosen**
31. Vaduganathan M, Bhatt DL, Cryer BL, et al. Proton-Pump Inhibitors Reduce Gastrointestinal Events Regardless of Aspirin Dose in Patients Requiring Dual Antiplatelet Therapy. J Am Coll Cardiol 2016;67:1661-71.**n; post hoc analysis**
32. Vaduganathan M, Cannon CP, Cryer BL, et al. Efficacy and Safety of Proton-Pump Inhibitors in High-Risk Cardiovascular Subsets of the COGENT Trial. Am J Med 2016;129:1002-5.**n; post hoc**
33. Washio E, Esaki M, Maehata Y, et al. Proton Pump Inhibitors Increase Incidence of Nonsteroidal Anti-Inflammatory Drug-Induced Small Bowel Injury: A Randomized, Placebo-Controlled Trial. Clin Gastroenterol Hepatol 2016;14:809-15.e1.**n; sample size**
34. Wei P, Zhang YG, Ling L, et al. Effects of the short-term application of pantoprazole combined with aspirin and clopidogrel in the treatment of acute STEMI. Exp Ther Med 2016;12:2861-4.**n; duration**
35. Yang M, He M, Zhao M, et al. Proton pump inhibitors for preventing non-steroidal anti-inflammatory drug induced gastrointestinal toxicity: a systematic review. Curr Med Res Opin 2017;33:973-80.**n; more up to date SR chosen**
36. Yi ZM, Qiu TT, Zhang Y, et al. Comparison of prophylactic effect of UGIB and effects on platelet function between PPIs and H2RAs combined with DAPT: systematic review and meta-analysis. Ther Clin Risk Manag 2017;13:367-77.**n; comparison**

22.7 Adverse events: Cardiovascular disease

1. Arana A, Johannes CB, McQuay LJ, et al. Risk of Out-of-Hospital Sudden Cardiac Death in Users of Domperidone, Proton Pump Inhibitors, or Metoclopramide: A Population-Based Nested Case-Control Study. Drug Saf 2015;38:1187-99.**n; study type**
2. Awaisu A, Hamou F, Mekideche L, et al. Proton pump inhibitor co-prescription with dual antiplatelet therapy among patients with acute coronary syndrome in Qatar. Int J Clin Pharm 2016;38:353-61.**n, outcomes are % of coprescribing and population**
3. Berger PB. Should proton pump inhibitors be withheld from patients taking clopidogrel? The issue that has been giving me heartburn! Circ Cardiovasc Qual Outcomes 2015;8:6-7.**n; publication type**
4. Bouziana SD, Tziomalos K. Clinical relevance of clopidogrel-proton pump inhibitors interaction. World J Gastrointest Pharmacol Ther 2015;6:17-21.**n; publication type**
5. Bundhun PK, Teeluck AR, Bhurtu A, et al. 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 Cardiovasc Disord 2017;17:3.**n, ander brondoc**
6. Chen KP, Lee J, Mark RG, et al. Proton pump inhibitor use is not associated with cardiac arrhythmia in critically ill patients. J Clin Pharmacol 2015;55:774-9.**n; population**
7. Choi YJ, Kim N, Jang IJ, et al. Pantoprazole Does Not Reduce the Antiplatelet Effect of Clopidogrel: A Randomized Controlled Trial in Korea. Gut Liver 2017;11:504-11.**n; sample size**
8. Dahal K, Sharma SP, Kaur J, et al. Efficacy and Safety of Proton Pump Inhibitors in the Long-Term Aspirin Users: A Meta-Analysis of Randomized Controlled Trials. Am J Ther 2017;24:e559-e69.**n; no access to full text**
9. Davis TME, Drinkwater J, Davis WA. Proton Pump Inhibitors, Nephropathy, and Cardiovascular Disease in Type 2 Diabetes: The Fremantle Diabetes Study. J Clin Endocrinol Metab 2017;102:2985-93.**n; outcome**
10. Depta JP, Lenzini PA, Lanfear DE, et al. Clinical outcomes associated with proton pump inhibitor use among clopidogrel-treated patients within CYP2C19 genotype groups following acute myocardial infarction. Pharmacogenomics J 2015;15:20-5.**n, genetic polymorfism not a research question**
11. D'Ugo E, Rossi S, De Caterina R. Proton pump inhibitors and clopidogrel: an association to avoid? Intern Emerg Med 2014;9:11-22.**n; not an SR**
12. Garcia Rodriguez LA, Johansson S, Nagy P, et al. Use of proton pump inhibitors and the risk of coronary events in new users of low-dose acetylsalicylic acid in UK primary care. Thromb Haemost 2014;111:131-9.**n, study design**
13. Gargiulo G, Costa F, Ariotti S, et al. Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6- or 24-month dual-antiplatelet therapy duration: Insights from the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY trial. Am Heart J 2016;174:95-102.**n; post hoc analysis**

14. Goldstein JL, Whellan DJ, Scheiman JM, et al. Long-Term Safety of a Coordinated Delivery Tablet of Enteric-Coated Aspirin 325 mg and Immediate-Release Omeprazole 40 mg for Secondary Cardiovascular Disease Prevention in Patients at GI Risk. Cardiovasc Ther 2016;34:59-66.**n; intervention**
15. Gracie DJ, Ford AC. The possible risks of proton pump inhibitors. Med J Aust 2016;205:292-3.**n; not an SR**
16. Gu RX, Wang XZ, Li J, et al. Effects of omeprazole or pantoprazole on platelet function in non-ST-segment elevation acute coronary syndrome patients receiving clopidogrel. Mil Med Res 2016;3:38.**n; outcome**
17. Hokimoto S, Akasaka T, Tabata N, et al. Impact of esomeprazole on platelet reactivity and clinical outcome according to CYP2C19 genotype in coronary heart disease patients during dual antiplatelet therapy. Thromb Res 2015;135:1081-6.**n; genetic polymorphisms**
18. Jensen BES, Hansen JM, Larsen KS, et al. Randomized clinical trial: the impact of gastrointestinal risk factor screening and prophylactic proton pump inhibitor therapy in patients receiving dual antiplatelet therapy. Eur J Gastroenterol Hepatol 2017;29:1118-25.**n; intervention**
19. Juurlink DN, Dormuth CR, Huang A, et al. Proton pump inhibitors and the risk of adverse cardiac events. PLoS One 2013;8:e84890.**n; study type**
20. Lozano I, Sanchez-Insa E, de Leiras SR, et al. Acute Coronary Syndromes, Gastrointestinal Protection, and Recommendations Regarding Concomitant Administration of Proton-Pump Inhibitors (Omeprazol/Esomeprazole) and Clopidogrel. Am J Cardiol 2016;117:366-8.**n; outcome**
21. Lu M. Report: Impact of drug combination of clopidogrel and pantoprazole In the prognosis of patients with transient ischemic attack. Pak J Pharm Sci 2017;30:217-21.**n, no access**
22. Mandurino-Mirizzi A, Leonardi S, Melloni C. Concomitant use of proton pump inhibitors and dual antiplatelet therapy for cardiovascular outcomes. Minerva Endocrinol 2017;42:228-37.**n, geen SR**
23. Nguyen LH, Lochhead P, Joshi AD, et al. No Significant Association Between Proton Pump Inhibitor Use and Risk of Stroke After Adjustment for Lifestyle Factors and Indication. Gastroenterology 2017.**n; comparison**
24. Nicolau JC, Bhatt DL, Roe MT, et al. Concomitant proton-pump inhibitor use, platelet activity, and clinical outcomes in patients with acute coronary syndromes treated with prasugrel versus clopidogrel and managed without revascularization: insights from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes trial. Am Heart J 2015;170:683-94.e3.**n; comparison**
25. Reinberg O. [Proton pump inhibitors (PPI): may be not as harmless as believed]. Rev Med Suisse 2015;11:1665-71.**n; not an SR**
26. Savarino V, Dulbecco P, Savarino E. Are proton pump inhibitors really so dangerous? Dig Liver Dis 2016;48:851-9.**n; not an SR**
27. Scott SA, Owusu Obeng A, Hulot JS. Antiplatelet drug interactions with proton pump inhibitors. Expert Opin Drug Metab Toxicol 2014;10:175-89.**n; expert opinion**
28. Serbin MA, Guzauskas GF, Veenstra DL. Clopidogrel-Proton Pump Inhibitor Drug-Drug Interaction and Risk of Adverse Clinical Outcomes Among PCI-Treated ACS Patients: A Meta-analysis. J Manag Care Spec Pharm 2016;22:939-47.**n; other SR selected**
29. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population. PLoS One 2015;10:e0124653.**n; methodology**
30. Sukhovershin RA, Cooke JP. How May Proton Pump Inhibitors Impair Cardiovascular Health? Am J Cardiovasc Drugs 2016;16:153-61.**n; not an SR**
31. Tran-Duy A, Vanmolkot FH, Joore MA, et al. Should patients prescribed long-term low-dose aspirin receive proton pump inhibitors? A systematic review and meta-analysis. Int J Clin Pract 2015;69:1088-111.**n; more comprehensive review selected**
32. Turkiewicz A, Vicente RP, Ohlsson H, et al. Revising the link between proton-pump inhibitors and risk of acute myocardial infarction-a case-crossover analysis. Eur J Clin Pharmacol 2015;71:125-9.**n, study design**
33. Vaduganathan M, Cannon CP, Cryer BL, et al. Efficacy and Safety of Proton-Pump Inhibitors in High-Risk Cardiovascular Subsets of the COGENT Trial. Am J Med 2016;129:1002-5.**n; post hoc analysis**
34. Wang Q, Ljung R, Lagergren J, et al. Prognosis of concomitant users of clopidogrel and proton-pump inhibitors in a high-risk population for upper gastrointestinal bleeding. BMC Pharmacol Toxicol 2014;15:22.**n, outcomes**
35. Wei P, Zhang YG, Ling L, et al. Effects of the short-term application of pantoprazole combined with aspirin and clopidogrel in the treatment of acute STEMI. Exp Ther Med 2016;12:2861-4.**n; short-term intervention**

36. Weisz G, Smilowitz NR, Kirtane AJ, et al. Proton Pump Inhibitors, Platelet Reactivity, and Cardiovascular Outcomes After Drug-Eluting Stents in Clopidogrel-Treated Patients: The ADAPT-DES Study. Circ Cardiovasc Interv 2015;8.**n; outcome**
37. Whellan DJ, Goldstein JL, Cryer BL, et al. PA32540 (a coordinated-delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) versus enteric-coated aspirin 325 mg alone in subjects at risk for aspirin-associated gastric ulcers: results of two 6-month, phase 3 studies. Am Heart J 2014;168:495-502.e4.**n; ouctome**
38. Yan Y, Wang X, Fan JY, et al. Impact of concomitant use of proton pump inhibitors and clopidogrel or ticagrelor on clinical outcomes in patients with acute coronary syndrome. J Geriatr Cardiol 2016;13:209-17.**n, outcomes**
39. Yi X, Han Z, Zhou Q, et al. Concomitant Use of Proton-Pump Inhibitors and Clopidogrel Increases the Risk of Adverse Outcomes in Patients With Ischemic Stroke Carrying Reduced-Function CYP2C19*2. Clin Appl Thromb Hemost 2018;24:55-62.**n, sample size**
40. Zou JJ, Chen SL, Tan J, et al. Increased risk for developing major adverse cardiovascular events in stented Chinese patients treated with dual antiplatelet therapy after concomitant use of the proton pump inhibitor. PLoS One 2014;9:e84985.**n; population**

22.8 Adverse events: Dementia

1. Corsonello A, Lattanzio F, Bustacchini S, et al. Adverse events of proton pump inhibitors: potential mechanisms. Curr Drug Metab 2017.**n; only one database searched**
2. Gracie DJ, Ford AC. The possible risks of proton pump inhibitors. Med J Aust 2016;205:292-3.**n; not an SR**
3. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf 2017;8:273-97.**n; only one database searched**
4. Ueberschaer H, Allescher HD. [Proton pump inhibitor - side effects and complications of long-term proton pump inhibitor administration]. Z Gastroenterol 2017;55:63-74.**n; not an sr**
5. Wijarnpreecha K, Thongprayoon C, Panjawatanan P, et al. Proton pump inhibitors and risk of dementia. Ann Transl Med 2016;4:240.**n; other more up to date SR chosen**

22.9 Adverse events: Community-acquired pneumonia

1. Abramowitz J, Thakkar P, Isa A, et al. Adverse Event Reporting for Proton Pump Inhibitor Therapy: An Overview of Systematic Reviews. Otolaryngol Head Neck Surg 2016;155:547-54.**n; SR of SR's; no re-analysis of original data**
2. Corsonello A, Lattanzio F, Bustacchini S, et al. Adverse events of proton pump inhibitors: potential mechanisms. Curr Drug Metab 2017.**n; only one database searched**
3. de la Coba Ortiz C, Arguelles Arias F, Martin de Argila de Prados C, et al. Proton-pump inhibitors adverse effects: a review of the evidence and position statement by the Sociedad Espanola de Patologia Digestiva. Rev Esp Enferm Dig 2016;108:207-24.**n; not clear whether search was systematic**
4. Filion KB, Chateau D, Targownik LE, et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. Gut 2014;63:552-8.**n; outcome too specific**
5. Gracie DJ, Ford AC. The possible risks of proton pump inhibitors. Med J Aust 2016;205:292-3.**n; not an SR**
6. Ho SW, Hsieh MJ, Yang SF, et al. Risk of Stroke-Associated Pneumonia With Acid-Suppressive Drugs: A Population-Based Cohort Study. Medicine (Baltimore) 2015;94:e1227.**n; stroke-associated pneumonia (<3 months after stroke)**
7. Johnson DA, Katz PO, Armstrong D, et al. The Safety of Appropriate Use of Over-the-Counter Proton Pump Inhibitors: An Evidence-Based Review and Delphi Consensus. Drugs 2017;77:547-61.**n; unclear search methodology**
8. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf 2017;8:273-97.**n; only one database searched**

22.10 Adverse events: Renal disease

1. Avinash A, Patil N, Kunder SK, et al. A Retrospective Study to Assess the Effect of Proton Pump Inhibitors on Renal Profile in a South Indian Hospital. J Clin Diagn Res 2017;11:Fc09-fc12.**n; sample size**

2. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf 2017;8:273-97.**n; only one database searched**
3. Paquot F, Krzesinski JM. [Proton-pump inhibitors and risk of kidney disease]. Rev Med Suisse 2017;13:1427-30.**n; not an sr**
4. Ueberschaer H, Allescher HD. [Proton pump inhibitor - side effects and complications of long-term proton pump inhibitor administration]. Z Gastroenterol 2017;55:63-74.**n; not an sr**
5. Wijarnpreecha K, Thongprayoon C, Chesdachai S, et al. Associations of Proton-Pump Inhibitors and H2 Receptor Antagonists with Chronic Kidney Disease: A Meta-Analysis. Dig Dis Sci 2017;62:2821-7.**n; more extensive SR found**
6. Yang Y, George KC, Shang WF, et al. Proton-pump inhibitors use, and risk of acute kidney injury: a meta-analysis of observational studies. Drug Des Devel Ther 2017;11:1291-9.**n; other more comprehensive SR was selected**

22.11 Adverse events: Clostridium difficile infection

1. Boghossian TA, Rashid FJ, Thompson W, et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database Syst Rev 2017;3:Cd011969.**n; outcomes**
2. Cao F, Chen CX, Wang M, et al. Updated meta-analysis of controlled observational studies: proton-pump inhibitors and risk of Clostridium difficile infection. J Hosp Infect 2018;98:4-13.**n; other more up to date SR chosen**
3. Eze P, Balsells E, Kyaw MH, et al. Risk factors for Clostridium difficile infections - an overview of the evidence base and challenges in data synthesis. J Glob Health 2017;7:010417.**n; review of SR's; no re-analysis**
4. Johnson DA, Katz PO, Armstrong D, et al. The Safety of Appropriate Use of Over-the-Counter Proton Pump Inhibitors: An Evidence-Based Review and Delphi Consensus. Drugs 2017;77:547-61.**n; unclear search methodology**
5. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf 2017;8:273-97.**n; only one database searched**
6. Oshima T, Wu L, Li M, et al. 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. J Gastroenterol 2018;53:84-94.**n; other more up to date SR chosen**
7. Villafuerte-Galvez JA, Kelly CP. Proton pump inhibitors and risk of Clostridium difficile infection: association or causation? Curr Opin Gastroenterol 2018;34:11-8.**n; not an sr**

22.12 Adverse events: Campylobacter and Salmonella infections

no exclusions

22.13 Adverse events: Gastric cancer

1. Johnson DA, Katz PO, Armstrong D, et al. The Safety of Appropriate Use of Over-the-Counter Proton Pump Inhibitors: An Evidence-Based Review and Delphi Consensus. Drugs 2017;77:547-61.**n; unclear search methodology**
2. Ko Y, Tang J, Sanagapalli S, et al. Safety of proton pump inhibitors and risk of gastric cancers: review of literature and pathophysiological mechanisms. Expert Opin Drug Saf 2016;15:53-63.**n; other review selected**
3. Krishnamoorthi R, Borah B, Heien H, et al. Rates and predictors of progression to esophageal carcinoma in a large population-based Barrett's esophagus cohort. Gastrointest Endosc 2016;84:40-6.e7.**n; study type**
4. Krishnamoorthi R, Singh S, Ragunathan K, et al. Factors Associated with Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2017.**n; study type**
5. Martin FC, Chenevix-Trench G, Yeomans ND. Systematic review with meta-analysis: fundic gland polyps and proton pump inhibitors. Aliment Pharmacol Ther 2016;44:915-25.**n; outcomes**
6. Niikura R, Hayakawa Y, Hirata Y, et al. Long-term proton pump inhibitor use is a risk factor of gastric cancer after treatment for Helicobacter pylori: a retrospective cohort analysis. Gut 2017.**n; publication type**

7. Reinberg O. [Proton pump inhibitors (PPI): may be not as harmless as believed]. Rev Med Suisse 2015;11:1665-71.**n; not an sr**

8. Ruetsch R, Juillerat P, Flatz A, et al. [Does long-term use of proton pump inhibitors promote premalignant lesions of the gastric mucosa?]. Praxis (Bern 1994) 2016;105:221-2.**n; outcome**
9. Schneider JL, Kolitsopoulos F, Corley DA. Risk of gastric cancer, gastrointestinal cancers and other cancers: a comparison of treatment with pantoprazole and other proton pump inhibitors. Aliment Pharmacol Ther 2016;43:73-82.**n; comparison**
10. Thota PN, Hajifathalian K, Benjamin T, et al. Lack of incremental effect of histamine receptor antagonists over proton pump inhibitors on the risk of neoplastic progression in patients with Barrett's esophagus: a cohort study. J Dig Dis 2017;18:143-50.**n; outcome**

22.14 Adverse events: Fractures

1. Abramowitz J, Thakkar P, Isa A, et al. Adverse Event Reporting for Proton Pump Inhibitor Therapy: An Overview of Systematic Reviews. Otolaryngol Head Neck Surg 2016;155:547-54.**n; SR of SR's; no re-analysis of original data**
2. Corsonello A, Lattanzio F, Bustacchini S, et al. Adverse events of proton pump inhibitors: potential mechanisms. Curr Drug Metab 2017.**n; only one database searched**
3. de la Coba Ortiz C, Arguelles Arias F, Martin de Argila de Prados C, et al. Proton-pump inhibitors adverse effects: a review of the evidence and position statement by the Sociedad Espanola de Patologia Digestiva. Rev Esp Enferm Dig 2016;108:207-24.**n; not clear whether search was systematic**
4. Gracie DJ, Ford AC. The possible risks of proton pump inhibitors. Med J Aust 2016;205:292-3.**n; not an sr**
5. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf 2017;8:273-97.**n; only one database searched**
6. Mossner J. The Indications, Applications, and Risks of Proton Pump Inhibitors. Dtsch Arztebl Int 2016;113:477-83.**n; not an sr**
7. Reinberg O. [Proton pump inhibitors (PPI): may be not as harmless as believed]. Rev Med Suisse 2015;11:1665-71.**n; not an sr**
8. Savarino V, Dulbecco P, Savarino E. Are proton pump inhibitors really so dangerous? Dig Liver Dis 2016;48:851-9.**n; not an sr**
9. Solomon DH, Diem SJ, Ruppert K, et al. Bone mineral density changes among women initiating proton pump inhibitors or H2 receptor antagonists: a SWAN cohort study. J Bone Miner Res 2015;30:232-9.**n; outcome**
10. Tolppanen AM, Taipale H, Tanskanen A, et al. Comparison of predictors of hip fracture and mortality after hip fracture in community-dwellers with and without Alzheimer's disease - exposure-matched cohort study. BMC Geriatr 2016;16:204.**n; comparison Alzheimer vs no Alzheimer**
11. Wu CH, Tung YC, Chai CY, et al. Increased Risk of Osteoporosis in Patients With Peptic Ulcer Disease: A Nationwide Population-Based Study. Medicine (Baltimore) 2016;95:e3309.**n; outcome osteoporosis**
12. Yang SD, Chen Q, Wei HK, et al. Bone fracture and the interaction between bisphosphonates and proton pump inhibitors: a meta-analysis. Int J Clin Exp Med 2015;8:4899-910.**n; more up to date SR was chosen**

23 References

1. Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG Clinical Guideline: Management of Dyspepsia. The American journal of gastroenterology 2017;112: 988-1013.
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4. Pinto-Sanchez MI, Yuan Y, Hassan A, Bercik P, Moayyedi P. Proton pump inhibitors for functional dyspepsia. The Cochrane database of systematic reviews 2017;11: Cd011194.
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6. Vaezi MF, Yang YX, Howden CW. Complications of Proton Pump Inhibitor Therapy. Gastroenterology 2017;153: 35-48.
7. Hill AB. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine 1965;58: 295-300.
8. Ioannidis JP. Exposure-wide epidemiology: revisiting Bradford Hill. Statistics in medicine 2016;35: 1749-62.
9. Guyatt G, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D. GRADE guidelines 6. Rating the quality of evidence--imprecision. Journal of clinical epidemiology 2011;64.
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11. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of G. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. The American journal of gastroenterology 2016;111: 30-50; quiz 1.
12. Whiteman DC, Appleyard M, Bahin FF, Bobryshev YV, Bourke MJ, Brown I, et al. Australian clinical practice guidelines for the diagnosis and management of Barrett's esophagus and early esophageal adenocarcinoma. Journal of gastroenterology and hepatology 2015;30: 804-20.
13. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014;63: 7-42.
14. Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. Canadian family physician Medecin de famille canadien 2017;63: 354-64.
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21. Catapani W, Guedes FS. A clinical trial assessing the efficacy of a therapeutic encounter versus traditional consultation in the management of functional dyspepsia. American Journal of Gastroenterology 2015;110: S751-2.
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