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„Risks of Long Term Use of Proton Pump Inhibitors “

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Beshoy Riffat Nan Abdelmeseh

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1. Introduction

Diseases of the gastrointestinal tract (GIT) tract are also called gastrointestinal disorders and they are of problems that occur and attack many sites of the digestive system starting from mouth and stomach, large and small intestines and cause uncomfortable symptoms such as bleeding, heart burn, hyperacidity, mal digestion, diarrhea and constipation. All these problems belong to many diseases which are known as:

1. mouth ulcer
2. Zollinger Ellison syndrome
3. peptic ulcer
4. duodenal ulcer

An overview of disorders associated with elevated secretion of gastric acid is shown as well as the associated problems, their mechanisms of secretion and the factors that affect these processes.

- physiology of stomach
- Layer of epithelium cells which have glands and pits. The two functional zones are oxyntic gland representing 80% of the stomach and pyloric gland representing 20% of stomach (Schubert 2008).
- Parietal cells which are located in oxyntic gland are responsible for secretion of hydrochloric acid and intrinsic factor (Cui and Waldum 2007).
 - Chief cells located in base of oxyntic gland secrete the digestive enzymes like pepsinogen and leptin (Bado et al. 1998).
 - Neuroendocrine cells contain hormones and agents that regulate the activity of parietal cells within the gland and also include D cells, A like cells, enterochromaffin cells (EC), enterochromaffin like cells (ECL).

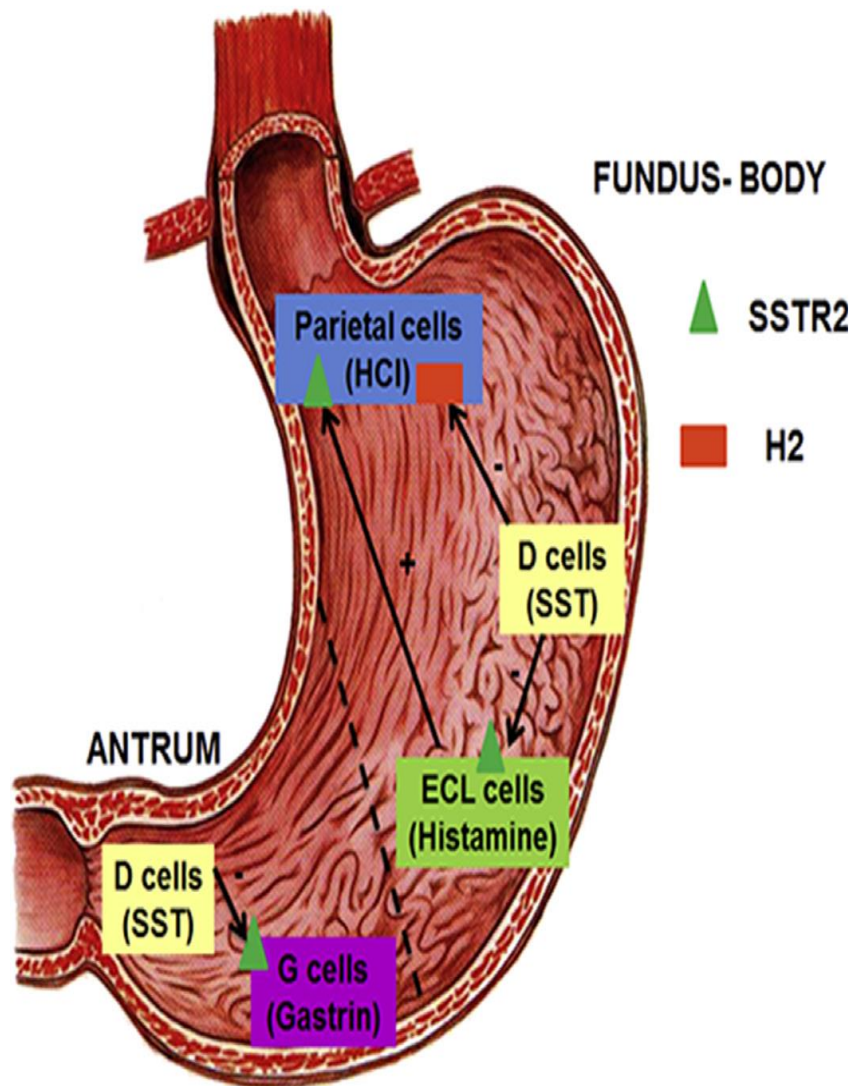


Fig. 1. Anatomic and functional areas of the stomach.

- Enterochromaffin cells (EC) contain atrial natriuretic peptide (ANP), somatostatin, serotonin, and adrenomedullin (Gower et al. 2003)
- A-like cells contain ghrelin and obestatin (Zhao et al. 2008)
- Enterochromaffin-like cells contain histamine (Prinz et al. 1993)

1.1 Mechanism of gastric secretion

- Parietal cells cause secretion of acid by a variety of factors related to food ingestion and regulated via central, peripheral, and cellular mechanisms (Cervero 1994).

- Most of vagal fibers supplying the stomach are afferent (Cervero 1994).
- The efferent fibers which called preganglionic neurons have indirect action of parietal cell, but postganglionic neurons which are located in the wall of the stomach have many neurotransmitters like (acetylcholine, gastrin releasing peptide, vasoactive intestinal peptide, nitric oxide and substance P. Through these messengers postganglionic neurons are able to regulate secretion of gastric acid directly or indirectly from the parietal cells (Smith et al. 2001).
- when these postganglionic messengers are released, they raise the level of intracellular (cAMP) and inositol triphosphate (IP3) and calcium (Sachs et. 2007).
- Induction of H^+/K^+ ATPase release the protons directly into lumen of the parietal cells and then reach the lumen of the gastric gland.

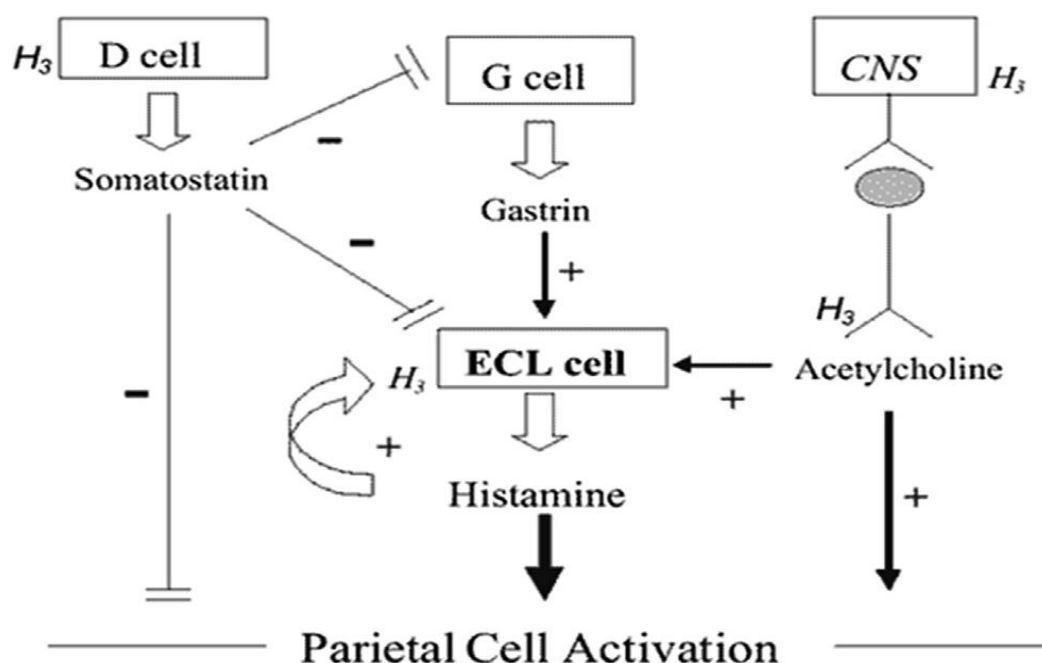


Fig. 2. Regulation mechanisms in gastric acid secretion.

The proton pump is the engine of gastric acid secretion or in another word known as H^+/K^+ ATPase, which produce H^+ ion into the lumen of the stomach and for the last step of the acid secretion two subunits are responsible:

- alfa subunit carries out the catalytic and transport function of the enzyme that reacts with ATP (Caplan et al.2007).
- beta subunit known as the smaller glycosylated protect enzyme from degradation is essential for functional stability of ATPase (Schubert 2008).

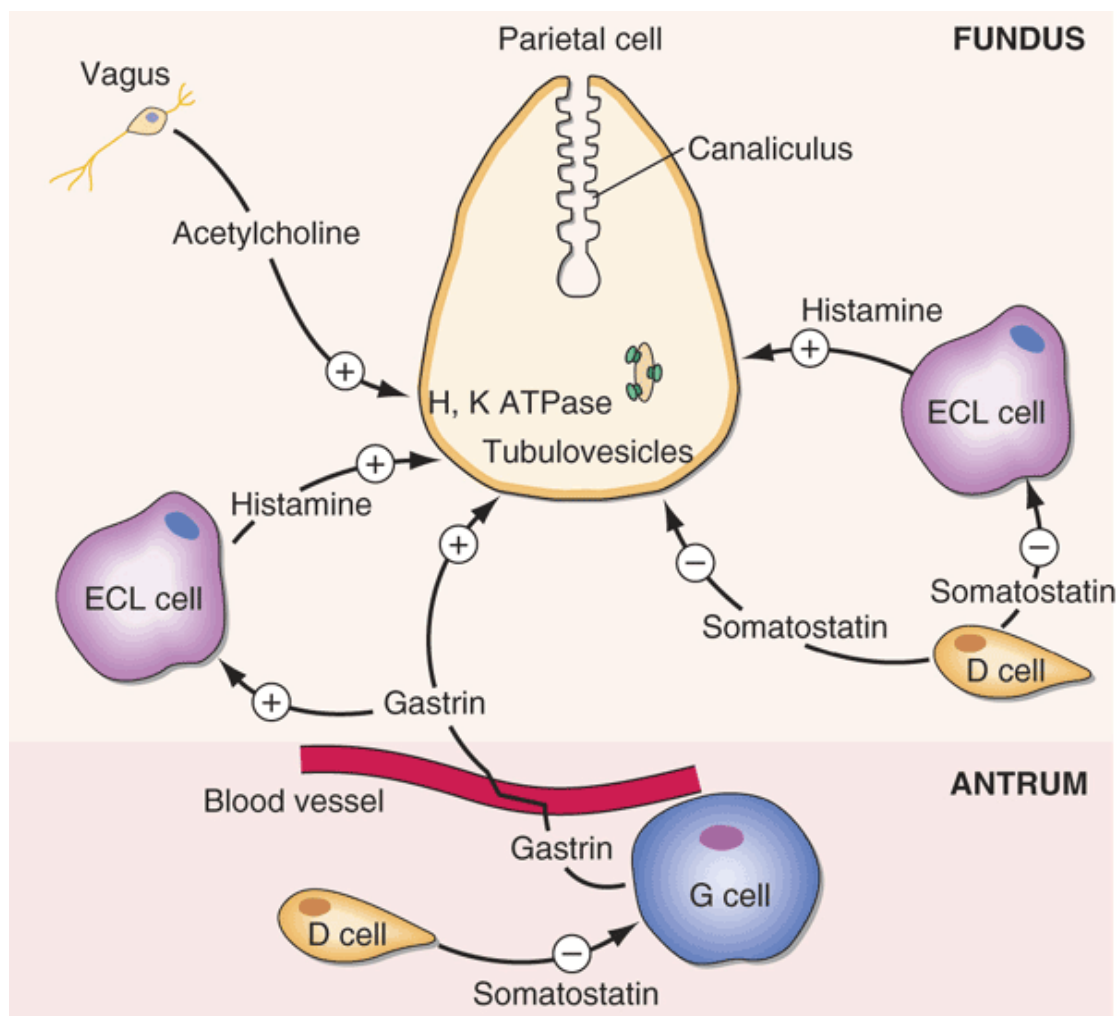


Fig 3: Parietal cell :production of H^+ ion from proton pump

1.2. Factors that affect and regulate gastric acid secretion

1. Histamine:

- a) has a positive effect on gastric acid release. It is found and produced in ECL cells which are located in the oxyntic mucosa and is considered as the most powerful stimulator of gastric acid secretion.
- b) it comes from decarboxylation of L- Histidine and acts on H₂ receptors by increasing the levels cAMP (Soll and Wollin 1979).
- c) H₃ receptors have an indirect effect on acid secretion by inhibition of somatostatin (Schubert 2008).

2. Gastrin

- a) the most potent endogenous stimulant of gastric acid in response to luminal amino acid comes from dietary intake (Hou and Schubert 2006).
- b) its effect is positive on the release and that comes from the fact that gastrin looks like cholecystokinin (CCK) due to C-terminal pentapeptide, therefore CCK1, CCK2 can recognize it and when those are stimulated in parietal cell causing a remarkable increasing in level of phospholipase C which elevates the level of intracellular Ca²⁺ (Kulaksiz et al..2000).
- c) gastrin indirectly has an effect by activation gene transcription of HDC that leads to an release of histamine (Zanner et al. 2002).

3. Acetylcholine

- a) has a positive effect on the release by two pathways:
 - 1. direct effect by binding to (M3) muscarinic receptors in parietal cells
 - 2. indirect effect by inhibition of somatostatin through activation of M2 and M4- receptors in D cells (Schubert 2008).

4. Ghrelin

- a) has a positive effect on the release by elevating histamine levels (Levin et al. 2005, Brzozowski et al. 2004).

5. Somatostatin

a) has a positive effect on the release of acid and has two forms:

somatostatin 14 found mainly in stomach and pancreas

somatostatin 28 found in small intestine

Both have an inhibitory effect on parietal cells stopping the release of histamine and gastrin from ECL cells and G cells (Altman et al. 2003)

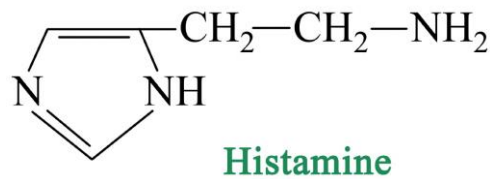


Fig 4.structure of histamine

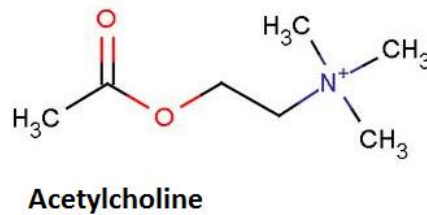


Fig 5 .structure of acetylcholine

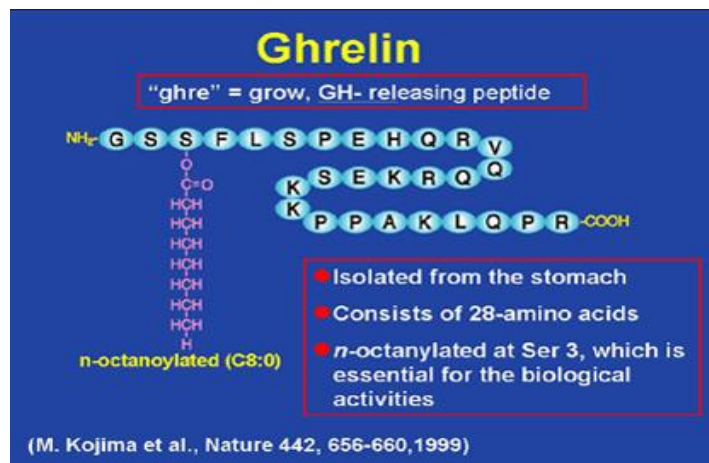


Fig 6.structure of ghrelin

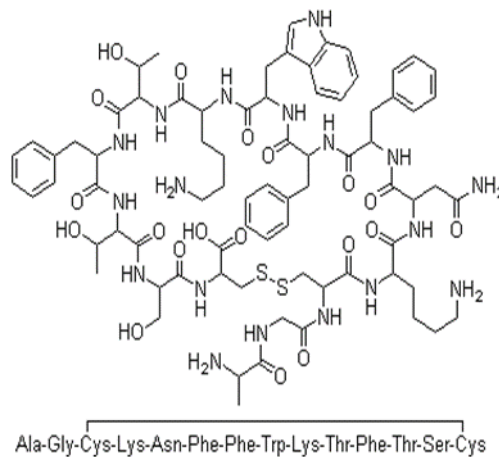


Fig 7: structure of somatostatin

1.3. Diseases associated with elevated levels of gastric acid

a) Gastroesophageal reflux disease (GERD)

GERD is the exposure of unprotected area of esophageal mucosa to gastric acid and pepsin and bile acid, due to the functional interaction between stomach and lower esophageal sphincter and nervous system leading to esophageal mucosal injury, which is usually called erosive esophagitis and always patient suffer from a complication like heart burn (Klauser et al. 1990, Richter 2007). Smoking and obesity increase incidence of GERD symptom like heart burn, belching and bloating. GERD is not life threatening but causes significant discomfort and increase risk of Barrett' s esophagus.

Gastroesophageal Reflux Disease (GERD)

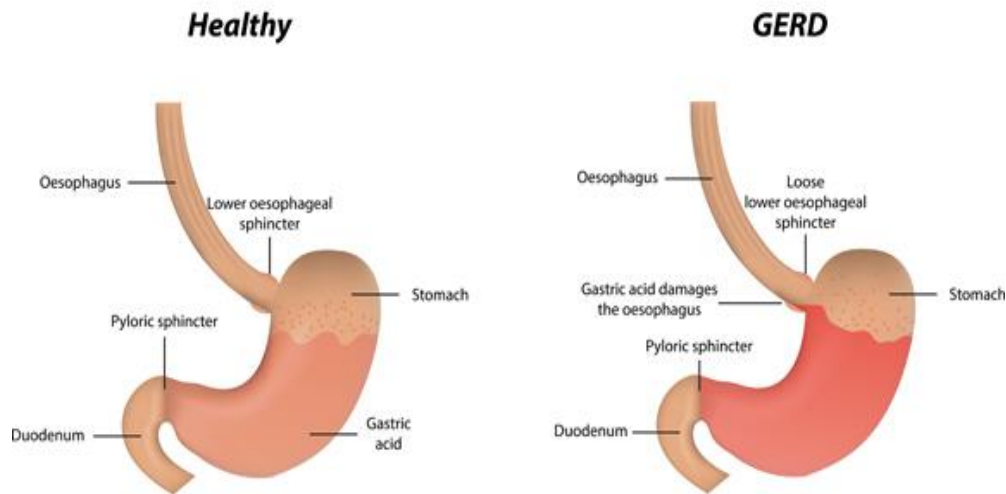


Fig 8: Difference between healthy stomach and stomach with GERD

b) Zollinger Ellison syndrom

in this disease a non beta cell tumor of pancreatic islets may produce gastrin in a sufficient quantity to stimulate secretion of HCl leading to severe gastroduodenal ulceration and other uncontrolled hyperchlorhydria.

ECL cell carcinoidis have been described in association with ZE syndrom.

The aim of the therapy in this case is to reduce gastric acid secretion. Therefore proton pump inhibitors are surely the drugs of first choice.

c) Peptic ulcer disease (PUD)

is a very common disease caused by

a) an imbalance between mucosal defence factors (somatostatin, prostaglandins, bicarbonates, calcitonin) and aggressive factors (acid, pepsin, *Helicobacter pylori*)

b) *Helicobacter pylori* and non steroidal antiinflammatory drugs

d) Duodenal ulcers

The etiology of most duodenal ulcers is due to *Helicobacter pylori* increased acid output and suppression of somatostatins (Robinson and horn 2005).

e) Stress related ulcers

Usually occur as result of severe systemic or CNS illness or trauma. Both acid and mucosal ischemia are involved in the etiology of stress ulcers.

f) *Helicobacter pylori* infection

Helicobacter pylori is gram negative rod shaped bacteria and has been associated with gastritis, PUD and gastric beta cell lymphoma.

40% of patient over 40 years with peptic ulcer are infected with *Helicobacter pylori*. The infection leads to impaired production of somatostatin from D cell which causes an increase in HCl and decrease of bicarbonate. *Helicobacter pylori* infections are now proven to be a risk factor of gastric cancer. Infection also causes inflammation of the antral gastric mucosa and its bacterial products may cause changes in endocrine function (Graham et al. 2002).

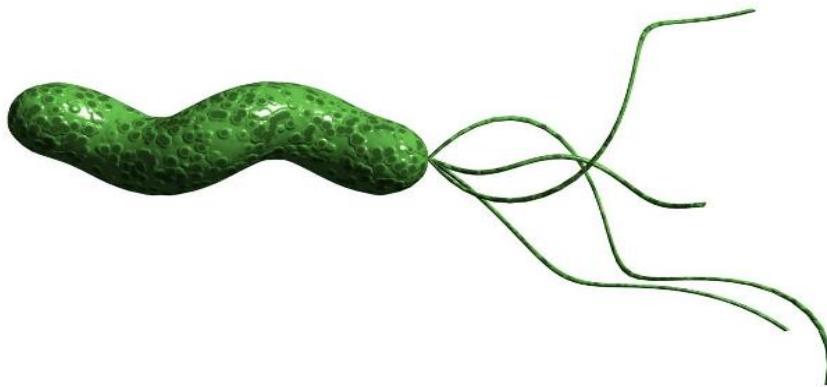


Fig 9 . *Helicobacter pylori*

1.4. Relation between the usage of NSAIDs and PUDs

NSAIDs are a major etiological factor associated with peptic ulceration in the world. It is estimated that approximately 1 % to 2% of patients taking NSAIDs will develop clinically significant ulceration.

Acetylsalicylic acid (Aspirine) may cause peptic ulcer through two mechanisms locally and systemically. Some drugs like diclofenac have an acidic nature, which have a direct local cytotoxic effect on mucosal epithelial cells and inhibit formation of gastric prostaglandins by blockade of COX1 enzyme. Using NSAIDs at same time with steroids or anticoagulant at age over 60 years consider a risk factor for increasing gastroduodenal injury (Lanza 1998)

NSAIDs induce ulcers more frequently in stomach lacking of mucosal defence mechanism (Hunt et al. 1995, Gambaro et al. 2003).

Starting treatment with NSAIDs in patients with infection of *H. pylori* increase risk and incidence of gastric ulcer (Huang 1996).

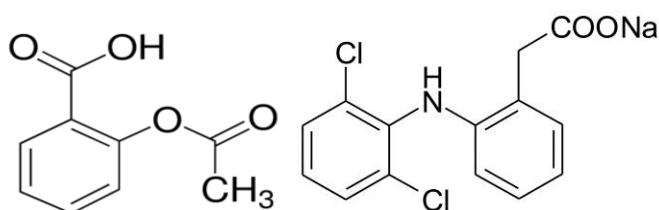


Fig 10: acetylsalicylic acid and diclofenac

1.5. Treatment of elevated gastric acid level

This treatment is based on suppressing of aggressive factors with

- a) Antacida
- b) Muscarinic receptor antagonists
- c) H₂ receptor antagonists
- d) Proton pump inhibitors (PPI)
- e) Eradication of *Helicobacter pylori*
- f) Prostaglandin analogues

a) Antacida

The primary action of this group on stomach is only a partial neutralization of gastric acid and inhibition of the proteolytic enzyme pepsin (Maton and Burton 1999).

Antacida are not currently used for the treatment of gastric peptic ulcer (Moayyedi et al. 2006). They show 10% improvement in GERD symptoms compared to placebo (Tran et al. 2007) and have an effective action in the prophylaxis of stress ulcers

They can cause drug interaction by changing of gastric pH (Maton et al. 1999). This effect is dose related. Calcium containing antacida can cause milk alkali syndrome leading to kidney failure or death (Picolos et al. 2005).

Magnesium containing antacida can cause diarrhea.

Aluminum antacida can cause encephalopathy and osteomalacia in end stage renal patients (National Kidney Foundation 2003).

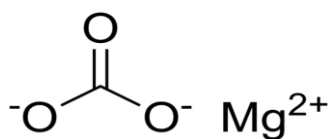


Fig 11. magnesium carbonate

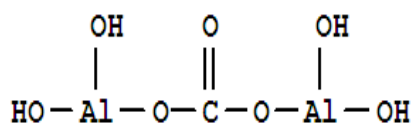


Fig 12. aluminium carbonate

b) Muscarinic receptor antagonists

Mode of action of this group is to block the M3 receptor which reduces gastric acid secretions for example pirenzepine.

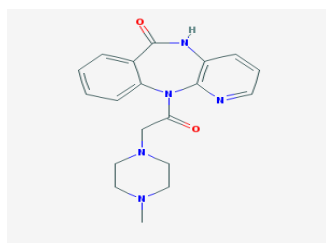


Fig 13 : pirenzepine

This group has many side effects, the most important one are parasympatholytic (atropin like) effects such as dry mouth, blurred vision and constipation..

c) H₂ receptor antagonists

They were described in 1972 (Black et al. 1972). This group has structural analogue of histamine and block H₂-receptors reversibly and decrease their tonic activation (Parsons and Ganellin 2006, Smith et al. 2001). All members of this group have a heterocyclic ring and reach peak concentration within 1-3 hours and are eliminated by renal mechanism, 30%-60% are excreted unchanged in urine. They can be used once daily at bed time to maximize action for treatment of nocturnal acid breakthrough (Pan et al. 2006). H₂-antagonists decrease H₂ receptors degradation (Osawa et al. 2005). Examples of this group are ranitidine or famotidine.

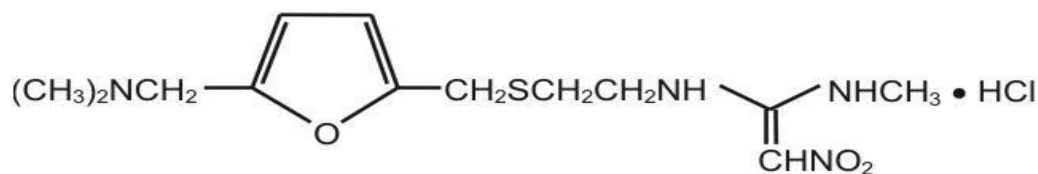


Fig 13 : structure of ranitidine

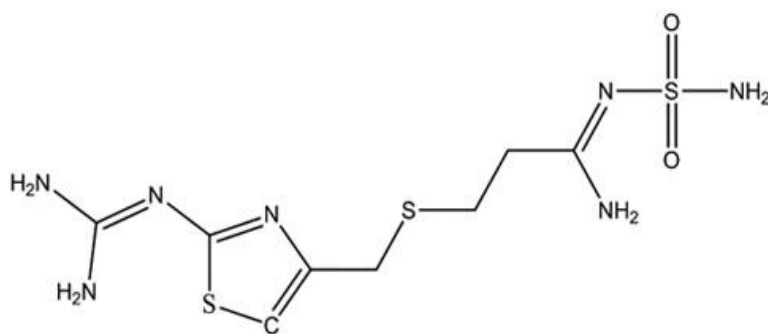


Fig 14 : famotidine structure

This drugs are usedfor peptic ulcer treatment and to remove symptoms of heart burn,but thea are not effective in controlled erosive esophagitis (Zacny et al. 2005). Ranitidine 75 mg and famotidine 10mg is able to reduce overnight gastric acidity for 12 hours (Grimley et al.1997). They are also used for treatment of symptomatic GERD (Tran et al. 2007), for prevention of NSAIDs induced injury.The standard dose reduces only duodenal, not gastric ulcer while double dose reduces risk of both (Rostom et al. 2002).Thea show a weak effect against non ulcer dyspepsia (Moayyedi et al. 2006). Cimetidine has an antiandrogenic effect, which causegyncomastia and impotence. H₂-antagonistsare not as effective as proton pump inhibitors (Khan et al. 2007). PPIs are superior to H₂-antagonist in preventing rebleeding of acut peptic ulcer and in ulcer symptoms and healing (Poynard et al. 1995, Walan et al. 1989)

d) Mucosal protective agents

Sucralfate

is an aluminum salt of sulfated sucrose and aluminum hydroxide. It binds to ulcerated tissue of gastric mucosa causing a cytoprotective effect (McCarthy 1991). It should be taken 30 to 60 minutes before the meals to enhance the process of binding effect.

It has similar effect in healing gastric and duodenal ulcer compared to H₂-antagonists (McCarthy 1991). It is also used for the prophylaxis of stress related injury, which is based on maintaining a lower intragastric pH and conserving the sterilizing effect of acidic stomach (Sesler 2007).

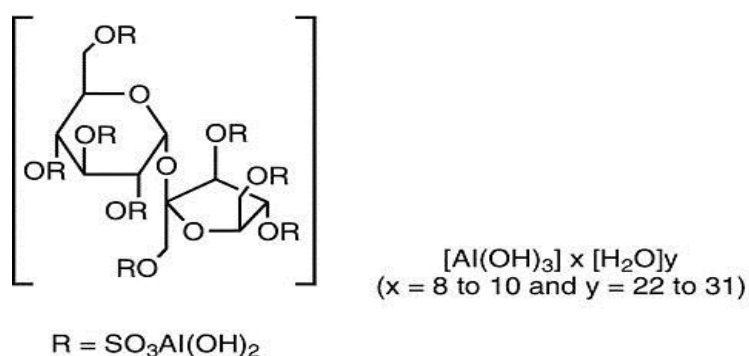


Fig 15: structure of sucralfate

Misoprostol

The theoretical basis for prostaglandin treatment is to overcome the systemic effect of NSAIDs and to enhance epithelial cell growth and repair (Duerksen 2003).

Only prostaglandin E₂ (Misoprostol) was approved by the FDA for prevention of NSAIDs related ulcer and designed to overcome the NSAIDs induced deficiency in prostaglandin in gastric mucosa. It is orally taken and reaches maximum plasma concentrations after 30 minutes with a half time 1.5 hours and its metabolites are renally excreted (Hooper et al. 2004).

Misoprostol is the only prostaglandin analog that has been demonstrated to reduce serious gastrointestinal complications from NSAIDs treatment (Hooper et al. 2004). It has been found to be superior to H₂-antagonists for prevention of gastric ulcer but not

for duodenal ulcer (Alex 2009 Rostom 2002). Misoprostol represent only 2% of medical therapy for NSAIDs users due to some common side effect like abdominal cramps and diarrhea leading to a stop of treatment (Laine et al. 2008).

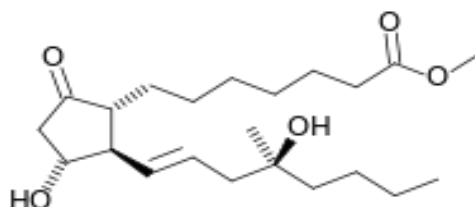


Fig 16 : structure of misoprostol

e) Eradication of *Helicobacter pylori* infection

Helicobacter pylori infection cause inflammatory gastritis and is a putative contributor to peptic ulcer disease, gastric lymphoma and adenocarcinoma. Eradication means a double or triple antimicrobial therapy. In combination with antisecretory drugs it is successfully used to treat peptic ulcer. Bismut compounds are also been included in regimen probably due to cytoprotective action. Triple therapy with metronidazole, a bismut compound and either tetracycline or amoxycillin for two weeks is recommended to treat *Helicobacter pylori* infections.

f) Proton Pump Inhibitors (PPIs)

The proton pump inhibitors are considered as the most potent inhibitors of gastric acid in due to inhibition of H⁺K⁺-ATPASE, which is the last step of the common pathway for gastric acid production (Sachs et al. 2007).

Some drugs of this group are:

omeprazole

lansoprazole

pantoprazole

rabeprazole

PPIs are weak bases and act as prodrug, which need an acidic environment in order to inhibit H^+K^+ -ATPase (Sachs et al. 2007). Members of this group share a common structure consisting of substituted pyridyl methyl sulfinyl benzimidazoles, that vary in terms of substitutions on either the pyridine or the benzimidazole rings (Huang and Hunt 1996). Due to its acid dissociation constant levels they can accumulate in the secretory channel of parietal cell, that means a higher concentration here compared to plasma. They become protonated and converted into an active sulfenamide which forms a disulfide bond with the alpha subunit of H^+K^+ -ATPase. Therefore the duration of action is long and the inhibitory mechanism does not depend on histamine, acetylcholine and gastrin stimulus for acid formation (Caplan 2007). In contrast to H_2 -antagonists PPIs decrease pepsin secretion.

Morning dosing of PPIs is associated with significantly improved acid suppression not like H_2 -antagonists (Chiverton et al. 1992, Mussig et al. 1997). The dose should be taken before breakfast because of the amount of H^+K^+ -ATPase in parietal cell is in very high concentrations due to fast and eating enhances it to become active.

Repeated dose of PPI increases its inhibitory effect and that occurs generally from the third day of treatment due to about 70% of pumps remain inhibited (Boparai et al. 2008). All group members undergo a metabolism via hepatic CYP2C19. Rabeprazole is unique as only 15% -20% of its metabolism involves by CYP2C19 (van Zanten et al. 2006).

All PPIs have a safety profile in both clinical trials and in post marketing pharmacovigilance (Salgueiro et al. 2006).

The main concerns regarding long term treatment with PPIs are prolonged hypergastrinemia and chronic hypochlorhydria, hip fractures (Yang et al. 2006), renal complications (Geevasinga et al. 2006) and community acquired pneumonia (Laheij et al. 2004).

PPIs can decrease bioavailability of drugs which acid dependent absorption like HIV protease inhibitors (Atazanavir), ampicillin, iron and digoxin.

Omeprazole is an inhibitor of CYP2C19 that can increase the level of some substances (diazepam, phenytoin) but not pantoprazole or esomeprazole.

The platelet inhibitory action of clopidogrel is also decreased (Siller et al. 2009, Gilard et al. 2008).

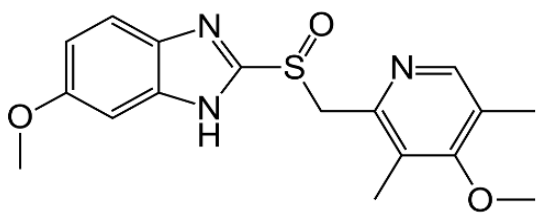


Fig 17: structure of omeprazole

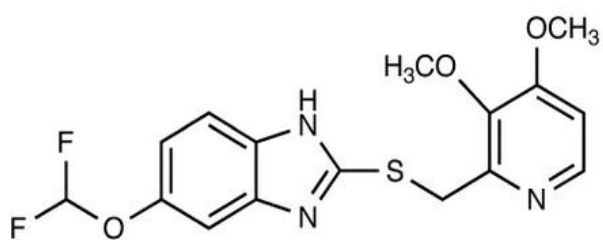


Fig 18: structure of pantoprazole

2. Aim of work

The aim of this work is to describe the gastrointestinal disorders and the treatment of these diseases. Furthermore the risks of longtime treatment with proton pump inhibitors should be discussed using the relevant literature.

3. Proton Pump Inhibitors and Myocardial Infarction

The primary indication of proton pump inhibitors is the treatment of GERD. In this field every year there are over 113 million PPI prescriptions are filled together with over the counter use with over 13 billion dollars world wide sales (Shah et al. 2015, Madanick et al. 2014, Katz 2010). About 21 million of patients in the USA only used one or more prescription of PPIs in 2009 making it the third highest seller in the country (US food and drug Administration FDA 2009, Shah et al. 2015).

In people with a history of an acute coronary syndrom treated with clopidogrel, which is antiplatelet agent used to reduce risk of ischemic events, and PPIs show a reduction of the efficacy of clopidogrel (Shah et al. 2015, CAPRIE 1996). There are many theories explaining and showing how the treatment with PPIs can enhance the risk of major adverse cardiovascular events amongst people with a history of acute coronary syndrom (Shah et al. 2015, Ho et al. 2009, Bhatt et al. 2010). The hypothesis depend on that the PPIs inhibit the hepatic isoenzyme (CYP2C19), which is responsible for the activation of clopidogrel, thereby interfering with its action to prevent clot formation leading to high risk of myocardial infarction and coronary thrombosis (Holmes et al. 2010).

However, some studies have associated the PPIs usage with high risk for cardiovascular patients, independently of clopidogrel use (Shah et al. 2015).

A reduction in the therapeutic benefit has been reported during treatment with another antiplatelet aspirin in patients with acute coronary syndrom (Goodman 2012).

It is possible that PPIs may reduce the absorption of antiplatelet drugs due to reduction of gastric pH, but at same time H₂ blocker make the same effect without risk of cardiovascular events (Adampoulos et al. 2009, Dunn et al. 2013).

Another explanation show risks of PPIs due to unknown mechanistic pathway. It was recently reported that PPIs inhibit the activity of dimethylarginine dimethylaminohydrolase enzyme (DDAH). The asymmetric dimethylarginine (ADMA) is considered as an endogenous molecule that inhibits the enzymatic activation of nitric oxide synthase (Shah et al. 2015, Cook et al. 2011).

The disturbance in endothelial nitric oxide synthase may cause an increase of vascular resistance and promotes inflammation and thrombosis (Shah et al. 2015, Cook et al. 2011).

ADMA is considered as a potent disease marker of major adverse cardiovascular events (Boeger et al. 2009).

The clinical study shows that PPIs increase the level of ADMA in the human endothelial cells by about 20%.

To date there is only one study, that has examined the risk of cardiovascular associated with PPIs using (Shih et al. 2014).

From the above concern there are data, that suggest that the risk coming from the usage of PPIs may apply or happen to people, who do not take antiplatelet agents and without any vascular diseases. Therefore a novel and recent validation was carried out (Shah et al. 2015, Nead et al. 2013).

For data mining analysis data sources were used from Stanford University, from Practice Fusion Inc. and one prospective source for survival analysis.

The Stanford Translation Research Integrated Database Environment (STRIDE) is a research and development project at Stanford University to create a standard base informatics platform supporting clinical and translational research. It contains data from 1.8 million patients, 19 million encounters, 35 million coded International Classification of Disease diagnosis and transcription reports totaling over 11 million unstructured clinical notes (Shah et al. 2015).

The Practice fusion Inc. is a free, web-based electronic health record system for clinicians. These data contain 1.1 million patients, 5.5 million coded diagnoses, 6.8 million prescriptions and 5.5 million unstructured clinical notes dating back to 2007.

Additionally the association of PPI use with cardiovascular mortality in Genetic Determinants of Peripheral Arterial Disease (Gene PAD) was examined. Gene PAD cohort is comprised of individuals, who underwent shortness of breath or an abnormal stress test at Stanford University and that was established in 2004 and included 1.5 million individuals (Shah et al. 2015, Nead et al. 2013).

Clinical data were used to screen the exposure to PPI associated with elevated risk for myocardial infarction in general population. The validation of data mining

approaches is performed by measuring predictive accuracy and is widely adopted in computer science (Halevy et al. 2009).

GERD) is the the primary indication for PPI. The authors took this fact to define the baseline population in their pipeline and excluded all patient under 18. They defined GERD by International Classification of Diseases, ninth revision (ICD-9) code for esophageal reflux (530.81) and heart burn (787.1) and UMLS code for GERD (C0017168) and myocardial infarction defined by ICD9 code 410, and more than 18 different UMLS codes including myocardial infarction (C0027051) and silent myocardial infarction (C0340324).

This study period included all data from 1994 through 2011 in STRIDE and from 2007 through 2012 in Practice fusion Inc. and defined two studies groups within the GERD baseline population in this period .

The first group study defined by taking PPIs including a sub group of patient that were not on clopidogrel. The other group examined H₂ blocker for treatment of GERD.

The data mining method works based on „beforeness“ of treatment with PPIs and given the uncertainty the exact times of treatment and the messy EMR data used. This is followed by a two steps process for detecting drug safety signals (Shah et al. 2015, Lependu et al. 2013).

First a raw association was calculated then followed by adjustment which involves matching on age, gender, length of observation, health status. The first step is useful for flagging putative signals, the second step was useful in reducing false alarm.

The first table show the balance of variables for patients on PPIs in the STRIDE dataset, the second the balance of variables in patients on H₂-blocker in the STRIDE dataset.

Variable	Before Matching			After Matching	
	Exposed (N = 32,363)	Unmatched controls (N = 38,114)	p-value	Matched controls (N = 32,099)	p-value
Demographics					
Age at indication (GERD), mean (sd)	54.88 (16.65)	53.47 (17.15)	<2.22e-16	54.52 (17.13)	0.005
Gender (male), n (%)	44.31	45.60	0.0006	44.61	0.44
Race, n (%)					
Asian	7.93	8.92	< 0.0001	8.33	0.13
Black	2.77	2.84	0.62	2.96	0.15
Other	11.82	11.58	0.33	11.92	0.71
Unknown	27.07	26.52	0.09	25.84	0.0001
White	50.41	50.14	0.49	50.95	0.16
Co-prescription					
Clopidogrel, n(%)	5.90	5.93	0.89	6.16	0.16
Other					
No. of unique diseases, n (%)					
1–28	7.72	12.78	<0.0001	7.30	0.34
29–41	9.45	9.67	0.34	8.87	0.002
42–56	10.16	10.07	0.72	9.98	0.42
57–74	10.44	10.12	0.16	10.27	0.46
75–95	10.26	9.76	0.03	10.28	0.91
96–121	9.93	9.66	0.23	10.35	0.08
122–157	10.47	9.62	0.0001	10.79	0.18
158–207	10.37	9.37	9.9e-06	10.64	0.26
208–294	10.53	9.62	6.3e-05	10.79	0.26
>294	10.67	9.33	3.8e-09	10.73	0.81
No. of unique drugs, n (%)					
1–9	5.78	14.23	<0.0001	5.80	0.92
10–15	9.18	10.03	0.0001	9.48	0.16
16–22	11.05	10.48	0.01	10.89	0.50
23–29	9.76	8.92	0.0001	9.51	0.29
30–38	10.93	9.37	8.0e-12	10.66	0.27
39–49	10.74	9.84	0.0001	10.94	0.33
50–64	10.80	9.43	1.7e-09	10.93	0.60
65–86	10.81	8.95	2.2e-16	10.48	0.15
87–123	10.74	9.12	9.5e-13	10.61	0.57
>123	10.21	9.63	0.009	10.70	0.05
Length of observation (days), n (%)					
1–9	8.97	10.92	<0.0001	8.37	0.007
10–102	9.90	10.05	0.52	9.59	0.17
103–364	9.72	10.25	0.02	9.89	0.48
365–816	9.95	10.02	0.77	10.21	0.25
817–1426	9.87	10.11	0.29	10.12	0.21
1427–2156	9.64	10.31	0.003	10.10	0.05
2157–3018	9.77	10.20	0.06	10.27	0.03
3019–3956	10.40	9.66	0.001	10.48	0.76

Table 1: Balance of variables for patients on PPIs in the STRIDE dataset (Shah et al. 2015)

Variable	Before Matching			After Matching	
	Exposed (N = 12,796)	Unmatched controls (N = 57,681)	p-value	Matched controls (N = 38,388)	p-value
Demographics					
Age at indication (GERD), mean (sd)	52.90 (16.85)	54.38 (16.95)	<2.22e-16	53.19 (16.74)	0.13
Gender (male), n (%)	42.76	45.50	1.38e-08	43.26	0.41
Race, n (%)					
Asian	9.27	8.28	0.0003	9.02	0.41
Black	3.41	2.68	2.55e-05	3.19	0.33
Other	11.80	11.67	0.67	11.60	0.61
Unknown	23.43	27.51	< 2.22e-16	24.24	0.12
White	52.09	49.86	4.70e-06	51.95	0.82
Co-prescriptions					
Clopidogrel, n(%)	6.99	5.67	7.1e-08	6.75	0.45
Other					
No. of unique diseases, n (%)					
1-28	6.05	11.44	< 0.0001	6.12	0.79
29-41	6.71	10.21	< 2.22e-16	6.83	0.68
42-56	7.92	10.60	< 2.22e-16	8.11	0.55
57-74	8.79	10.59	1.55e-10	9.22	0.21
75-95	9.14	10.17	0.0003	9.58	0.22
96-121	9.40	9.87	0.10	10.07	0.07
122-157	10.90	9.81	0.0003	11.88	0.01
158-207	11.46	9.47	9.59e-11	12.25	0.05
208-294	13.15	9.34	< 2.22e-16	13.19	0.92
>294	16.48	8.50	< 2.22e-16	12.75	< 2.22e-16
No. of unique drugs, n (%)					
1-9	4.01	11.83	< 0.0001	4.02	0.98
10-15	6.84	10.26	< 2.22e-16	6.78	0.85
16-22	8.33	11.25	< 2.22e-16	8.46	0.67
23-29	8.01	9.59	4.58e-09	8.24	0.48
30-38	9.91	10.12	0.47	10.68	0.04
39-49	10.37	10.20	0.58	11.18	0.03
50-64	10.90	9.87	0.0006	12.10	0.001
65-86	11.61	9.40	9.31e-13	12.63	0.008
87-123	13.29	9.10	< 2.22e-16	13.32	0.94
>123	16.73	8.38	< 2.22e-16	12.59	< 2.22e-16
Length of observation (days), n (%)					
1-9	6.56	10.81	< 0.0001	6.56	1
10-102	7.36	10.56	< 2.22e-16	7.40	0.90
103-364	8.45	10.35	7.87e-12	8.95	0.15
365-816	9.71	10.04	0.25	9.95	0.51
817-1426	9.97	10.01	0.91	10.24	0.47
1427-2156	10.44	9.90	0.07	10.61	0.65
2157-3018	10.68	9.84	0.005	10.70	0.97
3019-3956	11.80	9.60	1.17e-12	11.70	0.39
3957-5084	11.99	9.56	7.55e-15	11.69	0.46
>5084	13.04	9.33	< 2.22e-16	12.20	0.04

Table 2: Balance of variables in patients on H₂-blockers in the STRIDE dataset (Shah et al. 2015)

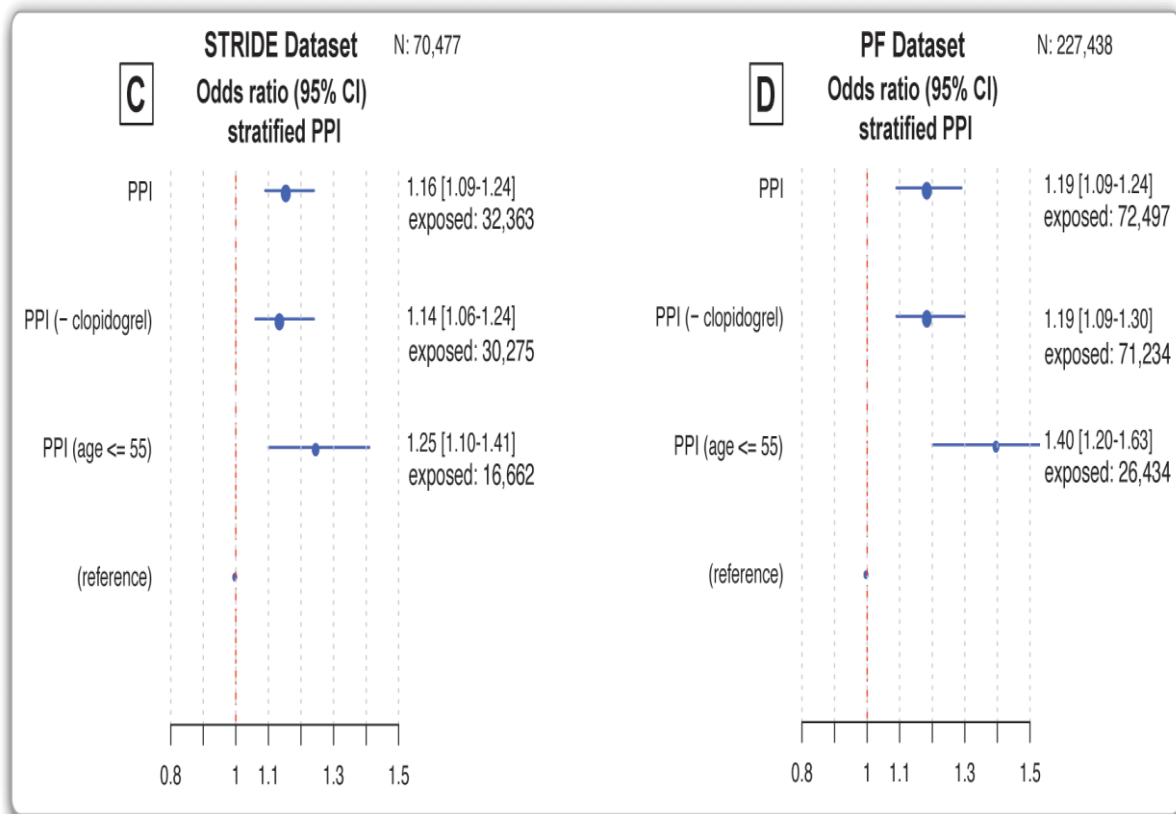
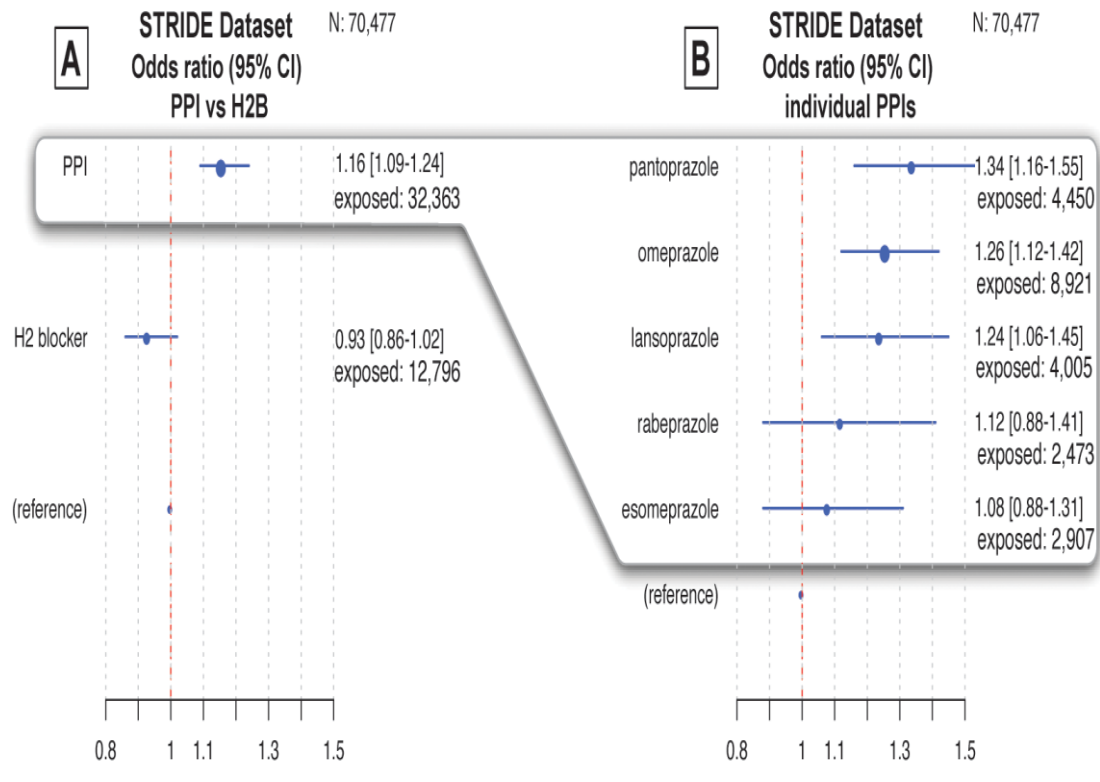


Fig 21: PPI use is associated with an increased risk for MI, regardless of age or clopidogrel use (Shah et al. 2015).

No association is identified for H₂-blocker use: In the figure, the dotted red line represents the reference point indicating no elevated risk for myocardial infarction (MI). The odds ratio and 95% confidence interval for each exposure are indicated by a blue dot and blue line, respectively, which are also represented numerically to the right of each fig. The size of the dot is proportional to the exposure size of each group (see Table 1). Fig A, derived from STRIDE (N = 70,477), shows that PPIs have a class-level effect for MI in the general population of patients with GERD. By comparison, H₂ blockers, an alternate treatment, have no association. Fig B breaks down the associations for each PPI individually. Figs C and D use stratification to show that the signals are corroborated in two independent datasets (STRIDE and Practice Fusion) and are robust in important subgroups. Fig C shows that, for the STRIDE dataset, when patients on clopidogrel are excluded, the associations are unchanged. Also, in lower-risk age groups for MI, the associations are still present. Similar trends are seen in these subgroups in the Practice Fusion (PF) dataset (N = 227,438) shown in Fig D (Shah et al. 2015).

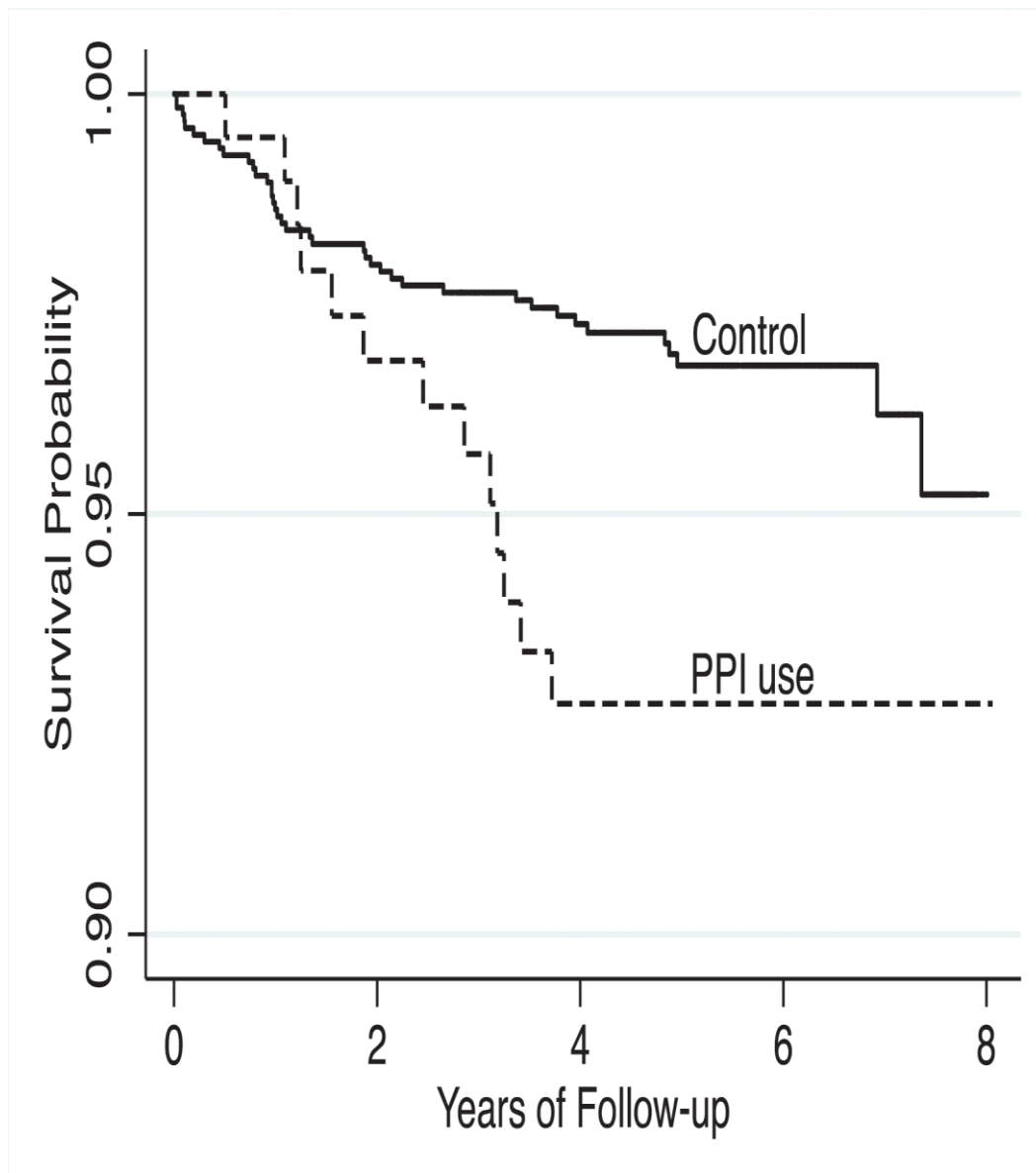


Fig. 22: Survival plot from the prospectively followed GenePAD study confirms that PPI use is associated adverse outcome (Shah et al. 2015).

The results illustrate, that the use of PPIs is associated with elevated risk of myocardial infarction in the general population and use of H₂-blockers do not show such risk independent of the clopidogrel use or the age.

The association is seen outside the high-risk populations previously examined in elderly or patients with ACS (Maggio et al. 2013).

The discovered results were compatible with the studied group of subject with coronary artery disease (Gilard et al. 2008).

While two prospectiv studies in post ACS patient failed to detect any relation between PPI use and myocardial infarction and stroke (Bhatt et al. 2010), the authors admit that their results donot deny a clinically effect on cardiovascular events due to the use pf PPIs.

In fact the two studies said that there is a high risk of myocardial infarction more than the normal and that concern is based on PPI decrease metabolism of clopidiogrel (Shah et al. 2015, FDA 2009).

The current study suggested that PPIs were associated with short term cardiovascular harm between taiwanse individuals (Shin et al. 2014).

and the previously point was compatible with the concern that PPIs reduced the cardioprotective effect of some drugs such as ticagrelor.

While this phenomenon might result from the effect of PPI absorption, it is also believed that H₂-blockers induce a similar reduction in gastric pH without increasing the cardiovascular risk (Shah et al. 2015).

PPIs have been reported to induce positive inotropic effect on myocrdial tissue and increase the cardiovascular risk factor homocysteine by inhibition the absorption of vitamin B12 (Sossala et al. 2011, Daval and Lentz 2005).

This observation demonstrates that PPI usage is associated with harm in general population like young and those who taking no antiplatelets. The PPIs refer to inhibition of DDAH activity that might explain how PPIs promote cardiovascular risk ,even in patient taking no clopidigrel (Tran et al. 2003).

This inhibition leads to an increase in intracellular ADMA in endothelial cells by 20% and a reduction of nitric oxide that explains the concern about using PPIs and the increased risk of myocardial infarction in the generalpopulation.

In conclusion this research used a novel analytical pipeline to associate PPI usage with risk of myocardial infarction in general population independent of clopidogrel use. This results and the preliniac results require an additional and more investigation (Shah et al. 2015, Leeper et al. 2013,Friedman et al. 2010).

4. Proton Pump Inhibitors and Community Acquired Pneumonia

Community acquired pneumonia is a common diagnosis associated with high morbidity rate. In 2006 alone over 4.2 million cases occurred in the USA (Lambert et al. 2010). The data come from medicare shown a 30 day mortality range from 3.8 to 8.5 depending of severity of disease (Lambert et al. 2015, Yu et al. 2012)

In 2011 omeprazole, the first discovered proton pump inhibitor (PPI), was the sixth most commonly prescribed drug in the USA with over 60 millions prescriptions (Lambert 2015, IMS institute for healthcare 2011, 2012)

Although the wide range use of PPIs in GERD, duodenal and peptic ulcers, the ambulatory setting suggests that 35% of patients receiving PPIs suffer from side effects associated with PPI-therapy including deficiencies of vitamins and minerals, hip fracture and diarrhea. Community acquired pneumonia (CAP) has been hypothesized as an additional side effect (Lambert et al. 2015, Pierson et al. 2002, Heidelbaugh et al. 2009)

A systemic review and meta analysis of many studies to show that treatment with PPIs associated with high risk of CAP depending on dose and duration of therapy was conducted.

The systematic review was carried out in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA), which consists of a 27 item checklist and a four phase flow diagram. and Meta-analysis of Observational Study in Epidemiology (MOOSE). The proposed checklist contains specifications for reporting meta analyses of observation studies in epidemiology, including background, search strategy, methods, results, discussion and conclusion (Lambert et al. 2015, Liberati et al. 2009, Stroup et al. 2000).

The PRISMA check list shows studies that could be excluded for more than one reason. Therefore the sum of exclusion reasons exceeds the total studies. Examples of studies lacking extractable data include abstracts without full results such as abstracts reporting a ratio without exposure outcome definitions or papers summarizing

outcome qualitatively in the text such as manuscripts reporting adverse event categories that grouped pneumonia among other events.

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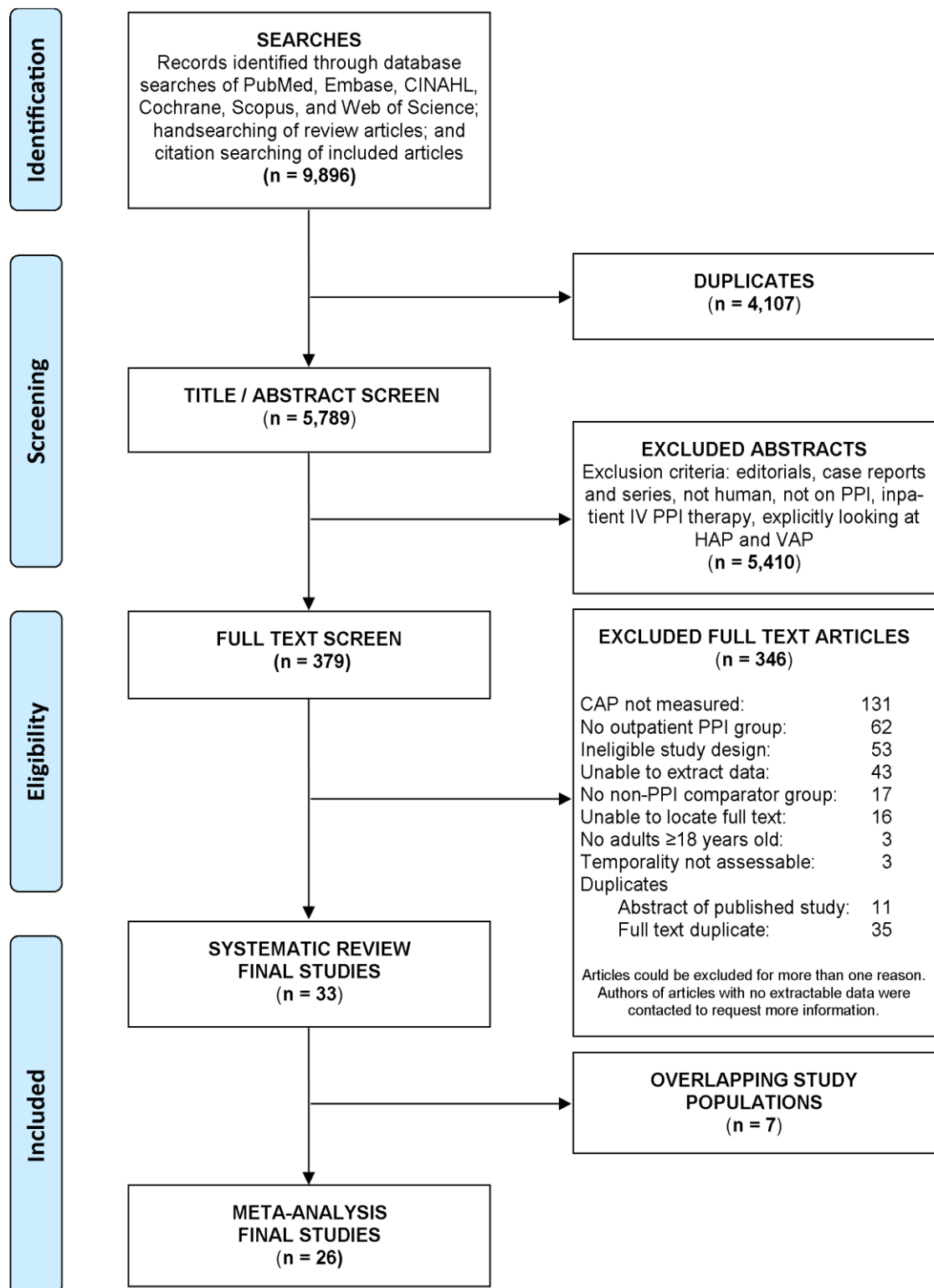


Fig 23: Flow diagram of study selection, adapted from PRISMA flow diagram (Lambert et al. 2015)

Systematic searches of MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus and Web of Science were performed.

The studies include data to calculate the risk of CAP among adult participants with and without exposure to PPI therapy. (Lambert et al. 2015, Anglemeyer et al. 2014, Shrier et al. 2007).

Studies in which less than 95% of participants were over 18 years old, also if PPIs were administered intravenously and also studies in which CAP preceded PPI exposure were excluded.

A modified version of the Newcastle-Ottawa-Scale was used to enhance the methodological quality of the studies (Lambert et al. 2015, Wells et al. 2013).

The primary results from meta-analysis were incident of CAP among population who were taking PPI. The secondary analysis evaluated the risk of CAP with H₂ receptor blockers and also the risk of hospitalization for CAP with PPI therapy. Therefore 3 subgroups of population were examined to make more specific investigations. Those treated with different PPI doses, different duration of PPI therapy (month and age categories, less than 65 years or more than 65 years).

Table 1. Qualitative analysis of 32 Studies under Systematic Review.

Author Year, Study Design	Location, Years of Conduct	Source of Cases	CAP setting	CAP Definition	# Cases / # Participants	Acid-suppression	Methods of Ascertainment	Ref.
Almirall 2008, Case-Control	Spain, 1999–2000	Patients >14 years old at 64 primary care centers	Inpatient or Outpatient	Medical record review with prescription of antibiotics and new radiological findings suggestive of infiltrate	1336 / 2662	PPI	PPI: Questionnaire; CAP: Medical, radiographic records	23
Chen 2013, Cohort	Taiwan, 1998–2008	CKD patients in Taiwan Health Insurance Research Database	Inpatient	Diagnostic codes (ICD-9)	619 / 8076	PPI	PPI: Prescription records; CAP: Diagnostic codes (ICD-9)	24
Dublin 2010, Case-Control	Washington, USA, 2000–2003	Adults 65–94 years old in Group Health Integrated healthcare delivery system	Inpatient or Outpatient	Diagnostic codes (ICD-9), confirmed by review of radiology and hospital records	1125 / 3360	PPI	PPI: Pharmacy database; CAP: Diagnostic codes (ICD-9), medical records	25
Ernst 2012, Case-Control	United Kingdom, 1997–2009	Anti-parkinsonian drug users 40–89 years old in the General Practice Research Database	Inpatient	Diagnostic codes (ICD-10)	1835 / 17923	PPI	PPI: Prescription records; CAP: Diagnostic codes (ICD-10)	26
Filion 2013, Cohort	Canada, UK, & USA, 1997–2010	New NSAID users ≥40 years old in eight research databases	Inpatient	Diagnostic codes (ICD-10)	5135 / 4238504	PPI	PPI: Pharmacy and prescription records; CAP: Diagnostic codes (ICD-10)	27
Gau 2010, Case-Control	Ohio, USA, 2004, 2006	Rural community hospital admissions ≥65 years old	Inpatient	Discharge diagnosis with radiographic confirmation	194 / 1146	PPI	PPI: Medication reconciliation, physician or nursing home notation; CAP: Diagnostic codes, medical records	28
Gulmez 2007, Case-Control	Funen, Denmark, 2000–2004	Government Patient Registries	Inpatient	Diagnostic codes (ICD-8 & ICD-10)	7642 / 41818	PPI	PPI: Pharmacy database; CAP: Diagnostic codes (ICD-8 & ICD-10)	29
Hennessy 2007, Case-Control	United Kingdom, 1987–2002	Adults ≥65 years old in the General Practice Research Database	Inpatient	Diagnostic codes (Read)	12044 / 60220	PPI	PPI: Prescription records; CAP: Diagnostic codes (Read)	30
Hermos 2012, Case-Control	USA, 1996–2007	New England Veterans Healthcare System	Inpatient or Outpatient	Diagnostic code (ICD-9) and pharmacy record of respiratory antibiotic prescription	1544 / 16964	PPI	PPI: Pharmacy database; CAP: Diagnostic codes (ICD-9), pharmacy records	31
Jena 2013, Cohort	USA, 1997–2007	Adults ≥30 years old in six employer-based insurance plans	Inpatient or Outpatient	Diagnostic codes (ICD-9)	16827 / 54490	PPI	PPI: Prescription drug claims database; CAP: Diagnostic codes (ICD-9)	32
Juthani-Mehta 2013, Cohort	Pennsylvania & Tennessee, USA, 1998–2008	Adults 70–79 years old in the Health, Aging, and Body Composition Study	Inpatient	Medical record review of radiography, respiratory symptoms, physical examination, and diagnostic codes (ICD-9)	193 / 1441	PPI	PPI: Patient pill bottles; CAP: Diagnostic codes (ICD-9), medical records	33
Lahelj 2003, Cohort	Netherlands, 2002	Outpatient endoscopy service and surrounding community	Inpatient or Outpatient	Patient report	6 / 405	PPI or H2RA	PPI: Self-report via questionnaire; CAP: Self-report via questionnaire	34
Lahelj 2004, Case-Control	Netherlands, 1995–2002	Integrated Primary Care Information (IPCI) project	Inpatient or Outpatient	Medical record review of radiography, microbiology or respiratory symptoms	475 / 5165	PPI	PPI: Prescription records, IPCI database; CAP: Medical record, IPCI database	35
Liu 2012, Case-Crossover	Taiwan, 1998–2007	Adults ≥18 years old with history of stroke and pneumonia hospitalization	Inpatient	Diagnostic codes (ICD-9)	13832 / 13832	PPI	PPI: Insurance database; CAP: Diagnostic codes (ICD-9)	36

(Continued)

Table 1. (Continued)

Author Year, Study Design	Location, Years of Conduct	Source of Cases	CAP setting	CAP Definition	# Cases / # Participants	Acid-suppression	Methods of Ascertainment	Ref.
Long 2013, Case-Control	USA, 1997–2000	ID patients <64 years old in the Life Link Health Plan Claims Database	Inpatient or Outpatient	Diagnostic codes (ICD-9) with antibiotic prescription or hospital admission	4658 / 23784	PPI	PPI: Outpatient pharmacy claims; CAP: Diagnostic codes (ICD-9), pharmacy records	37
Mastrorade 2009, RCT	USA, 2004–2008	Adults with poorly controlled asthma enrolled in ALA-ACRC	Outpatient	Not reported	1 / 402	PPI	PPI: Randomized per protocol; CAP: Adverse event reporting	38
Meijvis 2011, Case-Control	Netherlands, 2004–2010	Two teaching hospitals	Inpatient	New infiltrate on a chest radiograph with at least two clinical or laboratory findings consistent with pneumonia	430 / 2150	PPI	PPI: Pharmacy database; CAP: Medical admission records	39
Morris 2013, Cohort	USA, 2009–2011	Kidney transplant recipients at 3 hospitals	Inpatient or Outpatient	Positive sputum culture with medical record review for clinical correlation	4 / 211	PPI	PPI: Prescription records; CAP: Medical records, sputum culture	40
Muellerova 2012, Case-Control	United Kingdom, 1996–2005	CCPR patients ≥ 45 years old in General Practice Research Database	Inpatient or Outpatient	Diagnostic codes (Read)	1669 / 8814	PPI	PPI: Prescription records; CAP: Diagnostic codes (Read)	41
Myers 2009, Case-Control	United Kingdom, 2001–2002	Patients >40 years old in The Health Improvement Network (THIN)	Inpatient or Outpatient	Diagnostic codes (Read)	3 / 99 / 25863	PPI	PPI: Pharmacy records; CAP: Diagnostic codes (Read)	42
Nielsen 2012, Case-Control	Denmark, 1997–2009	Patients ≥ 15 years old in the Danish National Registry of Patients	Inpatient	Diagnostic codes (ICD-8 & ICD-10)	70814 / 76064	PPI	PPI: Prescription codes; CAP: Diagnostic codes (ICD-8 & ICD-10)	43
Pasina 2011, Cohort	Italy, 2006	Patients ≥ 65 years old admitted at 36 internal medicine wards	Inpatient	Diagnostic codes (ICD-9)	25 / 1332	PPI	PPI: Prescription codes; CAP: Diagnostic codes (ICD-9)	44
Quagliarello 2005, Cohort	New Haven, CT, USA, 2001–2003	Nursing home residents >65 years old	Inpatient or Outpatient	Compatible symptoms with radiographic findings	112 / 613	PPI or H2FA	PPI: Nursing home records; CAP: Medical & radiographic records	45
Ramsay 2013, Cohort	Australia, 2007–2011	Adults ≥ 65 years old, eligible for DVA services	Inpatient	Diagnostic codes (ICD-10)	6775 / 105407	PPI	PPI: Prescription records; CAP: Diagnostic codes (ICD-10)	46
Rodriguez 2009, Case-Control	United Kingdom, 2000–2005	Patients 20–79 years old in The Health Improvement Network (THIN)	Inpatient or Outpatient	Diagnostic codes (Read)	7297 / 17920	PPI	PPI: Pharmacy records; CAP: Diagnostic codes (Read)	47
Roughhead 2009, Cohort	Australia, 2002–2006	Patients ≥ 65 years old with full Veterans' Affairs benefits	Inpatient	Diagnostic codes (ICD-10)	13876 / 185533	PPI	PPI: Pharmacy records; CAP: Diagnostic codes (ICD-10)	48
Sarkar 2008, Case-Control	United Kingdom, 1997–2002	Patients ≥ 18 years old in General Practice Research Database	Inpatient or Outpatient	Diagnostic codes (Read or Oxford)	80086 / 879947	PPI	PPI: Prescription records; CAP: Diagnostic codes (Read or Oxford)	49
Schwinn 2011, RCT	Europe, Australia, Asia, Africa, Americas, 2007–2008	Aspirin users ≥ 18 years old with history or risk of peptic ulcer	Inpatient or Outpatient	Not reported	9 / 2426	PPI	PPI: Randomized per study protocol; CAP: Adverse event reporting	50
Sugano 2011, HCT	Japan, 2007–2008	Long-term low-dose aspirin users with history of ulcer	Inpatient	Not reported	1 / 461	PPI	PPI: Randomized per study protocol; CAP: Adverse event reporting	51
Sugano 2012, RCT	Japan, 2007–2009	Long-term NSAID users with history of ulcer	Inpatient	Not reported	6 / 366	PPI	PPI: Randomized per study protocol; CAP: Adverse event reporting	52

(Continued)

Table 1. (Continued)

Author Year, Study Design	Location, Years of Conduct	Source of Cases	CAP setting	CAP Definition	# Cases / # Participants	Acid-suppression	Methods of Ascertainment	Ref.
van de Garde 2006 (Thorax), Case-Control	United Kingdom, 1987–2001	Diabetic patients ≥ 18 years old in General Practice Research Database	Inpatient or Outpatient	Diagnostic codes (Read)	4719 / 20041	PPI or H2RA	PPI: Prescription records; CAP: Diagnostic codes (Read)	53
van de Garde 2006 (ERJ), Case-Control	Netherlands, 1995–2000	Adults >18 years old in the PHARMO record linkage system	Inpatient	Diagnostic codes (ICD-9)	1108 / 4925	PPI	PPI: Pharmacy database; CAP: Diagnostic codes (ICD-9)	54
van de Garde 2007 (J HTN), Case-Control	United Kingdom, 1987–2001	Diabetic patients ≥ 18 years old in General Practice Research Database	Inpatient or Outpatient	Diagnostic codes (Read)	4719 / 20041	PPI or H2RA	PPI: Prescription records; CAP: Diagnostic codes (Read)	55

ALA, American Lung Association; ACRC, Asthma Clinical Research Centers; CAP, community-acquired pneumonia; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, Connecticut; DVA, Department of Veterans' Affairs; H2RA, histamine-2 receptor-antagonist; IBD, inflammatory bowel disease; IPCI, Integrated Primary Care Information; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; RCT, randomized controlled trial; Ref., study reference number; USA, United States of America

The table above shows the analysis of 32 studies under systemic review (Lambert et al. 2015)

The study contains four major points:

- Systemic review
- Meta-analysis
- Sensitivity analyses
- Subgroup analyses

Systematic review

33 studies were carried out. The majority of them were of case control design (n= 18), 10 were cohorts, 4 randomized controlled trials, 1 case crossover study. Studies were done across the world.

For the majority of studies all available PPIs were used in the market for example 2 groups were treated with esomeprazole and 2 groups with lansoprazole. The other groups were treated with either PPI or H₂ receptor blocker (Lambert et al. 2015, Mastrorade et al. 2009, Scheiman et al. 2011, Sugano et al. 2011).

Those studies examining CAP within specific disease population, for examples persons who taking antiparkinson drugs, NSAIDs, persons with stroke history, persons with kidney transplantation (Lambert et al. 2015, Liu et al. 2012, Morris et al. 2013).

The meta analysis used data from 26 of the 33 studies including the systematic review. Those studies contain 6,351,656 (97%) participants and 226,769 (86.2%) cases of CAP (Lambert et al. 2015)

Meta Analysis

Out of 26 studies 15 reported statistically significant increased risk of CAP with PPI and this included 138,593 of total reported 226,769 cases of CAP (61,1%) (Lambert et al. 2015, Hermoset al. 2011, Jena et al. 2013).

11 reported show no significant association (Lambert et al. 2015).

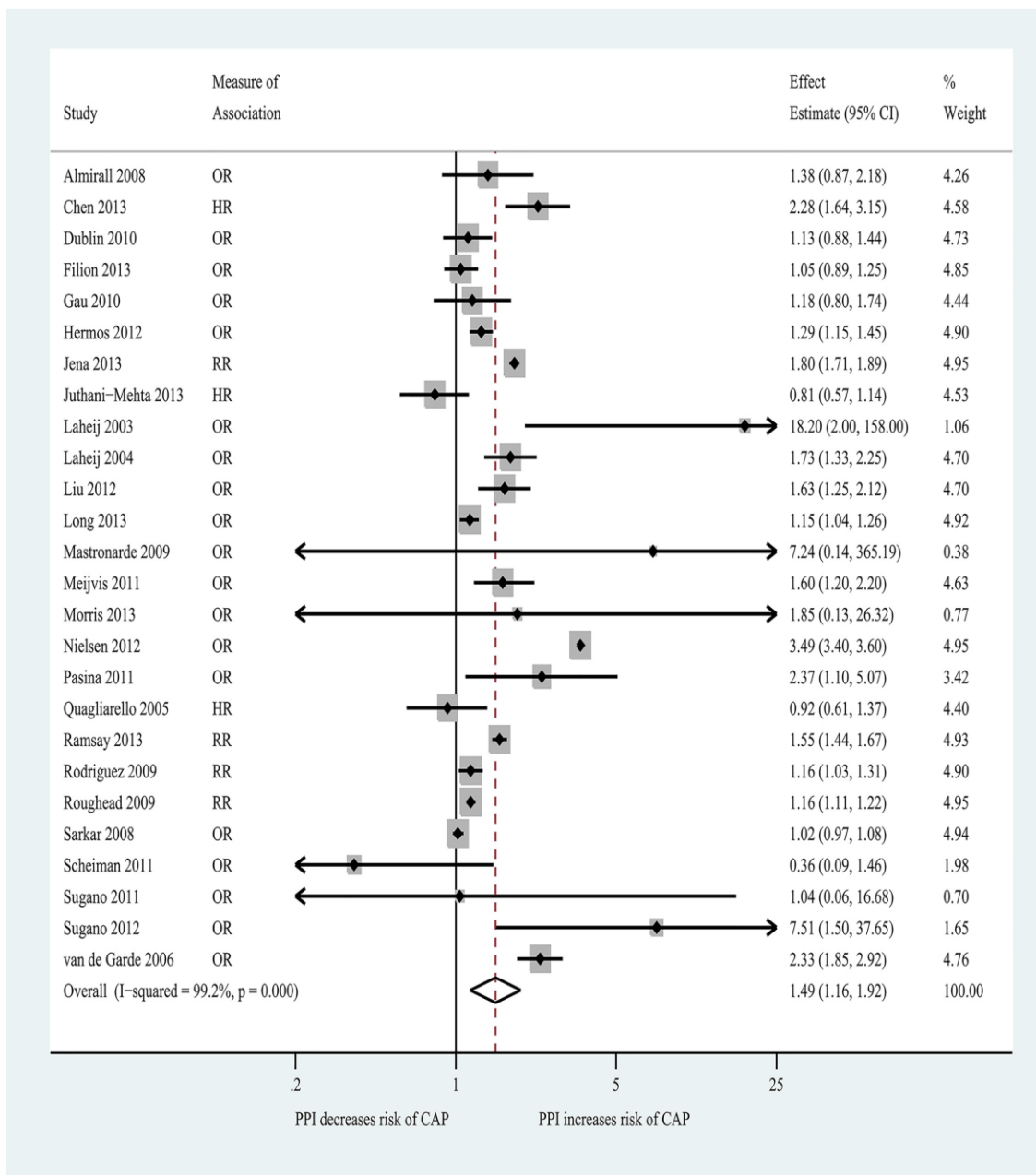


Table shows CAP risk with use of PPIs (Lambert et al. 2015).

The meta analysis identified a significantly increased risk of CAP with outpatient PPI use, with a pooled RR of 1.49. (Lambert et al. 2015, Pasina et al. 2011, Sugano et al. 2012, van de Garde et al. 2006)

Secondary Analyses

These analyses show the risk of hospitalization with CAP was 1.61 fold higher among PPI users as compared to non PPI users as a result of 16 studies used

(Lambert et al. 2015, Van de Garde et al. 2006)

8 studies show no significant CAP risk with H₂ receptor blocker compared to no acid suppression therapy (Lambert et al. 2015, Sarkar et al. 2008, Laheij et al. 2004).

Subgroup Analyses

The 8 studies show a risk of CAP with low dose PPI therapy as compared to no PPI therapy. Similar results were found to those taking a high dose PPI therapy.

The risk was increased during the first month of PPI therapy regardless of PPI patients age more than or less than 65 years (Lambert et al. 2015).

Table 2. Summary of Subgroup Analyses.

Subgroup		# of Studies	Pooled Effect Estimate	95% CI	I ² (%)	p-value for Heterogeneity	Reference
PPI Dose*	High	7	1.33	1.05–1.69	34.0	0.168	23,28,35,39,47,49,50
	Low	8	1.31	1.04–1.66	71.4	0.001	23,28,39,47,49,50,51,52
PPI Duration†	<1 month	6	2.10	1.39–3.16	72.5	0.003	23,35,39,47,49,51
	1–6 months	5	1.51	0.92–2.49	63.3	0.028	23,35,49,51,52
	>6 months	5	1.37	0.85–2.20	74.1	0.004	23,35,49,51,52
Age	<65 years	7	1.34	1.04–1.71	60.1	0.020	23,24,31,37,50,51,52
	>65 years	11	1.33	1.13–1.58	85.4	<0.001	23,24,25,28,31,45,46,48,50,51,52

* Dose is categorized as Low for doses $\leq$ 1 defined daily dose, High for doses $>$ 1 defined daily dose

† Duration refers to duration of time taking PPI prior to community-acquired pneumonia diagnosis

The table above shows the subgroups analyses (Lambert et al. 2015).

The systematic review of 33 studies and meta analysis of 26 studies show a 1.5 fold increased risk of CAP with patients used PPIs therapy, and is also associated with an increased risk for hospitalization with CAP by 1.6 fold.

No association was observed between H₂ receptor blocker use and CAP among the patient treated with H₂ blocker alone.

Some pathogenic mechanisms explain the association between PPI use and the incidence of CAP and said that decreased gastric acidity is associated with alteration of gut flora (Lambert et al. 2015, Williams et al. 2006, Dellipiani and Girdwood 1964). Due to reduced gastric acidity, the bacterial load increases in the stomach and elevates the pressure on the lower esophageal sphincter which may lead to retrograde movement of gastric contents up the esophagus. This reflux may then increase the risk of subsequent aspiration of both the gastric content and the bacteria and is of further interest in explaining the association between PPI use and CAP. A study by Altmann et al. (2003), which identified the presence of PPI in extragastric sites including the larynx and the lungs. Since PPI are absorbed and distributed throughout the systemic circulation that leads to a reduction in the acidity of the upper aerodigestive tract, thus resulting in increased bacterial colonization of the larynx, esophagus and lung. All of this increased the incidence of CAP (Lambert et al. 2015, Altman et al. 2003).

CAP risk was greatest during the first month of therapy (Lambert et al. 2015, Chey et al. 2009).

The risk of CAP does not depend on PPI dose or the participant age.

GERD a common indication for PPI therapy may directly increase the risk of CAP by increasing of microaspiration of gut flora (Lambert et al. 2015, Chey et al. 2009).

Jena et al. further explored the concept of confounding by using prescription drugs and medical claims data to demonstrate statistically significant associations between PPI use and some disease like osteoarthritis, chest pain and urinary tract infection.

Several meta analyses have sought to evaluate the relationship between PPI therapy and CAP.

Giuliano et al. (2012) conclude that patients prescribed PPIs had an increased risk for CAP, particularly at high PPI doses and soon after initiation of PPI therapy (Lambert et al. 2015).

Eom et al. (2011) found that patients taking any acid suppressant drugs were at increased risk of CAP or hospitalization pneumonia (Lambert et al. 2015).

This meta analyses enhance the existing literature by adding data from 19 studies that were not included in this investigation .

These 19 studies were identified through a combination of the broad,updated database search and unpublished data. This strengthened their subgroup and sensitivity analyses.

5. Summary

Problems of elevated gastric acid are very common and considered as the main cause of many diseases like peptic, duodenal ulcers and GERD.

A variety of drugs are prescribed for the treatment of these problems like antacids, H₂ receptor blockers and proton pump inhibitors (PPIs), which are considered as drugs of first choice and which are the most effective drugs.

In the last few years, there was some research that showed the risks of long time treatment of PPIs like myocardial infarction, community acquired pneumonia and hypomagnesemia. Primary results show that patients exposed to PPIs have a 1.16 fold increased association with myocardial infarction.

The use of PPIs is associated with a 1.5 fold increase of risk of community acquired pneumonia and hospitalization pneumonia with the highest risk within the first 30 days.

This results did not occur during treatment with H₂ receptor blockers.

All results are primary results and need further and more investigation in the future to get more and detailed insights in this discoveries.

From this research the use of PPIs should be done with caution especially when the duration time is long and the patients can use or shift to another type of antiseecretory drugs.

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histamine H₂-receptor antagonists or proton pump inhibitors for gastro-
oesophageal reflux disease patients. *Aliment Pharmacol Ther* 21:1299–1312

7. Curriculum Vitae

Name: Beshoy Riffat Nan Abdelmeseh

Birthday: 01-02-1983

Birthplace: Alexandria

Nationality: Egyptian

Education: Primary school at the Franciscan Sisters in Qena

Secondry school at El Shaied Abd Menaim Read

October 2004 Graduation from the Faculty of Pharmacy

Work experience: El Ezzapy Pharmacy Groups in Cairo (2005 - 2007)

Manager in DR. JACK pharmacy in Hurghada (2007 - 2011)