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HKU Finds that Long-term Use of Proton Pump Inhibitors is Associated with an Increased Risk of Stomach Cancer

Press Conference
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Speakers

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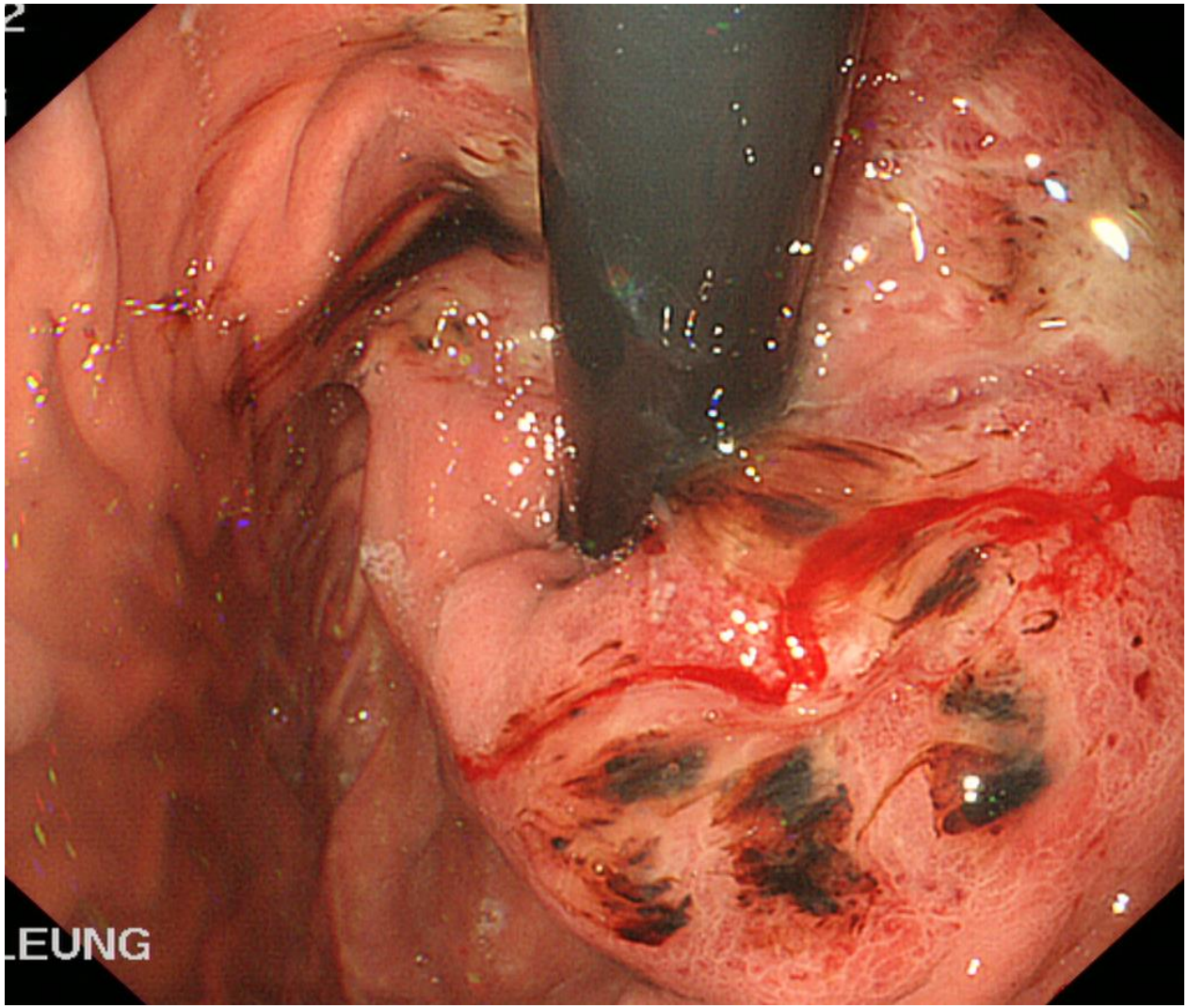
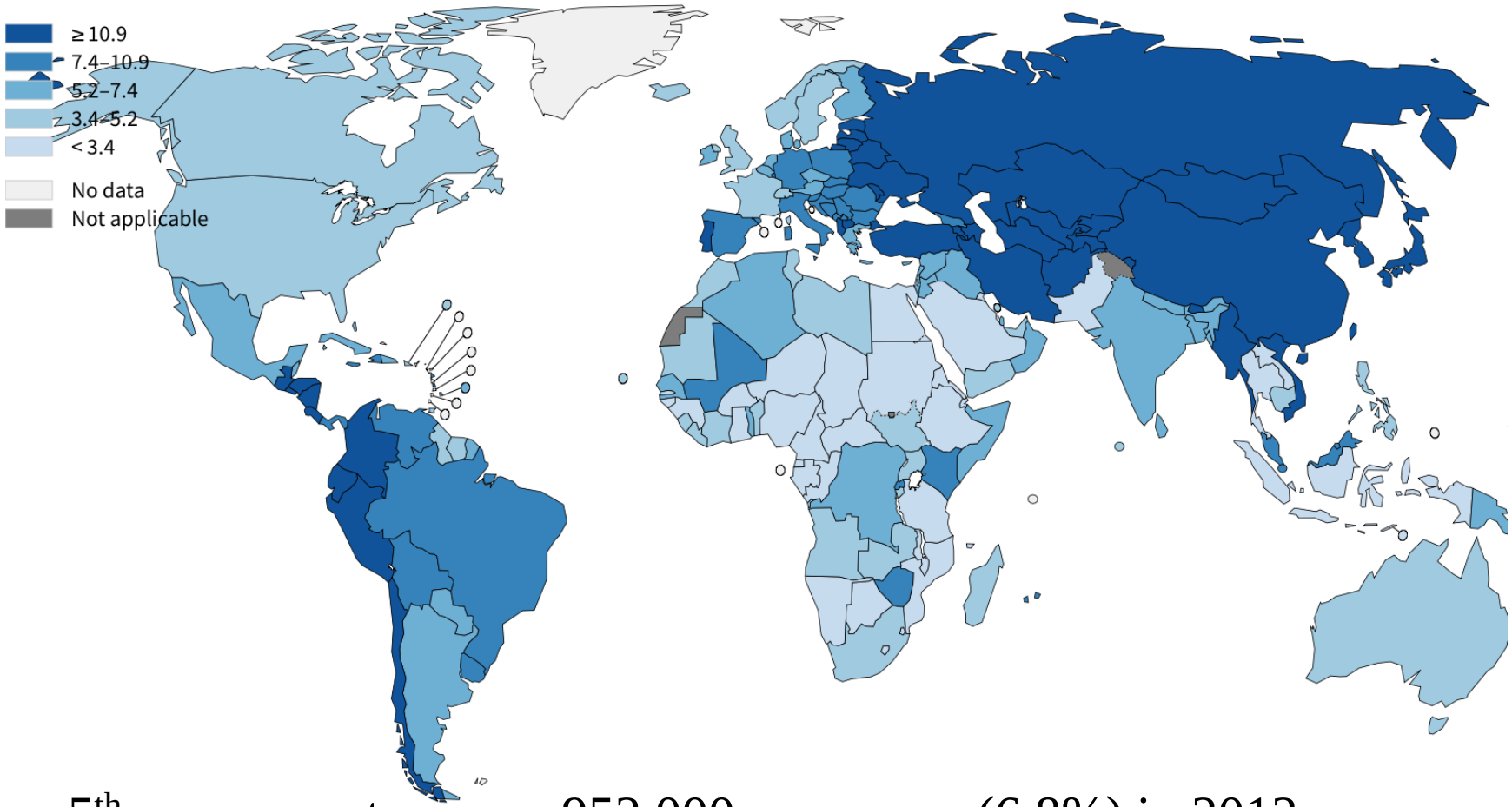
- Overview of stomach cancer
- What is Proton Pump Inhibitor (PPI)?
- Our study findings

Stomach cancer



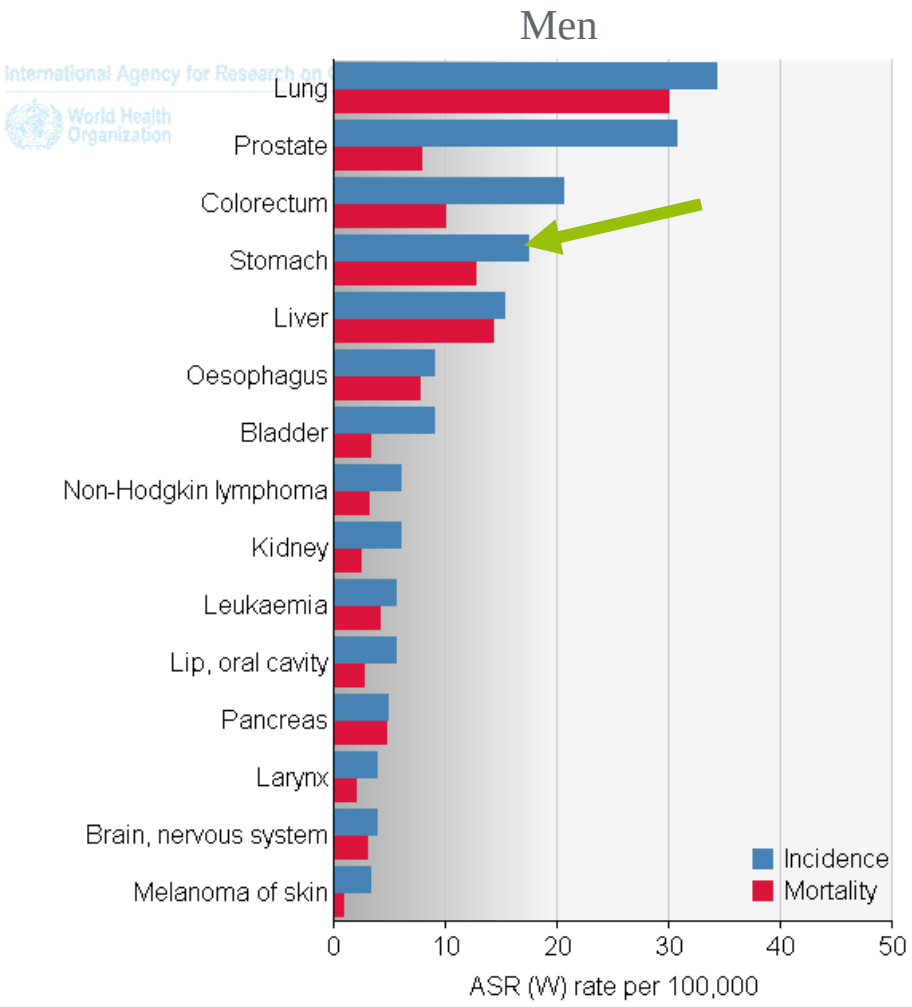
Stomach cancer in the world

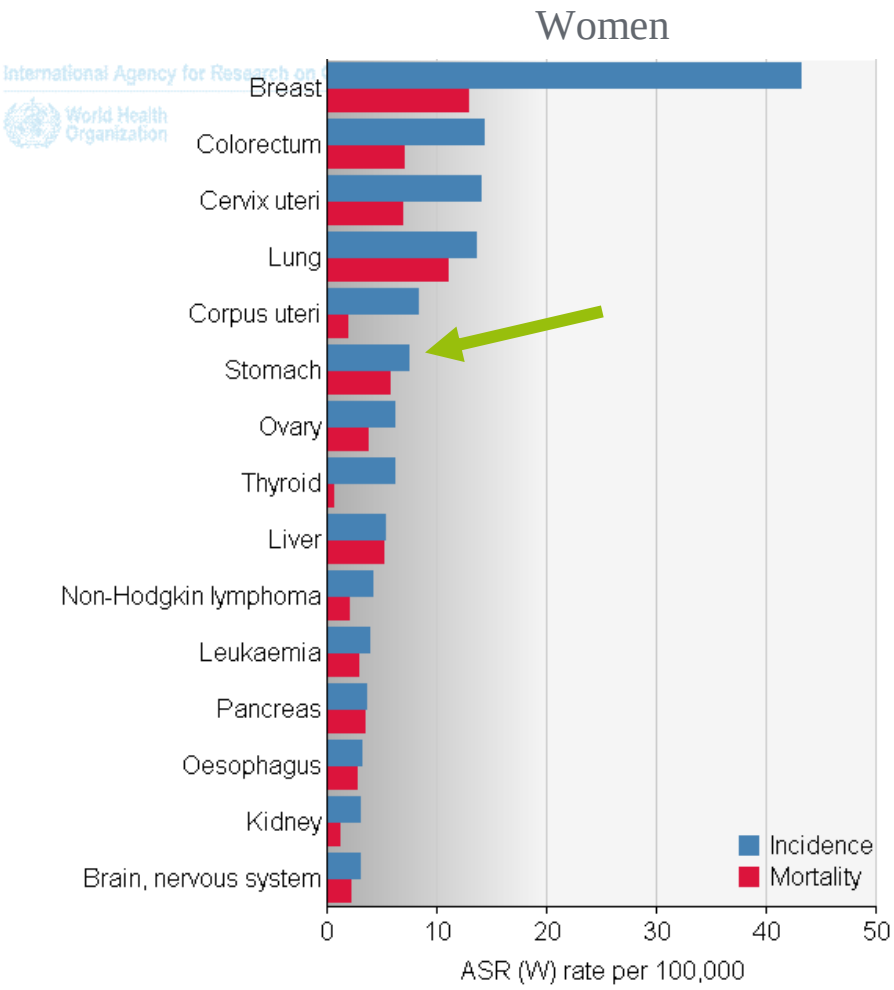


- 5th commonest cancer: 952,000 new cases (6.8%) in 2012
- 3rd leading cause of cancer death: 723,000 deaths (8.8%) in 2012

World Health Organization. Cancer Fact Sheets: Stomach Cancer

Stomach cancer: Global incidence and mortality





Stomach cancer in Hong Kong

Incidence in 2015 - Both Sexes

Both Sexes | Male | Female

Rank	Site	No.	Rel. Freq.	Crude rate*
1	Colorectum	5,036	16.6%	69.1
2	Lung	4,748	15.7%	65.1
3	Breast	3,920	12.9%	53.8
4	Prostate	1,831	6.0%	54.4
5	Liver	1,791	5.9%	24.6
6	Stomach	1,167	3.8%	16.0
7	Non-melanoma skin	1,018	3.4%	14.0
8	Corpus uteri	978	3.2%	24.9
9	Non-Hodgkin lymphoma	976	3.2%	13.4
10	Nasopharynx	876	2.9%	12.0
	All Sites	30,318	100.0%	415.8

Mortality in 2015 - Both Sexes

Both Sexes | Male | Female

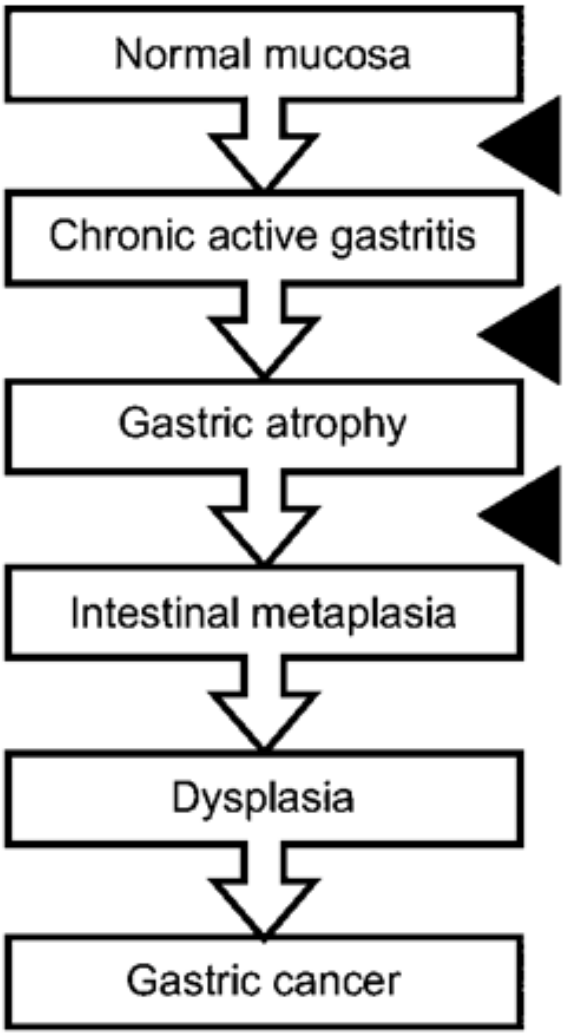
Rank	Site	No.	Rel. Freq.	Crude rate*
1	Lung	4,031	28.2%	55.3
2	Colorectum	2,073	14.5%	28.4
3	Liver	1,571	11.0%	21.5
4	Pancreas	691	4.8%	9.5
5	Stomach	669	4.7%	9.2
6	Breast	637	4.4%	8.7
7	Prostate	404	2.8%	12.0
8	Non-Hodgkin lymphoma	358	2.5%	4.9
9	Leukaemia	341	2.4%	4.7
10	Nasopharynx	327	2.3%	4.5
	All Sites	14,316	100.0%	196.3

Hong Kong Cancer Registry, Hospital Authority

Helicobacter pylori

- *H. pylori* has been classified by the International Agency for Research on Cancer (IARC) as a carcinogen in 1994
- The prevalence of *H. pylori* infection varies, ranging from <20% in some European countries to >80% in some African countries
- It is estimated that more than 4 billion people are infected with *H. pylori* in the world

Pathogenesis of stomach cancer



H. pylori

?? Proton pump inhibitors (PPIs)

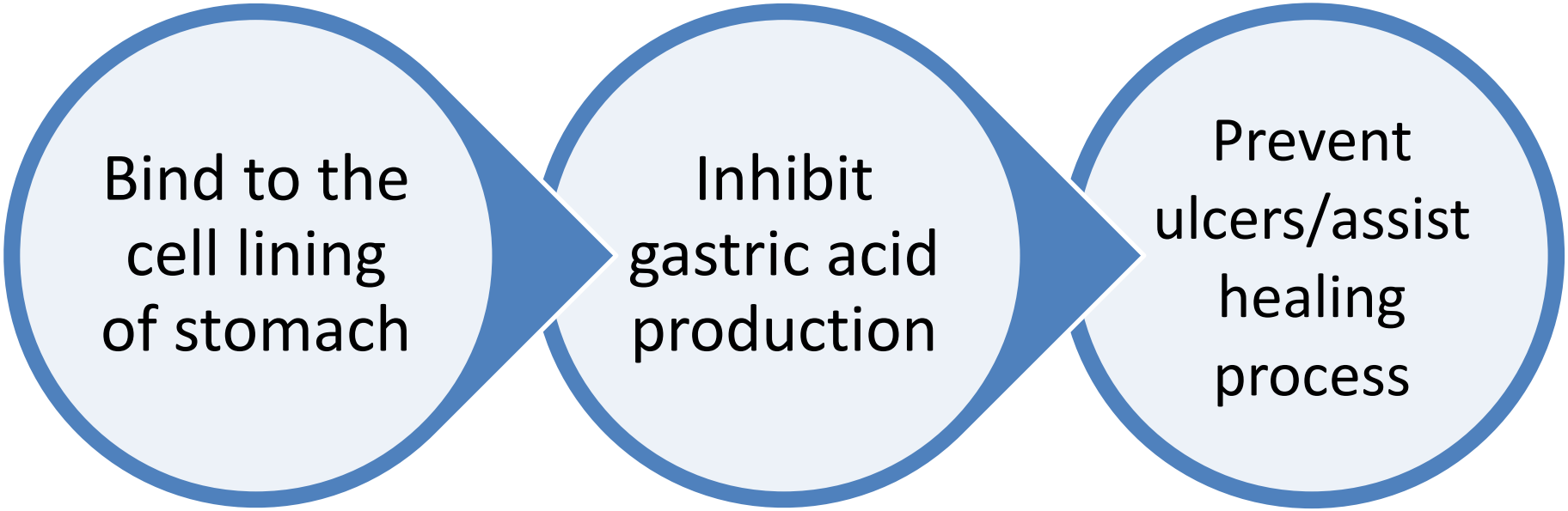
Achlorhydria, carcinogens

Kusters JG, et al. Clin Microbio Rev 2006

What are proton pump inhibitors (PPIs) ?

What are proton pump inhibitors (PPIs) ?

- Potent gastric acid suppressing agent
- Dexlansoprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, etc.

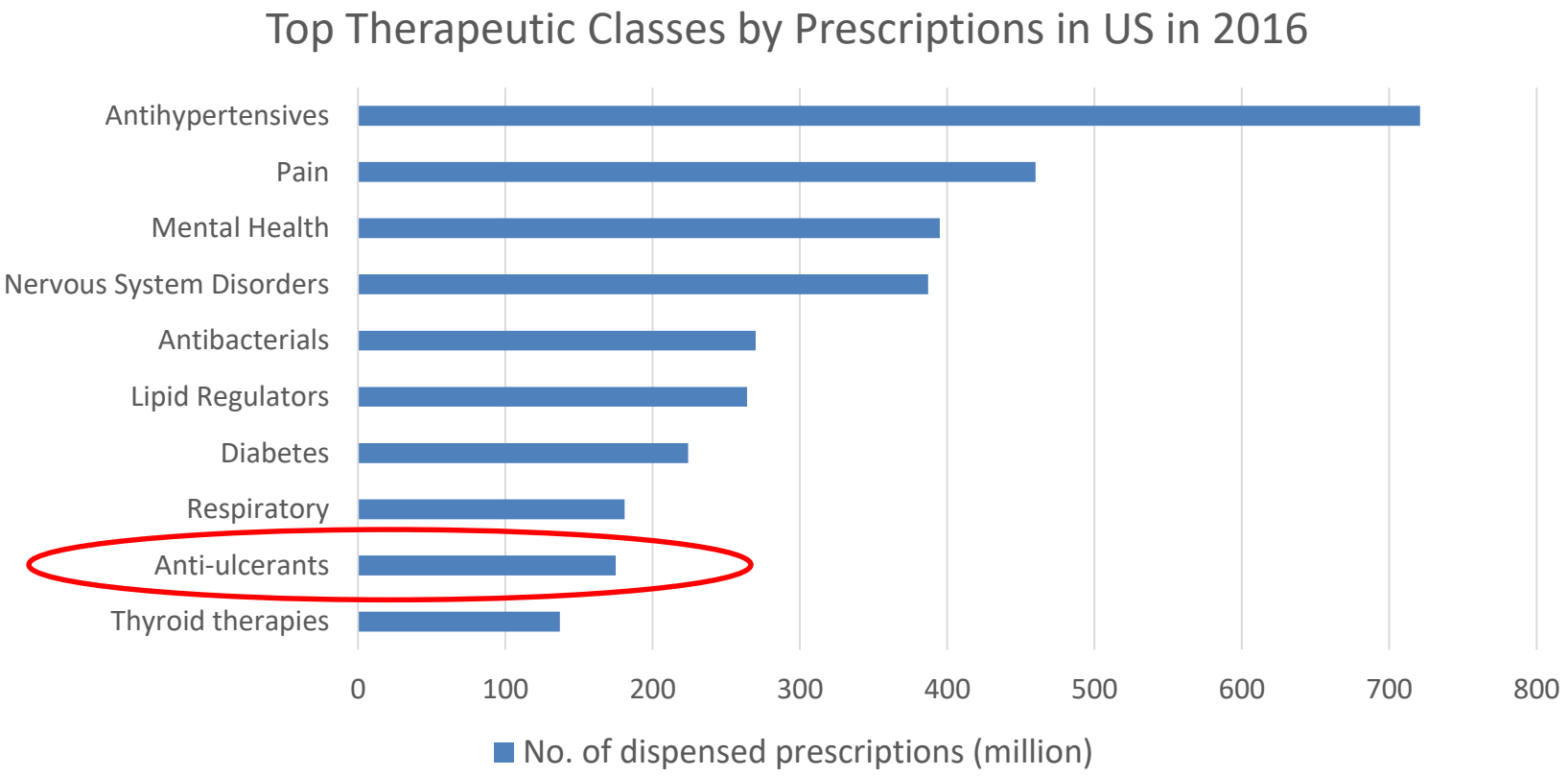


What are proton pump inhibitors (PPIs) ?

- Widely used in various gastrointestinal conditions
  - Indigestion
  - Acid reflux (heartburn)
  - Peptic ulcer disease (stomach / duodenum)
  - Prevent drug related ulcers
  - *H. pylori* eradication in triple therapy

What are proton pump inhibitors (PPIs) ?

- One of the top selling drug classes



Source: IQVIA, National Prescription Audit, Dec 2016

What are proton pump inhibitors (PPIs) ?

- One of the top selling drug classes

	No. of prescriptions for the most popular PPI in 2016
US	Omeprazole: 76 million prescriptions (Top 10 prescribed medicines)
UK	Omeprazole: 31 million prescriptions (Top 10 prescribed medicines)
HK	Pantoprazole: 1.6 million prescriptions

Source: QuintilesIMS Institute, National Health Service, Clinical Data Analysis and Reporting System

Adverse effects of PPIs

- Generally well tolerated
  - Mild headache
  - Constipation / diarrhoea
  - Wind (flatulence)
- Long term uses associated with
  - Bone fracture
  - *Clostridium difficile* infection
  - Pneumonia

Our Study

Research question

Will the use of PPIs increase the risk of stomach cancer even after successful *H. pylori* eradication?

Study on the association between PPIs use and stomach cancer (a population-based study)

Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study

Ka Shing Cheung,[1] Esther W Chan,[2] Angel Y S Wong,[2] Lijia Chen,[1] Ian C K Wong,[2,3] Wai Keung Leung[1]

ABSTRACT

Objective Proton pump inhibitors (PPIs) is associated with worsening of gastric atrophy, particularly in *Helicobacter pylori* (HP)-infected subjects. We determined the association between PPIs use and gastric cancer (GC) among HP-infected subjects who had received HP therapy.

Designs This study was based on a territory-wide health database of Hong Kong. We identified adults who had received an outpatient prescription of clarithromycin-based triple therapy between year 2003 and 2012. Patients who failed this regimen, and those diagnosed to have GC within 12 months after HP therapy, or gastric ulcer after therapy were excluded. Prescriptions of PPIs or histamine-2 receptor antagonists (H2RA) started within 6 months before GC were excluded to avoid protopathic bias. We evaluated GC risk with PPIs by Cox proportional hazards model with propensity score adjustment. H2RA was used as a negative control exposure.

Result Among the 63 397 eligible subjects, 153 (0.24%) developed GC during a median follow-up of 7.6 years. PPIs use was associated with an increased GC risk (HR 2.44, 95% CI 1.42 to 4.20), while H2RA was not (HR 0.72, 95% CI 0.48 to 1.07). The risk increased with duration of PPIs use (HR 5.04, 95% CI 1.23 to 20.61; 6.65, 95% CI 1.62 to 27.26 and 8.34, 95% CI 2.02 to 34.41 for ≥1 year, ≥2 years and ≥3 years, respectively). The adjusted absolute risk difference for PPIs versus non-PPIs use was 4.29 excess GC (95% CI 1.25 to 9.54) per 10 000 person-years.

Conclusion Long-term use of PPIs was still associated with an increased GC risk in subjects even after HP eradication therapy.

Significance of this study

What is already known on this subject?

- Although *Helicobacter pylori* eradication has been shown to reduce the risk of gastric cancer development, a considerable proportion of these individuals continues to progress to gastric cancer even after successful eradication of *H. pylori*.
- Previous studies have shown that the risk of gastric cancer was increased by 43% among PPIs users but the major confounding factor, *H. pylori*, was not adjusted in these analyses and the causal relationship may be biased.

What are the new findings?

- Long-term PPIs use was associated with a 2.4-fold increase in gastric cancer risk in *H. pylori*-infected subjects who had received eradication therapy.
- The risk of gastric cancer increases with the dose and duration of PPIs use.

How might it impact on clinical practice in the foreseeable future?

- Physicians should exercise caution when prescribing long-term PPIs to *H. pylori*-infected individuals even after successful eradication of *H. pylori*.

the world since the first PPI became available in the 1980s.[5] Although PPIs are generally consid-

Methods

- PPIs use after *H. pylori* eradication therapy (year 2003 – 2012)
- Stomach cancer development (up to year 2015)

Cheung KS, et al. Gut 2017

Characteristics of the study cohort

- Total patient number: 63,397
- Study observation period: 2003 - 2015
- Median follow-up: 7.6 years
- 153 (0.24%) developed stomach cancer
- Overall incidence rate: 3.2 per 10,000 person-years
- Median age at stomach cancer diagnosis: 71.4 years
- Median time from *H. pylori* therapy to stomach cancer development: 4.9 years

PPIs use and stomach cancer

- Definition of PPIs use: **< weekly use**
- PPIs users: 3271 (5.2%)
- Median duration of PPIs use: 2.7 years
- Incidence rate of stomach cancer: 8.1 per 10,000 person-years

- Compared with non-PPIs use, PPIs use was associated with an increased risk of stomach cancer by 2.4
- 4.3 excess stomach cancer cases per 10,000 person-years

- Use of H2-receptor antagonist, another less potent acid reducing drug, was not associated with an increase in stomach cancer risk (relative risk 0.72, statistically insignificant)

PPIs frequency and stomach cancer

Non-PPIs use
(< weekly use)

VS

Weekly to <daily PPIs use

relative risk: 2.44

VS

Daily PPIs use

relative risk: 4.55

PPIs duration and stomach cancer

Non-use
VS
Daily PPIs use

PPIs use ≥ 1 year	PPIs use ≥ 2 years	PPIs use ≥ 3 years
relative risk: 5.04	relative risk:6.65	relative risk:8.34

Conclusion

- Long-term PPIs use is associated with an increased stomach cancer risk even after *H. pylori* eradication
- A dose-response trend in terms of frequency and duration of PPIs treatment is noted
- PPIs are effective medications to treat various gastrointestinal diseases – PPIs use should not be discouraged
- Review of indications; use with the minimal dose, frequency and duration

Foreign media coverage

- Since online publication on 1 Nov 2017, study findings reported by >90 media globally, including
  - NY Times
  - The Guardian
  - Newsweek
  - The Times
  - American Gastroenterological Association

Acid reflux drug linked to more than doubled risk of stomach cancer – study

There are more than 50m prescriptions for proton pump inhibitors in the UK, though they have previously been linked to side-effects and increased risk of death

HEARTBURN AND ACID REFLUX DRUGS DOUBLE RISK OF STOMACH CANCER

BY KATE SHERIDAN ON 11/2/17 AT 1:24 PM

American Gastroenterological Association

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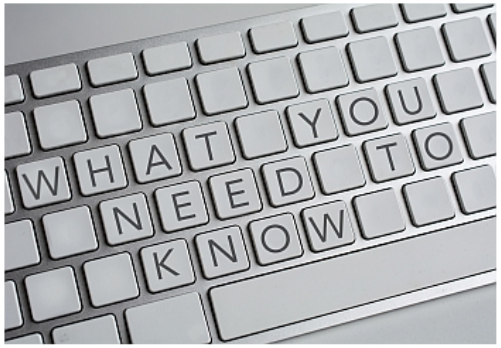
New PPI Study on Gastric Cancer Generates Media Attention

Nov. 2, 2017

AGA provides talking points to help your patients understand the science behind the PPI study.



The results of a new study about the use of proton pump inhibitors (PPIs) and their link to gastric cancer has been covered by various media outlets. This may cause your patients to question whether they should stay on or start using PPIs. Like all recent PPI studies, the information is important and interesting, but the results should not automatically alter practice, due to the limitations of the study's methodology.

The study, "Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study," published in *Gut*, concluded that even after Helicobacter pylori (H. pylori) eradication therapy, long-term use of PPIs was

Q & A Session