Long-term risks of PPIs:

What should I tell my patient?

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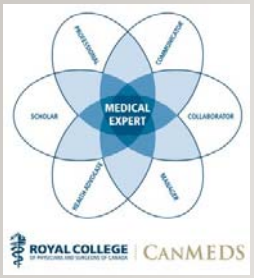


CDDW/CASL MEETING SESSION: *LONG-TERM RISKS OF PPIS*

CanMEDS Roles Covered in this Session:

✓	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS framework.)
✓	**Communicator** (as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)
✓	**Collaborator** (as *Collaborators*, physicians effectively work within a healthcare team to achieve optimal patient care.)
✓	**Manager** (as *Managers*, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)
✓	**Health Advocate** (as *Health Advocates*, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)
✓	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)

Long-term risks of PPIs:

What should I tell my patient?

Agenda

- Which are the long-term risks that PPIs have been associated with?
  - Quality (certainty) of evidence for 3 risks
- Methodological issues
- What should we tell our patients

Which are the long-term risks that PPIs have been associated with?

Methods: Systematic literature search (MEDLINE)

- Date: January 13, 2016
- Filters: English language; Humans
- ("proton pump inhibitor*" OR "proton-pump inhibitor*" OR PPI OR PPIs OR omeprazole OR lansoprazole OR pantoprazole OR rabeprazole OR esomeprazole OR dexlansoprazole)
  AND
  (safety OR safe OR risks OR "adverse effect*" OR "adverse drug reaction*" OR "adverse reaction*" OR "side effect*" OR fracture* OR osteoporosis OR difficile OR diarrhea OR infection* OR infectious OR pneumonia OR clopidogrel OR antiplatelet* OR "myocardial infarction*" OR "cardiovascular event*" OR "cardiovascular outcome*" OR stroke* OR "bacterial overgrowth" OR "spontaneous bacterial peritonitis" OR "microscopic colitis" OR "acute interstitial nephritis" OR calcium OR hypocalcaemia OR hypocalcaemia OR B12 OR "B 12" OR iron OR magnesium OR hypomagnesemia OR hypomagnesaemia)

Which are the long-term risks that PPIs have been associated with?

Results

- 7,257 articles (311 SR&MAs)

Which are the long-term risks that PPIs have been associated with?

- *C. difficile*-associated diarrhea
- Bone fractures
- Interaction with clopidogrel
- Interaction with methotrexate
- Hypomagnesemia
- Pneumonia / upper respiratory infections
- Enteric infections (other than CDAD)
- Dementia
- SBP in patients with cirrhosis
- Mortality in patients with cirrhosis
- Acute interstitial nephritis
- Chronic kidney disease
- Mortality after PEG insertion
- Acute myocardial infarction
- Microscopic colitis
- Vitamin B12 deficiency

Health Canada / FDA drug safety communications about PPIs

1. ***C. difficile*-associated diarrhea (CDAD)**
2. **bone fractures**
3. **interaction with clopidogrel**
4. **interaction with methotrexate**
5. **hypomagnesemia**

Overarching recommendation:

PPIs should be prescribed at the lowest dose and

shortest duration of therapy appropriate to the condition being treated

Health Canada / FDA drug safety communications

C. difficile-associated diarrhea (CDAD) and PPIs

- **HC (2012)**: “possible risk of CDAD”
- **FDA (2012):** “may be associated with an increased risk of CDAD”

Biological plausibility? May be …

C. difficile-associated diarrhea (CDAD) and PPIs

- Ingested *C. difficile* **vegetative forms** may survive in a stomach with reduced acidity (due to PPI use), but,
  ingested *C. difficile* **spores** survive in the gastric acid anyway

  Nerandzic MM et al. *Antimicrob Agents Chemother 2009*

- PPIs alter the gut microbiome, and this may promote CDAD

  Jackson MA et al. *Gut 2015*

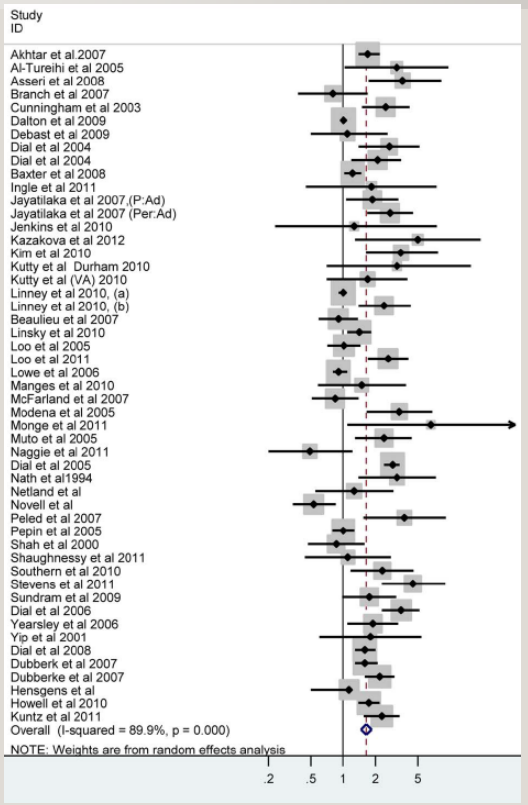
What is the evidence?

C. difficile-associated diarrhea (CDAD) and PPIs

Risk of CDAD

The most recent, methodologically-sound SR&MA:

- 51 observational studies
- OR **1.65**; 95% CI **1.47** to **1.85**
- Unexplained heterogeneity
- High risk of bias
  (residual confounding)
- Publication bias
- Quality (certainty) of evidence: **VERY LOW**



Tleyjeh IM et al. *PLoS ONE 2013*

What is the evidence?

C. difficile-associated diarrhea (CDAD) and PPIs

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NNH for:

hospitalized patients [14 days]

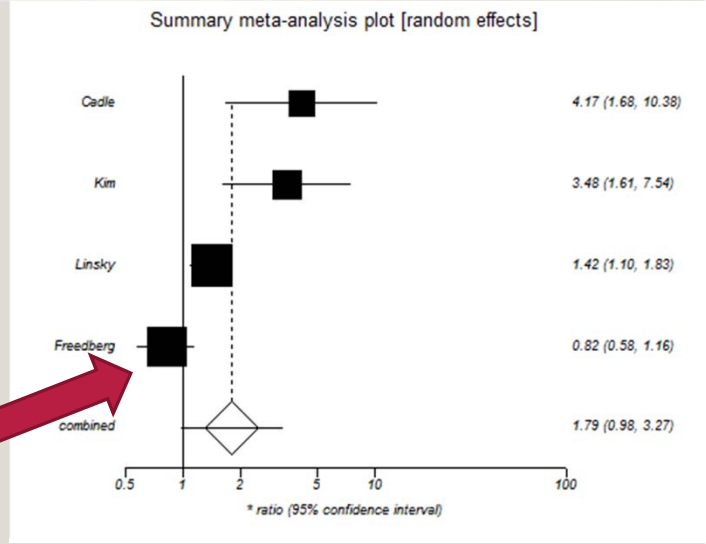
- on antibiotics: **50** (31 to 97)
- not on antibiotics: **367** (226 to 718)

general population [1 year]: **3925** (2412 to 7698)

Tleyjeh IM et al. ***PLoS ONE 2013***

What is the evidence?

C. difficile-associated diarrhea (CDAD) and PPIs



Risk of <u>recurrent</u> CDAD

This is a "cleaner", more homogeneous population (re baseline comorbidities).

The most recent SR&MA: **4** observ. studies

- OR **1.79** (**0.98** to **3.27**)
- Heterogeneity (explained)
- One study at low risk of bias:
  Freedberg AJG 2013; HR 0.82 (0.58 to 1.16)
- Quality (certainty) of evidence: **LOW**, for **<u>no</u>** association

Leontiadis GI. *Am J Gastroenterol 2013*

Health Canada / FDA drug safety communications

Bone fractures and PPIs

- **HC (2013):** “potential risk of bone fractures”
- **FDA (2013):** “possible increased risk of fractures”

CAG Position Statement

Bone fractures and PPIs

There is little to support the hypothesis that the association between PPI therapy and risk of fracture is causal.

Even if we assume that the association is causal, the [absolute] risk to patients is minimal.

Moayyedi P et al. *Can J Gastroenterol* 2013

Biological plausibility? No

Bone fractures and PPIs

- **Initial hypothesis: PPI use → ⇩ gastric acidity → → ⇩ Ca absorption → osteoporosis → fracture**
  - PPIs do **not** affect Ca absorption when Ca is taken with food (2 RCTs)
  - PPIs do **not** cause/worsen osteoporosis (1 RCT and 9 observ. studies)

Leontiadis GI et al. *Curr Treat Opt Gastroenterol* 2014

Other hypotheses:

- **Inhibition of osteoclasts →**
  → heterogeneous **increase** in bone mineral density →
  → impaired microfracture repair → fracture

Hansen KE et al. *J Bone Min Res* 2010

- Increased risk of falls (!)

Lewis JR et al. *J Bone Min Res* 2010

What is the evidence?

Bone fractures and PPIs

The most recent SR&MA: **Moayyedi P et al. *Can J Gastroenterol* 2013**

The most recent SR: **Leontiadis GI et al. *Curr Treat Opt Gastroenterol* 2014**

- 25 (plus 8) observational studies (and 1 RCT)
- Case-control studies: OR **1.21** (**1.07** to **1.38**)
- Cohort studies: OR **1.30** (**1.13** to **1.49**)
- Unexplained heterogeneity
- Similar results for studies at “not-so-high” risk of bias
- Quality (certainty) of evidence**: VERY LOW**

NNH = 2000
for 50-year-old Canadian women [1 year]

Health Canada / FDA drug safety communications

PPI-clopidogrel interaction

- **HC (2011):** PPIs known to strongly or moderately reduce Plavix effectiveness should be **avoided**. **Omeprazole** is one of these.
  - If a PPI must be used in a patient taking Plavix, **consider** a PPI that does not interact as strongly. **Pantoprazole** is one of these.

- **FDA (2010):** Avoid concomitant use of clopidogrel and **omeprazole** [or **esomeprazole** (2011)]. Reduced effectiveness of clopidogrel in patients who are **poor metabolizers** of the drug
  - Not all PPIs have the same inhibitory effect on CYP2C19 that is crucial for conversion of Plavix into its active form. **Pantoprazole** may be an alternative PPI for consideration. It is a weak inhibitor of CYP2C19.

Biological plausibility? Yes

PPI-clopidogrel interaction

Competitive inhibition in the hepatic CYP2C19 which converts

- PPIs to **inactive** metabolites
- the prodrug clopidogrel to its **active** metabolite

Kazui M et al. *Drug Metab Dispos* 2010

Pharmacokinetic and pharmacodynamic (platelet aggregation) studies

- 11 RCTs, 14 observ. studies
- Heterogeneity, unexplained
- Inconsistent results

clinical outcomes?

- Overall: it is possible that PPIs can adversely affect the pharmacokinetic and pharmacodynamic profile of clopidogrel.
- No evidence for differences between different PPIs

Leontiadis GI et al. *Gastrointest Endosc Clin N Am* 2011

What is the evidence?

PPI-clopidogrel interaction

Composite outcome of any major CV event

- 21 observ. studies: RD **0.02** (**0.01** to **0.03**)
  - Almost all: high risk of bias
  - Heterogeneity, unexplained
  - Quality (certainty) of evidence (for outcomes being worse on PPI Rx): **VERY LOW**

Gerson LB et al. *Dig Dis Sci* 2012

- 1 RCT: HR **0.99** (**0.68** to **1.44**)
  - Low risk of bias
  - Quality (certainty) of evidence (for no difference in outcomes)**:** **MODERATE** due to imprecision

Bhatt DL et al. *NEJM* 2010

What is the evidence?

PPI-clopidogrel interaction

Adverse GI events (hemorrhage, ulcer, perforation or obstruction)

- 7 observ. studies: OR **0.38** (**0.21** to **0.68**)
  - high risk of bias
  - No heterogeneity
  - Quality (certainty) of evidence: **VERY LOW**

Kwok CS et al. *Drug Saf* 2011

UGI bleeding (for patients taking clopidogrel and aspirin)

- 1 RCT: HR **0.13** (**0.03** to **0.56**)
  - Low risk of bias
  - Quality (certainty) of evidence: **HIGH**

Bhatt DL et al. *NEJM* 2010

Health Canada / FDA drug safety communications

PPI-methotrexate interaction

HC (2012)

The concurrent use of **high-dose** methotrexate (in the treatment of cancer) and of PPIs may increase methotrexate blood levels leading to side effects.

Health Canada / FDA drug safety communications

Hypomagnesemia and PPIs

FDA (2011)

- PPIs may cause hypomagnesemia if taken for prolonged periods of time

Methodological concerns: Studies on rare AEs of drugs

- **RCTs:** often impractical
- **Large-database observational studies** are needed, but:
  - cannot prove causation
  - may identify small **true** signals, but also small **erroneous** associations
  - Specific limitations:
    - **protopathic bias** (e.g. a patient with angina preceding a major CV event may be prescribed PPIs for misdiagnosed GERD)
    - **publication bias** (also: "*how many potential studies do not exist, when they could have readily been conducted*" JPA Ioannidis)
    - **channelling bias**
    - **confounding**

Channelling bias

Channelling bias: selection bias resulting from clinicians' tendency to prescribe treatment based on their perception of a patient's prognosis

Lobo FS et al. *Res Social Adm Pharm 2006*

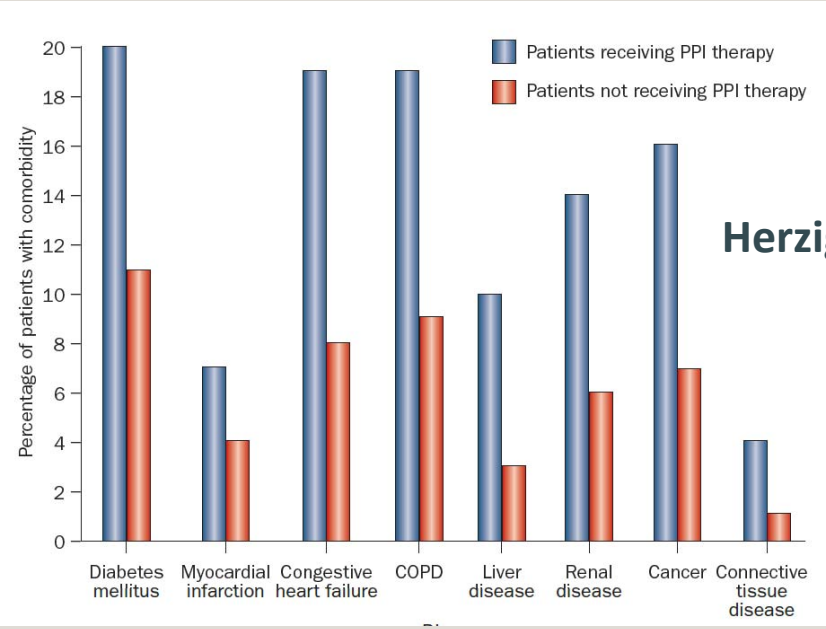
Two patients at the same risk for UGI bleeding, e.g. 5% per year.
Who is more likely to be prescribed a PPI (and stay on it)?

Chronic NSAIDs plus PMH of Hp-neg PUD

Chronic NSAIDs plus age 80 years

Channelling bias

- This is **exactly** what we see in every single observational study that assessed the long-term risks of PPIs:
  - PPI users are <u>consistently</u> sicker and frailer at baseline ("Table 1")



Herzig SJ et al. *JAMA* 2009

Leontiadis GI et al. *Curr Treat Opt Gastroenterol* 2014

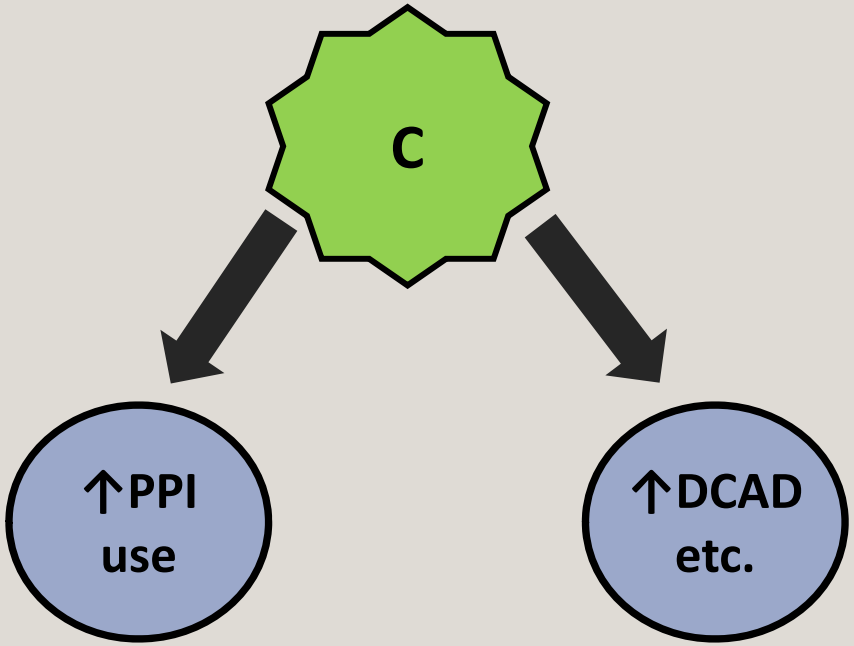
Channelling bias

- This is **exactly** what we see in every single observational study that assessed the long-term risks of PPIs:
  - PPI users are consistently sicker and frailer at baseline ("Table 1")
- Not a coincidence:
  - Studies on prescription patterns: old age, frailty, and comorbidities are "risk factors" for being on long-term PPI treatment.
    - Frail patients see physicians more often (surveillance bias)
    - Physicians may fear that frail patients are less likely to survive an upper GI bleed

Leontiadis GI et al. *Curr Treat Opt Gastroenterol* 2014

Confounding

- Frailer, sicker people are more likely be on PPIs
- Frailer, sicker people are more likely to develop fractures/ MIs/CDAD/etc. **anyway - irrespective of PPI use**.
- Frailty/comorbidity is a **confounder**



Residual confounding

- Almost all of these studies performed matching or statistical adjustment for confounders
  - Almost always the adjusted relative risk was smaller (than the unadjusted risk) or non-significant

Table 2 | The association between PPI therapy and fracture*

Study	% of patients with a fracture who received PPIs	% of controls who received PPIs	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Yang *et al.* (2006)[42]	3.94	2.38	1.77 (1.61–1.95)	1.4 (1.26–1.54)
Vestergaard *et al.* (2006)[43]	11.7	8	1.53 (1.50–1.56)	1.18 (1.12–1.43)
Targownik *et al.* (2008)[46‡]	1.7	0.9	2.53 (1.60–4.02)	1.92 (1.16–3.18)
Pouwels *et al.* (2010)[49]	4.5	2.9	1.62 (1.41–1.86)	1.20 (1.04–1.40)
Corley *et al.* (2010)[51§]	4.6	3.7	1.36 (1.27–1.46)	1.22 (0.96–1.54)

Leontiadis GI et al. *Curr Treat Opt Gastroenterol* 2014

Residual confounding

- Almost all of these studies performed matching or statistical adjustment for confounders
  - Almost always the adjusted relative risk was smaller (than the unadjusted risk) or non-significant
- Even the best adjusted or matched studies have measured most confounders as dichotomous variables.
  - oversimplification
  - The severity of each of the confounding factors/diseases should be measured as continuous or at least as ordinal variables, but such granularity cannot be obtained from large databases.

Leontiadis GI et al. *Curr Treat Opt Gastroenterol* 2014

How can we validate the results of an observational study that evaluated rare AEs of a drug?

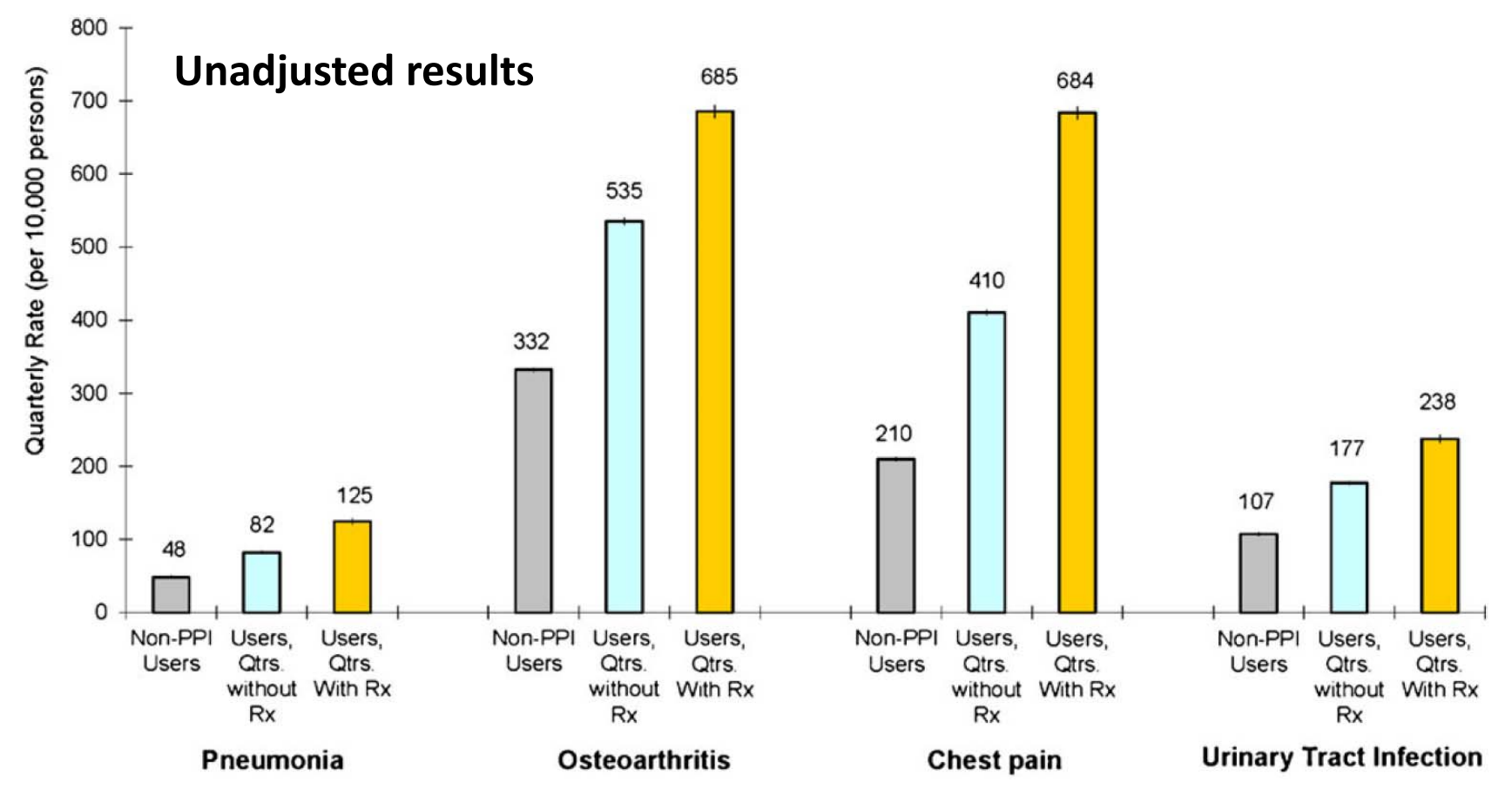
- With RCTs – not always feasible or ethical
- With pre-specified **falsification analyses**

Falsification approach

- Is the PPI-Community-Acquired Pneumonia (CAP) association confounded by unobserved patient and prescriber characteristics?
- Retrospective cohort study
  - 54,000 US individuals over 11 years
- **Falsification analyses**: testing for **implausible** associations between PPI use and
  - OA
  - chest pain
  - UTI
  - DVT
  - skin infection
  - RA

Jena AB et al. *J Gen Intern Med* 2012

Falsification approach



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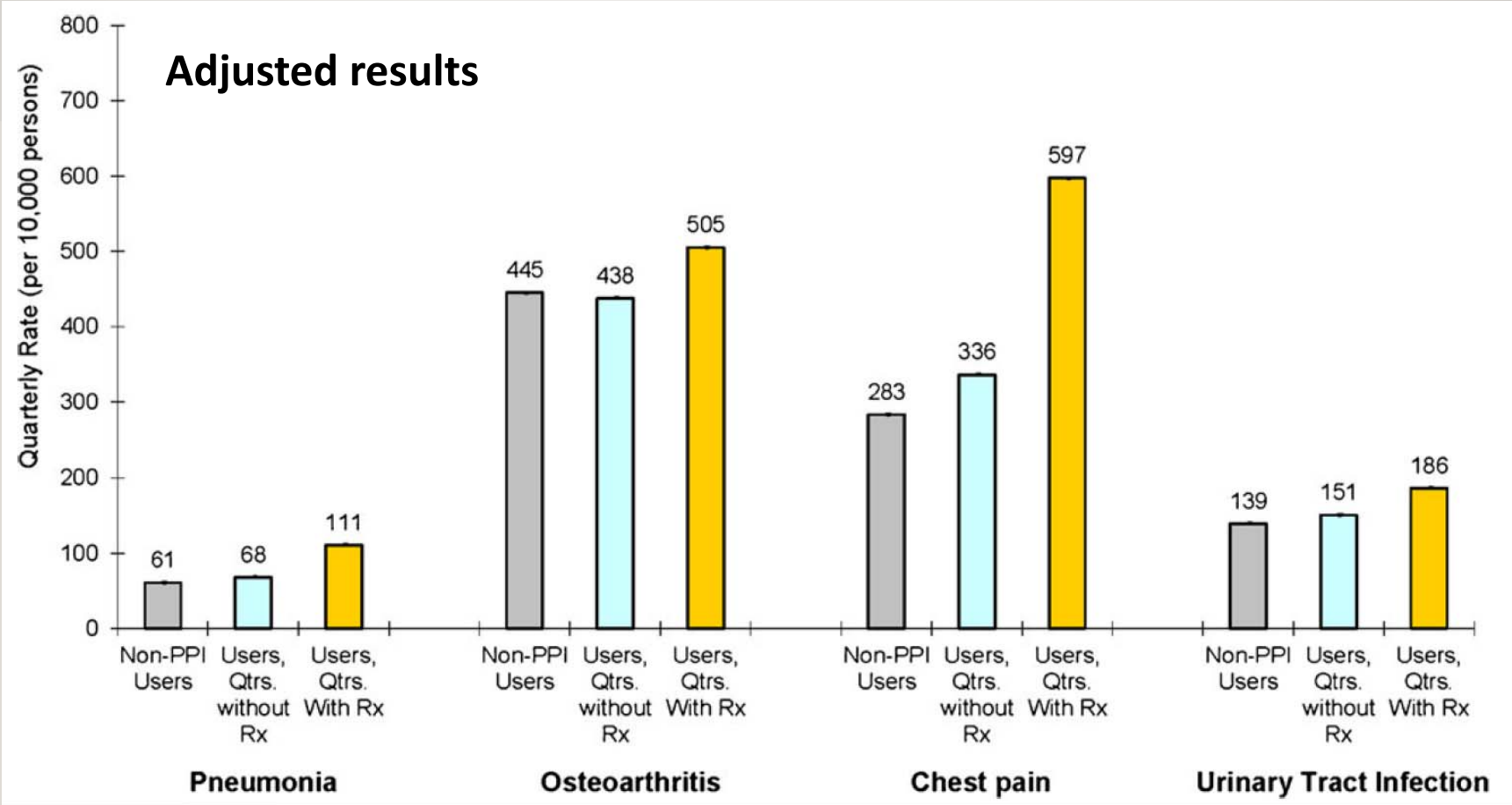

Jena AB et al. *J Gen Intern Med* 2012

Falsification approach

MCQ:

a) PPIs cause everything under the sun (OA, chest pain, UTI, DVT, skin infections, RA)

b) The observed association between PPI use and CAP is most likely confounded

Jena AB et al. *J Gen Intern Med* 2012

Are PPIs the only drugs associated with such long-term risks?

Associated with CAP:

- PPIs
- statins
- ACE-inhibitors
- digoxin
- amiodarone
- diuretics
- oral or inhaled corticosteroids
- zopiclone
- benzodiazepines

Remington LT et al. *Curr Opin Pulm Med* 2014
De Groot MCH et al. *Eur J Epidemiol* 2014

Associated with hip fractures:

- anti-Parkinson medications
- antidepressants
- medications for COPD
- bisphosphonates
- calcium
- vitamin D supplements

Rossini M et al. *Drugs Aging* 2014

The future?

- Large RCTs with several years follow up: unlikely to be conducted
  - MANAGE trial
    - partial factorial design 2x2 (dabigatran, omeprazole, placebo)
    - 2,000 pts with myocardial injury after noncardiac surgery
    - Duration: 1 year
    - may provide answers for not-too-rare, medium-term outcomes (CDAD, CAP)
- Many additional associations between PPIs and conditions common in older and frail people will be "discovered" soon
- In 5-10 years, the pendulum may be on the other side, with PPIs being used very cautiously in frail multi-morbid patients
- Alternative acid suppressive medications (H_2RAs, P-CABs): same fate as PPIs
- Consider: EUS-guided endoscopic hyper-selective vagotomy/block

Conclusions-1

- Observational studies have shown very modest associations between PPI therapy and several long-term risks
- **These associations are most likely spurious, due to residual confounding**
- However, we cannot exclude the possibility that some of these associations are causal

Conclusions-2

- We, physicians, should be aware of:
  - the potential risks of PPIs, and the quality of evidence
  - the clear indications for long term PPI use, and the quality of evidence
  - the fact that PPIs tend to be overused
- For each individual patient, we should:
  - weigh benefits against risks
  - assess if we should proactively (briefly) inform the patient about the benefits/risks balance
  - be prepared to discuss in detail and suggest online resources if asked
  - periodically re-assess
    - if the patient still needs long-term therapy
    - if the dose can be lowered
    - alternative treatments

Conclusions-3

- PPIs should not be withheld from patients who genuinely require them,

  but should be taken in the lowest effective dose and only for as long as clinically indicated.

- **The same is, of course, true for all medications.**

Thank you for your attention!

Each capsule contains your medication, plus a treatment for each of its side effects