

All You Need to Know About Proton Pump Inhibitors in 20 Minutes



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GI Update May 2014

Conflict of Interest

- Faculty: Mike Kolber
- Academic Family Physician with clinical work in Peace River, Alberta
- Relationships with commercial interests: None. No funding from industry, no grants or speakers honoraria or consulting fees
- Supported by University of Alberta department of Family Medicine and Alberta College of Family Physicians



Mr. Peter Paul Ingram

42 yo male programmer complains of daily post prandial (coffee, beer) retrosternal chest discomfort. As an evidence based health care provider, you:

- Give him **Esomeprazole** 40 mg / bid x 3 month x 3 repeats, "I gave him the most expensive (therefore the best), won't have to see him again for another year. Next patient nurse"
- Send him to the pharmacy for **OTC Ranitidine**
- Tell him to buy bottles of (and shares in) of **TUMS**
- Tell him to ↓ weight, ↓ **coffee, beer**, elevate head of the bed
- Give 8 - 12 weeks of your **cheapest PPI**, then re-evaluate

How many Canadians take PPIs?

- 27 million Rx's 2013
- All PPIs in top 50 Rx's in Canada
 - Panto #4, Rabrep #26, Esomep #27, Lansop #29, Omepr #50
- Dollars: Esomeprazole (Nexium) + Apo: \$380 million 2012
 - 2013 US: 5 BILLION (#1 for overall spending)

<http://www.canadianhealthcarenetwork.ca/pharmacists/news/special-reports/top-100-drugs-19660/4>

Appropriate PPI uses

- Short Term
 - Acute treatment UGI bleeding, PUD
 - ICU patients on ventilator / coagulopathy
- Long Term
 - GERD: earn your LT PPI!
 - Dyspepsia
 - Barrett's esophagus
 - Gastroprotection
 - Post PUD and GI bleeds

Inappropriate PPI Uses

- 60% may not have appropriate indication - long term PPI¹
- Admitted to medicine ward²
 - 40% put on, 50% discharged w PPI (10% had indication)
- Long term care³ : 27% advanced dementia
 - 18% took in last week of life!
- Asthma, cough, atypical ENT symptoms: does not work!^{4,5}
- Routine Post cholecystectomy

¹BMJ 2008;336:2, ²Ann Pharmacother 2006;40:1261, ³J Am Geriatr Soc 2010; 58; 880
⁴NEJM 2009;360:1487, ⁵Chest 2005; 128:1128

How well do PPIs work? Preventing NSAID associated PUD

- 40% chronic NSAID users → endoscopic ulcer¹
 - < 4% / year → clinical PUD
- Misoprostol 800 ug/d vs placebo²: RA + NSAIDs: 40%↓clinical PUD
 - ARD = 0.4% → NNT = 250 x 6 months
- PPI vs Placebo: > 3 / 12 NSAIDs use¹ (1' prevention)
 - Endoscopic ulcers: PPI 8%, placebo 20%, NNT = 9 over 3-6 months
- PPI vs H2Ant³: recurrent PUD (2' prevention)
 - PPI 28%, H2Ant 41%, NNT = 8 over 6 months
- PPI vs Misoprostol: current or recurrent PUD
 - Initial ulcer healing equal - better with high dose Miso⁴
 - PPI ↓ recurrent PUD @ 6 months: 39% vs 51%; NNT 8
 - AEs misoprostol > PPI (31% vs 16% (diarrhea))

¹Health Tech Assess 2007;11(51) ²Ann Int Med 1995;123:241 ³NEJM 1998;338: 719

⁴NEJM 1998;338: 727 ⁵Arch Intern Med. 2002;162:169

Who needs gastroprotection?

Risk factors for nonsteroidal anti-inflammatory drug (NSAID)-associated serious gastrointestinal adverse events

Characteristic	Odds ratio (95% CI)
History of ulcer complications	13.5 (10.3-17.7)
Multiple NSAIDs	9.0 (5.7-14.2)
High-dose NSAIDs	7.0 (5.2-9.6)
Concomitant anticoagulant use	6.4 (2.9-14.6)
Age ≥ 70 years	5.6 (4.6-6.9)
Age ≥ 60 years	3.1 (2.5-3.7)
Concomitant corticosteroid use	2.2 (1.4-3.5)
History of cardiovascular disease	1.8 (1.1-3.2)

Data from references 12, 13, 27 and 28

Can J Gastro 2002; 16: 231

Who Needs Gastroprotection?

Table 1. Patients at increased risk for NSAID GI toxicity

High risk
1. History of a previously complicated ulcer, especially recent
2. Multiple (≥2) risk factors
Moderate risk (1-2 risk factors)
1. Age >65 years
2. High dose NSAID therapy
3. A previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants
Low risk
1. No risk factors

H₂ glycer is an independent and additive risk factor and needs to be addressed separately (see text and recommendations).

Table 2. Summary of recommendations for prevention of NSAID-related ulcer complications

	Low	Moderate	High
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID+PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk* (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

*Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for H₂ glycer, and if the infection is present, eradication therapy should be given.

Am J Gastroenterol 2009; 104:728

Do PPIs work for GERD? '3-6-9 rule'

HEARTBURN EXAMPLE

PATIENTS WHO RESPOND IN THE PPI GROUP

≈ 65% AT 4 WEEKS, 85% AT 8 WEEKS

PATIENTS WHO RESPOND TO H2RA

≈ 40% AT 4 WEEKS, 55% AT 8 WEEKS

PATIENTS WHO RESPOND IN THE PLACEBO GROUP

≈ 15% AT 4 WEEKS, 30% AT 8 WEEKS

8-9/10 PATIENTS WILL RESPOND TO A PPI
3 OF THESE IMPROVED NOT BECAUSE OF A DRUG
AN ADDITIONAL 2-3 OF THESE WOULD HAVE IMPROVED WITH AN H2RA

COCHRANE LIBRARY CD003244

Cochrane Systematic Reviews 2007, Issue 2. Art. No.: CD003244

GERD Are PPIs equally effective?

- Depends who takes you golfing!
- Individual patient responses

Khan, Cochrane Systematic Reviews 2007, CD003244

If all the same → use the cheapest! 90 days cost – Alberta 2014

• Rabeprazole 20mg:	\$35
• Omeprazole 20mg:	\$50
• Lansoprazole 30mg:	\$55
• Pantoprazole 40mg:	\$55
• Tecta 40 mg:	\$85
• Nexium 40mg:	\$195
• Ranitidine 150mg bid:	\$45

PRICE COMPARISON OF COMMONLY PRESCRIBED PHARMACEUTICALS IN ALBERTA 2014

What about BID PPI?

- No difference c/w OD PPI¹
- 25% Nova Scotians, 23% US Veterans started on BID PPI^{2,3}
- Reserve BID for patients with classic GERD still symptomatic on once daily PPI

¹ Khan, Cochrane Reviews 2007, CD003244, ² Gastro 2004 April; 126(4) Supp 2: W1277, A603
³ J Gen Intern Med 2013 DOI: 10.1007/s11606-013-2345-0

GERD: How long initial treatment? Earn your Long Term PPI!

- Try ~ 8 -12 weeks and re-evaluate¹
- If better with PPI and non-pharm → dc PPI
- If symptoms recurrence → restart
 - daily or less frequent
 - On demand

¹Armstrong Can J Gastro 2004 (19): 15

On Demand PPIs

- **Most GERDs are NERDs!**
 - 60-70% GERDs: No esophagitis on endoscopy²
 - On demand = daily PPIs for patients w/o visible esophagitis¹
 - *On demand should work in most patients*
- GERDs followed long term³
 - 80% PPIs: 50% daily, 30% on demand

¹Aliment Pharm 2007; 26: 195, ²Can J Gastro 2004 (19): 15, ³Aliment Pharm 2007; 25: 715

Can patients stop PPIs?

- Yes, 27% of PPI users x 4 years → successfully dc¹
- Predictors of stopping: older age and dyspeptics²
 - Less successful: heartburn

¹Aliment Pharm 2006 ;24: 945 ²Am J Gastro 2009; 104:527

Stopping PPIs Cold Turkey or taper?

- RCT taper vs. not taper off PPIs
 - More successful in getting off PPIs (31 vs 22%; NSS)¹
- 120 healthy volunteers (no GERD sx)
 - RCT to placebo or PPI then dc
 - 20% developed GERD sx after dc PPI
- I taper!

¹Aliment Pharm 2006 ;24: 945 ²Gastroenterology 2009;137:80

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Proton pump inhibitors: risk of bone fractures

Starting date: April 4, 2011
Expiring date: April 4, 2011
Subcategory: Drug
Type of communication: Informational
Source of report: Health Canada
Audience: General Public, Healthcare Professionals
Identification number: 302011

What you should do

If you are taking PPIs and are at risk of osteoporosis, or are unsure of whether you are at risk, please consult your healthcare professional. Health Canada has previously communicated with consumers and healthcare professionals about the risk of bone fractures associated with long-term use of proton pump inhibitors (PPIs).

Related articles

- FDA Drug Safety Update: Risk of Low Magnesium Levels Associated with Long-Term Use of Proton Pump Inhibitors (3/1/09)
- FDA Drug Safety Update: Possible Increased Risk of Fractures of the Hip, Wrist, and Ankle with the Use of Proton Pump Inhibitors (5/25/05); updated 3/23/07
- FDA: Possible Fracture Risk with High Dose, Long-term Use of Proton Pump Inhibitors (FDA press release 3/23/07)

PPI Potential Adverse Effects

- Gastrointestinal
 - Nuisance diarrhea, lymphocytic colitis
 - C. diff. and c. diff recurrence
- Pneumonia
- Osteoporosis, hip #
- VB12 deficiency, hypomagnesemia, interstitial nephritis

PPI and GI AEs

- Nuisance diarrhea: 5-10%
 - microscopic colitis¹
- Clostridium difficile: ORs: 1.93² to 2.05³
- Patients with C Diff: risk of recurrence ↑ with PPI⁴
 - PPI 25.2% no PPI 18.5%, ARD ~ 7% NNH = 15
- Risk of recurrence > initial, PPI > H2A

¹ Aliment Pharmacol Ther 2010; 32: 1124

² Am J Gastro 2012; 107:1011 ³ Am J Gastro 2007;102:2047

⁴ Arch Intern Med. 2010;170(9):772

Putting it all together PPI and C diff³

- Community¹ 1/10000 ADD PPI → 1 extra case
- Hospital admissions²
 - Without antibiotics 5 / 1000 ADD PPI → 5 extra cases
 - With antibiotics 42/1000 ADD PPI → 36 extra cases
- On PPI at admission 53/1000 ADD Abx → 45 extra cases

Community risk low: do they really need PPI during admissions? (especially if contemplating Abx)

¹BMC Inf Dis 2011, 11:194, ²NEJM 2011;365:1693, ³Am J Gastro 2012; 107:1011

PPI and pneumonia

- CAP Rates: primary care 360,000 patients x 7 years¹
 - Non PPI users 0.6% / year vs current PPI users 2.5%
 - Adjusted: **1 additional case per 100 patients / year**
- SR PPIs² or Acid ↓ meds³ : OR 1.36 (1.12–1.65)
 - Higher dose PPI → ↑ risk^{1,3}
 - New starts (< 30 days) > LT use?⁵
- Recurrent CAP⁴: if start PPI after 1st pneumonia
 - 15% vs 8% no PPI → ARD = 7%, NNH = 15 over 5 years

Overall risk low, if pneumonia → limit concomitant PPI

¹JAMA 2004;292:1955 ²Aliment Pharmacol Ther 2010; 31: 1165

³CMAJ 2011. DOI:10.1503, ⁴Am J Med 2010 123, 47, ⁵Ann Intern Med. 2008;149:391-398.

PPI and fractures

Systematic Review	# of Studies	RR / OR with PPI	RR / OR with H2ANT	Comments
BMJ 2012 ¹	11	1.30 (1.25, 1.36)	NR	
Ann Fam Med 2011 ²	11	1.29 (1.18, 1.41)	1.10 (0.99-1.23)	Overall fracture
Am J Med 2011 ³	11	1.30 (1.19-1.43)	1.12 (0.97-1.30)	Hip fracture
Am J Gastro 2011 ⁴	16	1.25 (1.14, 1.37)	NR	Hip fracture ST use > LT use
Eur J Gastro 2011	7	1.24 (1.15, 1.34)	NR	Hip only
Bone 2011	12	1.23 (1.11, 1.36)	1.12(0.99–1.27)	Hip

¹Khalili, BMJ 2012;344:e372 doi: 10.1136, ²Eom, Ann Fam Med 2011;9:257

³Yu, Am J Medicine 2011; 124:519, ⁴Ngamruengphong, Am J Gastroenterol 2011; 106:1209

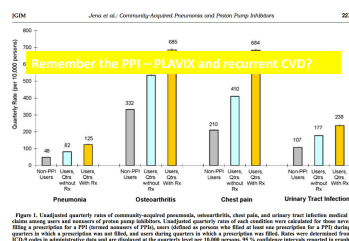
⁵Ye, Eur J Gastro Hepat 2011; 23:794, Kwok, Bone 2011; 48 : 768

Putting it all together Attributable Fracture risk

- Nurses Health Study: prospective cohort, 80,000 healthy US nurses, mean 66 years, data on PPI / Hip # for 8 years¹
 - Hip fracture risk not on PPI = **1.5 / 1000**
 - Hip fracture risk on PPI = **2 / 1000**
 - Absolute risk difference = **0.5 / 1000**
 - NNH = 2000 x 8 years for 1 additional hip fracture
 - Smoking ↑ risk > PPI and duration of use
 - Risk ~ baseline if stop > 2 years

BMJ 2012;344:e372 doi: 10.1136

Are PPI associated Adverse Events due to residual confounding?



J Gen Intern Med 2012; 28(2):223–30
 Bhatt, NEJM 2010;363:1909

Summary PPIs

- Earn your LT PPI, **cheapest**, lowest dose (on demand)
- Clean up the: “I don’t know why I take PPIs”
 - Taper, then DC
- Adverse Events:
 - Attributable risks low, but a ton of people on them...
 - Limit potential AEs by judicious use of PPIs
 - Patient with C diff, CAP, osteoporosis or hip # → consider stopping PPI if possible