Clinical Question 8

- Do proton pump inhibitors cause bone loss?

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Learning Objectives

Upon completion of this module, participants will be better able to:

- Explain the impact of co-morbidities on the risk profile of patients with osteoporosis
- Explain how osteoporosis therapies may mitigate the impact of proton pump inhibitors on the risk of bone loss and fragility fractures
- Describe why treatment with proton pump inhibitors may be associated with bone loss and increased fracture risk
- Mitigate the impact of medication-related factors which may increase the risk of bone loss and fragility fractures

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Clinical Question 8

Do proton pump inhibitors cause bone loss?

Proton pump inhibitors are widely used in older patients. Some but not all studies recognize risk for declines in BMD and increases in fracture risk.

Clinical Vignette

- Femoral neck BMD T-score is -3.6
- Currently on oral bisphosphonate (risedronate 35 mg weekly) for the past 2 years
- On a PPI for GERD for the last 4 years. (Gastroscopy showed mild gastritis and esophagitis). Her friends in Florida told her that they heard that her stomach pill is horrible for bones. She stopped and now is unable to sleep at night due to severe heartburn but is concerned about potential long-term side effects of PPI drug therapy
- H2 blocker is not able to control her symptoms

Maria
63 years old

What is Maria's risk of osteoporotic fracture?

1. Low
2. Moderate
3. High

Clinical Vignette

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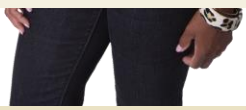
- H2 blocker is not able to control her symptoms

Maria
63 years old

What treatment advice would you discuss with Maria?

1. Ignore her friends' advice
2. Restart PPI and continue risedronate
3. Restart PPI and change OP therapy to denosumab
4. Stop all OP therapy and just take Vit D and Calcium



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Proton Pump Inhibitors (PPIs)

- PPIs are potent acid suppressing medications used to treat gastro-intestinal (GI) conditions:

Common uses of Proton Pump Inhibitors	
→ Prevent recurrent GERD symptoms	→ Complications of Barrett's esophagus
→ Complications of peptic stricture	→ Complications related to NSAIDs
→ Complications of esophageal stricture	

- PPIs may potentially reduce absorption of calcium carbonate[1,2]
- Some retrospective studies have shown long-term PPI is associated with increased risk of hip fractures,[2,3] particularly at high doses; other studies have found no association[4,5]
- For patients with osteoporosis using PPIs:
  - → Ensure optimal calcium and vitamin D supplementation
  - → Prescribe the lowest effective PPI dose, review indication periodically
  - → Consider alternate formulation of calcium (e.g., calcium citrate)

1. O'Connel, MB, et al. (2005) *Am J Med* 118, 778-781. 2. Targownik LE, et al. (2008) *CMAJ* 179, 319-326. 3. Yang YX, et al. (2006) *JAMA* 296, 2947-2953. 4. Pouwels S. et al. (2011) *Osteoporosis Int.* 22, 903-910 5. Grey SL, et al. (2010) *Arch Intern Med* 170, 765-771.

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Proton Pump Inhibitors and Fracture

- PPIs are potent suppressors of gastric acid
- A meta-analysis of 12 observational studies (1,521,062 patients) showed increased fractures with PPI use (OR 1.2; 1.11 – 1.3 P<0.001)
- No difference in fracture risk seen with H2 Blockers
- Risk appears dependent on duration of therapy, decreases following D/C
- Pathophysiology unknown, may be due to impaired calcium absorption associated with decreased gastric acidity
- May be due to impaired absorption of calcium carbonate in presence of higher gastric
- Calcium carbonate best absorbed in acidic pH
- Long-term PPI use is associated with increased fall risk
- PPI may directly affect osteoclast proton pump
- Need prospective RCT data – Only observational data present

Kwok et al 2011 ; Lewis 2014

OR = odds ratio; pts = patients; D/C = discontinuation; MOA = mode of action; OC = osteoclasts; RCT = randomized clinical trial

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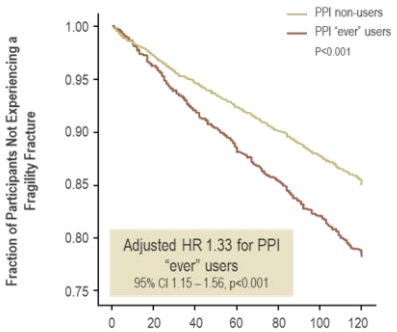
PPI Use is Associated with Increased Fracture

- **Potential mechanisms by which PPI therapy causes an increase in fracture risk include†:**
  - → Interference with Ca^{2+} absorption
  - → Direct action of PPI in skeletal cells (osteoclasts)



Kaplan–Meier curve showing unadjusted fragility fracture-free survival by PPI use (defined as PPI ever use).

PPI = proton pump inhibitor. P-value from the log rank test.
†Exact mechanism is not understood

Fraser LA, et al. (2013) *Osteoporosis Int*. 24,1161-1168.

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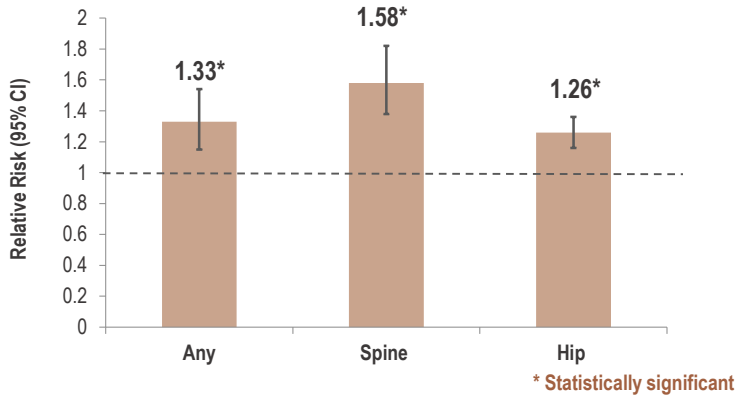
Meta-analysis of Fracture Risk with PPI from Observational, Case-control and Cohort Studies

Meta-analysis of 18 international observational case-control and cohort studies (n = 244,109 fracture cases)



Zhou B et al. (2016) Osteoporos Int 27, 339-347.

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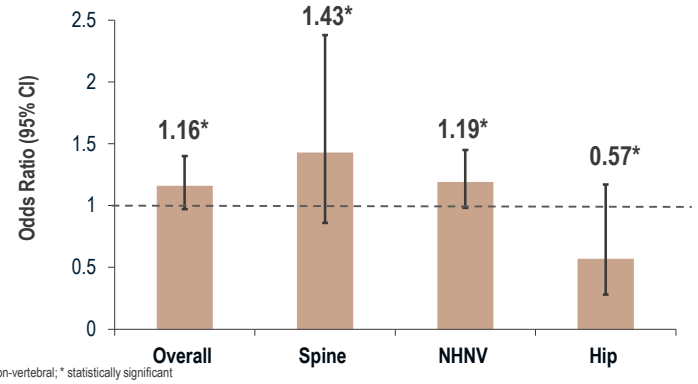
PPI Use and Fracture in a Prospective Observational Study: PPI Use Associated with Numerically Higher Risk of Overall, Clinical Spine and Non-Hip/Non-Vertebral Fractures

Global Longitudinal Study of Osteoporosis in Women (GLOW)
Multivariable regression model predicting Year 3/Year 5 fracture.
(n=2,715)



NHNV = non-hip-non-vertebral; * statistically significant

Adachi JD, et al. (2013) *ASBMR*, Oral presentation, OP 1049.

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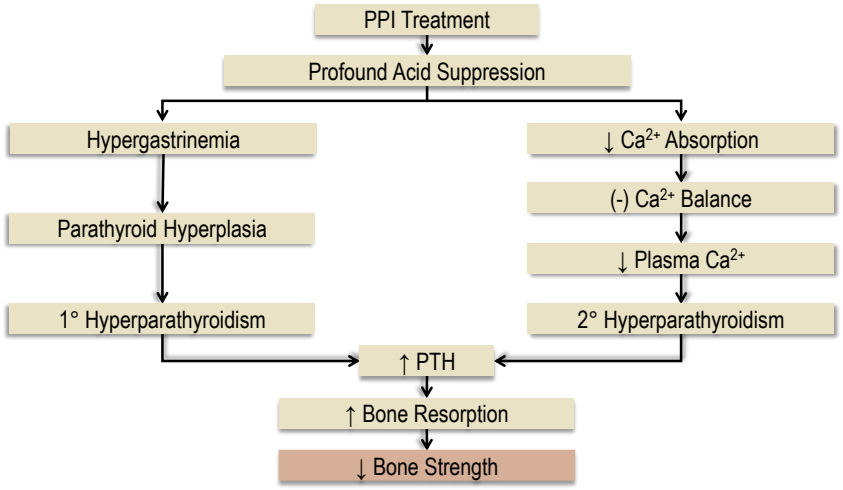
Proposed Mechanism of PPI on Bone Metabolism



Adapted from: Yang YX. (2012) *Curr Gastroentrol Rep.*, 14, 473 – 479.

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Risk of Fracture with PPI Use: Health Canada Statement – April 4, 2013

PPI Treatment May be Associated With a Small:	OP-related Risk Factors that May Contribute to Increased Risk:
→ ↑ risk of OP-related hip fracture	→ Age
→ ↑ risk of OP-related wrist fracture	→ Gender
→ ↑ risk of OP-related spine fracture	→ Presence of health conditions

The risk of fracture was higher in patients who received multiple daily doses of PPIs and therapy for a year or longer

Health Canada Alert April 2013. Proton Pump Inhibitors: Risk of Bone Fractures. Available at: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/26523a-eng.php. Last accessed March 17, 2017.

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PPI Product Monographs Continue to Reflect Health Canada Guidance*

- Several observational studies suggest PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.
- The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (>1 year).
- Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Accessed March 17, 2017.
Product Monographs of Losec (omeprazole magnesium), Nexium® (esomeprazole magnesium trihydrate), Tecta® (pantoprazole magnesium), Pantoloc® (pantoprazole sodium), Pariet® (rabeprazole sodium), Prevacid® (lansoprazole), Dexilant® (dexlansoprazole)

Discussion: Clinical Takeaways

1. PPIs are potent acid suppressing medications used to treat gastrointestinal (GI) conditions[1]
2. Gastric acid suppression may also reduce the bioavailability of calcium for intestinal absorption leading to increased bone resorption[1]
3. PPI use is associated with a modest risk of fragility fracture[2,3]
4. Health Canada suggests physicians monitor patients with risk factors for osteoporosis who use PPIs[3]

1. Yang YX. (2012) Curr Gastroenterol Rep 14, 473–479. 2. CAG Position Statement: Hip Fracture and Proton Pump Inhibitor Therapy – A 2013 update.
3. Health Canada Alert April 2013. Proton Pump Inhibtors: Risk of Bone Fractures. Available at: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/26523a-eng.php.