

Appendix 3: Ranges of frequency ratios for harms associated with proton pump inhibitors, and related references

Harm	Frequency ratios (and confidence intervals)	Reference
Increased risk of fractures (overall)	RR- 1.14 (1.06, 1.24) – 1.29 (1.18, 1.41)	[1–4]
Increased risk of spine fracture	RR- 1.07(1.01,1.14) – 1.56 (1.31, 1.85)	[2–4]
Increased risk of hip fracture	RR- 1.16 (1.07, 1.27) – 1.30 (1.19, 1.43)	[2–6]
<i>Clostridium difficile</i> infections	RR- 0.9 (0.90,1.50) – 5.0 (1.3, 19.4)	[7–12]
<i>Clostridium difficile</i> -related diarrhoea	RR- 2.04 (1.93, 2.17) – 2.74 (1.85, 4.07)	[13,14]
<i>Campylobacter</i> infections	RR - 3.5 (1.1, 12.0) – 11.7 (2.5,54.0)	[12]
<i>Salmonella</i> infections	RR - 4.2 (2.2, 7.9) – 8.3 (4.3,15.9)	[12]
Community-acquired pneumonia	RR- 1.17 (1.11, 1.24) – 1.65 (1.25, 2.19)	[15–17]
Hospitalisation for community-acquired pneumonia	RR - 1.05 (0.89,1.25)	[17]
Gastric cancer	OR- 1.39 (1.19, 1.64)	[18]
Gastric atrophy	OR - 1.50 (0.59, 3.80)	[19]
Intestinal metaplasia	OR - 1.46 (0.43, 5.03)	[19]
Simple ECL hyperplasia	OR - 5.01 (1.54, 16.26)	[19]
Focal ECL hyperplasia	OR - 2.48 (0.44, 14.13) - 3.98 (1.31, 12.16)	[19,20]
Colorectal cancer	OR - 1.08 (0.96, 1.20)	[21]
Corporal chronic inflammation	OR - 1.30 (0.68, 2.48)	[20]
Increased risk of vascular events among patients taking clopidogrel	RR- 1.10 (0.75, 1.61) – 1.60 (1.07, 2.40)	[22–31]
Bacterial peritonitis	RR- 2.22 (1.28 – 3.83) – 3.15 (2.09, 4.74)	[32–35]
Small intestine bacterial overgrowth	RR- 2.82 (1.24, 4.21)	[36]

References:

1. Eom CS, Park SM, Myung SK, Yun JM, Ahn JS. Use of Acid-Suppressive Drugs and Risk of Fracture : A Meta-analysis of Observational Studies. *Ann Fam Med*. 2011;257–67.
2. Kwok CS, Yeong JK-Y, Loke YK. Meta-analysis: risk of fractures with acid-suppressing medication. *Bone*. 2011;48(4):768–76.
3. Yu EW, Bauer SR, Bain PA, Bauer DC. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med*. 2011;124(6):519–26.

4. Tsoi KK, Ng SC, Wong MC, Hirai HW, Lam T, Chan FKL. S-210. *Gastroenterology*. 2011;140(5):S-210.
5. Cardinal L, Shankar U, Sharma S, Masood WM. Effect of Proton Pump Inhibitors on the Risk of Hip Fracture: Systematic Review and Synthesis. *Clin Gastroenterol Hepatol*. 2011;9(2):184.
6. Ngamruengphong S, Leontiadis GI, Radhi S, Nugent K. Use of Proton Pump Inhibitors and Fracture: Meta-Analysis of Observational Studies. *Gastroenterology*. 140(5):S-731.
7. Kwok CS, Arthur AK, Anibueze CI, Cavallazzi R, Singh S LY. Proton pump inhibitors and associated risk of clostridium difficile infection: A systematic review and meta-analysis of observational studies. *Br J Clin Pharmacol*. 2012;73(6):985.
8. Deshpande A, Pant C, Pasupuleti V, Rolston DDK, Jain A, Deshpande N, et al. Association between proton pump inhibitor therapy and Clostridium difficile infection in a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(3):225-33.
9. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol*. 2012;107(7):1011-9.
10. Tleyjeh I, Bin Abdulhak A, Riaz M et al. Association between acid-suppression therapy and clostridium difficile infection: A systematic review and meta-analysis. *Clin Microbiol Infect*. 2012;18:113.
11. Tleyjeh IM, Bin Abdulhak A a, Riaz M, Alasmari F a, Garbati M a, AlGhamdi M, et al. Association between proton pump inhibitor therapy and clostridium difficile infection: a contemporary systematic review and meta-analysis. *PLoS One*. 2012;7(12):e50836.
12. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther*. 2011;34(11-12):1269-81.
13. Shukla S, Shukla A, Guha S, Mehboob S. S1230 Use of Proton Pump Inhibitors and Risk of Clostridium difficile-Associated Diarrhea: A Meta-Analysis. *Gastroenterology*. 2010;138(5):S-209.
14. Gupta A, Attar BM, Agarwal R, Tsoi KK, Ng SC, Wong MC, et al. S-210. *Gastroenterology*. 2009;140(5):S-210.
15. Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. *Aliment Pharmacol Ther*. 2010;31(11):1165-77.
16. Eom C-S, Jeon CY, Lim J-W, Cho E-G, Park SM, Lee K-S. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *Can Med Assoc J*. 2011;183(3):310-9.
17. Lambert A a, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell T a. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. *PLoS One*. 2015;10(6):e0128004.
18. Ahn JS, Eom C-S, Jeon CY, Park SM. Acid suppressive drugs and gastric cancer: a meta-analysis of observational studies. *World J Gastroenterol*. 2013 Apr;19(16):2560-8.
19. Song H, Zhu J, Lu D. Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions (Review). *Cochrane database sys rev*. 2014;(12):CD010623.
20. Layli E, Nasserri-Moghaddam S. Meta-analyses: Does Long-term PPI use Increase the Risk of Gastric Premalignant Lesions? *Arch Iran Med*. 2013;16(8):449-58.

21. Ahn JS, Park SM, Eom CS, Kim S, Myung S-K. Use of Proton Pump Inhibitor and Risk of Colorectal Cancer: A Meta-analysis of Observational Studies. *Korean J Fam Med*. 2012;33(5):272–9.
22. Collet J-P, Hulot J-S, Sweeny J, Montalescot G. TCT-456: Use Of Proton Pump Inhibitor Is Associated With Increased Mortality In Coronary Artery Disease Patients Exposed To Clopidogrel: A Systematic Metanalysis. *Am J Cardiol*. 2009;104(6):168D.
23. Hakeem A, Bhatti S, Karmali K, Rothenberg F, Vandivier RH. Weighing the Evidence of Harm With Ppi+ Clopidogrel Versus Clopidogrel Alone for Secondary Prevention of Cad-Meta Analysis of Randomized Trials and Observational Studies Comprising Over 50,000 Patients. *J Am Coll Cardiol*. 2010;55(10):A137.E1282.
24. Kwok CS, Loke YK. Meta-analysis : the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther*. 2010;31(8):810-23.
25. Jo S, Lim H, Choi Y, Kim S, Kim H, Han S, et al. A meta-analysis of 43,432 patients: concomitant use of proton pump inhibitor with clopidogrel is associated with increased death and myocardial infarction in patients receiving PCI. *J Am Coll Cardiol*. 2010;66(15 Suppl B):B100-B101.
26. Siller-Matula JM, Jilma B, Schrör K, Christ G, Huber K. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. *J Thromb Haemost*. 2010;8(12):2624–41.
27. Ngamruengphong S, Leontiadis GI, Crowell MD, Chaliki HP, Sharma VK. T1078 Risk of Adverse Cardiovascular Events With Concomitant use of Clopidogrel and Proton Pump Inhibitors(PPI): Systematic Review and Meta-Analysis of Observational Studies. *Gastroenterology*. 2010;138(5):S–483.
28. Kwok CS, Jeevanantham V, Dawn B, Loke YK. No consistent evidence of differential cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: meta-analysis. *Int J Cardiol*. 2013;167(3):965–74.
29. Chen M, Wei J, Xu Y, Liu X, Huang D. A Meta-Analysis of Impact of Proton Pump Inhibitors on Antiplatelet Effect of Clopidogrel. *Cardiovasc Ther*. 2012;30:227–33.
30. Huang B, Huang Y, Li Y, Yao H, Jing X, Huang H, et al. Adverse cardiovascular effects of concomitant use of proton pump inhibitors and clopidogrel in patients with coronary artery disease: a systematic review and meta-analysis. *Arch Med Res*. 2012 Apr;43(3):212–24.
31. Focks JJ, Brouwer MA, Oijen MGH Van, Lanas A, Bhatt DL, Verheugt FWA. Concomitant use of clopidogrel and proton pump inhibitors : impact on platelet function and clinical outcome- a systematic review. *Heart*. 2013;99(8):520–7.
32. Trikudanathan G, Israel J, Cappa J, O’Sullivan DM. Association between proton pump inhibitors and spontaneous bacterial peritonitis in cirrhotic patients - a systematic review and meta-analysis. *Int J Clin Pract*. 2011;65(6):674–8.
33. Deshpande A, Pasupuleti V, Thota P, Pant C, Mapara S, Hassan S, et al. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *J Gastroenterol Hepatol*. 2013;28(2):235–42.
34. Mapara S, Deshpande A, Thota P et al. Pharmacologic acid suppression is associated with spontaneous bacterial peritonitis in patients with cirrhosis: A meta-analysis. *J Hosp Med*. 2012;7:S53.

35. Devaki P, Njei B, Nrusimhadri N DI. Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: A meta-analysis of epidemiologic evidence. *Hepatology*. 2012;56:952A.
36. Lo W-K, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. *Clin Gastroenterol Hepatology*. 2013;11(5):483–90.