

Appendix: Details of studies used in meta-analysis and of supplementary analysis

Studies of PPI Use and Hip Fracture			
Author, Year	Study Design / Cohort	No. of Subjects / Cases	Follow up and Outcome
Vestergaard, 2006 ¹	Case-control study of Danish national population	124,655 cases / 373,962 controls	All fractures during study period of Jan 2000 to December 2000.
Yang, 2006 ²	Nested case-control General Practice Research Database (GPRD).	13,556 cases / 135,386 controls	Hip fracture during study period between May 1987 to March 2003.
Kaye, 2008 ³	Nested case-control General Practice Research Database (GPRD).	1,098 cases/10,923 controls Individuals with no risk factor.	First hip fractures after at least 2 years of follow-up.
Targownik, 2008 ⁴	Retrospective matched cohort study of the Population Health Research Data Repository of Manitoba, Canada	15,792 cases of fracture / 47,289 controls	Osteoporotic fractures with > 7 years of follow up.
Yu, 2008 ⁵	Prospective Study of Osteoporotic Fractures (SOF)	4808 women with 451 hip fractures; 234 on PPI 5407 men with 98 hip fractures; 487 on PPI	Osteoporotic fractures Mean follow-up time 7.6 yrs (1986/88-1996) for women and 5.6 yrs (2000/02-2007) for men.
De Vries, 2009 ⁶	Retrospective cohort study General Practice Research Database (GPRD).	234,144 PPI user, 166,798 H2 blocker users and 67,309 bisphosphonate users	All fractures, hip fracture, and vertebral fracture; mean duration of follow p in all groups > 3 years
Corley, 2010 ⁷	Nested case-control Kaiser Permanente Database.	33,752 cases / 130,471 controls	Hip fracture during study period between Jan 1995 and Sept 2007.
Pouwels, 2010 ⁸	Case control study Dutch PHARMO	6,763 cases /26,341 controls	Hip or femur fractures with mean follow-up of 4.1 years.
Gray, 2010 ⁹	Prospective analysis Women's Health Initiative	161,806 women, 3396 used PPI; 1500 hip fractures	All fractures including, hip, spine, forearm and wrist and bone mineral density measurements. Mean follow up 7.8 years.
Chiu, 2010 ¹⁰	Nested cases-control study Taiwan National Health Insurance Database	1241 cases of hip fracture; 1241 controls	Newly diagnosed hip fractures in 2005 and 2006

Present study, 2011	Prospective analysis Nurses' Health Study	79, 899 post-menopausal women	Hip fractures > 7 years of follow up.
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REFERENCES

1. Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. *Calcif Tissue Int.* Aug 2006;79(2):76-83.
2. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA.* Dec 27 2006;296(24):2947-2953.
3. Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. *Pharmacotherapy.* Aug 2008;28(8):951-959.
4. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ.* Aug 12 2008;179(4):319-326.
5. Yu EW, Blackwell T, Ensrud KE, et al. Acid-suppressive medications and risk of bone loss and fracture in older adults. *Calcif Tissue Int.* Oct 2008;83(4):251-259.
6. de Vries F, Cooper AL, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving acid-suppressant medication alone and in combination with bisphosphonates. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Dec 2009;20(12):1989-1998.
7. Corley DA, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology.* Jul;139(1):93-101.
8. Pouwels S, Lalmohamed A, Souverein P, et al. Use of proton pump inhibitors and risk of hip/femur fracture: a population-based case-control study. *Osteoporos Int.* Jun 29.
9. Gray SL, LaCroix AZ, Larson J, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med.* May 10;170(9):765-771.
10. Chiu HF, Huang YW, Chang CC, Yang CY. Use of proton pump inhibitors increased the risk of hip fracture: a population-based case-control study. *Pharmacoepidemiol Drug Saf.* Nov 2010;19(11):1131-1136.

Supplementary Analysis:

In sensitivity analyses, we included fractures associated with high trauma and observed no change in our effect estimates. Regular use of PPI was associated with a fully-adjusted hazard ratio for all hip fractures, including those associated with high trauma of 1.37 (1.14 to 1.64). We also explored the possibility that using time-varying covariates in our model might lead to inadequate control for confounders and therefore performed analyses using only baseline information on all covariates. This approach did not materially alter our effect estimates (fully-adjusted hazard ratio 1.36, 1.13 to 1.63).