



CANADIAN ASSOCIATION OF GASTROENTEROLOGY
L'ASSOCIATION CANADIENNE DE GASTROENTEROLOGIE

CAG/ACG National Office, 2902 South Sheridan Way, Oakville, ON, Canada L6J 7L6

Telephone: (905) 829-2504 Toll free: 1-888-780-0007 Fax: (905) 829-0242

E-mail: cagoffice@cag-acg.org Website: <http://www.cag-acg.org>

CAG Position Statement:
Hip fracture and proton pump inhibitor therapy

Paul Moayyedi for the CAG Clinical Affairs Committee

There has been recent media attention to the possibility that long term proton pump inhibitor (PPI) prescribing may be linked to an increased risk of hip fracture according to a data from UK (1) and Canadian databases (2). The Canadian Association of Gastroenterology (CAG) has prepared the following position statement on the association between PPI therapy and hip fracture in light of this evidence. This position statement is outlined in greater detail elsewhere (3).

Yang et al. (1) reported a nested case control study using the UK General Practice Research Database (GPRD) which selected patients over the age of 50 with an incident hip fracture and age and sex matched controls. There were 13,556 hip fracture cases and 135,386 controls and PPI therapy for more than one year was associated with an increased risk of hip fracture (adjusted odds ratio (OR) = 1.44; 95% confidence intervals (CI) = 1.30 to 1.59). Targownik et al (2) reported a further nested case control study using the Manitoba Population Health Research Data Repository where 15,792 patients with osteoporosis-related fractures were compared to 47,289 controls. There was no overall association between PPI use and fracture until after 5 or more years of exposure where the risk of osteoporotic fracture became significant (adjusted OR = 1.62; 95% CI = 1.02 to 2.58). Similarly the risk of hip fracture became significant after seven years of exposure (adjusted OR = 4.55; 95% CI = 1.68 to 12.29).

The clinical significance of this is uncertain as extrapolation of these figures (assuming 1.8 per 1000 develop a hip fracture (1)) suggests that 1263 patients need to be treated with PPI for more than one year to develop one excess hip fracture although the number needed to harm may be much lower after seven years according to the Canadian study.

These studies use reputable databases and are rigorously conducted and analyzed appropriately. The discussions in both of these articles suggest quite strongly that the association they have found is likely to be causal. Large databases provide a wonderful opportunity to evaluate benefits and harms of medical interventions but caution needs to be exercised before assuming the latest finding represents a risk to patients. The ready availability of databases means that literally millions of associations can be tested and even within a particular hypothesis there are a variety of approaches to splitting the data (e.g. duration of therapy, dose of therapy, length of follow up, age of patients, male versus female). Researchers and journals are prone to emphasize positive findings and tend to underplay the role of chance or confounding factors. These issues are less likely to be important if a consistent association is found and an accompanying editorial (4) to the Canadian study also cites a third Danish database study that supports an association between PPI therapy and fracture (5). It is interesting to note that the Danish study had a much larger number of cases than the other two studies (124,655 cases) and yet had much more muted conclusions and was published in a lower impact factor journal.

The Danish study was circumspect in their conclusions as there were inconsistencies in the data and no dose response. For example there seemed to be an increased risk with taking < 25 doses of PPI in one



CANADIAN ASSOCIATION OF GASTROENTEROLOGY
L'ASSOCIATION CANADIENNE DE GASTROENTEROLOGIE

CAG/ACG National Office, 2902 South Sheridan Way, Oakville, ON, Canada L6J 7L6

Telephone: (905) 829-2504 Toll free: 1-888-780-0007 Fax: (905) 829-0242

E-mail: cagoffice@cag-acg.org Website: <http://www.cag-acg.org>

year with a lower (but still statistically significant) risk in those taking one dose per day for a year. There seemed no biologically plausible hypothesis why such infrequent use of PPI therapy would be associated with an increased risk of fracture. There are also inconsistencies with the UK and Canadian study. The UK study reported an increased risk of hip fracture after one year of PPI therapy and there seemed to be little increase in risk over the next 4 years whereas the Canadian study only found a significant association after 7 years. Targownik et al. suggest that perhaps the UK database included patients that had in fact been taking PPIs for much longer but this is speculation.

Furthermore a Canadian cohort study (6) followed up elderly patients in Ontario on warfarin (n=52,701), thyroid replacement (n=40,555), oral corticosteroids (n=43,915) and PPI therapy (n=60,383) for five years. There was no increased risk of hip fracture in those taking warfarin compared to PPI therapy (adjusted OR = 0.94; 95% CI = 0.81 to 1.09) but there was an increased risk with corticosteroid therapy compared to PPI therapy (adjusted OR = 1.44; 95% CI = 1.21 to 1.70). It could be that warfarin is also associated with an increased risk of hip fracture but it is interesting that Targownik et al. found little increase in risk of fracture in those taking anticoagulants (14.5% of fracture cases taken anticoagulants compared with 13.4% controls).

Finally there is the issue of biological plausibility. It has been proposed that acid suppression may reduce calcium absorption and increase the risk of fracture (1). The role of pH in calcium absorption is however controversial. The dissolution of calcium carbonate is pH dependent *in vitro* although the clinical significance of this is uncertain given that calcium is absorbed in the small intestine where the pH is non-acidic whatever the pH of the stomach. A review of the literature (7) identified 7 randomized trials that evaluated calcium absorption with acid suppression in health subjects or those with ulcer disease. There were major methodological issues with many of the studies and they were all small. Four studies found no impact on calcium absorption whilst three reported decreased absorption. Further work is needed in this area but there are no conclusive data that would make the association between fracture and PPI biologically plausible. Furthermore some research suggests that PPI therapy may inhibit bone resorption (8) which might protect against fracture risk.

PPIs are one of the most well tolerated classes of drugs on the market. They have also improved the quality of life of countless patients with acid related disease. There are risks in prescribing any drug and this should be born in mind by all prescribing clinicians. PPI therapy should only be prescribed for indications where there is proven or likely benefit and the need for these drugs should be reviewed on a regular basis. This applies particularly to the frail and elderly, patients with multiple comorbidities and those taking a number of different medications where the possibility for drug interactions increases. This message applies to all drugs clinicians prescribe including PPI therapy. Current data would not support particular care in prescribing PPI therapy due to concern about risk of hip fracture. There is no persuasive evidence that the association is causal although this can never be excluded as a possibility.

The Canadian Association of Gastroenterology encourages health professionals to keep continually updated on the medical literature and will endeavour to disseminate further guidance if more information on the possible harms of PPI therapy becomes available.



CANADIAN ASSOCIATION OF GASTROENTEROLOGY
L'ASSOCIATION CANADIENNE DE GASTROENTEROLOGIE

CAG/ACG National Office, 2902 South Sheridan Way, Oakville, ON, Canada L6J 7L6

Telephone: (905) 829-2504 Toll free: 1-888-780-0007 Fax: (905) 829-0242

E-mail: cagoffice@cag-acg.org Website: <http://www.cag-acg.org>

References

1. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; 296: 2947-53.
2. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ* 2008; 179: 319-26.
3. Moayyedi P, Cranney A. Hip fracture and proton pump inhibitor therapy: balancing the evidence for benefit and harm. *American Journal of Gastroenterology* 2008; in press
4. Richards JB, Goltzman D. Proton pump inhibitors: balancing the benefits and potential fracture risks. *CMAJ* 2008; 179: 306-7.
5. Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. *Calcified Tissue International* 2006; 79: 76-83.
6. Mamdani M, Upshur RE, Anderson G, Bartle BR, Laupacis A. Warfarin therapy and risk of hip fracture among elderly patients. *Pharmacotherapy* 2003; 23: 1-4.
7. Wright MJ, Proctor DD, Insogna KL, Kerstetter JE. Proton pump-inhibiting drugs, calcium homeostasis, and bone health. *Nutrition Reviews* 2008; 66: 103-8.
8. Tuukkanen J, Vaananen HK. Omeprazole, a specific inhibitor of H⁺-K⁺-ATPase, inhibits bone resorption in vitro. *Calcified Tissue International* 1986; 38: 123-5.