CANADIAN ASSOCIATION OF GASTROENTEROLOGY
L'ASSOCIATION CANADIENNE DE GASTROENTEROLOGIE
CAG/ACG National Office, 224 – 1540 Cornwall Road, Oakville, ON, Canada L6J 7W5
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 – a 2013 update

Paul Moayyedi, Bsc, MB ChB, PhD, MPH, FRCP, FRCPC, AGAF, FACG
Yuhong Yuan, MSc, MD, PhD
Grigorios Leontiadis, MD, PhD
on behalf of the CAG Clinical Affairs

Health Canada have recently provided an information update on proton pump inhibitor (PPI) therapy and risk of fracture in April 2013 (1) stating "Several scientific studies suggest that PPI therapy may be associated with a small increased risk for fractures of the hip, wrist, or spine related to osteoporosis, a disease resulting in the weakening of bones. The risk of fracture was higher in patients who received multiple daily doses of PPIs and therapy for a year or longer. Additional risk factors for osteoporosis, such as age, gender and the presence of other health conditions, may also contribute to the increased risk of fractures. At Health Canada's request, manufacturers of all PPIs marketed in Canada have updated the drug labels for their products to include information on this risk."

The Canadian Association of Gastroenterology provided a position statement on PPI therapy and risk of hip fracture in 2008 (2) and we have updated this in light of the recent Health Canada statement. Large administrative databases are a useful tool to assess possible benefit or harms of health care interventions but given that billions of associations can be measured with these databases then highly statistically significant findings will inevitably occur by chance. Added to this problem is that any association may simply be due to confounding factors and not due to the health care intervention causing the disease (e.g. a database study may find that steroid inhaler therapy increases the risk of lung cancer but this may simply due to smokers are more likely to have lung disease (and be given steroid inhalers) and smoking causes lung cancer). Associations between health care interventions and risk of harm are therefore being reported almost every week and it is therefore very difficult for the clinician to know what associations that are likely to be causal and what are likely to be spurious. There is no simple answer to this problem as epidemiological data can never prove or disprove a hypothesis. Hill (3) has described nine factors that make an association more likely to be causal. We have previously evaluated the evidence for PPI therapy and risk of fracture according to the most important of these factors namely strength of the association, biological plausibility, specificity, consistency of the association, and evidence of a dose response relationship (4). We have conducted an updated systematic review evaluating PPI therapy and risk of fracture that will be submitted to a peer reviewed journal and have used these data to assess CAG position on the use of PPI therapy and risk of fracture.

Strength of the association

There has been a wealth of data published since the 2008 CAG position statement on PPI therapy and hip fracture risk. Our systematic review identified 13 case control studies (5-17) evaluating 1,101,595

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participants. PPI use was associated with fracture with an odds ratio (OR) = 1.21 (95% confidence intervals (CI) 1.07 to 1.38). There were also 12 cohort studies (18-29) evaluating 834,442 participants over 3,712,891 patient years of follow up. Overall these cohort studies suggested PPI therapy was associated with an increased risk of fracture (relative risk (RR) = 1.30; 95% CI = 1.13 to 1.49). Overall the data therefore suggest that PPI therapy may increase the risk of fracture although the effect is very modest and any association may be due to confounding factors. Studies usually did adjust for some confounding factors but data available from databases is limited and residual confounding cannot be excluded.

Biological plausibility

The association between PPI therapy and fracture risk would be strengthened if a biologically plausible mechanism could explain the association. The original paper that highlighted concerns regarding acid suppression and fracture (6) suggested this could be due to PPI therapy reducing the absorption of calcium. In our systematic review there were 4 studies (18, 20, 22, 27) that also assessed the impact of PPI therapy on bone mineral density involving 178,686 subjects and none of these studies found any significant association between PPI therapy and bone mineral density (BMD) with PPI users having very similar BMD to non-users. An additional Canadian study (30) involving 7,720 participants also found no association between PPI therapy and the presence of osteoporosis or with BMD loss over time. The association between PPI therapy and fracture therefore does not have a plausible biological explanation with current data.

Evidence of a dose response relationship

An association is more likely to be causal if more of the risk factor leads to a higher risk of disease. There were three case control studies (9, 12, 16) that evaluated a dose response in terms of patients taking <1 defined daily dose (DDD), 1 DDD, and > 1 DDD. There was some evidence that moving from <1 DDD to PPI therapy once per day was associated with an increased risk (OR 1.14 versus 1.31) but little evidence that increasing to >1 DDD had any increased risk (OR = 1.40) with no statistically significant (p=0.51) difference between the OR for subjects taking 1DDD and those taking higher doses. This was supported by one cohort study (19) that also showed no dose response for PPI therapy.

Another approach for dose response is to evaluate duration of therapy. This was more difficult to assess as studies used slightly different cut-off definitions but there was no significant impact of duration of PPI therapy in four case controls studies (6, 7, 9, 12) (OR for < 1 year of use = 1.25, OR for 1-5 years = 1.32, OR for > 5 years = 1.31). There was also no significant impact of duration of PPI therapy in three cohort studies (19, 22, 24) (RR for < 1year of use = 1.19, 1-5 years = 1.20, > 5 years = 1.21). There is therefore little evidence to support the Health Canada statement that the risk of fracture with PPI therapy increased with multiple doses and longer duration of therapy when all data is evaluated.

Specificity of the association

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If PPI therapy was the only drug therapy that increased the risk of fracture then this would strengthen the hypothesis that the association was causal. However there are numerous drugs that have been associated with fracture. Yang et al. (6) found antipsychotics, antiparkinsonian, and antiseizure drugs were all associated with increased risk of hip fracture. Attention has also focused on the risk of thyroxine replacement and fracture (31) and warfarin has also been implicated (32). Drugs with diverse modes of action are therefore all associated with increased risk of fracture and not of all of these have clear mechanisms by which they would exert effects on bone metabolism. This raises the possibility that the association between PPI therapy and fracture risk is spurious and relates to ill patients on a number of medications (including PPI therapy) are at increased risk of having fractures.

Consistency of the data

An association is more likely to be causal if different investigators, in varying populations using different methodologies obtain similar results. This is not the case with PPI therapy and fracture. In our systematic review 6 case control studies were negative and 7 were positive and this is reflected in the statistics, which suggest 94% of the variation in the data is not due to chance. We have explored reasons for heterogeneity and this remains unexplained. Three of the cohort studies were negative and 9 were positive and again 88% of the variation in the data was not explained by chance. We could not identify any factors that explained variations in study results.

What are the risks of fracture with PPI therapy?

There is little to support the hypothesis that the association between PPI therapy and risk of fracture is causal. Even if we assume the association is causal the risk to patients is minimal. Using the OR taken from the meta-analysis of case control studies and a risk calculator developed by WHO (33) then approximately 2,000 Canadians (we used a 50 year old Canadian woman with normal bone density as a baseline) would need to be given PPI therapy to cause one additional fracture in a given year. Of course the number needed to harm falls as the risk of fracture rises but it is important to emphasize that three cohort studies (19, 23, 27) evaluating high risk cohorts of patients taking bisphosphonates found no increased risk of fracture in those taking PPI therapy (RR fracture = 0.89; 95% CI = 0.67 to 1.17).

The data from this systematic review can also be pooled to assess the proportion of fractures in these cohorts that are attributable to PPI therapy. The population attributable fraction is calculated as approximately 1%. In other words if PPI use was stopped in the community this would only reduce the fractures in the community by approximately 1%. This seems an extremely modest impact on fracture rates particularly when the association may be spurious and suggests that we should not be overly concerned regarding PPI therapy in public health terms.

Conclusions

There have been numerous studies on the risk of fracture with PPI therapy since the CAG position statement in 2008. These data however do not change the conclusions of the original position statement. Current data would not support particular care in prescribing PPI therapy due to concerns

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about risk of fracture. The risk is extremely modest and there is no persuasive evidence that even this risk is causal and the association could be spurious. As with all medications PPIs should only be given when there are clear indications that the benefit of therapy outweighs the risk.

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