Proton pump inhibitors therapy and risk of hip fracture: a systematic review and meta-analysis


CRD summary
The authors concluded that results indicated that proton pump inhibitors therapy had potential to increase the risk of hip fracture. The reliability of the authors’ conclusion is limited by potential for publication bias and the unclear quality and small number of included studies.

Authors' objectives
To assess the association between proton pump inhibitors therapy and hip fracture.

Searching
PubMed, EMBASE and The Cochrane Library were searched to June 2010 for studies in any language. Search terms were reported.

Study selection
Cohort and case-control studies that compared the risk of hip fractures between users of proton pump inhibitors and users of non-proton pump inhibitors were eligible for inclusion.

Included studies were conducted in Netherlands, USA, UK, Canada and Denmark. Dosages and durations of proton pump inhibitors varied; further details were reported in the paper. Patient ages varied from over 18 years to 50 years or older.

Two reviewers independently assessed studies for inclusion; disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology checklist; only studies of high quality were included.

The authors did not state how many reviewers assessed study quality.

Data extraction
Two reviewers independently extracted data to enable calculation of odds ratios (ORs) and 95% confidence intervals (CIs). Disagreements were resolved by consensus.

Methods of synthesis
Pooled odds ratios and corresponding 95% CIs were calculated using random-effects meta-analysis where there was evidence of statistical heterogeneity; otherwise a fixed-effect model was used. Heterogeneity was assessed using X² and I². Subgroup analysis explored the influence of region, dosage and duration of proton pump inhibitors (short duration, less than one year; medium duration, one to three years; long duration, over three years). Publication bias was assessed using funnel plots and Egger test.

Results of the review
Seven studies providing eight comparisons (1,166,069 participants) were included: two prospective studies, two retrospective cohort studies, two case-control studies and one nested-case control study.

Proton pump inhibitor therapy was associated with a statistically significant increase in the risk of hip fracture (OR 1.24, 95% CI 1.15 to 1.34, I²=44%; eight comparisons).

No evidence of publication bias was found.

Subgroup analyses taking into account the region where the study was conducted and the duration of the study found
similar results to the main analysis except for studies with a duration of three to six years, where the result was no longer significant.

**Authors’ conclusions**
Findings indicated that proton pump inhibitors therapy had potential to increase the risk of hip fracture.

**CRD commentary**
The review question was clearly stated with respect to eligible study designs and interventions; eligible patients and outcomes were not predefined. Three major databases were searched. No efforts were made to search grey literature sources so some relevant papers may have been missed. Study selection and data extraction were conducted in duplicate which minimised potential for reviewer error and bias; no such process was applied during quality assessment so the possibility of reviewer error and bias could not be ruled out. Study quality was assessed using appropriate criteria but the results were not reported so the quality of the included studies was unclear. Included study designs were liable to potential biases.

The statistical methods used to combine data appeared appropriate. Sample sizes in the included studies were large.

The reliability of the authors’ conclusion is limited by the potential for publication bias and the unclear quality and small number of included studies.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further long-term studies (matched cohort studies or randomised controlled trials) were needed to assess the incidence of osteoporotic fractures. Further long-term studies were needed to assess the association between proton pump inhibitors and risk of hip fractures.

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