CRD summary
This well-conducted review concluded that there was some evidence for a modest association between proton-pump inhibitor use and risk of fractures, which was not seen with histamine-2 receptor antagonist use. These conclusions are likely to be reliable, although the results may only be applicable to elderly patients at relatively high risk of fractures.

Authors' objectives
To determine whether there is an increased risk of fractures with proton-pump inhibitors and histamine-2 receptor antagonists.

Searching
MEDLINE and EMBASE were searched up to September 2010 with no language restrictions; an automatic PubMed update search was set up. Search terms were reported. Bibliographies of included studies and relevant review articles were screened.

Study selection
Case-control or cohort (prospective or retrospective) studies that evaluated the association of fracture risk with concomitant proton-pump inhibitor or histamine-2 receptor antagonist exposure were eligible for inclusion. Studies had to report sufficient data to estimate odds ratios (ORs) for this association.

Included studies were conducted in general practices, clinical centres, hospitals, and general populations, in the USA, UK, Netherlands, Europe, Canada, and Denmark. The mean age of patients ranged from 43 to 79 years (where reported); in some studies most patients were aged 70 years or older. The proportion of men ranged from 0 to 100%.

Two reviewers independently selected studies for inclusion. Any disagreements were resolved by discussion.

Assessment of study quality
Three reviewers independently assessed study quality based on participant selection, follow-up, ascertainment of exposure, and definition and monitoring of adverse outcomes. Any disagreements were resolved by discussion.

Data extraction
Three reviewers independently extracted data to calculate odds ratios together with 95% confidence intervals (CIs). Where possible, data were extracted on adjusted odds ratios, otherwise raw data were used to calculate unadjusted estimates. If studies reported multiple data sets, the data from the largest sample of cases were extracted. Data were extracted separately for different classes of fracture (vertebral, hip or overall). Authors were contacted for additional information where necessary. Disagreements were resolved by discussion.

Methods of synthesis
Summary odds ratios, together with 95% confidence intervals, were estimated using random-effects models. Data were pooled separately according to fracture risk. The effect of duration of exposure was investigated by comparing estimates within studies of longer and shorter durations of exposure. Indirect comparisons were made between proton-pump inhibitors and histamine-2 receptor antagonists exposed patients using Bucher's statistical method. Heterogeneity was assessed using $I^2$.

Results of the review
Twelve studies reported in 11 articles (n=1,521,062 patients) were included in the review. These included four prospective cohort studies, two retrospective cohort studies and six case-control studies (including 3 nested case-control studies). Duration of follow-up ranged from 6.5 weeks to 7.8 years, where reported. All except one of the studies adjusted for potential confounding variables, although not all of these adjusted for all potential confounders. Eleven
studies were based on electronic databases of patient cohorts (based prescription claims and diagnostic codes for fractures), so they were at risk of misclassification or inconsistent recording of exposures.

Proton-pump inhibitor use was associated with an increased risk of spine fractures (OR, 1.50, 95% CI 1.32 to 1.72; four studies; $I^2=0\%$), hip fractures (OR 1.23, 95% CI 1.11 to 1.36; 10 studies; $I^2=72\%$) and overall fractures (OR 1.20, 95% CI 1.11 to 1.30; 11 studies; $I^2=78\%$). Longer duration of proton-pump inhibitors use (more than 3 years) was associated with a greater increased risk of fracture.

There was no association between histamine-2 receptor antagonist use and the risk of spine fractures (three studies; $I^2=0\%$), hip fractures (nine studies; $I^2=75\%$) or overall fractures (nine studies; $I^2=82\%$).

Analysis based on indirect comparisons showed an increased risk of spine fractures with proton-pump inhibitors compared with histamine-2 receptor antagonists (OR 1.58, 95% CI 1.31 to 1.89), but no significant difference in the risk of hip or overall fractures. One study reported a direct comparison and showed an increased risk of hip fractures with proton-pump inhibitors compared with histamine-2 receptor antagonists (OR 1.34, 95% CI 1.14 to 1.38).

Authors’ conclusions
There was some evidence for a modest association between proton-pump inhibitor use and risk of fractures, which was not seen with histamine-2 receptor antagonist exposure. The association was most consistent for spine fractures, while there was substantial heterogeneity in the magnitude of risk for other fractures.

CRD commentary
The review addressed a focused question supported by clearly defined inclusion criteria. The literature search was adequate for published studies but specific attempts were not made to locate unpublished data, so there was a possibility of publication bias. Appropriate steps were taken to minimise bias and errors at all stages of the review process.

Study quality was assessed using appropriate criteria and the results of the assessment were reported. Appropriate methods were used to pool data, but there was substantial heterogeneity for some analyses which was not adequately investigated.

The authors’ cautious conclusions, which acknowledge the heterogeneity between studies, are supported by the data and are likely to be reliable, although results may only be generalisable to elderly patients at relatively high risk of fractures.

Implications of the review for practice and research
Practice: The authors stated that clinicians who are concerned about patients with high fracture risk may wish to consider the option of histamine-2 receptor antagonists instead of proton-pump inhibitors.

Research: The authors stated that a randomised trial of patients on proton-pump inhibitor therapy and histamine-2 receptor antagonist therapy would be ideal, but that such trials would have to be very large and of long duration to capture enough cases of fracture to demonstrate an effect. Future studies should consider risk factors for fractures and the indication for proton-pump inhibitor therapy and adjust for this in the analysis.

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