Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies
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CRD summary
This review found evidence that proton-pump inhibitor use increased the risk of fracture. No conclusive evidence was found for an association between histamine-2 receptor antagonists and fractures. The review was well conducted but the available evidence was limited to non-randomised observational studies, so there is a potential for bias in the analyses and the results may not be conclusive.

Authors' objectives
To investigate the association between the use of acid-suppressive drugs and the risk of fracture.

Searching
PubMed, EMBASE and The Cochrane Library were searched without language restrictions from inception to December 2010; search terms were presented.

Study selection
Studies were eligible for inclusion if acid-suppressive drugs were used, including proton-pump inhibitors and histamine-2 receptor antagonists, and the association with any type of bone fracture reported. Randomised and observational studies were eligible.

The identified studies were conducted from 1991 to 2007, mostly in European or American populations. Most studies used proton-pump inhibitors and histamine-2 receptor antagonists; some used proton-pump inhibitors alone or histamine-2 receptor antagonists alone. All but one study recorded hip fractures. Some studies reported spinal, forearm, femoral and wrist fractures.

Two reviewers independently assessed the studies for eligibility.

Assessment of study quality
Quality assessment of case-control and cohort studies was performed using the Newcastle-Ottawa scale. Studies with a score of 7 or more (out of a total of 11) were deemed to be of high quality.

It was probable, but not explicitly stated, that two reviewers independently assessed study quality.

Data extraction
Data on fracture incidence were extracted on adjusted odds ratios (ORs) or relative risks (RRs), with confidence intervals (CIs). Factors adjusted for in the analysis were identified. Odds ratios and relative risks were assumed to be equivalent because of the rarity of fractures. The focus was on the longest period of use reported in each study.

Two reviewers independently extracted data and differences were resolved by consensus.

Methods of synthesis
Studies were combined in random-effects meta-analyses using the DerSimonian-Laird method. Heterogeneity was assessed using I².

Subgroup analyses were performed to investigate the effect on the outcome of type of study, study quality, variables used for adjustment, type of drug used, type of fracture, drug dose, and sex.

The potential for publication bias was investigated by creating funnel plots and using the Egger test.

Results of the review
Three cohort, five case-control and three nested case-control studies were included in the review. The total number of patients was in excess of 700,000 (study sizes ranged from approximately 760 to 390,000, where reported). No
randomised controlled trials were identified. Study quality scores ranged from 4 to 9 (out of 9) in case-control studies and from 7 to 8 in cohort studies.

Proton-pump inhibitors were found to increase fracture risk (adjusted OR 1.29, 95% CI 1.18 to 1.41; I²=69.8%; 10 studies). This increase was found for all types of study and levels of study quality. There was an increased risk of hip fracture (OR 1.31, 95% CI 1.11 to 1.54; nine studies) and vertebral fracture risk (OR 1.56, 95% CI 1.31 to 1.85; three studies), but no association with other types of fracture. There was no evidence of a differential effect due to dose or sex.

Histamine-2 receptor antagonists were not associated with fractures overall (OR 1.10, 95% CI 0.99 to 1.23; I²=86.3%; seven studies). An association was identified in the two cohort studies (OR 1.08, 95% CI 1.02 to 1.13) and in two nested case-control studies (OR 1.20, 95% CI 1.13 to 1.28), but not in other case-control studies. A significant association was found in the three high-quality studies (OR=1.13, 95% CI 1.05 to 1.21), but not the low-quality studies. There was no evidence of a differential effect due to type of fracture or dose.

Further subgroup and sensitivity analyses were reported.

There was no evidence of publication bias in any meta-analysis.

Authors' conclusions
There was evidence that the long-term use of proton-pump inhibitors increased the risk of fractures. There was no evidence that the use of histamine-2 receptor antagonists increased the risk of fractures.

CRD commentary
Inclusion criteria for the review were explicitly stated. Relevant sources were searched for studies. Relevant studies may have been missed as it was unclear whether unpublished studies were sought, but there was no evidence of publication bias. Appropriate action was taken to minimise error and bias in the review processes.

Quality assessment was undertaken using a standard checklist, reported in full, and taken into account in the analyses. The studies were appropriately synthesised in meta-analyses and differences between studies were investigated. The authors' conclusions generally reflect the evidence presented. All the included studies were non-randomised observational studies, so there was a possibility that the results were biased because of unidentified confounding factors. While the authors concluded that there was no evidence of an association between histamine-2 receptor antagonists use and fractures, a significant association was identified in cohort studies and in high-quality studies, so whether there was an association remained uncertain.

This review was well conducted, but the available evidence was limited to non-randomised observational studies, so there is a potential for bias in the analyses and the results may not be conclusive.

Implications of the review for practice and research
Practice: The authors stated that the use of proton-pump inhibitors should be carefully considered for patients who have an increased risk of fracture due to, for example, their age. The authors also stated that it was not necessary to treat to the point of an achlorhydric state, so dose should carefully chosen to achieved the desired goals.

Research: The authors suggested that large-scale observational studies and randomised trials should be conducted specifically to investigate the long-term effects of acid-suppressive drugs on fractures, including studies using histamine-2 receptor antagonists.

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