Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies

Abstract

This meta-analysis evaluated the association between proton pump inhibitor or histamine$_2$-receptor antagonist use and fractures primarily in older adults.

Ten publications reporting 11 observational case-control or cohort studies were considered eligible for analysis.

The summary effect estimate for risk of hip fracture was modestly increased among individuals taking PPIs (RR 1.30, 95% CI 1.19–1.43). There was also an increase in spine (RR 1.56, 95% CI 1.31–1.85) and any-site fractures (RR 1.16, 95% CI 1.04–1.30) among PPI users.

These findings were similar in both men and women and after stratification by duration of use. In contrast, H2RA use was not significantly associated with increased risk of hip fracture (RR 1.12, 95% CI, 0.97-1.30).

In this meta-analysis of observational studies, PPIs modestly increased the risk of hip, spine, and any-site fractures, whereas H2RAs were not associated with fracture risk. The possibility of residual confounding cannot be excluded. Further skeletal evaluation should be considered for patients who are taking proton pump inhibitors and also at risk for osteoporotic fracture.

Introduction

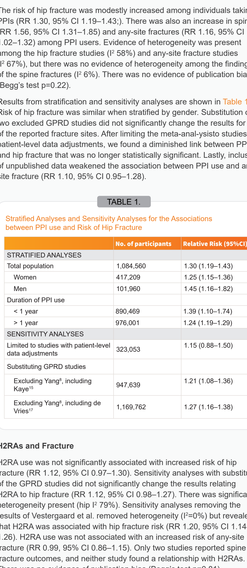
The Food and Drug Administration (FDA) published an advisory (updated March 23, 2011) communicating the possible increased risk of fractures with the use of high dose and/or long-term proton pump inhibitors.

Study Selection

Thus a total of 10 publications involving 11 studies were included in the meta-analysis (Figure 1). One relevant but as yet unpublished study was identified and included in the sensitivity analysis using data reported in abstract only.

FIGURE 1.

Flowchart of the literature search



PPIs and Fracture

The risk of hip fracture was modestly increased among individuals taking PPIs (RR 1.30, 95% CI 1.19–1.43;). There was also an increase in spine (RR 1.56, 95% CI 1.31–1.85) and any-site fractures (RR 1.16, 95% CI 1.02–1.32) among PPI users. Evidence of heterogeneity was present among the hip fracture studies (I^2 58%) and any-site fracture studies (I^2 67%), but there was no evidence of heterogeneity among the findings of the spine fractures (I^2 6%). There was no evidence of publication bias (Begg's test p=0.22).

Results from stratification and sensitivity analyses are shown in Table 1. Risk of hip fracture was similar when stratified by gender. Substitution of the two excluded GPRD studies did not significantly change the results for any of the reported fracture sites. After limiting the meta-anal-ysisto studies with patient-level data adjustments, we found a diminished link between PPI use and hip fracture that was no longer statistically significant. Lastly, inclusion of unpublished data weakened the association between PPI use and any-site fracture (RR 1.10, 95% CI 0.95–1.28).

TABLE 1.

Stratified Analyses and Sensitivity Analyses for the Associations between PPI use and Risk of Hip Fracture

	No. of participants	Relative Risk (95%CI)
STRATIFIED ANALYSES		
Total population	1,084,560	1.30 (1.19–1.43)
Women	417,209	1.25 (1.15–1.36)
Men	101,960	1.45 (1.16–1.82)
Duration of PPI use		
< 1 year	890,469	1.39 (1.10–1.74)
> 1 year	976,001	1.24 (1.19–1.29)
SENSITIVITY ANALYSES		
Limited to studies with patient-level data adjustments	323,053	1.15 (0.88–1.50)
Substituting GPRD studies		
Excluding Yang[4], including Kaye[15]	947,639	1.21 (1.08–1.36)
Excluding Yang[4], including de Vries[17]	1,169,762	1.27 (1.16–1.38)

H2RAs and Fracture

H2RA use was not significantly associated with increased risk of hip fracture (RR 1.12, 95% CI 0.97–1.30). Sensitivity analyses with substitution of the GPRD studies did not significantly change the results relating H2RA to hip fracture (RR 1.12, 95% CI 0.98–1.27). There was significant heterogeneity present (hip I^2 79%). Sensitivity analyses removing the results of Vestergaard et al. removed heterogeneity (I^2=0%) but revealed that H2RA was associated with hip fracture risk (RR 1.20, 95% CI 1.14-1.26). H2RA use was not associated with an increased risk of any-site fracture (RR 0.99, 95% CI 0.86–1.15). Only two studies reported spine fracture outcomes, and neither study found a relationship with H2RAs. There was no evidence of publication bias (Begg's test p=0.81).

Effect of Duration and Dose

The increase in hip fracture risk persisted after stratification by short-term (1 < year) and long-term (> 1 year) proton pump inhibitor use (Table 1). Several studies also analyzed further stratification beyond 1 year of duration, but these effects could not be quantitatively pooled because of the use of inconsistent strata across studies. Yang et al (n=148,942) found increasing risk of fracture with increasing duration of proton pump inhibitor use over several years. Targownik et al (n=63,081) similarly noted a duration effect, although the authors did not find a statistically significant increased risk of fracture until 5 or more years of proton pump inhibitor exposure. In contrast, several other studies (pooled n=359,133) did not find a consistent trend in fracture risk with prolonged duration of proton pump inhibitor or histamine-receptor antagonist use.

Dose effects were unable to be quantitatively pooled because of incompatible definitions of dose and medication exposure across studies. Four studies (pooled n=348,751) reported increased fracture rates with higher doses of proton pump inhibitor or histamine2-receptor antagonist, whereas Vestergaard et al (n=498,942) did not find evidence of a significant dose-response relationship. Two studies (n=662,840) determined that fracture risk diminishes after discontinuation of proton pump inhibitor for more than 1 or 2 years. On the other hand, 1 smaller study (n=2482) found evidence of persistently increased risk of fracture despite discontinuation of proton pump inhibitor.

Discussion

In this study level meta-analysis, proton pump inhibitor use was associated with a modestly increased risk of hip fractures. Spine fractures were more frequent among individuals taking proton pump inhibitors, and there also was a slight increase in risk of any-site fractures. These findings were similar in both men and women. Although the FDA advisory based on non-quantitative review of the data states that "patients at highest risk for fractures . . . used a PPI for one year or more," our systematic meta-analysis incorporating additional unpublished data suggests that short-term use (<1 year) and longer use (>1 year) were similarly associated with increased fracture risk. Parallel examination of histamine$_2$-receptor antagonist use did not find any statistically significant association with fracture.

4.7% of hip fractures might be attributable to PPI use.

PPI use is even more common among the population most at risk for fracture: older adults, and those who have been prescribed bisphosphonates.

Use of bisphosphonates did not mitigate the increased fracture risk associated with PPI use. Association of PPI use and fracture is only evident among adults who have major osteoporotic risk factors.

In this meta-analysis, we observed an increased risk of fracture that was present even with PPI use of <1 year. There may be a mechanism that has direct effects upon bone mineralization or bone quality and is not necessarily mediated by bone density changes. In vitro studies suggest that proton pump inhibitors may have a direct effect on bone via inhibition of the osteoclastic H+ ATPase pump, but this would lead to inhibition of bone resorption. Clinical trials have reported conflicting results on the effect acid suppression and biochemical measurements of bone resorption in humans.Furthermore,discordant effects on bone mineral density have been reported.

Prolonged PPI use can lead to vitamin B12 deficiency, which might increase risk of falls by causing peripheral neuropathy. B12 deficiency has also been linked to high homocysteine levels, which may disrupt collagen cross-linking and is associated with increased fracture risk. PPI use might also lead to hypomagnesemia, which may independently predispose to fractures. Additional studies of acid suppression and skeletal outcomes, particularly randomized trials, are needed to test these hypotheses.

Conclusions

PPI use modestly increased the risk of hip, spine, and any-site fractures, whereas H2RA use was not associated with increased fracture risk.

The biological mechanism is not yet clear, and we cannot rule out the possibility of residual confounding.

But even a slight increase in fracture risk due to PPIs may lead to a large number of additional fractures on a public health scale.

Reference

1. Elaine WY, Scott RB, Bain PA, Douglas CB. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 inter national studies. Am J Med. 2011 June ; 124(6):519-526.doi:10.1016/j.amjmed.2011.01.007.