ONLINE EXCLUSIVE

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Q/ What are the risks of long-term PPI use for GERD symptoms in patients > 65 years?

EVIDENCE-BASED ANSWER

A/ THE USE OF PROTON PUMP INHIBITORS (PPIs) to control gastroesophageal reflux disease (GERD) is significantly associated with an increased risk of cardiovascular events such as acute myocardial infarction and myocardial ischemia, especially with treatment longer than 8 weeks (strength of recommendation [SOR]: **A**, systematic review of randomized, controlled trials [RCTs]). This summary is based on data extrapolated from studies on all adults because there is limited evidence that specifically addresses patients older than 65 years.

Adults taking PPIs also appear to be at increased risk of *Clostridium difficile* infection, community-acquired pneumonia (CAP; with use for < 30 days), and fracture (SOR: **B**, systematic reviews of heterogeneous prospective and retrospective observational studies).

Evidence summary

A 2017 meta-analysis of 16 RCTs examined the risk of cardiovascular events in 7540 adult patients taking PPIs for GERD (mean ages 45-55 years).[1] The primary outcome was cardiovascular events—including acute myocardial infarction, myocardial ischemia, angina pectoris, cardiac failure, and coronary artery stenosis—and cardiac disorders.

Analysis of pooled data found that PPI use was associated with a 70% increase in cardiovascular risk (relative risk [RR] = 1.7; 95% confidence interval [CI], 1.13-2.56; number needed to harm [NNH] = 241) when compared with controls (placebo, H_2 blocker, or surgery). A subgroup analysis found that PPI use for longer than 8 weeks was associated with an even higher risk of adverse cardiovascular events (6 trials, 2296 patients; RR = 2.33; 95% CI, 1.33-4.08; NNH = 67) when compared with controls. The meta-analysis wasn't limited by heterogeneity ($I^2 = 0$).

C difficile infection risk is higher for PPI users

A 2016 meta-analysis of 23 observational studies (19 case-control, 4 retrospective cohort; 186,033 patients) examined the risk of hospital-acquired *C difficile* infections in adults prescribed PPI for any indication.[2] PPI exposure varied from use at time of diagnosis or hospitalization to any use within 90 days. Of the 23 studies, 16 reported sufficient data to calculate the mean age for the patients which was 69.9 years.

The risk of *C difficile* infection was found to be higher with PPI use than no use (pooled odds ratio [OR] = 1.81; 95% CI, 1.52-2.14). Although a significant association was found across a large group, the results were limited by considerable heterogeneity ($I^2 = 82\%$).

Risk of community-acquired pneumonia also increases with PPI use

A 2015 systematic review and meta-analysis of 33 trials (18 case-control, 10 cohort, 4 RCTs, and 1 case-crossover study) examined the risk of CAP in adult patients prescribed PPI for any indication for durations ranging from less than 1 month to > 6 months.[3] The systematic review was distilled to 26 studies because of overlapping study populations.

These 26 studies included 226,769 cases of CAP among 6,351,656 patients. The primary outcome was development of CAP, the secondary outcome was hospitalization for CAP.

PPI use, compared with no use, was associated with an increased risk of developing CAP (pooled OR = 1.49; 95% CI, 1.16-1.92) and an increased risk of hospitalization for CAP (pooled OR = 1.61; 95% CI, 1.12-2.31).

In a subgroup analysis for age, patients older than 65 years were also found to have an increased risk of developing CAP with PPI use (11 trials, total number of patients not provided; OR = 1.33; 95% CI, 1.13-1.58). Despite the significant associations of PPI use with risk revealed in the primary, secondary, and subgroup analyses, the results were limited by marked heterogeneity, with an $I^2 > 99\%$.

Hip and vertebral fracture risk is associated with PPIs

A 2011 systematic review and meta-analysis investigated the risk of fracture in adult patients taking PPIs for any indication.[4] The analysis included 10 observational studies (4 cohort, 6 case-control) with a total of 223,210 fracture cases. The authors examined the incidence of hip, vertebral, and wrist or forearm fractures.

No significant association was found between PPI use and wrist or forearm fracture (3 studies; pooled OR = 1.09; 95% CI, 0.95-1.24). A modest association was noted between PPI use and both hip fractures (9 trials; OR = 1.25; 95% CI, 1.14-1.37) and vertebral fractures (4 trials; OR = 1.5; 95% CI, 1.32-1.72).

Subgroup analysis didn't reveal evidence of an effect of duration of PPI use on fracture. Investigators didn't conduct subgroup analysis of different patient ages. Final results were limited by significant heterogeneity with an I^2 of 86%.

Recommendations

A 2015 American Geriatrics Society Beers Criteria update recommends limiting PPI use because of increased risk of *C difficile* infections and fractures. It also recommends against using PPIs for longer than 8 weeks except for high-risk patients (such as patients taking oral corticosteroids or chronic nonsteroidal anti-inflammatory drug users), patients with Barrett's esophagitis, or patients who need maintenance after failure of a drug discontinuation trial or H_2 blockers (quality of evidence, high; SOR, strong).[5]

Editor's takeaway: Despite limited evidence specific to patients over age 65, or perhaps because the majority of the studied populations were younger, increased caution should be exercised in the use of PPIs. JFP

References

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Extrapolation from studies on all adults suggests a significant link between proton pump inhibitors and higher risk of cardiovascular events—especially with treatment > 8 weeks.