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

Evidence-based answers from the Family Physicians Inquiries Network

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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, H2 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 (I² = 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 (I² = 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.
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.