# Proton Pump Inhibitors Are Associated With Increased Risk of Site-Specific Nonunion After Open Reduction Internal Fixation

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INTRODUCTION:

Nonunion is generally defined as a fracture that fails to heal within nine months and shows no progression toward healing over three consecutive months. Beyond its physical limitations, nonunion is associated with significant reductions in quality of life, chronic pain, and increased risk of long-term opioid use. While risk factors such as metabolic comorbidities and medications (ex: NSAIDs, opioids) have been linked to impaired healing. Proton pump inhibitors (PPIs), widely prescribed for acid-related gastrointestinal disorders, have come under scrutiny due to emerging association with calcium absorption, disrupted bone metabolism, and increased fracture risk. PPI use has risen substantially in the past decade, particularly in those over age 55, making it critical to assess their potential impact on fracture healing.

Although prior studies have reported a link between PPI use and nonunion, these have focused primarily on femoral and tibial fractures, without stratification by fracture location or patient demographics. This study represents the first large scale, multi-bone analysis evaluating PPI-associated nonunion risk across surgically managed long bone fractures, with site-specific and age-stratified analysis.

METHODS: We conducted a retrospective cohort study using the TriNetX US Collaborative Network. Adults ≥ 18 years undergoing operative fixation of humerus, radius/ulna, femur, or tibia/fibula fractures between 2015-2023 were included. PPI exposure was defined as use within 30 days postoperatively. Nonunion was assessed between 90 days and 2 years post-op using ICD codes. Propensity score matching (1:1) accounted for demographics, comorbidities, and medication use. Absolute risk, risk ratios (RR), hazard ratios (HR) were calculated; Kaplan-Meier analysis assessed nonunion-free survival.

RESULTS: Among 410,433 patients, 48,408 received PPIs. After matching, PPI use was significantly associated with higher nonunion rates in tibia/fibula (4/44% vs. 2.20% p<0.0001; RR: 2.075) and radius/ulna (3.36% vs. 1,88%, p<0.0001; RR: 1.853) fractures. Femur and humerus showed elevated rates in PPI users but did not reach significance. The strongest effect was observed in younger patients. In tibia/fibula fractures, PPI users aged 18-44 had >10-fold increased risk of nonunion (HR: 10.865). Similar but less pronounced age-related trends were seen in radius/ulna fractures, with the greatest risk seen in patients aged 18-44 (RR: 2.79, p<0.0001).

DISCUSSION AND CONCLUSION:

Our findings confirm that PPI use is associated with increased risk of nonunion following operative fixation, with the strongest effects observed in tibia/fibula and radius/ulna fractures. These findings suggest that impaired angiogenesis and altered bone remodeling – both potential effects of PPIs – may disproportionately affect bones with limited vascularity. The strikingly elevated risk in younger patients challenges assumptions about their resilience to metabolic disruption and highlights the importance of dynamic bone turnover in healing.

Given the widespread use of PPIs, these results underscore the need for careful practice, especially in patients with fracture prone to nonunion. Future research should investigate the mechanisms by which PPIs impair healing and explore safer strategies for managing acid-related gastrointestinal disorders in orthopedic populations.