

# Do Systemic Bisphosphonates Affect the Risk of Aseptic Loosening and Revision After Primary Total Knee Arthroplasty? A Systematic Review and Meta-Analysis

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**Introduction:** Although Total Knee Arthroplasty (TKA) is a highly successful procedure, 2% of patients require revision of their primary TKA at 2 years and around 3% of patients require revision within 5 years [1]. Postoperative bone loss significantly increases the risk for TKA failure [2]. Bisphosphonates such as alendronate, risedronate, and zoledronic acid are therapies that can be used to help prevent bone mineral density (BMD) loss [3]. Bisphosphonates inhibit the mevalonate pathway in osteoclasts, inducing apoptosis and ultimately the inhibition of bone resorption [4]. The primary aim of this systematic review and meta-analysis is to determine whether the use of systemic bisphosphonates influences the rate of revision after primary TKA.

**Methods:** This systematic review was carried out following PRISMA guidelines to identify studies in PubMed, Cochrane Library Database, and Grey Literature between January 2009 and July 2025 that assessed the effect of bisphosphonates on revision procedures and outcomes following primary TKA. This analysis included a total of 426,920 patients (378,836 women), and the certainty of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, which considers risk of bias, inconsistency, indirectness, imprecision, and publication bias. A meta-analysis was performed using a random effects model to compare risk of revision surgery, aseptic loosening, and periprosthetic fracture between patients who did or did not receive postoperative systemic bisphosphonates, with significance set at  $p < 0.05$ .

**Results:** After screening 253 initial results, 4 studies met the inclusion/exclusion criteria, all being retrospective cohorts using general bisphosphonates postoperatively, with an average follow-up duration of more than 3 years. A total of 104,530 patients received bisphosphonates postoperatively, while 322,088 patients did not receive any therapy. Of the four studies that assessed all-cause revision, bisphosphonate use significantly decreased the odds of revision ( $p = 0.0046$ , CI: 0.255-0.779, OR= 0.446) with substantial heterogeneity ( $p < 0.0001$ ,  $I^2 = 95.5\%$ ) (Figure 1). Of the two studies that assessed aseptic loosening, it was deemed that there was no significant difference between the two groups based on the random effects model ( $p = 0.184$ , CI: 0.348-1.226, OR=0.653) with substantial heterogeneity ( $p < 0.0001$ ,  $I^2 = 96.2\%$ ) (Figure 2). Of the two studies that evaluated periprosthetic fracture, it was deemed that there was no significant difference between the two groups ( $p = 0.418$ , CI: 0.001-9374, OR=2.332) with substantial heterogeneity ( $p < 0.0001$ ,  $I^2 = 94.9\%$ ) (Figure 3).

**Discussion:** This meta-analysis determined that use of systemic bisphosphonates following primary TKA reduces the odds of revision by approximately 55%. However, effects on aseptic loosening and periprosthetic fracture were not significant and were limited by the available studies. The high heterogeneity does, however, limit the certainty of our analysis, and further randomized controlled trials are needed to validate this finding.

**SIGNIFICANCE/CLINICAL RELEVANCE:** Postoperative bisphosphonate use appears to reduce the risk of revision after primary TKA by inhibiting bone resorption. Surgeons may want to consider prescribing bisphosphonates as a postoperative therapy to extend implant longevity.

**References:** [1] Marsh JD, McClure JA, Lanting BA, Vasarhelyi EM, MacDonald SJ, Naudie DDR, et al. J Arthroplasty. 2024;39(3):689-94.e3. [2] Soltanihafshejani N, Bitter T, Verdonschot N, Janssen D. J Orthop Res. 2024;42(1):90-9. [3] Baron R, Ferrari S, Russell RG. Bone. 2011;48(4):677-92. [4] Bellido T. J Clin Invest. 2024;134(6):e179942.

## Images and Tables:

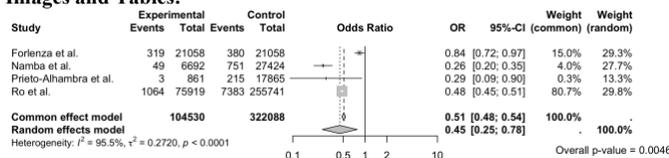


Figure 1. All-cause revision forest plot. “Experimental” indicates systemic bisphosphonate use (general, unspecified).

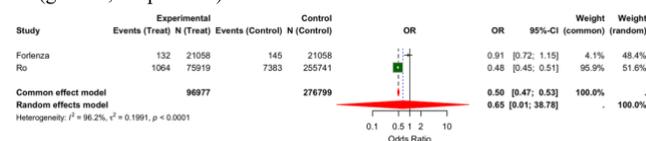


Figure 2. Loosening forest plot. “Experimental” indicates systemic bisphosphonate use (general, unspecified).

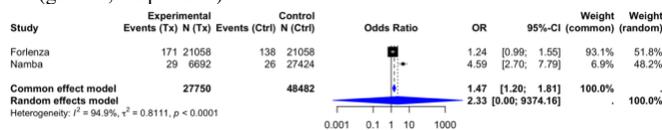


Figure 3. Periprosthetic fracture forest plot. “Experimental” indicates systemic bisphosphonate use (general, unspecified).