Effectiveness of Pharmacological Interventions Versus Placebo or No Treatment for Osteoporosis in Patients With CKD Stages 3-5D: Editorial Summary of a Cochrane Review

Takashi Hara, Yasukazu Hijikata, and Yukiko Matsubara

Osteoporosis is an important comorbidity in patients with chronic kidney disease (CKD). Compared with individuals who do not have CKD, the prevalence of osteoporosis and the risk of fractures is higher in individuals with CKD.[1,2] Major bone fractures in patients with CKD are a global health care burden and are often associated with high rates of hospitalization, death, and high health care–associated costs.[3,4]

The conditions associated with CKD complicate the diagnosis and treatment of osteoporosis. Impaired skeletal strength in patients with CKD occurs via a different mechanism: the so-called CKD–mineral and bone disorder (MBD). Bone disorders caused by CKD-MBD are termed renal osteodystrophy, a form of osteoporosis and a complex heterogeneous disorder of bone quality and density. Although bone biopsy is the gold standard diagnostic tool for renal osteodystrophy, it has limited availability, and it is not suitable for repeated evaluations. Though several agents are effective for the treatment of osteoporosis in the general population,[5] the use of anti-osteoporotic drugs may lead to adynamic bone disease in patients with CKD,[6] making treatment for osteoporosis in such patients an area of high unmet need.

The 2017 KDIGO guideline on CKD-MBD represented a dramatic paradigm change in the diagnosis and treatment of osteoporosis in patients with CKD.[7] The guideline recommends measuring bone mineral density (BMD) to assess fracture risk in patients with CKD-MBD and/or clinical risk factors for osteoporosis. In addition, the guideline removed the requirement for bone biopsy before initiating antiresorptive therapy for osteoporosis because of the need to individualize the use of these drugs in patients with CKD. The guideline changed the way nephrologists think about osteoporosis and its treatment in patients with CKD; nonetheless, there is no clear direction for how nephrologists should manage their patients.[8]

In a Cochrane Review[9] we assessed the effectiveness of pharmacological interventions versus placebo or no treatment for osteoporosis in patients with CKD stage 3 to stage 5 treated with dialysis (CKD 3-5D). We provide a summary of its findings here.

We searched the Cochrane Kidney and Transplant Registry through January 25, 2021, for randomized controlled trials (RCTs) and quasi-RCTs of pharmacological interventions for osteoporosis in people with CKD 3-5D. We conducted a pairwise random-effects meta-analysis to estimate the efficacy and safety of pharmacological therapy. The risk of bias was evaluated using the Cochrane risk of bias tool, and the certainty of evidence was ascertained using GRADE.[10]

Findings

Seven studies (48 records; 9,164 participants) were included in this study. The sample sizes ranged from 50 to 4,973, and 5 studies were included in the subgroup of large studies. All studies included postmenopausal women exclusively. Five studies (42 records; 9,054 patients) included patients with CKD 3a-4. Two studies (6 records; 110 patients) included patients undergoing hemodialysis or with CKD 5 but not receiving dialysis. For all participants, CKD-MBD was stable or controlled at baseline. A total of 5 anti-osteoporotic drugs were identified: abaloparatide, alendronate, denosumab, raloxifene, and teriparatide. The follow-up duration ranged from 8 to 54 months.

We were unable to perform the qualitative analysis as planned because most of the studies reported both vertebral and nonvertebral or clinical fracture. Therefore, we divided "fracture at any site" into "vertebral fracture by radiography" and "clinical fracture" (defined as any site fractures with fracture-related symptoms).

Patients With Osteoporosis and CKD 3-4

Anti-osteoporotic drugs may reduce the risk of vertebral fracture (risk ratio [RR], 0.52 [95% CI, 0.39-0.69]; low certainty evidence due to a serious risk of bias and inconsistency) (Fig 1A). Anti-osteoporotic drugs probably make little or no difference to the risk of clinical fracture (RR, 0.91 [95% CI, 0.79-1.05]; moderate certainty evidence due to a serious risk of bias) (Fig 1B) and adverse events (RR, 0.99 [95% CI, 0.98-1.00]; moderate certainty evidence due to a serious risk of bias). We were unable to include studies for BMD at the femoral neck, lumbar spine, or total hip in the meta-analysis because they only reported the percentage change in BMD in the intervention group.

Patients With Osteoporosis and CKD 5-5D

The anti-osteoporotic drug raloxifene may slightly improve lumbar spine BMD (mean difference, 0.03 [95% CI, 0.03-0.04]; low certainty evidence due to a serious risk of bias and indirectness). No adverse events were reported in either study. It is uncertain whether raloxifene can reduce the risk of clinical fractures (RR, 0.33 [95% CI, 0.01-7.87]; very low certainty evidence due to a serious

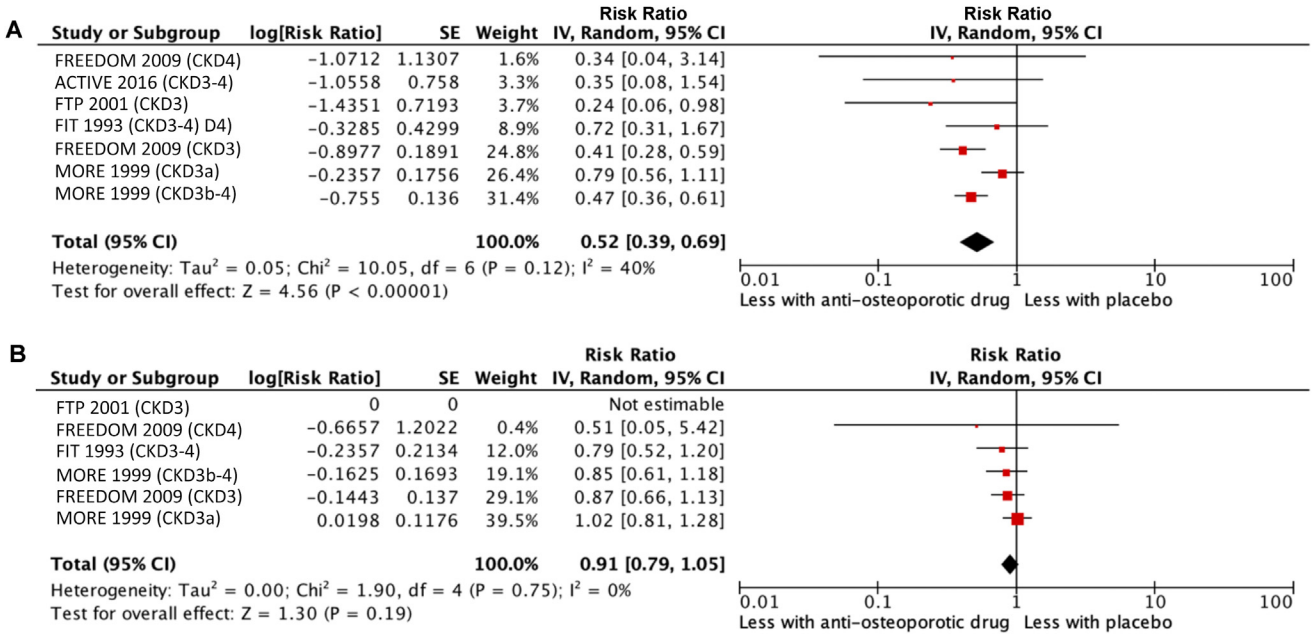

Figure 1. Forest plot of anti-osteoporosis drugs (abaloparatide, alendronate, denosumab, raloxifene, and teriparatide) versus placebo for patients with osteoporosis and CKD stages 3-4 for (A) vertebral fracture by radiography and (B) clinical fracture. Abbreviations: CKD, chronic kidney disease; IV, inverse variance; SE, standard error. Original graphics © 2021 The Cochrane Collaboration; adapted from Hara et al[9] with permission of the copyright holder.

risk of bias and serious imprecision). It is unclear whether raloxifene improves femoral neck BMD (mean difference, 0.01 [95% CI, 0.00-0.02]; very low certainty evidence due to a serious risk of bias, inconsistency, and indirectness). The effect of raloxifene in reducing the risk of death remains uncertain (RR, 1.00 [95% CI, 0.22-4.56]; very low certainty evidence due to a serious risk of bias and imprecision).

Conclusions

For patients with CKD 3-4, anti-osteoporotic drugs may reduce the risk of vertebral fracture with low certainty. Moderate certainty evidence suggests that anti-osteoporotic drugs have little or no effect on the risk of clinical fractures and adverse events. For patients with CKD 5-5D, it is unclear whether raloxifene reduces the risk of clinical fracture and death because the certainty of this evidence is very low. Raloxifene may slightly improve lumbar spine BMD (low certainty evidence). Because the certainty evidence is very low, it is uncertain whether raloxifene improves BMD in the femoral neck. There is a need for larger studies involving men, children with CKD, and people with unstable CKD-MBD to determine the effectiveness of each anti-osteoporotic drug at various stages of CKD.

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Support: There was no specific funding for this editorial summary. Cochrane Kidney and Transplant supported the development of the original Cochrane Review.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: We thank Narelle Willis and Tess Cooper of Cochrane Kidney and Transplant for their help in coordinating this summary.

Prior Publication: This editorial summary is based on the Cochrane Review previously published in the *Cochrane Database of Systematic Reviews* (CDSR) 2021, Issue 7, https://doi.org/10.1002/14651858.CD013424.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback; the CDSR should be consulted for the most recent version of the review.

Peer Review: Received April 26, 2022 in response to an invitation from the journal. Direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form May 24, 2022.

Publication Information: © 2022 by the National Kidney Foundation, Inc. Published online October 31, 2022 with doi: 10.1053/j.ajkd.2022.05.020

References

1. Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int.* 2000;58(1):396-399. doi:10.1046/j.1523-1755.2000.00178.x

2. Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol*. 2006;17(11):3223-3232. doi:10.1681/ASN.2005111194
3. Tentori F, McCullough K, Kilpatrick RD, et al. High rates of death and hospitalization follow bone fracture among hemodialysis patients. *Kidney Int*. 2014;85(1):166-173. doi:10.1038/ki.2013.279
4. Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM. Hip fracture in patients with non-dialysis-requiring chronic kidney disease. *J Bone Miner Res*. 2016;31(10):1803-1809. doi:10.1002/jbmr.2862
5. Crandall CJ, Newberry SJ, Diamant A, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. *Ann Intern Med*. 2014;161(10):711-723. doi:10.7326/M14-0317
6. Amerling R, Harbord NB, Pullman J, Feinfeld DA. Bisphosphonate use in chronic kidney disease: association with adynamic bone disease in a bone histology series. *Blood Purif*. 2010;29(3):293-299. doi:10.1159/000276666
7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2017;7(1):1-59. doi:10.1016/j.kisu.2017.04.001
8. Khairallah P, Nickolas TL. Updates in CKD-associated osteoporosis. *Curr Osteoporos Rep*. 2018;16(6):712-723. doi:10.1007/s11914-018-0491-3
9. Hara T, Hijikata Y, Matsubara Y, Watanabe N. Pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D. *Cochrane Database Syst Rev*. 2021;(7):CD013424. doi:10.1002/14651858.CD013424.pub2
10. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol*. 2011;64(4):380-382. doi:10.1016/j.jclinepi.2010.09.011