Effectiveness of Pharmacological Interventions for Treatment of Osteoporosis in Patients With CKD 3-5D: No Clear Choices

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Fractures are a debilitating injury associated with extended rehabilitation, long-term pain, and considerable costs. Just half of patients with a hip fracture regain their mobility and their prefracture level of independence.[1] As the population ages, predictions about increasing numbers of fractures are staggering: from 1.7 million fractures in 1990 to 6.3 million in 2050.[2] Studies in patients with chronic kidney disease (CKD) stages 3 and 4 (CKD 3-4),[3-6] on dialysis,[7,8] and after transplantation[9,10] all show that patients with CKD have a 2- to 100-fold increase in fracture risk compared to age- and sex-matched individuals without CKD. CKD and osteoporosis are highly co-prevalent. In analyses of NHANES data, the prevalence of osteoporosis was 2-fold greater among patients with than without an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2,[5] and among patients with osteoporosis the prevalence of a Cockcroft-Gault equation–calculated creatinine clearance (CL_{cr}) ≤ 35 mL/min was ∼80% for women and 50% for men >60 years of age.[11] After a major fracture requiring hospitalization, mortality increases 100% in patients on dialysis.[12,13] and health care–associated costs after fracture exceeded $600 million in 2010 in patients with CKD.[14]

The high co-prevalence of osteoporosis and CKD guarantees that many nephrologists will need to know how to effectively treat low bone mineral density (BMD) and prevent fractures. In that regard, KDIGO recommends pharmacologic strategies be used in the general population.[15] However, data supporting the efficacy of these antifracture treatments in CKD populations are suboptimal. The US Food and Drug Administration (FDA) registry trials excluded de facto kidney disease, and other studies in patients with CKD had sample sizes too small to assess a fracture outcome. In general, the sample sizes needed to assess a fracture outcome are in the thousands.

In this issue of *AJKD*, a Cochrane Review Editorial Summary[16] reports on a systematic review and meta-analysis of 7 studies that investigated the efficacy of antifracture treatments in patients with CKD. The studies were parallel randomized clinical trials with sample sizes ranging from 50 to 4,973—in total 9,164 participants (all postmenopausal women) with osteoporosis and CKD 3-5D.[17-23] Five studies included patients with CKD 3-4,[17-20,23] and 2 included patients with CKD 5-5D.[22,23] Five pharmacologic interventions were investigated: the anabolic agents abaloparatide and teriparatide; the antiresorptives alendronate and denosumab; and the selective estrogen receptor modulator raloxifene. All studies were judged to be at an overall high risk of bias.

The primary outcomes included (1) incidence of fracture at any site; (2) mean change in BMD measured by dual-energy radiographic absorptiometry of the femoral neck, total hip, lumbar spine, and distal radius; (3) all-cause mortality; (4) incidence of adverse events; and (5) quality of life. The findings of the review were inconclusive for all outcomes.

For patients with CKD 3-4, antiosteoporotic drugs may reduce the risk of vertebral fracture (risk ratio [RR], 0.52 [95% CI, 0.39-0.69]; low certainty evidence). Antiosteoporotic drugs probably make little or no difference on the risk of both clinical fracture (RR, 0.91 [95% CI, 0.79-1.05]) and adverse events (RR, 0.99 [95% CI, 0.98-1.00]), both with moderate certainty evidence. There were no studies that could be used to assess treatment efficacy for BMD.

For patients with CKD 5-5D, it was uncertain whether raloxifene reduced the risk of clinical fracture (RR, 0.33 [95% CI, 0.01-7.87]; very low certainty evidence). Although raloxifene may yield improved BMD at the lumbar spine (mean difference, 0.03 [95% CI, 0.03-0.04]; low certainty evidence), it remained uncertain whether it improved BMD at the femoral neck (mean difference, 0.01 [95% CI, 0.00-0.02]). The included studies reported no adverse events. It was uncertain whether raloxifene reduced the risk of death (RR, 1.00 [95% CI, 0.22-4.56]; very low certainty evidence).

The overall conclusion of the investigation was that among postmenopausal women with CKD 3-4, antiosteoporotic drugs may reduce the risk of vertebral fracture. For patients with CKD 5-5D, raloxifene may slightly improve bone strength. Because these conclusions are based on limited and biased data, they do not provide much improvement over the status quo to support using these agents in patients with CKD.

An unfortunate, but not unexpected, outcome of this study would be to interpret these data as evidence that there is no rationale to treat patients with CKD for osteoporosis or fracture prevention. Because this conclusion would leave at-risk patients vulnerable to preventable events, it is relevant to briefly consider the individual studies included in the analysis to better understand their limitations and bias (Table 1). All studies were conducted in women, thus providing no information for almost half of patients with CKD. The predialysis studies included

Table 1. Findings and Limitations of the Included Studies

Study	CKD Stage	Comparisons	Efficacy	Limitations
FREEDOM 2009	3-4	Denosumab vs placebo	- Denosumab increased BMD at the hip and femoral neck in pts with CKD3-4 and at the spine in pts with CKD3	- All pts post-menopausal women - Just 17/7808 with CKD4 - CKD due to age-related eGFR declines - PTH levels normal - BMD of the total hip and radius not included - QOL not reported
ACTIVE 2016	3-4	Abaloparatide vs teriparatide vs placebo	- Abaloparatide and teriparatide increased BMD at all skeletal sites vs placebo - At the spine, abaloparatide increased BMD more in pts with eGFR <60 vs >60 - BMD increases at other skeletal sites independent of eGFR	- All pts postmenopausal women - Only 27 pts with eGFR < 37 - CKD due to age-related eGFR declines - PTH levels normal - Low fracture rates—low heterogeneity - BMD of the total hip and radius not included - QOL not reported
FPT 2001	3-4	Teriparatide vs placebo	- Teriparatide increased spine and femoral neck BMD vs placebo	- All pts postmenopausal women - CKD defined as CL_{cr} < 80 mL/min - PTH levels normal - BMD of the total hip and radius not included - QOL not reported - Incomplete outcomes data
FIT 1993	3-4	Alendronate vs placebo	- Alendronate increased BMD at the spine and hip - BMD increases at the total hip were higher in pts with eGFR < 45 - Increases in BMD at other skeletal sites independent of eGFR	- All pts postmenopausal women - PTH levels normal - BMD of the total hip and radius not included - QOL not reported
MORE 1999	3-4	Raloxifene vs placebo	- Raloxifene increased BMD at the spine and femoral neck - Raloxifene reduced risk of vertebral fractures	- All pts postmenopausal women - PTH levels normal - BMD of the total hip and radius not included - QOL not reported - Incomplete outcomes data
Haghverdi 2014	5-5D	Raloxifene vs placebo	- Raloxifene increased BMD of lumbar spine and femoral neck	- All pts postmenopausal women - BMD of the total hip and radius not included - Sample size too small to test for antifracture efficacy - QOL not reported - Adverse events not reported
Hernandez 2003	5-5D	Raloxifene vs placebo	- Raloxifene increases trabecular BMD	- All pts postmenopausal women - BMD of the total hip and radius not included - Sample size too small to test for antifracture efficacy - QOL not reported - Adverse events not reported

Abbreviations: ACTIVE, Abaloparatide Comparator Trial in Vertebral Endpoints; BMD, bone mineral density; CKD, chronic kidney disease; CL_{cr}, creatinine clearance; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); FIT, Fracture Intervention Trial; FPT, Fracture Prevention Trial; FREEDOM, A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis; MORE, Multiple Outcomes of Raloxifene Evaluation; PTH, parathyroid hormone; pts, patients; QOL, quality of life.

secondary analyses of 5 large FDA registry trials that were not designed or conducted to test drug efficacy in patients with CKD. The eligibility criteria for these studies excluded patients with a frank diagnosis of CKD or hyperparathyroidism, or with elevated serum creatinine. Although CL_{cr} or eGFR may have been at a low level in some participants, they likely had age-related declines in kidney function rather than the types of CKD or CKD–mineral and bone disorder that we treat in our clinics. Thus, whether these studies are applicable to patients with true CKD is debatable.

Several trials had insufficient numbers of patients with moderate to severe CKD to use standard KDIGO CKD stage stratifications, and some did not have adequate fracture events in the CKD categories for valid statistical testing. For example, in FREEDOM, the registry trial for the use of denosumab in women with postmenopausal osteoporosis, use of the MDRD Study equation identified only 17 patients with CKD 4 out of a total of 7,808 participants—and there were no fractures in any these patients.[17] In FPT, the registry trial for teriparatide, due to the small number of fracture events, CKD was defined as a Cockcroft-Gault CL_{cr}

cutoff of <80 mL/min,[20] which would be considered normal in the absence of kidney damage. Similarly, ACTIVE, a 3-way comparison trial between abaloparatide, teriparatide, and placebo had only 11, 6, and 8 patients with an eGFR < 37 mL/min/1.73 m^2 in each group, respectively, and fracture event rates were low.[18] By contrast, FIT, the registry trial for alendronate, had an adequate sample size to test a CL_{cr} cutoff of 45 mL/min and demonstrated significant spine and nonspine fracture risk reduction for patients below this threshold.[19] In the 2 studies conducted in patients with CKD 5-5D, the overall numbers of patients (N = 110) were too small to test for antifracture efficacy.[21,22]

Did these agents improve BMD? BMD is an important surrogate outcome for fracture. From the general population we know that increases in BMD T-scores predict a lower future fracture risk. Recent data from the long-term extension study of FREEDOM shed light on the relationship between increases in BMD and decreases in fracture risk.[24] Nonvertebral fracture risk reduction plateaued up to a total hip T-score of −2.0, which was associated with a 1-year fracture incidence of 2%. Furthermore, a 1.0 unit increase in BMD T-score was associated with a decrease in fracture risk up to but not greater than −2.0. If we believe that increases in BMD lower fracture risk, even in patients with CKD, then we have some rationale to treat at-risk patients.

Unfortunately, Hara et al could not include BMD change data from studies of patients with CKD 3-4 due to methods of BMD reporting (ie, percent change). However, in all the original trials, BMD increased in patients with CKD. In FIT, BMD at the spine and hip increased in the treatment versus placebo group, BMD increases at the total hip were higher in participants with eGFR < 45 mL/min/1.73 m^2, and increases in BMD at other skeletal sites were independent of eGFR. In FREEDOM, denosumab increased BMD at the hip and femoral neck in participants with CKD 3-4 and at the spine in those with CKD 3. In ACTIVE, abaloparatide and teriparatide increased BMD at all skeletal sites compared with placebo. At the spine, abaloparatide resulted in greater BMD increases in participants with an eGFR of <60 versus >60 mL/min/1.73 m^2, and BMD increases at other skeletal sites were independent of eGFR. In FPT, teriparatide increased spine and femoral neck BMD compared with placebo in all eGFR subgroups (30-49, 50-79, ≥80 mL/min/1.73 m^2) independent of kidney function. In the 2 studies of patients with CKD 5-5D, BMD was preserved or improved at the spine and hip in participants randomized to raloxifene versus placebo.

The information from Hara et al is challenging to digest and translate into clinical practice because of the significant data limitations and high risk of bias for the parent studies. Most of the studies do not fully reflect the CKD seen in nephrology practice, and due to small sample size some reported no fracture events in any of the CKD subgroups for either the active drug or placebo groups. Thus, our opinion is that these data are best interpreted as "not definitive." Ultimately, the Hara et al study supports a call to action. A meta-analysis can only be as good as the quality of the studies included, and the main limitation of the work of Hara et al is the poor quality of the available trials for fracture prevention in CKD.

The high co-prevalence of osteoporosis and CKD means that all of us will encounter these patients in our clinical practice, and we still lack the data needed to support our treatment decisions. Thus, we need well-powered trials in the patients we see in our clinics and reporting of raw data and adherence to NIH data-sharing guidelines so that meta-analyses can be conducted to answer questions that cannot be fully investigated by small trials. Only then will we be able to answer the incredibly important question of how to lower fracture risk in patients with CKD.

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