Renal Bone Disease and Bone Histomorphometry

Daniel L. Hurley, MD, FACE¹ and Robert A. Wermers, MD, FACE¹
¹Division of Endocrinology, Diabetes, Metabolism and Nutrition
Mayo Clinic, Rochester, MN, USA

AACE Endocrine University
March 07, 2018
DISCLOSURES

• Industry support
  – None

• Off-label drug use:
  – None
OBJECTIVES

1. To understand the complexities of chronic kidney disease & mineral bone disease (CKD-MBD), to include bone histomorphometry (i.e., bone volume, turnover, and mineralization)
2. Review the limitations of OP therapy in CKD-MBD
3. Review the indications of bone biopsy in CKD-MBD
4. Recognize the value of bone histomorphometry in the assessment of CKD-MBD
Chronic Kidney Disease (CKD)

- 9th leading cause of death in the U.S.A.
  - 20 million with CKD
    - 8.3 million with moderate-severe CKD
    - 0.3 million require hemodialysis

- **Risk factors**
  - Diabetes, hypertension, older age
  - Drug toxicity, autoimmune disease, renal infection/obstruction, acute renal failure
CKD Prevalence and Risk Factors
In Stage 3-4 CKD


*Stage 3 GFR <60, Stage 4 <30 mL/min. Coresh J. Am J Kidney Dis 2003;41:1
Prevalence of CKD in Diagnosed T2DM

Diabetes-related Renal Disease Is the Leading Cause of Kidney Failure in the United States (38% of T2DM in stages 1-4 CKD)

*Pathologic abnormalities or markers of damage, including blood or urine tests or imaging studies.

5-Year Outcomes of CKD-MBD are Poor

- **Subjects**: n = 27,998 patients with eGFR <90 mL/min, with 5-year follow up from 1996 to 2001

- **Outcome**: death is more likely than progression to hemodialysis in stages 2 through 4 CKD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR mL/min/1.73m²</th>
<th>Progression to ESRD</th>
<th>Cumulative Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>60 - 89</td>
<td>1.1 %</td>
<td>19.5 %</td>
</tr>
<tr>
<td>3</td>
<td>30 - 59</td>
<td>1.3 %</td>
<td>24.3 %</td>
</tr>
<tr>
<td>4</td>
<td>15 - 29</td>
<td>19.9 %</td>
<td>45.7 %</td>
</tr>
</tbody>
</table>

Keith. *Arch Intern Med* 2004;164:659
CKD-MBD Pathophysiology

Stages of secondary HPT development

1. Increased FGF23, and phosphate retention

CKD-MBD Pathophysiology
Stages of secondary HPT development

2. Inhibition of 1,25-dihydroxyvitamin D synthesis

- Due to ↑’d P, ↑’d FGF23, and loss of nephrons
- Results in ↓’d intestinal calcium absorption, hypocalcemia, ↓’d CaSR activity, and ↑’d PTH release due to a lack of inhibition of PTH secretion

CKD Progression
Calcitriol and 2º HPT

CKD-MBD Pathophysiology

Stages of secondary HPT development

3. Reduction in PT gland vitamin D receptor (VDR)
   – Due to ↓’ed 1,25-dihydroxyvitamin D levels

4. Reduction in PT gland calcium sensing receptor (CaSR)
   – ↑’er serum calcium required to inhibit PTH release

5. Increased PT gland size (hyperplasia)
   – Due to loss of 1,25(OH)2D-mediated inhibition of parathyroid growth from loss of PT gland VDR, loss of PT gland CaSR, and increase in EGF synthesis
   – PTH resistance due to uremia, acidosis, ↑P, and ↓ active vitamin-D
Complications of CKD

• Mineral & bone disorders
  – 1,25-dihydroxy vitamin D deficiency
  – Hyperphosphatemia
  – Secondary and tertiary HPT
  – Bone loss and fractures

• Cardiovascular disease

• Hypertension

• Anemia

• Infections and immune compromise
Complications in CKD-MBD

↓ Vitamin D Receptors  ↓ Ca-Sensing Receptors

↑ PTH  ↓ Ca++  ↓ 1,25D  ↑ Pi

Systemic Toxicity
CVD
Hypertension
Inflammation
Calcification
Anemia
Immunologic

Renal Failure

Bone Disease
Bone pain
Fracture
Marrow fibrosis
Erythropoietin resistance
CKD Morbidity and Mortality
What the endocrinologist should know

• Morbidity
  – 60% greater risk of cardiovascular disease
    • CAD, CHF, CVA or TIA
  – Mineral Bone Disorders occur early
    • Secondary HPT affects 25% of hemodialysis patients¹

• Mortality
  – 5-10 times more likely to die than reach ESRD

¹Byrnes C. *Pharmacotherapy* 2005;25(5):709
CKD morbidity/mortality


Age-standardized rates of death, CVD events, and hospitalizations from any cause according to the estimated glomerular filtration rate (eGFR) among 1,120,295 ambulatory adults.

Panel A – Death
Panel B – CVD Events
Panel C – Hospitalizations
### Lab Assessment of CKD

**eGFR preferred over serum creatinine**

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>sCreat. mg/dl</th>
<th>eGFR</th>
<th>CKD Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>M</td>
<td>B</td>
<td>1.3</td>
<td>91</td>
<td>1</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>B</td>
<td>1.3</td>
<td>74</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>W</td>
<td>1.3</td>
<td>75</td>
<td>2</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>W</td>
<td>1.3</td>
<td>61</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>B</td>
<td>1.3</td>
<td>67</td>
<td>2</td>
</tr>
<tr>
<td>55</td>
<td>F</td>
<td>B</td>
<td>1.3</td>
<td>55</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>W</td>
<td>1.3</td>
<td>56</td>
<td>3</td>
</tr>
<tr>
<td>55</td>
<td>F</td>
<td>W</td>
<td>1.3</td>
<td>45</td>
<td>3</td>
</tr>
</tbody>
</table>

*eGFR= estimated glomerular filtration rate; B=black, W=white, M=male, F=female*
Evaluation of MBD in CKD

• BCM of BTO

  – Biochemical markers (BCM) of bone turnover (BTO) are difficult to interpret in stage 4-5 CKD
    • Urine retention of collagen crosslinks (CTX)
    • Bone alkaline phosphatase (BAP) not renally excreted

  – Possible causes of BAP elevation
    • HPT, secondary or tertiary
    • Vitamin D deficiency
    • Osteomalacia
    • Fracture

KDIGO Clinical Practice Guidelines. Kid Int 2009;Suppl 113:S1-S130.
Evaluation of MBD in CKD

• DXA BMD
  – Bone density measurement may be difficult to interpret in patients with stage 4-5 CKD

• FRAX
  – May underestimate fracture risk in patients with T2DM

KDIGO Clinical Practice Guidelines. Kid Int 2009;Suppl 113:S1-S130.
PTH and Bone Loss

CKD Stages 2-4

BMD reduced at all sites: L-sp 6.3%, Fn-Hip 12.1%, Dist-Radius 5.7%.

Rix M. Kidney Int 1999;56:1084
Evaluation of MBD in CKD

• Iliac-crest bone biopsy
  – Patients with stage 3-5 CKD should be considered for bone biopsy if they have unexplained
    • fractures,
    • bone pain,
    • hypercalcemia,
    • hypophosphatemia,
    • or suspected aluminum toxicity (rare)

KDIGO Clinical Practice Guidelines. Kid Int 2009;Suppl 113:S1-S130.
Classification of Renal Bone Disease

• ‘Renal Osteodystrophy’ (ROD)
  – High turnover (HTO) renal osteodystrophy
    Hyperparathyroidism/Osteitis fibrosa cystica
  – Low turnover (LTO) renal osteodystrophy
    – Osteomalacia (OM)
    – Adynamic bone disease (ADB)
  – Mixed bone disease

• Other types of bone disease in CKD
  – Osteoporosis (OP)
  – Glucocorticoid-induced bone loss (GIO)
## TMV Classification of CKD-MBD

### KDIGO Position Statement¹

<table>
<thead>
<tr>
<th>Turnover (T)</th>
<th>Mineralization (M)</th>
<th>Volume (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Framework For Classification of CKD-Mineral and Bone Disease

<table>
<thead>
<tr>
<th>Type²</th>
<th>Laboratory (+)</th>
<th>Bone Disease</th>
<th>Vascular-Soft Tissue Calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LB</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>LC</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>LBC</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

¹Moe S, et al. Kidney International 2006; 69:1945-1953. ²L: laboratory abnormalities (of calcium, phosphate, parathyroid hormone, alkaline phosphatase or vitamin D metabolism); B: bone disease (abnormalities of turnover, mineralization, volume, linear growth or strength); C: calcification of vascular or other soft tissues. KDIGO, Kidney Disease Improving Global Outcomes
TMV System for CKD-MBD

Used to define and reclassify ‘renal osteodystrophy’

- Each axis represents one of the descriptors in the TMV classification (T-turnover, M,-mineralization and V-bone volume)
- Many patients with CKD-MBD cluster in areas shown by the Figure bars:
  - **OM**, osteomalacia, is currently described as low-BTO with abnormal M. The V may be low to medium, depending on the CKD severity and duration and other factors affecting bone.
  - **AD**, adynamic bone disease, is currently described as low-BTO with normal M, and V in this example is at the lower end of the spectrum but other patients with normal M and low-BTO will have normal V.
  - **Mild HPT**, hyperparathyroidism, and **OF**, osteitis fibrosa, are currently used distinct categories, but actually represent a range of abnormalities along a continuum of medium to high-BTO, and any V depending on CKD duration.
  - **MUO**, mixed uremic CKD-MBD, is variably defined internationally. In the graph example, it is depicted as high-BTO, normal V, with abnormal M.

The TMV classification system more precisely describes the range of pathologic abnormalities in CKD-MBD. [BTO, bone turnover; CKD, chronic kidney disease; MBD, mineral & bone disease.]

Bone Turnover (BTO) and CKD-MBD

(A) Normal BTO, (B) Low BTO due to Osteomalacia, (C) Very Low BTO due to Adynamic Bone Disease, (D) High BTO with osteitis fibrosa due to Hyperparathyroidism

(A) In normal BTO (2 BMUs shown), osteoblast bone formation equals osteoclast bone resorption.

(B) In osteomalacia (2 BMUs shown), osteoid accumulates on most bone surfaces due to a defect in mineralization (i.e., calcification). Potential etiologies include chronic metabolic acidosis, vitamin D deficiency, and excess FGF-23.

(C) Adynamic bone disease is a form of very low BTO (only 1 BMU shown) with little osteoid formed.

(D) High BTO (3 BMUs) is often related to hyperparathyroidism, with disease severity highly correlated to the degree of PTH elevation.

Spectrum of Metabolic Bone Disease in CKD*

Adynamic Bone (27%)  OM (7%)  2º HPT (3%)  Osteitis Fibrosis (50%)

Mixed ROD (13%)

Increased Bone Turnover (Hyperparathyroidism)

Decreased Bone Turnover (Calcium, Vitamin D, Aluminum)

*Hruska K. *NEJM* 1995;333:166
Normal Bone Turnover

Normal mineralized bone, osteoid and cellular elements (Goldner stain)

Normal tetracycline single and double label (fluorescence microscopy)
High Bone Turnover

Activation frequency (Ac.f.) >0.72/year and/or BFR/BS >3.80 mm³/cm² per year (L-Goldners, R-Toluidine Blue)
High Bone Turnover

(Above) Hyperparathyroidism and increased bone turnover (Ac.f) and osteoclast number

(Below) Osteitis Fibrosa with aggressive (multinucleated) osteoclastic resorptive activity
Bone Formation Lamellar vs Woven Bone

(Above) Normal bone turnover.

(Right) Under conditions of rapid bone turnover, as in CKD-MBD (right figure) osteoid may be deposited in a disorganized fashion and is called **woven bone** in contrast to **lamellar bone**.
Low Bone Turnover

Activation frequency (Ac.f.) <0.49/year and/or BFR/BS < 1.80 mm$^3$/cm$^2$ per year

Absent Tetracycline label (fluorescence microscopy)
Osteomalacia (OM)

OM: abnormal mineralization of newly formed collagen matrix, resulting in excessive accumulation of un-mineralized osteoid.
Osteomalacia (OM)

- Excessive accumulation (volume and thickness) of osteoid, and decreased cellular elements.

- Un-mineralized osteoid, diminished Tetracycline label (fluorescence microscopy).
Bone Histology in CKD-MBD

Prevalence of degree of BTO and amount of cancellous bone volume in patients with stage-5 CKD, on HD

Data from 630 bone biopsies of adult patients with stage-5 CKD requiring HD, and evaluated by histomorphometry and analyzed using the turnover (T), mineralization (M), and volume (V) NKF-KDIGO classification system.

Management of CKD-MBD

• Diagnostic evaluation
  – Estimate glomerular filtration rate (GFR)
  – Identify and treat reversible causes of renal dysfunction

• Management
  – Early referral to nephrologist
  – Identify and treat complications of CKD¹,²
    • Control of PTH and the Ca X P product (K/DOQI goal <55 mg²/dL² in stage 3-5 CKD)

²Bailie G. *Pharmacotherapy* 2005;25(12):1687-1707
Medical Management of CKD-MBD

1. **Nutritional deficiencies**
   - Ergocalciferol (D2) or cholecalciferol (D3) if 25-OH vitamin D <30 ng/mL, but will not ↓ PTH

2. **Phosphorus and calcium management**
   - Dietary P intake 0.8 - 1.0 g/day (meat and dairy)
   - Use (non-aluminum) phosphate binder with meals
     - Calcium carbonate, calcium acetate
       - Do not exceed 1500 mg/day elemental calcium
     - Calcium and aluminum free polymer (Sevelamer)
       - No hypercalcemia; ↓’es LDL-cholesterol, $$$
Medical Management of CKD-MBD

3. Active Vitamin D analog (VDA) therapy early to ↓PTH, ↓Ca X P <55 mg²/dL² and improve bone health
   - ↓transcription of PTH gene; ↓PTH synthesis
   - Agents: calcitriol, alfacalcidol or doxercalciferol, and paricalcitol

4. Cinacalcet added to VDA, if needed to control PTH
   - ↑es CaSR sensitivity to extracellular Ca⁺²; ↓es PTH
   - FDA approved for stage-5 CKD & hemodialysis
## NKF-K/DOQI Recommendations

### Treatment of Stage 3-4 CKD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Phosphorus (mg/dL)</th>
<th>Calcium (mg/dL)</th>
<th>PTH (pg/mL)</th>
<th>VDA Treatment if PTH* remains above goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>&lt;4.6</td>
<td>&lt;8.4</td>
<td>35-70</td>
<td>Vitamin D Analog (VDA):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Calcitriol 0.25 mcg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Doxercalciferol 2.5 mcg 3X per week</td>
</tr>
<tr>
<td>4</td>
<td>&lt;4.6</td>
<td>&lt;9.5</td>
<td>70-110</td>
<td>• Paricalcitol 1 mcg/day, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 mcg 3X per week</td>
</tr>
<tr>
<td>5</td>
<td>&lt;5.5</td>
<td>&lt;10.2</td>
<td>150-300</td>
<td></td>
</tr>
</tbody>
</table>

*PTH levels and VDA treatment guidelines based on the concern of possible adynamic bone disease.

# Efficacy Oral Vitamin D Analogs

**CKD Stage 3-4**

<table>
<thead>
<tr>
<th>Vit D Analog Mean Dose (mcg/day)</th>
<th>Duration (wks) Patients (n)</th>
<th>% PTH Suppression at 6 months</th>
<th>% Patients with PTH ↓ ≥ 30%</th>
<th>Study Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitriol 0.25-1.0 mcg</td>
<td>52 wks n=25</td>
<td>25%</td>
<td>(na)</td>
<td>PTH suppression not primary goal; ↑sCa++ common at 0.75-1 mcg/day</td>
</tr>
<tr>
<td><strong>2nd Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfacalcidol 104 wks n=89</td>
<td>28%</td>
<td></td>
<td>(na)</td>
<td>Dose titration to achieve high normal sCa++ treatment goal</td>
</tr>
<tr>
<td><strong>2nd Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxercalciferol 1.8 mcg</td>
<td>24 wks n=27</td>
<td>46%</td>
<td>74%</td>
<td>PTH suppression primary treatment goal</td>
</tr>
<tr>
<td><strong>3rd Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paricalcitol 1.4 mcg</td>
<td>24 wks n=108</td>
<td>42%</td>
<td>91%</td>
<td>PTH suppression primary treatment goal</td>
</tr>
</tbody>
</table>

## Safety of Oral Vitamin D Analogs
### CKD Stage 3-4

<table>
<thead>
<tr>
<th>Vitamin D Analog</th>
<th>% Change in sCa++ at 6 Months</th>
<th>% Patients with sCa++ &gt; 10.5</th>
<th>% Increase in Ca X P Product</th>
<th>% Increase in Urine Ca++ at 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Generation Calcitriol</td>
<td>8%</td>
<td>64%</td>
<td>(na)</td>
<td>139%</td>
</tr>
<tr>
<td>2nd Generation Alfacalcidol</td>
<td>3%</td>
<td>15%</td>
<td>(na)</td>
<td>41%</td>
</tr>
<tr>
<td>2nd Generation Doxercalciferol</td>
<td>5%</td>
<td>4%</td>
<td>12%</td>
<td>42%</td>
</tr>
<tr>
<td>3rd Generation Paricalcitol</td>
<td>1%</td>
<td>2%</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Osteoporosis Medication Studied in CKD

Systematic review and meta-analysis

- Literature search: 13,692 records from database
  - 13 trials evaluated drug therapy with BMD or fractures among a total of 9850 patients with CKD
    - 6 studies among kidney transplant recipients patients
    - 2 studies with stage 3 to 5 CKD, not on dialysis
    - 2 studies with patients receiving dialysis
    - 4 subgroup analyses of PM patients with CKD in RCT’s
      (1 head-to-head trial comparing 2 bisphosphonates; the other trials were placebo-controlled)
  - Patients in most studies were given concomitant calcium or vitamin D supplements or both
  - Study durations ranged from 8 to 36 months.

RCT, randomized controlled trial. LM. Wilson et al., Ann Intern Med. doi:10.7326/M16-2752
# Osteoporosis Medication Studied in CKD

<table>
<thead>
<tr>
<th>Drug Use in RCT</th>
<th>Study group</th>
<th>Follow-up</th>
<th>Significant % BMD difference vs PBO (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiresorptive vs Placebo</strong></td>
<td>CKD stage</td>
<td>Months</td>
<td>L-spine</td>
</tr>
<tr>
<td>ALN</td>
<td>(2007 Jamal)</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>(2010 Toussaint)</td>
<td>3-4</td>
<td>18</td>
</tr>
<tr>
<td>RAL</td>
<td>(2008 Ishani)</td>
<td>3-5</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>(2014 Haghwerdi)</td>
<td>5/HD</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(2003 Hernandez)</td>
<td>HD</td>
<td>12</td>
</tr>
<tr>
<td>Dmab</td>
<td>(2011 Jamal)</td>
<td>3-4</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>(2016 Bonani)</td>
<td>post-K-Tx</td>
<td>12</td>
</tr>
<tr>
<td>APD</td>
<td>(2003 Coco)</td>
<td>post-K-Tx</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(2009 Walsh)</td>
<td>post-K-Tx</td>
<td>24</td>
</tr>
<tr>
<td><strong>Anabolic vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPT</td>
<td>(2007 Miller)</td>
<td>2-3</td>
<td>21</td>
</tr>
</tbody>
</table>

ALN, alendronate. APD, amino-propylidinedisphosphonate. Dmab, denosumab. RAL, raloxefene. TPT, teriparatide. ns, non-significant. LM. Wilson et al., Ann Intern Med. doi:10.7326/M16-2752
Osteoporosis Medication Studied in CKD

Appendix Figure. Pooled rates of vertebral fractures among patients with CKD.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Intervention Population</th>
<th>Timing, wk</th>
<th>Events/Total, n/N Placebo</th>
<th>Events/Total, n/N Intervention</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates vs. placebo</td>
<td>Coco et al, 2003 (26)</td>
<td>Paml</td>
<td>Transplant recipients</td>
<td>52</td>
<td>2/28</td>
</tr>
<tr>
<td></td>
<td>Walsh et al, 2009 (27)</td>
<td>Paml</td>
<td>Transplant recipients</td>
<td>104</td>
<td>6/47</td>
</tr>
<tr>
<td></td>
<td>Torregrosa et al, 2010 (31)</td>
<td>Rise</td>
<td>Transplant recipients</td>
<td>52</td>
<td>6/49</td>
</tr>
<tr>
<td></td>
<td>Smerud et al, 2012 (30)</td>
<td>Iban</td>
<td>Transplant recipients</td>
<td>52</td>
<td>1/63</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 0.0%; P = 0.67)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates vs. placebo</td>
<td>Jamal et al, 2007 (28)</td>
<td>Alen</td>
<td>Stage 3 CKD</td>
<td>144</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Toussaint et al, 2010 (29)</td>
<td>Alen</td>
<td>Stage 3-4 CKD</td>
<td>78</td>
<td>1/25</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 0.0%; P = 0.57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene vs. placebo</td>
<td>Ishani et al, 2008 (34)</td>
<td>Ralox</td>
<td>GFR &lt;45 mL/min/1.73 m²</td>
<td>156</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Ishani et al, 2008 (34)</td>
<td>Ralox</td>
<td>GFR 45–59 mL/min/1.73 m²</td>
<td>156</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Haghverdi et al, 2014 (32)</td>
<td>Ralox</td>
<td>Dialysis, stage 5 CKD</td>
<td>32</td>
<td>1/30</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 0.0%; P = 0.68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide vs. placebo</td>
<td>Miller et al, 2007 (35)</td>
<td>Terl</td>
<td>Stage 2–3 CKD</td>
<td>84</td>
<td>37/199</td>
</tr>
<tr>
<td>Denosumab vs. placebo</td>
<td>Jamal et al, 2011 (36)</td>
<td>Deno</td>
<td>Stage 3 CKD</td>
<td>156</td>
<td>92/1309</td>
</tr>
<tr>
<td></td>
<td>Jamal et al, 2011 (36)</td>
<td>Deno</td>
<td>Stage 4 CKD</td>
<td>156</td>
<td>3/33</td>
</tr>
</tbody>
</table>

NR, not reported. LM. Wilson et al., Ann Intern Med. doi:10.7326/M16-2752
Osteoporosis Medication Studied in CKD
Systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Bisphosphonates vs. Placebo</th>
<th>Raloxifene vs. Placebo</th>
<th>Teriparatide vs. Placebo</th>
<th>Denosumab vs. Placebo</th>
<th>Ibandronate vs. Risedronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3 (280) -4.8% to 0%</td>
<td>1 (60) 0%</td>
<td>0 studies</td>
<td>1 (90) 0%</td>
<td>1 (69) 0%</td>
</tr>
<tr>
<td>Cardiovascular disease events</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>1 (2875) 0% to 3%†</td>
<td>0 studies</td>
</tr>
<tr>
<td>Infections</td>
<td>1 (129) -12.1% to 0.7%‡</td>
<td>0 studies</td>
<td>0 studies</td>
<td>2 (2955) -4.9% to 27.2%‡</td>
<td>0 studies</td>
</tr>
<tr>
<td>Renal adverse events</td>
<td>4 (373) -18.1% to 0%</td>
<td>0 studies</td>
<td>1 (83) -1.5% to 0.9%§</td>
<td>1 (90) 4.1%</td>
<td>1 (69) 0%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>0 studies</td>
<td>0 studies</td>
<td>1 (83) -1.5% to 0.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>1 (129) -3.9%</td>
<td>0 studies</td>
<td>1 (83) 17.7% to 24.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1 (93) 8.6%</td>
<td>0 studies</td>
<td>0 studies</td>
<td>1 (90)</td>
<td>12 events vs. 1 event</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
</tr>
<tr>
<td>Gastrointestinal adverse events</td>
<td>2 (179) -8% to 4%</td>
<td>0 studies</td>
<td>0 studies</td>
<td>1 (90) 1.4% to 20.5%</td>
<td>0 studies</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
<td>0 studies</td>
</tr>
</tbody>
</table>

* The risk difference was calculated by subtracting the percentage of participants experiencing an adverse event in the placebo or control group from the percentage experiencing an adverse event in the treatment group.
† Across different subgroups of patients with chronic kidney disease.
‡ Across different types of infections.
§ Across different types of renal adverse events and different treatment groups.
| Across different treatment groups.  |

LM. Wilson et al., Ann Intern Med. doi:10.7326/M16-2752
Osteoporosis Medication Studied in CKD

Systematic review and meta-analysis

• **Review Limitations:** results may have limited applicability to the general population of patients with CKD
  
  – Bisphosphonates and denosumab were the only drugs studied in men
  
  – Most of the evidence for raloxifene, teriparatide, and denosumab is from subgroup analyses of trials of PM women; some of these excluded women with elevated creatinine levels
  
  – T2DM, an important risk factor for fractures, and prevalent among patients with CKD, was not well reported in the studies, and could influence the meta-analysis findings
  
  – Many trial subjects were also likely receiving a calcium and/or vitamin D supplements, although several studies did not fully report on there use

PM, postmenopausal. RCT, randomized controlled trial.

LM. Wilson et al., Ann Intern Med. doi:10.7326/M16-2752
Osteoporosis Medication in CKD-MBD

Summary

• More research is needed to determine the best options for patients across the spectrum of CKD
  – To improve BMD and prevent fractures with minimal risk for adverse outcomes
  – Especially in stage 3 to 5 CKD
    • Studies should be adequately powered to show a reduction in the risk for fractures and should have sufficient follow-up (≥3 years)

PM, postmenopausal. RCT, randomized controlled trial. LM. Wilson et al., Ann Intern Med. doi:10.7326/M16-2752
Thank You!

hurley.daniel@mayo.edu