Disclosures

- None
Review

- Calcium and Vitamin D
- Bisphosphonate Atypical Femur Fractures
- Denosumab safety and efficacy data
- New treatments on the Horizon
  - Odanacatib
  - Romosozumab
  - Blosozumab
  - Abaloparatide
Do Calcium supplements cause Coronary Heart disease?

Metanalysis of CVD events reported in calcium supplement trials (Ca intake ≥1500 mg/d)

RR for MI = 1.27 (p=0.038)
RR for MI, stroke or sudden death= NS

Bolland, Reid BMJ 2010

Bolland, Reid BMJ 2011
Calcium supplementation: no effect on risk of MI or CAD

5 year RCT of 1000 mg/d calcium supplement in 1460 older women with 4 years additional follow-up

MI or ASCVD death
RR = 0.9  NS

If preexisting CVD, data suggest a slight decrease in risk

Lewis, Prince et al JBMR, 2011
A Prospective Study of Calcium Supplement Intake and Risk of Cardiovascular Disease in Women

- Julie Paik, Brigham and Women's Hospital, Harvard Medical School, USA
Prospective Study of Calcium Supplement and CV Risk

- 74,272 women in Nurses’ Health Study (1984-2006) free of CVD and cancer at baseline.
- 22 years of follow-up- 4,857 CV events occurred (2,634 CHD and 2,223 stroke events).
- Age-adjusted RR of CVD was 0.67 (95% CI 0.62, 0.72) for women taking >500mg/day of calcium supplements compared to no calcium supplements.

Paik et al. ASBMR 2012
The Women’s Health Initiative (WHI) Calcium plus Vitamin D Supplementation Trial: Health Outcomes 5 years after Trial Completion

- Jane Cauley, University of Pittsburgh Graduate School of Public Health, USA

ASBMR 2012
WHI Calcium/Vit D Supplementation: 5 yrs after Trial

- WHI 1000 mg calcium with 400 IU Vit D₃ (CaD) versus PBO in 36,282 women age 50 to 79 yrs
- After 7 yrs, CHD was similar in the 2 groups.
- Analysis was extended 5 additional yrs of follow-up among 86% of participants, CaD, n=15025 and PBO, n=14837.

Cauley et al. ASBMR 2012
WHI Calcium/Vit D Supplementation: 5 yrs after Trial

- No difference in CVD or disease mortality in the post-intervention period.
- In WHI long-term follow-up, no CVD endpoints were increased 5 years after the end of the trial.
  - Vertebral fractures remained lower 5 years after stopping the Ca –VitD supplement protocol.
- There are no long-term CV, cancer or bone adverse events associated with having taken Ca and Vit D supplements.

Cauley et al. ASBMR 2012
Calcium and Vitamin D: Moderate Dose Recommendations

**DIETARY CALCIUM AND FRACTURES**

**VITAMIN D AND MORTALITY**

Warensjö E et al, BMJ 2011;342:d1473

Melamed ML et al, Arch Intern Med 2008;168:1629-1637
Calcium and vitamin D Intakes

- **Total** calcium intake of 1000-1200 mg/day (from diet, supplements or both)
- No need for aggressive over-supplementation of calcium
- Vitamin D 1000-4000 mg/day
- For high-risk patients, measure 25-OH D
- Optimal level of vitamin D is not known, but levels of 30-50 ng/ml are reasonable
Osteonecrosis of the Jaw (ONJ):
Osteonecrosis of the Jaw (ONJ): Definition

- A confirmed case of bisphosphonate-associated ONJ is defined as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider
  - in a patient who was receiving or had been exposed to a bisphosphonate,
  - who had not had radiation therapy to the craniofacial region.

ASBMR Task Force on Bisphosphonate-Associated ONJ
ONJ and Bisphosphonates

- Estimated incidence in osteoporosis patients 1:10,000-1:100,000
- Current guidelines for the American Dental Association (2011) emphasize the health consequences of osteoporosis, benefits of bisphosphonate and low risk of ONJ in osteoporosis patients receiving bisphosphonates
Atypical Fractures of Femoral Diaphysis
Time Trends for Femur Fractures in the U.S.

National Hospital Discharge Survey (1996-2006)
- Hip fracture rates decreased by 33%
- Subtrochanteric, femoral shaft, and lower femur rates remained stable.

Nationwide Inpatient Sample (1996-2007)
- Hip fracture rates decreased by 30% in women and 20% in men
- Subtrochanteric fragility fracture rates increased by 20% in women while unchanged in men.
- For every decline of 100 hip fractures there was an increase of one subtrochanteric fragility fracture.

Nieves et al, Osteoporos Int. 2010 Mar;21(3):399-408.
Wang et al, JBMR 2010 (online) and abstract 1029
Bisphosphonate Use and Atypical Fractures of the Femoral Shaft

- Risk is approximately 1/1000 patients after 5 years of use
- Up to 50% of cases are bilateral
- After bisphosphonate withdrawal, the risk decreases by 70% per year *
- The pathogenesis of these fractures is still unknown

Dell et al, ASBMR 2010 (Kaiser Permanente)
Wylie et al JAMA Feb 23, 2010
2014 Update: ASBMR Task Force on Atypical Femur Fractures

Location: below lesser trochanter, above supracondylar flare
Major Features (four of five)
• Trauma: little or none
• Direction: lateral transverse, may be oblique on the medial side
• Comminution: little or none
• Complete fractures: may have a medial spike; incomplete fractures involve only the lateral cortex
• Localized periosteal reaction/thickening of the lateral cortex
Minor features (none required)
• Generalized increase in cortical thickness of the shaft
• Prodromal symptoms such as dull aching pain in groin or thigh
• Bilateral incomplete or complete fractures and symptoms
• Delayed fracture healing

Shane E et al, JBMR 2014;29:1-23
Subtrochanteric Stress Fracture Associated with a Typical Cortical Stress Reaction
Diagnosis of Atypical Femur Fractures

- The most important aspect of diagnosis is to have a high index of suspicion for these fractures in patients taking long-term bisphosphonates who complain of thigh pain.
Diagnosis of Atypical Femur Fractures

- Radiographs of the involved areas must be taken immediately, and if the radiograph is negative, further studies including MRI and/or technetium bone scans should be obtained to completely exclude fracture.

- If a fracture is found, because 50 to 75% of these fractures can be bilateral, imaging of the contralateral side should always be undertaken.
Drug Holiday

- Temporary withholding of bisphosphonate after at least 3-5 years in appropriate patients
  - NOT “stopping treatment”
  - ONLY applies to bisphosphonates
- Very little data, many opinions
- Periodic re-evaluation of balance of benefits and risks
- End drug holiday when fracture risk is again high
  - T-score ≤-2.5, high fracture risk by FRAX

FDA Guidance on Bisphosphonates

...decisions to continue treatment must be based on individual assessment of risks and benefits and on patient preference. In this regard, patients at low risk for fracture (e.g., younger patients without a fracture history and with a bone mineral density approaching normal) may prove to be good candidates for discontinuation of bisphosphonate therapy after 3 to 5 years, whereas patients at increased risk for fracture (e.g., older patients with a history of fracture and a bone mineral density remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy.

- Bisphosphonates do not have to be discontinued after 3-5 years in patients at high risk of fractures

Algorithm for Management of Long-Term Bisphosphonate Therapy

Post-menopausal women treated with oral (≥ 5 yrs) or IV (≥ 3 yrs) BPs but <10 years

Hip, spine, or multiple other osteoporotic fractures before or during therapy

Yes
Continue BP, or change to alternative anti-fracture therapy
Reassess every 2-3 years

No
Hip BMD T-Score ≤ -2.5 or High fracture risk

Yes
Continue BP for up to 10 yr, or change to alternative anti-fracture therapy
Reassess every 2-3 years

No
Consider Drug Holiday
Reassess every 2-3 years

Teriparatide Once weekly Effects on Fracture Risk

Fujita et al., CTI, 2014
PTH (1-84) and Alendronate Alone or in Combination

Teriparatide + Denosumab

Leder BZ et al. J Clin Endocrinol Metab. 2014 Feb 11: [Epub ahead of print]
Ten Years of Denosumab Treatment in Postmenopausal Women With Osteoporosis: Results From the FREEDOM Extension Trial: ASBMR 2015

Key Inclusion Criteria for the Extension:
- Completed the FREEDOM study (completed their 3-year visit, did not discontinue investigational product, and did not miss > 1 dose)
- Not receiving any other osteoporosis medications

International, multicenter, open-label, single-arm study
Ten Years of Denosumab Treatment in Postmenopausal Women With Osteoporosis: Results From the FREEDOM Extension Trial: ASBMR 2015

- **Lumbar Spine**: Extension 21.7%<sup>c</sup> (Placebo: a, b; Denosumab: a, b)
- **Total Hip**: Extension 9.2%<sup>c</sup> (Placebo: a; Denosumab: b)

Graphs show percentage change from baseline over study years.
Why do we need more therapies for osteoporosis?

- **No optimally effective drug yet**
  - No agent restores bone strength and fracture risk to “normal”

- **Poor adherence to certain drugs**
  - Inconvenient dosing regimens
  - GI intolerance

- **High expense of certain drugs**

- **Patient concerns about safety**, especially the long-term safety of bisphosphonates
### Fracture Risk Reduction in Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Medication</th>
<th>Spine</th>
<th>Nonvertebral</th>
<th>Hip</th>
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<tr>
<td>Estrogen</td>
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<tr>
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<tr>
<td>Ibandronate</td>
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<tr>
<td>Zoledronate</td>
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<td>Teriparatide</td>
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<tr>
<td>Denosumab</td>
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</tbody>
</table>

No head-to-head trials compare fracture outcomes
New Therapies for Osteoporosis

- **Antiresorptive**
  - Odanacatib

- **Anabolics**
  - Romosozumab
  - Blosozumab
  - Abaloparatide (PTHrp analog)
Cathepsin K inhibition: Resorbing Osteoclast

Chloride-bicarbonate exchanger

Osteoclast

Bone

Collagen

Cathepsin K

Lysosomal enzymes

$\alpha_2\beta_2$ Integrin
Calcitonin & Receptor
CIC-7
Lysosomes
Cat K
RANK/RANKL
V-ATPhase
Cathepsin K

- Cathepsin K is a lysosomal cysteine protease highly expressed in and highly selective for the osteoclast.
- Cathepsin K is collagenolytic, and capable of degrading Type-I collagen (90% of bone matrix), osteopontin and osteonectin.
Genetic Deficiency of Cathepsin K: Pychnodysostosis

- Short stature, high bone mass with skeletal fragility
- Cathepsin K deficient mice have osteopetrosis
Odanacatib

- Selective and reversible inhibitor of Cathepsin K, thus inhibiting collagen matrix dissolution
- Unlike other antiresorptives, odanacatib permits persistent osteoclast viability and cellular activity (levels of TRAP5b - a marker of osteoclast number - do not change with Odanacatib treatment)
Odanacatib, a Cathpsin-K inhibitor for osteoporosis:
A Two-year Study in Postmenopausal Women with Low Bone Density

J Bone Miner Res 2010:25;937-47
Inhibition of Cathepsin K: Odanacatib:
Phase II- randomized, double-blind, placebo-controlled trial

- 1-year dose finding trial with 1-year extension
- 320 women, mean age: 64 ± 7.8
- Doses: Placebo, 3, 10, 25, 50 mg once weekly
- Primary Hypothesis: LS BMD at 24 months
- Other end points: bone turnover markers

Bone HG et al. J Bone Min Res 2010;25:937
Odanacatib: BMD Percent Change from Baseline at 18 Months

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Biochemical Markers at 18 Months

Geometric Mean Percent Change from Baseline at Month 18

Bone Resorption
- u-NTx
- s-CTx

Bone Formation
- s-BSAP
- s-P1NP

Placebo
- ODN 3 mg
- ODN 25 mg
- ODN 50 mg
- ODN 10 mg

Effects of Anti-resorptive Agents on Bone Remodeling

Not a head-to-head comparison

% decrease from baseline of serum CTX and serum BSAP at 24 months

Alendronate ¹  Denosumab ¹  Odanacatib ²

Proposed mechanisms for osteoclast-osteoblast coupling

Direct cell-cell contact Ephrin B2-Ephrin B4
Release of OC stimulatory factors Wnt 10b, BMPs, and sphingosine-1 phosphate

B Therapy with bisphosphonates, denosumab
Release of growth factors from bone matrix
Net effect on bone formation
Osteoclast
Osteoblast
Direct effects

C Therapy with ODN and other CatK inhibitors
Release of growth factors from bone matrix
Net effect on bone formation
Osteoclast
Osteoblast
Direct effects

Adapted from Khosla S. JBMR 2012:27;506
Potential mechanisms of antiresorptive drugs

Odanacatib Phase III Fracture Trial

- 3 year DB trial of 16,231 postmenopausal women
- Odanacatib 50 mg once weekly vs placebo
- All patients received 5600 IU vit. D weekly
- Three primary endpoints: morphometric vertebral fractures, nonvertebral fractures and hip fractures
- Event driven trial after 237 hip fractures accrued
- In July 2012, the study was stopped by the DSMB due to the fact that the trial met its efficacy endpoint
Odanacatib Anti-Fracture Efficacy and Safety in Postmenopausal Women With Osteoporosis

Long-Term Odanacatib Fracture Trial (LOFT)

- Comparison of ODN 50 mg/wk orally vs PBO
  - > 16,000 women ≥ 65 years
  - BMD T score -2.5 at the total hip (TH) or femoral neck (FN) or with a prior radiographic vertebral fracture (VFx) and a T score -21.5 at the TH or FN
- Primary end points: new morphometric vertebral (VFx), hip, and clinical nonvertebral fractures
  - Reduction in fractures at 6 months and later
  - BMD increased; change from baseline at 5 years: LS 11.5% vs. 0.3%; hip 5.7% vs -3.8%
  - Fractures: 54% decline in spine; 47% decline in hip; 23% decline in nonvertebral (P < .001 for all)

Safety and Tolerability of Odanacatib Therapy

• No respiratory side effects or atrial fibrillation
• No ONJ in either PBO or ODN
• 5 cases of atypical femoral fractures (0.1%) in ODN vs 0 in PBO (avg T-score -4.4)
• No difference in CV mortality
• More strokes (19; 0.2%) in ODN than in PBO (8; 0.1%)
• Morphea-like skin lesions: 12 in ODN (5/10,000 patient-years) and 3 in PBO; 5/12 ODN and 2/3 in PBO got better

Wnt Signaling Pathways

- A group of signal transduction pathways comprised of 19 secreted Wnt glycoproteins
- These regulate a vast array of biological processes including embryonic cell development and migration, cell homeostasis and tumor suppression and oncogenesis
- Three Wnt signaling pathways have been characterized:
  - the Canonical (β-catenin dependent) Wnt pathway,
  - the noncanonical Wnt calcium pathway
  - the noncanonical Wnt planar cell polarity pathway
Wnt/LRP5/β-Catenin Pathway in Bone Formation

- Wnt/LRP5/β-catenin pathway is essential for:
  - Osteoblast proliferation, differentiation, and survival
Dikkopf-1 (Dkk-1) in association with Kremen and Sclerostin bind LRP5 and LRP6. Soluble frizzled-related protein (sFRP-1) binds Wnt and prevents its interaction with frizzled.
Sclerostin

- Protein product of the gene SOST, and is expressed principally in the osteocyte
- It is a negative regulator of the Wnt/B-catenin pathway by binding to LRP5 and LRP6

Sclerostin staining in Osteocytes
Poole K et al. FASEB 2005
“Genetic” Bone Disorders involving the Wnt pathway

- **Loss-of-function of LPR5-**
  - Osteoporosis Pseudoglioma Syndrome

- **Gain-of-function of LPR5-**
  - High bone mass

- **Sclerosteosis** - loss-of-function of the SOST gene encoding Sclerostin

- **Van Buchem’s disease** - 52-kb deletion of the downstream promoter of SOST
Sclerosteosis
Inhibition of Sclerostin- Advantages

- Extracellular target amenable to the use of biologics
- Highly selective for bone: expression is limited to osteocytes
- Absence of sclerostin is known to result in marked increases in bone mass and strength
- Haplo-insufficiency of sclerostin results in more moderate increase in bone mass
Sclerostin Antibody

Diagram A:
- WNT
- Scl
- DKK1
- LRP5/6
- LRP4
- ↓ Wnt Signalling
- ↓ Bone Formation

Diagram B:
- DKK1-Ab
- Scl
- ↑ Wnt Signalling
- ↑ Bone Formation
Sclerostin MAb Increases BMD in Rats

1.5-year-old rats 1 year post-ovariectomy
MAb 25 mg/kg 2x/wk x 5 wk
PTH 1-34 100 mcg/kg 5x/wk x 5 wk

Inhibition of Sclerostin With AMG 785 in Postmenopausal Women With Low Bone Mineral Density: Phase 2 Trial Results

McClung MR, ASBMR 2012
Sclerostin-Ab (Romosozumab) in PMO: Phase 2 Results

- 12 month trial of 419 Women, 55 to 85 years old with Lumbar spine, Total Hip, or Femoral Neck T-score –2.0 to –3.5.
- Randomized to AMG 785 (Romosozumab)
  - 70 mg Q month
  - 140 mg Q month
  - 210 mg Q month
  - 140 mg Q 3 month
  - 210 mg Q3 month
- Placebo
- Open-label active comparators:
  - 70 mg/w Alendronate or 20 µg/d TPTD

McClung MR, ASBMR 2012
Sclerostin-Ab (Romosozumab) in PMO: Phase 2 Results
Effects of 2 Years of Treatment With Romosozumab Followed by 1 Year of Denosumab or Placebo: Results

- 15.7% increase in BMD at LS at 24 months
- Improvement continued in year 3 for the denosumab group

Randomized treatment group up to month 24.
BL = baseline.
Romosozumab in PMO: Phase 2 Results - Safety

- AEs balanced with exception of injection site reactions
  - 4% placebo
  - 12% Romosozumab
- Romosozumab antibodies
  - Ab in 20%, neutralizing Ab in 3%

McClung MR, ASBMR 2012
#1143 Keaveny et al. Romosozumab Increased Estimated Strength by FEA at the Lumbar Spine at Month 12

- Whole bone: Placebo (n = 27) -3.9%, Teriparatide (n = 28) 27.3%**, Romosozumab (n = 24) 18.5%
- "Cortical": Placebo (n = 27) -2.0%, Teriparatide (n = 28) 16.2%, Romosozumab (n = 24) 28.8%**
- Trabecular: Placebo (n = 27) -6.0%, Teriparatide (n = 28) 21.4%, Romosozumab (n = 24) 26.0%*

Data are LS means and 95% CIs. *P < 0.05 compared with placebo; †P < 0.05 compared with teriparatide. ANCOVA model adjusting for baseline QCT FEA value and geographic region.
Teriparatide 20 µg QD, romosozumab 210 mg QM.
#1143. Keaveny et al. Romosozumab Increased Estimated Strength by FEA at the Hip at Month 12

Data are LS means and 95% CIs. *P < 0.05 compared with placebo; †P < 0.05 compared with teriparatide.  
ANCOVA model adjusting for baseline QCT FEA value and geographic region.  
Teriparatide 20 μg QD, romosozumab 210 mg QM.
Effect of Blosozumab on Bone Mineral Density

- Blosozumab, 52-week phase 2 trial in postmenopausal women; LS T score -2.0 to -3.5

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Increase in BMD at LS, %</th>
<th>P value</th>
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<tr>
<td>270 mg/2 wk</td>
<td>17.7</td>
<td>&lt; .001</td>
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<tr>
<td>180 mg/2 wk</td>
<td>14.9</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>180 mg/4 wk</td>
<td>8.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Placebo</td>
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<td></td>
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</tbody>
</table>

- 52-week follow-up with no blosozumab treatment

Effect of Blosozumab on BMD: 52 week follow-up off treatment after 52 weeks of treatment

Open bars indicate mean % change from study baseline at 52 weeks of treatment. Striped hatching indicates mean % change from study baseline through week 104. *P < .001. †P < .05 compared with placebo.
Q4W = blosozumab every 4 weeks; Q2W = blosozumab every 2 weeks. P values are corrected Dunnett’s adjusted P values.
Safety Concerns with Manipulation of the WNT Pathway

- WNT pathway is ubiquitous and involved in multiple cell functions
- Potential for excess bone formation (entrapment palsies, increased intracranial pressure).
- Reassuring that heterozygous carriers of Sclerosteosis and Van Buchem’s do not demonstrate these problems
- Potential for osteosarcoma (deletion of Wnt inhibitory factor-1 can lead to osteosarcoma in mice)
**Abaloparatide**

**Bone effects of PTH vs PTHrP**

- **Parathyroid hormone (PTH)** (Teriparatide)
  - PTH receptor
  - $R^0$ conformation (locks PTH)
  - Adenylyl cyclase
  - G protein
  - cAMP
  - Sustained increase in cAMP
  - Bone resorption $\geq$ Bone formation

- **PTH-related protein (Abaloparatide)**
  - PTHrP
  - $R^0$ conformation (transient PTHrP binding)
  - Adenylyl cyclase
  - G protein
  - cAMP
  - Transient increase in cAMP
  - Bone formation $>$ Bone resorption

Effect of abaloparatide on BMD in Postmenopausal Women

- International MC, RDBPC 24 week trial
- Intervention: 222 pts with PMO treated with ABA (20, 40, or 80ug sc qd), TPD (20ug sc qd), or placebo (PBO)
- Outcome: BMD increase by DXA

Abaloparatide increases BMD at all sites more than PBO

Leder BZ, et al. J Clin Endocrinol Metab 2015; 100: 697
Phase 3 Trial Design of Abaloparatide Clinical Trial

N = 2463

Randomization

- Placebo
- Abaloparatide 80 mcg Daily SC
- Teriparatide 20 mcg Daily SC

M  6  12  18

Miller et al, Endo Soc 3-15
#1053: Williams, Fitzpatrick et al. Effects of Abaloparatide on Major Osteoporotic Fracture Incidence in Postmenopausal Women with Osteoporosis - Results of the Phase 3 ACTIVE Trial

-70%*

-55%†

*P=0.0004, abaloparatide vs placebo.

†P=0.031, abaloparatide vs teriparatide.

Teriparatide NS vs placebo.
Summary

- We now standardized methods to identify patients with osteoporosis at high risk of fracture (DXA and FRAX)
- We have effective and safe medications to treat, with more on the way
- Unfortunately, less women and men are being tested today with DXA, and still only 20% of eligible patients are being treated