AACE
25th Annual Scientific and Clinical Congress

Osteoporosis Treatment: Then and Now

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Portland, Oregon, USA

Orlando, FL
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Disclosures

I am disclosing financial relationships as follows:

Advisory Boards: Amgen, Merck, Radius

Honorarium for speaking: Amgen, Merck

Michael McClung, MD 2016
Congratulations, AACE

THE AMERICAN ASSOCIATION of CLINICAL ENDOCRINOLOGISTS
AACE Annual Scientific 25th & Clinical Congress

Join us for our 25th Annual Meeting in ORLANDO

Celebrate the Journey

MAY 25 - 29, 2016
Osteoporosis: THEN and NOW

THEN: 1992 – the year of the first AACE meeting – in Orlando

Images courtesy of Dr David Dempster
Osteoporosis: THEN and NOW

THEN: 1992 – the year of the first AACE meeting – in Orlando

Earlier milestones

1942– Albright realized that
• women with osteoporosis were in negative calcium balance due to poor calcium absorption and excessive renal calcium loss
• estrogen therapy improved calcium balance

1948– Albright-Reifenstein textbook

Fuller Albright

Images courtesy of Dr. David Dempster
Osteoporosis: THEN and NOW

- 1960-64: Frost and Parfitt describe process of bone remodeling
- 1977: ASBMR founded, but osteoporosis was a very small part of the scientific program
- 1986: Dempster's photos depict osteoporosis

Images courtesy of Dr. David Dempster
Osteoporosis: *THEN and NOW*

- 1978: estrogen approved to treat osteoporosis
- 1984: injectable calcitonin approved as osteoporosis therapy
- 1985-90: epidemiology of fracture and relationship to BMD
- 1985-88: clinical trials with fracture endpoints begun
- 1987: DXA introduced
- 1989-92: large clinical trials begun
1992

- Osteoporosis was one of the “osteopenic” conditions
- Osteoporosis diagnosed when older women presented with height loss or pain due to vertebral fractures
- No definition or diagnostic tests
- Available treatments
  - estrogen
  - injectable calcitonin
  - oral etidronate (off label)
  - sodium fluoride
The Science of Osteoporosis: 1992-2010

1993: relationship of BMD to fracture risk

Efforts to prevent hip fractures should focus on women with low hip bone density.

The Science of Osteoporosis: 1992-2010

• 1993: relationship of BMD to fracture risk
• 1994: WHO definition of osteoporosis

<table>
<thead>
<tr>
<th>WHO Diagnostic Category*</th>
<th>T-Score</th>
</tr>
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<tbody>
<tr>
<td>Normal bone mass</td>
<td>≥ -1</td>
</tr>
<tr>
<td>Low bone mass</td>
<td>−1 &gt; -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ -2.5</td>
</tr>
<tr>
<td>Established osteoporosis</td>
<td>≤ -2.5 and fracture</td>
</tr>
</tbody>
</table>
The Science of Osteoporosis: 1992-2010

- 1993: relationship of BMD to fracture risk
- 1994: WHO definition of osteoporosis
- 1995: alendronate reduces vertebral fracture risk – and licensed for treatment

Pivotal Phase 3 study

Incidence of vertebral fracture at 3 years

<table>
<thead>
<tr>
<th>Incidence of Vertebral Fracture (%)</th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of Vertebral Fracture at 3 years</td>
<td>6.2%</td>
<td>2.8%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

The Science of Osteoporosis: 1992-2010

- 1993: relationship of BMD to fracture risk
- 1994: WHO definition of osteoporosis
- 1995: alendronate reduces vertebral fracture risk – and licensed for treatment
- 1998: clinical guidelines appear

**National Osteoporosis Foundation - 1998**

Treatment for osteoporosis recommended in all postmenopausal women with

T-score -2.0 or lower

or

T-score ≤ -1.5 and another risk factor

**AACE Guidelines - 2001**

- adult with fragility fracture
- T-score < -2.5
- T-score < -1.5 + risk factors
The Science of Osteoporosis: 1992-2010

- 1993: relationship of BMD to fracture risk
- 1994: WHO definition of osteoporosis
- 1995: alendronate reduces vertebral fracture risk – and licensed for treatment
- 1998: clinical guidelines appear
- 1999-2004: more drugs licensed
- 2004: ONJ
- 2007: Atypical fracture
- 2008: FRAX introduced
- 2010: denosumab licensed
Osteoporosis is a consequence of an imbalance in bone remodeling with bone formation lagging behind resorption.

- Anti-remodeling agents – 90% of market
  - bisphosphonates
  - estrogen agonist/antagonist (raloxifene)
  - RANK ligand inhibitor (denosumab)
- Remodeling stimulating (anabolic) agents
  - teriparatide (PTH 1-34)
Osteoporosis Therapies

OBJECTIVES

1. improve bone strength
2. reduce risk of fracture

BENEFITS

1. effective protection from fractures
   - vertebral fracture by 60-70%
   - hip fracture by 40-50%
   - non-vertebral fracture by 20-35%
2. in general are well tolerated
3. in clinical trials, have been very safe

Fracture Risk with Osteoporosis Treatment

HORIZON Study

- Spine: Placebo 70%, Zoledronic acid 25%
- Hip: Placebo 40%, Zoledronic acid 25%
- Non-spine: Placebo 20%, Zoledronic acid 41%


FREEDOM Study

- Spine: Placebo 20%, Denosumab 68%
- Hip: Placebo 41%, Denosumab 41%
- Non-spine: Placebo 25%, Denosumab 20%

Osteoporosis Therapies

1. Fracture protection
   - begins within months of starting therapy
   - continues with long-term therapy
   - wanes when treatment is stopped
Alendronate:
Cumulative Incidence of Clinical Vertebral and Hip Fracture
Phase 3: FIT Trial

Clinical Vertebral Fracture  Hip Fracture

Zoledronic Acid and Denosumab
Incidence of Morphometric Vertebral Fracture

HORIZON Study

- Placebo
- Zoledronic acid

FREEDOM Study

- Placebo
- Denosumab

Zoledronic Acid and Denosumab
Cumulative Incidence of Hip Fracture

HORIZON Study

FREEDOM Study

Osteoporosis Therapies

1. Fracture protection
   • begins within months of starting therapy
   • persists with long-term therapy
   • wanes when treatment is stopped
Long Term Alendronate Therapy

Mean Percent Change (± SE)

Placebo
ALN 10 mg

Urinary N-telopeptide

Total Hip BMD

Years

Fracture Protection with Risedronate Persists with Long Term Therapy

Fracture protection persists with long term therapy

VERT-MN: Radiographic Vertebral Fracture*

Incidence per Year (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ris 5 mg</th>
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</thead>
<tbody>
<tr>
<td>Years 0-3</td>
<td>7.6%</td>
<td>4.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ 49%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*P=0.001</td>
</tr>
<tr>
<td>Years 4-5</td>
<td>12.3%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ 59%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*P=0.011</td>
</tr>
<tr>
<td>Years 6-7</td>
<td>3.8%</td>
<td>3.8%</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

Subjects switched to risedronate 5 mg at end of year 5

Mellstrom DD et al. *Calcif Tissue Int.* 2004;75:462-8
Vertebral Fractures with Zoledronic Acid

Fracture protection persists with long term therapy

Years 1-3
- PBO: 10.9% (310/2853)
- ZOL: 3.3% (92/2822)
- P = <0.001

Years 4-6
- Core study: 3.3% (92/2822)
- Extension study: 3.0% (14/469)

Denosumab Treatment
Total Hip BMD and Nonvertebral Fractures Through 10 Years

Percentage Change From Baseline

Total Hip

FREEDOM Extension

9.2% change
7.4% change

Yearly Incidence of Nonvertebral Fractures (%)

Placebo Cross-over Denosumab Long-term Denosumab

Study Year

Years of Denosumab Treatment

Bone HG et al. ASBMR; Seattle, WA; October 12, 2015; #LB-1157
Osteoporosis Therapies

1. Fracture protection
   • begins within months of starting therapy
   • persists with long-term therapy
   • wanes when treatment is stopped
     – even with bisphosphonates
Discontinuing Osteoporosis Treatments

- Skeletal benefit of most drugs disappears quickly upon discontinuation of treatment
  - estrogen
  - raloxifene
  - calcitonin
  - teriparatide
  - denosumab

![Graph showing LS BMD: Mean Percent Change from Baseline](image)


Stopping Alendronate Therapy

Changes over 5 years are within the LSC

Mean Percent Change (± SE)

Lumbar spine

Total Hip

Years

0 1 2 3 4 5 6 7 8 9 10

Years

0 1 2 3 4 5 6 7 8 9 10

ALN 10 mg
ALN 20 mg/ALN 5 mg/Placebo

Clinical Vertebral Fractures in FLEX Study

Cumulative Incidence of Fractures (%)

- **ALN 5 years → Placebo 5 years**: 5.4%
- **Alendronate 10 years**: 2.5%

Relative Risk (RR) ↓ 55%
P = 0.013

Years Since FIT:

<table>
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<tr>
<th>ALN/PLB</th>
<th>437</th>
<th>436</th>
<th>425</th>
<th>412</th>
<th>398</th>
<th>387</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALN/ALN</td>
<td>662</td>
<td>660</td>
<td>646</td>
<td>631</td>
<td>615</td>
<td>597</td>
</tr>
</tbody>
</table>

OC

Vertebral Fractures with Zoledronic Acid

Absolute risk of new vertebral fracture if therapy is stopped = 1%/year

P = 0.0348

Osteoporosis Therapies

1. Fracture protection
   - begins within months of starting therapy
   - persists with long-term therapy
   - wanes when treatment is stopped
     - even with bisphosphonates

2. No drug yet “cures” osteoporosis
   - long-term treatment is required
Risks and Concerns with Long-term Therapy

**Bisphosphonates**

- Hypocalcemia
- Intolerance
  - upper GI symptoms: *oral drugs*
  - acute phase reaction: *IV drugs*
  - bone and muscle pain
- Inflammatory eye problems
- Atrial fibrillation
- Esophageal cancer: *oral drugs*
- Osteonecrosis of the jaw
- Atypical fractures

**No increase with long-term therapy**

**Unproven relationship; minimal evidence of increased risk with long-term therapy**

**Concern here of risk of long-term therapy**
Benefit:Risk Profile of Bisphosphonate Treatment for 10 Years

73 year old woman
FN T-score -2.7
63% with vertebral fracture

- Vertebral Fracture Prevented *
  - 23% after 10 years

- Hip Fracture Prevented *
  - 3.3% after 10 years

- Atypical Femoral Fracture **
  - 0.11% after 10 years

** From Dell RM et al. *J Bone Miner Res* 2012;27:2544-50
Optimize the Benefit:Risk Ratio

- Treat patients who will receive the most benefit
  - at high risk for fracture
- Avoid long-term therapy in low risk patients
- Avoid treatment in patients at risk for adverse effects
- Individualize treatment to match the patient

Risk of Fracture

Benefit

Risk

Low

High
Osteoporosis Therapy - 2016

Summary

• We have effective tools to diagnose osteoporosis and to identify patients at high risk of fracture.

• In patients with osteoporosis, our current treatments can effectively and quickly reduce fracture risk.

• While all drugs have side effects, the incidence of serious complications from our therapies is quite low.

• As a result the benefit:risk ratio of therapy is high – when patients at high risk are treated.

McClung M. Personal opinion, 2016
Osteoporosis Therapy - 2016
How Are We Doing?

- Adherence to therapy is very poor

58% discontinued therapy
Osteoporosis Therapy - 2016
How Are We Doing?

- Adherence to therapy is very poor
- Number of BMD tests is declining – despite increase in number of patients over age 65
- Number of prescriptions for osteoporosis drugs has decreased by >40% since 2008
- Treatment gap – even for the most obvious patients – has widened since 2002


Between 2000 and 2013, number of women age 65 and older has increased from 35 million to 44.7 million
Osteoporosis Therapy - 2016

How Are We Doing?

Are You Kidding?

“The dominant approach to hip fracture prevention (i.e., drugs) is neither viable as a public health strategy nor cost effective”.


Overdiagnosis of Osteoporosis?

The 5 Most Commonly Overdiagnosed Conditions

- CKD
- Low T
- Pre-dementia
- Thyroid cancer
- Crazy tests
  - BMD
  - Total body scans
  - MRI for back pain and headache
Osteoporosis Therapy - 2016

*Where Did We Go Wrong?*

1. Lost focus on treating patient at high risk
2. NOF guidelines not supported by the osteoporosis community
   - not known to primary care physicians
   - not implemented
3. Too many fracture endpoints
4. Destructive debates among competing drug companies
5. Criticism of DXA – especially by epidemiologists
6. Confusion among doctors and patients

NO CONSISTENT, BELIEVABLE VOICE
Osteoporosis Therapy - 2016
Where Are We Going?

Advances in Health Care Delivery

1. Development of Fracture Liaison Services
   “Capture the Fracture” (IOF)
   “Own the Bone” (AOA)
   “2 Million 2 Many” (NBHA)

2. Discussion of the “Treat-to-Target” concept
   Therapies will be chosen on their probability of getting an individual patient to a “target”

FNIH Meta-regression
Change in Total Hip BMD vs Reduction in Hip Fracture

MORE (RAL)
FIT II (ALN)
HIP (RIS)
FREEDOM (DMAB)
Clodronate

Bubble size ~ to n fractures in study

*Courtesy of Dr D Black et al, ASBMR 2015

OOC

*Bubble size ~ to n fractures in study

Between group difference in BMD change
+1% BMD change = -11.11% in RR (95% CI -14.54% to -7.54%, p = 0)
Large, Progressive Increases in HIP BMD

**Total Hip BMD**
- Placebo
- Denosumab 60 mg QM

**Femoral Neck BMD**
- Placebo
- Odanacatib 50 mg QW

Percentage Change from Baseline
- 9.2%
- 9.8%
Relationship Between Total Hip T-score on Therapy and Non-vertebral Fracture Risk

- 5.0
- 6.0

DMAb (N = 3612)

Incidence of non-vertebral fracture at 1 year (%)

- 3.0
- 2.5
- 2.0
- 1.5
- 1.0
- 0.5

Total Hip T-score

Ferrari S et al. ASBMR 2015
Osteoporosis Therapy - 2016

Where Are We Going?

Improved Imaging Techniques

- Trabecular bone structure
- High resolution pQCT
- Algorithms to estimate cortical porosity
- Mapping of cortical thickness and mass
- Finite element analysis – estimated bone strength surrogate for fracture in clinical trials
- new “target” for treatment
Osteoporosis Therapy - 2016
Where Are We Going?

New Drugs

1. Cathepsin K inhibition

2. Sclerostin inhibition
Cathepsin K Inhibition

- Cathepsin K, the major proteolytic enzyme of osteoclasts

- Odanacatib
  - very specific inhibitor of cathepsin K
  - inhibits bone resorption without decreasing osteoclast number and function – thus preserving bone formation
  - in pre-clinical studies, increased endocortical and periosteal bone formation; increased cortical thickness and strength

- Convenient once weekly oral dosing in clinical studies

References:
Cathepsin K Inhibitor: Odanacatib

Phase 2: Bone Mineral Density

A Lumbar Spine

B Total Hip

Cathepsin K Inhibitor: Odanacatib
Phase 3: Fracture Risk Reduction

- In LOFT study, odanacatib 50 mg po once weekly significantly reduced fracture risk in women with osteoporosis

- Relative risk reduction (%), 95% (confidence interval)
  - spine 54% (2.3% vs 7.2%)
  - hip 47% (0.7% vs 1.2%)
  - non-vertebral * 23% (6.5% vs 8.0%)

* Time-dependent decrease in non-vertebral fracture risk

- Final adjudication of safety events expected soon

McClung M et al. ASBMR 2014
Sclerostin Inhibition

- Sclerostin – an osteocyte-derived inhibitor of bone formation
- Romosozumab
  - humanized anti-sclerostin antibody
  - in pre-clinical studies, normalized bone mass, structure and strength
- Administered SQ once monthly in clinical studies

Sclerostin Inhibitor: Romosozumab

Phase 2 Study: Bone Mineral Density

Data are LS means and 95% CIs.

Bone Mineral Density – Year 3
*Romosozumab Discontinuation: Transition to Denosumab*

**Lumbar Spine**
- Romosozumab 210 mg QM*: 15.7% from Baseline
- Denosumab 60 mg Q6M: 19.4% from Baseline
- Placebo*: 7.1% from Baseline

**Total Hip**
- Denosumab 60 mg Q6M: 6.0% from Baseline
- Placebo Q6M: 7.1% from Baseline

McClung MR et al. ASBMR 2014.
**Sclerostin Inhibitor: Romosozumab**

*Phase 3: Fracture Risk Reduction*

*Phase III studies are underway*
- evaluation of safety will be important

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3 extension</th>
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<tbody>
<tr>
<td>Romosozumab</td>
<td>Denosumab</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Placebo</td>
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<td>Denosumab</td>
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*ClinicalTrials.gov Identifier: NCT01575834*

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*ClinicalTrials.gov Identifier: NCT01631214*
Osteoporosis Treatment
*The Near Future*

- Sequential therapy
  - For patients with severe osteoporosis, a sequential treatment regimen will be used

Finite interval of anabolic agent followed by an anti-remodeling drug

- Anabolic agent
  - 6-12 months
- Anti-remodeling Drug
  - 6-24 months
- Anabolic agent
  - 6-12 months

Target met
- Continue or “drug holiday”

Target not met
- Change to more potent drug

Bisphosphonate
- 3-5 years
Osteoporosis Treatment - 2016
State of the Art

- We understand much but not all of how bone loss occurs and how osteoporosis develops
- We have very effective tools for diagnosing osteoporosis and for estimating fracture risk in individual patients
- We have several classes of effective treatments to prevent bone loss and to reduce fracture risk
However, our patients, physician colleagues and health care systems do not share our interest and are not aware of how much we know and can do.

- Most patients with fractures are not being evaluated
- Most patients with osteoporosis are not treated
- Most patients begun on therapy stop within 6-12 months
Osteoporosis Treatment - 2016
*Where Are We Going?*

- Better measures of bone strength and fracture risk
- Drugs with long dosing intervals – improved adherence
- New drugs are that may actually “cure” osteoporosis
  -- *but*
- We need to translate our scientific advances into daily clinical practice
  - Help primary care colleagues feel comfortable approaching the question of osteoporosis
    - clearer guidelines
    - secondary prevention services
  - Help patients appreciate the relative benefits vs risks of osteoporosis treatments
  - Help payers recognize the effectiveness of our current strategies

*OOC*
Osteoporosis Treatment - 2016

**Action Plan**

- Osteoporosis community MUST
  - Re-engage the medical community about the importance and urgency of treating patients at high risk for fracture

- Communicate
  - more consistently about treatment strategies
  - more clearly about the effectiveness of our current treatments
  - more loudly about the very favorable benefit:risk ratio
Osteoporosis no longer has to happen.

Effective management of patients with osteoporosis can now be based on solid clinical data – *on Science* - not just opinion.

The ART of managing osteoporosis is still important.

Beneficiaries of these advances and our work will be our patients.
Thank you, AACE

Michael R. McClung, MD, FACP, FACE
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Working to prevent Bone Attacks
OREGON OSTEOPOROSIS CENTER