Confronting the Challenges of Osteoporosis: NEW APPROACHES AND EMERGING TREATMENTS

SUNDAY, APRIL 2, 2017
6:00–7:45 AM
Hyatt Regency Orlando
Regency Ballroom R

CHAIR
Michael McClung, MD
Oregon Osteoporosis Center,
Portland, OR

FACULTY
João Lindolfo Borges, MD
Universidade Catolica de Brasilia,
Brazil
David Kendler, MD, FRCPC
Professor of Medicine
University of British Columbia, Canada
Clifford J. Rosen, MD
Senior Scientist
Director, Center for Clinical & Translational Research
Maine Medical Center Research Institute

AGENDA
Where Are We? Current State of Care in Osteoporosis
How Are We Doing? Contemporary Challenges (and Crisis)
Where Are We Going? How New Drugs and Genetics will Impact Management

LEARNING OBJECTIVES
Upon completing this activity, learners will be able to:
• Summarize current clinical challenges in the diagnosis and management of osteoporosis and discuss common barriers to success
• Apply current guidelines and state of care methods when assessing and treating patients at risk for low trauma fractures or living with osteoporosis
• Discuss the mechanism of action, benefits, and limitations of emerging osteoporosis therapies, and recognize the potential impact of current trials on practice

CME CREDITS: 1.75 AMA PRA Category 1 Credits™
This activity is supported by an educational grant from Amgen
SYMPOSIUM AGENDA

Confronting the Challenges of Osteoporosis: New Approaches and Emerging Treatments
Sunday, April 2, 2017

6:00 – 6:05 AM  Welcome and Introduction
                 Michael R. McClung, MD

6:05 – 6:25 AM  Where Are We? Current State of Care in Osteoporosis
                 David Kendler, MD, FRCPC

6:25 – 6:45 AM  How Are We Doing? Contemporary Challenges in Osteoporosis
                 Clifford J. Rosen, MD

6:45 – 7:05 AM  Where Are We Going? How New Drugs and Genetics Will Impact Management
                 João Lindolfo Borges, MD

7:05 – 7:15 AM  Summary
                 Michael R. McClung, MD

7:15 – 7:40 AM  Q&A and Panel Discussion

7:40 – 7:45 AM  Closing
                 Michael R. McClung, MD

FACULTY

Michael R. McClung, MD – Program Director
Director, Oregon Osteoporosis Center
Portland, OR

João Lindolfo Borges, MD
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Universidade Catolica de Brasilia
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Professor of Medicine (Endocrinology)
University of British Columbia
Vancouver, Canada

Clifford J. Rosen, MD
Director, Maine Medical Center Research Institute
Scarborough, ME
Michael R. McClung, MD – Program Director

Dr. Michael McClung is the founding director of the Oregon Osteoporosis Center. He graduated from Rice University in Houston and from the University of Texas Southwestern Medical School in Dallas. After training in Internal Medicine at Parkland Hospital in Dallas, he completed a fellowship in Endocrinology at the National Institute of Health in Bethesda, Maryland. He has served on the faculty at the Oregon Health Sciences University and in the Department of Medical Education at Providence Portland Medical Center. Dr. McClung has helped plan, conduct, and report many of the major clinical trials in the field. He serves on the editorial board of several journals. He is active in numerous professional organizations and currently serves on the Board of the International Osteoporosis Foundation and the North American Menopause Society. His major interests are the management of patients with osteoporosis and other metabolic bone diseases and helping younger physicians develop their interests in this field.

João Lindolfo Borges, MD

Dr. João Lindolfo Borges is Professor of Endocrinology at the Universidade Católica de Brasília (Catholic University of Brasilia). He is the Director of the Centro de Pesquisa Clínica do Brasil (Brazilian Clinical Research Center). Dr. Borges received his M.D. from Universidade Brasília (University of Brasilia), and his fellowship was at the University of Virginia, Charlottesville, Virginia. Dr. Borges was the Vice-president of the Brazilian Society of Endocrinology and Metabolism. He was president of the Brazilian Society of Clinical Densitometry, president and founder of the Latin-American Society of Clinical Densitometry. Dr. Borges served as board member of the International Society for Clinical Densitometry (ISCD) for six years. He served as a committee member of the American Association of Clinical Endocrinologists and Endocrine Society. He has received numerous awards including the ISCD Physician of the year and Fellow of the American College of Endocrinology. Dr. Borges was a member of editorial board of several journals including Journal of Clinical Densitometry.
David Kendler, MD, FRCPC

Dr. Kendler graduated from the MD program at the University of Toronto in 1977. After completing a rotating internship in Toronto, he practiced for several years in Canada, Botswana, and New Zealand. He returned to Internal Medicine training in 1983 in Christchurch, New Zealand and in 1984 joined the Internal Medicine program in Halifax, Canada. In 1985 he moved to Vancouver to complete Internal Medicine and Endocrinology training at the University of British Columbia. After a 2-year thyroid immunology Fellowship in New York, he returned to the University of British Columbia Faculty of Medicine where he is now a Professor of Medicine in Endocrinology. He has led osteoporosis programs at Children and Women’s Hospital and St. Paul’s Hospital. He is the director of Prohealth Clinical Research, a major North American centre for clinical trials in the area of osteoporosis. He serves on the Scientific Advisory Council of Osteoporosis Canada and Chairs the Western Osteoporosis Alliance. He is a Past-President of the International Society for Clinical Densitometry. He is a member of the Committee of Scientific Advisors of the International Osteoporosis Foundation and is co-Chair of the Western Osteoporosis Alliance. He has been awarded the John Bilezikian ISCD Global Leadership Award. He has served on the Board of Directors of the Canadian Menopause Society. He has published over 120 peer-reviewed papers on osteoporosis therapies, osteoporosis risk assessment, and autoimmune thyroid disease.

Clifford J. Rosen, MD

Dr. Rosen is a clinical and translational scientist who runs a basic laboratory funded by 3 NIH grants related to bone-fat interactions. He also oversees clinical trials and is on the executive committee of the D2d trial studying the effects of vitamin D supplementation on the prevention of Type 2 Diabetes. Dr. Rosen has over 365 publications in peer-reviewed journals and is an associate editor at The New England Journal of Medicine as well as director of clinical and translational medicine at Maine Medical Center Research Institute.
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The Endocrine Society has achieved Accreditation with Commendation.

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LEARNING OBJECTIVES
Upon completion of this educational activity, learners will be better able to:

- Summarize current clinical challenges in the diagnosis and management of osteoporosis and discuss common barriers to success
- Apply current guidelines and state of care methods when assessing and treating patients at risk for low trauma fractures or living with osteoporosis
- Discuss the mechanism of action, benefits, and limitations of emerging osteoporosis therapies, and recognize the potential impact of current trials on practice

TARGET AUDIENCE
This continuing medical education activity should be of substantial interest to endocrinologists, endocrine fellows, and healthcare professionals who treat patients with bone and calcium disorders.

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As a provider of continuing medical education (CME) accredited by the Accreditation Council for Continuing Medical Education, the Endocrine Society has a policy of ensuring that the content and quality of this educational activity are balanced, independent, objective, and scientifically rigorous. The scientific content of this activity was developed under the supervision of the Endocrine Society's Special Programs Committee (SPC). The commercial supporter(s) of this activity have no influence over the planning of this CME activity.

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**Michael R. McClung, MD:** Consultant, Radius Health, Inc., Amgen; Speaker, Amgen

**David Kendler, MD, FRCP:** Research Support, Amgen; Speaker, Amgen, Eli Lilly & Company, GlaxoSmithKline; Consultant, Eli Lilly & Company; Investigator, Eli Lilly & Company, AstraZeneca; Advisory Group Member, Pfizer, Inc.

The faculty reported the no relevant financial relationship: **Clifford J. Rosen, MD, João Lindolfo Borges, MD**

The following SPC member who reviewed content for this activity reported the relevant financial relationships:

**E Michael Lewiecki, MD:** Consultant, Amgen, Merck, Eli Lilly, Radius Health, Shire, Abbvie and Alexion; Speaker, Alexion, Shire; Research Grant Support, Amgen, Eli Lilly, Merck

The following SPC Committee members reported financial relationships:

**Zahid Ahmad, MD:** Research Support, Regeneron, FH Foundation; Consultant, Regeneron; Speaker, Amgen, Genzyme, Sanofi

**Andrew Ahmann, MD:** Research Support, Dexcom, Lexicon, Medtronic, Novo Nordisk; Consultant, Dexcom, Novo Nordisk, Trividia Health

**Giuseppe Barbessino, MD:** Spouse, employee of Genzyme

**John Carmichael, MD:** Research Support, Novo Nordisk, Chiasma, Novartis, Pfizer, Strongbridge Biopharma; Speaker, Novartis; Advisory Board, Pfizer, Chiasma, Ionis Pharmaceuticals

**Natalie Cusano, MD:** Research Support, Shire; Speaker, Shire

**Joan Han, MD:** Research Support, Rhythm Pharmaceutical

**Alan Kelly, MD:** Speaker, Eli Lilly

**Lisa Nachtigall, MD:** Consultant, Ipsen, Novartis, Corcept; Grant Support/Investigator, Chiasma

**Neda Rasouli, MD:** Research Support, Novo Nordisk, Calibra, INTARCIA Therapeutics, GlaxoSmithKline, Bristol Meyer Squibb, AstraZeneca /Amylin, Ionis Pharmaceuticals, Boehringer Ingelheim

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The following SPC members reported no relevant financial relationships: **Connie Newman, MD,**

**Amy Rothberg, MD**

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ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT
This activity is supported by an educational grant from Amgen.

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WHERE ARE WE?
CURRENT STATE OF CARE IN OSTEOPOROSIS

David Kendler, MD, FRCP
Where Are We? Current State of Care in Osteoporosis

David Kendler MD
Professor of Medicine
University of British Columbia
Vancouver Canada

Orlando, April 2017

Osteoporosis 2017

- Understanding of the epidemiology of bone loss and fracture
  - Better tools for patient evaluation: diagnosis and fracture risk assessment
  - Targeting of high risk patients to effective therapies; importance of secondary fracture prevention.
  - Guidelines for testing and treatment initiation
  - Guidelines for management of glucocorticoid, aromatase inhibitor, androgen deprivation, male

- Awareness of the physiology and pathophysiology of postmenopausal and age-related bone loss
  - Bone resorption and bone formation; cortical bone loss

- Current treatments
  - Antiresorbers: estrogen, SERM, bisphosphonates, denosumab
  - Anabolic: teriparatide

Fractures from Osteoporosis are more Prevalent than Heart Attack, Stroke and Breast Cancer Combined

![Fracture Prevalence in Canadian Women](image)

Fracture Risk and ease of case-finding

The majority of post-menopausal women (84%*) have not suffered a fragility fracture

Strategies to case-find new and prior fracture patients could identify up to 50% of all potential hip fracture cases from 16% of the population

Fracture Liaison Services


Risk of major osteoporotic fracture after initial fracture (REYKJAVIK STUDY)

N. C. Harvey, H. Johannsson, K. Siggeirsdottir, A. Olof, V. Guðnason, E. McCallion, G. Sigurdsson, J. A. Karlsson, University of Southampton, Southampton, United Kingdom

- 18872 men and women
- 5039 patients <1 first fracture
- 2029 patients <2 first fractures
- Risk of a second MOF:
  - Increased by 4% for each year of age
  - 45% higher for women than men
  - Increased immediately after the first fracture: RR 3.1 (95% CI 2.3, 3.9) at 1 year
  - Remains higher than the prediction throughout follow-up: RR 2.1 (95% CI 1.3, 3.5) at 10 years

Figure: Risk of a MOF after a score of 10 or greater (WHO) or Risk of a repeat MOF over 10 years.

BMD and Fracture: More to the Story

BMD distribution vs. Osteoporotic Fracture Rates/Number

<table>
<thead>
<tr>
<th>BMD T-scores</th>
<th>60</th>
<th>45</th>
<th>30</th>
<th>20</th>
<th>15</th>
<th>10</th>
<th>5</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture rate per 1000 person-years</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
</tbody>
</table>


North American Menopause Society Treatment Recommendations

Postmenopausal women and men over age 50:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 after excluding secondary causes
- Low bone mass (-1 to -2.5) FRAX 10 year probability
- Hip fracture ≥ 3% or
- Any osteoporosis fracture ≥ 20%


Definitions of osteoporosis

Osteoporosis can be defined clinically and by DXA

Clinical definition
Frailty fracture especially hip or spine

Densitometric definition
T-score < -2.5 at spine, total hip in a postmenopausal woman or man over age 50

10-year fracture risk

Calculation Tool

Osteoporosis Canada Guidelines: Therapy

First line therapies

- Alendronate, risedronate, zoledronic acid, estrogen, raloxifene, denosumab and teriparatide

First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women*

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Antiresorptive Therapy</th>
<th>Bone Formation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Vertebral</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Hip</td>
<td>√</td>
<td>-</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

*For postmenopausal women, **indicates first line therapy and Grade 1 recommendation. For non-postmenopausal treatment, alendronate, risedronate, and ibandronate are recommended. For postmenopausal treatment, alendronate, risedronate, and zoledronic acid are recommended. For non-vertebral fractures, non-vertebral fractures are a composite endpoint including hip, pelvic, ribs, humerus, radius, and clavicle. **Hormone therapy (estrogen) can be used as first line therapy in women with menopausal symptoms.

2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. OBG Obstet Gynecol 2010
Early increased incidence of vertebral fracture correlating with early trabecular bone loss
Later increased incidence of hip fracture correlating with accumulation of trabecular and cortical bone loss

Zoledronic Acid After Hip Fracture: Subsequent Fracture Risk Over Time

As Trabecular and Cortical Bone Loss Progresses, Vertebral and Hip Fracture Rates Increase Exponentially

Early increased incidence of vertebral fracture correlating with early trabecular bone loss
Later increased incidence of hip fracture correlating with accumulation of trabecular and cortical bone loss

Zoledronic Acid After Hip Fracture: Subsequent Fracture Risk Over Time

The same effect is seen for risedronate (data not shown)


BMD is Sustained with Long-Term Bisphosphonate Therapy

Pre-menopausal Post-menopausal

Progression osteoporosis

Hip Cross Section

The same effect is seen for risedronate (data not shown)


Zoledronic Acid After Hip Fracture: Subsequent Fracture Risk Over Time

The same effect is seen for risedronate (data not shown)

No Significant Difference in Fracture Risk Between Year 6 and 9 on Zoledronic Acid

Results show continued efficacy in both groups, yet do not provide evidence of benefit from continuing ZOL infusions for more than 6 years.


Serum bone turnover markers were not affected by different duration of ZOL infusions at year 6 and 9.

**Table:**

<table>
<thead>
<tr>
<th>Year</th>
<th>Change in BMD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z9</td>
<td>-2.0</td>
</tr>
<tr>
<td>Z6P3</td>
<td>-1.3</td>
</tr>
<tr>
<td>Z6</td>
<td>0.0</td>
</tr>
<tr>
<td>Z3</td>
<td>2.3</td>
</tr>
<tr>
<td>P3</td>
<td>3.7</td>
</tr>
<tr>
<td>P1</td>
<td>5.4</td>
</tr>
<tr>
<td>P0</td>
<td>7.7</td>
</tr>
</tbody>
</table>

**Graph:**

- **All Clinical Fractures:**
  - Year 6: 0%
  - Year 9: 0%

- **NS:** not significant

**Figures:**

- **HORIZON:** 6 years Zol then 3 years placebo (N=95)
- **9 years Zol** (N=95)

**References:**


**SERMs**

Selective Estrogen Receptor Modulators

- **Agonist**
  - Bone
  - CVS

- **Antagonist**
  - Breast
  - Uterus

**Figures:**

- **Bone CVSBreast Uterus SERMs**
  - Selective Estrogen Receptor Modulators Agonist Antagonist


**Table:**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Hip BMD</th>
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<tbody>
<tr>
<td>Z9</td>
<td>+4.6%</td>
</tr>
<tr>
<td>Z6P3</td>
<td>+3.7%</td>
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</tbody>
</table>

**Graph:**

- **Mean % Difference at 9 years, 0.96% (-1.07, 2.98), P = 0.351**

**Figures:**


**References:**


**Figures:**

- **Ralphofene and Invasive Breast Cancer**
  - 8 Years MORE and CORE (N=2641)
  - **RR = 0.51 (95% CI, 0.35-0.73)**
  - **49%**

**Table:**

<table>
<thead>
<tr>
<th>Years</th>
<th>Cumulative incidence per 1000 woman</th>
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<tr>
<td>0</td>
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<td>2</td>
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<td>4</td>
<td>7.4</td>
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<tr>
<td>6</td>
<td>11.5</td>
</tr>
<tr>
<td>8</td>
<td>15.3</td>
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</tbody>
</table>

**Graph:**

- **Raloxifene and Invasive Breast Cancer**
  - **8 Years MORE and CORE (N=2641)**
  - **RR = 0.66 (95% CI, 0.55-0.81)**
  - **34%**

**Table:**

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo</th>
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<tr>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>4</td>
<td>7.1</td>
</tr>
<tr>
<td>6</td>
<td>11.1</td>
</tr>
<tr>
<td>8</td>
<td>15.6</td>
</tr>
</tbody>
</table>

**Graph:**

- **Denosumab**
  - RANK•Ligand inhibitor

- **FREEDOM Extension**
  - **Long-term•Denosumab**
  - **Cross-over•Denosumab**

**Table:**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Total Hip BMD</th>
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<tbody>
<tr>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>6.4</td>
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<tr>
<td>3</td>
<td>9.2</td>
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<td>4</td>
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<td>9</td>
<td>26.0</td>
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<td>10</td>
<td>28.8</td>
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**Graph:**

- **Ralphofene and Invasive Breast Cancer**
  - **8 Years MORE and CORE (N=2641)**
  - **RR = 0.51 (95% CI, 0.35-0.73)**
  - **49%**

**Table:**

<table>
<thead>
<tr>
<th>Years of Denosumab Treatment</th>
<th>Percentage change from baseline</th>
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<td>1</td>
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<td>2</td>
<td>1.4%</td>
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<td>2.6%</td>
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<td>9</td>
<td>9.8%</td>
</tr>
<tr>
<td>10</td>
<td>11.0%</td>
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</table>

**Graph:**

- **Denosumab**
  - **Total Hip BMD and Nonvertebral Fractures Through 10 Years**
  - **FREEDOM**
  - **Extension**

**Table:**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Normalized Incidence of Nonvertebral Fractures</th>
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<tbody>
<tr>
<td>1</td>
<td>0.1</td>
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<td>0.9</td>
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<tr>
<td>10</td>
<td>1.0</td>
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</table>
### Rare Risks Associated with Bisphosphonate Use and Other Health Outcomes

#### Meta-analysis | Vertebral Fracture

<table>
<thead>
<tr>
<th>First Line</th>
<th>Odds ratio Lower Limit</th>
<th>Upper Limit</th>
<th>P-Value</th>
<th>Odds ratio and 95% CI Lower</th>
<th>Upper</th>
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<td>0.19</td>
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<td>Raloxifene</td>
<td>0.57</td>
<td>0.39</td>
<td>0.83</td>
<td>0.00</td>
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<tr>
<td>Bazedoxifene</td>
<td>0.61</td>
<td>0.32</td>
<td>1.18</td>
<td>0.14</td>
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<tr>
<td>Ibandronate</td>
<td>0.62</td>
<td>0.37</td>
<td>0.98</td>
<td>0.04</td>
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<tr>
<td>Calcium</td>
<td>0.71</td>
<td>0.45</td>
<td>1.12</td>
<td>0.14</td>
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<tr>
<td>Vitamin D</td>
<td>0.96</td>
<td>0.59</td>
<td>1.58</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Vitamin D+Calcium</td>
<td>0.99</td>
<td>0.74</td>
<td>1.41</td>
<td>0.95</td>
<td></td>
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</tbody>
</table>

#### Meta-analysis | Non-Vertebral Fracture

<table>
<thead>
<tr>
<th>First Line</th>
<th>Odds ratio Lower Limit</th>
<th>Upper Limit</th>
<th>P-Value</th>
<th>Odds ratio and 95% CI Lower</th>
<th>Upper</th>
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<tbody>
<tr>
<td>Teriparatide</td>
<td>0.50</td>
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<td>Risedronate</td>
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<tr>
<td>Zoledronate</td>
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<td>0.55</td>
<td>0.84</td>
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<tr>
<td>Denosumab</td>
<td>0.74</td>
<td>0.56</td>
<td>0.94</td>
<td>0.03</td>
<td></td>
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<tr>
<td>Alendronate</td>
<td>0.78</td>
<td>0.66</td>
<td>0.92</td>
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<td>Bazedoxifene</td>
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<td>Ibandronate</td>
<td>0.88</td>
<td>0.43</td>
<td>1.64</td>
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<td>Raloxifene</td>
<td>0.90</td>
<td>0.76</td>
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<td>Calcium</td>
<td>0.94</td>
<td>0.84</td>
<td>1.02</td>
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<tr>
<td>Vitamin D</td>
<td>1.00</td>
<td>0.82</td>
<td>1.22</td>
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<tr>
<td>Vitamin D+Calcium</td>
<td>1.01</td>
<td>0.82</td>
<td>1.20</td>
<td>0.93</td>
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#### Safety of Long-term Anti-resorptive Treatment

<table>
<thead>
<tr>
<th>Zoledronic Acid (HORIZON ext)</th>
<th>RIS (n=135)</th>
<th>Placebo (n=130)</th>
<th>Odds ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>P-Value</th>
<th>Odds ratio and 95% CI Lower</th>
<th>Upper</th>
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</thead>
<tbody>
<tr>
<td>Any serious AE</td>
<td>24.4%</td>
<td>30.0%</td>
<td>0.78</td>
<td>0.66</td>
<td>0.92</td>
<td>0.00</td>
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#### Denosumab (FREEDOM & Exp) 5 years

<table>
<thead>
<tr>
<th>FREEDOM</th>
<th>Vasectomy Fracture</th>
<th>Vertebral Fracture</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 1-3</td>
<td>Fracture (n=3880)</td>
<td>Fracture (n=3880)</td>
<td>0.09</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>10.4</td>
<td>10.2</td>
<td>10.7</td>
</tr>
<tr>
<td>Discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=130)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serious AEs</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=135)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Questions


*Includes atrial fibrillation, antiarrhythmic block first degree, bundle branch block left, bundle branch block right, arrhythmias, atrioventricular extrasystoles, conduction disturbances, and ventricular extrasystoles.*
HOW ARE WE DOING?
CONTEMPORARY CHALLENGES IN OSTEOPOROSIS

Clifford J. Rosen, MD
How Are We Doing?

Contemporary Challenges (and Crisis ?)”

Clifford J Rosen MD
rosenc@mmc.org

Conflicts of Interest

• Associate Editor of New England Journal of Medicine
• Editor of UpToDate-
• Board of Reviewing Editors- eLife
• Alexion Pharmaceuticals: Partial Post Doctoral funding

Outline

• The ‘perfect storm’: osteoporosis medicine
• State of the Treatment:
• Drugs for Osteoporosis- Why and Why Not?
• Vitamin D testing and osteoporosis management
• Challenges

The Perfect Storm - Crises in Osteoporosis Pharmacotherapy

The Number of Women Tested for BMD Has Declined

The American Journal of Medicine: Clinical Research Study

Trends and Disparities in Osteoporosis Screening Among Women in the United States, 2008–2014

Katherine M. Stiegler, PhD, MPH,1* Pamela S. Harris, MSAP
1AMF Public Policy Institute, Washington, DC; “American Federation of Teachers, Washington, DC."

CLINICAL RESEARCH STUDY

The American Journal of Medicine

Trends and Disparities in Osteoporosis Screening Among Women in the United States, 2008–2014

Katherine M. Stiegler, PhD, MPH,1* Pamela S. Harris, MSAP
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Figure 3 Trends in osteoporosis screening by age among women enrolled in commercial or Medicare Advantage plans, 2008–2014.
Post Screening: Osteoporosis Management 2017

Patient days of therapy (PDOT) have declined

>50% since 2008 in the U.S.¹
- 60% of women have taken themselves off therapy (40% stopped after Dr’s recommendation)²
- 25% of women cite “negative news” around OP meds as the number one reason (20% cite “fear/concern of SEs”; 30% cite “concern of long-term safety”)³

The impact is starting to be felt:
- Decade-long trend of declining hip Fx in elderly women is leveling off ²
- Patients who stop Tx (> 1 year) have a higher incidence of Fx⁴

MEDicare data.

- The Media

WELL WOMAN

New Cautions About Long-Term Use of Bone Drugs

By TARA PARKER-POPE  MAY 9, 2012 6:32 PM  May 9, 2012 6:32 pm

An X-ray shows a fracture in the femur of a woman 60-69 years old.

In an unusual move that may prompt millions of women to rethink their use of popular bone-building drugs, the Food and Drug Administration published an analysis that suggested caution about long-term use of the drugs, but fell short of issuing specific recommendations.

The F.D.A. warning, published in The New England Journal of Medicine online on Wednesday, was prompted by a growing debate over how long women should continue using the drugs, known as bisphosphonates, which are sold as generic versions of brands like Fosamax and Boniva, as well as Novartis's Reclast.

Typical Morphologic Characteristics of Atypical Fractures from Case Report

A. Transverse

C. Cortical thickening

B. Cortical beaking

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from indirect trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features: A. Fracture pattern pictured with an arrow measuring 30 degrees to highlight transverse fracture. B. The arrow pointing out the un cortical beak. C. Hypertrophied cortices outlined.

Neviaser et al J. Ortho trauma 2008
Media Reports and the Interpretations

- 99% of stories are focused on the importance of holistic lifestyle changes for OP fracture prevention (exercise, nutrition, supplements)
- 6% of articles discuss consequences of Fx (of >250 stories, <20 characterize the impact of a fracture on a person’s life)
- Mainstream media drives the conversation. After first reports (2002-3) in scientific literature of potentially serious side-effects associated with bisphosphonates were published, no change in internet search patterns. However, from 2006-2010, search spikes clearly aligned with negative mainstream media coverage.

Prevalence of Bisphosphonate Use in the US Over the last 2 decades

The Disconnect: Efficacy vs Effectiveness

- We have good if not great drugs that are efficacious- But Are they effective?
- Patients who stop Tx (> 1 year) have a higher incidence of Fx- failure of drug?

Reminders: Osteoporosis Rxs work in trials

Mainstream Media’s Impact on Patient Days of Therapy and Hip Fractures

Adverse Publicity: Effect on Oral Bisphosphonate Use in USA

All Clinical Fractures in Women with Existing Vertebral fractures


Wysowski DK, -Rosenblatt personal communication Greene P. Bone. 2013;57:423-428

Black, et. al, Lancet, 1996
Hip Fractures: Women with Existing Vertebral Fractures

% of women with any clinical fracture

tMonths of Follow-up

Placebo
Alendronate

Relative hazard: 0.49 (0.23, 0.99)

2.2%
1.1%


Risedronate and Fracture Risk

New Vertebral Fractures
New Nonvertebral Fractures*

Incidence (%)
0 4 8 12 16

16.3%
11.3%
8.4%
5.2%

RR = 0.59 (0.43-0.82)
RR = 0.60 (0.39-0.94)

PBO
5 mg

* Osteoporotic fractures only, Harris, et al, JAMA, 1999.

Studies of Long Term Bisphosphonate Use (BMD primary endpoint)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Design</th>
<th>N</th>
<th>Follow-up years</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT Long-Term Extension (FLEX)</td>
<td>Alendronate (5 &amp; 10 mg/day)</td>
<td>1099</td>
<td>5+5=10</td>
<td></td>
</tr>
<tr>
<td>HORIZON-PFT Ext.</td>
<td>Zoledronic acid (5 mg/year)</td>
<td>1233</td>
<td>3+3=6</td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td>Risedronate weekly</td>
<td>164</td>
<td>3+3+3=9</td>
<td>Small, non-randomized, adherent only</td>
</tr>
</tbody>
</table>

Long term effect of bisphosphonates before and after drug holiday

<table>
<thead>
<tr>
<th>Study</th>
<th>Alendronate years</th>
<th>Risedronate years</th>
<th>Zolendronate year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>PL 21% AL 11%</td>
<td>0-3 PL 32% RIS 20%</td>
<td>0-3 PL 20% Z 10%</td>
</tr>
<tr>
<td>5-10</td>
<td>AL/AL 18% AL/PL 17%</td>
<td>4-5 R/R 19% PL 32%</td>
<td>4-6 Z/Z 9% clinical Z/P 12% Z/P 6%</td>
</tr>
<tr>
<td></td>
<td>6-7 R/R 13%</td>
<td>0-9 Z/P 9% clinical Z/P 12% Z/P 6%</td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>15-20</td>
<td>0-9 Z/P 7% morph NS Z/P 4% NS</td>
<td></td>
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</table>

Denosumab Treatment: Vert Fractures

Cummings, NEJM 2009
Baron, unpublished communication

The LOFT TRIAL: Odanacatib vs PBO

- 16,000 subjects enrolled in 3yr trial; 6000+ finished 5 yr extension, PBO vs OD -1.2 billion$
- Spine BMD -2.7, FN BMD -2.7, 46% had vert frx
- OD: 52% reduction in vert frx, 48% reduction in hip fracture, 25% in non-vert frx, 67% reduction in clin vert frx
- BMD increase at year 5 for OD: 10.9% LS, 10.5% Total hip
- But AFF present in 0.3% of OD and only 0.1% for PBO; adjudication resulted in AFF in OD (10) and 0 in PBO
- Significantly greater risk of fatal stroke from TIMI adjudication

Unpublished data 2016

Exorbitant price tag leads to exorbitant profits
$7,200 per year to treat 2002
$42,000 per year to treat 2017
Indeed, the future looks bright for Forteo. As predicted by Pharmacor’s June 2009 osteoporosis report, by 2018 Forteo sales may reach close to the $2 billion mark.
NIH Funding and New Studies

- Single center investigator initiated studies are becoming much rarer
  - NIH
  - Industry
- NIH funding for multi-center NIH trials on osteoporosis therapy- almost non-existent
- NIH support for young clinical investigators is marginally limping along
- NIH funding is in huge jeopardy
- NIAMS Clinical Trials Review Panel: 7 years in existence, very few osteoporosis submitted grants;
  - Now including observational studies

Testing for Vitamin D in Routine Physician Visits 2014: Low Value?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>395,657</td>
<td>45,216</td>
<td>440,873</td>
</tr>
<tr>
<td>% Patients</td>
<td>89.7%</td>
<td>10.3%</td>
<td>100%</td>
</tr>
</tbody>
</table>

10% Patients Seeing a Primary Doctor in Maine Get Vit D levels without indication

| Medicare Paid Amount for Vitamin D Test 2014: | $40.40 |
| $53,879 |
| $2,176,712 |
Summary and Challenges

- Osteoporosis medicine is in a crisis mode
- Few want to prescribe less want to stay on drug, yet the drugs work
- Are we performing low value testing rather than high value
- True prevalence rates are needed; closer attention to informed decision making with patients
- Physician education!!!!
WHERE ARE WE GOING?
HOW NEW DRUGS AND GENETICS WILL IMPACT MANAGEMENT

João Lindolfo Borges, MD
Where Are We Going? How genetics and new drugs will impact management
Joao Lindolfo C Borges

Disclosure
Clinical trials
Amgen, Radius, Sanofi, Novartis, MSD, Lilly, AZ, Novartis, Abbvie, Jansen, Kowa, Intarcia
Consulting
Shire, Ache
Speaking
Shire, Ache

The search for THE osteoporosis Genes

VDR Gene (12q12-14)

• VD modulates intestinal calcium absorption, osteoclastic and osteoblastic activities, PTH production.
• VDR mediates the biological actions of 1,25(OH)2D3.
• Mutations in VDR gene cause rickets, low bone mass, hypocalcemia and hyperparathyroidism


ER-α Gene (6q25)

• ER-α mediates the physiologic effects of the estrogen.
• Estrogen resistance due to a nonsense mutation in ER-α gene causes severe osteoporosis.


COLIA1 Gene (17q21-q22)

• COLIA1 gene encodes the α1(I) protein chain of type I collagen, the most abundant extracellular bone matrix protein.
• Mutations in the coding regions of the COLIA1 gene result in osteogenesis imperfecta.
• COLIA1 knock-out mice has low bone mass and high-risk fractures.

The search for genes linked to osteoporosis

- Genes Emerging for rare monogenic disorders.
- Genes Identified Through Extreme Cases of Osteoporosis.
- Genes Identified Through Genome-Wide Association Studies (GWAS).

Genes Identified Through Genome-Wide Association Studies (GWAS)

- 95 candidate genes
- 30% associated with Wnt signaling pathway

Genetics of osteoporosis

One Size Does Not Fit All

New drugs on the horizon

Search on Clinicaltrials.gov

Results

- 80 studies listed
**Results**

- 80 studies listed

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Comparison of PF708 and Forteo in Osteoporosis Patients</td>
<td>Osteoporosis</td>
<td>Drug: Teriparatide (PF708); Drug: Teriparatide (Forteo)</td>
</tr>
<tr>
<td>The Deferasirox-calcium-vitamin D3 Therapy for Postmenopausal</td>
<td>Postmenopausal</td>
<td>Drug: Deferasirox and calcium-vitamin D3; Drug: Calcium-vitamin D3</td>
</tr>
<tr>
<td>Osteoporosis (PMOP)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**What is in the near future?**

1. Abaloparatide
2. Romosozumab

**Abaloparatide**

- Parathyroid hormone-related peptide (PTHrP) analog (1-34) is a protein with homology to parathyroid hormone (PTH).
  - The peptide selectively binds to the RG conformation of PTH type 1 receptor
  - The hypothesis is that Abalo would have a more pronounced anabolic bone action than teriparatide

**The ACTIVE Trial:**
Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial

**Study Background**

- ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints)¹
  - 18 months of abaloparatide-SC compared with placebo and open-label teriparatide
  - Multicenter, multinational, double-blind, placebo-controlled
  - 2463 postmenopausal women aged 49 to 86 were enrolled
    - With prior radiographic vertebral or recent (< 5 yrs prior) nonvertebral fracture
      - T-score ≤ -2.5 at spine or femoral neck and age ≤ 65
      - T-score ≤ -2.0 if age >65
    - No prior fracture required if age >65 and T-score ≤ -3.0 and > -5.0

**ACTIVE Trial Design**

International, randomized, placebo- and active-controlled trial

ACTIVE: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=821)</th>
<th>Abaloparatide-SC (n=824)</th>
<th>Teriparatide (n=818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.7</td>
<td>68.9</td>
<td>68.8</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79.8</td>
<td>80.5</td>
<td>78.9</td>
</tr>
<tr>
<td>Asian</td>
<td>16.0</td>
<td>15.5</td>
<td>16.7</td>
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<tr>
<td>Black or African American</td>
<td>2.8</td>
<td>3.2</td>
<td>2.9</td>
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<tr>
<td>Other</td>
<td>1.5</td>
<td>0.8</td>
<td>1.5</td>
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<tr>
<td>Baseline prevalent vertebral fracture (%)</td>
<td>22.9</td>
<td>21.5</td>
<td>26.9</td>
</tr>
<tr>
<td>Prior nonvertebral fracture history (%) within 5 years</td>
<td>32.4</td>
<td>30.1</td>
<td>29.3</td>
</tr>
<tr>
<td>Patients with no history of prior fracture, %</td>
<td>37.4</td>
<td>37.0</td>
<td>37.7</td>
</tr>
<tr>
<td>Lumbar spine BMD T-score</td>
<td>-2.9</td>
<td>-2.9</td>
<td>-2.9</td>
</tr>
<tr>
<td>Total hip BMD T-score</td>
<td>-1.9</td>
<td>-1.9</td>
<td>-1.9</td>
</tr>
<tr>
<td>Femoral neck BMD T-score</td>
<td>-2.2</td>
<td>-2.2</td>
<td>-2.1</td>
</tr>
</tbody>
</table>


Serum Biomarkers of Bone Turnover

BMD Changes at Vertebral and Nonvertebral Sites

Risk Reduction of New Vertebral Fractures

Risk Reduction of Nonvertebral Fractures

Risk Reduction of Clinical Fractures

*P < 0.01 vs. placebo; †P < 0.001 abaloparatide vs. teriparatide.
Error bars indicate median interquartile ranges.
Adapted from Miller et al. JAMA. 2016; 316:722-733.

*Includes all ITT patients who had pretreatment and postbaseline evaluable radiologic assessments. †P < 0.001 vs placebo.
Based on cumulative Kaplan-Meier estimates ITT at 19 months.

Risk Reduction of Nonvertebral Fractures

ITT Population N=2463

Proportion of Patients with Nonvertebral Fractures, %

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=821)</th>
<th>Abaloparatide-SC (n=824)</th>
<th>Teriparatide (n=818)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.7% (n=33)</td>
<td>2.7% (n=18)</td>
<td>3.3% (n=24)</td>
</tr>
</tbody>
</table>


Risk Reduction of Clinical Fractures

ITT Population N=2463

Proportion of Patients with Clinical Fractures, %

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=821)</th>
<th>Abaloparatide-SC (n=824)</th>
<th>Teriparatide (n=818)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.3% (n=95)</td>
<td>4.9% (n=27)</td>
<td>4.8% (n=35)</td>
</tr>
</tbody>
</table>

Risk Reduction of Major Osteoporotic Fractures

ITT Population N=2463

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients with Major Osteoporotic Fractures, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.2% (n=94)</td>
</tr>
<tr>
<td>Abaloparatide-SC</td>
<td>1.5% (n=110)</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>3.1% (n=33)</td>
</tr>
</tbody>
</table>

Based on cumulative Kaplan-Meier estimates ITT at 19 months.

Time Event to Osteoporosis Fracture

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at risk</th>
<th>Time to Event, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>820</td>
<td>0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24</td>
</tr>
<tr>
<td>Abaloparatide-SC</td>
<td>822</td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>818</td>
<td></td>
</tr>
</tbody>
</table>


Safety and Adverse Events

Safety Population N=2460

<table>
<thead>
<tr>
<th>Treatment</th>
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<th>Abaloparatide-SC n=822</th>
<th>Teriparatide n=818</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatment-emergent adverse events</td>
<td>87.6%</td>
<td>89.4%</td>
<td>88.9%</td>
</tr>
<tr>
<td>Serious treatment-emergent adverse events</td>
<td>11.0%</td>
<td>9.7%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.6%</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>6.1%</td>
<td>9.9%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Discontinuation due to &gt;7.0% BMD decrease</td>
<td>6.5%</td>
<td>0.5%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Hypercalcemia (prespecified)</td>
<td>0.4%</td>
<td>3.4%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Adverse events of special interest</td>
<td>Orthostatic hypotension</td>
<td>16.4%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>3.5%</td>
<td>2.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Faint</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>0.5%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

*Serum albumin-corrected calcium value ≥10.7 mg/dL at any time point, prespecified safety endpoint.
†P = 0.006 abaloparatide-SC vs teriparatide; ‡P < 0.001 vs placebo.

Summary

• In postmenopausal women with osteoporosis, 18 months of subcutaneous abaloparatide compared with placebo significantly:
  • Increased BMD at the lumbar spine, total hip, and femoral neck
  • Reduced the risk of vertebral and nonvertebral fractures
  • Reduced the risk of clinical and major osteoporotic fractures (exploratory endpoints)
• Abaloparatide-SC had an acceptable safety profile
  • No differences were seen between the placebo, abaloparatide and teriparatide groups in adverse events, serious adverse events, or deaths
  • The incidence of hypercalcemia was higher with abaloparatide-SC compared to placebo (3.0% vs 0.1%). A lower incidence of hypercalcemia was observed with abaloparatide-SC compared with teriparatide (3.6% vs 6.0%)
Summary II

• The early increase in P1NP and less prominent increase in s-CTX support the idea that abaloparatide might have an enhanced net anabolic effect compared to teriparatide.

Eighteen Months of Treatment with Subcutaneous Abaloparatide Followed by 6 Months of Treatment With Alendronate in Postmenopausal Women With Osteoporosis: Results of the ACTIVExtend Trial

Felicia Cosman, Paul D Miller, Gregory C Williams, Gary Hattersley, Ming-yi Hu, Ivo Valter, Lorrae A Fitzgerald, Iente, Just Rits, Claus Christansen, John P Bilezikian, and Dennis Black


**ACTIVEExtend Study Objectives**

- **Primary Endpoint:**
  - Percentage of participants who sustained 1 or more new morphometric vertebral fractures between ACTIVE baseline and 6 months after starting alendronate in the Abaloparatide-SC/Alendronate group vs the Placebo/Alendronate group
  - Percentage of patients who sustained 1 or more new morphometric vertebral fractures between baseline of ACTIVExtend and 6 months into extension study is an exploratory outcome
- **Secondary Endpoints:**
  - Incidence and time to first event for nonvertebral, major osteoporotic, and clinical fractures
  - Percentage change in lumbar spine (LS), total hip (TH), and femoral neck (FN) BMD assessed from the baseline of ACTIVE to 6 months of ACTIVExtend
  - In a subset of participants, changes in serum markers of bone turnover (s-PINP and s-CTX)

**ACTIVE and ACTIVExtend Trial Design**

ACTIVE n=2463

ACTIVExtend n=1139

(againing 92% of patients eligible to enroll)

6-month planned interim analysis

19^*

25^†

43

ACTIVE n=2463

ACTIVExtend n=1139

Placebo (n=821)

Alendronate 70 mg QW (n=558)

Abaloparatide-SC 80 μg daily SC (n=824)

Teriparatide 20 μg daily SC (n=615)

6-month planned interim analysis

19^*

25^†

43

*1-month gap in treatment was allowed for rollover from ACTIVE to ACTIVExtend. Investigators and patients remained blinded to original treatment assignment for 6 months of the extension.

**Time to First Nonvertebral Fractures From ACTIVE Baseline Through 6 Months of ACTIVExtend**

**Time to First Major Osteoporotic Fracture From ACTIVE Baseline Through 6 Months of ACTIVExtend**
**Time to First Incident Clinical From ACTIVE Baseline through 6 Months of ACTIVExtend**

- **Patients with ≥ 1 clinical fractures (%):**
  - Abaloparatide-SC/Alendronate HR=0.55 (95% CI, 0.33-0.92); Logrank p=.02

**Conclusions**

- The sequence of 18 months of abaloparatide followed by 6 months of alendronate improved BMD and decrease fracture risk rapidly throughout the skeleton.
- Sequential abaloparatide followed by alendronate is a treatment option for patients at high risk for osteoporosis-related fractures.

### Transdermal Abaloparatide

- Phase 2 clinical trial of abaloparatide administered via a coated transdermal microarray delivery system in healthy postmenopausal women with osteoporosis.

### Transdermal Abaloparatide and Spine BMD

- Mean Standard Error of the Mean (SEM) Percent Change from Baseline at weeks 12 and 24 in Total Spine BMD:
  - https://www.sec.gov/Archives/edgar/data/1428522/000104746914005588/a2220482zex-99_1.htm#13ZCY11623_4

### Transdermal Abaloparatide and Hip BMD

- Mean Standard Error of the Mean (SEM) Percent Change from Baseline at weeks 12 and 24 in Total Hip BMD:
  - https://www.sec.gov/Archives/edgar/data/1428522/000104746914005588/a2220482zex-99_1.htm#13ZCY11623_4

### Wnt Signaling Pathway

- Sclerostin and DKK1 Inhibit Wnt Signaling
- Antibodies to Sclerostin and DKK1 Stimulate Wnt Signaling

Clinical Studies of Humanized Monoclonal Antibodies to Sclerostin for Osteoporosis

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type</th>
<th>Company</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romosozumab *</td>
<td>IgG2</td>
<td>Amgen/UCB</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Biosozumab</td>
<td>IgG4</td>
<td>Lilly</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>BPS804 **</td>
<td>IgG2</td>
<td>Novartis/Mereo</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

* EVENITY™
** Orphan drug designation for osteogenesis imperfecta granted by FDA and EMA


Romosozumab
Humanized monoclonal antibody to sclerostin

Romo Phase 2 Trial

- Randomized, placebo-controlled, parallel-group study in 419 postmenopausal women with low BMD (T-score from -2.0 to -3.5 at LS, TH, or FN)
- Subjects received various doses SC Romo Q1M or Q3M, SC PBO, or open-label ALN or TPT
- Primary endpoint: percentage change from baseline in LS BMD at 12 months

Randomization Schema

Romo Increased BMD (Superior to ALN and TPT)
Romo Increased P1NP and Decreased CTX


Romo Phase 2 Conclusions

- Romo Q1M and Q3M resulted in a rapid large increase in BMD, transient increase in P1NP, and sustained decrease in CTX.
- BMD increase with Romo was greater than with PBO, ALN, and TPT.


Romo Phase 2 Conclusions

- Romo Q1M and Q3M resulted in a rapid large increase in BMD, transient increase in P1NP, and sustained decrease in CTX.
- BMD increase with Romo was greater than with PBO, ALN, and TPT.


Romo Phase 2 Extension: 3 Years

- 24 Months of Romo or PBO – Transition to Dnab or PBO

McClung MR et al. ASBMR 2014.

Romo Phase 2 Extension: BMD Year 3

- 24 Months of Romo or PBO – Transition to Dnab or PBO

McClung MR et al. ASBMR 2014.

FRAME Study Design

- Fracture Study in Postmenopausal Women with Osteoporosis (FRAME)
- Phase 3 RCT in 7180 women with PMO randomized to Romeo 210 mg SC Q1M or PBO for 1 year followed by open label Dnab 60 mg Q6M in both groups for 1 year.
- Co-primary end points: cumulative incidences of new VF at 12 months and 24 months.

**FRAME Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 3,591)</th>
<th>Romosozumab (N = 3,589)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>70.8 (6.9)</td>
<td>70.9 (7.0)</td>
</tr>
<tr>
<td>BMD T-score, mean (SD)</td>
<td>–2.7 (1.0)</td>
<td>–2.7 (1.0)</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>–2.5 (0.5)</td>
<td>–2.5 (0.5)</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, %</td>
<td>18.0%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Number of prevalent vertebral fractures, %</td>
<td>13.8%</td>
<td>14.1%</td>
</tr>
<tr>
<td>1</td>
<td>4.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Most severe vertebral fracture grade, %</td>
<td>10.5%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Mild</td>
<td>7.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Moderate</td>
<td>21.8%</td>
<td>21.7%</td>
</tr>
<tr>
<td>Prior nonvertebral fracture on or after age 45, %</td>
<td>10.5%</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

**FRAME: LS and TH BMD Through Month 12**

![Graphs showing BMD changes over time](Cosman F et al. ASBMR Oral Presentation. 2016.)

**FRAME: % Change in Serum P1NP and CTX with Romo and PBO Through Month 12**

![Graph showing % change in serum P1NP and CTX](Cosman F et al. ASBMR Oral Presentation. 2016.)

**FRAME: New VFs Through Month 12 (Co-Primary Endpoint)**

![Graph showing new vertebral fractures](Cosman F et al. ASBMR Oral Presentation. 2016.)

**FRAME: Time to First Clinical Fracture Through Month 12**

![Graph showing time to first clinical fracture](Cosman F et al. ASBMR Oral Presentation. 2016.)

**FRAME: Other Key Fracture Endpoints Through Month 12**

![Table showing subject incidence](Cosman F et al. ASBMR Oral Presentation. 2016.)
**FRAME: Lumbar Spine and Total Hip BMD Through Month 24**

**FRAME: New Vertebral Fracture Through Month 24 (Co-Primary Endpoint)**

**FRAME: Time to First Clinical and Nonvertebral Fracture Through Month 24**

**FRAME: Romosozumab Safety Overview**

**FRAME Conclusions**

- **Romo for 12 months compared with PBO (RRR)**
  - New vertebral fracture: 73% (p < 0.001)
  - Clinical fracture: 36% (p = 0.008)
  - Nonvertebral fracture: 25% (p = 0.096)
- Over 24 months, Romo-to-Dmab compared with PBO-to-Dmab (RRR)
  - New vertebral fracture: 75% (p < 0.001)
  - Clinical fracture: 33% (nominal p = 0.002; adjusted p = 0.096)
  - Nonvertebral fracture: 25% (nominal p = 0.029; adjusted p = 0.057)
- **Safety**
  - Injection site reactions: Romo 5.2%, PBO 2.9%

---

Phase 3 placebo-controlled study evaluating the efficacy and safety of romosozumab in treating men with osteoporosis (BRIDGE)
Summary

• Sclerostin is an inhibitor of Wnt signaling that diminishes osteoblastic bone formation.
• Anti-sclerostin therapy with romosozumab increases osteoblastic bone formation, increases BMD, and decrease fracture risk.
• Anti-sclerostin therapy is a potential strategy for managing osteoporosis and other skeletal disorders.

Final Conclusion

• Genetics studies will allow the design of "custom-made" drugs.
• There is light at the end of the tunnel!
• Two promising drugs were developed.
SUMMARY

- From large epidemiological studies and sophisticated high resolution imaging studies, we now have a very good knowledge about what osteoporosis is.
- We have excellent clinical tools for diagnosing osteoporosis and assessing fracture risk.
- The combination of non-skeletal approaches and the appropriate use of any of several pharmacological agents substantially reduces the risk of important clinical fractures and, in some cases, mortality.
- We know how and have both tools and guidelines to select the right patients for treatment to optimize the benefit risk ratio.

SUMMARY

- The collective focus of our education and clinical research should be on translating the advances that clinical research has provided us into practical, meaningful approaches that will be accepted and used in daily practice of primary care colleagues as well as specialists.
  - help primary care colleagues feel comfortable approaching the question of osteoporosis.
  - clearer guidelines.
  - secondary prevention services to optimize treatment benefit.
  - help patients appreciate the relative benefits vs risks of osteoporosis treatments.
  - help payers recognize the effectiveness and cost effectiveness of our current strategies when used appropriately.

SUMMARY

- Novel, exciting drugs and new tools for evaluation will soon be available.
- These new drugs and tools will not solve the “crisis” in osteoporosis.

SUMMARY

- Despite these important advances over the past 25 years,
  - most patients at risk for osteoporosis are not being screened.
  - most patients at high risk of fracture are not being treated.
  - patients who do begin therapy stop about a short time.
- Osteoporosis is not viewed as important clinical issue.
- The effectiveness of our treatments is not appreciated.
- The concern over rare safety issues is not considered in the context of the benefit provided.
- Confusion exists about the appropriate strategies for long-term management.

Osteoporosis Treatment - 2017
Action Plan

- Osteoporosis community MUST
  - Re-engage the medical community about the importance, urgency and effectiveness 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 Treatment - 2017

Summary

- 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.

Photo courtesy of Dr McClung