Conflict of Interest
Jonathan D. Adachi

Consultant/Speaker
• Actavis
• Amgen
• Eli Lilly
• Merck

Clinical Trials
• Amgen
• Eli Lilly
• Merck
• Novartis

Stock
• None to declare
Objectives

- Understand the benefits and risks of OP therapy
- Determine who should be given a drug holiday or treatment interruption
- Define “Treat to target” versus standard goal therapy
How do you identify patients at high risk of fracturing?
Who is at high fracture risk?

• Those with a fracture
  – Incident
  – Prevalent

• Those with a low t-score
  – -3.0 lumbar spine
  – -2.5 femoral neck
Fracture Risk Prediction: Importance of age, BMD and Spine Fracture

Krege JH et al. Bonekey 2013
What is the data regarding treatment efficacy?
Alendronate reduces vertebral, Non-vertebral, and Hip Fractures

Cochrane meta-analysis: Patient incidence of fracture and weighted relative risk for fractures after treatment with 10 mg alendronate

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Percentage of Patients With Fractures (%)</th>
<th>n (Participants)</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral Fracture</td>
<td>8.5%</td>
<td>7156</td>
<td>0.55 (0.45–0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-vertebral Fracture</td>
<td>5.6%</td>
<td>9481</td>
<td>0.84 (0.74–0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>4.0%</td>
<td>9807</td>
<td>0.61 (0.40–0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Risedronate Reduces Vertebral, Non-vertebral, and Hip Fractures

Cochrane meta-analysis: Patients’ incidence of fracture and weighted relative risk for fractures after treatment with 5 mg risedronate

Zoledronic Acid Reduces Vertebral, Non-vertebral, and Hip Fractures

RCT: HORIZON 3 year Pivotal Fracture Trial in PMO women

**Incidence rate**

**3-year cumulative event rates based on Kaplan-Meier estimates.**

Denosumab Reduces Vertebral, Non-vertebral, and Hip Fractures in Women With PMO

RCT: FREEDOM 3 year Pivotal Fracture Trial in PMO women

- **Vertebral Fracture**:
  - Placebo: 7.2% (n = 264/3691)
  - Denosumab: 2.3% (n = 86/3702)
  - Reduced Risk: 68%
  - RR 0.32 (95% CI, 0.26–0.41) p<0.001 vs placebo

- **Non-vertebral Fracture**:
  - Placebo: 8.0% (293/3906)
  - Denosumab: 6.5% (238/3902)
  - Reduced Risk: 20%
  - RR 0.80 (95% CI, 0.67–0.95) p=0.01 vs placebo

- **Hip Fracture**:
  - Placebo: 1.2% (43/3906)
  - Denosumab: 0.7% (26/3902)
  - Reduced Risk: 40%
  - RR 0.60 (95% CI, 0.37–0.97) p=0.04 vs placebo

*Crude incidence
†Kaplan-Meier estimate of incidence

Hormone Therapy Prevents Vertebral, Non-vertebral, and Hip Fractures in Postmenopausal Women

RCT: WHI study with postmenopausal women treated with hormone therapy for 5.2 years

- Clinical Vertebral Fracture: HR 0.66 (95% CI, 0.44–0.98)
- Non-vertebral Fracture: HR 0.77 (95% CI, 0.69–0.86)
- Hip Fracture: HR 0.66 (95% CI, 0.45–0.98)

CI = confidence interval, HR = hazard ratio, RRR = relative risk reduction

HT = daily combined estrogen and progestin

Raloxifene Reduces Vertebral Fractures

RCT: MORE Study in postmenopausal women for 3 years

- **No Pre-existing Vertebral Fractures**
  - Low-risk Population
    - Placebo: 4.5% (68/1522)
    - Raloxifene 60 mg/day: 2.3% (35/1490)
    - RRR 50%
- **Pre-existing Vertebral Fractures**
  - High-risk Population
    - Placebo: 21.2% (163/770)
    - Raloxifene 60 mg/day: 14.7% (113/769)
    - RRR 30%

Relative risk of non-vertebral, including hip, fractures was not significant (RR 0.9, 95% CI, 0.8–1.1)

Meta-analysis of 7 Raloxifene clinical trials reported fracture reductions results consistent with results from the MORE study; overall odds ratio of 0.60

2. Seeman E, et al. *Osteoporos Int.* 2006;17:313
Teriparatide Reduces Risk of Vertebral and Non-vertebral Fractures in Women With PMO

RCT: Effect of daily PTH for 18 months on vertebral and non-vertebral fractures

- *Includes hip fracture
- RR 0.35 (95% CI, 0.22–0.55)
  - p<0.001 vs placebo
- RR 0.47 (95% CI, 0.25–0.88)
  - p=0.02 vs placebo

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

Based on GRADE A evidence as assessed in the Osteoporosis Canada 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada\(^1\)

<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></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vertebral</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Hip</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Non-Vertebral</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*For postmenopausal women, ✓ indicates first line therapies and Grade A recommendation. **Hormone therapy (estrogen) can be used as first-line therapy in women with menopausal symptoms.
In Clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

Keypoint

- Numerous therapies with fracture efficacy
- Parenteral therapies seem to have greater efficacy
  - Teriparatide
  - Denosumab
  - Zoledronic acid
Treatment Failure?
Treatment Failure

- 60 yr old women with FN-BMD of -3.5
- Treated with Actonel with a loss in BMD after 2 years of treatment
- How do you explain the bone loss?
Adherence

• On further questioning she admits to sometimes forgetting to take her medication on an empty stomach
• Stomach upset that she had resolved with taking it with a meal
Actonel DR Formulation

Bypasses esophagus and stomach and delays release until the small intestine, where the pH >5.5

Intended to reduce the binding of risedronate with dietary calcium

Mean Percent Change from Baseline in Lumbar Spine BMD

Percent change from baseline (intent to treat [ITT])
least square means (+/- standard error [SE])

At all time points, increases in BMD were statistically significant vs. baseline

* In the per protocol analysis at Week 104, 35 mg DR was associated with statistically greater increase than Actonel® 5 mg daily; 95% CI = -1.811; -0.220
† At endpoint (end of study), 35 mg DR was associated with statistically greater increase than Actonel® 5 mg daily; 95% CI = -1.762; -0.355
Ŧ including Last Observation Carried Forward (LOCF) patients

35 mg DR before breakfast is not shown

At all time points, increases in BMD were statistically significant compared to baseline.

* At Week 104, 35 mg DR was associated with statistically greater increase than Actonel® 5 mg daily; 95% CI = -1.179; -0.110

† At endpoint (end of study), 35 mg DR was associated with statistically greater increase than Actonel® 5 mg daily; 95% CI = -1.030; -0.014

Ŧ Including Last Observation Carried Forward (LOCF) patients

35 mg DR before breakfast is not shown

Keypoint

- Adherence remains our greatest challenge with only between 20-40 % adherent to therapy at 1 year
- Oral bisphosphonates need to be taken on an empty stomach, half an hour prior to food
Generic bisphosphonates?
Case Report - NY

- 62 year female with OP, LS T-score -3.0, commenced on Fosamax 70 mg weekly in May 2002.
- Followed on annual basis, tolerated her medication well. LS T-score of -2.61 in Sept 2004.
- Aug 2005, switched from Fosamax to apo-ALN, told this was Fosamax.
- Jan 2006, gave a history of severe stomach upset, 10-15 pounds of weight loss.
• Had normal upper GI endoscopy, colonoscopy and small bowel follow through MRI and CT abdomen negative.
• Didn’t link her GI problems to apo-ALN as she was told this was Fosamax and had never had any problems.
• D/C’d apo-ALN, problems resolved. Rechallenged recurred.
• Started on novo-ALN.
• With novo-ALN had problems with stomach pain, that persisted even with a PPI.
• Switched to Actonel 35 mg without difficulty.
Generic ALN, AE’s and Efficacy

Grima D et al. BMC Musculoskeletal Disorders 2010, 11:68
<table>
<thead>
<tr>
<th>Tablet and dose</th>
<th>Lot number</th>
<th>Average disintegration time in seconds (SD)</th>
<th>Number of tablets tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novo-Alendronate 70mg</td>
<td>A34021</td>
<td>12.7 (1.09)</td>
<td>18</td>
</tr>
<tr>
<td>Apo-Alendronate 70mg</td>
<td>(L) JD 7416</td>
<td>25.7 (5.59)</td>
<td>20</td>
</tr>
<tr>
<td>Actonel 35mg</td>
<td>425314</td>
<td>101.2 (20.56)</td>
<td>20</td>
</tr>
<tr>
<td>Fosavance 70mg</td>
<td>Y 1382</td>
<td>378.0 (60.5)</td>
<td>20</td>
</tr>
<tr>
<td>Fosamax 70mg</td>
<td>Y1277 &amp; Y1498</td>
<td>147.4 (50.47)</td>
<td>20</td>
</tr>
</tbody>
</table>

Olszynski WP et al. J Bone Miner Res 2010;25;S125
Esophagitis due to bisphosphonates.
Severe, extensive hemorrhagic ulcerations and inflammatory exudates, which were still present in the distal esophagus on the ninth day of hospitalization.

Panel B shows concentric esophageal-wall thickening (arrow) suggestive of transmural inflammation.
The irregularity of the mucosa is consistent with esophagitis (black arrows). The distal esophagus is strictured (white arrow).
Bisphosphonate Associated Contact Stomatitis

Rubegni NEJM 2006;355:22 e25
Keypoint

• Generic bisphosphonates may lead to increased GI side effects
• This may be related to rapid disintegration of the generics
Atypical Femoral Fracture

- 65 yr old female, 8 yrs of BP therapy
- Complaining of bilateral thigh pain
- Constant dull ache
What would you do next?
Incomplete Atypical Femoral Fracture
Bilateral incomplete AFFs on plain film and bone scan
Incomplete AFF with focal lateral cortical thickening on plain film CT demonstrates a focal lucent cleft / fracture line
Complete AFF treated with lateral compression plate with subsequent failure and ultimate Gamma nail.
Subtle incomplete AFF’s on plain film (A and B) areas of increased uptake on bone scan (C) and focal lucent cleft identified with CT (D)
Bilateral incomplete AFFs on MRI showing focal cortical thickening and periosteal/surface edema
Atypical Fractures of the Femoral Diaphysis in Postmenopausal Women Taking Alendronate

For every 100 or so reduction in typical hip fractures, there was an increase of one subtrochanteric fragility fracture.

Wang et al. JBMR 2011;26:553-560
Effect of Teriparatide on Fracture Healing in Patients with Non-Displaced Incomplete Atypical Femur Fractures

Angela Cheung, UHN
TPTD and Fracture Healing in Patients with AFF

- 13 pts with incomplete AFF treated with TPTD.
- All PMP women, mean age 68.6 (57.5-81.0) yrs
  - 9 Caucasians,
  - 2 Southeast Asians,
  - 2 South Asian
- 8/13 had previous complete AFF.
- Average duration of BP 12.6 yrs (3.0-28.0).
- Mean BMD T-scores at diagnosis of AFF were:
  - LS -1.87
  - TH -1.14
  - FN -1.85
TPTD and Fracture Healing in Patients with AFF

• TPTD therapy mean 13.4 months (1.4 to 20.2).
• 3 pts prophylactic surgical repair (2 for progression of fracture and 1 for preference).
• 10 patients:
  – 5 radiographic improvement,
  – 4 had no change and
  – 1 progressed despite TPTD.
• Unclear whether TPTD improves fracture healing in patients with incomplete non-displaced AFFs.
“Importantly, the results of our study should not deter clinicians and patients from using bisphosphonates in appropriate patients.”

Park-Wyllie et al. JAMA. 2011;305(8):783-789
• Atypical femoral fractures while devastating, are rare
• Often present bilaterally
• Tend to occur in Asians, with longer duration of use and relatively good BMD’s
• Teriparatide might be of benefit
Osteonecrosis of the Jaws Associated With the Use of Bisphosphonates

**FIGURE 1.** Exposed necrotic maxillary bone in a patient receiving zolendronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr. Jay Neugarten, New Hyde Park, NY.)
Are there any dental benefits to bisphosphonate therapy?
Early Dental Implant Stability Correlates With Bone Turnover in BP Exposed Patients

Objective:
To assess the relationship between dental implant stability and bone turnover in patients with or without BP exposure
Early Dental Implant Stability Correlates With Bone Turnover in BP Exposed Patients

Study Design & Methods
Descriptive “best practice” prospective cohort study
Participants were asked to discontinue BPs around dental implant placement

Investigations
• Implant stability was assessed at surgery and 8 weeks later by resonance frequency analysis (RFA ISQ value), with values > 50 considered adequate
• sCTX measurement before treatment and at 1 and 8 weeks post-implant surgery
Results

• RFA ISQ demonstrated association between lower bone turnover and short-term implant stability in the “past/current” BP user group
• Studies with a larger population and longer follow-up are required to determine improvement in implant stability with antiresorptive medicines
Early Dental Implant Stability Correlates With Bone Turnover in BP Exposed Patients

Clinical implications

- In the era of ONJ, warnings have been raised in practicing dental procedures in subjects receiving BP’s.
- Current or previous use of BP’s is not detrimental for the stability of dental implant procedures.
- The greater the suppression bone resorption with BP’s, greater the short-term implant stability.
- BP treatment may became a therapeutic strategy to improve dental implant stability in patients at risk of poor surgical outcomes if confirmed in long-term studies.

BP: bisphosphonate, RFA ISQ: reference frequency analysis implant stability quotient.
Brown et al Can Fam Phys 2014;60:324-333

Risks of major osteoporotic fracture and other rare events

- Major osteoporotic fracture in high-risk women: 3100
- Major osteoporotic fracture in moderate-risk women: 1600
- Major osteoporotic fracture in low-risk women: 650
- Fatal MVA: 8.4
- Death by murder: 1.62
- Bis-AFF (2 y): 2
- Bis-AFF (8 y): 78
- Bis-ON*: 1.03

INCIDENCE PER 100,000 PERSON-YEARS
Keypoint

• Benefits of therapy even in relatively low risk individuals outweigh the risks of rare events like ONJ and atypical fractures
Should we suggest a drug holiday after several years treatment?
Drug Holiday

• Who should be considered for a drug holiday?
• Who should not be considered for a drug holiday?
• How long should the drug holiday last?
Effects of Continuing or Stopping Alendronate After 5 Years of Treatment The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial


JAMA. 2006;296:2927-2938
Effects of Continuing or Stopping Alendronate After 5 Years of Treatment The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

Figure 4. Survival Curve for Time to First Nonvertebral Fracture and Time to First Clinical Vertebral Fracture

- Nonvertebral Fractures
  - Alendronate (Fleeced)
  - Placebo

- Clinical Vertebral Fractures
  - RR, 0.45 (95% CI, 0.24-0.86)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>437</td>
<td>632</td>
</tr>
<tr>
<td>12</td>
<td>429</td>
<td>642</td>
</tr>
<tr>
<td>24</td>
<td>410</td>
<td>649</td>
</tr>
<tr>
<td>36</td>
<td>396</td>
<td>688</td>
</tr>
<tr>
<td>48</td>
<td>373</td>
<td>696</td>
</tr>
<tr>
<td>60</td>
<td>358</td>
<td>693</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; RR, relative risk.
Between-treatment Comparison of the Proportion of Patients with Morphometric Vertebral Fractures Between Year 3 and Year 6 (ITT)

- **P = .03, **P = .03, relative risk reduction vs Z3P3; n = the number of patients in the analysis population with x-rays at Year 3 and Year 6
- †ITT = intention to treat, Z3P3 = ZOL for 3 years and placebo for 3 years, Z6 = ZOL for 6 years
Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday


Curtis et al. Osteoporos Int 2008;19:1613-1620
Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday

Results

- 9,063 women
- Hip fracture incidence
  - discontinued 8.43 versus
  - continued 4.67 per 1000 person years (p=0.016).
Who should *not* be considered for a BP drug holiday

- osteoporotic femoral neck BMD at discontinuation (ie, T-score ≤ -2.5),
- a history of fragility fracture, or prevalent vertebral fracture associated with increased risk of fracture
- high-risk patients with osteoporotic BMD or history of fragility fracture (including prevalent vertebral fracture) *should not* be candidates for BP drug holiday

Brown et al Can Fam Phys 2014;60:324-333
When and for whom should BP holidays be considered?

<table>
<thead>
<tr>
<th>FRACTURE RISK</th>
<th>CLINICAL PROFILE AND TESTS</th>
<th>IS A BISPHOSPHONATE HOLIDAY APPROPRIATE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt; 10% 10-y risk)</td>
<td>• No important clinical risk factors for fracture</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• Assess femoral neck BMD</td>
<td>• At low future fracture risk, should be withdrawn from therapy</td>
</tr>
<tr>
<td></td>
<td>• Request lateral spine x-ray scan to investigate for any subclinical vertebral fractures</td>
<td>• Monitor at extended intervals (3-5 y)</td>
</tr>
<tr>
<td>Moderate (10%–20% 10-y risk)</td>
<td>• Assess clinical risk factors for fracture</td>
<td>• Maybe</td>
</tr>
<tr>
<td></td>
<td>• Assess femoral neck BMD</td>
<td>• If vertebral fractures are found, stratify patient as high risk and continue bisphosphonate therapy</td>
</tr>
<tr>
<td></td>
<td>• Request lateral spine x-ray scan to investigate for any subclinical vertebral fractures</td>
<td>• If there is no previous history of fragility fracture, a drug holiday can be considered if femoral neck BMD T-score is &gt; -2.5 and there are no other important clinical risk factors</td>
</tr>
</tbody>
</table>

Brown et al Can Fam Phys 2014;60:324-333
Keypoint

• High risk individuals should not be given a drug holiday
• Low risk individuals or those should probably be given a drug holiday
Long-term Effects of Prolia
Long-term effects of Prolia

- 70 yr old women with osteoporosis and prior vertebral fractures
- Treated ALN for 3 yrs, switched to Prolia 3 years ago due to further fractures
- Excellent response to Prolia with ↑ in BMD
- She has heard about side effects, wants to know about the long-term effects of Prolia
- What go you tell her?
The Effect of Denosumab on Fracture Risks at 36 Months

The Percent Change in Bone Mineral Density Over 36 Months With Denosumab

Bone Mineral Density Substudy  n = 441

Lumbar Spine

Mean Percent Change in BMD

Study Months

Total Hip

Mean Percent Change in BMD

Study Months

Denosumab 60 mg Q6M

Placebo

Intent-to-treat, last observation carried forward analysis

*P < 0.001 for denosumab vs. Placebo

FREEDOM Extension Study Design
International, multicenter, open-label, single-arm study

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.
Continued DMAb Treatment in the FREEDOM Extension for Up to 7 Years

• Maintained reduction in bone turnover
• Was associated with a low incidence of nonvertebral and clinical vertebral fractures
• Remained well tolerated

Objective

• To evaluate if continued DMAb treatment in year 4 and beyond is associated with a further reduction in nonvertebral fracture incidence compared with the first 3 years of treatment.
Methods

Nonvertebral fracture rates and rate ratios were calculated in subjects who enrolled into the FREEDOM extension

Rates per 100 subject-years and rate ratios using GEE Poisson regression were adjusted for age, total hip BMD T-score, weight, and history of nonvertebral fracture at the beginning of DMAb treatment. Treatment group was included in the model for the combined (long-term + cross-over groups) analysis only.
Yearly Nonvertebral Fracture Incidence With DMAb Treatment for Up to 7 Years

Long-term DMAb Treatment

Cross-over DMAb Treatment

n = number of subjects who have \( \geq 1 \) nonvertebral fracture. Percentages for nonvertebral fractures are Kaplan-Meier estimates.
Nonvertebral Fracture Rate Ratios: Long-term DMAb Subjects

Rate Ratio (95% CI) = 0.74 (0.59–0.95)  
P = 0.016

Fracture Rate per 100 Subject-years (95% CI)

First 3 Years: 1.98
4th Year: 1.43
Years 4-7: 1.45

Fractures n = 140
DMAb Treatment
33
119

N = 2343

N = number of subjects who did not miss >1 dose of DMAb during FREEDOM and enrolled into the extension.
Nonvertebral Fracture Rate Ratios: Cross-over DMAb Subjects

Fracture Rate per 100 Subject-years (95% CI)

- **Rate Ratio (95% CI) = 0.48 (0.29–0.79)**
- **P = 0.004**

**Fractures n = 114**

- **First 3 Years: 2.20**
- **4th Year: 1.03**

**N = 1730**

*N = number of subjects who did not miss >1 dose of DMAb during the first 3 years in the extension.*
Summary

• When DMAb was continued beyond 3 years of therapy, the nonvertebral fracture rate during year 4 was significantly further decreased compared with the first 3 years of treatment.

• When DMAb was continued for up to 7 years, the nonvertebral fracture rate remained significantly decreased compared with the first 3 years of treatment.
What is the safety data available for patients on 6 years of denosumab therapy?

Exposure-adjusted Subject Incidence of AEs

<table>
<thead>
<tr>
<th></th>
<th>FREEDOM Study</th>
<th>EXTENSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Years 1-3 N = 3883</td>
<td>Prolia® (denosumab) Years 1-3 N = 3879</td>
</tr>
<tr>
<td>All AEs</td>
<td>156.1 (3614)</td>
<td>154.3 (3598)</td>
</tr>
<tr>
<td>Infections</td>
<td>30.7 (2113)</td>
<td>29.3 (2052)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1.6 (167)</td>
<td>1.8 (187)</td>
</tr>
<tr>
<td>Eczema</td>
<td>0.6 (67)</td>
<td>1.1 (119)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt; 0.1 (3)</td>
<td>0.0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>10.4 (974)</td>
<td>10.6 (1002)</td>
</tr>
<tr>
<td>Infections</td>
<td>1.3 (134)</td>
<td>1.5 (160)</td>
</tr>
<tr>
<td>Cellulitis or erysipelas</td>
<td>&lt; 0.1 (1)</td>
<td>0.1 (12)</td>
</tr>
</tbody>
</table>

Osteonecrosis of the jaw (ONJ) and atypical femoral fracture have been reported.¹ ²

N = number of subjects who received ≥ 1 dose of investigational product. Treatment groups are based on the original randomized treatments received in the Pivotal Phase 3 Fracture Study. Rate = exposure-adjusted subject incidence per 100 subject-years. n = total number of subjects with an AE. AEs coded using MedDRA v13.0. AE = adverse events.

¹ Adapted from Brown JP, et al. Presented at: ACR; November 5-9, 2011; Chicago, Ill.
² Data on file, Amgen.
Hip Fracture

All FREEDOM study participants

FREEDOM study participants aged 75 and older

No. at Risk
Placebo 3906 3799 3672 3538 3430 3311 3221
Denosumab 3902 3796 3676 3566 3477 3397 3311

No. at Risk
Placebo 1236 1196 1133 1082 1024 975 942
Denosumab 1235 1192 1147 1099 1054 1027 987
Change in Cortical Mass Surface Density (mg/cm²)

Change in cortical mass (mg/cm²) surface density over 36 months

Placebo Group

anterior

posterior

$p<0.05$  $p>0.05$

Change in cortical mass (mg/cm²) surface density over 36 months

Denosumab Group

$p<0.05$  $p>0.05$
Change in Cortical Thickness (mm) over 36 months

Change in cortical thickness (mm) over 36 months

$0 < 0.05$  $p > 0.05$

Placebo Group

Denosumab Group
Keypoint

• Ongoing therapy with denosumab results in ongoing treatment benefit.
What about combination therapy?
Combination Therapy

• 75 yr old female:
  – on ALN for 3 years
  – multiple vertebral fractures
  – FN-BMD <-4.0
  – presents with history of recent hip fracture
• Pt. has heard about combination therapy
• What do you recommend?
Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial

ASBMR 2012 Update
DATA Study

1 Year Change in BMD

P<0.0001

P=0.0005

P<0.001

P=0.013

BMD % change

Spine

Total Hip

Femoral Neck

DMAD
TPTD
Both

Tsai et al. Lancet 2013
Combined Dmab and TPTD in PMO: The DATA Study

- Unlike concomitant TPTD and BPs, TPTD and DMAB increased BMD at the hip and spine more than either drug alone.
- DMAB-TPTD co-administration may be an important treatment option in patients at high risk of fracture.

Tsai et al. Lancet 2013
Introduction

- Selective serotonin receptor inhibitors (SSRIs), proton pump inhibitors (PPIs) and glucocorticoids (GCs) are associated with increased fracture risk.
- The complications of GCs are well known, with more recent attention being paid to the commonly used medications, SSRIs and PPIs.
Which therapy or combination of therapies has the greatest risk for fracture?

a) SSRI
b) PPI
c) Glucocorticoids
d) SSRI and glucocorticoids
e) PPI and glucocorticoids
Adjusted Odds Ratios and 95% CIs for Any Fracture in Year 3 or 5, by Drug Therapy

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI (n=568)</td>
<td>1.59 (1.23-2.04)</td>
</tr>
<tr>
<td>GC (n=747)</td>
<td>1.05 (0.90-1.23)</td>
</tr>
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<td>PPI (n=643)</td>
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<tr>
<td>GC, SSRI and PPI (n=502)</td>
<td>1.72 (1.19-2.48)</td>
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Adjusted Odds Ratios and 95% CIs for Hip Fracture in Year 3 or 5, by Drug Therapy

<table>
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<tr>
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<tbody>
<tr>
<td>SSRI (n=50)</td>
<td>0.45 (0.14-1.49)</td>
</tr>
<tr>
<td>GC (n=74)</td>
<td>0.87 (0.53-1.43)</td>
</tr>
<tr>
<td>PPI (n=61)</td>
<td>0.53 (0.26-1.08)</td>
</tr>
<tr>
<td>GC and SSRI (n=54)</td>
<td>1.73 (0.74-4.05)</td>
</tr>
<tr>
<td>GC and PPI (n=63)</td>
<td>1.27 (0.68-2.39)</td>
</tr>
<tr>
<td>SSRI and PPI (n=48)</td>
<td>0.26 (0.04-1.94)</td>
</tr>
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<td>GC, SSRI and PPI (n=52)</td>
<td>1.31 (0.48-3.55)</td>
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</table>
Adjusted Odds Ratios and 95% CIs for Spine Fracture in Year 3 or 5, by Drug Therapy

- SSRI (n=58): 1.99 (0.99-4.03)
- GC (n=91): 1.71 (1.13-2.60)
- PPI (n=68): 1.35 (0.80-2.28)
- GC and SSRI (n=54): 2.53 (1.13-5.68)
- GC and PPI (n=74): 2.93 (1.75-4.89)
- SSRI and PPI (n=51): 2.08 (0.78-5.55)
- GC, SSRI and PPI (n=50): 1.73 (0.58-5.17)
Adjusted Odds Ratios and 95% CIs for Non-Hip, Non-Spine Fracture in Year 3 or 5, by Drug Therapy

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Results
Single medication use

- SSRI use was the only therapy associated with a statistically significant increase in overall and non-hip, non-vertebral fractures and while not statistically significant with spine fractures
- GCs were significantly associated with spine fractures
- PPIs, were not statistically significantly associated with fractures
Results
Combination Medication Use

• Significant increases in spine fractures seen with:
  – SSRIs and GCs
  – GCs and PPIs
  – GCs, PPIs and SSRIs

• Significant non-hip, non-spine fractures seen with:
  – SSRI’s and GCs
  – SSRIs and PPIs
  – PPIs and GCs
  – SSRIs, GCs and PPIs
The calcium controversy
Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial
Subgroup analysis for the risk of cardiovascular disease with calcium supplements

Loretta T Radford, Mark J Bolland, Greg D Gamble, Andrew Grey, Ian R Reid
Calcium Meta-analysis

Myocardial Infarction

HR 1.31 (95% CI: 1.02-1.67; p=0.035)

Calcium Meta-analysis

Stroke

HR 1.20 (95% CI: 0.96-1.50; p=0.11)

WHI

Myocardial Infarction

HR: 1.22 (95% CI: 1.00-1.50; p=0.054)

WHI

Stroke

HR: 1.17 (95% CI: 0.95-1.44; p=0.14)
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
WHI Calcium/Vit D Supp’n: 5 yrs after Trial

- No difference in CVD or disease mortality in the post-intervention period.
- Vertebral fractures 13% lower with CaD vs PBO, HR=0.87; 95% CI (0.76, 0.98).
- Among postmenopausal women followed for up to 12 yrs, CaD was associated with a decreased risk of vertebral fractures
  - Little effect on other skeletal and non-skeletal outcomes.
• Calcium supplementation may be of fracture benefit
• Calcium supplementation may be associated with CVS events
• Daily calcium requirements should be met through diet if possible
• For those at high risk for fracture, calcium alone is not enough
Does treatment reduce mortality?
Zoledronic Acid Reduced Risk of All-cause mortality by 28% Over Time


Hazard ratio, 0.72; (95% CI, 0.56-0.93)

P = 0.0117

Zoledronic acid (N=1054)
Placebo (N=1057)
Fig. 2  Mortality for survivors of hip fracture according to bisphosphonate treatment (Kaplan–Meier analyses)
Bolland J Clin Endocrinol Metab 95: 1174–1181, 2010
Centre (J Clin Endocrinol Metab 96: 0000–0000, 2011)
Keypoint

- Treatment not only reduces fractures and fracture related morbidity, but it reduces mortality
Summary

• While there are controversies around treatment, there is no doubt that the benefits of therapy out weigh the risks, so treatment should be considered for all high risk individuals