Issues that Perplex Us: Atypical Femur Fractures
What to do in Clinical Practice

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Disclosures

Industry:

- Amgen, Ipsen, Regeneron (grants to institution for research studies and/or honoraria)

Non-industry:

- International Society of Clinical Densitometry – 2019 Position Development Conference task force member (in charge of AFF guidelines); Canadian Panel Chair
- ASBMR International Task Force on AFF, member
- Endocrine Society – clinical practice guideline committee member
- Osteoporosis Canada – clinical practice guideline committee member

Learning Objectives

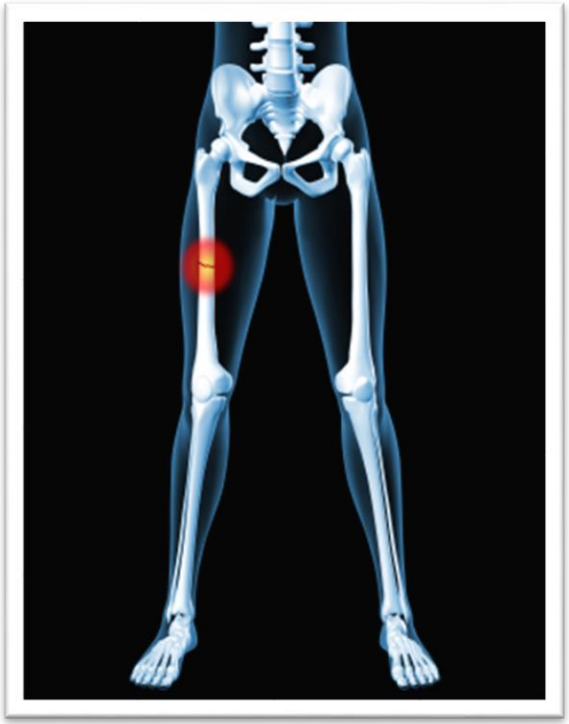
At the end of the session, participants will be able to:

1) Identify an atypical femur fracture
2) Discuss risk of developing atypical femur fracture
3) Manage patients with atypical femur fractures

IDENTIFY AFF

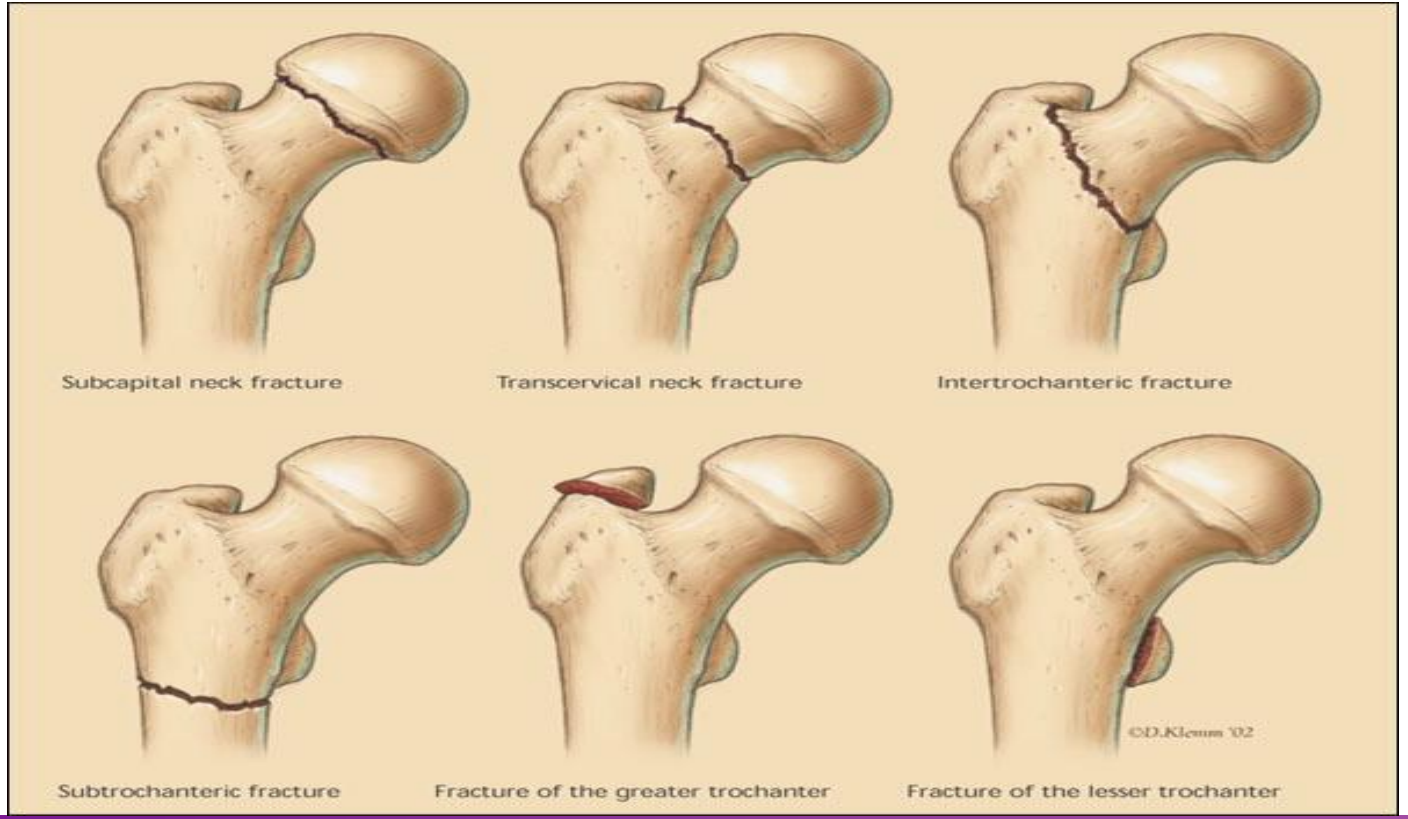
ATYPICAL FEMUR FRACTURE

Atypical femur fractures (AFF)



- low-trauma stress fractures
- in subtrochanteric or shaft region of the femur
- specific radiographic findings
- associated with bisphosphonates and denosumab therapy

Hip Fractures



PERSPECTIVE

JBMR

Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research

Elizabeth Shane,* David Burr,* Peter R Ebeling, Bo Abrahamsen, Robert A Adler, Thomas D Brown, Angela M Cheung, Felicia Cosman, Jeffrey R Curtis, Richard Dell, David Dempster, Thomas A Einhorn, Harry K Genant, Piet Geusens, Klaus Klaushofer, Kenneth Koval, Joseph M Lane, Fergus McKiernan, Ross McKinney, Alvin Ng, Jeri Nieves, Regis O'Keefe, Socrates Papapoulos, Howe Tet Sen, Marjolein CH van der Meulen, Robert S Weinstein, and Michael Whyte

Journal of Bone and Mineral Research, Vol. 25, No. 11, November 2010, pp 2267-2294

REVIEW

JBMR®

Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research

Elizabeth Shane*, David Burr*, Bo Abrahamsen, Robert A Adler, Thomas D Brown, Angela M Cheung, Felicia Cosman, Jeffrey R Curtis, Richard Dell, David W Dempster, Peter R Ebeling, Thomas A Einhorn, Harry K Genant, Piet Geusens, Klaus Klaushofer, Joseph M Lane, Fergus McKiernan, Ross McKinney, Alvin Ng, Jeri Nieves, Regis O'Keefe, Socrates Papapoulos, Tet Sen Howe, Marjolein CH van der Meulen, Robert S Weinstein, and Michael P Whyte

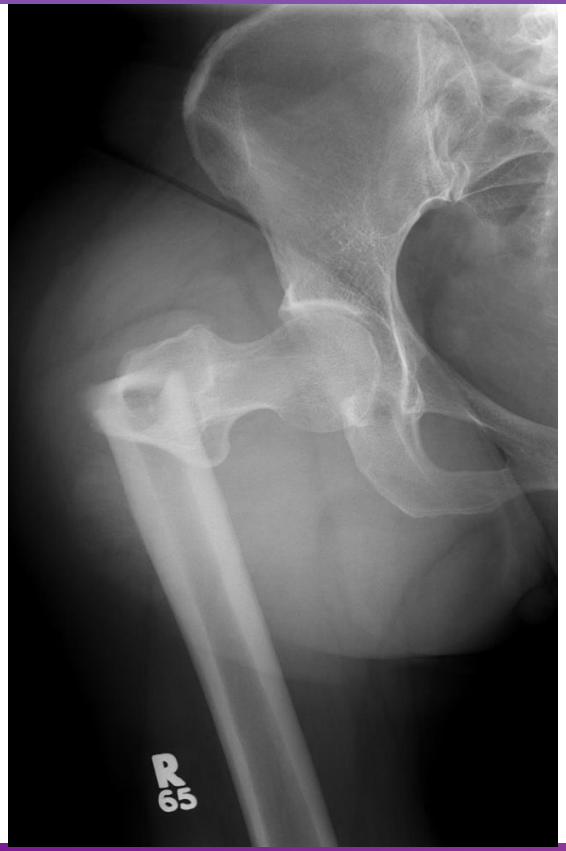
Journal of Bone and Mineral Research, Vol. 29, No. 1, January 2014, pp 1-23

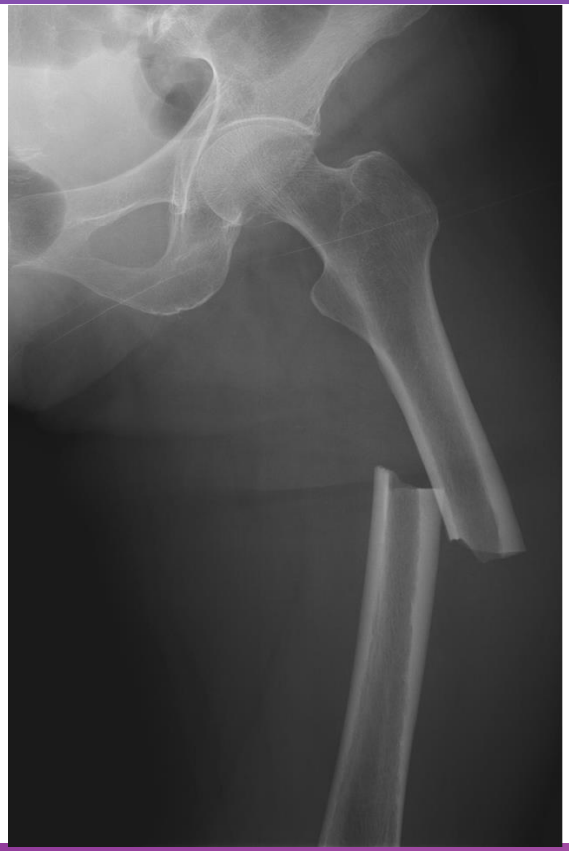
AFF: ASBMR Case Definition 2013

- Major features (4 out of 5 criteria):
  - Below lesser trochanter, above supracondylar flare
    1. Little or no trauma
    2. Transverse (or mostly transverse) ~~or short oblique configuration~~
    3. Non-comminuted (or minimally comminuted)
    4. Complete fractures extend through both cortices and may have a medial spike; Incomplete fractures involve only the lateral cortex
    5. Localized periosteal or endosteal reaction of the lateral cortex

- Minor features (none required):
  - Generalized increase in cortical thickness
  - Delayed healing
  - Prodromal symptoms such as dull aching pain in groin or thigh
  - Bilateral fractures and symptoms

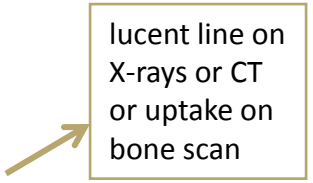
Imaging





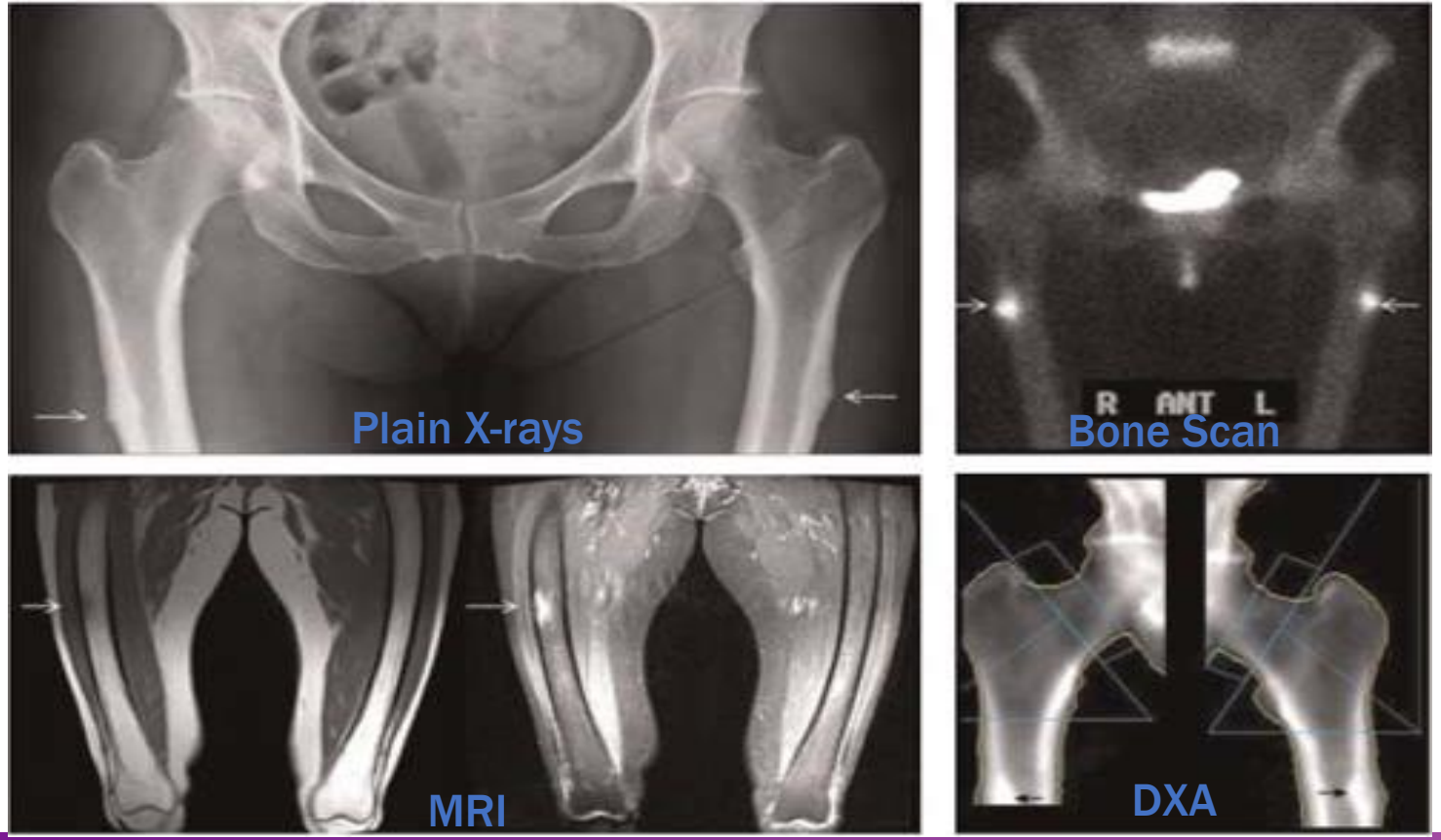
2013 (2014) ASBMR Case Definition for Incomplete AFF

- Major features (4 out of 5 criteria):
  - Below lesser trochanter, above supracondylar flare
    1. Little or no trauma
    2. Transverse (mostly) ~~or short oblique configuration~~
    3. Non-comminuted (minimally)
    4. Complete fractures extend through both cortices and may have a medial spike; Incomplete fractures involve only the lateral cortex
    5. Localized periosteal or endosteal reaction of the lateral cortex



- Minor features (none required):
  - Generalized increase in cortical thickness
  - Delayed healing
  - Prodromal symptoms such as dull aching pain in groin or thigh
  - Bilateral fractures and symptoms

Imaging using other modalities

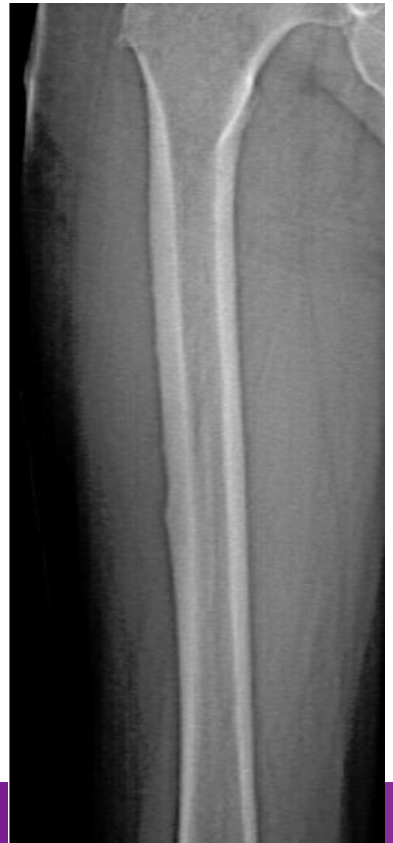


Internatonal Society for Clinical Densitometry 2019 PDC – Detection of AFF

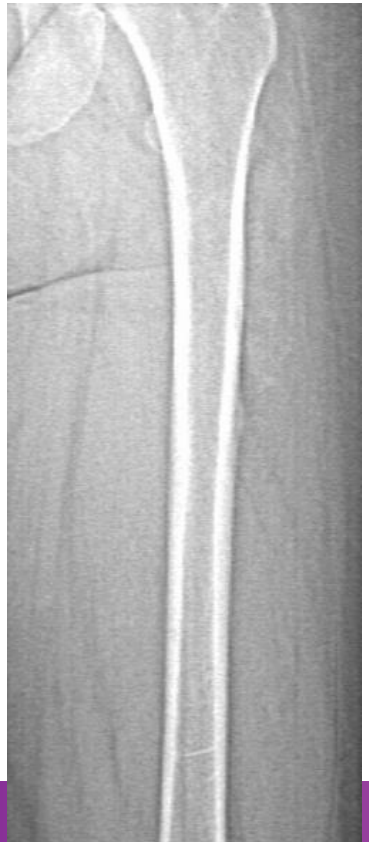
1) Full-length Femur Imaging (FFI) for detection of AFF
2) Reporting physicians to comment on presence or absence of abnormalities in the spectrum of AFFs for all hip and femur scans
3) Consider bilateral FFI in patients who have had 3 or more years of potent antiresorptive therapy, especially in those on long term glucocorticoid therapy

Which of these is an incomplete AFF?

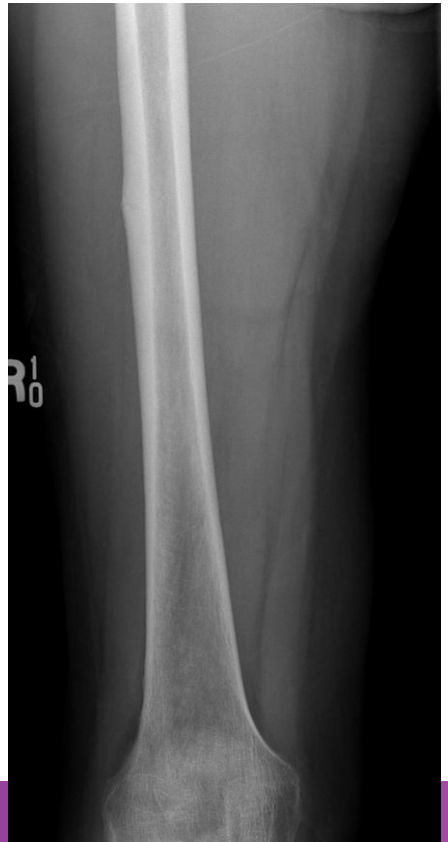
1.) Patient D



2.) Patient E



3.) Patient F



Densitometer based femur imaging

Fig. 2. Densitometer-based full-length femur imaging (FFI). (**a**) Single-energy scan showing beaking (arrows). (**b**) Dual-energy scan showing focal cortical periosteal and endosteal reactions at the lateral cortex (arrow; image: courtesy of Diane Krueger). (**c**) Image from densitometer-based full-length femur imaging (FFI).

RISK

ATYPICAL FEMUR FRACTURE

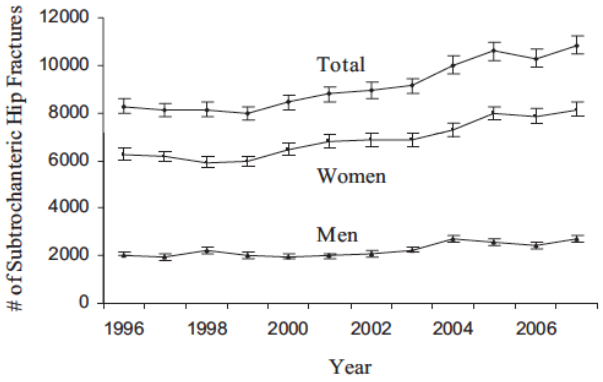
ORIGINAL ARTICLE

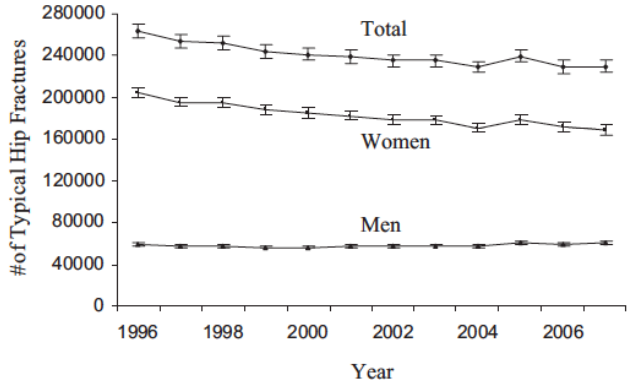
JBMR

Trends in Incidence of Subtrochanteric Fragility Fractures and Bisphosphonate Use Among the US Elderly, 1996–2007

Zhong Wang and Timothy Bhattacharyya

Intramural Research Program, National Institute of Arthritis, Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA





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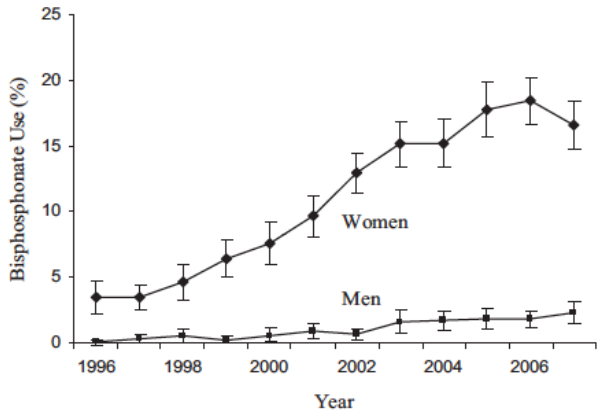

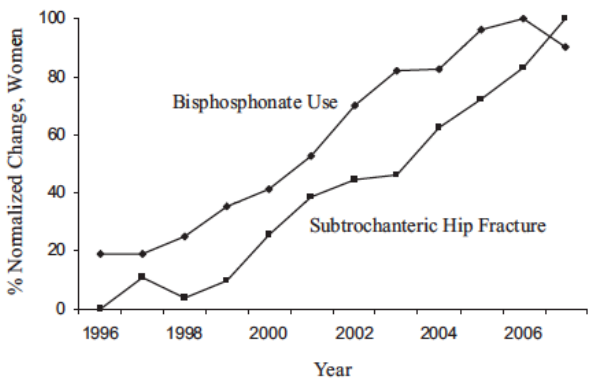

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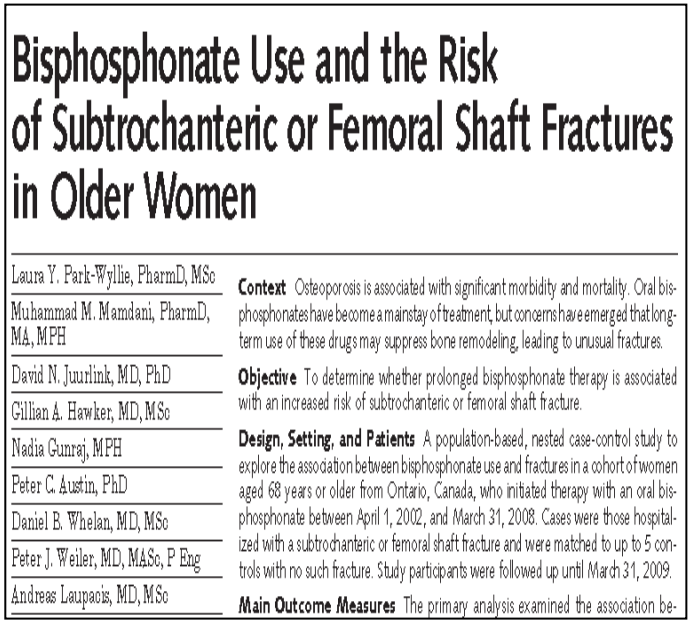
- "In the context of declining typical hip fractures among the US elderly, we observed small but significant increases in the incidence of subtrochanteric fragility fractures"
- "we estimated that for every 100 or so reduction in typical femoral neck or intertrochanteric fractures, there was an increase of one subtrochanteric fragility fracture."

Incidence of Complete AFFs

Ontario CANADA Data



Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women

Laura Y. Park-Wyllie, PharmD, MSc
Muhammad M. Mamdani, PharmD, MA, MPH
David N. Juurlink, MD, PhD
Gillian A. Hawker, MD, MSc
Nadia Gunraj, MPH
Peter C. Austin, PhD
Daniel B. Whelan, MD, MSc
Peter J. Weiler, MD, MASc, P Eng
Andreas Laupacis, MD, MSc

Context Osteoporosis is associated with significant morbidity and mortality. Oral bisphosphonates have become a mainstay of treatment, but concerns have emerged that long-term use of these drugs may suppress bone remodeling, leading to unusual fractures.

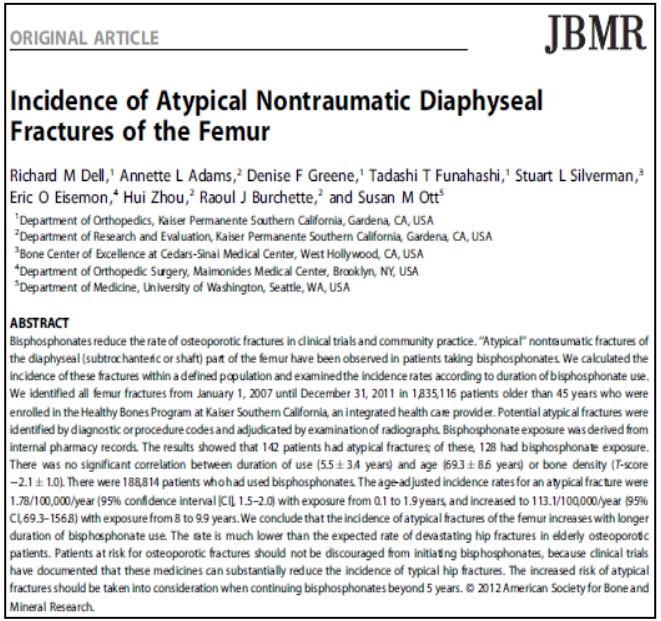
Objective To determine whether prolonged bisphosphonate therapy is associated with an increased risk of subtrochanteric or femoral shaft fracture.

Design, Setting, and Patients A population-based, nested case-control study to explore the association between bisphosphonate use and fractures in a cohort of women aged 68 years or older from Ontario, Canada, who initiated therapy with an oral bisphosphonate between April 1, 2002, and March 31, 2008. Cases were those hospitalized with a subtrochanteric or femoral shaft fracture and were matched to up to 5 controls with no such fracture. Study participants were followed up until March 31, 2009.

Main Outcome Measures The primary analysis examined the association be-

~1-2/1000 py after 6 - 7 years

Kaiser Permanente California Data



ORIGINAL ARTICLE

JBMR

Incidence of Atypical Nontraumatic Diaphyseal Fractures of the Femur

Richard M Dell,[1] Annette L Adams,[2] Denise F Greene,[1] Tadashi T Funahashi,[1] Stuart L Silverman,[3] Eric O Eisemon,[4] Hui Zhou,[2] Raoul J Burchette,[2] and Susan M Ott[5]

[1]Department of Orthopedics, Kaiser Permanente Southern California, Gardena, CA, USA
[2]Department of Research and Evaluation, Kaiser Permanente Southern California, Gardena, CA, USA
[3]Bone Center of Excellence at Cedars-Sinai Medical Center, West Hollywood, CA, USA
[4]Department of Orthopedic Surgery, Maimonides Medical Center, Brooklyn, NY, USA
[5]Department of Medicine, University of Washington, Seattle, WA, USA

ABSTRACT

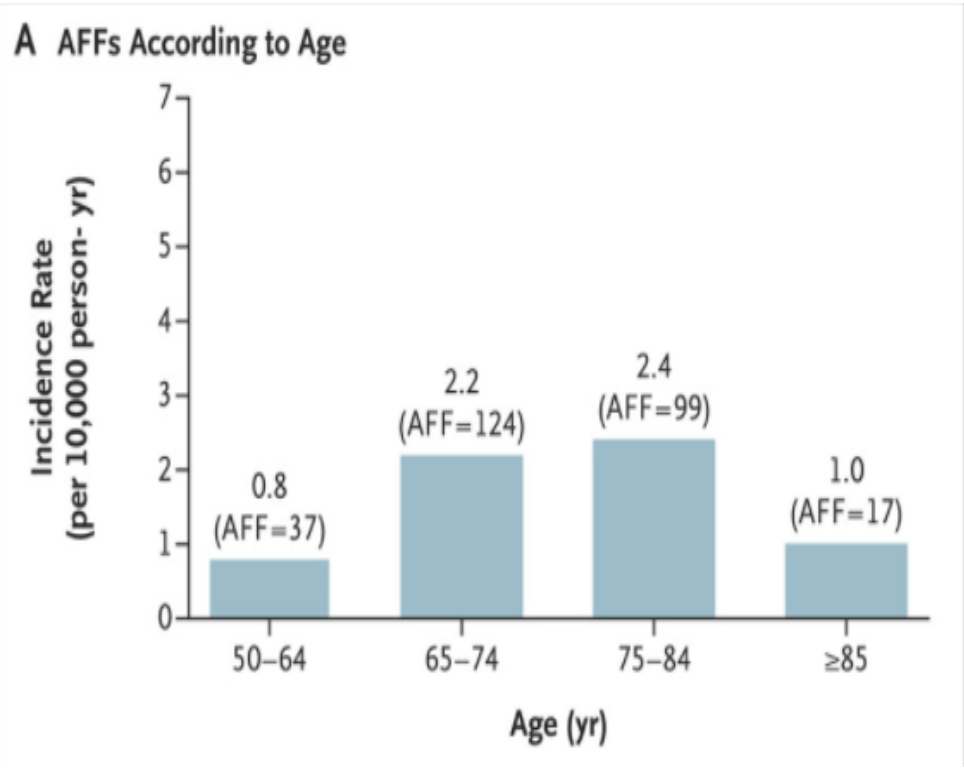
Bisphosphonates reduce the rate of osteoporotic fractures in clinical trials and community practice. "Atypical" nontraumatic fractures of the diaphyseal (subtrochanteric or shaft) part of the femur have been observed in patients taking bisphosphonates. We calculated the incidence of these fractures within a defined population and examined the incidence rates according to duration of bisphosphonate use. We identified all femur fractures from January 1, 2007 until December 31, 2011 in 1,835,116 patients older than 45 years who were enrolled in the Healthy Bones Program at Kaiser Southern California, an integrated health care provider. Potential atypical fractures were identified by diagnostic or procedure codes and adjudicated by examination of radiographs. Bisphosphonate exposure was derived from internal pharmacy records. The results showed that 142 patients had atypical fractures; of these, 128 had bisphosphonate exposure. There was no significant correlation between duration of use (5.5 ± 3.4 years) and age (69.3 ± 8.6 years) or bone density (*T*-score −2.1 ± 1.0). There were 188,814 patients who had used bisphosphonates. The age-adjusted incidence rates for an atypical fracture were 1.78/100,000/year (95% confidence interval [CI], 1.5–2.0) with exposure from 0.1 to 1.9 years, and increased to 113.1/100,000/year (95% CI, 69.3–156.8) with exposure from 8 to 9.9 years. We conclude that the incidence of atypical fractures of the femur increases with longer duration of bisphosphonate use. The rate is much lower than the expected rate of devastating hip fractures in elderly osteoporotic patients. Patients at risk for osteoporotic fractures should not be discouraged from initiating bisphosphonates, because clinical trials have documented that these medicines can substantially reduce the incidence of typical hip fractures. The increased risk of atypical fractures should be taken into consideration when continuing bisphosphonates beyond 5 years. © 2012 American Society for Bone and Mineral Research.

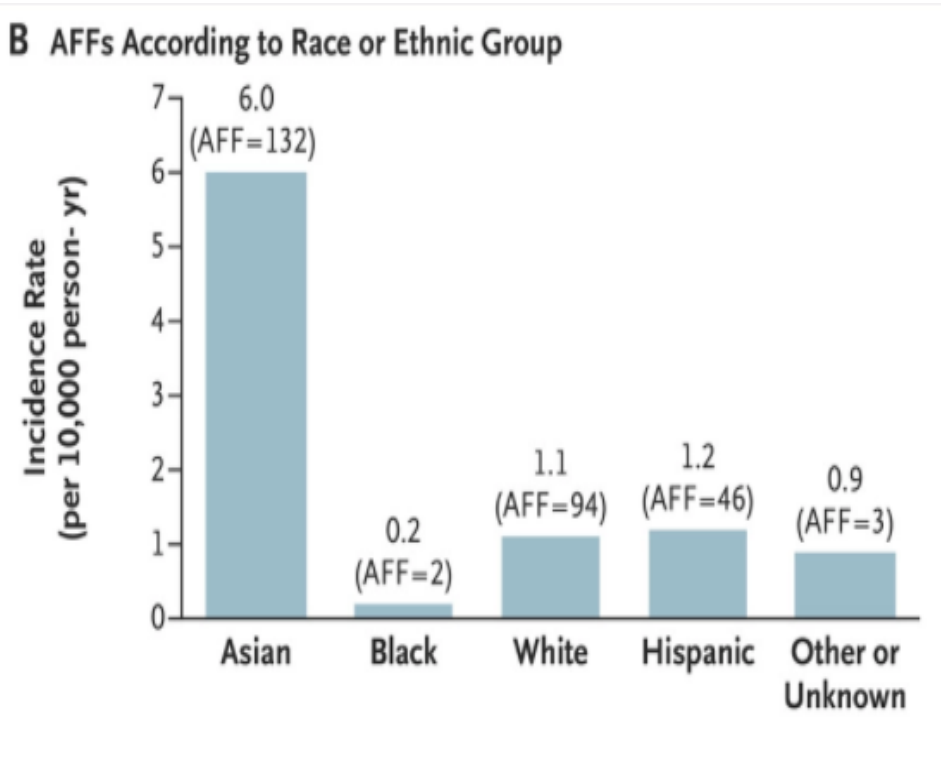
~1/1000 py after 8 - 9.9 years

Risk Factors for AFFs

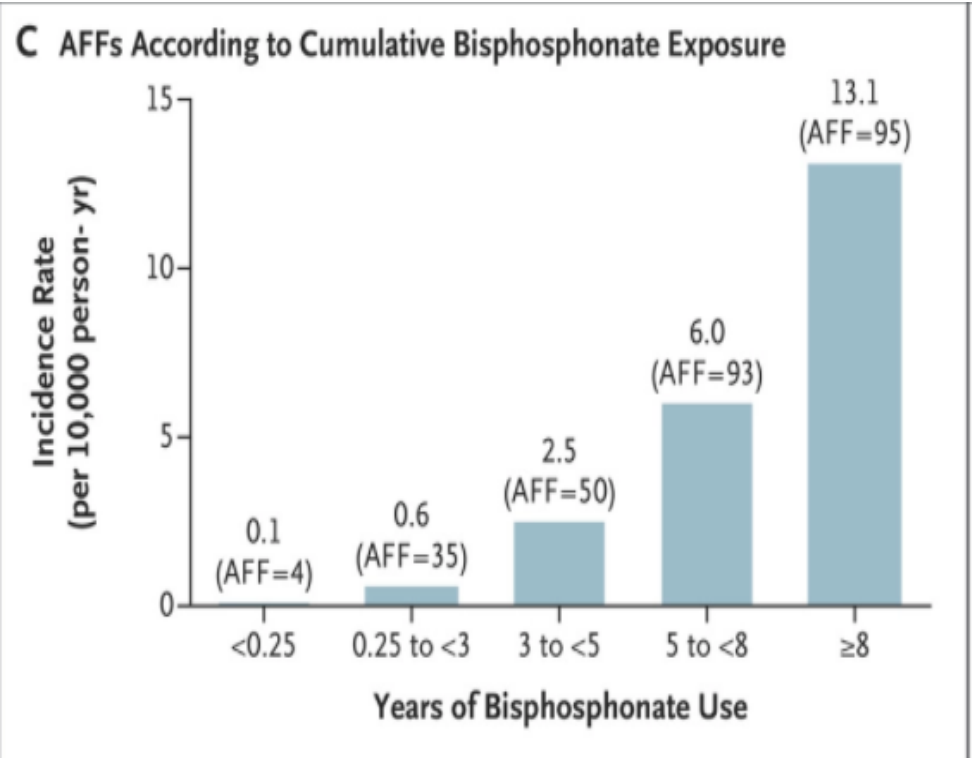
- Younger women
- Osteopenic (can vary)
- Asian race
- Long duration of BP therapy
- Multiple anti-resorptive medications
- Glucocorticoid use
- Rheumatoid arthritis
- Varus hip angle, bow-leg deformity, small diameter

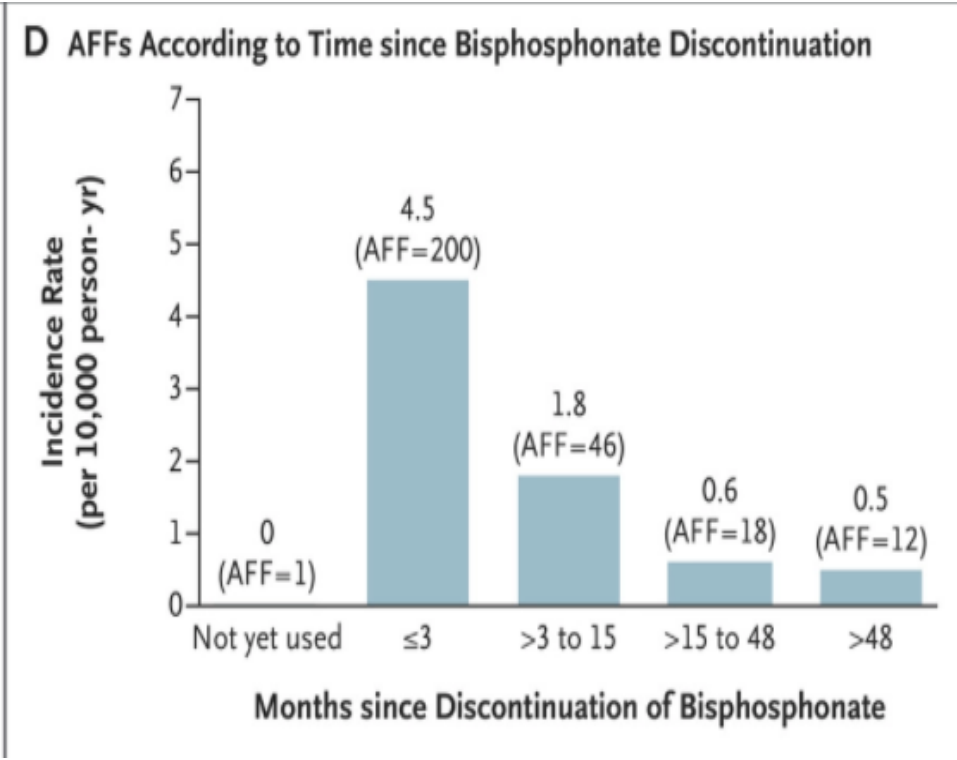
Risk Factors for AFFs





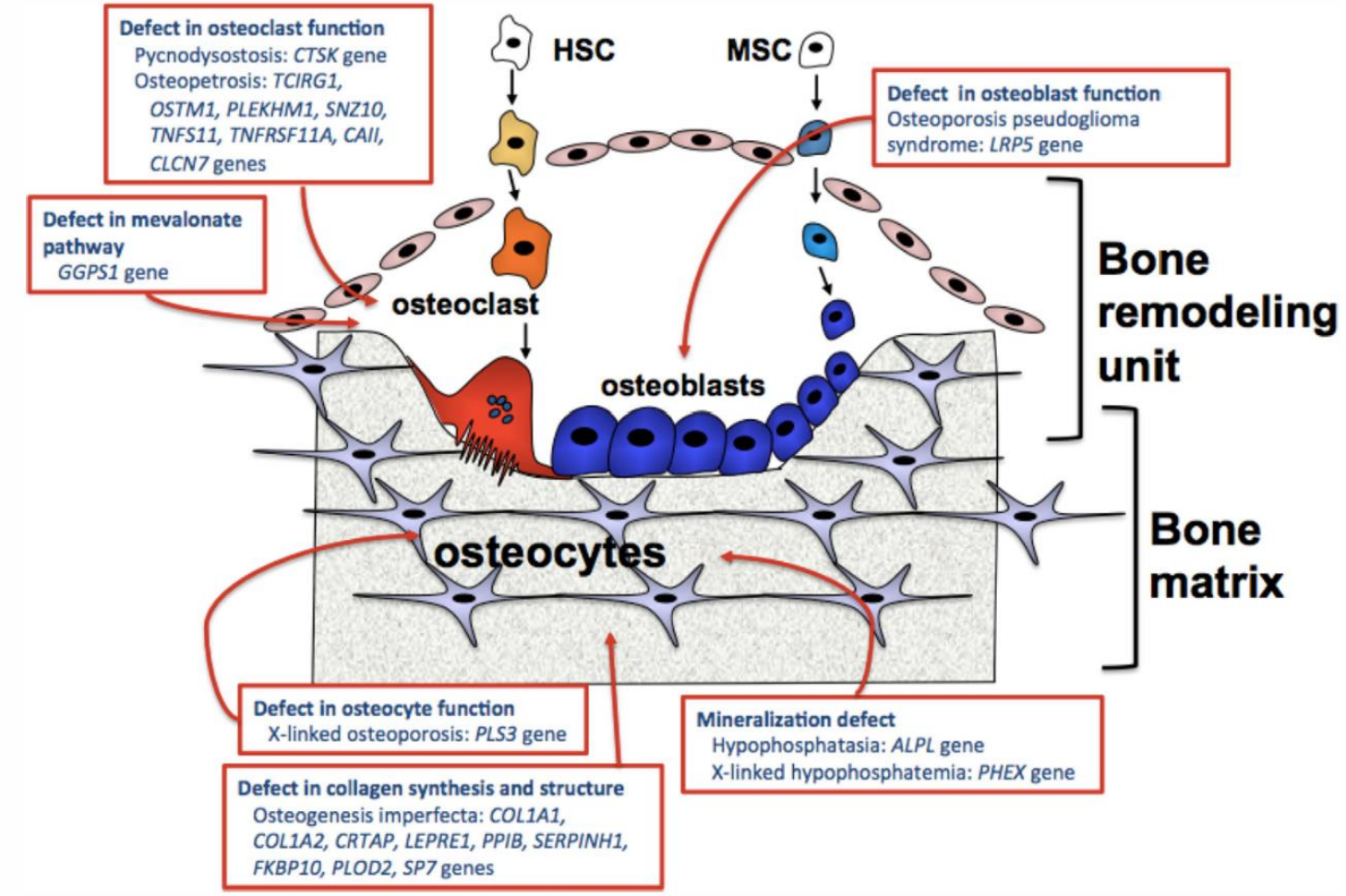
Risk Factors for AFFs





Pathogenetic Mechanisms

- Effect of suppression of bone remodeling on:
  - Bone's material properties – collagen, AGEs, increased tissue mineral density etc.
  - Healing of stress fractures
- Relationship of hip and lower limb geometry
- Genetic susceptibility – collagen abnormality, low bone turnover at baseline, etc…


Defect in osteoclast function
Pycnodysostosis: CTSK gene
Osteopetrosis: TCIRG1, OSTM1, PLEKHM1, SNZ10, TNFS11, TNFRSF11A, CAII, CLCN7 genes
Defect in mevalonate pathway
GGPS1 gene
HSC
MSC
Defect in osteoblast function
Osteoporosis pseudoglioma syndrome: LRP5 gene
osteoclast
osteoblasts
Bone remodeling unit
Bone matrix
osteocytes
Defect in osteocyte function
X-linked osteoporosis: PLS3 gene
Mineralization defect
Hypophosphatasia: ALPL gene
X-linked hypophosphatemia: PHEX gene
Defect in collagen synthesis and structure
Osteogenesis imperfecta: COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, SERPINH1, FKBP10, PLOD2, SP7 genes

AFF: Key Clinical Feature

ASBMR Task Force review

- 75% have prodromal pain
  - These features are fundamentally different from common osteoporotic femur fractures and strongly suggest a distinct pathogenesis

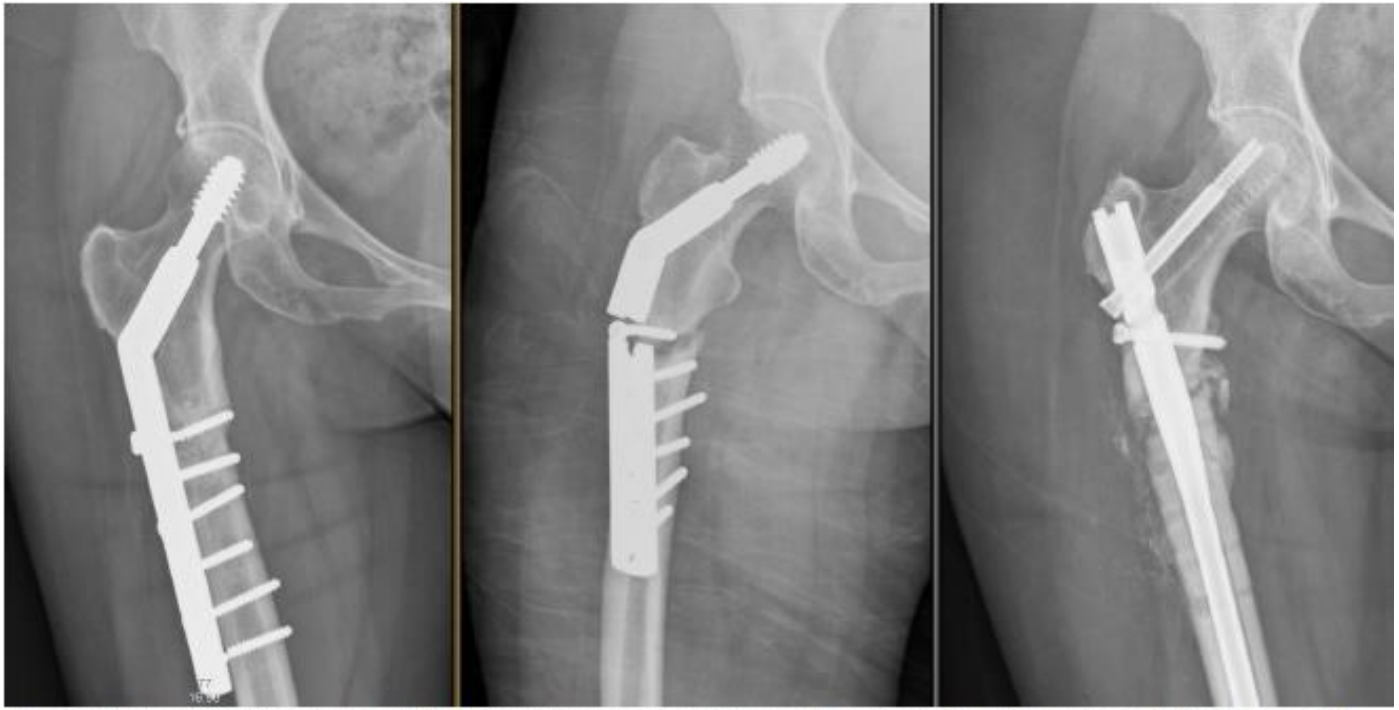
Ontario AFF Cohort (n~400)

- ~80-85% have prodromal symptoms: pain, ache, weakness, loss of function

MANAGE PATIENTS

ATYPICAL FEMUR FRACTURE

Surgical Management: IMR



Complete AFF treated with lateral compression plate, with subsequent failure and ultimately treated with a Gamma nail.

Current ASBMR Task Force Recommendations

STOP

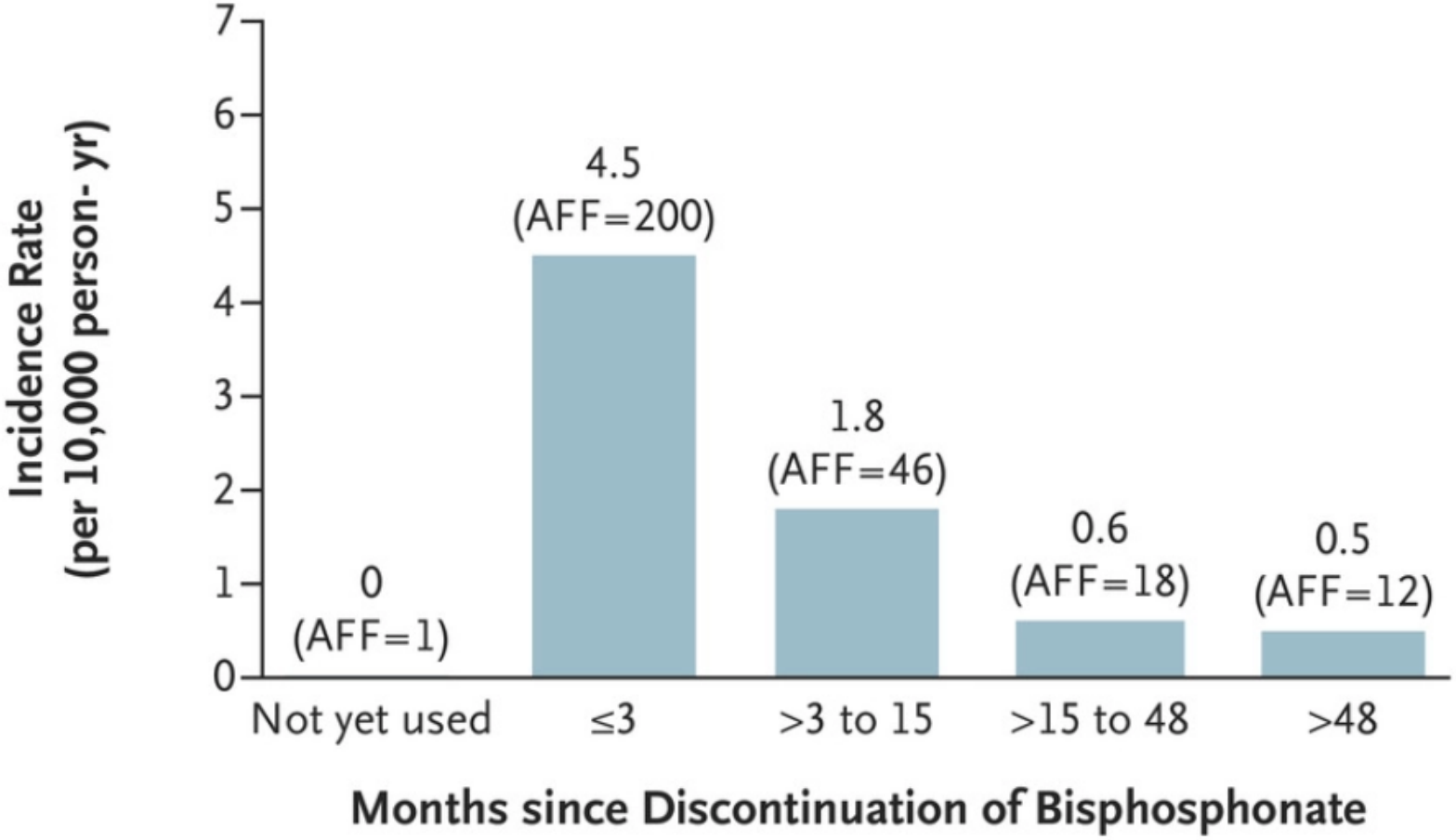
anti-resorptive therapy

(bisphosphonates and denosumab)

IMAGE

Contralateral femur

Kaiser Permanente Southern California Data



Current ASBMR Task Force Recommendations

FOR INCOMPLETE AFFs ➔

Consider prophylactic nailing

+/- teriparatide

>>Decrease weight-bearing (treat like a stress fracture)

IMPLICATIONS FOR YOUR OSTEOPOROSIS PRACTICE

ATYPICAL FEMUR FRACTURE

POINTS to consider:

- Fractures are common
- Bisphosphonates, denosumab, teriparatide, romosozumab are all effective therapies
- Use a sequential combination of anabolic and antiresorptive therapy
- Adverse effects (such as MVFx, AFF, ONJ) are rare

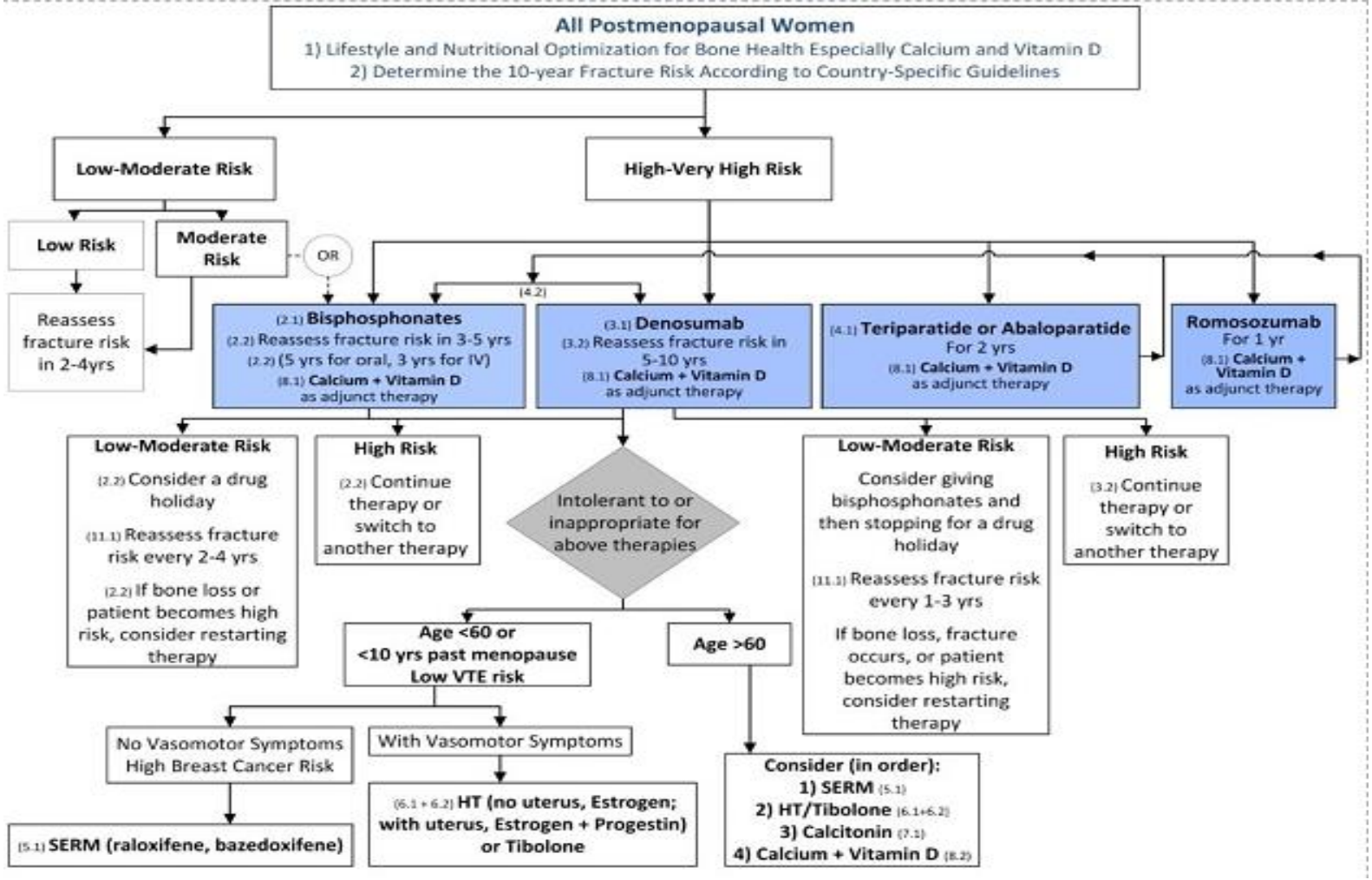
JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline FREE

Richard Eastell, Clifford J Rosen ✉, Dennis M Black, Angela M Cheung, M Hassan Murad, Dolores Shoback

The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 5, May 2019, Pages 1595–1622, https://doi.org/10.1210/jc.2019-00221

Published: 25 March 2019 **Article history** ▾


All Postmenopausal Women
1) Lifestyle and Nutritional Optimization for Bone Health Especially Calcium and Vitamin D
2) Determine the 10-year Fracture Risk According to Country-Specific Guidelines
Low-Moderate Risk
High-Very High Risk
Low Risk
Moderate Risk
OR
Reassess fracture risk in 2-4yrs
(4.2)
(2.1) Bisphosphonates
(2.2) Reassess fracture risk in 3-5 yrs
(2.2) (5 yrs for oral, 3 yrs for IV)
(8.1) Calcium + Vitamin D
as adjunct therapy
(3.1) Denosumab
(3.2) Reassess fracture risk in 5-10 yrs
(8.1) Calcium + Vitamin D
as adjunct therapy
(4.1) Teriparatide or Abaloparatide
For 2 yrs
(8.1) Calcium + Vitamin D
as adjunct therapy
Romosozumab
For 1 yr
(8.1) Calcium + Vitamin D
as adjunct therapy
Low-Moderate Risk
(2.2) Consider a drug holiday
(11.1) Reassess fracture risk every 2-4 yrs
(2.2) If bone loss or patient becomes high risk, consider restarting therapy
High Risk
(2.2) Continue therapy or switch to another therapy
Intolerant to or inappropriate for above therapies
Low-Moderate Risk
Consider giving bisphosphonates and then stopping for a drug holiday
(11.1) Reassess fracture risk every 1-3 yrs
If bone loss, fracture occurs, or patient becomes high risk, consider restarting therapy
High Risk
(3.2) Continue therapy or switch to another therapy
Age <60 or <10 yrs past menopause Low VTE risk
Age >60
No Vasomotor Symptoms High Breast Cancer Risk
With Vasomotor Symptoms
(5.1) SERM (raloxifene, bazedoxifene)
(6.1 + 6.2) HT (no uterus, Estrogen; with uterus, Estrogen + Progestin) or Tibolone
Consider (in order):
1) SERM (5.1)
2) HT/Tibolone (6.1+6.2)
3) Calcitonin (7.1)
4) Calcium + Vitamin D (8.2)

Internatonal Society for Clinical Densitometry 2019 PDC – Detection of AFF

1) Full-length Femur Imaging (FFI) for detection of AFF
2) Reporting physicians to comment on presence or absence of abnormalities in the spectrum of AFFs for all hip and femur scans
3) Consider bilateral FFI in patients who have had 3 or more years of potent antiresorptive therapy, especially in those on long term glucocorticoid therapy

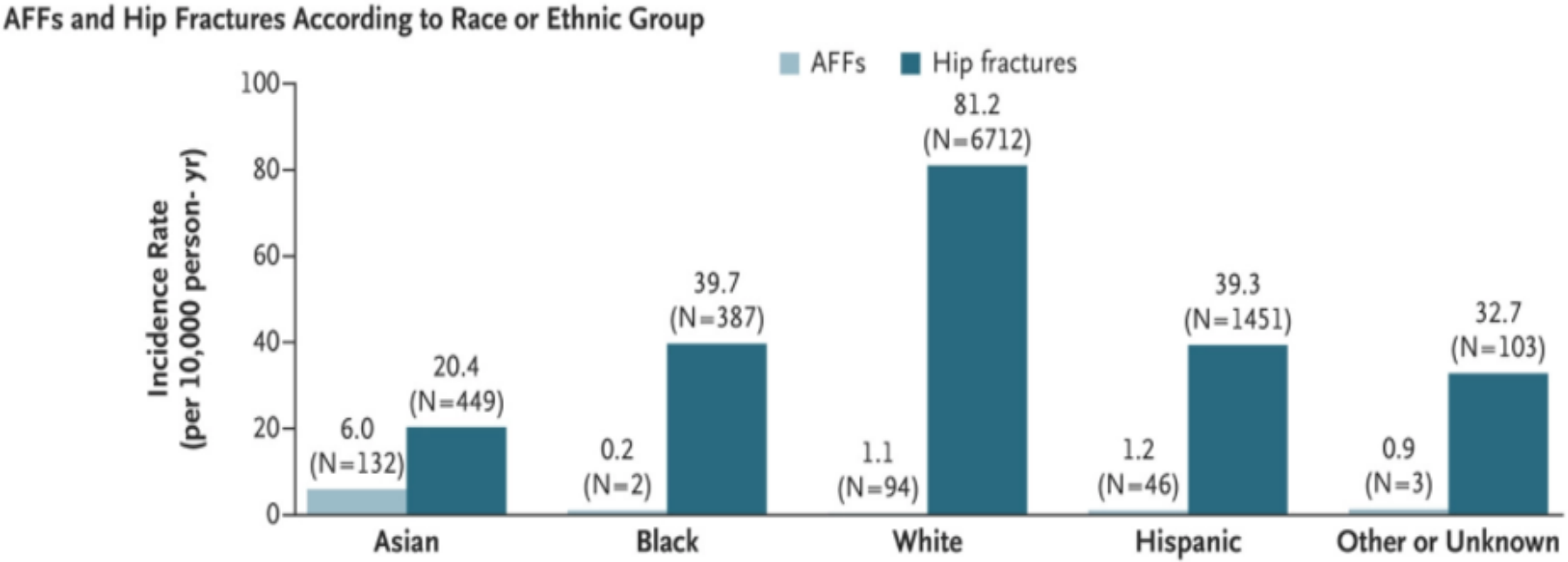
How do we communicate the real risk to patients?

1. Low:
   - Complete AFFs – ~1/1000 patient years after 6-10 years
   - Incomplete AFFs -- ? ~1/100

2. Drug treatment according to fracture risk – benefit/risk ratio

3. Reassess drug therapies after 3-5 years, consider drug holiday for stable moderate (and ? high) risk patients

Special Considerations for Asians



Important Points

1. AFFs are rare (but incomplete AFFs may be more common)

2. Patients at high risk for osteoporotic fracture should be treated

3. Stop potent antiresorptive therapies for patients with AFFs

4. Consider bisphosphonate drug holidays for those who have been on potent bisphosphonates after 3-5 years, especially those who are not at high risk for fractures.

If your patient has an AFF:

1. stop potent antiresorptive therapy
2. decrease weight bearing activities
3. consider bone formation therapies if patients need therapies to prevent osteoporotic fractures

Summary

1) Identify an atypical femur fracture
2) Discuss risk of developing atypical femur fracture
3) Manage patients with atypical femur fractures
4) Implications for your practice in Osteoporosis

Thank you!

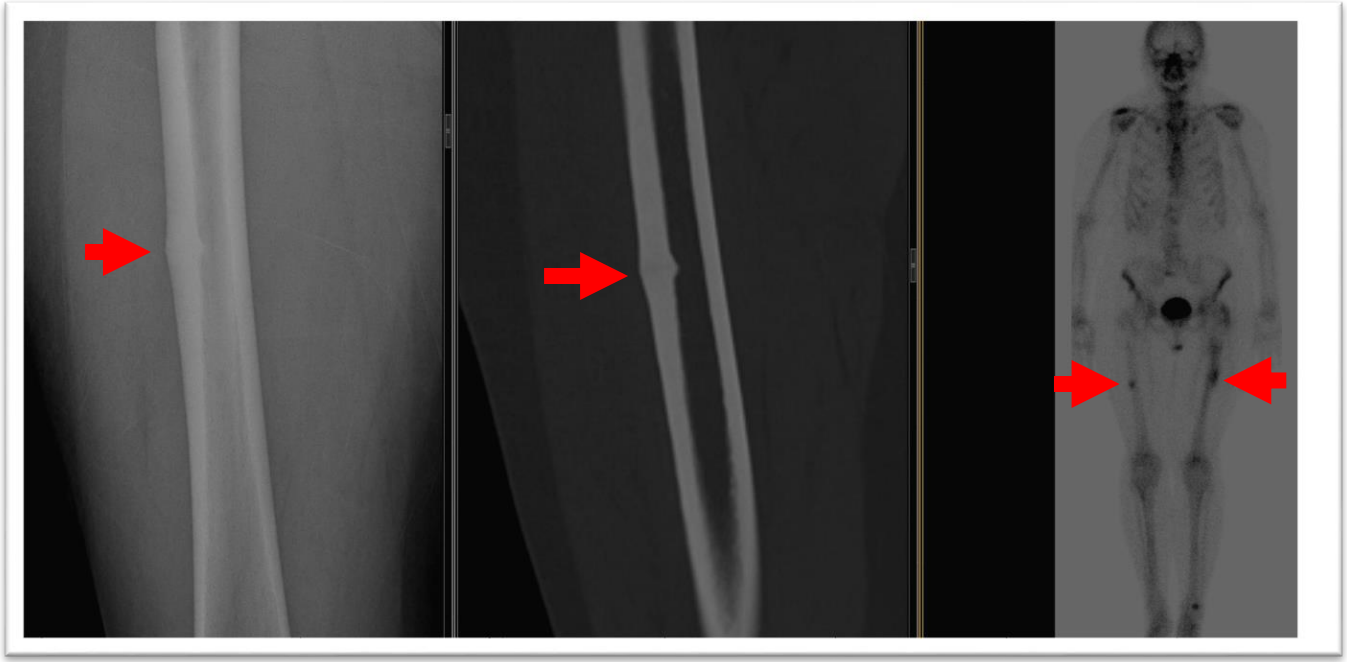
 angela.m.cheung@gmail.com

 Visit: osteoconnections.com

 Facebook/OsteoporosisUHN

 Twitter/OsteoUHN; Twitter/AngelaMCheung

Other imaging modalities



X ray

CT scan

Bone scan

ISCD 2019 PDC: Detection of iAFFs

1. Can DXA systems detect iAFFs or abnormalities in the spectrum of AFF?

2. What densitometer-based test should be used for the detection of abnormalities in the spectrum of AFF, and how should it be analyzed, interpreted and reported?

3. In which patient population should densitometer based full length femur imaging (FFI) be used to screen for abnormalities in the spectrum of AFF?

Cheung AM et al, J Clin Densitom. 2019 Oct - Dec;22(4):506-516

ISCD 2019 PDC: Detection of iAFFs

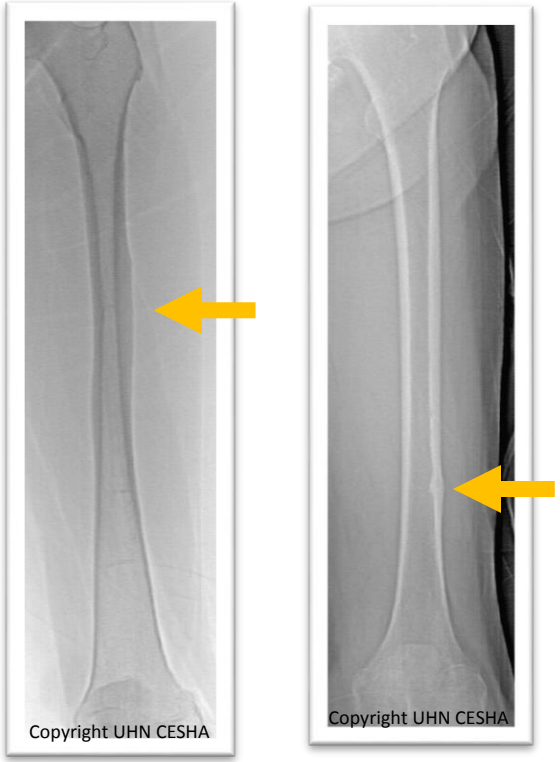
1. Can DXA systems detect iAFFs or abnormalities in the spectrum of AFF? YES

2. What densitometer-based test should be used for the detection of abnormalities in the spectrum of AFF, and how should it be analyzed, interpreted and reported? FFI

3. In which patient population should densitometer based full length femur imaging (FFI) be used to screen for abnormalities in the spectrum of AFF?

ISCD Official position 2:
(i.e. how should we screen? How should we report?)

- If the purpose is to detect abnormalities in the spectrum of AFF, then full length femur imaging (FFI) is recommended over both default-length femur imaging and extended-length femur imaging



Cheung, A et al. 2019. J Clin Densitom 22: p.510

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   Consider those on >3 yrs of potent anti-resorptive therapy, especially those on glucocorticoid therapy

Management of osteoporosis care of patients who need dental surgery. Considerations related to ONJ

Arthur C. Santora II, MD, PhD

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Disclosures

Merck & Co. Inc.

- Former employee – Stock, pension

Entera Bio, Ltd.

- Chief Medical Officer / Consultant

Myovant Sciences

- Consultant

CSR Pharma Group Inc.

- Consultant

Objectives

Review

- Cased definition of Osteonecrosis of the Jaw (ONJ)
- Epidemiology of ONJ
  - Association of drugs that inhibit osteoclasts with ONJ
- Mechanism of action and pharmacokinetics of bisphosphonates and denosumab

ONJ risk management in osteoporosis patients

- Prior to starting treatment
- During long-term treatment
- Prior to an elective dental procedure

Case Definition of Osteonecrosis of the Jaw (ONJ)

- **ONJ** is defined as an area of exposed bone in the oral cavity that does not heal within 8 wk following identification by a healthcare provider in a patient who has not had radiation therapy in the craniofacial region or evidence of local malignancy.[1]
- **AR**(antiresorptive-related)**ONJ** is defined as ONJ in a patient who has been receiving or has been exposed to a bisphosphonate or denosumab.[1]
- **MR**(medication-related)**ONJ** is defined as ONJ in a patient who has been receiving or has been exposed to a bisphosphonate, denosumab or antiangiogenic therapy.[1,2]
- MRONJ, ARONJ and ONJ often used interchangeably, and another name (e.g., osteomyelitis osteonecrosis) used to describe ONJ when there is no history of medication use)

1. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.
2. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 2014;72:1938-56.

Staging Antiresorptive-related ONJ

- Patients with **Stage 1** disease have exposed bone and are asymptomatic with no evidence of significant adjacent or regional soft tissue inflammation or infection. [1]
- **Stage 2** disease is characterized by exposed bone with associated pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection. [1] (2° is an assumption)
- **Stage 3** disease is characterized by exposed bone associated with pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection, **in addition to** a pathologic fracture, an extraoral fistula or oral-antral fistula, or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus.[1]

1. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.

ONJ Incidence and Pathophysiology

Incidence

- Cancer: 1% to 2% / person-year (zoledronic acid and denosumab) 5- to 10-fold higher in combination with antiangiogenic agents [1]
- Osteoporosis: 0.15% to < 0.001% / person-years of exposure [1]

"The pathophysiology of ONJ is not well understood." [1]

- Case definition requires both bone necrosis **and delayed healing**
- Trauma (e.g., tooth extraction, dentures) and Infection may cause necrosis
- Neither bisphosphonates nor denosumab are established direct causes of bone necrosis
- Active osteoclasts are required for sequestration and sloughing of necrotic bone in the jaw

1. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.

Risk Factors for ONJ in Patients with Osteoporosis [1]

Tooth Extraction

Poor dental health

- Lack of routine care by a dentist
- Caries requiring extraction
- Periodontitis
- Chronic infection of bone
- Ill-fitting dentures
- Sjogren's and other causes of decreased saliva

Tori /Exostoses - thin mucosa overlying periosteum

Smoking

Diabetes

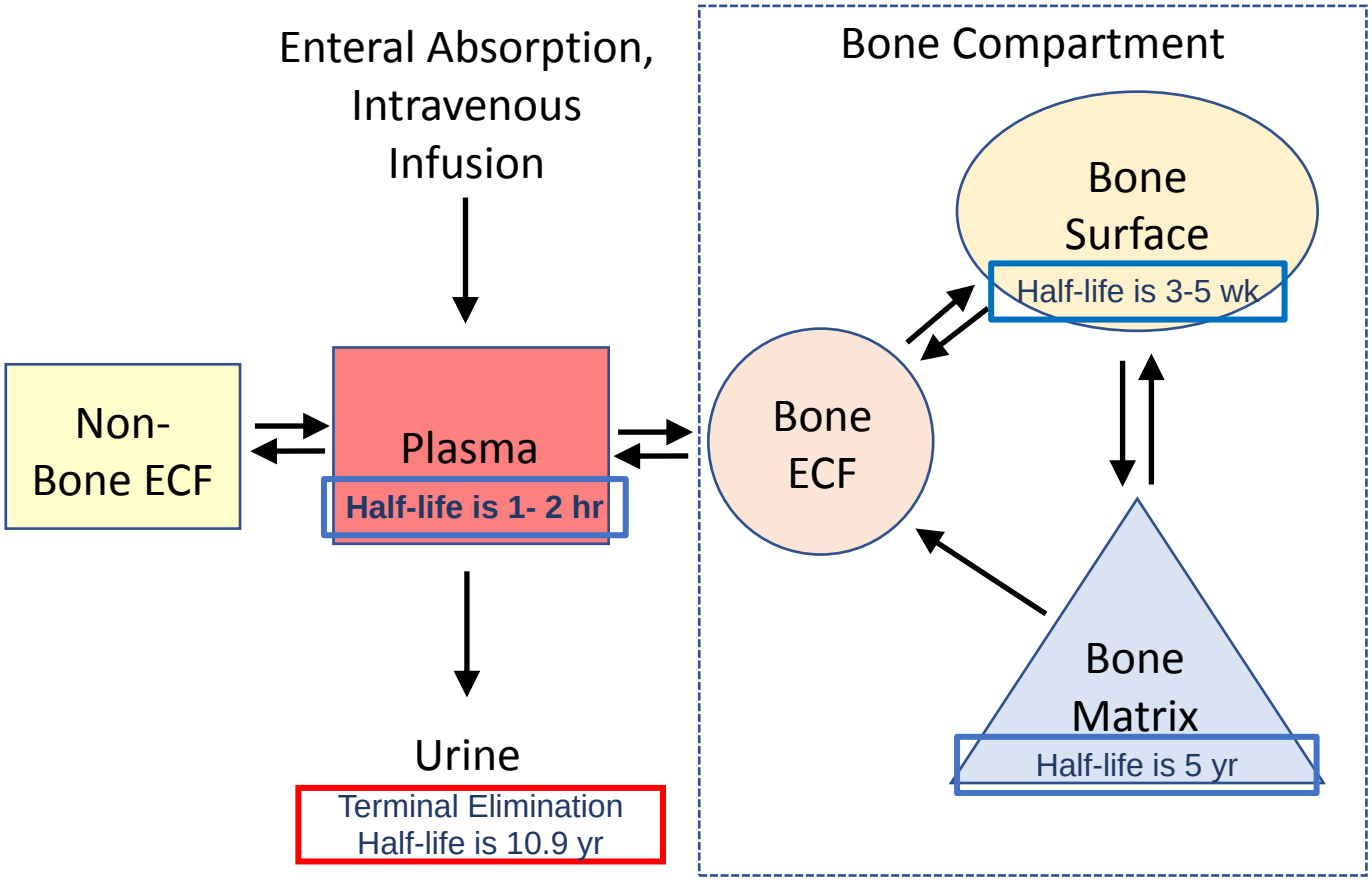
Glucocorticoids – Infection and AVN

Factor V Leiden and other causes of thrombosis [2]

Dental Implants may lead to diagnosis but may not be causal

1. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.
2. Glueck CJ, McMahon RE, Bouquot JE, Triplett D, Gruppo R, Wang P. Heterozygosity for the Leiden mutation of the factor V gene, a common pathoetiology for osteonecrosis of the jaw, with thrombophilia augmented by exogenous estrogens. J Lab Clin Med 1997;130:540-3.

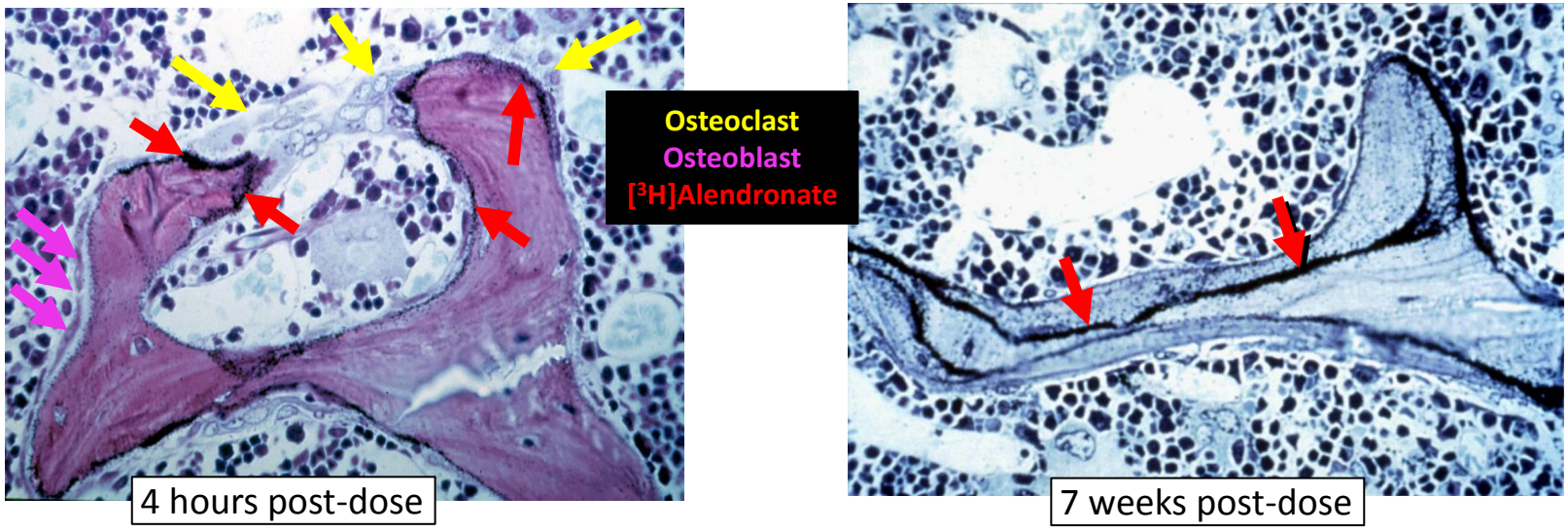
Bisphosphonate Kinetics



Bisphosphonate Distribution on Bone Surfaces

- Absorbed alendronate is rapidly cleared from blood ($T_{½}$= 1-2 hr)
  - 50 % rapidly excreted in urine
  - No soft tissue accumulation
  - 50 % on bone surfaces concentrated under osteoclasts
  - **Only alendronate on bone surfaces under osteoclasts is pharmacologically active**

- Estimated $T_{½}$ on the surface of bone is 2 to 5 weeks
- Alendronate on the surface of bone is either
  - Slowly released into blood, or
  - Trapped (≈65% that initially distributed to bone) within newly formed bone where it is not pharmacologically active

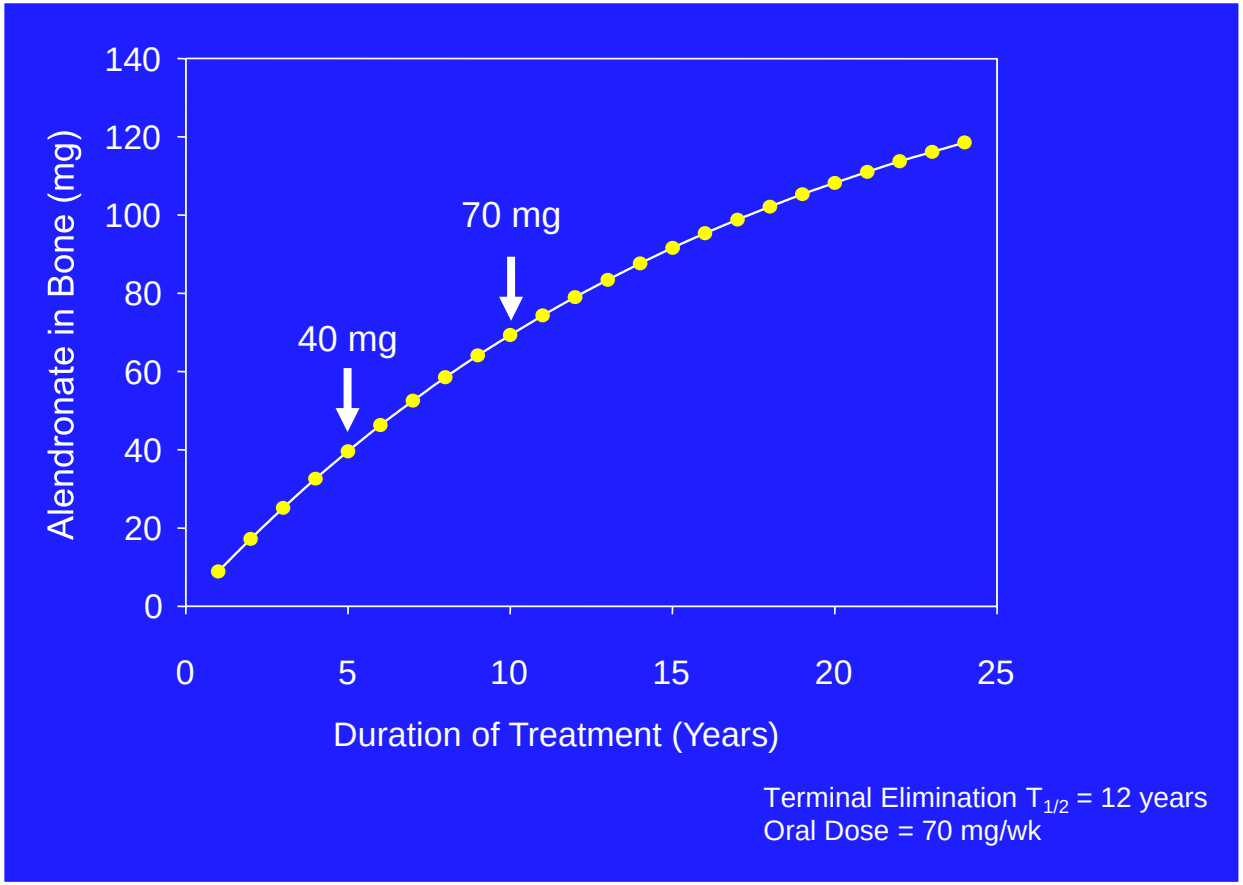


Masarachia et al. Bone 1996; 19:281–290

Why are Drug Holidays Possible After Long-Term Bisphosphonate use?

- After treatment is interrupted, no “new” bisphosphonate is delivered to bone surfaces
- Bisphosphonate retained in bone that formed during prior dosing will be “recycled” and released after treatment is discontinued
- The amount of recycled drug is a function of previous daily/weekly dose and years of treatment
- Recycled bisphosphonate will prevent or at least slow post-treatment bone loss for months to years post treatment.

Estimated Bone Accumulation of Alendronate During Long-term Administration



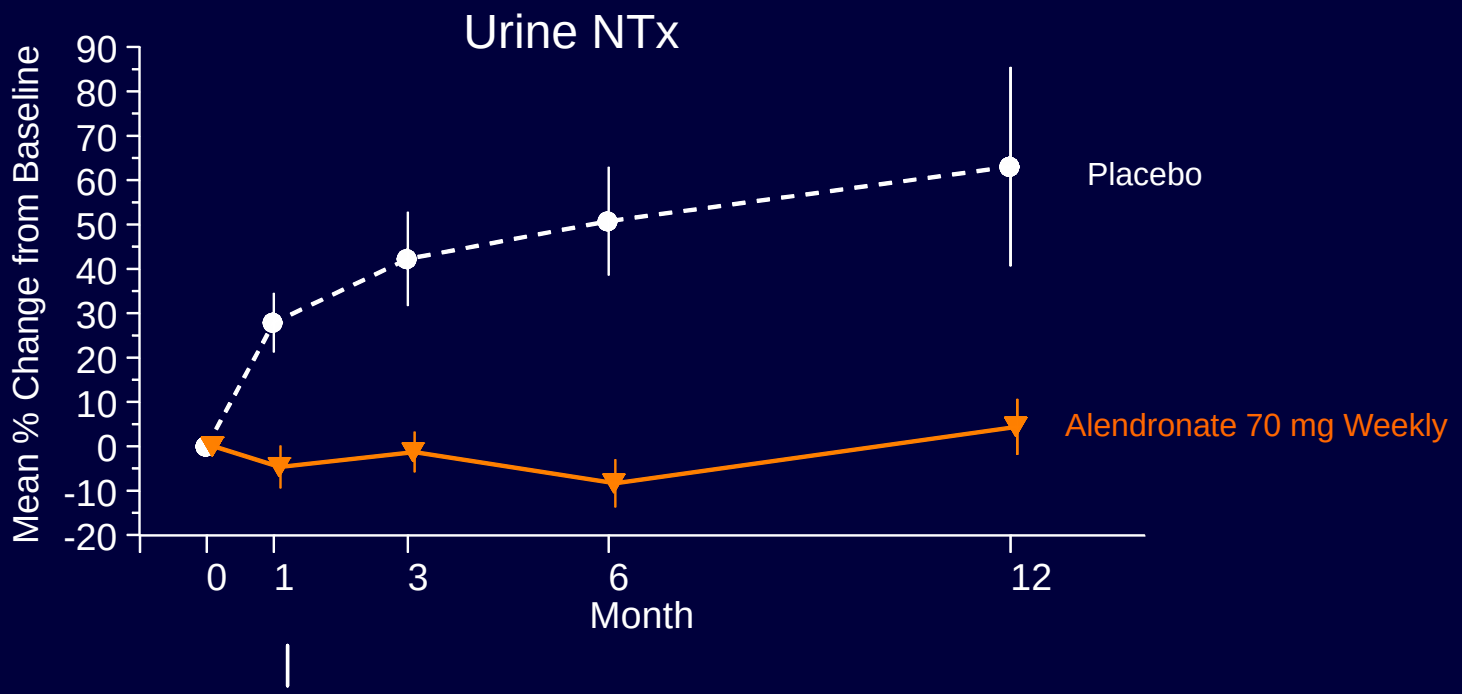
Bone Remodeling Changes after Discontinuation of Long-Term Bisphosphonate Treatment

- **Mathematical modeling** of alendronate release from bone suggests that the amount released will be insufficient to fully prevent bone loss if discontinued after 5 to 10 years
  - After **5 years** of treatment with alendronate 70 mg weekly, the amount released from bone each week is approx. the same as that absorbed after a **12.8 mg weekly** dose
  - After **10 years** of treatment with alendronate 70 mg weekly, the amount released from bone each week is approx. the same as that absorbed after a **17.5 mg weekly** dose
- **Clinical studies** of effects of discontinuation of long-term oral alendronate treatment on biochemical markers of bone remodeling and BMD have confirmed this prediction

Langdahl et al. J Bone Min Res 2012; 27: S120
Cosman et al. Osteoporos Int. 2016; 27:377-86
Bone, et al. N Engl J Med 2004:350;1189-1199
Black et al. JAMA. 2006; 296: 2927-38

Bone Resorption Increases Quickly After Long-Term Treatment is Discontinued

Patients Previously Treated with Bisphosphonates for ~5 Years



Urine NTx= Urine N-Telopeptides of type 1 collagen to creatinine ratio (bone resorption marker).
The figure represents the LS Geometric Mean ± SE.
Prior use of bisphosphonates: mean 6.0 years, median 5.2 years.

Presented at ASBMR Meeting in October 2012 Plenary Poster 0377
Langdahl et al. J Bone Min Res 2012; 27: S120

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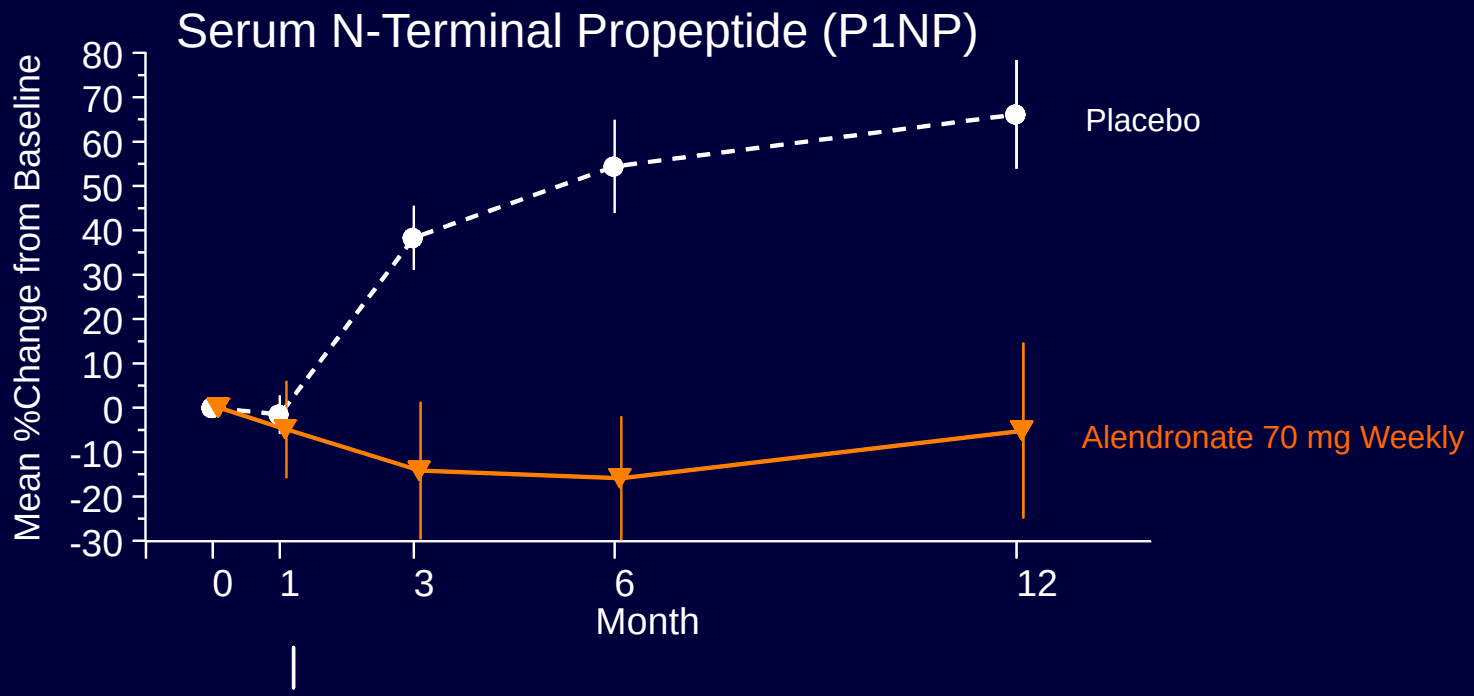

P1NP = Serum N-Terminal Propeptide of Type 1 Collagen (bone formation marker)
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Denosumab PK and PD [1]

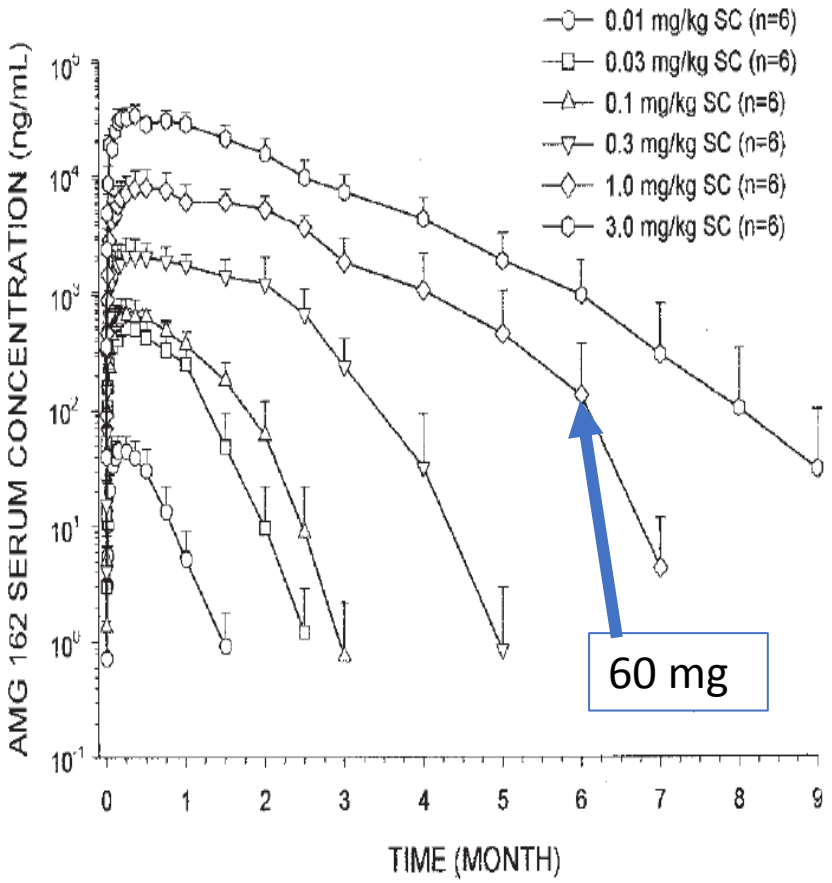

FIG. 2. The serum concentration profile of AMG 162 (ng/ml) over time. Data are presented as mean and SE [1]

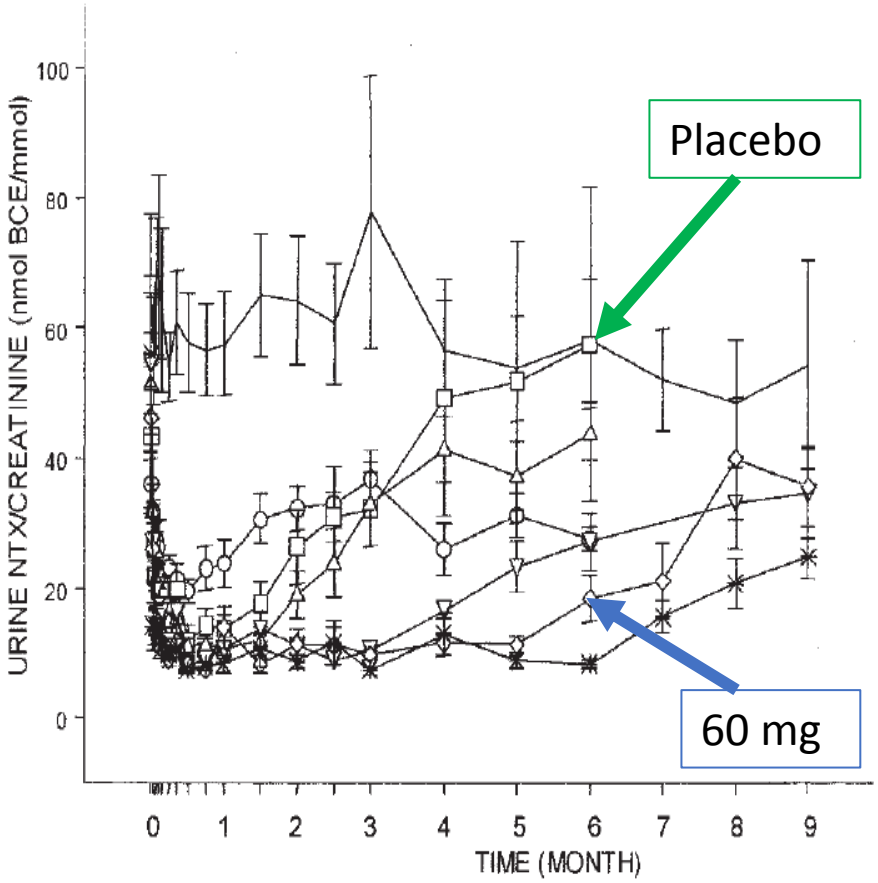

FIG. 1. Changes in a second morning void urinary NTX/creatinine (nmol BCE/mmol creatinine) over time. Mean and SE [1]

1. Bekker PJ, Holloway DL, Rasmussen AS, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res 2004;19:1059-66.

ONJ Risk Management in Osteoporosis Patients Prior to starting treatment [1]

Dental history and PE

- History of tooth extractions or periodontitis
- Missing or carious teeth
- Gum recession and/or inflammation

Current and prior dental care

- Personal oral hygiene
- **Established relationship with a dentist with scheduled prophylaxis**

Review ONJ as a potential risk with each patient and address modifiable risks (e.g., smoking)

Determine whether either dental extraction or implants are planned or needed

- Offer to communicate with your patient's dentist/oral surgeon to coordinate dental and osteoporosis care
- **Strongly consider delaying start of antiresorptive osteoporosis drugs until invasive dental procedures have been completed**

Do not initiate antiresorptive osteoporosis drug therapy in a patient with an active dental abscess or osteitis/osteomyelitis until appropriately treated by a dentist / oral surgeon.
- long-term treatment with an appropriate antibiotic(s) often required

1. Personal "Expert Opinion" not experimentally validated
2. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.
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ONJ risk management in osteoporosis patients During long-term treatment [1]

- Review dental history and PE
- Confirm scheduled exams and prophylaxis by a dentist
- Determine whether either dental extraction or implants are planned
  - Offer to communicate with your patient's dentist/oral surgeon to coordinate dental and osteoporosis care
- Review ONJ as a potential AE and discuss modifiable risk

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2. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.
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ONJ risk management in osteoporosis patients Prior to an elective dental procedure [1]

Review dental history and PE

Determine what dental procedure(s) is/are planned

- Crowns and restorations with no bone trauma do not carry a risk of ONJ
- Some periodontal procedures are low-risk (patient's periodontist should decide)

Dental Extractions and Implants

- Coordinate with dentist / oral surgeon
- Time procedure 6-months after prior denosumab dose and 9- to 12-months after prior zoledronic acid infusion
- Interrupt oral bisphosphonates 2 to 3 months prior to procedure
- Once dentist / oral surgeon confirms procedure site has healed, resume antiresorptive on schedule

Do not delay emergent dental procedures required to treat acute infections

1. Personal "Expert Opinion" not experimentally validated
2. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.
3. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 2014;72:1938-56.

ONJ Bibliography

1. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.
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3. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 2014;72:1938-56.
4. Ruggiero SL. Diagnosis and Staging of Medication-Related Osteonecrosis of the Jaw. Oral Maxillofac Surg Clin North Am 2015;27:479-87.
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9. Peters E, Lovas GL, Wysocki GP. Lingual mandibular sequestration and ulceration. Oral Surg Oral Med Oral Pathol 1993;75:739-43.
10. Ryu JI, Kim HY, Kwon YD. Is implant surgery a risk factor for osteonecrosis of the jaw in older adult patients with osteoporosis? A national cohort propensity score-matched study. Clin Oral Implants Res 2021;32:437-47.
11. Varoni EM, Lombardi N, Villa G, Pispero A, Sardella A, Lodi G. Conservative Management of Medication-Related Osteonecrosis of the Jaws (MRONJ): A Retrospective Cohort Study. Antibiotics (Basel) 2021;10.