

Balancing the Risks and Benefits of Osteoporosis Treatment: part I: 3 to 5 years treatment

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2

Risks and benefits of initiating osteoporosis treatment

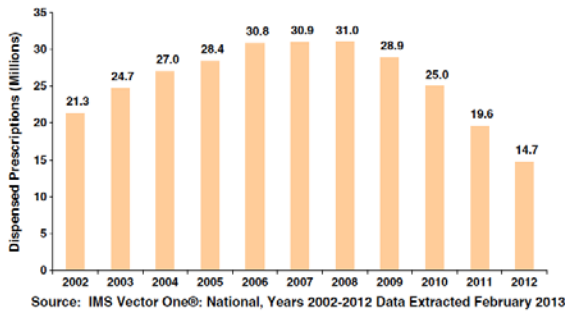
Short-term treatment (3-5 years)

- Benefits (fracture reductions)
- Risks (ONJ, AFF)
- Benefits vs. risk

3



Adverse Publicity: Effect on Oral Bisphosphonate Use in USA



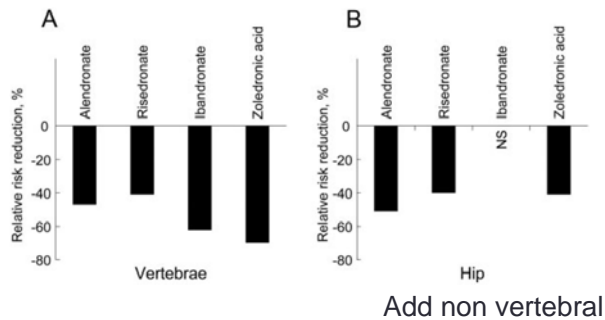
Wysowski DK, Greene P. *Bone*. 2013;57:423-428

Background Short-term Txmt: Osteoporosis Treatments Reduce Fractures for 3 to 5 Years

- Many large and well conducted clinical trials (>80,000 participants)
- 3 to 5 years
- Works especially well in people with osteoporosis and especially BMD <-2.5
- Bisphosphonates, Denosumab, newer treatments

6

Bisphosphonates Reduce Fracture Risk up to 5 Years



Khosla S, et al. *J Clin Endocrinol Metab* 97: 2272-2282, 2012

Benefits of Therapy: Fractures prevented in 10,000 osteoporotic women treated for 3 years*

	Fractures prevented
Hip	112
Spine	545
Non-vertebral	164
	822

Based on results from from large RCTS: FIT, HORIZON, VERT NA, others

* Like women in FIT, HORIZON, FREEDOM trials

8

What about Safety?

Impactful recent safety concerns:

- Osteonecrosis of the jaw (ONJ)
- Atypical femur fractures

9

ONJ and oral Bisphosphonates: Summary from ASBMR report, 2007

- Very rare in osteoporosis patients (1 in 10,000 to 100,000)
 - Higher in oncology use
- Invasive bone procedures (extraction) strongest risk factor. Weaker risk factors include:
 - > age 65, periodontitis, dentures,
- Little evidence that doses used for osteoporosis increase risk of ONJ
 - If so, VERY low risk
- 2012 ADA report (Hellstein et al) has helped to put concerns into perspective

Atypical subtrochanteric fractures: Case Reports and Case Studies

- First identified in case reports and case series (2006-2010)
 - NY and Singapore
- Associated with bisphosphonates?

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FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal 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 arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the uncortical beak. C, Hypertrophied cortices outlined.

Lenart et al NEJM 2008/ Goh J Bone Joint Sur. 2007

Morphologic Characteristics of Atypical Fractures from Case Reports



FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal 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 arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the uncortical beak. C, Hypertrophied cortices outlined.

Neviaser et al J. Ortho trauma 2008

ASBMR Task Force on Atypical Femur Fracture (2010/2014*)

- Begun in 2009, first published 2010
- Updated report (2014)
- Careful review of ever-growing literature
- Created a case-definition to standardize reporting and research

*Shane, et. al. JBMR, 2010 & 2013

ASBMR Task Force Case Definition for Atypical Femur Fracture (Update 2013)*

- Major Criteria (must have ≥ 4)
 - Location: Below lesser trochanter above distal metaphyseal flare
 - Transverse or short-oblique (from x-ray)
 - Minimal or no trauma
 - Non- or minimally comminuted
 - Localized reaction in lateral cortex
- Minor Criteria (may be present)
 - Increased cortical thickness (generalized)
 - Prodromal symptoms (pain in thigh/groin)
 - Bilateral
 - Delayed healing

*Shane, et. al. JBMR, 2010/2013

What types of Studies Assessing Incidence of AFF and Relationship to BP use?

- 1) Individual case reports and case series (from 2007)
 - Total > 230 cases published
 - 2) Observational/epidemiologic studies (Canada, Denmark, US, Sweden, other countries)
 - Mostly sets of cases compared to controls
 - A couple of cohort studies
 - 3) A bit of data from RCT's
- 2013: meta-analysis of bisphosphonates and atypical fracture (Gedmintas, JBMR, 2013)

2 of the largest epidemiologic studies

1. Swedish study (Schilcher)
2. Kaiser NW, U.S. (Feldstein)

Both:

- Population based
- Reviewed individual x-rays from fracture patients

Schilcher et al, NEJM 5/11
Feldstein, JBMR 2012

How many fractures are atypical? Swedish data, 2008

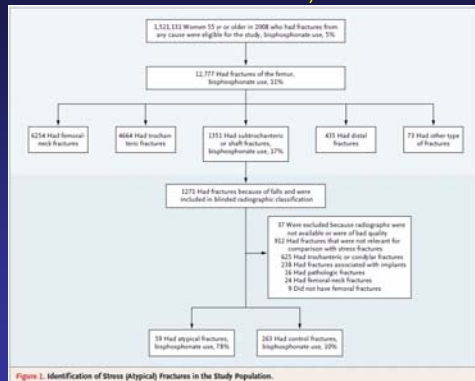


Figure 1. Identification of Stress (Atypical) Fractures in the Study Population.

* Schilcher, et al. NEJM 2011

17

Swedish study of Bisphosphonates and Atypical Fracture

- All hip fractures in Sweden 2008 (12,777)
- ICD-10 (S722 and S723) in National Register
 - Subtrochanteric or femoral shaft (n=1271)
- 1234 X-rays Retrieved /reviewed for AFF, ASMBR-like criteria
- Link to pharmaceutical register (3 yrs only)

Schilcher et al, NEJM 5/11

What is the incidence of AFF?

- Seemingly simple question
- Quite complex, no clear answer
 - Depends on definition of AFF
 - Depends on population studied. Not many population-based studies
 - How many treated with bisphosphonates?
- Incidence estimates (women > age 50) range from ~1 to 15 per 10,000

A different question: How common are AFF compared to all hip fractures??

19

Swedish study: How many with AFF?

- 1.5 million Swedish women > age 55
- ~12,777 femur fractures in 2008
- 322 met review criteria for subtrochanteric/FS
 - 59 atypical

Schilcher et al, NEJM 5/11

A handle on number of AFF's per hip fracture?

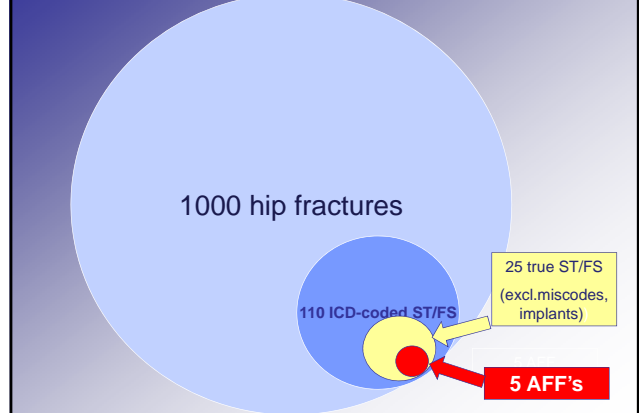
- Schilcher and Feldstein are only population-based studies with x-ray evaluation
- ASMBR (2010-like) evaluations

Study	Hip fractures	AFF fractures*	AFF per 1000 hip
Schilcher	12,700	59	4.6
Feldstein	5034	22	4.4

- Use this number to compute risks for BP treatment for 3-5 years

21

How common are AFF compared to all hip fractures?
From Swedish study of Schilcher et al. (NEJM, 2011)

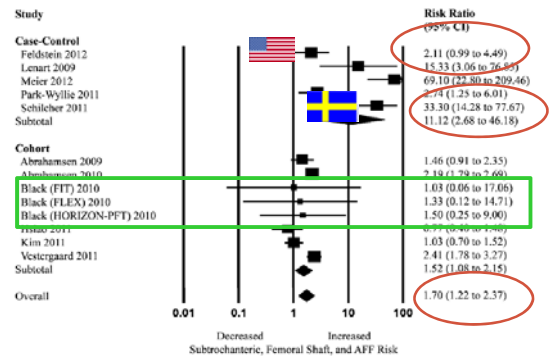


How Strong is relationship of bisphosphonates to AFF fracture risk?

- Wildly varying relative risks for bisphosphonate use:
- Swedish studies: Relative risk > 65 (!)
- Kaiser NW study: Relative risk = 2.1

Feldstein, Black, et al. JBMR 2012

2013 Meta-analysis of atypical femur fracture studies: 13 case-control and cohort studies*



*Gedmintas L, et al J Bone Miner Res. 2013

Risks for AFF

- Incidence of AFF: 5 AFF per 1000 hip fractures
- Vary assumptions for relative risk of BP use and AFF.
 - Meta analysis: 1.7 (1.2, 2.4)
 - Other sources: 11.8

Gedmintas....

Benefits vs. Risks of BP treatment

Scenario:
Treat 10,000 osteoporotic women for 3 years

27

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Table 3. Number of Patients Who Would Need to Be Treated for 3 Years with Bisphosphonates to Prevent One Fracture versus the Hypothetical Number Associated with an Increase of One Atypical Femur Fracture.¹⁰

Variable	No. Needed to Treat (3 yr) [†]	No. of Events Prevented per 1000 Patients Treated (3 yr)
Type of fracture		
Any nonvertebral, including hip	35	29
Hip	90	11
Vertebral fracture (morphometric)	14	71
Any fracture		100
	No. Needed to Harm (3 yr) [‡]	No. of Atypical Femur Fractures Associated with Treating 1000 Women for 3 Yr
Hypothetical relative risk of atypical femur fracture		
1.2	43,300	0.02
1.7	12,400	0.08
2.4	6,200	0.16
11.8	800	1.25

Black, Rosen. NEJM 1/16

Benefits vs. Risk, 10,000 women treated 3 years

	Fractures prevented	RR for AFF	AFF caused
Hip	112		
Spine	545		
Non-vertebral	164		
	822		
		1.7	0.1
		12 (worst case)	1.2

29

BP treatment: the Bottom Line

Benefits for BP and other osteoporosis treatment (for 3-5 years) far outweigh any risks, even allowing for some risk of AFF.

What about treatment beyond 5 years?.... Stay tuned.

30

Long-term treatment: Controversies and unresolved questions..Where to start?

- Can we predict risk of AFF? (very interesting)
 - Use prior AFF (or focal thickening), duration of treatment, time since therapy, gender, race (asian high?) (need data..Rick Dell, Kaiser Calif. DB)
- Optimal sequential LT therapy (and combo)
- Benefits of long term use of bisphosphonates and other therapies
- Do A-R's cause AFFs? If so, how long and what is magnitude of risk?
- Does treatment now prevent fractures in 20 years?
- How to decide when to stop therapy and how long should drug holiday be? When to restart?

Thanks for listening!



32