

Osteoporosis Update

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Disclosure Information

- I have the following financial relationships to disclose:
 - Consultant on a Data Monitoring Committee for Merck Sharpe & Dohme
- I will not discuss off label use and/or investigational drug use in my presentation

Controversies & FAQ in Osteoporosis

- Who to screen among younger postmenopausal women?
- How to define osteoporosis in men?
- Who to screen among older men?
- How often to screen and when to stop screening?
- Should patients with osteopenia receive drug treatment?
- How long to treat with bisphosphonates?

Who to Screen: Women Age 50-64

- No data available on benefit of drug treatment beginning at age 50-64 and continuing over 3-4 decades
- Despite rapid rates of bone loss during menopausal transition, fracture risk for any given BMD much lower in younger vs. older women

5-Yr Probability of Fracture in Postmenopausal Women According to Baseline Age

Age, years	Clinical Vertebral Fracture, %	Hip Fracture, %	Other Fractures, %
50-54	0.3	0.0	1.7
55-59	0.5	0.2	2.1
60-64	1.0	0.2	3.1
65-69	1.6	0.8	4.3
70-74	2.5	1.6	6.3
75-79	3.8	4.0	7.6
80-84	3.8	6.9	10.9
85-89	3.8	16.7	14.2

Who to Screen: Women Age 50-64

- Early drug treatment leads to prolonged duration of use-increased risk of net harms
- Overtreating younger women when fracture risk low leaves them with fewer options in their 70s, when hip fracture risk increases exponentially

Who to Screen: Women Age 50-64

- Risk assessment to select younger postmenopausal women for screening uncertain
- Current clinical guidelines encourage BMD testing in younger women with risk factors for fracture, but no agreement regarding which factors to choose
- Other approaches include use of weight alone (e.g. <70 kg), use of age and weight (e.g. OST) and use of fracture risk assessment tool (e.g. FRAX)
- USPSTF (2011) recommended screening women age 50-64 at increased fracture risk as defined by FRAX cutpoint

Osteoporosis Self-Assessment Tool (OST)

- Simple risk calculator designed to identify individuals more likely to have low BMD
- OST score = [wt (kg) - age (yrs)] X 0.2
- OST score < 2 proposed as cutoff to select younger postmenopausal women for BMD testing

Cadarette SM et al. Osteoporos Int 2004; 15:361-366

Gourlay ML et al. Osteoporos Int 2005; 16:921-927

USPSTF Approach to Select Women 50-64 for BMD Testing

- Select women aged 50-64 yrs for BMD testing who have $\geq 9.3\%$ 10-yr probability of major osteoporotic fracture as calculated by FRAX tool
- Rationale for threshold: 65 year old white woman, average height and weight (5 ft 5 in; 150 lbs), no additional risk factors

Comparison of OST vs. USPSTF Approach in Women Age 50-64

- 36% (OST<2) vs. 15% (USPSTF approach, FRAX >9.3%) of women selected for BMD testing

Untreated Participants (n=2163)	Identification of Osteoporosis (Femoral Neck BMD T-score ≤ -2.5)			
	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	AUC (95% CI)
OST <2 (tool based on age & weight)	79	70	15	0.75
USPSTF (FRAX ≤ 9.3)	33	86	14	0.60

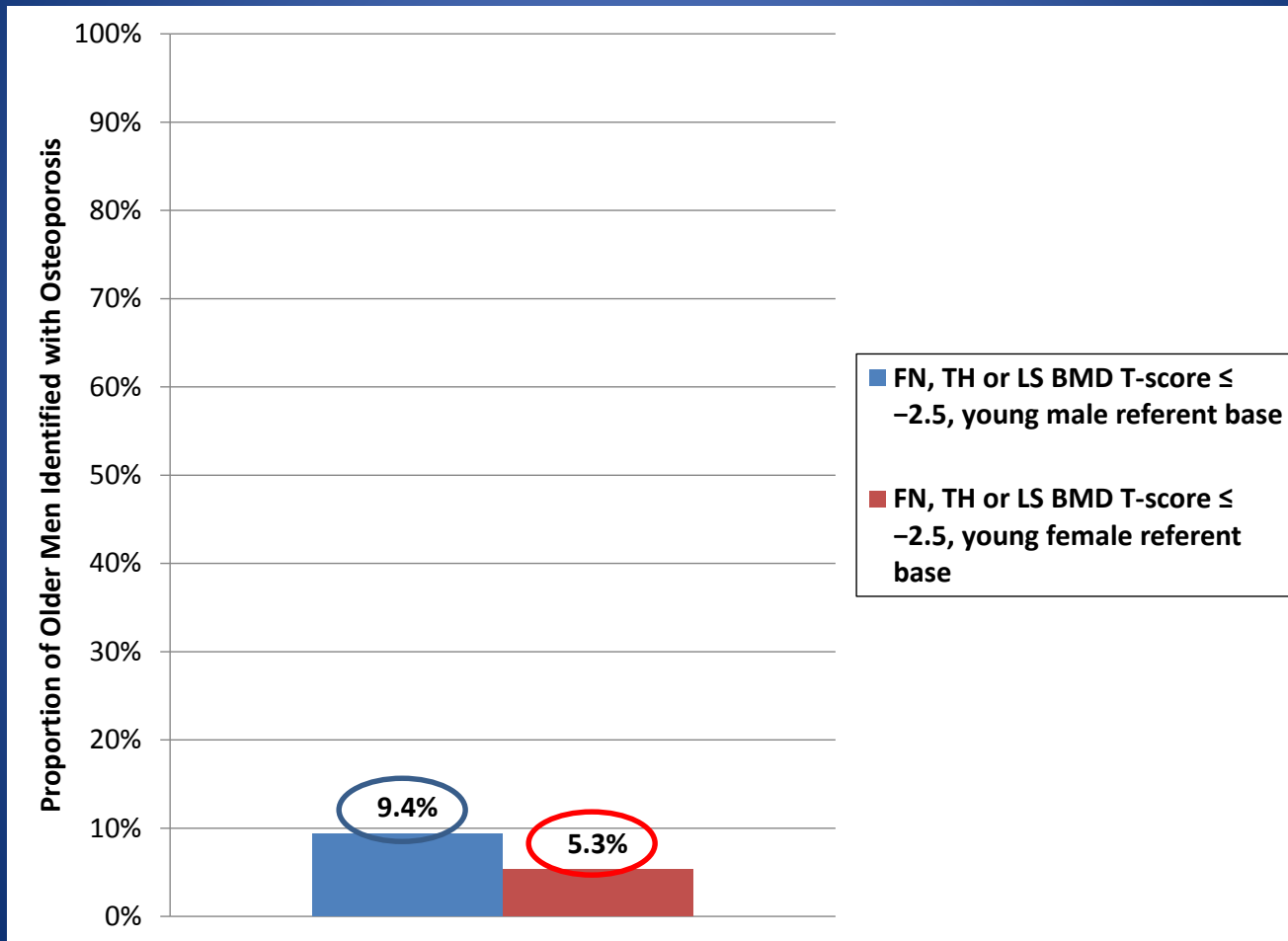
Who to Screen: Women Aged 50-64

- Complex risk assessment tools do not perform any better than simple tools in selecting younger postmenopausal women for BMD testing
- Despite accelerated bone loss associated with menopause, rates of major fracture events are **LOW**
- “Need a baseline” is not strong rationale for ordering BMD test
- **IF** drug treatment will be initiated for T-score ≤ -2.5 , consider use of OST to determine if BMD testing is warranted

How to Define Osteoporosis in Men

- BMD cutoff value in men to identify osteoporosis has been controversial (male specific vs. female specific cutoff value?)
- At femoral neck:
 - 0.592 g/cm² is male specific T score of -2.5
 - 0.558 g/cm² is female specific T score of -2.5

Proportion of Older Men Identified with Osteoporosis



How to Define Osteoporosis in Men

- Similar relative risk of fracture per unit ↓ in hip BMD in men and women
- For any given absolute value of hip BMD, age-adjusted hip fracture rates similar in men and women
- Diagnosis of osteoporosis in men should be based on same BMD cutoff value used in women, **female specific T score -2.5 or below**

Who to Screen: Older Men

- No RCT in men has demonstrated benefit of drug treatment in reducing clinical fractures
- BMD testing proposed in older men to prevent fractures largely because it is accepted strategy in older women

Who to Screen: Older Men

- Some guidelines recommend BMD testing in all men ≥ 70 yrs and in men 50-69 yrs with clinical risk factors
- ACP (2007): BMD testing in men at increased risk of osteoporosis who are candidates for drug treatment
- USPSTF (2011): No recommendation, but men most likely to benefit from screening have 10-year probability of major osteoporotic fracture $\geq 9.3\%$
- Other potential approaches include use of wt alone (BMI < 20 to 25), age and wt (OST)

Qaseem A et al. Ann Intern Med 2008; 148:680-684

US Preventive Services Task Force. Ann Intern Med 2011; 154:356-364

Comparison of OST vs. USPSTF Approach in Men Aged ≥ 70

- 65% (OST) vs. 45% (USPSTF) selected for BMD testing

Untreated Participants (n=4053)	Identification of Osteoporosis (T-score ≤ -2.5 at Hip or Spine)		
	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)
OST (<2) (tool based on age & weight)	83 (77-87)	36 (35-38)	7 (6-8)
USPSTF (FRAX ≤ 9.3)	59 (52-66)	59 (57-60)	7 (6-9)

- AUC over full range of tool: 0.68 for OST vs. 0.62 for FRAX

Who to Screen: Older Men

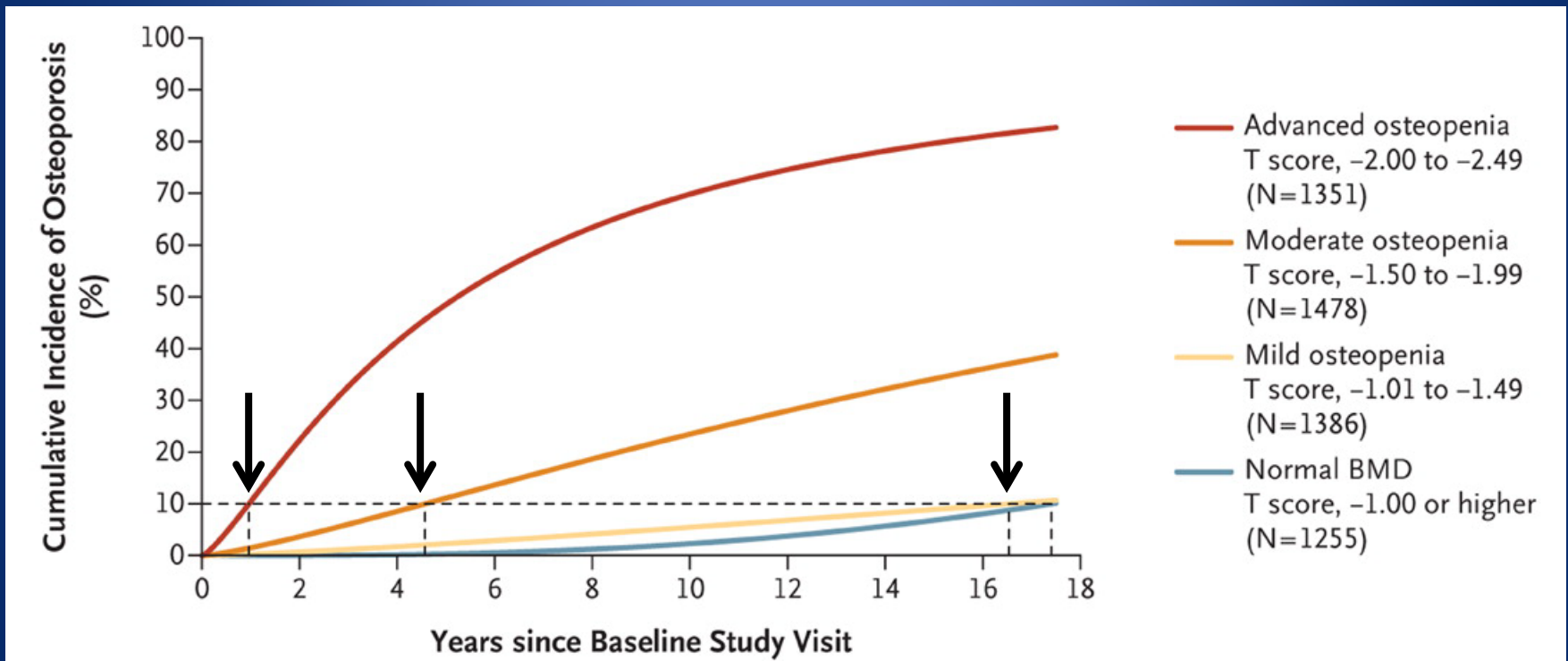
- Recommendations for universal screening of all men age ≥ 70 may be premature
- OST performs better than more complex FRAX-based strategy to select older men for BMD testing
- Additional research on development and validation of risk assessment tools is warranted

How Often to Screen Older Adults

- Bone loss accelerates with advancing age in both sexes
- Paucity of data to guide decisions about the interval between BMD tests

How Often Should Older Women Be Screened?

Unadjusted Cumulative Incidence of Osteoporosis According to Baseline T-Score Range



How Often Should Older Men Be Screened?

Time for 10% of Men without Osteoporosis to Transition to Osteoporosis

Baseline T-score range	Osteoporosis events, n (%)	Time interval for 10% of ppts to develop osteoporosis	
		Unadjusted years (95% CI)	Adjusted years (95% CI)
> -1.50 (normal BMD or mild osteopenia)	9/4203 (0.21)	–	–
- 1.50 to - 1.99 (moderate osteopenia)	35/680 (5.15)	8.57 (6.67, 10.99)	8.51 (6.67, 10.86)
- 2.00 to - 2.49 (advanced osteopenia)	73/352 (20.74)	2.59 (2.03, 3.30)	2.68 (2.12, 3.40)

How Often to Screen Older Adults

- Baseline BMD is **MAJOR** determinant of BMD testing interval in older adults without osteoporosis at initial assessment
- Lower the BMD at initial assessment, shorter the rescreening interval

When to Stop Screening?

- Age to stop or decrease use of BMD testing has not been examined
- Women with high BMD T-scores (e.g. > -1.5) have very low risk of fracture before estimated time to death and benefit less from rescreening
- Women with low BMD T-scores (e.g. between -2.0 and -2.5) have high risk of fracture before estimated time to death and benefit more from rescreening
- Age to stop may be lower in men vs. women due to higher competing risk of mortality

Who to Treat: RCT Evidence for Drug Treatment to Prevent Fracture (Fx)

- In postmenopausal women with BMD T-score ≤ -2.5 or existing radiographic vertebral fxs:
 - Some drug treatments (bisphosphonates and denosumab) lower risk of clinical fxs incl hip fxs
 - Several drug treatments lower risk of new radiographic vertebral fxs
- IV zoledronic acid lowers risk of clinical fxs among patients with recent hip fx

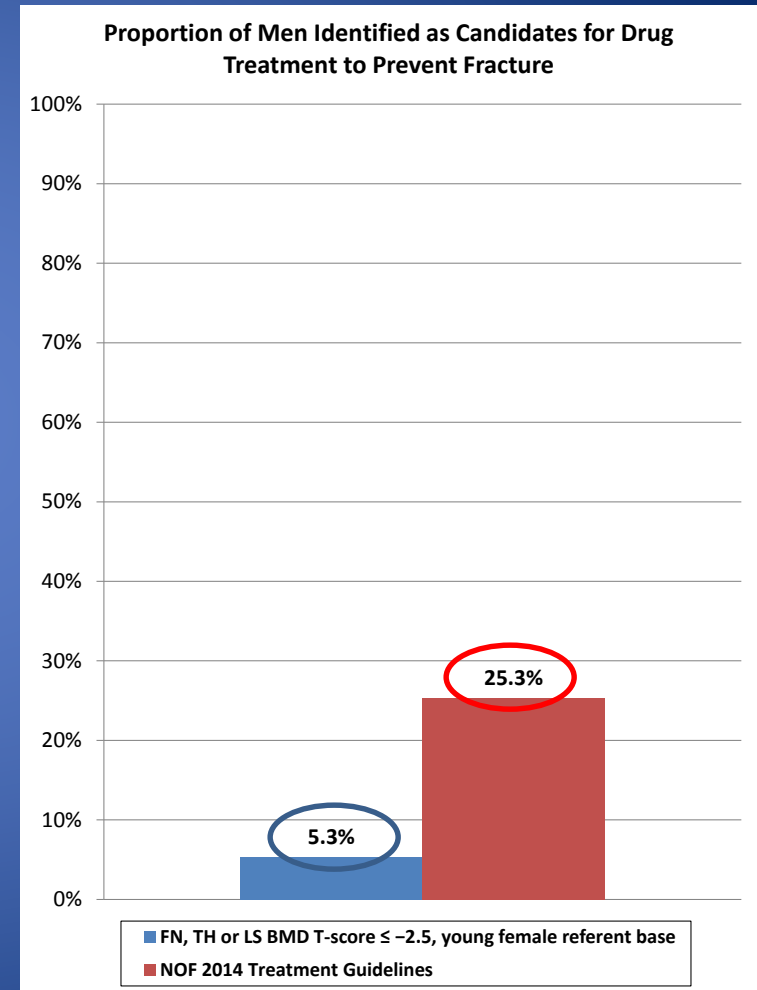
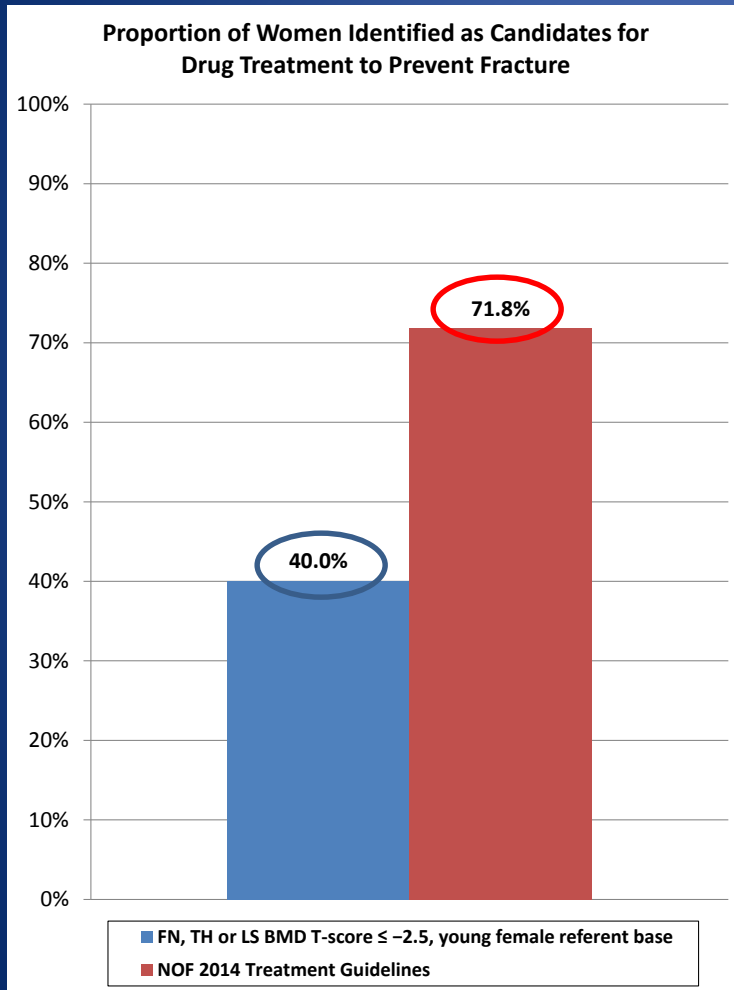
Expanding Indications for Drug Treatment to Prevent Fracture

- Some US guidelines (NOF, Endocrine Society) endorse use of FRAX thresholds to aid in decision whether or not to initiate drug treatment in adults aged ≥ 50 yrs with osteopenia (T-score between -1.0 and -2.5)
 - 10 yr hip fx probability $\geq 3\%$
 - 10 yr major osteoporotic fx (MOF) probability $\geq 20\%$

Movement to Broaden Criteria by Which Osteoporosis is Diagnosed

- National Bone Alliance 2014 Position Paper
 - “Postmenopausal women and men ≥ 50 yrs should be diagnosed with osteoporosis if they have elevated risk for future fractures”
 - Increased fracture risk defined as 10 yr hip fx probability $\geq 3\%$ or 10 yr MOF probability $\geq 10\%$

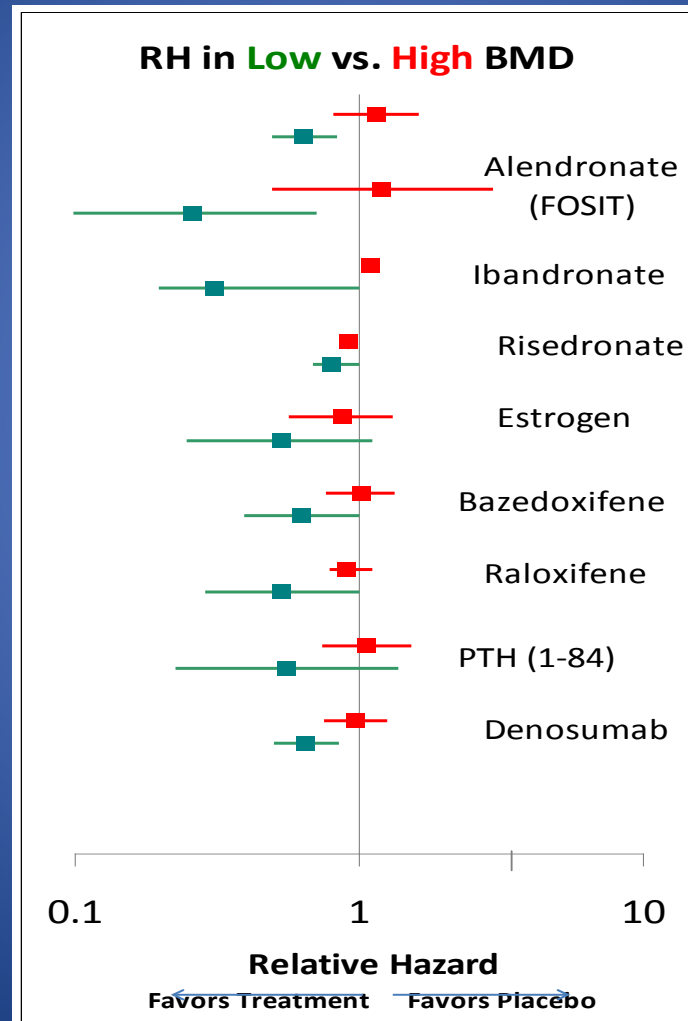
Proportion of Older Adults Identified as Candidates for Drug Treatment to Prevent Fracture



Effect of Alendronate Treatment on Risk of Clinical Fractures According to BMD T-score

BMD T-score	Placebo, n/N (%)	Alendronate, n/N (%)	RH (95% CI)
< -2.5	159/812 (19.6)	107/819 (13.1)	0.64 (0.50-0.82)
-2.5 to -2.0	87/710 (12.3)	92/726 (12.7)	1.03 (0.77-1.39)
-2.0 to -1.6	66/696 (9.5)	73/669 (10.9)	1.14 (0.82-1.60)

Relative Hazard of Clinical Fracture According to Treatment and BMD



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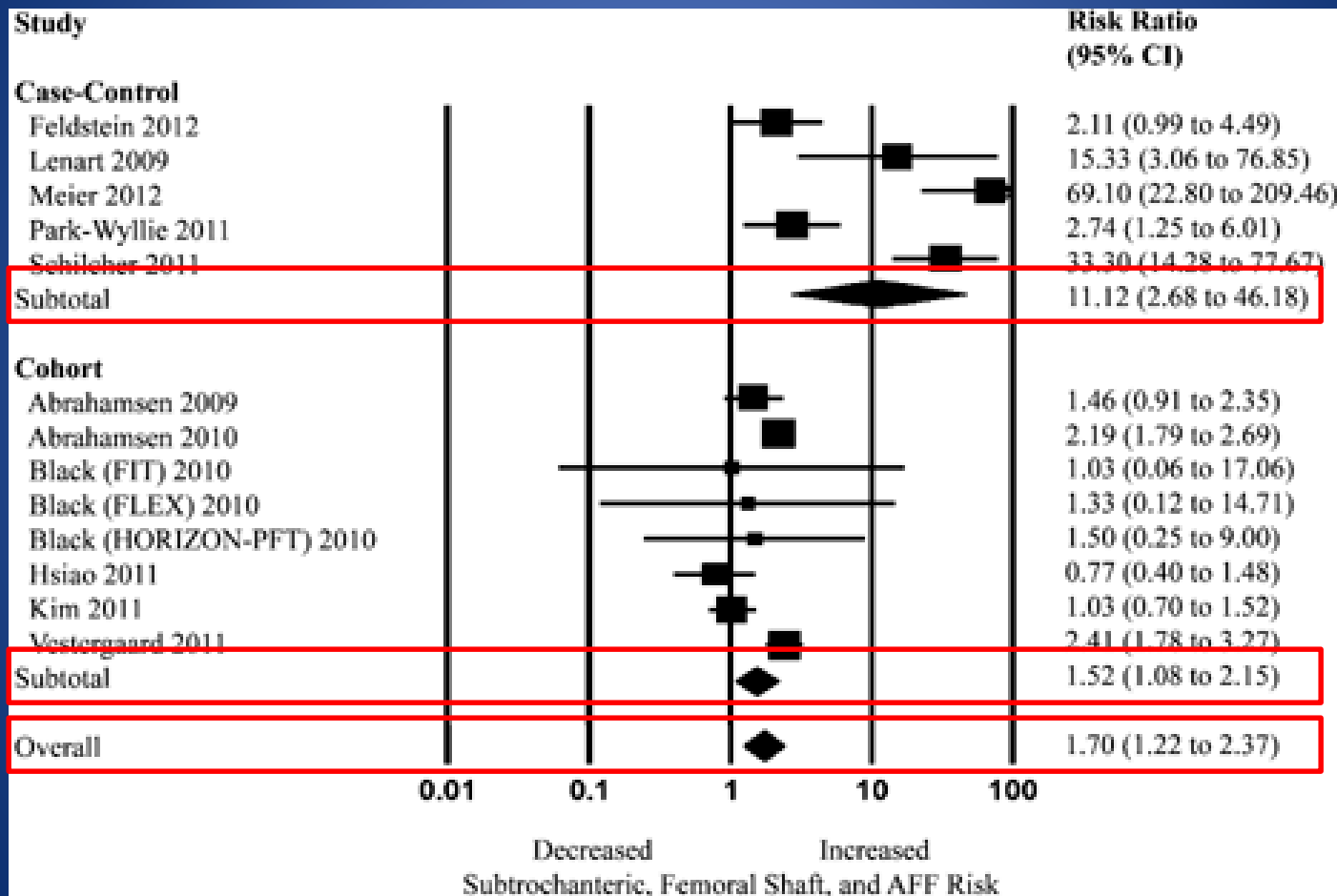
What about Patients with BMD T-score > -2.5 ?

- Effectiveness of drug treatment in reducing clinical fxs among middle-aged and older adults without prevalent vertebral fxs and T-score > -2.5 unproven
- Adoption of NOF FRAX treatment thresholds labels a substantial proportion of older adults with a problem that might not benefit from drug treatment
- RCT are warranted to determine if drug treatment is efficacious among patients with T scores > -2.5 selected on the basis of high fracture risk

How Long to Treat with Bisphosphonates?

- Potential long-term safety issues:
 - ONJ, atypical femoral fractures (AFF)
- ONJ incidence very low (<1 case per 10,000 patient treatment years)
- AFF are rare events in the general population (3 AFF vs. 103 hip fxs per 10,000 person-yrs)
- Concerns of many women regarding these adverse effects have become a barrier to treatment initiation and adherence

Association of Bisphosphonate Use with AFF



Effect of Stopping vs. Continuing Alendronate Treatment on Fracture Risk

- Among older women who used alendronate for 5 yrs, those randomized to placebo vs. those randomized to alendronate for additional 5 yrs had
 - Similar rate of nonvertebral fx and new radiographic vertebral fx
 - Higher rate of clinical vertebral fx

Effect of Stopping vs. Continuing Zoledronic Acid Treatment on Fracture Risk

- Among older women who received zoledronic acid annually for 3 yrs, those randomized to placebo vs. those randomized to zoledronic acid for additional 3 yrs had
 - Similar rate of nonvertebral fx and clinical vertebral fx
 - Higher rate of new radiographic vertebral fx

Fracture Risk Prediction After Bisphosphonate Discontinuation

- Older age and lower hip BMD (BMD T score ≤ -2.3) at time of discontinuation of alendronate were associated with higher risk of clinical fractures after discontinuation
- Follow-up BMD measurements 1 yr after alendronate discontinuation and bone turnover markers 1-2 yrs after discontinuation were not associated with fracture risk after discontinuation

How Long to Treat with Bisphosphonates?

- Drug holiday should be considered in women after 3-5 yrs of oral bisphosphonates or 2-3 yrs of IV bisphosphonates
- Women with low BMD (e.g. T-scores ≤ -2.5) at this time point or those who experienced major osteoporotic fracture on treatment should consider continuing treatment
- No data to support periodic monitoring of BMD or bone turnover markers during holiday

How Long to Treat with Bisphosphonates?

- Among women on drug holiday, reassess BMD and fracture risk 3-5 yrs after discontinuation
- Further research warranted to quantify fracture risk after discontinuation and to determine best practice strategy for patients who remain at high fracture risk after discontinuation

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"I think we can rule out osteoporosis."