Osteoporosis
Year in Review and Case Studies

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Case 1

It's hard enough to get control of this blood sugar – do I really have to address bone health?

- 56yo female with Type 2 DM since the age of 30 presents in routine follow up
  - Her diabetes is complicated by microalbuminuria and mild to moderate peripheral neuropathy
- The only change in medical history is that she stepped awkwardly off of a curb while walking her dog last fall and fractured her distal tibia
- She underwent menopause at the age of 49; she has never had a fracture before
- She does not require steroids, has no family history of osteoporotic fracture, quit smoking in 1983
- She has had no height loss from her youth
- She has never had a DXA; she doesn't take any vitamins or supplements

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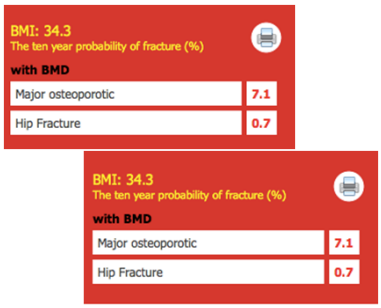
Case 1

- PE: BMI 35 (64”, 200#)
  - Height unchanged over the past 6 years
  - No kyphosis on exam
  - 1/4 monofilament bilat
- HgbA1C 8.8%
- Nl Creat and TSH
- Vitamin D 36
- Total calcium 9.8 with normal albumin
- PTH 96 pg/mL (normal 14 – 72)

- DXA results:
  - LS 1-4: T-score -1.6
  - LTH: T-score -1.2
  - LFN: T-score -1.8

FRAX Score: With out “secondary”



BMI: 34.3
The ten year probability of fracture (%)
with BMD
Major osteoporotic
7.1
Hip Fracture
0.7

What do we make of this secondary hyperparathyroidism?

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Diabetes and Bone Disease

- There is an increased risk for fracture in diabetics compared with normoglycemic controls
- The degree of bone loss differs between Type 1 and Type 2
- Often see higher BMD in Type 2 – due to weight
  - Insulin is a growth factor in bone, and insulin is often started later in adult life in Type 2 diabetics
  - Type 1 diabetics may never achieve peak bone mass, given onset in youth and adolescence
- Bone fragility seems to contribute to fracture risk independent of BMD, especially in Type 2 DM
- Hyperglycemia contributes to hypercalciuria and secondary hyperparathyroidism
- Advanced glycation end-products contribute to bone fragility

Tuominen JT et al. Diabetes Care 1999; 22:1196
Verhaeghe J, et al. J Bone Miner Res 1994; 9:1657
Melton LJ et al. J Bone Miner Res 2008; 23:1334

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Diabetes and Bone Disease

- WHI Observational Study of 93,676 postmenopausal women, those with Type 2 DM (n+5285) had an increased risk of fracture after f/u compared with women without[1]
- Association between risk of fracture and longer DM duration, presence of retinopathy, neuropathy, and + insulin treatment has been seen repeatedly
- BMD is often lower in Type 1 DM and higher in Type 2 DM, compared with control non-diabetic cohorts, but fracture risk is higher in all types of diabetics compared with nondiabetics[2]
- Neuropathy specifically increases fracture risk through localized bone loss at the foot and ankle, and also reduced proprioception with increased risk for falls

[1]Bonds DE, et al. J Clin Endrocrinol Metab 2006; 91:3404
[2]Vestergaard P, et al. Osteoporos Int 2007; 18:427

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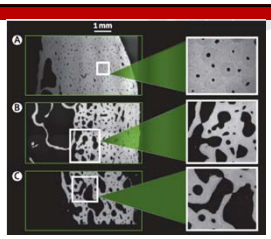
Diabetes and Bone Pathogenesis



- Why the increased fracture despite normal or increased BMD?
- Advanced glycation end-products (AGEs)
  - Increased collagen glycosylation may contribute to fragility of diabetic bone – this is not measurable with BMD
- Diabetic renal/uremic disease
  - Hyperparathyroidism, also adynamic bone disease with more end-stage renal disease
- Increased cortical porosity[1]
  - Studies of HR-pQCT in 332 participants with and without diabetes in the Hertfordshire Cohort Study
  - More porous bone seen in cortical areas of distal radius and distal tibia
  - AGEs causing oxidative stress and inflammatory response?

[1]Paccou J, et al. Calcif Tissue Int , December 2015, ePub ahead of print
Zebaze RM et al. The Lancet 2010;375:1729-36

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Evaluation of bone disease in the diabetic patient

- Consider DXA measurement in postmenopausal women prior to the age of 65 with diabetes, and men with diabetes with any other risk factor for fracture
- Evaluate for secondary cause of bone loss, and have a low threshold for ordering 24 hour urine to r/u hypercalciuria
- Can we use FRAX?[1]
  - Currently there is no FRAX manipulation or consideration of the presence of diabetes
  - Meta-analysis of SOF, MrOS and the Health ABC Research data shows for a particular FRAX score, in diabetics the fracture risk is higher
  - Use of FRAX will likely underestimate fracture risk

Schwartz AV, Black DM et al. JAMA 2011; 305:2184

Bone Disease and DM: Treatment

- Despite long-standing observation that there is an increased incidence of fracture in diabetics, no studies have looked particularly at therapy for osteoporosis in diabetes
- PPAR activators likely enhance adipogenesis but decrease osteogenesis – if possible, thiazoladinediones should be avoided in diabetics with osteoporosis or fractures
- Small subsets of larger studies have shown no difference in the fracture reduction potential of both alendronate and raloxifene in those with Type 1 and Type 2 diabetes
- NOF recommendations: follow larger treatment recommendations as outlined in the Clinician's Guide to Prevention and Treatment
- Remember the importance of calcium supplementation, replace vitamin D deficiency, emphasize smoking cessation, consider PT referral for fall reduction (especially in those with retinopathy or neuropathy or myopathy), avoid sedentary lifestyle

Denosumab (Prolia) – ongoing Phase III trial data

- Fully human monoclonal antibody to the receptor activator of nuclear factor-kb ligand (RANKL) that blocks its binding to RANK
- Inhibits development and activity of osteoclasts
- Decreases bone resorption, increases bone density
- RANKL expressed on precursors of osteoblasts, marrow stromal cells and activated T cells

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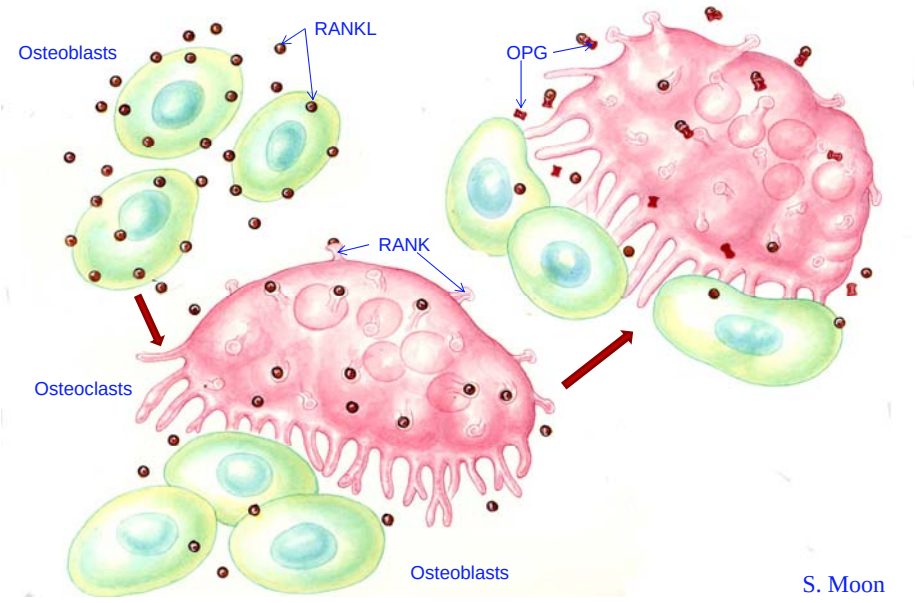
RANKL Pathway Involvement in Bone Remodeling



S. Moon

Table 1. Baseline Characteristics of the Subjects.*

Variable	Denosumab (N=3902)	Placebo (N=3906)
Age		
Mean — yr	72.3±5.2	72.3±5.2
Group — no. (%)		
<70 yr	1030 (26.4)	1028 (26.3)
70–74 yr	1637 (42.0)	1642 (42.0)
≥75 yr	1235 (31.7)	1236 (31.6)
Body-mass index†	26.0±4.1	26.0±4.2
Region — no. (%)‡		
Western Europe	1761 (44.8)	1773 (45.1)
Eastern Europe	1374 (34.9)	1355 (34.4)
Latin America	472 (12.0)	462 (11.7)
North America	282 (7.2)	297 (7.5)
Australia and New Zealand	44 (1.1)	48 (1.2)
T score		
Lumbar spine	−2.82±0.70	−2.84±0.69
Total hip	−1.89±0.81	−1.91±0.81
Femoral neck	−2.15±0.72	−2.17±0.71
Prevalent vertebral fracture — no. (%)		
Yes	929 (23.8)	915 (23.4)
No	2864 (73.4)	2854 (73.1)
Unreadable or missing data	109 (2.8)	137 (3.5)
Serum 25-hydroxyvitamin D — ng/ml§	23.1±11.7	22.9±11.3

FREEDOM Trial
Baseline characteristics

3- year trial of denosumab in postmenopausal osteoporosis

Cummings S et al, NEJM, August 2009, 756 - 765

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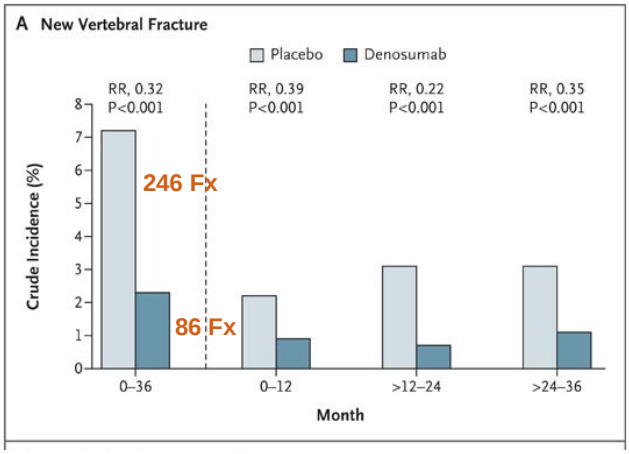
FREEDOM Trial: Incidence of new Vertebral Fracture



Cummings S et al, NEJM, August 2009, 756 - 765

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Denosumab Freedom Data

- As of 9/2013, exposure was 1,252,566 patient years
- See persistent suppression of bone turnover markers, ongoing increase in bone density and sustained fracture reduction
  - Four post-marketing reports of AFF, as defined by ASBMR
    - All had previously been on bisphosphonates
  - 32 cases of ONJ, as defined by AAOMS
  - 5 reports of analyphylaxis – none fatal
- Conclusion:
  - Postmarketing safety surveillance has not shown any unexpected findings
  - The benefits are greater than the risks
  - It remains an important choice for fracture reduction in the treatment of postmenopausal osteoporotic women at moderate to high risk for fracture
    - Especially if they have difficulty with oral bisphosphonates, intolerant or unresponsive to other therapies, or have renal insufficiency

Geller M, Wagman RB, etc. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Disease, April 2014, OC40
Osteoporosis International 2014

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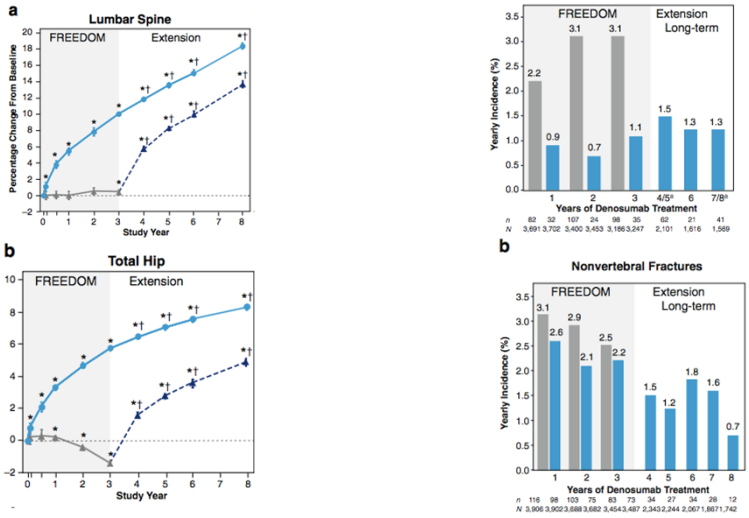
Denosumab FREEDOM Extension Trial (8 year data)



Papapoulos S, Lippuner K, Bone HG et al. Osteoporos Int 2015; 26:2773-2783

Case Report:

- 62yo WF presents for her yearly exam
- She's not had any height loss, no personal history of fracture
- Smokes "6 cigarettes a day"
- Mom broke her hip at age 78
- Normal menstrual history; 3 pregnancies
- Should you order a bone density test, or is it too soon?
- DXA: LS T-score -1.8, Fem Neck -2.1

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NOF Screening Guidelines

- DXA:
  - Women ≥65
  - Men ≥70
  - Postmenopausal women and men aged 50-69 based on risk factor profile
  - Postmenopausal women and men over age 50 who have had a fragility fracture
  - Screening of premenopausal women decided individually by clinician
  - Only to be done at facilities using accepted quality assurance
- Vertebral Imaging:
  - All women ≥70 and all men ≥80 with DXA T-score < -1.0
  - Women ≥65 and men ≥70 if T-score ≤ -1.5
  - In those with low trauma fracture in adulthood
  - Those with height loss 1.5" or more
    - Or a documented height loss of ≥ 0.8" based on reliable office measurement
  - Recent or ongoing long term glucocorticoid treatment

* Can be VFA or lateral thoracic and lumbar spine plain x-ray

www.nof.org; Clinician's Guide to Prevention and Treatment of Osteoporosis, updated 4/2014

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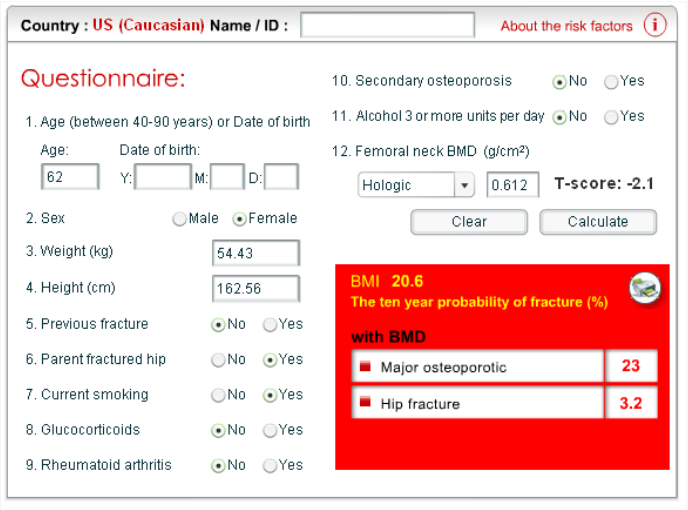


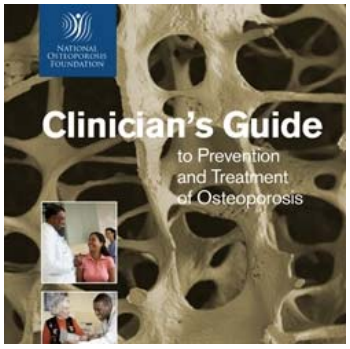
She has significant risk for fracture, and you decide to start her on alendronate.

Four years later . . .

- Has received bisphosphonates 4 years
- Clinically no change – except that she's quit smoking!
- Bone density over the past five years:
  - LS – increased by 5% - now -1.7
  - Total hip – increased by 4%; now -1.6

When can you consider stopping therapy?

2014 NOF Recommendations



- "No pharmacologic therapy should be considered indefinite in duration. After the initial treatment period, which depends on the pharmacologic agent, a comprehensive risk assessment should be performed. There is no uniform recommendation that applies to all patients, and duration decisions need to be individualized."

www.nof.org/ clinician's guide Updated April, 2014

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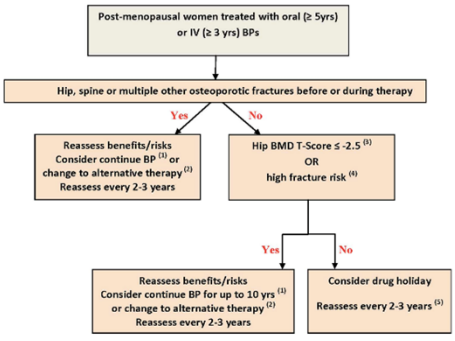
Drug Holiday

- 10 years of alendronate and 6 years (sequential) of zoledronic acid reduce the risk of vertebral compression fracture better than 5 and 3 years, respectively (FLEX and HORIZON)
- However, 5 years of aln and 3 years of zol followed by 2-4 year 'holiday' continues to reduce vert Fx risk better than never being treated
- Continued therapy longer than 5 years (oral) or 3 years (IV) may be indicated for people at highest risk for fracture
- BTMs (BSAP, CTx, P1NP) are likely not useful for risk stratification, but could be useful to time re-starting therapy



"Managing Osteoporosis in Patients on Long-term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research"

Black DM et al. JAMA 2006;296:2927-2938.
Bone HD et al. N Engl J Med 2004;350:1189-1199
Adler RA, Sellmeyer DE, et al. J Bone Miner Res 2016;31:16-35

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Risks of Bisphosphonates

- ONJ – first described in 2003 – definition by AAOMS:
  1) Exposed, necrotic bone in the maxillofacial region that has been present for at least 8 weeks despite appropriate therapy
  2) Exposure to potent antiresorptive agents, such as bisphosphonates or denosumab
  3) No history of radiation to the jaw
- Incidence of ONJ – 1/10,000 – 1/100,000 with oral bisphos
  - Associated with poor oral hygiene, smoking, diabetes, concomitant glucocorticoids, chemotherapy – see a trend of increasing incidence with time of exposure to bisphos
  - Associated with invasive dental procedures such as extractions or implants
- AFF – first described in 2005
  - Diagnosis: subtrochanteric, often with prodromal groin or lateral thigh pain, often occurs with no preceding trauma, originates at the lateral part of the cortex
  - Definite association with length of time of exposure to bisphosphonates – esp >5 yrs
  - Incidence lower than ONJ

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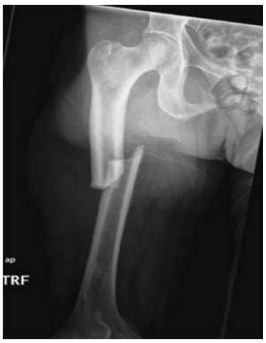
Atypical Femoral Fracture

- Patients on therapy for more than 3 years with thigh or groin pain should undergo imaging to identify stress reactions or fractures
- The risk of AFF seems to fall substantially within the first year after stopping therapy (Dell, et al)
- One study has shown improved fracture healing in 5 patients who received teriparatide for 6 months after fracture, vs. 9 patients who had slower healing and nonunion with conservative mgmt (Chiang CY)
- Case reports reveal those with AFFs that are later introduced to denosumab have developed recurrent AFF



McClung M. Clinical Ob Gyn 2013;56:743-748.
Dell RM, Adams AL, et al. J Bone Miner Res. 2012;27:2544-2550
Chiang CY, Zebaze RM, et al. Bone. 2013;52:360-365

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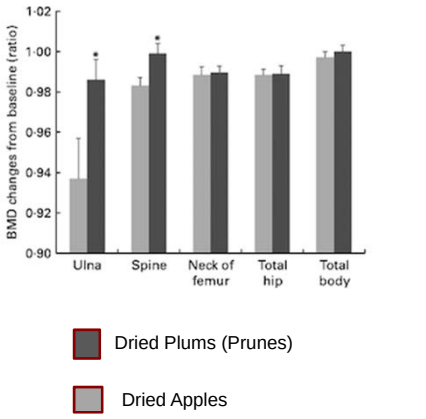
I really don't want to take any of those drugs. What else can I do?

- Dried Prunes – 65 PM women ate dried apples and 65 ate dried prunes x 1year
- Saw significant improvement in the prune group at the ulna and lumbar spine
- All groups took calcium and vitamin D
- Prunes have anti-oxidants but also Boron
- Subsequent studies have shown suppression of RANKL and sclerostin expression in the prune group



Hooshmand S, Arjmandi BH, et al. Br J Nutr 2011;106:923-930
Hooshmand S, Brisco JR et al. Br J Nutr 2014;112:55-60

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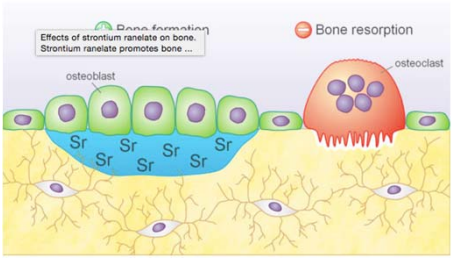
Other therapies - Strontium Ranelate

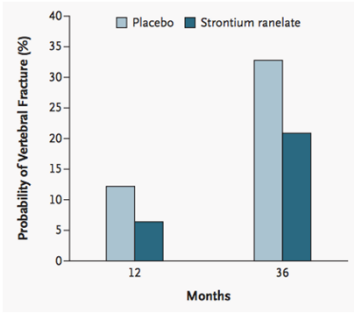
- Orally active agent with two atoms of stable strontium (Sr) and an organic moiety (ranelic acid)
- Simultaneously promotes osteoblastic bone formation and inhibits osteoclastic bone resorption – an 'anabolic' therapy
  - Strontium bonds to the extracellular domain of the calcium sensing receptor (CaSR) present in both osteoblasts and osteoclasts
- Can rebalance bone remodeling in favor of bone formation
- Strontium has been shown to be incorporated into the mineralized matrix formed during treatment

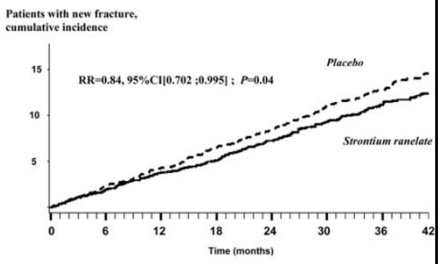


Querida W, Rossi AL, et al. Micron 2016;80:122-134

Strontium – Fracture Prevention

- Fracture data: two Phase III trials in postmenopausal women
- Dosing: 2grams strontium ranelate for three years
  - SOTI trial, Spinal Osteoporosis Therapeutic Intervention trial
  - TROPOS – Treatment of Peripheral Osteoporosis trial
  - Significant reductions in vertebral and non-vertebral fractures
  - Subsequent follow up trials have shown persistent fracture reduction after 5 and ten years of therapy.





Meunier PJ, Roux C, et al. NEJM, 2004;320:459-469
Reginster JY, Seeman E, et al. J Clin Endo Metab 2005;90:2816-2822

Strontium – Safety Concerns

- Strontium has been approved by the European Medicines Agency (EMA) for the treatment of osteoporosis
- April 2013 regulatory re-evaluation procedure was begun when it was noted that in increase in MI was observed in pooled analyses of safety *data from all randomized* controlled trials with strontium
  - Fu… cardiac risk was particularly pronounced in those wit…
  - Ne… ontium co… ***contrain…*** ***current*** tre… ***hy…*** ***or…***
- Stront… een app…
- NOF…
  - N… e treatment of osteoporosis
  - Tr… n is not fully understood
  - Pl… rontium ranelate made by Sevier is the or… ffect of strontium has not been studied in … s containing strontium salts

Reginster JY, Bran… 7-1671
www.nof.org/ clinician's guide Updated April, 2014

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In Summary

- Reviewed the latest data on pathophysiology of metabolic bone disease in diabetes
- Updated our information on the ongoing Phase III and extension trial of denosumab
- Explored the latest recommendations regarding ONJ, AFF and employing drug holidays
- Expand our information of the role of Strontium Ranelate in our osteoporosis treatment armamentarium

Hungry for more information on metabolic bone disease? Come to ***Bone Day 2016!***
Friday, November 4, 2016 here at the BRT

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