

Prevention and Treatment of Osteoporosis (What more do we need to know?)

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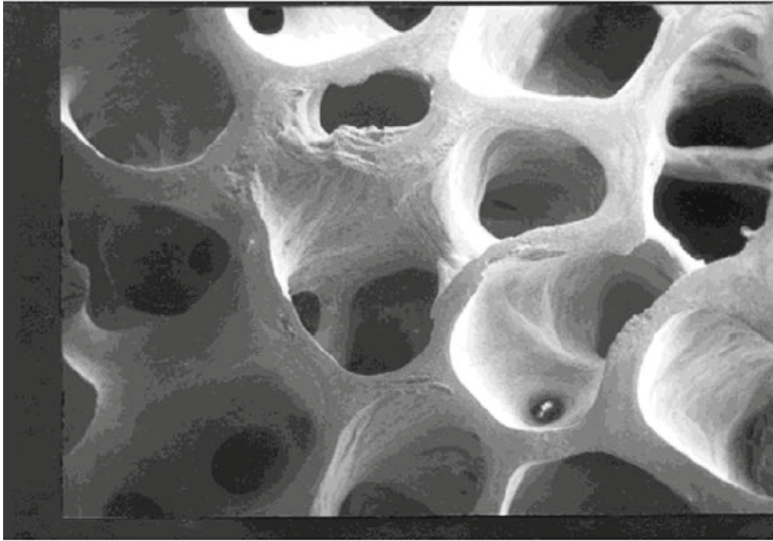
University of Montreal Hospital Center



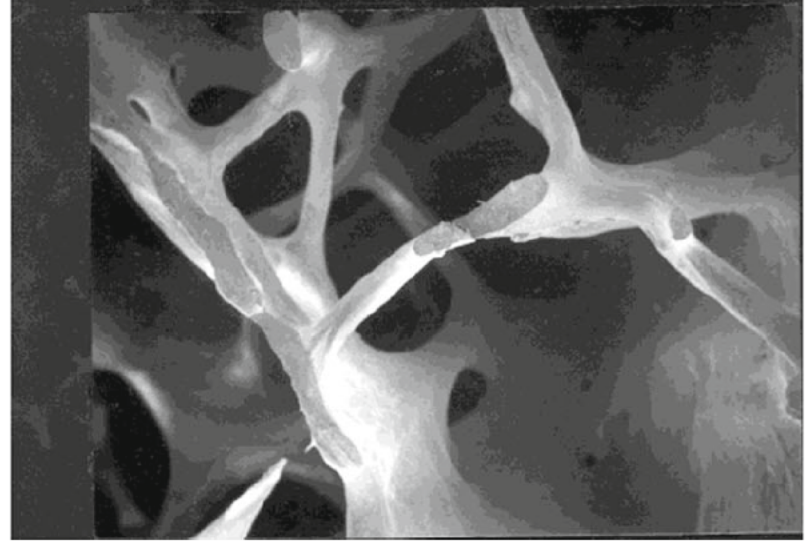
Disclosures

- Received honorarium as a consultant and funding for research (institution)
 - Amgen
 - Astellas
 - AstraZeneca
 - BMS
 - Bayer
 - Janssen
 - Sanofi

What are we trying to prevent/treat



Normal bone



Osteoporotic bone

Why Screen and Treat?

Risk and consequences of Osteoporosis



Peak bone mass achieved¹

Later

Earlier

Bone loss¹

Gradual

Accelerated after
menopause

**Hip Fractures²
Lifetime Risk**

4.6%

12.1%

**Vertebral Fracture
Prevalence³**

21.5%

23.5%

**Mortality 1 year post hip
fracture⁴**

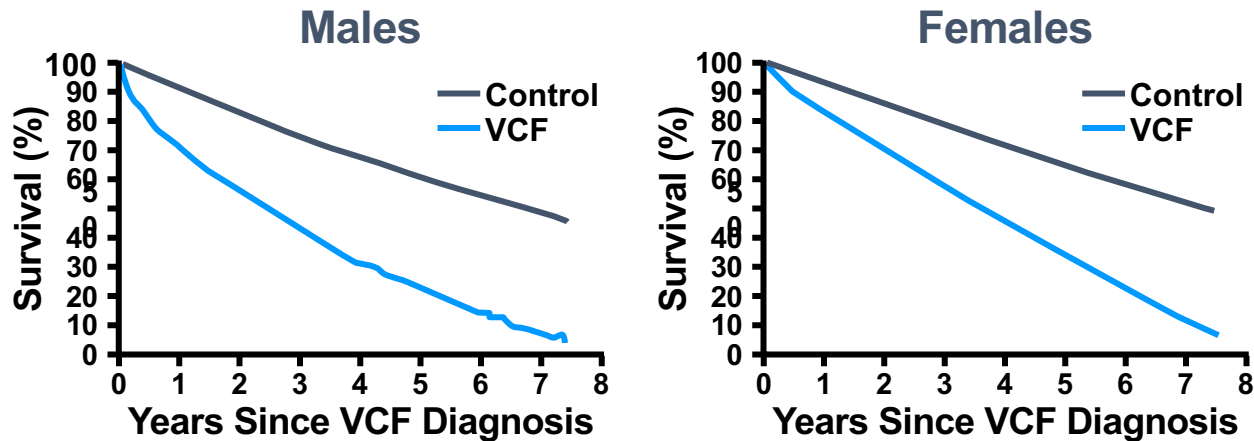
31-38%

12-28%

Seeman E. *J Appl Physiol.* 2003;95(5):2142-2151. 2. Hopkins RB, et al. *Osteoporos Int.* 2012;23(3):921-7.
3. Jackson SA, et al. *Osteoporos Int.* 2000;11:680-687. 4. Papaioannou A, et al. *Osteoporos Int.* 2008;19(4):581-587.

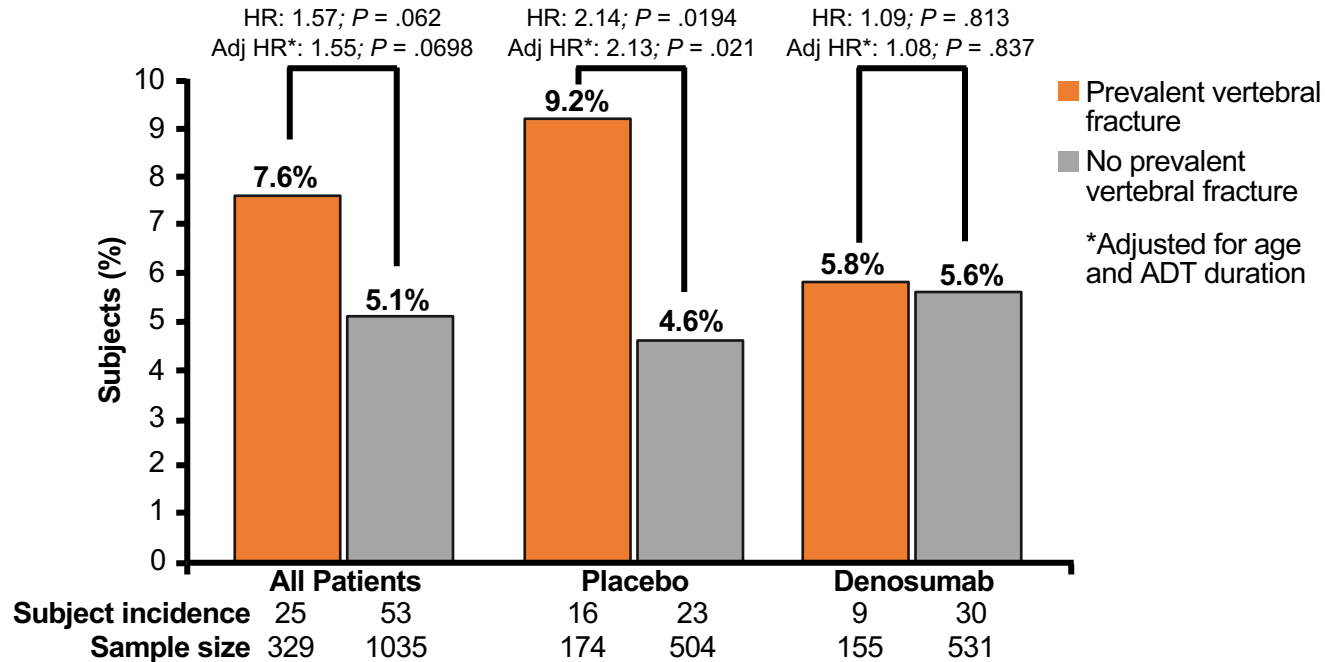
Mortality

Patients with Vertebral Compression Fracture



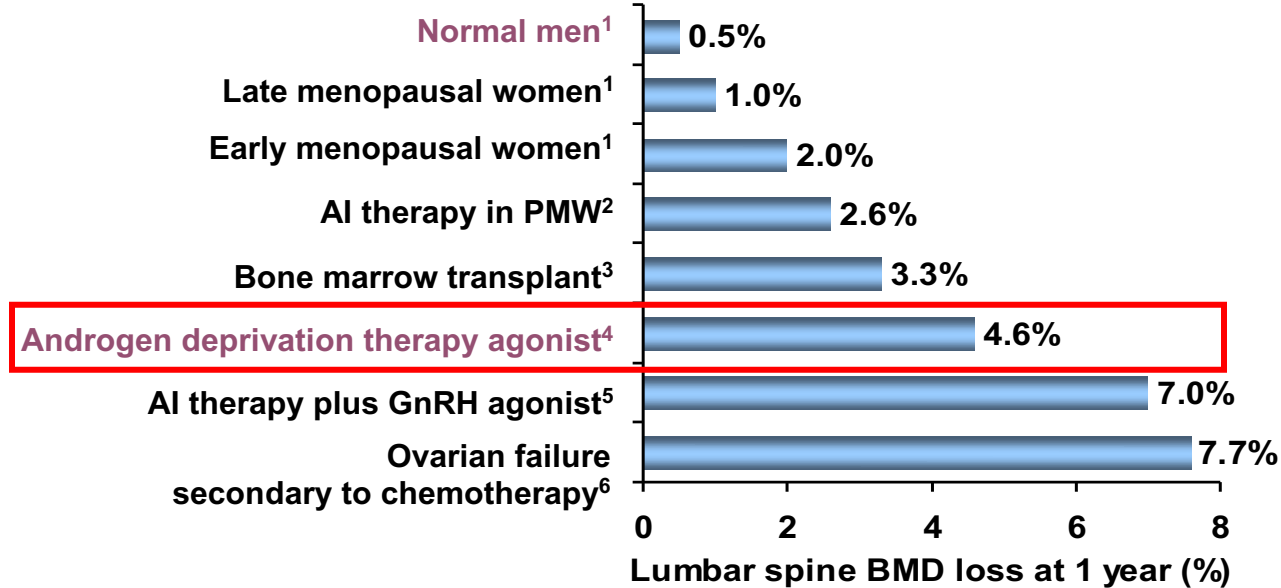
- overall mortality twice that of the matched controls (N=97,142)

Prevalent Vertebral Fracture at study entry Denosumab phase 3 study in nmHSPC



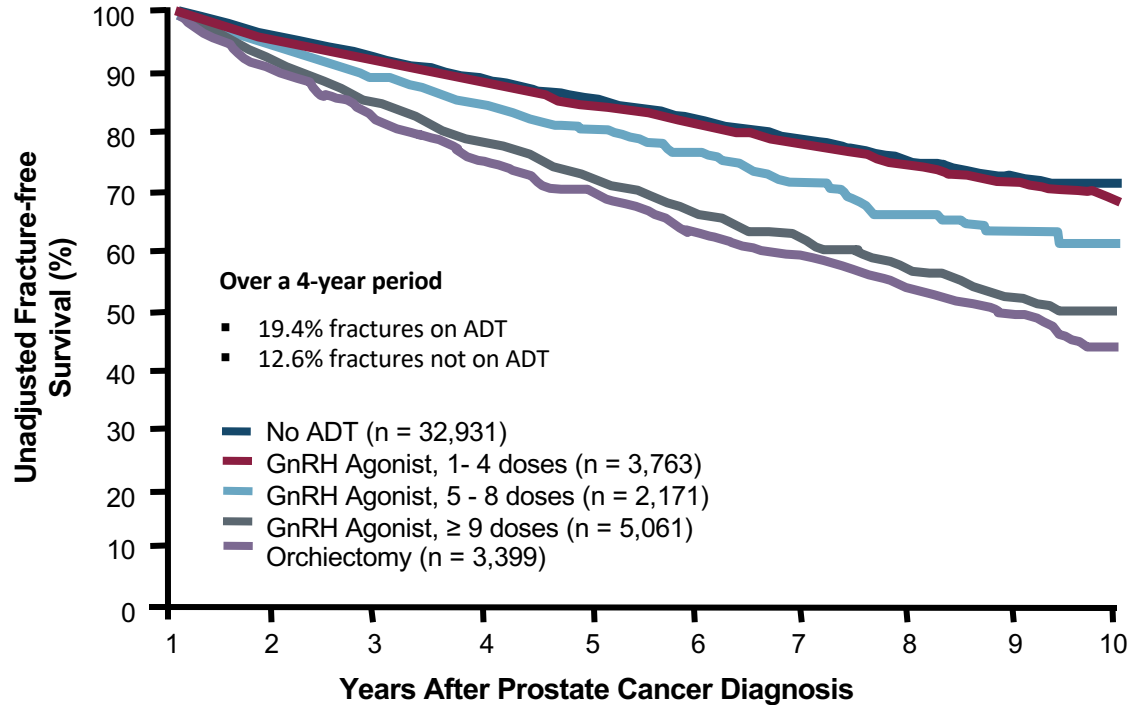
Impact of ADT

ADT is Associated with Significant Bone Loss

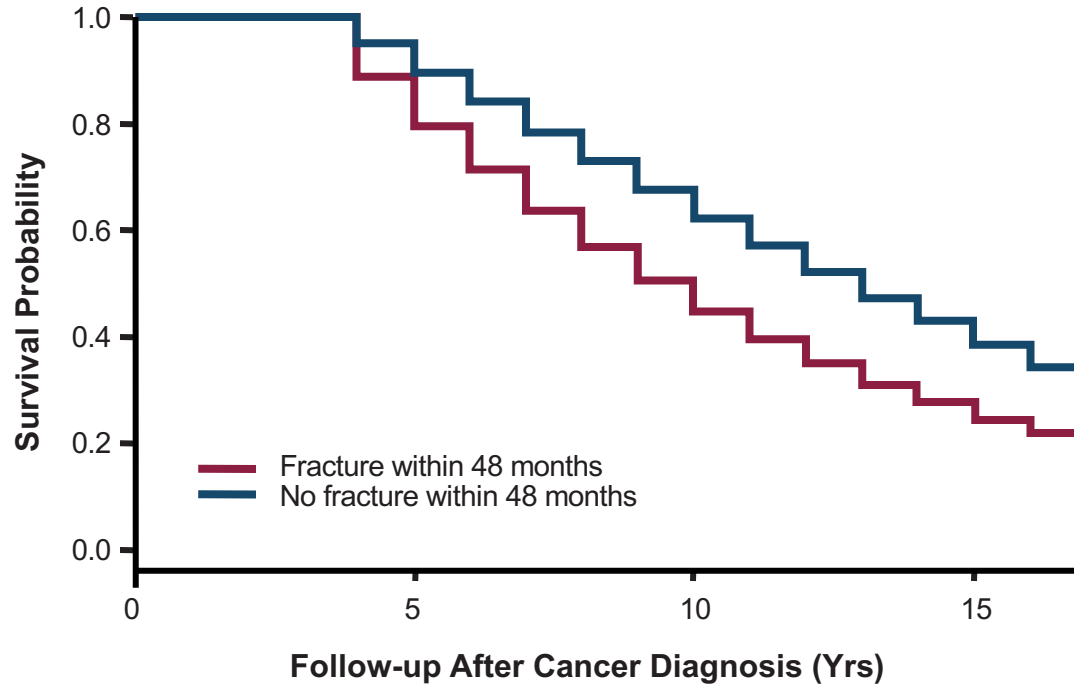


1. Kanis. *Osteoporosis*. 1997;22; 2. Eastell et al. *J Bone Miner Res*. 2002;17(suppl 1):S165; 3. Lee et al. *J Clin Endocrinol Metab*. 2002;87:329; 4. Maillefert et al. *J Urol*. 1999;161:1219; 5. Gnant. *Breast Cancer Res Treat*. 2002;76(suppl 1):S31. Abstract 12; 6. Shapiro et al. *J Clin Oncol*. 2001;19:3306.

ADT Leads to Increased Fracture Rates (SEER)



Effect of Fracture on Survival Among Men with Prostate Cancer: From the SEER Database of Men on ADT



Calculating fracture risk

Canadian Association of Radiologists and Osteoporosis Canada Risk (CAROC) Assessment tool

10-year Risk Assessment for Men (CAROC Basal Risk)

Age	Low Risk	Moderate Risk	High Risk
50	above -2.5	-2.5 to -3.9	below -3.9
55	above -2.5	-2.5 to -3.9	below -3.9
60	above -2.5	-2.5 to -3.7	below -3.7
65	above -2.4	-2.4 to -3.7	below -3.7
70	above -2.3	-2.3 to -3.7	below -3.7
75	above -2.3	-2.3 to -3.8	below -3.8
80	above -2.1	-2.1 to -3.8	below -3.8
85	above -2.0	-2.0 to -3.8	below -3.8

Fragility fracture of prolonged steroid use increases risk by 1 category



Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: **Canada**

Name/ID:

[About the risk factors](#)

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth

Age:

Date of Birth:

Y:

M:

D:

2. Sex

☐

Male

☐

Female

3. Weight (kg)

4. Height (cm)

5. Previous Fracture

☒

No

☐

Yes

6. Parent Fractured Hip

☒

No

☐

Yes

7. Current Smoking

☒

No

☐

Yes

8. Glucocorticoids

☒

No

☐

Yes

9. Rheumatoid arthritis

☒

No

☐

Yes

10. Secondary osteoporosis

☒

No

☐

Yes

11. Alcohol 3 or more units/day

☒

No

☐

Yes

12. Femoral neck BMD (g/cm²)

Select BMD



Clear

Calculate



Weight Conversion

Pounds ➔ kg

Convert

Height Conversion

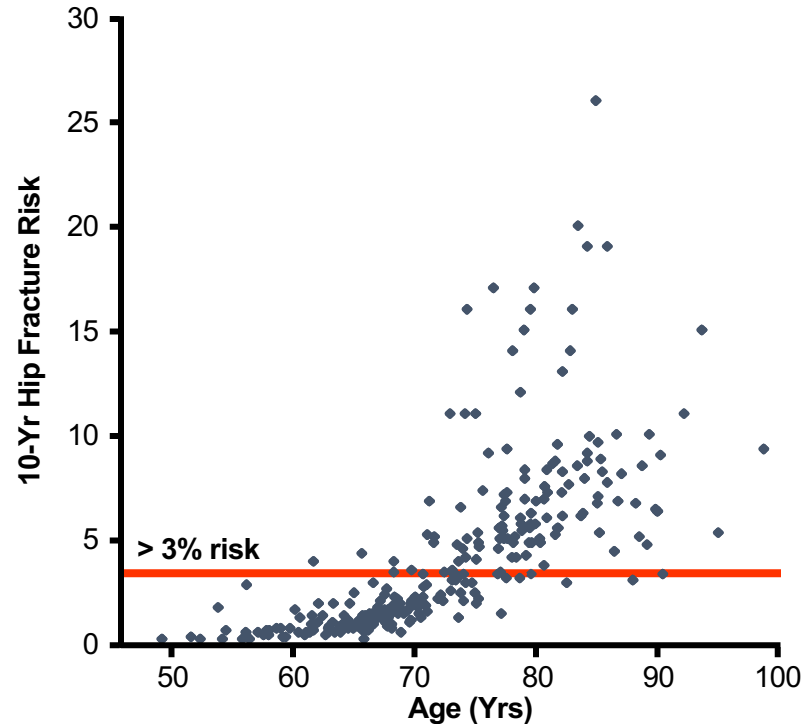
Inches ➔ cm

Convert

00834571

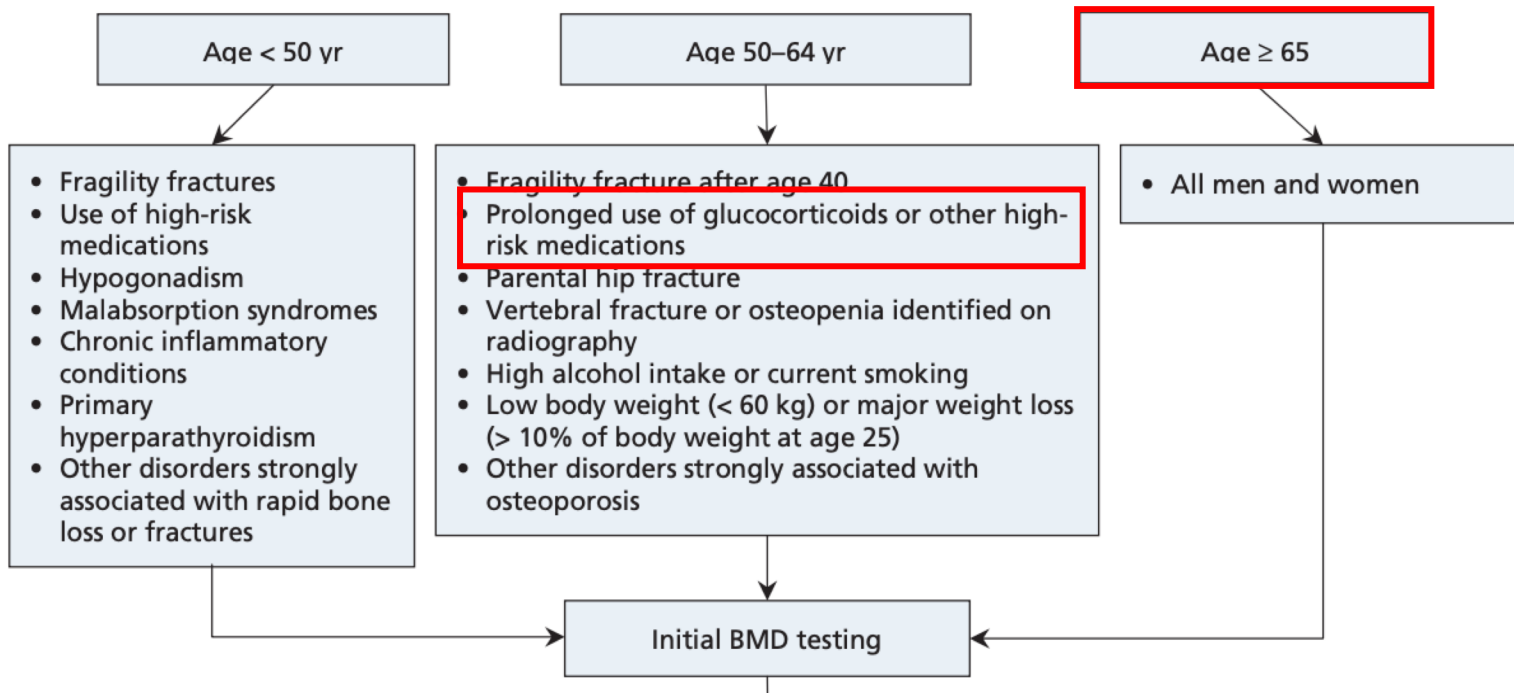
Individuals with fracture risk
assessed since 1st June 2011

FRAX 10-Yr Hip Fracture Risk by Age in Men Receiving ADT for Prostate Cancer

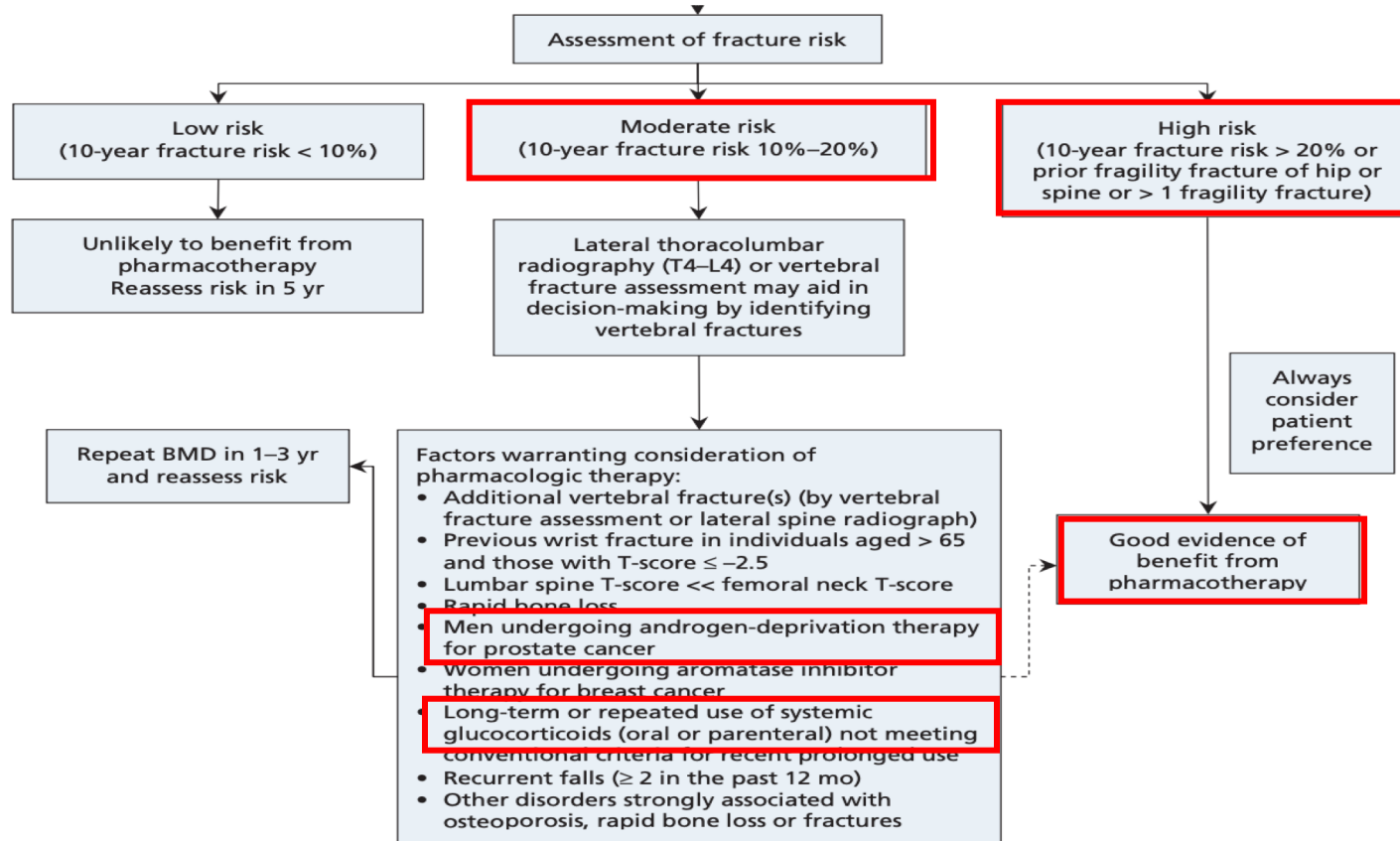


General Guidelines: BMD for who?

Encourage basic bone health for all individuals over age 50, including regular active weight-bearing exercise, calcium (diet and supplements) 1200 mg daily, vitamin D 800–2000 IU (20–50 µg) daily and fall-prevention strategies



General Guidelines: Who to treat?



Treatment options

Everyone knows **HOW**

The problem is **DECIDING** to screen and treat

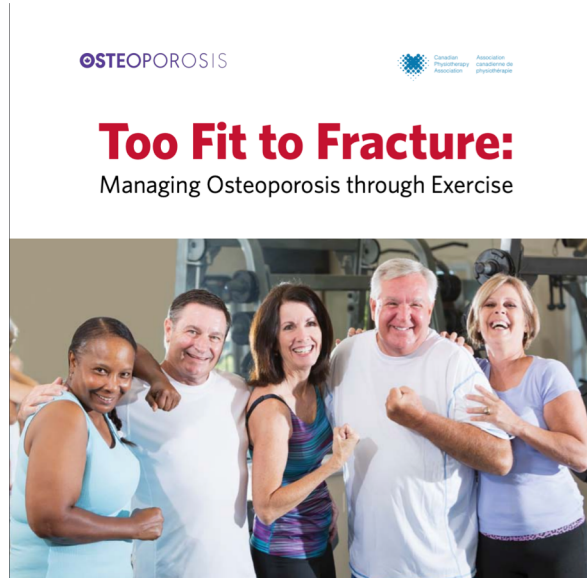
Are patients getting enough calcium?

Table 9 Estimating daily dietary calcium intake

Step 1: Estimate calcium intake from calcium-rich foods^a

Product	# of servings/day	Estimated calcium/serving, in mg	Calcium in mg
Milk (8 oz.)	_____	×300	= _____
Yogurt (6 oz.)	_____	×300	= _____
Cheese (1 oz. or 1 cubic in.)	_____	×200	= _____
Fortified foods or juices	_____	×80 to 1,000 ^b	= _____
			Subtotal = _____
Step 2: Add 250 mg for nondairy sources to subtotal above			+250
			Total calcium, in mg = _____

Exercise: Yes but how?



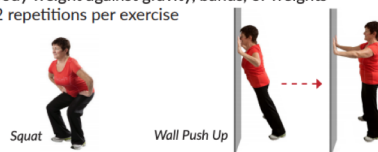
Exercise

Too Fit to Fall or Fracture

Strength Training

 At least 2 days/week

- ▶ Exercises for legs, arms, chest, shoulders, back
- ▶ Use body weight against gravity, bands, or weights*
- ▶ 8 - 12 repetitions per exercise



Try these to get started:

- Classes at YMCA/community centre
- Consult a physical therapist/kinesiologist
- Contact Osteoporosis Canada



Balance Exercises

 Every day

- ▶ Tai Chi, dancing, walking on your toes or heels
- ▶ Have a sturdy chair, counter, or wall nearby, and try (from easier to harder): shift weight from heels to toes while standing; stand heel to toe; stand on one foot; walk on a pretend line



Posture Awareness

 Every day

- ▶ Gently tuck your chin in and draw your chest up slightly
- ▶ Imagine your collarbones are wings - spread your wings slightly without pulling your shoulders back



Aerobic Physical Activity

 At least 150 mins/week

- ▶ Bouts of 10 mins or more, moderate to vigorous intensity*
- ▶ You should feel like your heart is beating faster and you are breathing harder
- ▶ You might be able to talk while doing it, but not sing

Examples:

- Brisk walking
- Dancing
- Jogging
- Aerobics class

Strength Training (more examples)

 At least 2 days/week

Other exercises include:

- ▶ Upright row
- ▶ Step up



What are spine sparing strategies?

Spine sparing strategies help "spare" the spine from injury. Injuries to the spine can occur when we bend forward or twist the spine quickly or repeatedly, or if we lift something heavy, bend far forward (e.g., tying shoes) or twist the torso all the way to the side. Bending or twisting while holding a weighted object (e.g., groceries, grandchild) is also risky.

Spine sparing strategies:

- ▶ Bend with your hips and knees, not your spine
- ▶ Turn your whole body rather than twisting your spine



Ready to learn more?

Osteoporosis Canada has developed tools to help you get too fit to fracture!

- ▶ Download a free booklet, one-page summary, and other tools
- ▶ Watch videos about exercise, balance training, and safe physical activity
- ▶ Watch webcasts by expert researchers

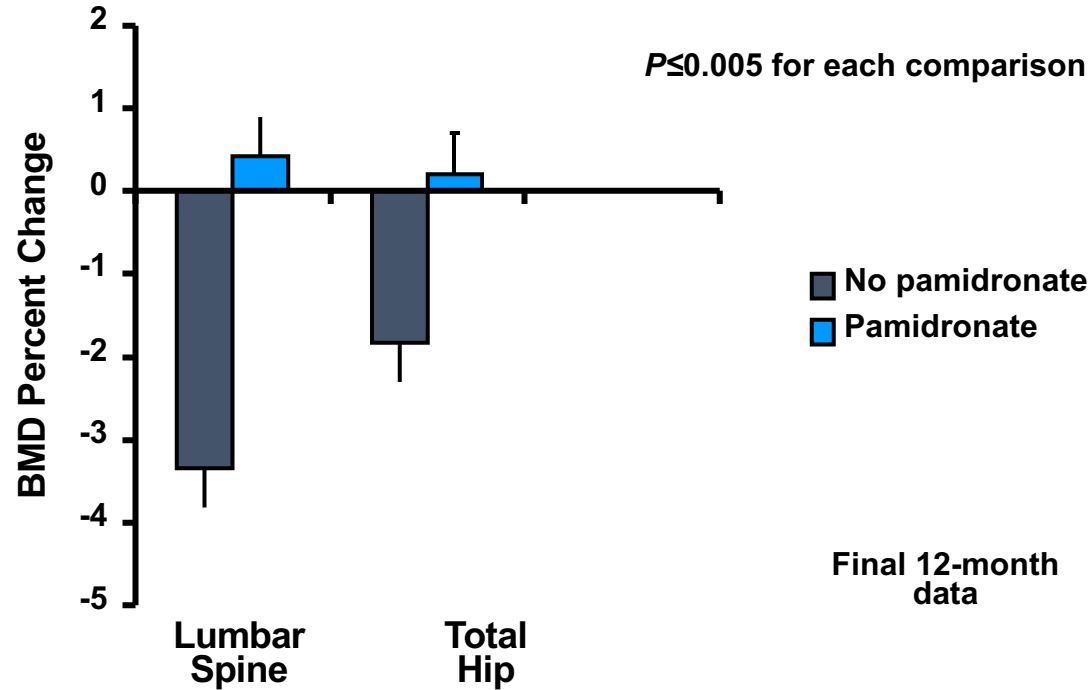
<http://www.osteoporosis.ca/osteoporosis-and-you/too-fit-to-fracture/>

Not online? No problem! Just call the hotline number below to order a free booklet.

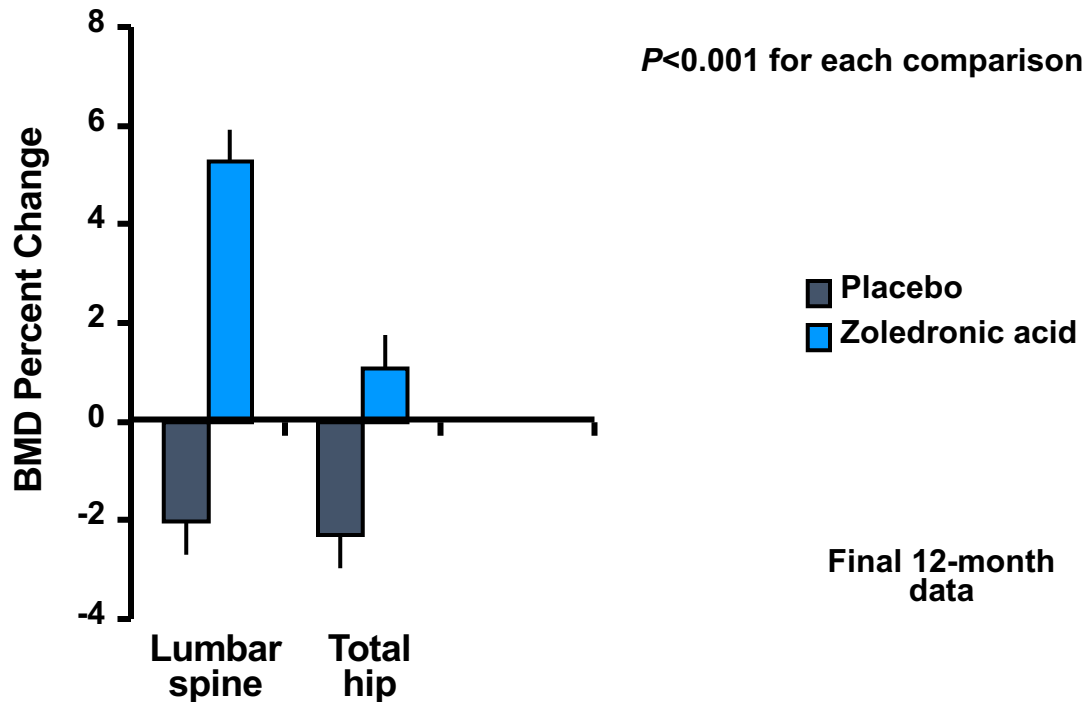
Bone health agents

Basically they all work

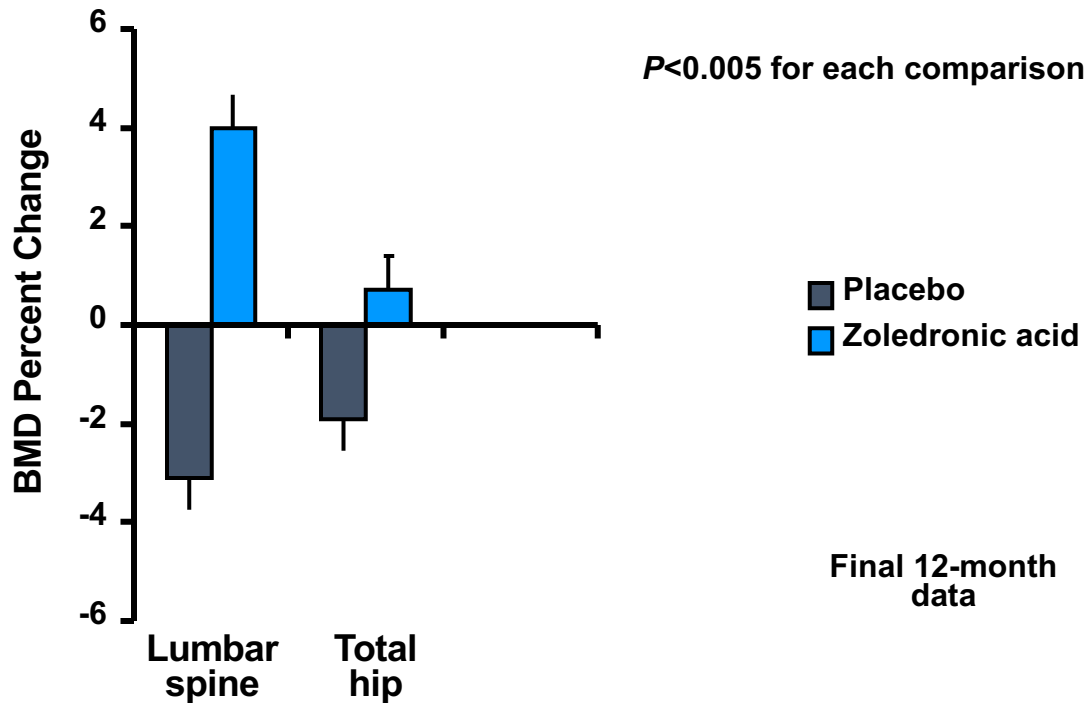
Pamidronate IV q 3months (n=47)



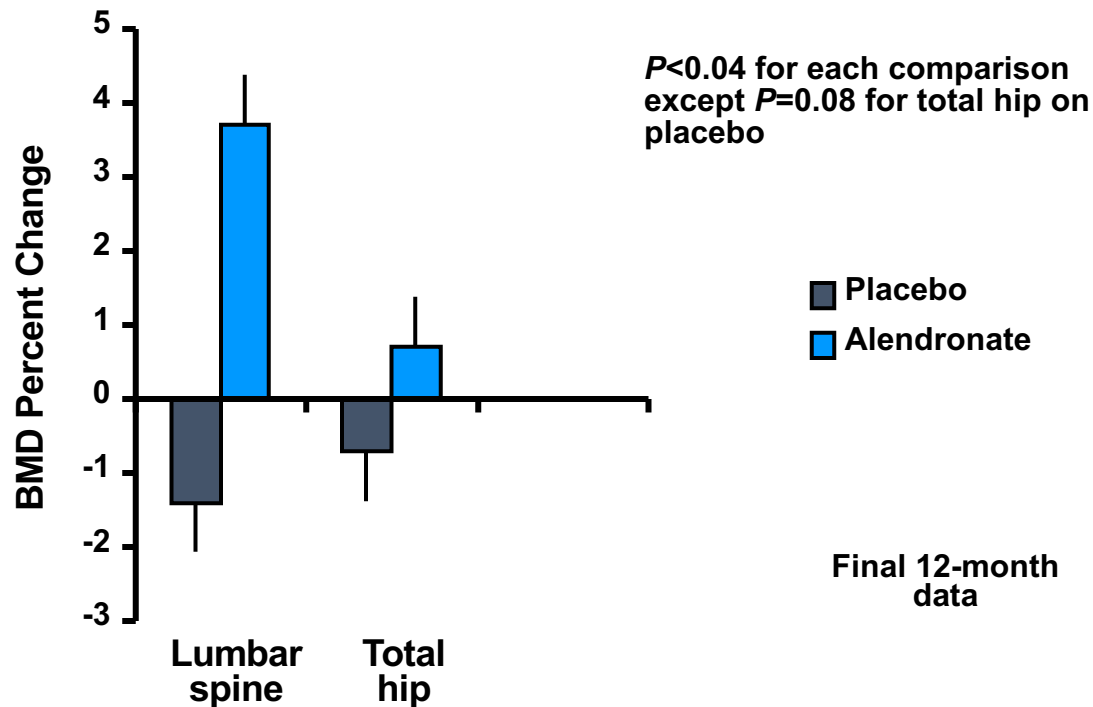
Zoledronic Acid IV q 3 months (n=106)



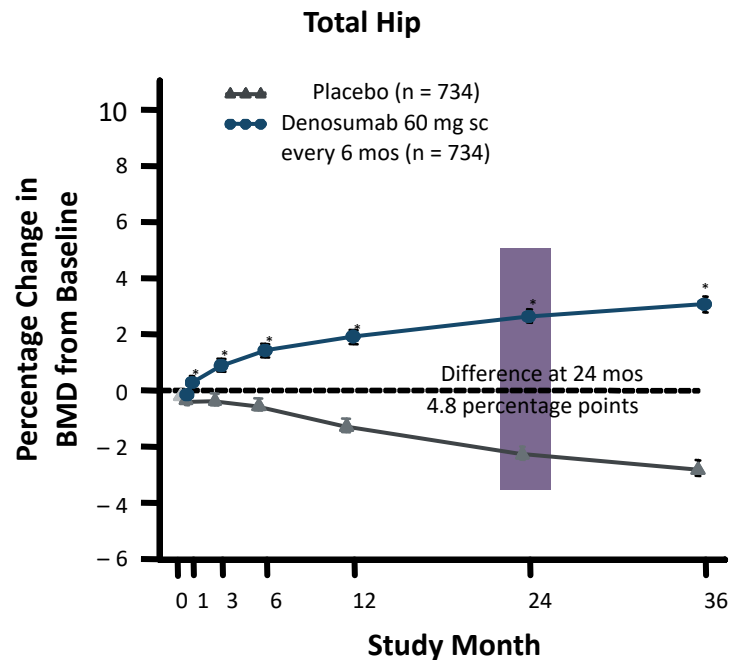
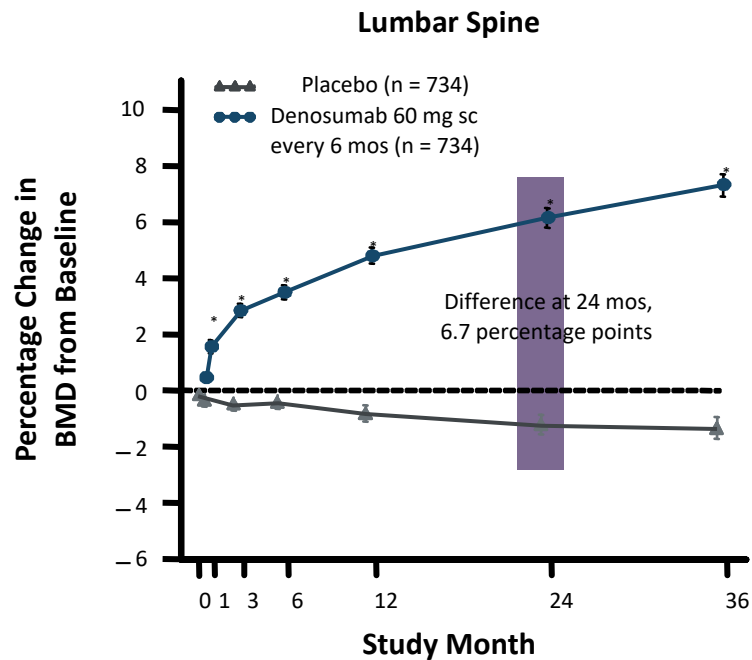
Zoledronic Acid IV q 12 Months (n=40)



Alendronate PO weekly (n=112)



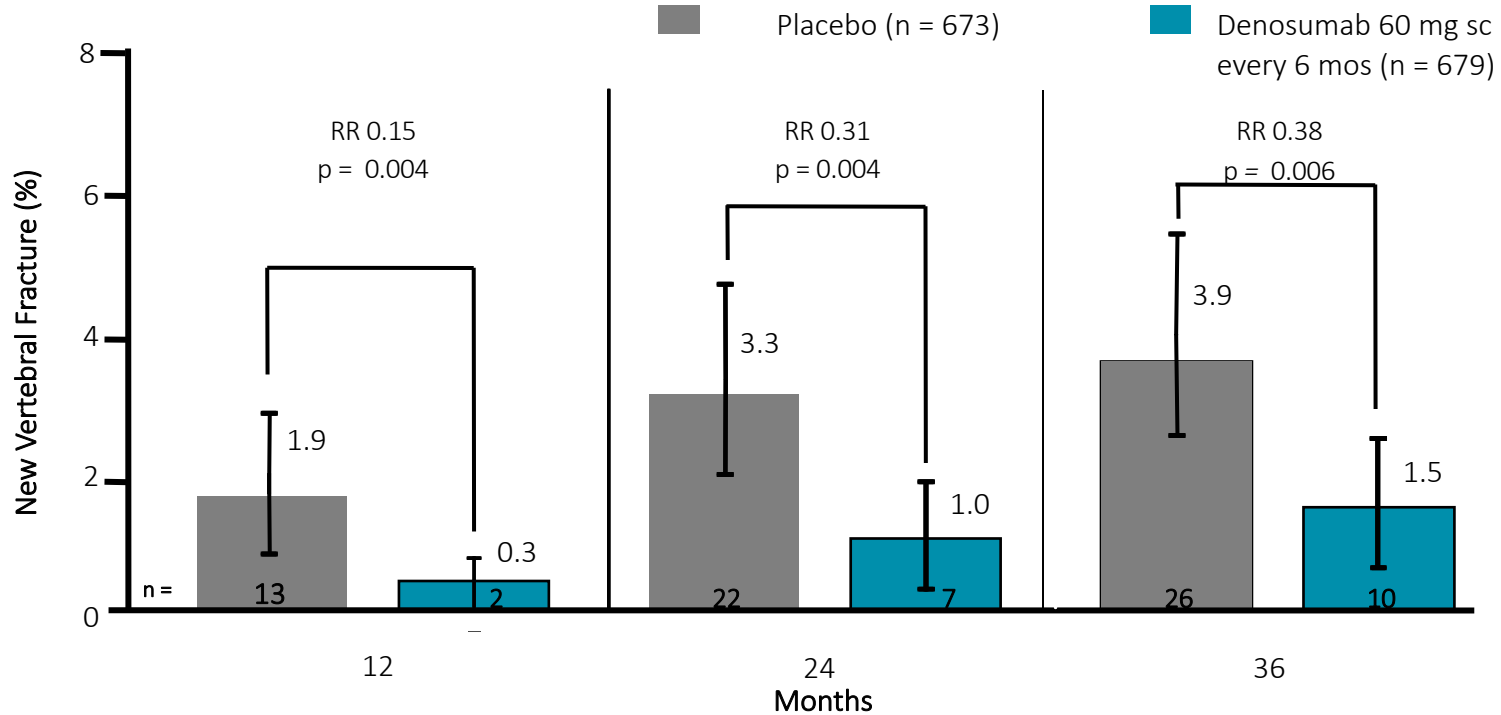
Denosumab 60mg q 6 months (n=1468)



p < 0.001 at all measured sites

Denosumab 60 q 6 months

New Vertebral Fractures at 3 years



Basic Principles

- **BMD:** for patients on long term ADT
- **Vitamin D:** 800-2000 IU/day
- **Calcium:** Diet +/- supplements for > 1200/day
- **Exercise:** Important but will it get done?
- **Smoking:** STOP
- **Alcohol:** limit < 2 drinks/day
- **Medication** if high risk: Bisphosphonates or Denosumab

Fractures and Impact of bone protective agents in recent studies

What can we learn?

ERA 223 (NCT02043678)

Study population

- Patients with bone-predominant mCRPC (≥ 2 bone metastases)
- Asymptomatic or mildly symptomatic
- ECOG PS of 0 or 1
- No prior chemotherapy for CRPC or AR antagonists
- No known brain or visceral metastases

Accrual dates 3/2014 – 8/2016

Target Accrual
N=800

1:1
Randomisation,
Double blind

Abiraterone acetate 1000 mg qd and
prednisone/prednisolone 5 mg bid (AAP)
+ **Radium-223**
55 kBq/kg IV every 4 weeks for 6 cycles

Stratification factors

- Geographical region
- Use of bone health agents*
- Total ALP level at baseline (ALP <90 vs. ≥ 90 U/L)

Abiraterone acetate 1000 mg qd and
prednisone/prednisolone 5 mg bid (AAP)
+ **Matching placebo**

Primary endpoint

- SSE-FS

Secondary endpoints

- OS
- rPFS
- Time to chemotherapy
- Time to opiate use for cancer pain
- Safety

Exploratory endpoints

- PSA response
- Time to PSA progression
- ALP response
- Time to ALP progression
- HRQoL

Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline;
Initiation during study was prohibited to prevent confounding effects.

389 events were required to detect a 39% increase in SSE-FS using a test with a 2-sided alpha of 0.05, 90% power and 1:1 randomisation

ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiological progression-free survival; SSE-FS, symptomatic skeletal event-free survival.

Smith M *et al.* Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

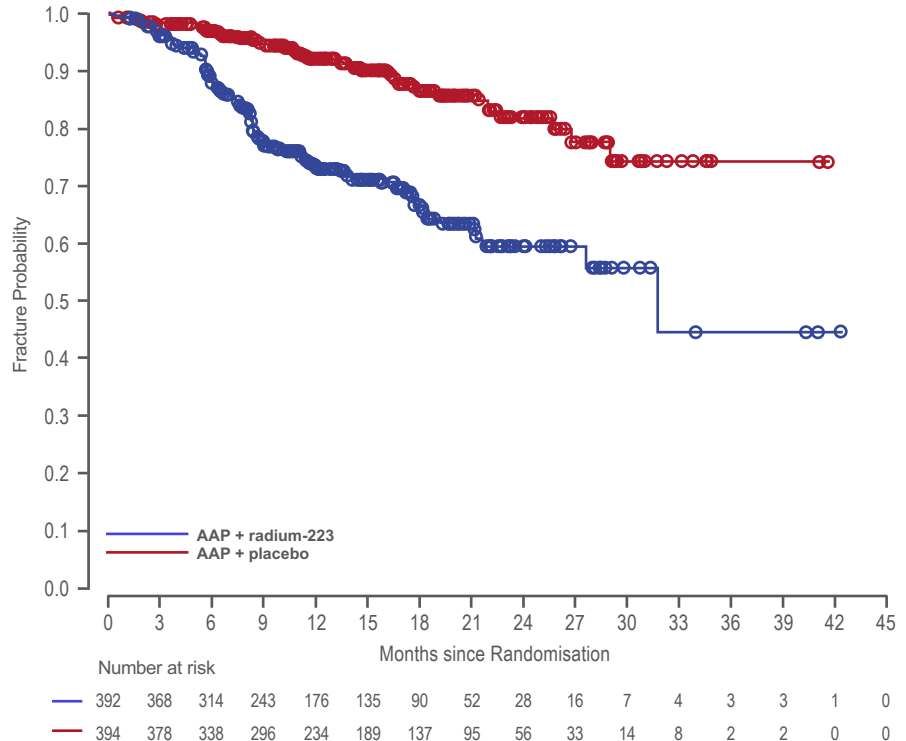
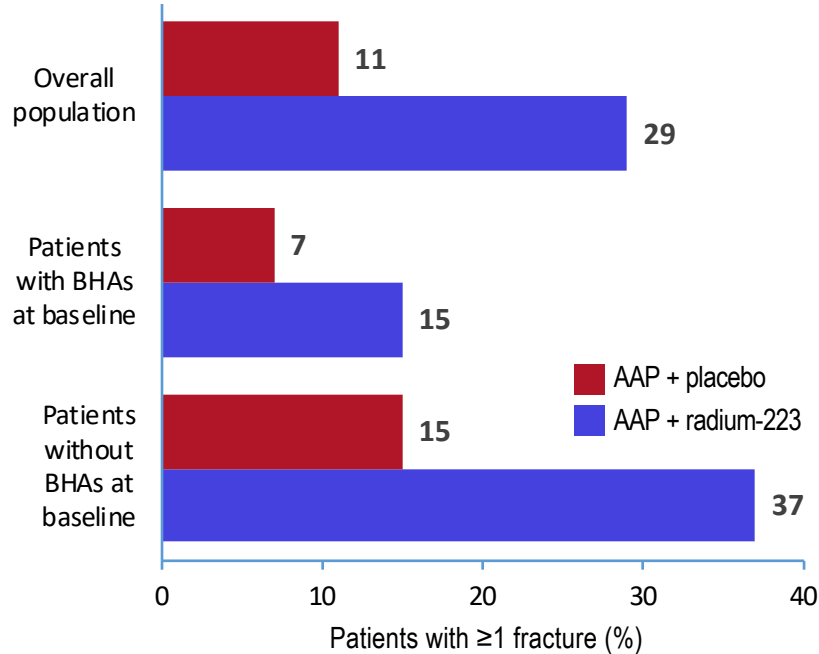
Most Frequent Treatment-Emergent Adverse Events

TEAEs in ≥15% of patients in either group, n (%)	AAP + radium-223 N=392			AAP + placebo N=394		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Back pain	133 (34)	23 (6)	0	121 (31)*	16 (4)	0
Fatigue	89 (23)	4 (1)	0	79 (20)	6 (2)	0
Arthralgia	80 (20)	4 (1)	0	75 (19)	5 (1)	0
Fracture†	103 (26)	35 (9)	1 (0.3)	38 (10)*	12 (3)	0
Hypertension	59 (15)	43 (11)	0	78 (20)	51 (13)	1 (0.3)
ALT increased	69 (18)	29 (7)	5 (1)	59 (15)	28 (7)	0
Constipation	56 (14)	1 (0.3)	0	72 (18)	0	0
Diarrhoea	65 (17)	4 (1)	0	60 (15)	7 (2)	0
Nausea	66 (17)	1 (0.3)	0	59 (15)	1 (0.3)	0
AST increased	61 (16)	18 (5)	1 (0.3)	53 (14)	16 (4)	0
Peripheral oedema	51 (13)	2 (0.5)	0	61 (16)	0	0
Anaemia	57 (15)	24 (6)	0	46 (12)	11 (3)	0

No grade 5 TEAEs reported in ≥10% of patients; *Grade of severity missing for one patient; †Compound term for events of femoral neck, femur, humerus, lumbar vertebral, osteoporotic, pathological, radius, rib, spinal compression, stress, thoracic vertebral, tooth, traumatic and ulna fracture.

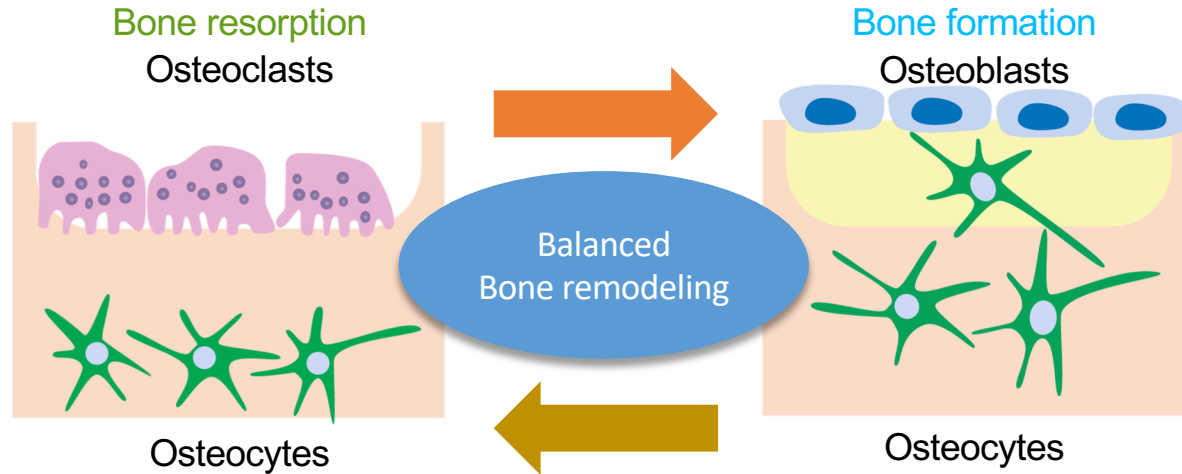
AAP, abiraterone acetate and prednisone/prednisolone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Fractures Occurring on study: early event

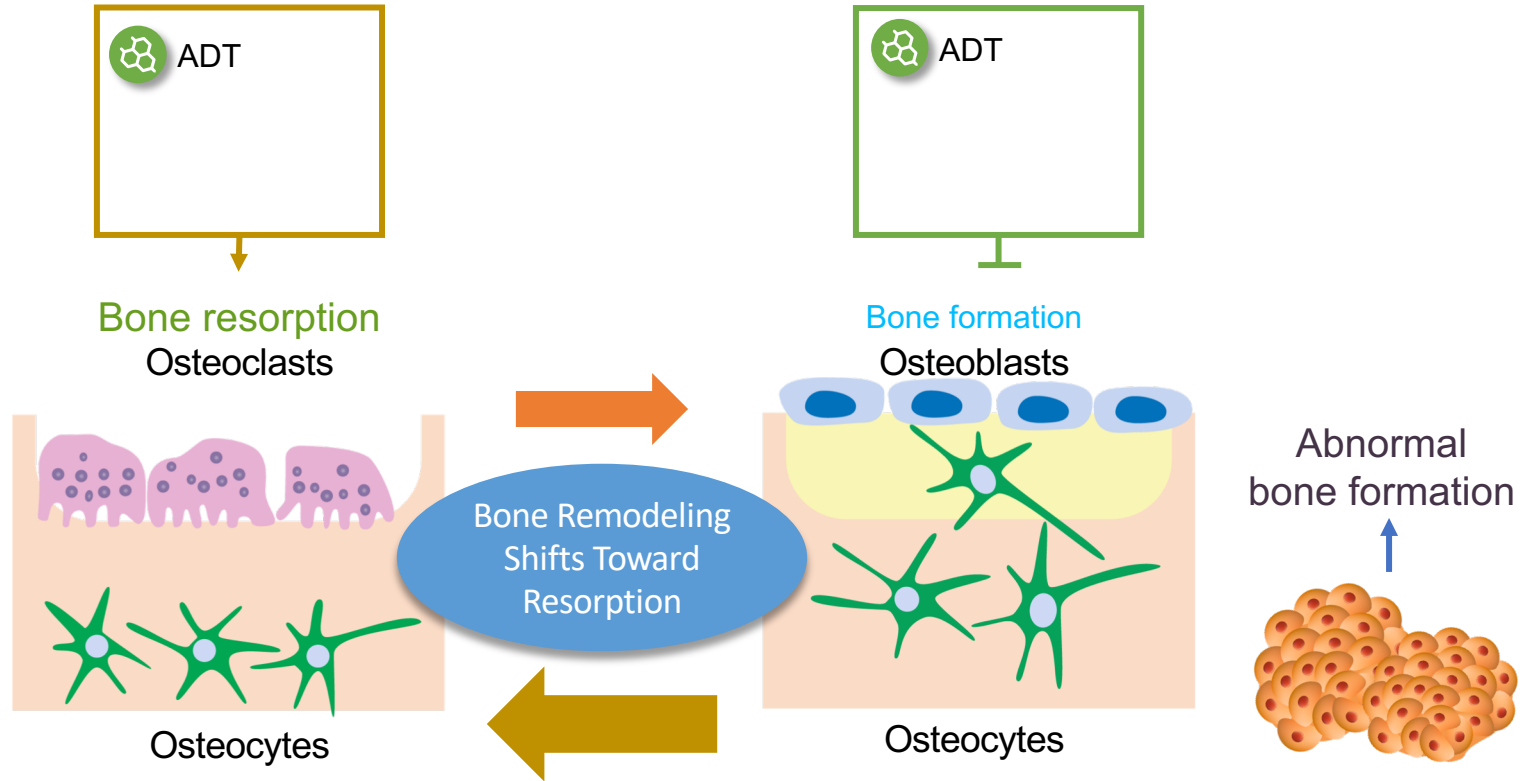


Why the high fracture rate?

Normal bone remodeling



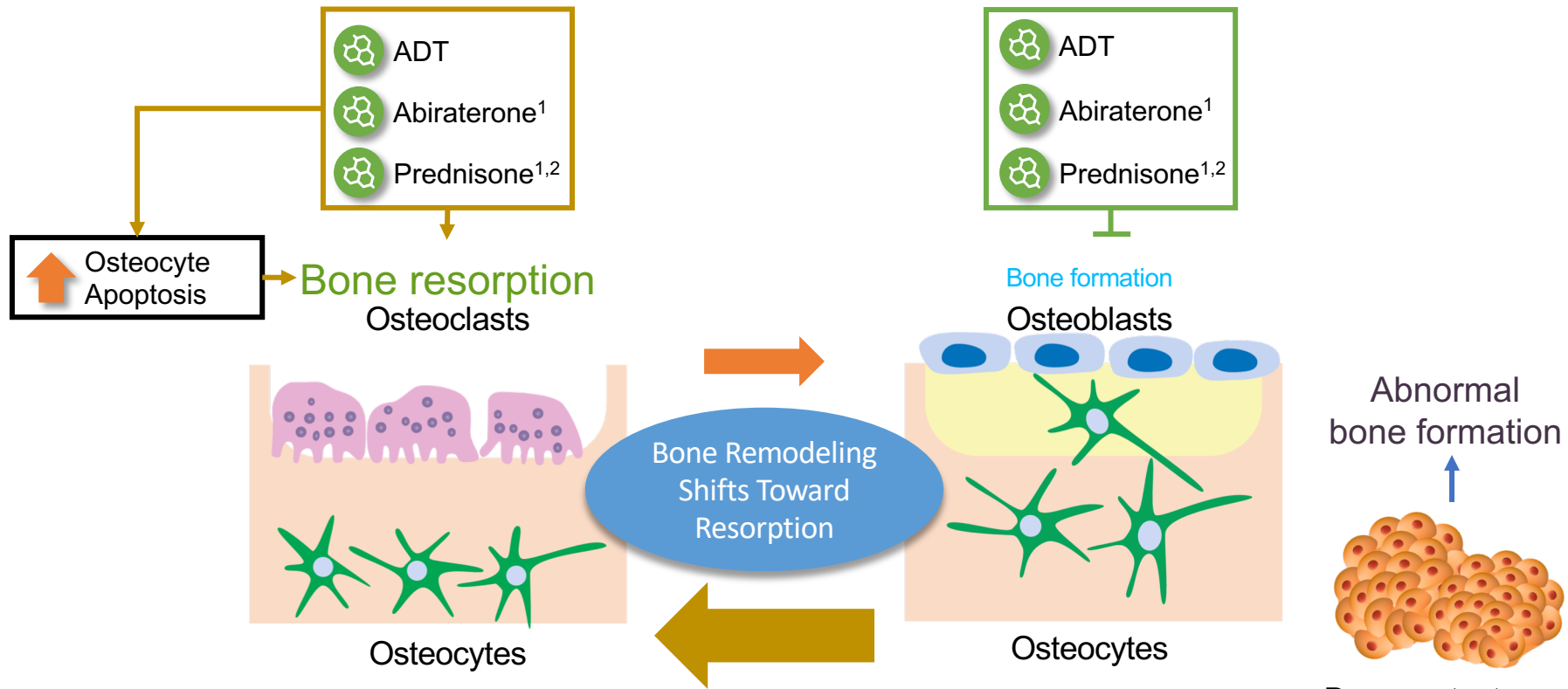
ADT Shifting the Balance Toward Bone Resorption



ADT, androgen deprivation therapy; BHA, bone health agent.

1. Sambrook PN et al. *Ann Rheum Dis* 2003;62:1215–1217. 2. Auchus RJ et al. *Oncologist* 2014;19:1231–1240. 3. Suominen MI et al. *Clin Cancer Res* 2017;23:4335–4346.

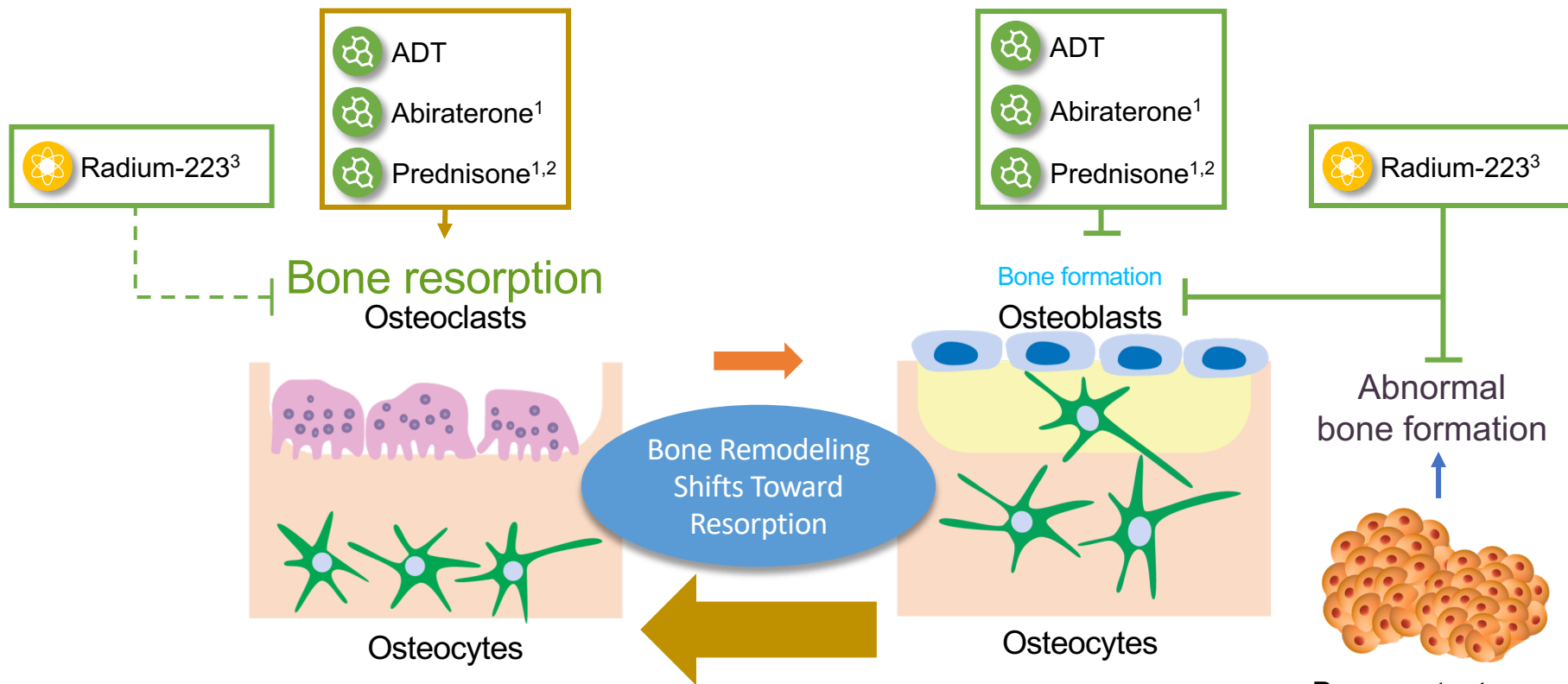
Abiraterone/Pred Osteoclast Activation and Inhibit Osteoblasts



ADT, androgen deprivation therapy; BHA, bone health agent.

1. Sambrook PN et al. *Ann Rheum Dis* 2003;62:1215–1217. 2. Auchus RJ et al. *The Oncologist* 2014;19:1231–1240. 3. Suominen MI et al. *Clin Cancer Res* 2017;23:4335–4346.

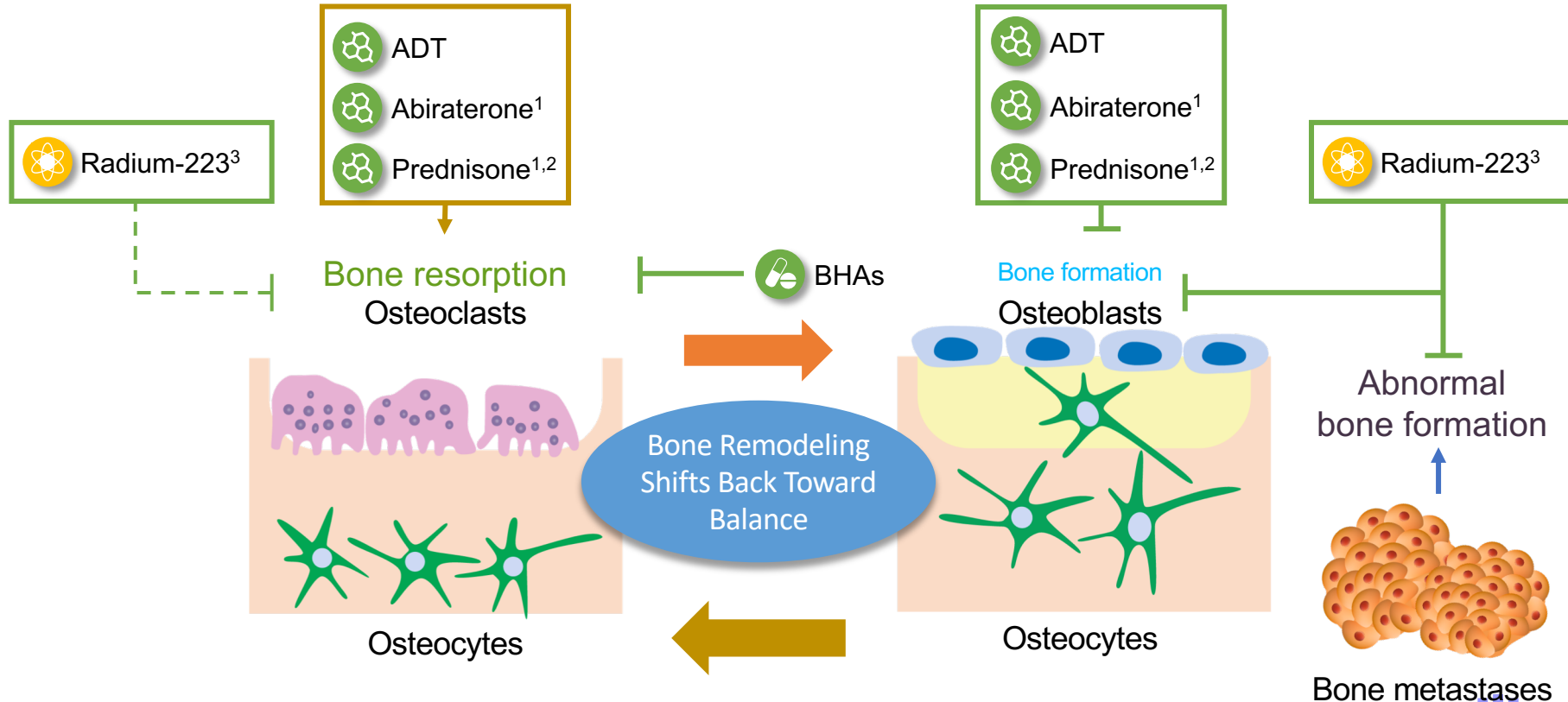
Radium-223 inhibits osteoblasts with further ↑ in bone resorption



ADT, androgen deprivation therapy; BHA, bone health agent.

1. Sambrook PN et al. *Ann Rheum Dis* 2003;62:1215–1217. 2. Auchus RJ et al. *Oncologist* 2014;19:1231–1240. 3. Suominen MI et al. *Clin Cancer Res* 2017;23:4335–4346.

Bone Health Agents ↓ Bone Resorption Partially Restoring Balance

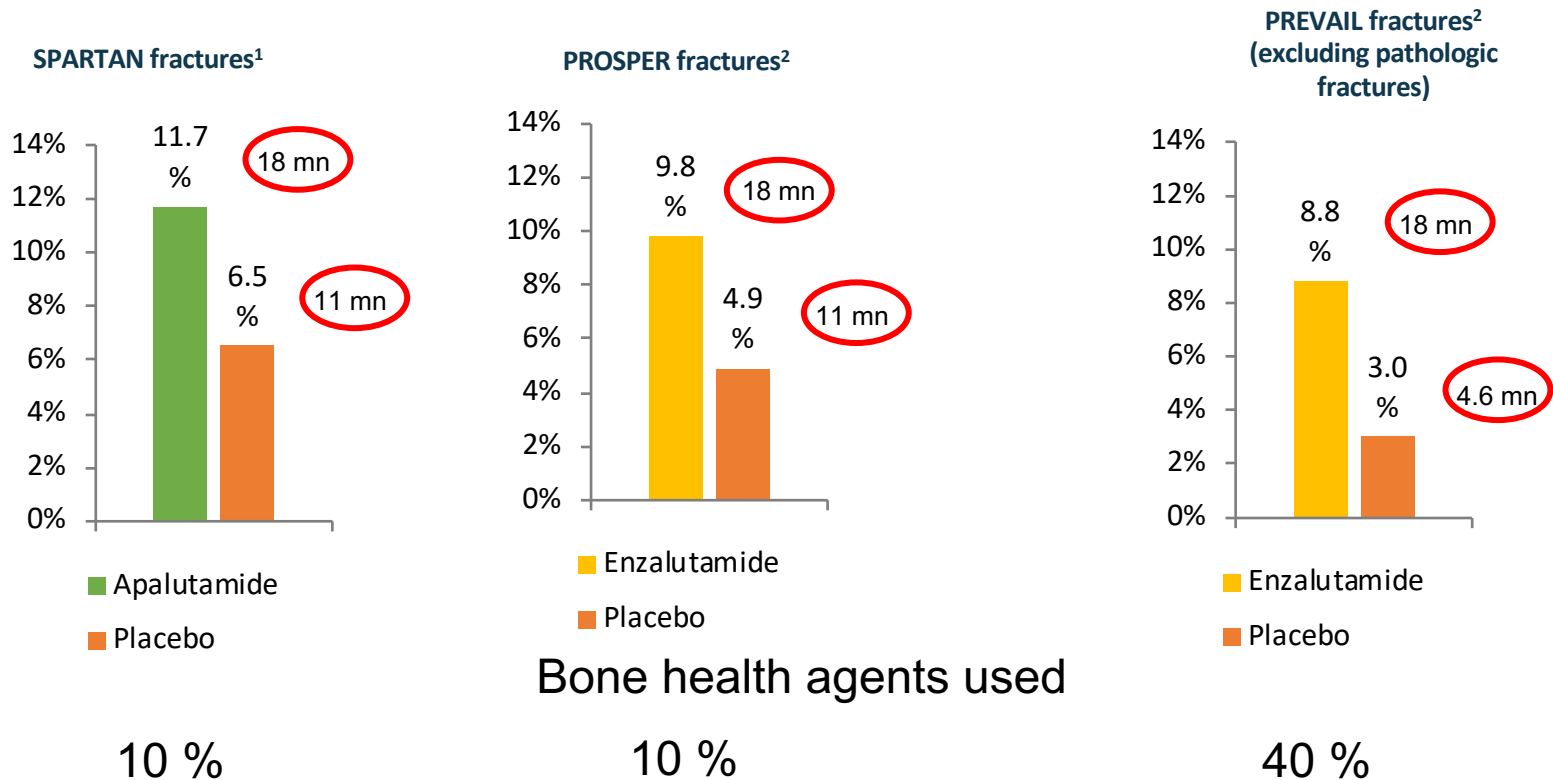


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Is this unique to
abiraterone/prednisone?

Fractures in phase III studies with new AR pathways inhibitors



USPI, U.S. prescribing information.

1. Smith MR *et al.* *N Engl J Med* 2018; doi:10.1056/NEJMoa1715546 [Epub ahead of print]. 2. Xtandi (enzalutamide) [prescribing information]. Astellas Pharma US, Inc., Northbrook, IL. July 2018. 3. Zytiga (abiraterone acetate) [prescribing information]. Janssen Biotech, Inc., Horsham, PA. February 2018. 4. Erleada (apalutamide) [prescribing information]. Janssen Products, LP, Horsham, PA. February 2018.

EORTC GUCG 1333 (PEACE III)

Study population

- Patients with bone-predominant mCRPC (≥ 2 bone metastases)
- Asymptomatic or mildly symptomatic
- WHO PS of 0 or 1
- No prior treatment with, cyp17 inhibitors, enzalutamide, Ra233, other radionuclotides, hemibody radiotherapy
- No known brain or visceral metastases

Target Accrual
N=560

1:1
Randomisation,

Enzalutamide 160 mg qd

Radium-223
55 kBq/kg IV every 4 weeks for 6
cycles

Stratification factors

- Country
- Baseline pain (BPI worst pain 0-1 vs 2-3)
- Prior docetaxel (yes vs no)
- Use of bone health agents*

Enzalutamide 160 mg qd

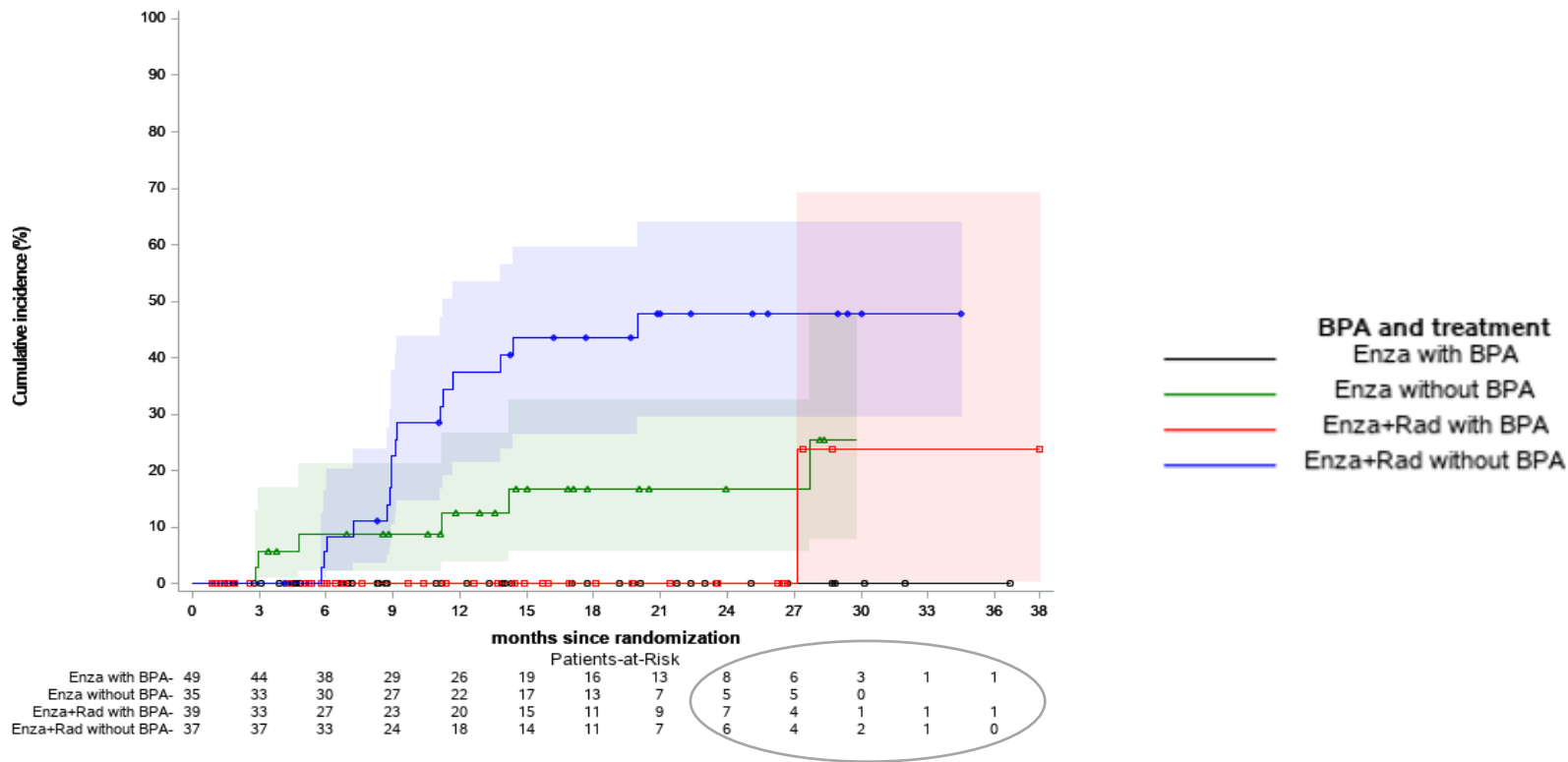
Primary endpoint

- rPFS

Secondary endpoints

- OS
- DSS
- SSE
- Time to initiation of next systemic anti-neoplastic therapy
- PFS2
- Brief Pain Inventory (BPI), (EQ-5D-5L)

Cumulative incidence fractures by treatment arm and use of bone protecting agents

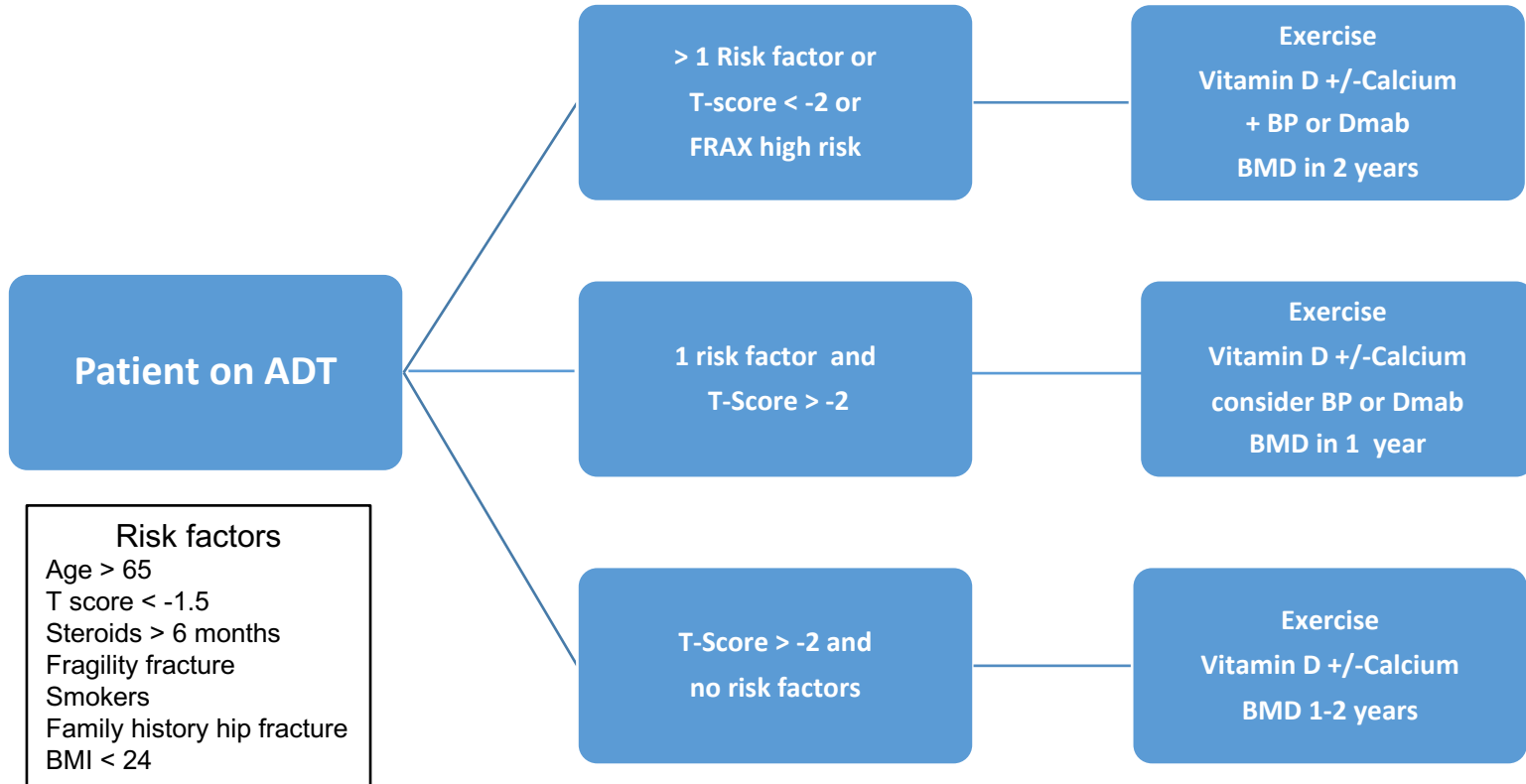


Bone fractures and cumulative incidence

Time point	Treatment and use of bone protecting agents			
	With exposure to BPA		Without exposure to BPA	
	Enza+Rad (N=39)	Enza (N=49)	Enza+Rad (N=37)	Enza (N=35)
	Cum Incidence (95% CI)*	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
3 months	0 (-)	0 (-)	0 (-)	5.7 (1.0-16.7)
6 months	0 (-)	0 (-)	5.6 (1.0-16.3)	8.8 (2.2-21.0)
9 months	0 (-)	0 (-)	22.6 (10.6-37.3)	8.8 (2.2-21.0)
12 months	0 (-)	0 (-)	37.4 (21.8-53.1)	12.4 (3.9-26.2)
15 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)
18 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)

* the one fracture in this group occurred at month 27

Proposed Approach for men on ADT



Conclusion

- Bone health is not cool but...
- ADT increases bone loss and fracture risk
- New treatment options for advanced PCa may increase risk
 - more likely due to increased time on therapy and survival
- Due to its MOA Radium 223 requires BHA
- Basic principles need to be adhered
 - patients on ADT: at least vitamin D and encourage exercise
 - Identify patients at risk and intervene as needed

We can do better