

Fracture Risks with ADT use in Patients with Prostate Cancer

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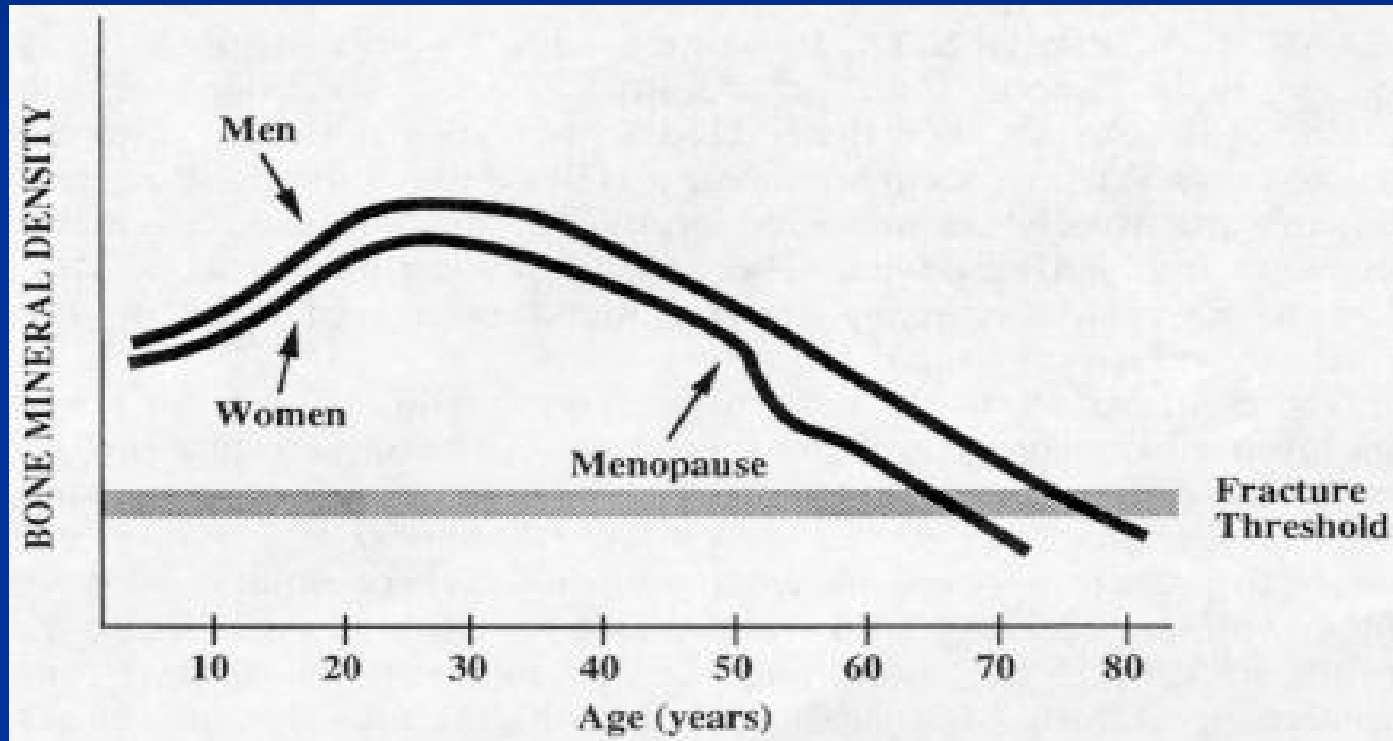
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Why Is This Topic Important?

- **Osteoporosis results in 350,000 hip fractures each year in the US**
- **This number is expected to double by 2025**
- **Annual direct costs of osteoporotic fractures are estimated at \$17 billion**

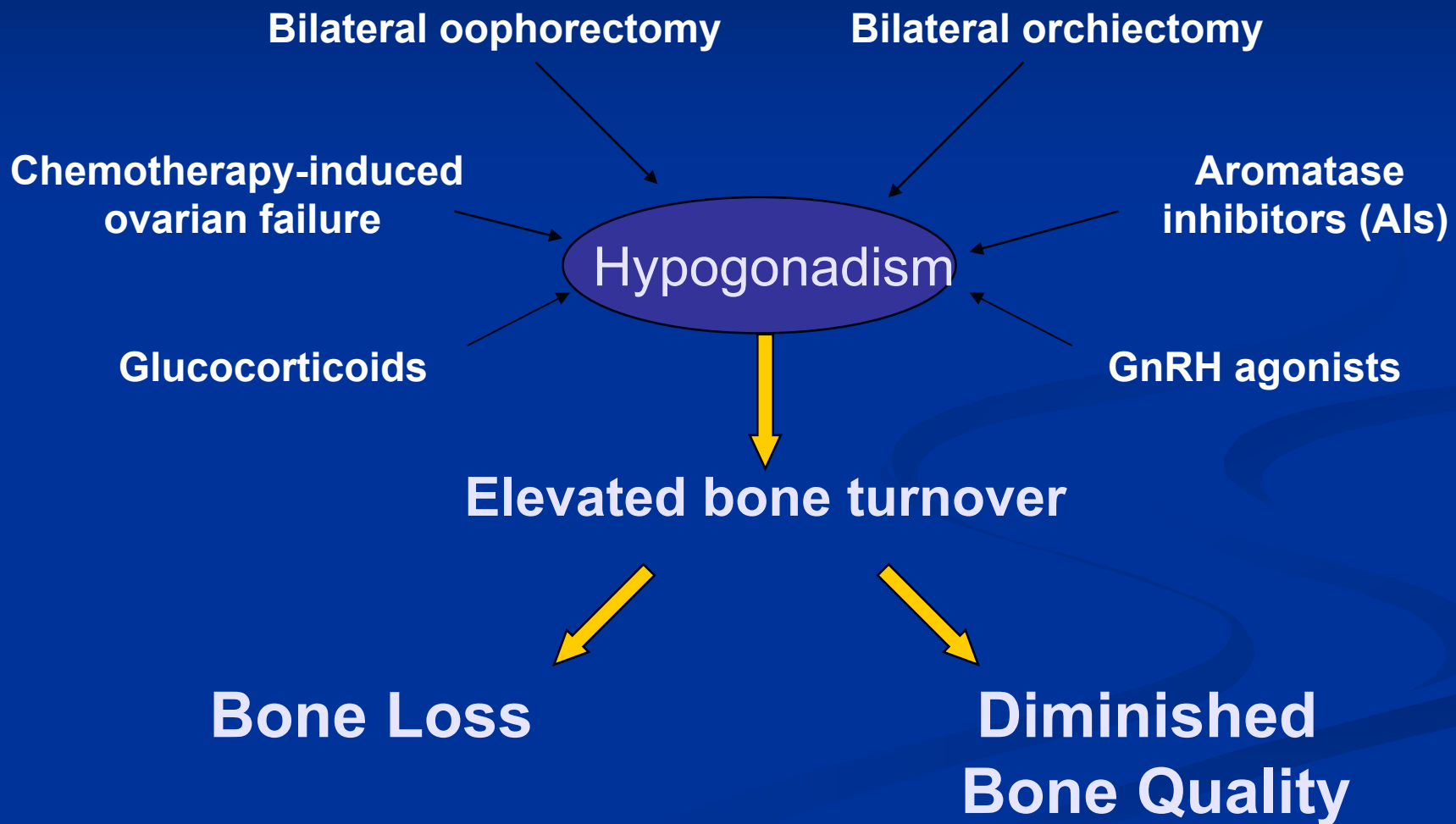
Bone Mineral Density by Age and Gender



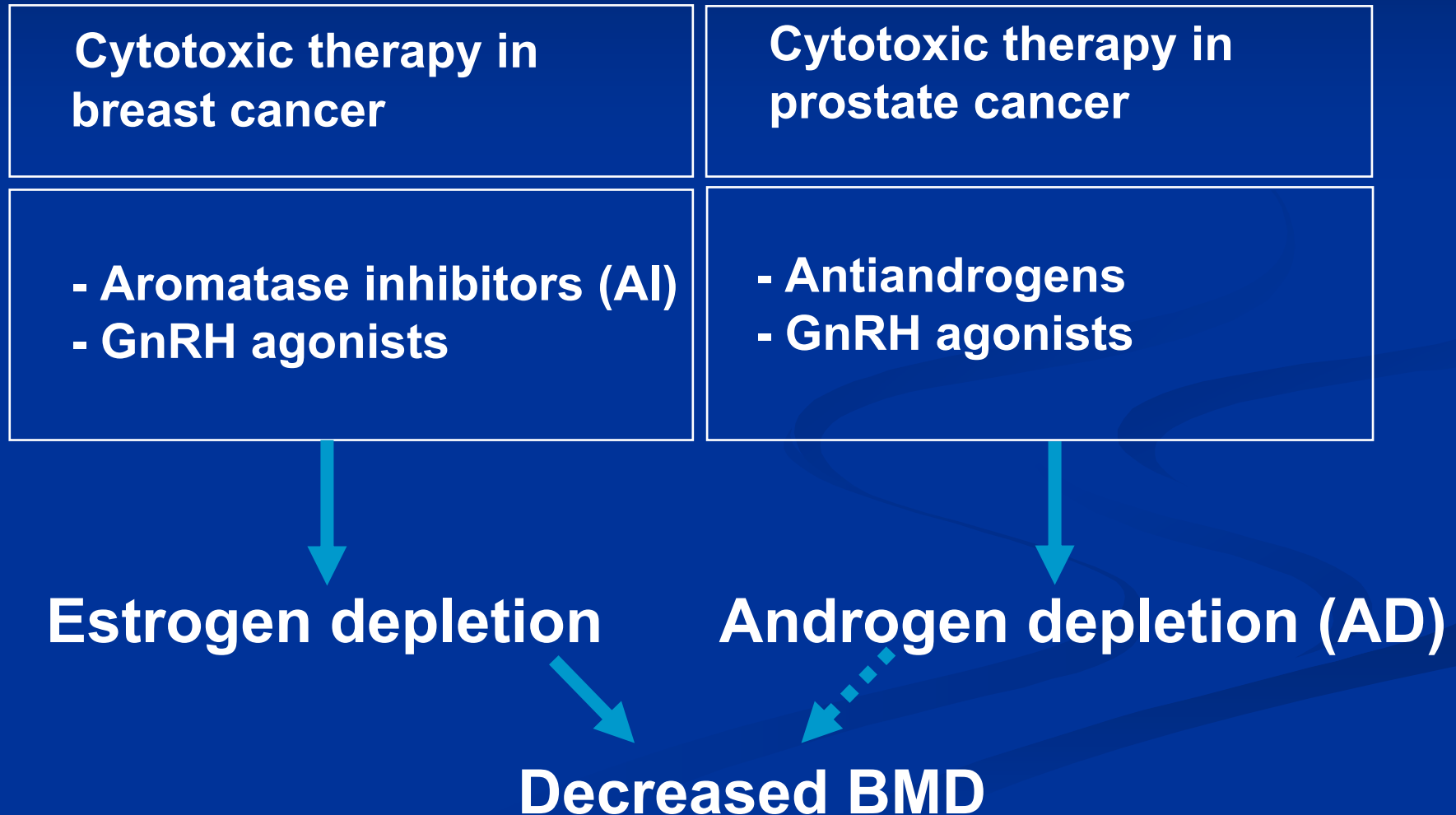
Magnitude of risk of Osteoporosis in Men

- Longitudinal studies show a 0.5% to 1% loss in cortical bone in men in later life^{1,2}
- Bone loss occurs more rapidly in older men and causes hip / spine fractures in men > 75 years^{2,3}

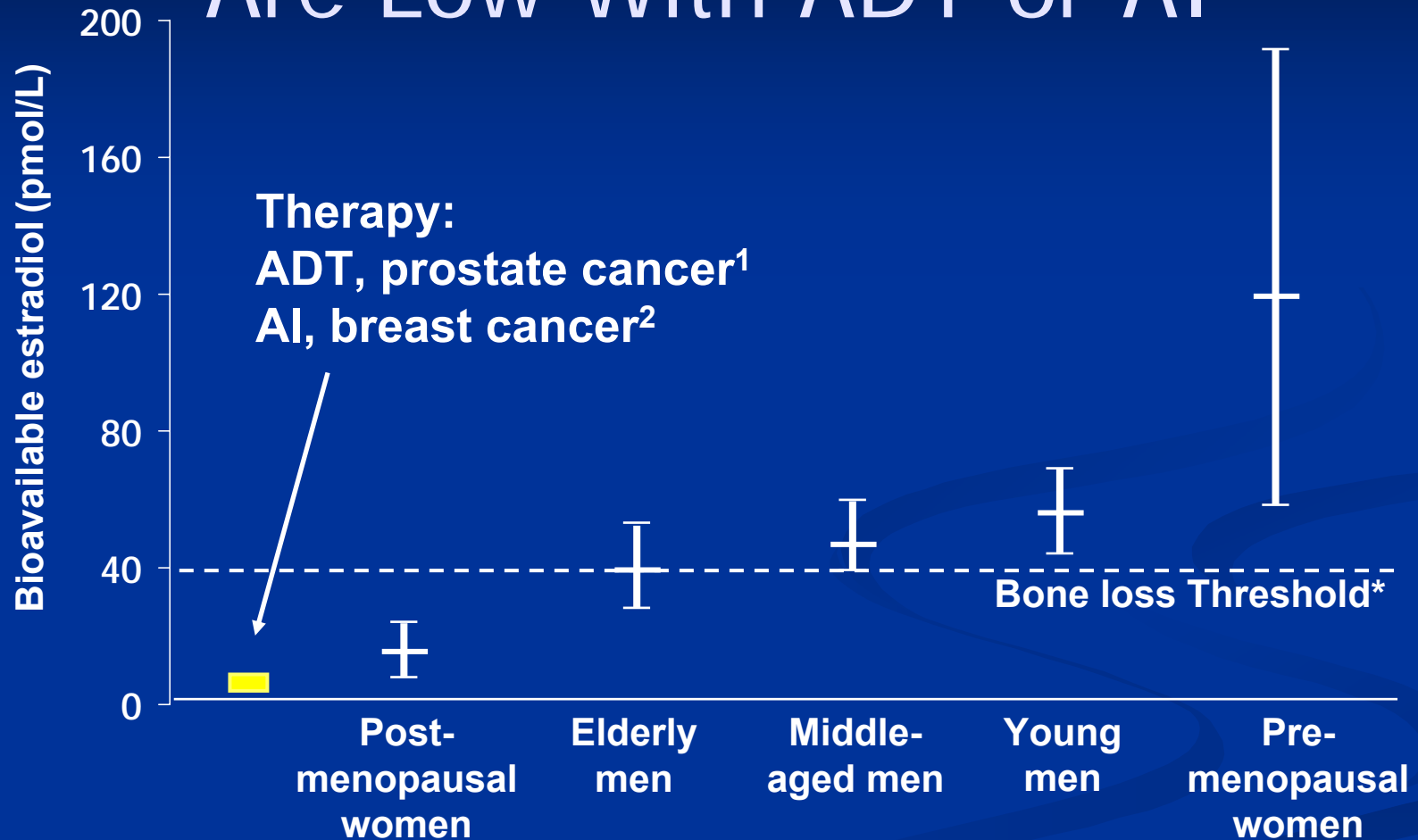
Causes of Cancer Treatment-Induced Bone Loss (CTIBL)



Effects of Cytotoxic Therapy in Patients With Breast and Prostate Cancer



Bioavailable Estradiol Concentrations Are Low With ADT or AI



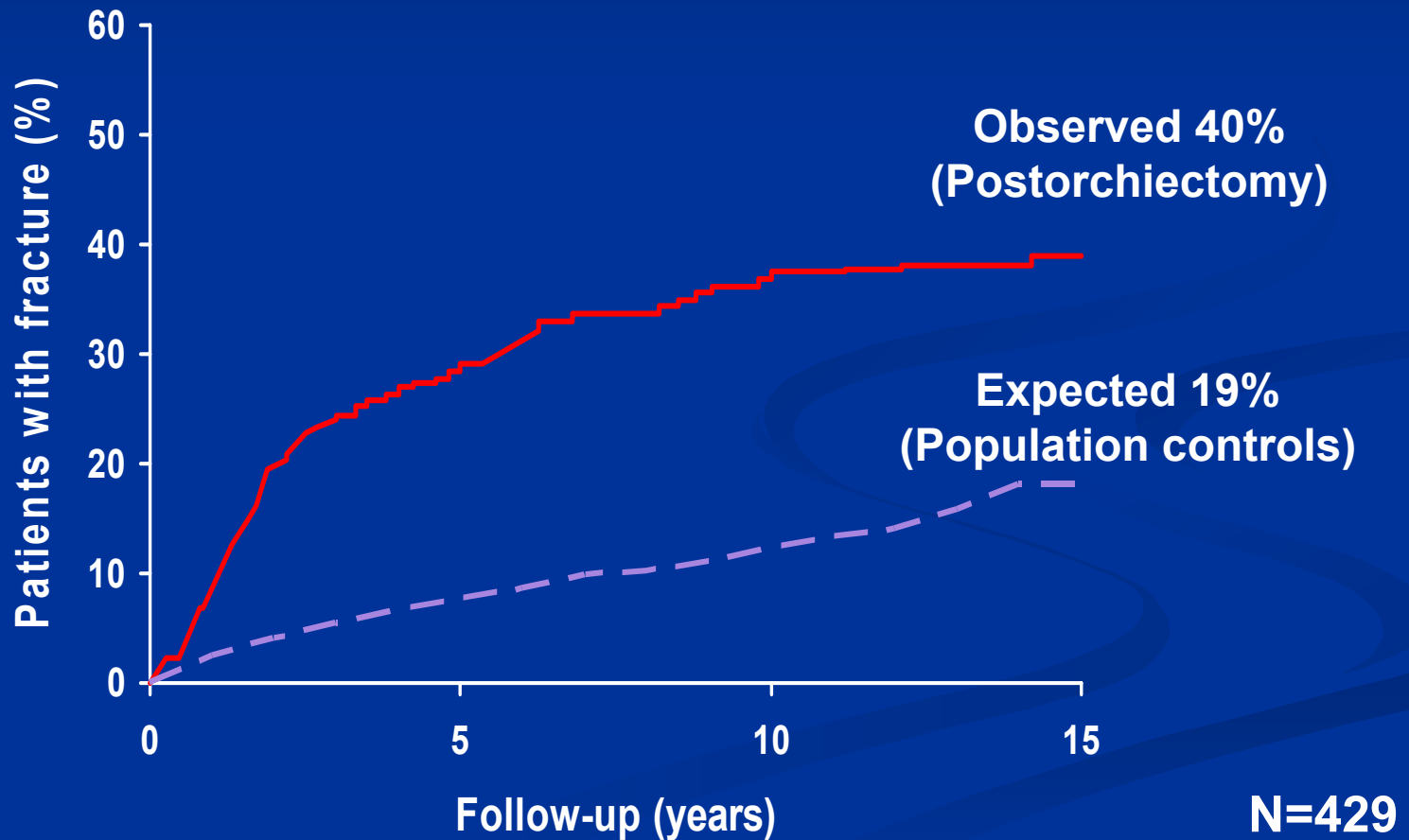
*Based on regression analysis of radius/ulna BMD vs bioavailable E₂ in elderly men.

1. Adapted from Khosla S et al. *J Clin Endocrinol Metab.* 2001;86:3555-3561. 2. Smith MR et al. *J Clin Endocrinol Metab.* 2002;87:599-603. 3. Hesmati HM et al. *J Bone Miner Res.* 2002;17:172-178.

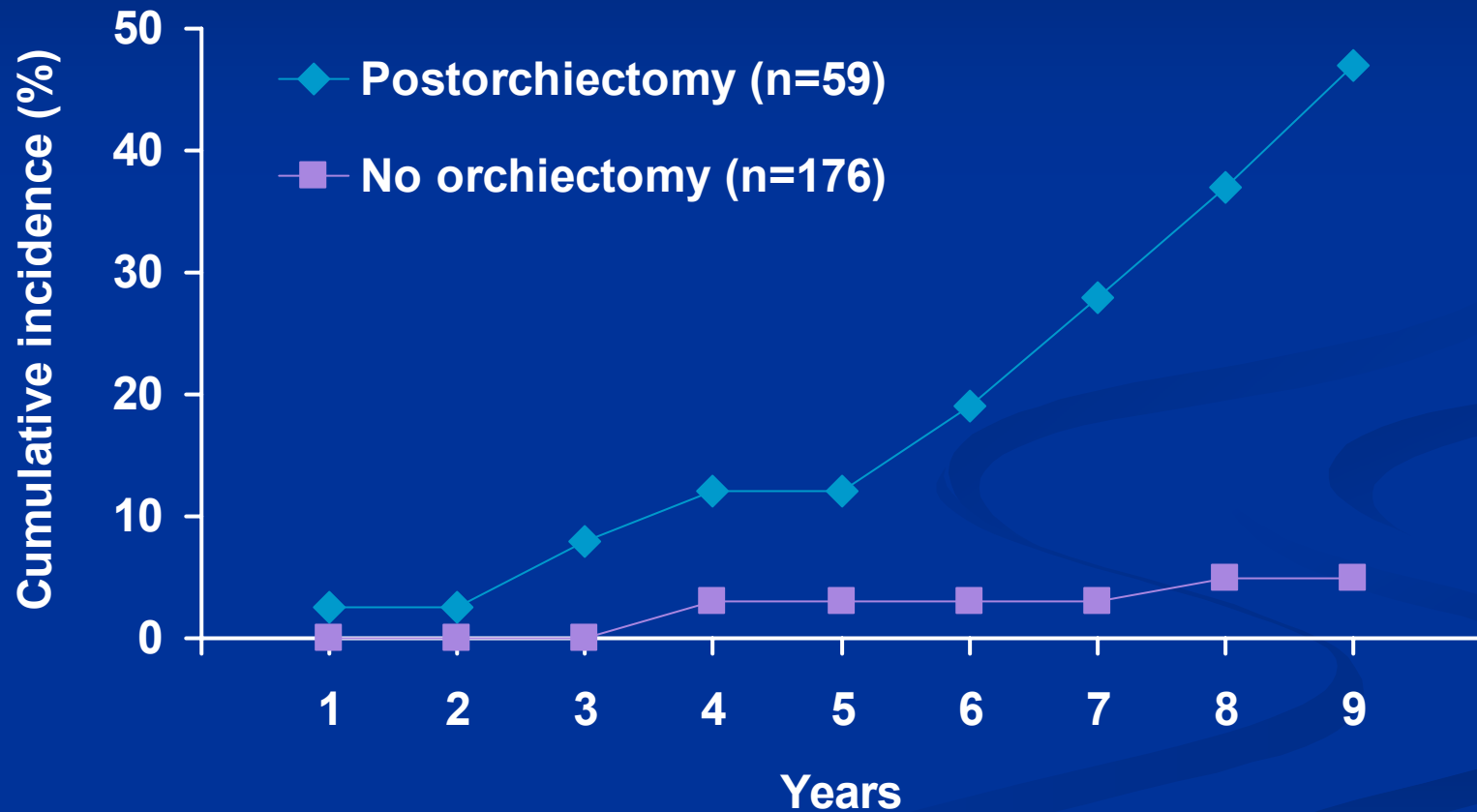
Bone loss in patients with Prostate Cancer with ADT

- Osteopenia and Osteoporosis occurs in 10-25% of men with prostate cancer prior to initiation of hormonal therapy^{1,2,3}
- Studies show that once ADT is initiated, average femoral neck BMD decreases 7.6% by 1 year¹
- A study of intermittent ADT begun with 9 months of ADT reported a 2.7% decrease in hip BMD, which stabilized during the off-therapy period¹

Bilateral Orchiectomy and Increased Fracture Incidence in Men



Androgen Deprivation Therapy (ADT) and Increased Fracture Incidence



Recommendations for Assessing Bone Health in At-Risk Patients: Summary

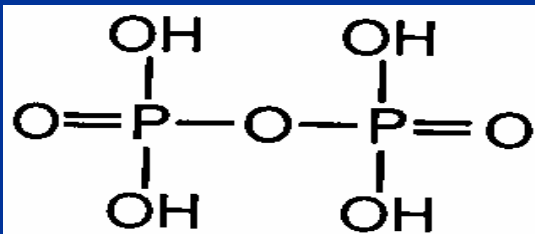
- **All men on ADT should be screened at baseline and yearly thereafter according to some authors**

Treatment of Bone Loss in the Adjuvant Setting

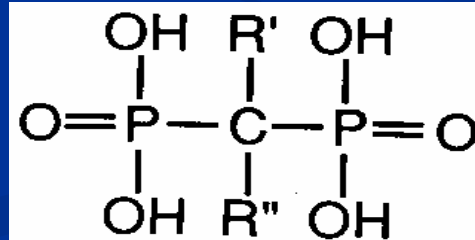
Bisphosphonates

- Analogues of inorganic pyrophosphate
- Inhibitors of osteoclast activity
- Oral and IV forms

<u>Drug</u>	<u>Generatio n</u>	<u>Relative Potency</u>
Etidronate	1st	1
Clodronate		10
Tiludronate	2nd	10
Alendronate		100
Pamidronate		100-1000
Risedronate	3rd	1000-10,000
Ibandronate		1000-10,000
Zoledronate		10,000+



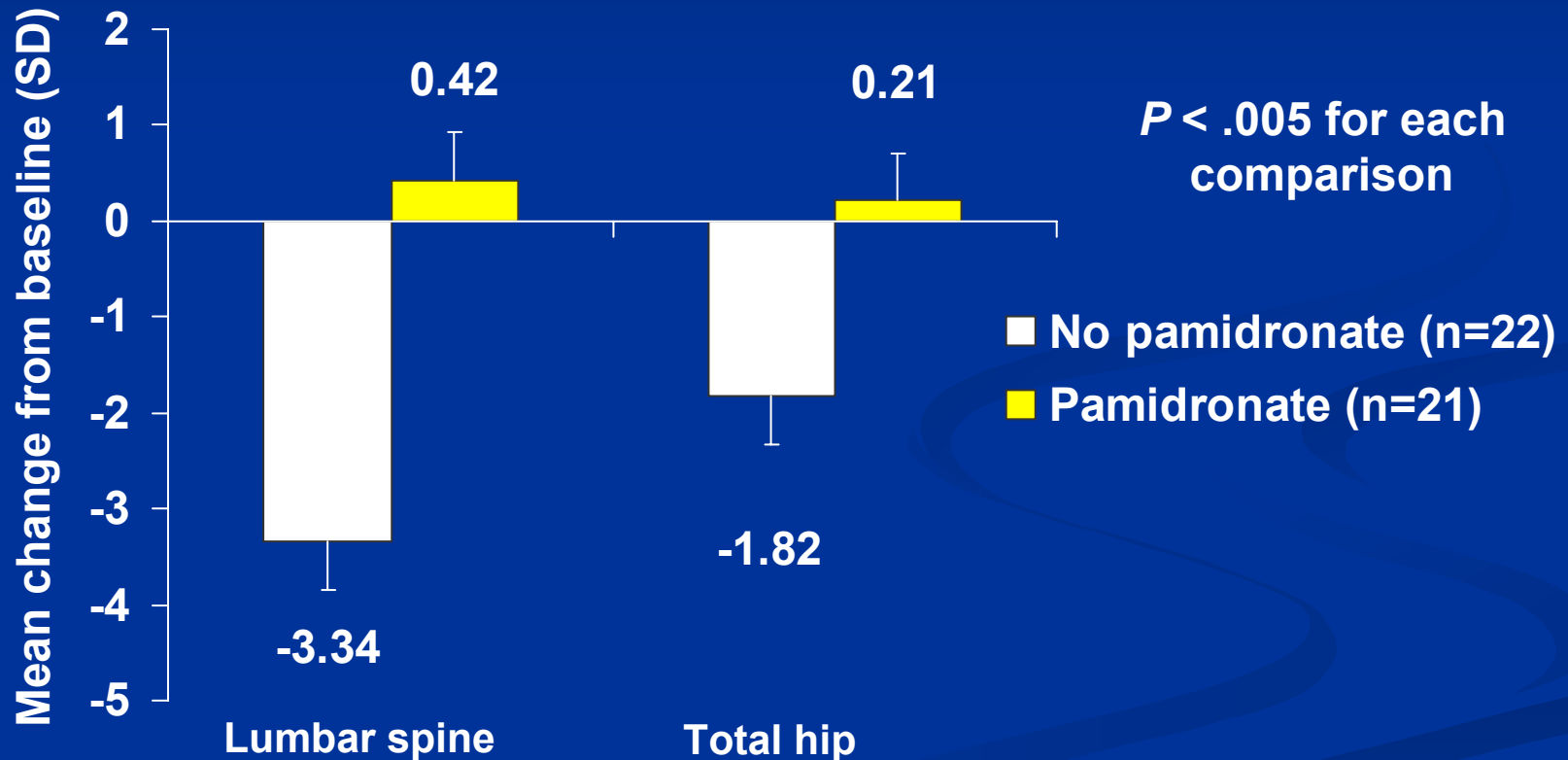
Pyrophosphate



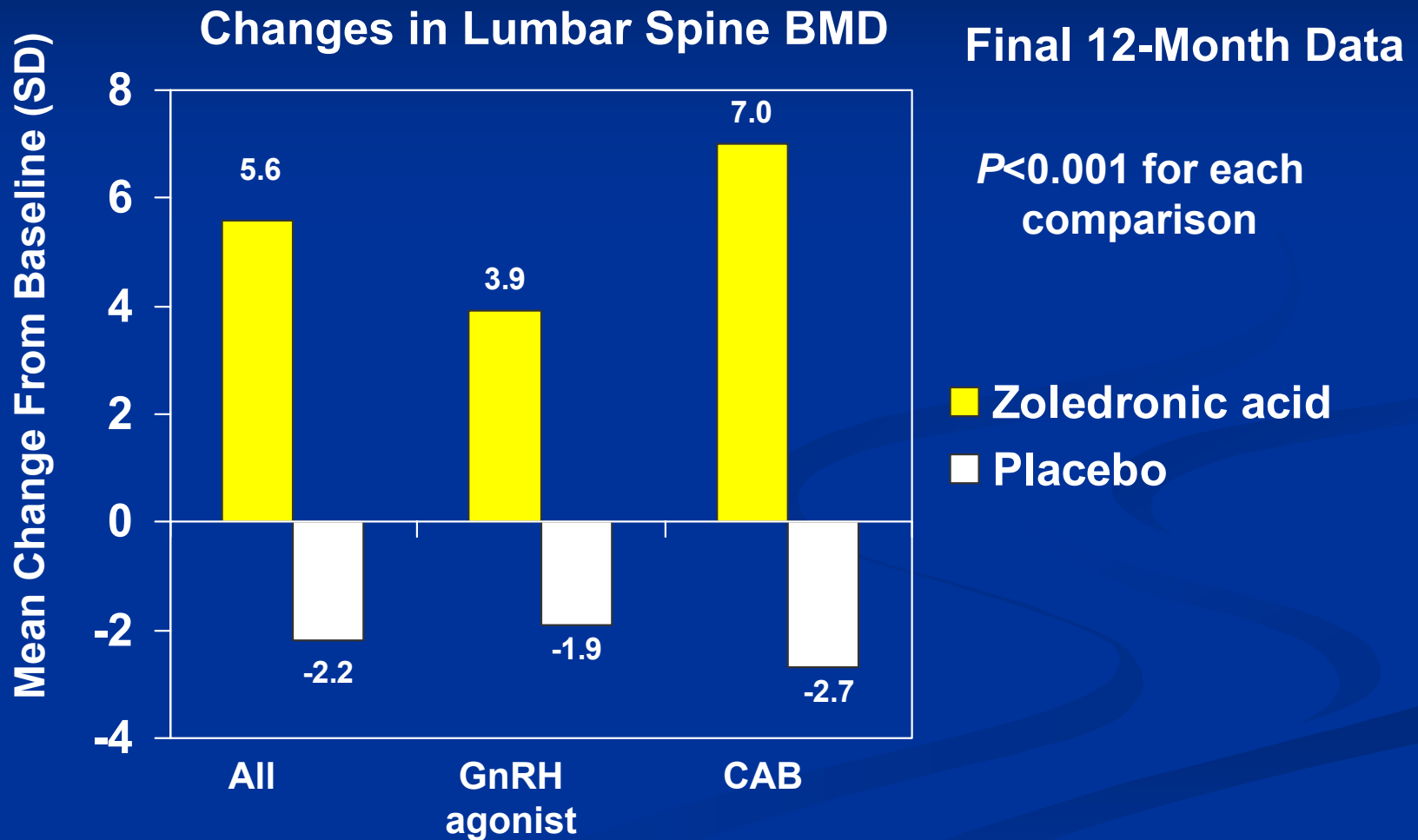
Bisphosphonate

Pamidronate and ADT-Induced Bone Loss in Men With Localized Prostate Cancer

12-Month Data



Zoledronic Acid Increases BMD in Patients With Locally Advanced Prostate Cancer on ADT



CAB=combined androgen blockade.

Smith MR et al. *J Urol*. 2003;169:2008-2012.

Zoledronic Acid Subsequent to ADT in Patients with Prostate Cancer

Study Design

- Men (n=122) with prostate cancer without bone metastases treated with androgen deprivation therapy (ADT)
- After treatment with ADT \leq 12 months, randomization to zoledronic acid 4mg or placebo, IV, every 3 months. T-score \geq -2.5 or less at 1 more measured sites

Outcomes:

- Primary End points: Change in femoral neck and lumbar spine bone mineral density (BMD)
- Secondary Endpoints: Change in serum bone specific alkaline phosphatase and urine N-telopeptide levels

Zoledronic Acid Subsequent to ADT in Patients with Prostate Cancer

Results:

- Zoledronic acid increased BMD in all three sites compared to placebo:
 - FN by 3.6% (p=.0004)
 - TH by 3.8% (p<.0001)
 - LS BMD by 6.7% (p<.0001)
- Effects were not differentiated according to ADT therapy duration at all three sites
- Mean BSAP and NTx were decreased significantly in the zoledronic group (each p<.0001) and increased in placebo group (p<.0001 and p=.004) respectively

FN=Femoral Neck; TH= Total Hip; LS=Lumbar Spine; BMD=Bone Mineral Density
BSAP=Bone specific alkaline phosphatases; NTx=N-telopeptide levels

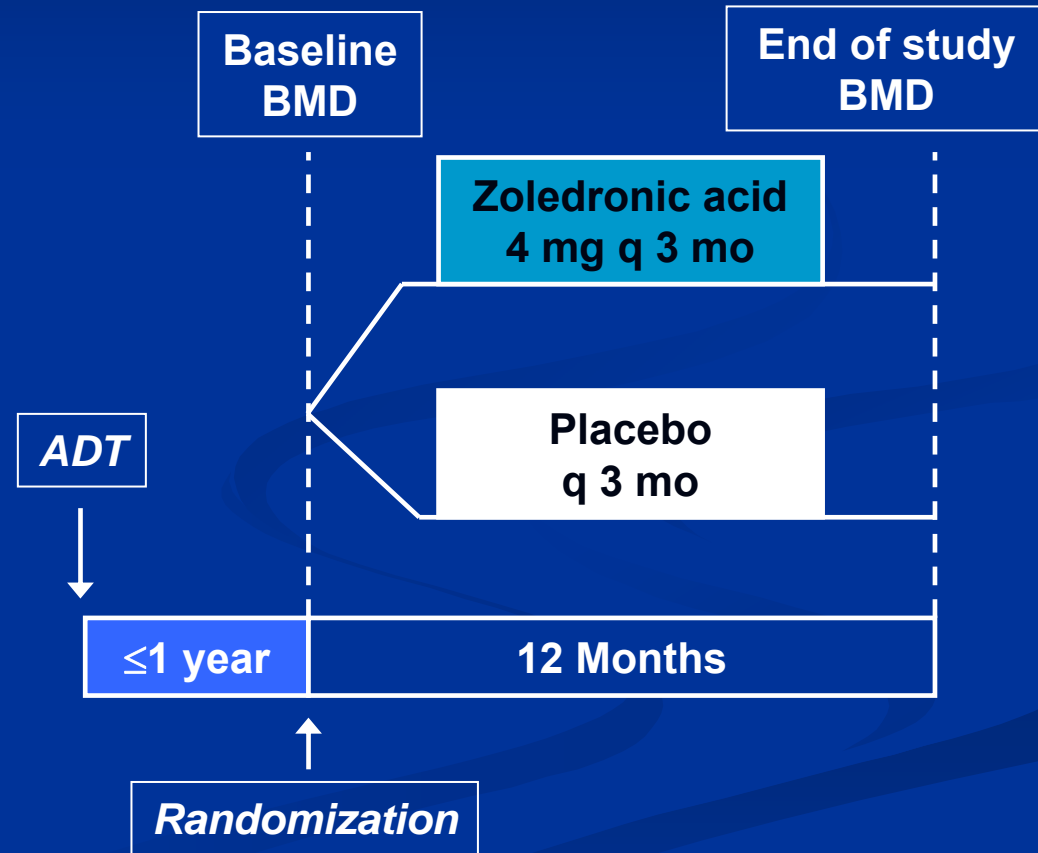
Conclusions

- Intermittent administration of zoledronic acid within the first 12 months of ADT prevents bone loss and increases BMD in patients with prostate cancer without bone metastases.
- Results similar to earlier study by Smith et al, where the effect of Zoledronic acid on BMD in patients with non-metastatic PC in whom ADT was initiated at study enrollment
- This finding that zoledronic acid remains effective in men on ADT for up to 1 year supports current recommendations for periodic DEXA monitoring and initiation of bisphosphonate therapy in men with decreasing BMD

ASCO 2006 Updates

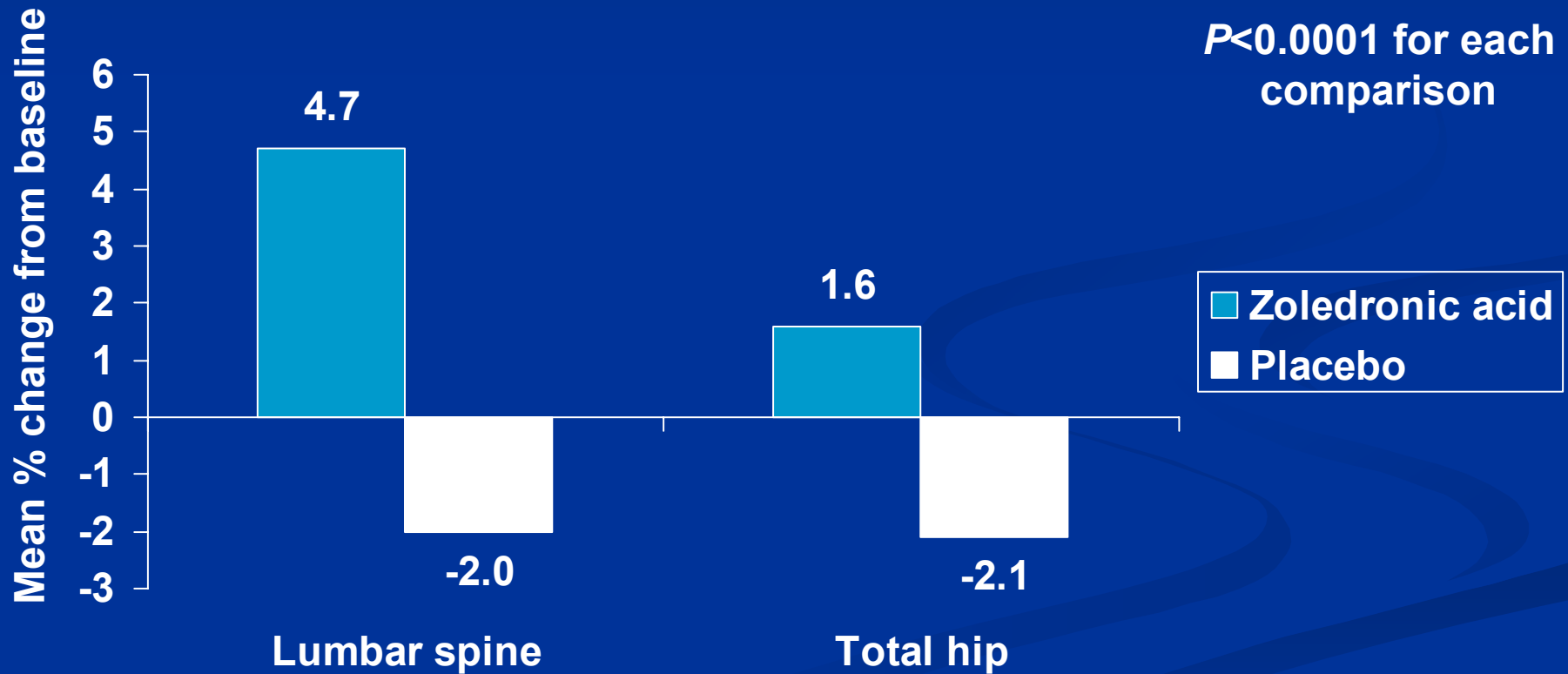
Zoledronic Acid to Prevent Further Bone Loss: US 45 Study Design

- Men (n=222) with prostate cancer treated with androgen deprivation therapy (ADT)
 - Treated with ADT ≤ 1 year at randomization to ADT plus zoledronic acid or placebo
 - T-score ≥ -2.0
- End points: lumbar spine bone mineral density (BMD) and total hip BMD at baseline and 52 weeks; N-telopeptide, and bone-specific alkaline phosphatase at baseline, every 12 weeks, and at 52 weeks; safety



Zoledronic Acid Increases Bone Mineral Density (BMD) in Men With Prostate Cancer Receiving Androgen Deprivation Therapy ≤ 1 year (US 45)

Changes in BMD from baseline



Abstract 4515—Oral Presentation

Presenter: Michaelson

Annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: A randomized placebo-controlled trial

Study Design

- Open-label 12-month study of men with nonmetastatic prostate cancer (N = 44) who were receiving GnRH therapy were randomly assigned to ZOL (4 mg IV once) or placebo

Abstract 4515—Oral Presentation

Presenter: Michaelson

Results

- Mean lumbar spine BMD significantly increased by 4.0% \pm 0.9 in men treated with ZOL and decreased by 3.1% \pm 0.7 in men who received placebo ($P < .001$)
- Mean BMD of the total hip decreased by 1.9% \pm 0.7 in men who received placebo and decreased by only 0.7% \pm 0.6 in men treated with ZOL ($P = .005$)
- ZOL significantly decreased serum NTX compared with placebo throughout the study ($P < .005$)

Abstract 14643—Publication Only

Presenter: Lam

Oral bisphosphonates fail to prevent bone loss from androgen deprivation therapy in men with prostate cancer

- Retrospective study of alendronate and risendronate in men initiating ADT (N = 22)
- Overall, the mean annual change in BMD was -7.77% ($P = .0003$)
 - 9/22 men maintained or gained bone density (-1.26% to $+5.95\%$)
 - 13/22 men lost $\geq 6.03\%$ (-6.03% to -23.2%)
 - There were no unexpected toxicities or fractures
- In this retrospective study, prophylactic oral bisphosphonates did not protect against accelerated ADT-induced bone loss in men with prostate cancer

DEXA for Measuring BMD

Dual-energy x-ray absorptiometry (DEXA):

- Provides a 2-dimensional measure of bone density
- Office-based procedure
- Central DEXA
 - Gold standard
 - Measures spine, hip, or total body BMD
- Peripheral DEXA
 - Measures wrist, heel, or finger BMD



World Health Organization (WHO): Criteria for Assessing Bone Density

Diagnosis	T-score
Normal	> -1
Osteopenia	-1 to -2.5
Osteoporosis	≤ -2.5
Severe osteoporosis	≤ -2.5 T-score and ≥ 1 fragility fracture

Markers for Assessing Bone Turnover

Bone Formation Markers	
Bone alkaline phosphatase (ALP)	Serum
Osteocalcin (OC)	Serum
Bone Resorption Markers	
C-telopeptides of type I collagen (CTX)	Urine
Deoxypyridinoline (D-Pyr)	Urine
N-telopeptides of type I collagen (NTx)	Urine
Pyridinoline (Pyr)	Urine

Summary

- Bone loss is highly prevalent in men with prostate cancer at initial diagnosis, and initiating ADT results in accelerated bone resorption, leading to bone loss and an increased risk of fracture.
- They are also at high risk for disease progression and bone metastases that can result in significant skeletal morbidity, including pathologic fracture, spinal cord compression, and debilitating bone pain requiring additional therapy.
- Zoledronic acid, has increased BMD in men receiving ADT and is the only bisphosphonate that has shown statistically significant reductions in skeletal morbidity in patients with bone metastases from prostate cancer.