

# Postmenopausal Osteoporosis

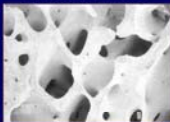
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Diabetes and Metabolism  
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## Objectives

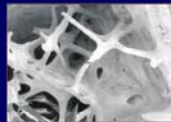
- Review the definition of osteoporosis and its health care impact
- Overview of diagnosis and evaluation
- Discuss available therapeutic options, pharmacologic and non-pharmacologic
- Finish up with a few cases

## Osteoporosis: Definition

Normal Bone



Osteoporotic Bone



©2005, David W. Dempster, PhD

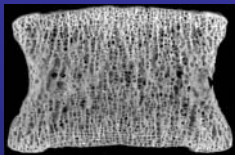
### NIH Definition:

"Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture"

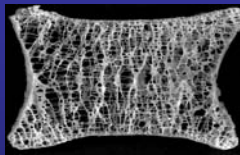
1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA*. 2001;285:785-795.



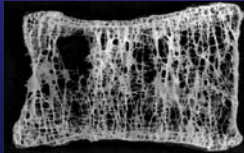
Normal



Moderate Osteoporosis



Severe Osteoporosis



Courtesy Dr. A. Boyde

## Vertebral Fractures Have Significant Consequences for Patients, Including Dorsal Kyphosis

### Vertebral Fractures

- ▶ Associated with
  - Acute and chronic pain
  - Kyphosis and height loss
  - Impaired function
  - Increased morbidity and mortality
  - Increased fracture risk



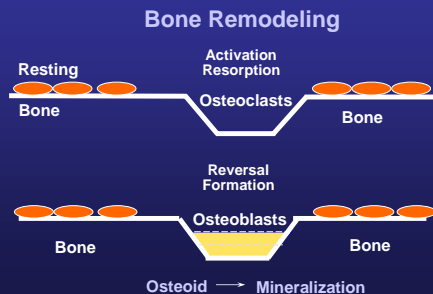
Image reprinted with permission from Whitehead MI, et al. *A Slide Atlas of Menopause*. London, UK: Parthenon Publishing Group; 1993.  
Delmas PD, et al. *J Bone Miner Res*. 2005;20:557-563.

## Hip and Other Non-Vertebral Fractures Have Significant Consequences

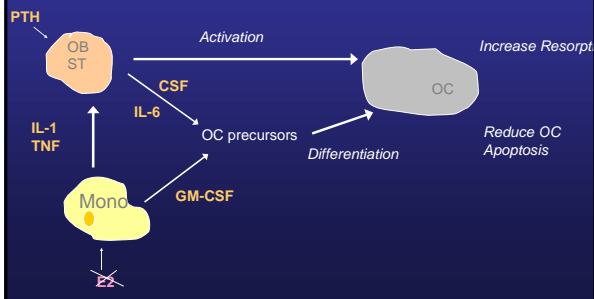
- ▶ Hip fracture associated with
  - Loss of ambulatory status in 30% of patients
  - Increased morbidity and mortality
  - Increased fracture risk
  - Major reason for admission to chronic care facilities
- ▶ Non-vertebral fractures
  - Pain
  - Increased risk of future fractures

National Osteoporosis Foundation. Available at: <http://www.nof.org/osteoporosis/diseasefacts.htm>. Accessed August 13, 2007.

## Pathophysiology of Osteoporosis



## Local Mechanism of Estrogen Effects on Bone Loss



## Genetics of Osteoporosis

- Twin and family studies show high heritability of bone structure: 60-80%
- Fracture risk also quite heritable
  - Eg: wrist fractures have been found to be 25-50% heritable
- Osteoporosis development is multifactorial with several genes involved

## Tools for Studying Genetics of Osteoporosis:

- Human Genome Project
- Extensive SNP databases
- International HapMap resource
- International consortiums pooling large, well-characterized data sets

## Genetics, cont

- Goal of finding a few specific genes that contribute significantly to osteoporosis:
  - Predicting fracture risk
  - Assessing a likely response to treatment: "pharmacogenomics"
  - Further personalizing approach to a patient with osteoporosis

Will genetic information enhance these goals beyond readily measurable clinical factors?

## Clinical Presentation of Osteoporosis

- ▶ Usually asymptomatic and undiagnosed
- ▶ Signs and symptoms
  - Low-trauma fractures of spine, wrist, or hip
  - Loss of height
  - Kyphosis (rounded back)
  - Acute or chronic back pain
- ▶ Diagnostic tests
  - Bone mineral density measurement
  - Spine x-ray or morphometry



Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, Md: US Department of Health and Human Services; 2004:187-217.

## NOF Screening guidelines

- All women >65yo
- Women <65yo with one or more risk factors for osteoporotic fracture (other than estrogen deficiency)
- Postmenopausal women with a fracture
- Women who are considering therapy
- Screening of men, pre-menopausal women and non-white women decided individually



## Why DEXA?

- High precision
- Short scanning time
- Low radiation dose
- Scans both spine and hip
- \*\*The test used in most clinical trials, so clinical usefulness and interpretation is most well-known and studied – also the normative database is the largest

## Uses of BMD by DEXA

- Diagnosis of Osteopenia or Osteoporosis
  - Postmenopausal women
  - Glucocorticoid use
  - Metabolic bone disease
  - Osteopenia on plain radiograph
  - Previous fragility fracture or loss of height
- Prognosis – fracture risk assessment
- Monitor therapeutic response

## Diagnosis – T-score WHO criteria

- Normal -  $\geq -1$
- Osteopenia -  $< -1$  and  $> -2.5$
- Osteoporosis -  $\leq -2.5$
- “Severe” Osteoporosis -  $\leq -2.5$  + Hx Fx
- \*\*Osteoporosis is also diagnosed in patients with a history of fragility fracture, regardless of BMD

## Osteoporotic Fracture Risk

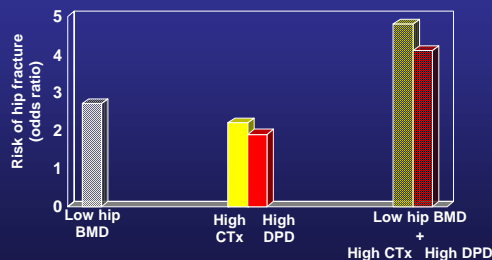
- Personal History of Fx
- Family history of Fx after age 50
- Weight <127#
- Current Smoker
- Age
- White Race
- Alcoholism
- Low physical activity
- Recurrent falls
- Dementia

History is an important diagnostic tool in osteoporosis evaluation!

## Bone Turnover Markers and Fracture Risk

- BMD is only a “snapshot” of bone – doesn’t indicate RATE of bone loss
- Significant correlation between markers and rates of bone loss
- Those with a higher rate of bone loss develop osteoporosis faster and are more likely to fracture
- Bone Specific Alkaline Phosphatase and serum C-telopeptide most useful

## Predicting hip fracture risk with BMD and markers



Garnero et al, J Bone Miner Res, 1996

## Likely Best Use of Bone Turnover Markers

- Predict fracture occurrence
- Select specific therapy for patients
- Predict increases in bone mass on therapy
- Monitor effectiveness of therapy
- To Be Continued . . .

## Vertebral Fracture Assessment

- Densitometric spine imaging performed to detect vertebral fractures
- Consider its use:
  - Height loss (historical)  $\geq 1.5$  inches
  - Hx of fracture after age 50
  - Commitment to long term steroids
  - History/findings suggestive of vertebral fracture

[www.iscd.org](http://www.iscd.org) 2005 Official Positions



VFA

Baseline 2 yr-Follow-up

## Initial Laboratory Evaluation

- Searching for abnormalities that, when treated, decrease the relative risk of fracture
- Evaluate for secondary causes of bone loss and increased bone turnover

## Laboratory evaluation

- Calcium, Magnesium, phosphorous
- PTH
- **25(OH) vitamin D**
- 24 hour urine calcium and creatinine
- TSH
- SPEP
- Chem 7

## Non-pharmacologic Intervention: Nutrition

- Peak bone mass attainment in puberty and young adulthood the greatest time of impact for nutrition on bone health
- Nutritional recommendations for North American adults include 3 dairy servings per day
- Lactose intolerance, Soda “substitution”
- High salt diet increases calciuria

## Calcium

- Probably best absorbed as citrate
- Intestinal absorption of calcium plateaus at 500mg
  - Divide doses to bid or tid
- Dairy products provide 250 – 300mg per serving: 8oz glass milk, 8oz yogurt, 16oz cottage cheese or 1oz hard cheese





## Fracture Reduction with Vitamin D

- Significant reduction only observed in the studies where treatment dose was 700-800IU/day
- Greater fracture reduction was achieved with higher serum 25(OH)vitD levels
  - 26% reduction in hip fractures
  - 23% reduction in non-vertebral fractures
- 35% reduction in falls with improvement in muscle strength

## Exercise

- Nurses Health Study: Walking 4hr/week decreased hip fx by 41% over those walking <1 hr/week<sub>1</sub>
- High intensity weight lifting, one hour twice a week significantly increased LS and TP BMD<sub>2</sub>
- Likely has minimal effect on BMD but is key for muscle strength and fall prevention

1: Feskanich et al JAMA 2002 Nov 13;288(18):2300-6.  
 2: Nelson et al JAMA 1994 Dec 28; 272(24), pp 1909-14

## Treatment recommendations: NOF

- Start therapy at T-score <-2 if no other risk factors
- Start therapy at T-score <-1.5 if risk factors are present
  - This is also a great “grey” zone where bone turnover markers are helpful!

## Who do we treat?

- NOF Clinician’s Guide to Prevention and Treatment of Osteoporosis, March 2008
- Consider treatment in all PM women and men over 50yo with
- Low bone mass at Total hip, Lumbar Spine or Femoral neck (T-score -1.0 to -2.5) and
  - 10yr hip Fx probability  $\geq 3\%$  or
  - 10 yr probability of all major osteoporotic related fracture of  $\geq 20\%$
  - Using FRAX

Country : US(Caucasian) Name / ID:  About the risk factors ⓘ

**Questionnaire:**

1. Age (between 40-90 years) or 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 more units per day:  No  Yes

12. Femoral neck BMD:  Select

The World Health Organization Fracture Risk Assessment Tool [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)



www.shef.ac.uk/FRAX/

Country: **US(Caucasian)** Name / ID:  About the risk factors ⓘ

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth  
 Age: 47 Y:  M:  D:   
 2. Sex:  Male  Female  
 3. Weight (kg): 65.6  
 4. Height (cm): 171.4  
 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 more units per day:  No  Yes  
 12. Femoral neck BMD: T-score: -1.6

Clear Calculate

**BMI: 22.3**  
 The ten year probability of fracture (%)  
 with BMD

Major osteoporotic	5.9
Hip fracture	1.5

The World Health Organization Fracture Risk Assessment Tool. www.shef.ac.uk/FRAX

### Effects of Bisphosphonates on Osteoclast Function

**Normal Osteoclast**

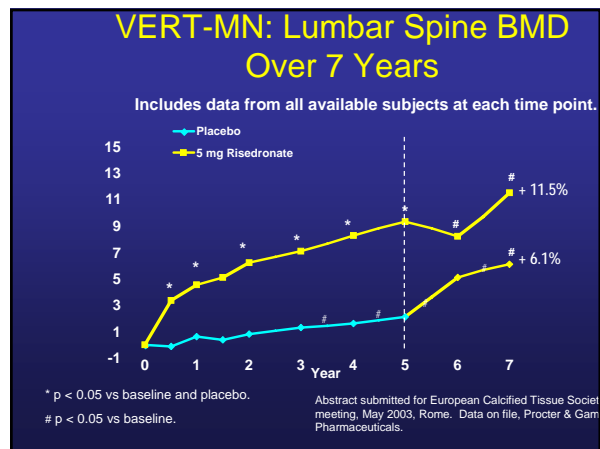
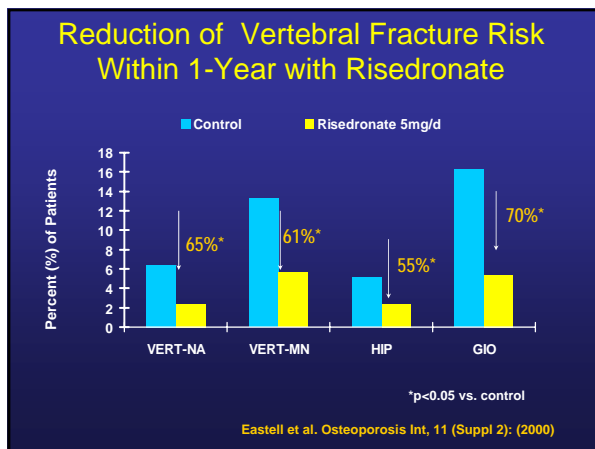
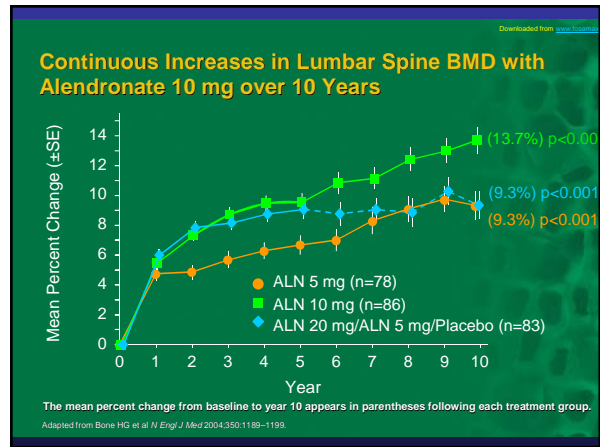
**Osteoclast Following Uptake of Bisphosphonate**

Loss of ruffled border<sup>1</sup>  
 Cytoskeletal disorganization<sup>1</sup>  
 Cell death by apoptosis<sup>2</sup>  
 Altered vesicular trafficking<sup>3</sup>

- Sato, H, et al. *J Clin Invest*. 1991;88:2095-2105.
- Hughes DE, et al. *J Bone Miner Res*. 1995;10:1478-1487.
- Rogers H. *Curr Pharm Des*. 2003;9:2643-2656.

## Alendronate (Fosamax)

- Fracture Intervention Trial (FIT)
  - In all pts with T-score <-1.6, sig reduction in vertebral fractures
  - In pts with T-score <-2.5, or 1 or more previous fragility fractures, sig reduction hip and all clinical fractures



## Reclast (zoledronic acid)

- IV infusion
- 5mg infused over 15 minutes
- Once yearly dosing

## HORIZON Pivotal Fracture Trial: Overview and Study Design

- ▶ Objective: To evaluate the potential of once yearly Reclast to decrease fracture risk in postmenopausal women with osteoporosis
- ▶ 3-year, randomized, double-blind, placebo-controlled clinical trial
  - 7736 women from 239 clinical centers in 27 countries
- ▶ Treatment
  - Annual infusion of either Reclast or placebo
  - Calcium 1000–1500 mg/d; vitamin D 400–1200 IU/d
- ▶ Follow-up visits at 6, 12, 24 and 36 months
  - Telephone interviews every 3 months

Black DM, et al. *N Engl J Med.* 2007;356:1809-1822.

Please see full prescribing information.

## HORIZON Pivotal Fracture Trial: Baseline Characteristics

	Reclast (n = 3875)	Placebo (n = 3861)
Stratum I, n (%)	3045 (78.6)	3039 (78.7)
Stratum II, n (%)	830 (21.4)	822 (21.3)
Mean (SD) age, years	73.1 (5.3)	73.0 (5.4)
Femoral neck T-score, n (%)		
≤ -2.5	2814 (72.6)	2734 (70.8)
Prevalent vertebral fracture, n (%)		
1 or more	2416 (62.3)	2477 (64.2)
Prior bisphosphonate use	565 (14.6)	557 (14.4)

Adapted from Black DM, et al. *N Engl J Med.* 2007;356:1809-1822.

Please see full prescribing information.

## Reclast Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I)

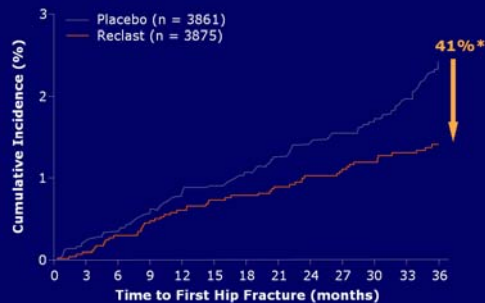


\*P < .001, relative risk reduction vs placebo (95% confidence interval)

Adapted from Black DM, et al. *N Engl J Med.* 2007;356:1809-1822.

Please see full prescribing information.

## Reclast Reduced Cumulative 3-Year Risk of Hip Fractures (Strata I + II)



\*P = .0024, Relative risk reduction vs placebo (95% confidence interval)

Adapted from Black DM, et al. *N Engl J Med.* 2007;356:1809-1822.

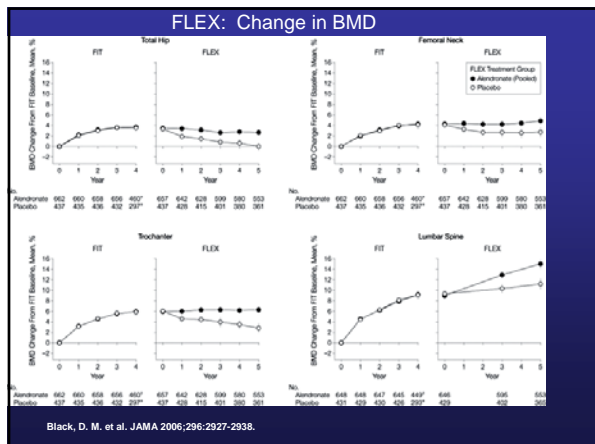
Please see full prescribing information.

## Doctor, will I ever be able to stop my osteoporosis medicine?

- Fracture Intervention Trial Long-term Extension (FLEX)
  - FIT Trial participants, on Aln for at least 3 years, randomly placed on placebo or alendronate for five more years
    - 60% had hx clinical fractures since menopause
    - \*\*Women at the highest risk for fx were excluded\*\*
  - 1099 women were enrolled
  - BMD at LS, TH, FN; bone turnover markers, fractures and AEs were evaluated

Black DM et al. *JAMA.* December 27, 2006; 296:2927-2938





### Case 1

- 68yoWF presents with mid-thoracic pain after pulling a fitted sheet onto her bed
- Height loss of 2.5" since youth
- PE with mild kyphosis, focal pain palpable at T10
- Labs all normal; plain X-ray with compression fracture at T10
- Does she have a diagnosis yet? What do you do?



### Case 1

- She DOES have osteoporosis
- DO get a BMD for serial evaluation of therapy
  - L<sub>2-4</sub> T-score  $-3.2$ ; total hip T-score  $-2.7$
- Begin antiresorptive therapy: bisphosphonate
  - Spend time counseling her on use!
- RDA calcium and vitamin D
- Pain control then physical therapy

### Case 2

- 53yo WF requests BMD for health maintenance
- PMHx: GERD, treated HTN
- Menopause at age 49; no symptoms; never on HT
- PE: normal, weight 142#, no kyphosis, no bony pain, height 5'4" unchanged from high school

### Case 2, cont

- BMD:
  - L<sub>1-4</sub> T-score  $-1.8$
  - Total hip T-score  $-2$
  - Femoral neck T-score  $-2.1$

Now What?

## Case 2, cont

- **More History!**
  - Never a smoker
  - Mother without any fractures; pt broke her left arm at age 12 after flying off a bike, no others
  - Works out 4 days a week, never falls
- Screen for secondary causes of bone loss
- Start RDA calcium – citrate as on a PPI
- Start RDA Vitamin D – 800IU/d
- Repeat BMD in 2 years

## Case 3

- 68yoWF with Crohn's on chronic prednisone
- On RDA calcium and vitamin D
- On bisphosphonate for four years
  - BSAP 8
- Workup for secondary causes is negative; spine T-score –3.5
- Has had three new compression fractures in the last two months

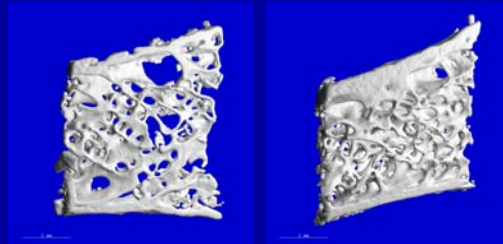
## Teriparatide (Forteo)

- 1-34 PTH, synthetic
- Anabolic agents – main action is to stimulate osteoblasts
- Daily subcut injection, 20mcg
- Very expensive - \$20/d; \$6,000/year
- Osteosarcoma warning

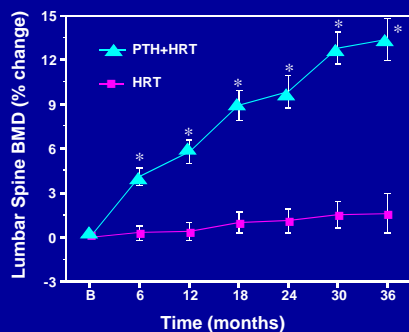
## 64 Year-Old Woman (M H)

**Before PTH(1-34)**  
 Ct.Th: 0.32 mm  
 CD: 2.9/mm<sup>3</sup>

**After PTH(1-34)**  
 Ct.Th: 0.42 mm  
 CD: 4.6/mm<sup>3</sup>



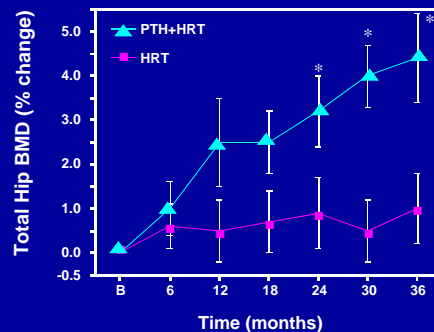
## Change in Lumbar Spine BMD



Cosman, et al JBMR 2001

\*P<0.05

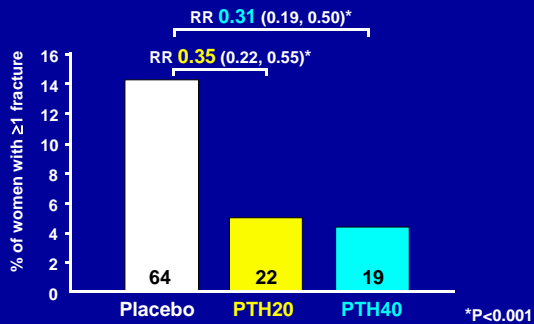
## Change in Total Hip BMD



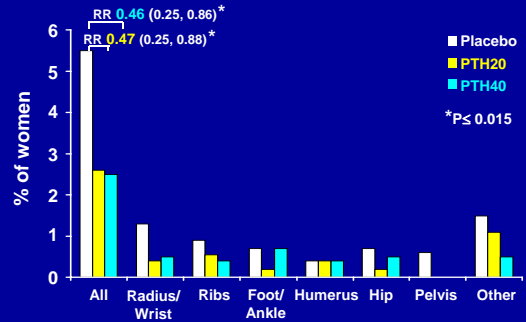
Cosman, et al. JBMR 2001

\*P<0.05

## Teriparatide Reduces the Risk of Vertebral Fractures - GHAC



## Teriparatide Reduced Nonvertebral Fragility Fractures - GHAC



## Serial Monitoring

- Spine – significant gains from treatment can usually be seen in one year
  - Hip often takes 18-24 months
- See changes ( $\uparrow$  or  $\downarrow$ ) in six months with patients on glucocorticoids
- ISCD recommends yearly BMD until bone mass stable or improving, then every two years