Welcome!

FLS Bone Health ECHO® TeleECHO Clinic

We will be recording this TeleECHO Clinic for educational and quality improvement purposes.

By participating in this clinic you are consenting to be recorded.

- If you do not wish to be recorded, please email andrea.medeiros@nof.org at least one week prior to the TeleECHO Clinic you wish to attend.
- Please type in your name, location, and email address in the chat.

Some helpful tips:

- Please mute your microphone when not speaking

- Position webcam effectively

- Communicate clearly during clinic:
    - Speak clearly
    - Use chat function

Project ECHO's goal is to protect patient privacy

To help Project ECHO accomplish that goal, please only display or say information that doesn't identify a patient or that cannot be linked to a patient.

References:

For a complete list of protected information under HIPAA, please visit www.hipaa.com

Common HIPAA Identifier Slip-Ups and Easy Ways to Protect Patient Privacy

- 1st – **Names:** Please do not refer to a patient's *first/middle/last name* or use any *initials*, etc. Instead please use the *ECHO ID*.

- 2nd – **Locations:** Please do not identify a patient's *county, city or town*. Instead please use only the patient's *state* if you must or the *ECHO ID*.

- 3rd – **Dates:** Please do not use any dates (like *birthdates*, etc.) that are linked to a   patient. Instead please use only the patient's *age* (unless > 89)

- 4th – **Employment:** Please do not identify a patient's *employer*, work *location* or *occupation*. Instead please use the *ECHO ID*.

- 5th – **Other Common Identifiers:** Do not identify patient's *family* members, *friends, co-workers, numbers, e-mails*, etc.

Goal-directed Treatment*
to Prevent Fractures

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*AKA Treat-to-Target

Acknowledgements/Disclosures

- Developed in collaboration with Dr. Mike Lewiecki and Dr. Felicia Cosman

- Support from ASBMR and NOF

- Financial interests: consultations with Amgen and Radius, who have treatments that may benefit from Goal-directed Treatment

- Grant/Research/Speaker's Bureau: Amgen

Developing goals for osteoporosis

- An ASBMR-U.S. NOF Task Force
- Included several specialties and countries

Goal-Directed Treatment for Osteoporosis: A Progress Report From the ASBMR-NOF Working Group on Goal-Directed Treatment for Osteoporosis

Steven R Cummings,[1] Felicia Cosman,[2] E Michael Lewiecki,[3] John T Schousboe,[4] Douglas C Bauer,[5] Dennis M Black,[6] Thomas D Brown,[7] Angela M Cheung,[8] Kathleen Cody,[9] Cyrus Cooper,[10] Adolfo Diez-Perez,[11] Richard Eastell,[12] Peyman Hadji,[13] Takayuki Hosoi,[14] Suzanne Jan De Beur,[15] Risa Kagan,[16] Douglas P Kiel,[17] Ian R Reid,[18] Daniel H Solomon,[19] and Susan Randall[20]

Learning Objectives

Understand the fundamentals of Goal-directed treatment to prevent fractures

1. What is the difference between selecting initial drug treatment for in standard vs. goal-directed treatment?

2. At a follow-up visit, what is the purpose of measuring BMD in standard vs. goal-directed treatment?

3. Why obtain spine imaging in patients who will be given drug treatment?

Outline

- Standard vs. goal directed drug treatment
  - Selection of initial treatment
  - Follow-up of treatment
- Issues

When to consider goal-directed treatment

- For patients who meet the criteria for starting drug therapy to prevent fractures

- It is most useful in patients who have a hip BMD T-score below -2.5

  - For example, patients who have suffered a fracture and have osteoporosis by BMD

- Goal-directed treatment is intended to rationalize the selection of initial treatment

- The approach to follow-up to monitor patients applies to patients who received drug treatment to prevent fractures

Standard approach

- Start based on BMD and/or FRAX score
- Prescribe 1st line drug, usually bisphosphonate
- BMD in 1-2 years to check 'response'
- If 'responding', continue
- If not, consider switching to another drug
- A bisphosphonate "holiday' after 5 years

Two cases

Ms. O.

56 year old woman

- 2 years ago: wrist fracture while jogging
  - No medical or risk factors; BMI 25
  - BMD: femoral neck (FN) T-score: -2.7, spine -2.4
- Started alendronate
- Now: routine follow-up visit

Ms. O.

56 year old woman

2-year follow-up

- No subsequent fracture

- T-score   3 yrs ago   current

   FN   -2.7   -2.4

   Spine   -2.4   -2.2

- She is responding. Continue.

- Consider a drug holiday at 5 years of treatment

Mrs. S.

77 y.o. white woman

- – Humerus fracture

- – Controlled hypertension and heart failure

- – No other risk factors

- – BMD: FN T-score = -3.4, Spine = -3.1

- FRAX$_{hip\ fx}$ = 12%, FRAX$_{major}$ = 26% per 10 years

- Prescribed alendronate

Mrs. S.
Follow-up

2 years of alendronate

- T-score   2 yrs ago   current

   FN   -3.4   -3.1

   Spine   -3.1   -2.7
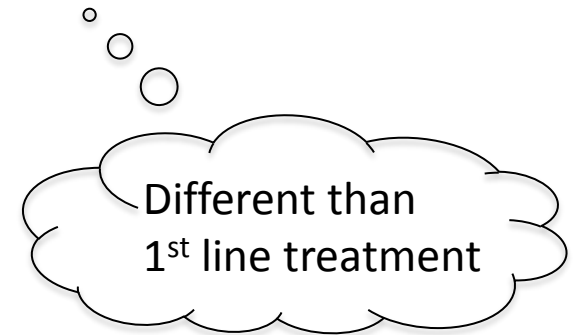
- No fracture

- She is 'responding'

- Continue

What's wrong?

What's wrong?

- Despite 'responding' alendronate she has a very high risk of fracture
- She has a very high risk of fracture next year

Goal-directed treatment

1. Set a goal with the patient
2. Choose the treatment that has a reasonable chance reaching that goal
3. Reassess every 2 years

Different than 1st line treatment

Set a goal

- If the main reason to treat is a low BMD, then goal should be BMD value
- If the main reason is a high fracture risk, the goal should be a low risk of fracture
- The goal may be both

BMD goal

- Set a T-score goal of ≤ -2.5 at the femoral neck or total hip
  - Or at the lumbar spine

Why a T-score > -2.5?

- Higher than the level for starting treatment:

Extension of the Fracture Intervention Trial (FLEX):

- If FN T-score remains ≤ -2.5, continuing treatment reduces clinical vertebral fracture risk

- When FN T-score reaches > -2.5, there is little benefit in continuing treatment, so stop[1,2]

1. Alendronate: Schwartz AV et al. J Bone Miner Res. 2010;25:976-982.
2. Zoledronate: Cosman F et al. J Clin Endocrinol Metab. 2014. Epub;
Black DM et al. J Bone Miner Res. 2012;27:243-254.

Fracture risk goal

- Free of fractures. For at least 3-5 years.

- A risk below the treatment threshold for starting drug treatment

- Good correlation between hip BMD and fracture risk on treatment
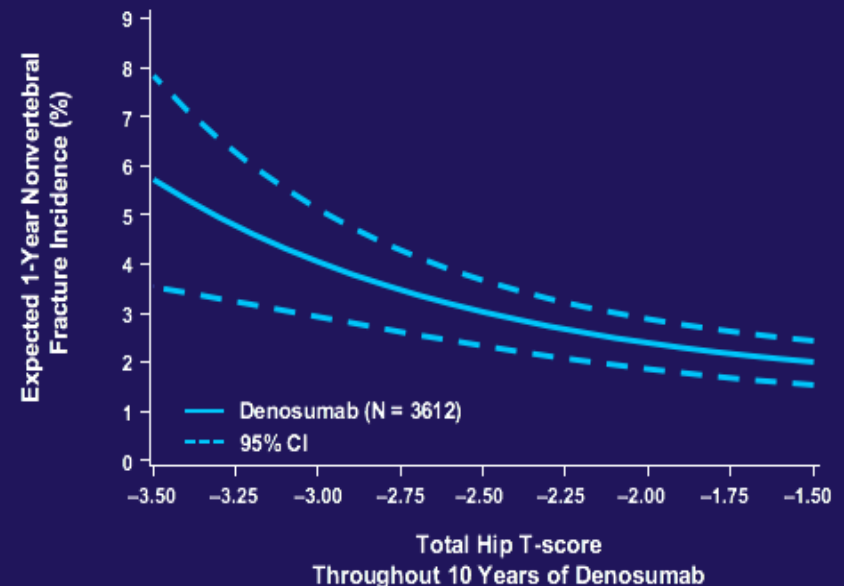 - Use FN BMD in FRAX for 10 year risks

Recent analyses: BMD achieved during treatment correlates with fracture risk

ARCH and FREEDOM: Total Hip T-score and Subsequent Nonvertebral Fracture Incidence
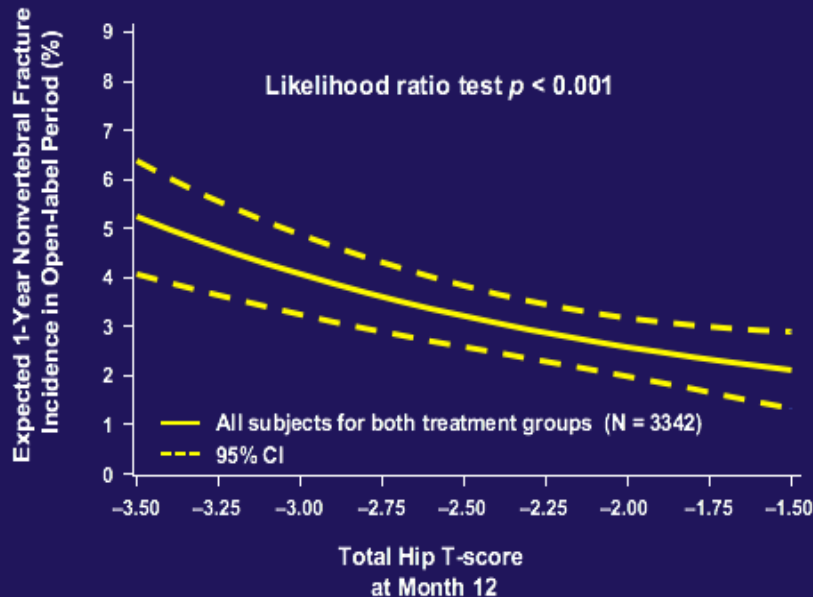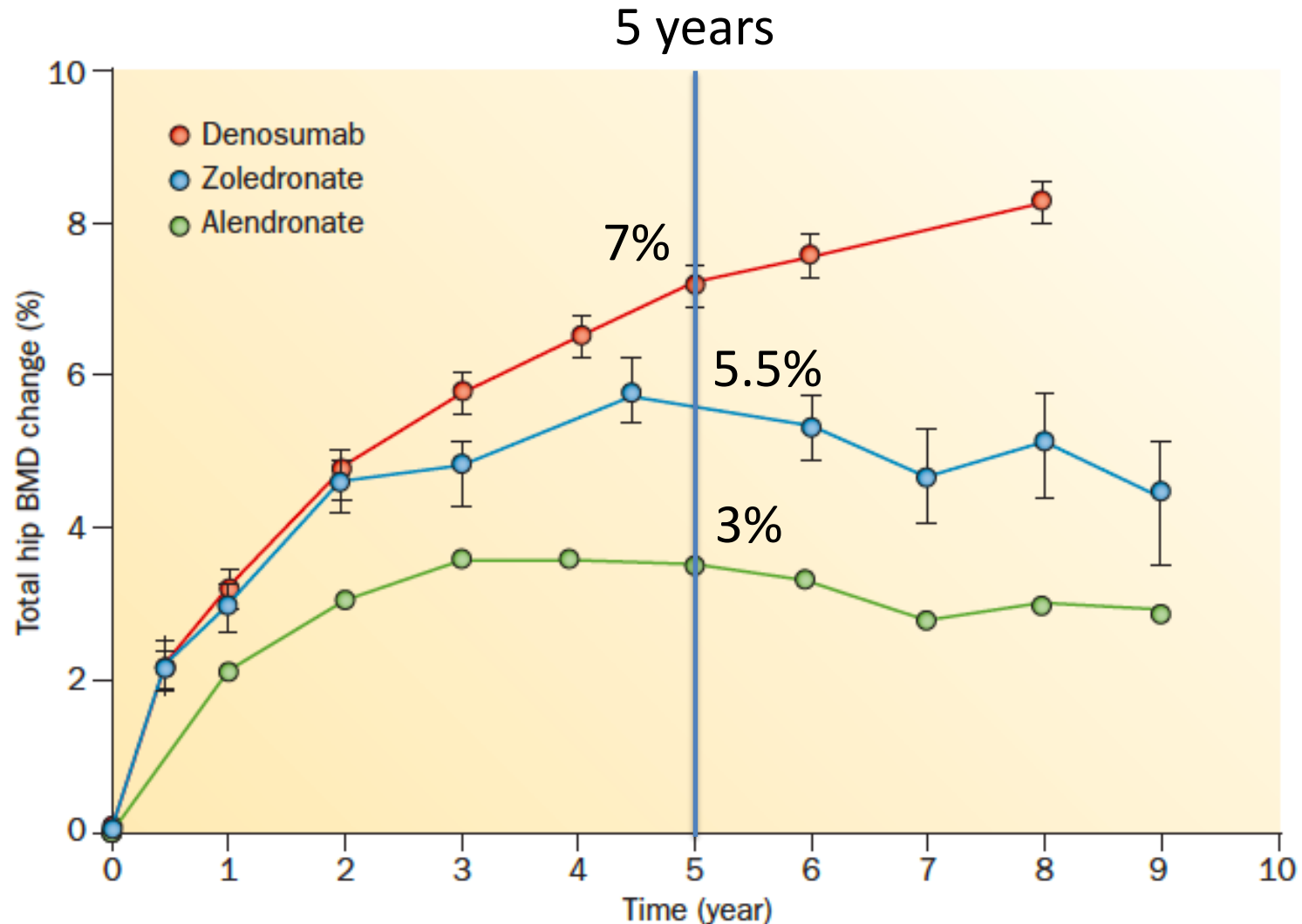
Choosing initial treatment to reach the patient's BMD goal

Most patients

- >50% chance of reaching hip T>=2.5 by 5 years

Very high 1-year risk

- >50% chance of reaching T>-2.5 by 1 year
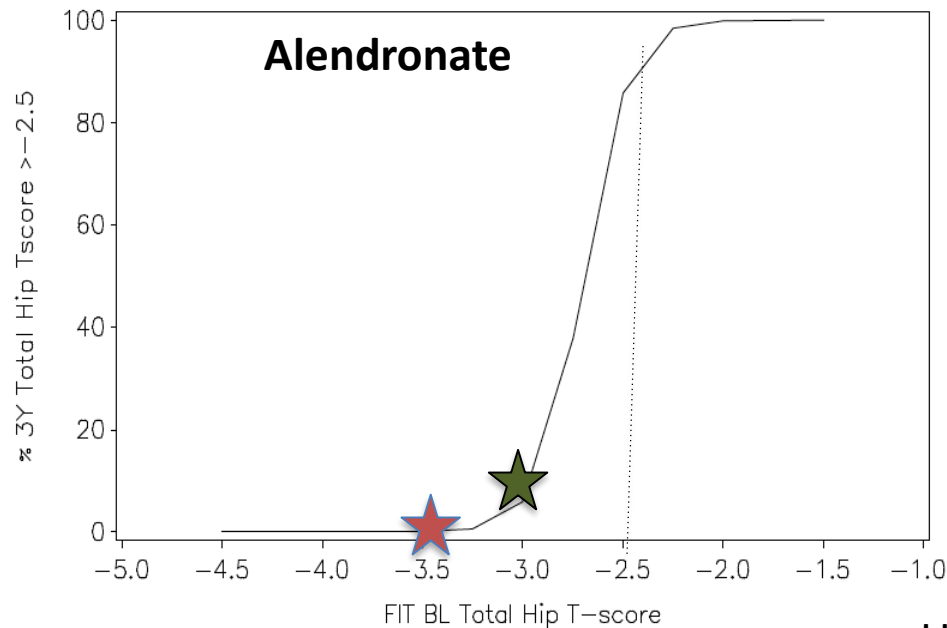
Long-term increases in total hip BMD

5 years

Reid, *Nat.Rev. Endocrinol* 2015;11:418-428

Chances of reaching T >-2.5 goal by 3 years with alendronate

Start T-score   Chance

-3.0   ~10-15%

-3.5   ~1-2%

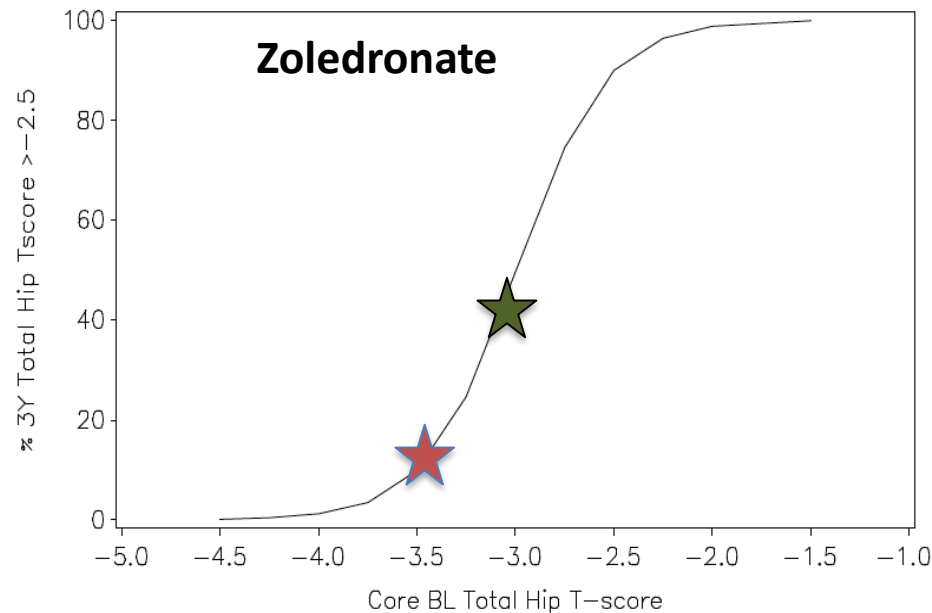
Unpublished data from FIT.

Chances of reaching T >-2.5 goal by 3 years with zoledronate
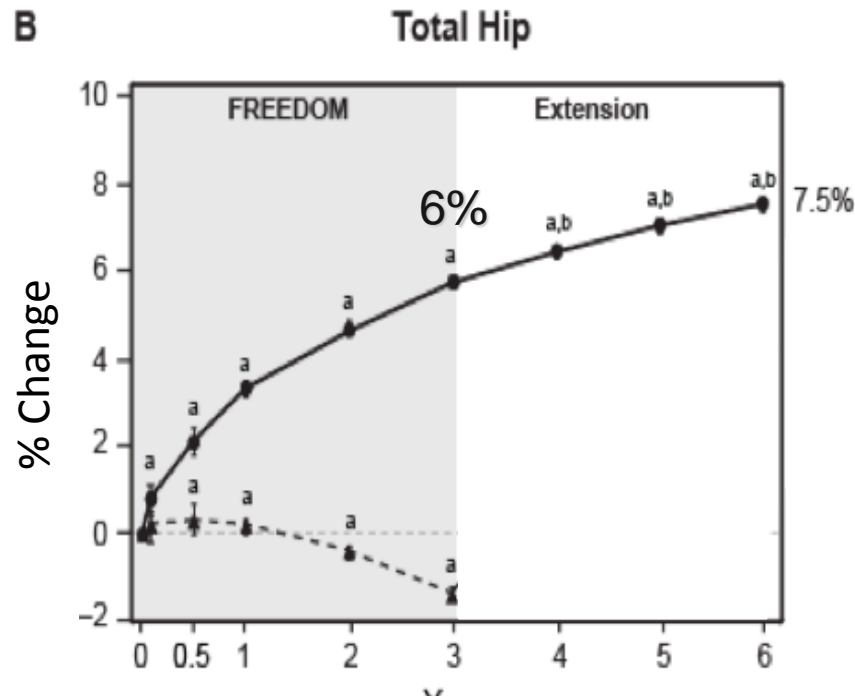
Start T-score   Chance

-3.0   ~40%

-3.5   ~10%

Unpublished data from HORIZON.

Chances of reaching T >-2.5 goal by 3 years with denosumab
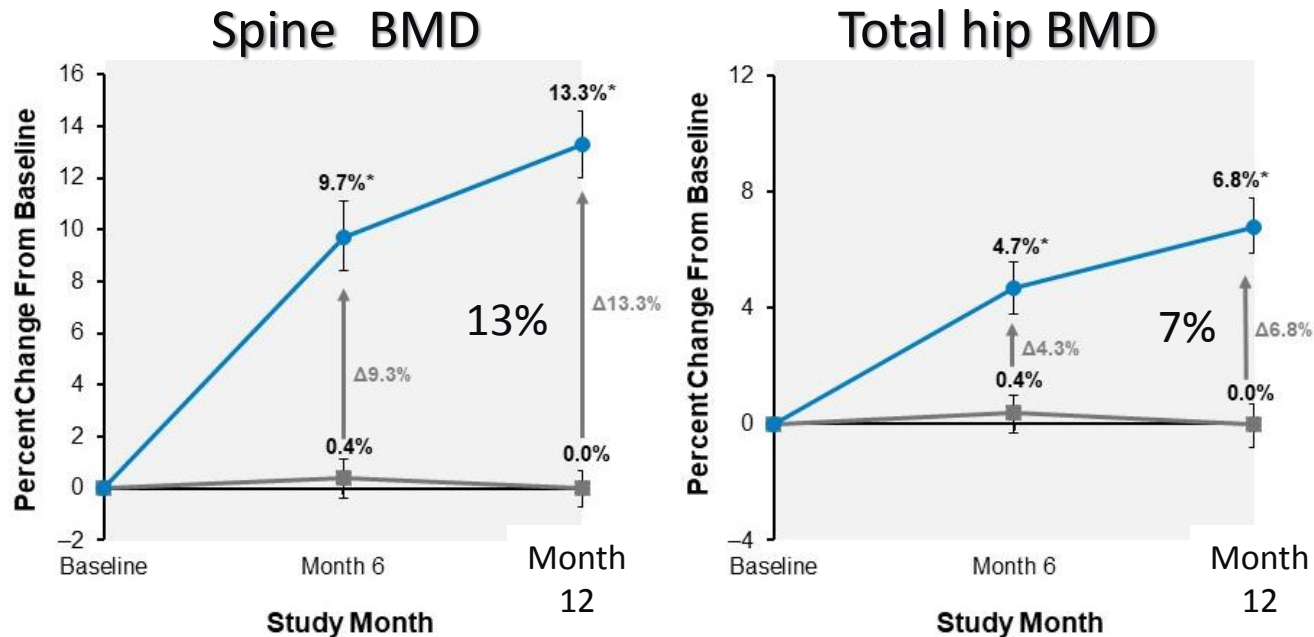
Start T-score	Chance
-3.0	~50%
-3.5	~25%

B **Total Hip**

Patients with high 1 year risk
Romosozumab vs. Placebo (FRAME)

Spine BMD — Total hip BMD

Chance of reaching T> -2.5 at 1 year

Start T-score = 3.0   Spine: > 80%

Hip: ~50%

Fracture risk goal

- If the primary reason for starting treatment is a high risk of fracture, then ideally, the goal would be a level of fracture risk below the risk threshold for initiating treatment.

Fracture risk goal

- Free of major fracture for at least 5 years
- An ideal outcome
- Occurrence of a fracture indicates a 2-4 fold increase in risk of another
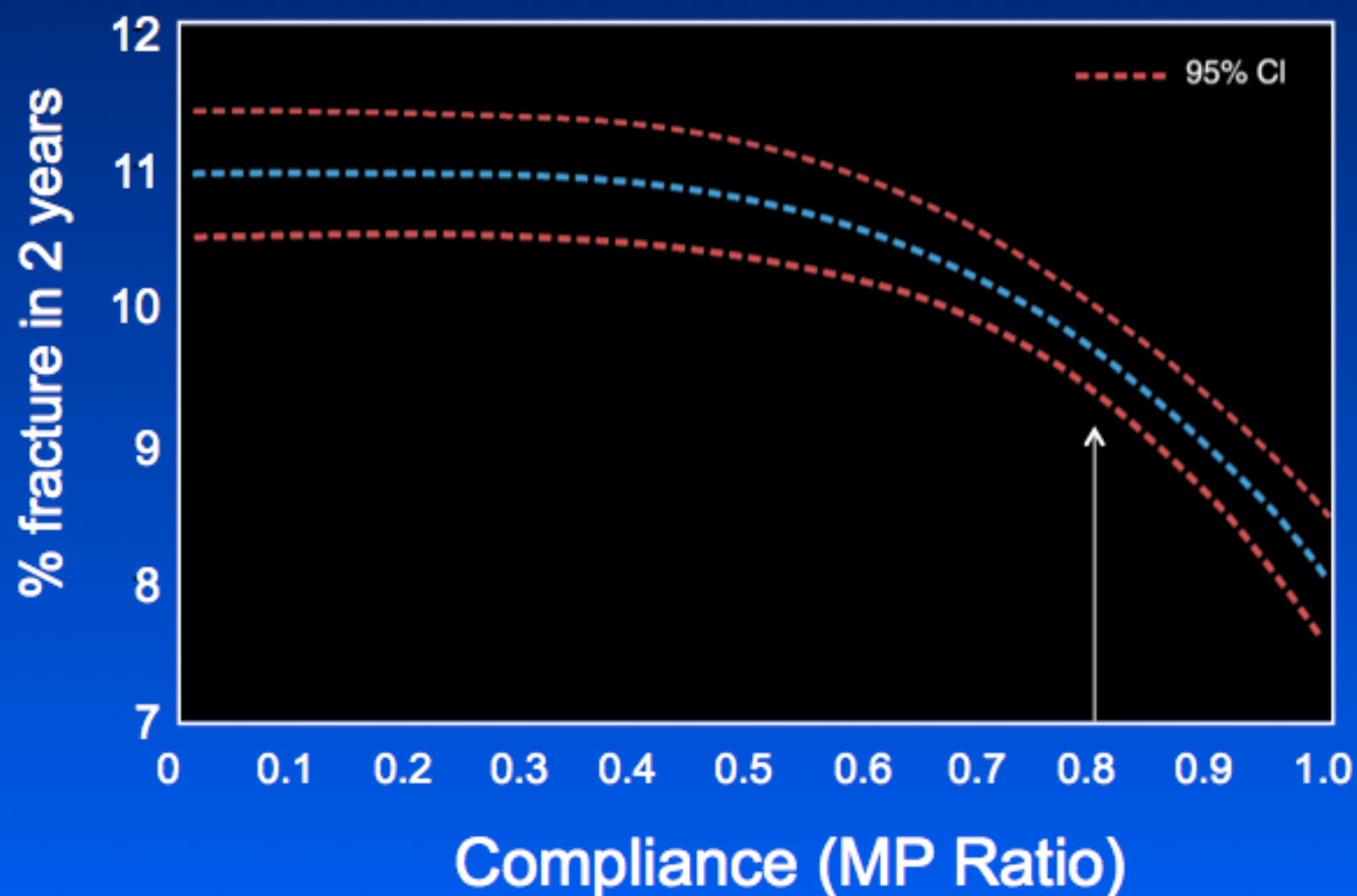
Follow-up

Follow-up

- Patients receiving treatment should be assessed within 3-5 years for achievement of the treatment goal*

  * Follow-up sooner for adherence

Principles of follow up for achievement of goals

1. Has the patient **adhered** to treatment?

    – If poor adherence persists, consider zoledronate or denosumab

    – Aim for at least 80% adherence

[1]Cosman et al JCEM 2014 2

About half the benefit of treatment is lost if compliance falls below 80%

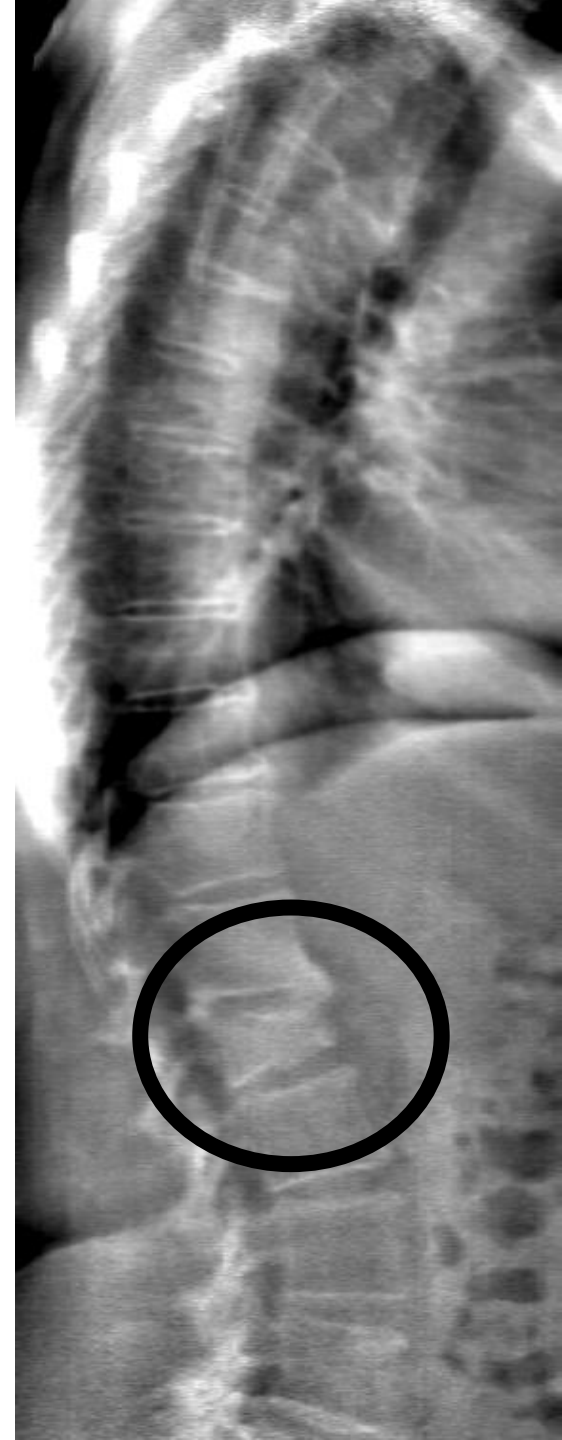Siris et al. Mayo Clin Proc 2006;81:1013

Principles of follow up for achievement of goals

1. Has the patient adhered to treatment?

2. Has the patient developed a new vertebral fracture?

3. Has the patient had a nonvertebral fracture?

Obtain spine VFA or x-ray

- Measure height at baseline

- VFA or x-ray at baseline

- Follow-up
  - Measure height
  - >3 cm loss indicates high risk of a new fracture
  - Obtain VFA or x-ray

- Or, repeat VFA or x-ray

Cosman F et al OI 2014
Schousboe J et al. J Clin Densitometry 2006;9:133–143

Has a vertebral fracture occurred?

- A vertebral fracture during treatment means a 5-fold risk of another vertebral fracture[1]

- Consider switching to a treatment that has greater efficacy for vertebral fracture
  - Denosumab, zoledronate, denosumab, teriparatide and abaloparatide decrease vertebral fracture risk by > 65%

[1]Cosman et al JCEM 2014

Principles of follow up for achievement of goals

1. Has the patient adhered to treatment?

2. Has the patient developed a new vertebral fracture?

3. Has the patient had a nonvertebral fracture?

Principles of follow up for achievement of goals

1. Has the patient adhered to treatment?

2. Has the patient had a nonvertebral fracture?
   - A fracture during treatment with indicates a 2 – 3 fold increased risk of another nonvertebral fracture[1,2]
   - Consider switching to a more potent treatment

1. Cosman et al JCEM 2014   2. Data presented by Adolfo Diez Perez

Principles of follow up for achievement of goals

1. Has the patient adhered to treatment?

2. Has the patient developed a vertebral fracture?

3. Has the patient had a nonvertebral fracture?

4. Measure BMD
   - Has she achieved her BMD goal?
   - If not, what is the chance she will reach that goal with current treatment?

If BMD goal is achieved

- Once the T-score goal is achieved BMD should be maintained above that level.

- If target T-score >-2.5 achieved with a bisphosphonate

  - Stop treatment

  - Reassess BMD periodically

  - Restart if / when T-score is below -2.5

If BMD goal is achieved with non-bisphosphonate therapy

- For non-bisphosphonate treatments, like denosumab, BMD declines rapidly after treatment is stopped.

- After achieving the goal, treatment should be continued with an agent that maintains BMD

  - Bisphosphonate, raloxifene

Stopping denosumab

- Within 2 months
  - The risk of any vertebral fracture increases to untreated levels
  - An increased risk of multiple vertebral fractures
- Have a system to ensure denosumab is given on time
- If stopped, start an antiresorptive, such as a bisphosphonate (or raloxifene?) within 2-3 months after the scheduled treatment

BMD goal is not achieved

- If T-score is still less than -2.5, what is the probability of achieving the goal with continued therapy?
- If <50%, switch to more potent agent
  - If on a bisphosphonate, consider denosumab
  - Consider bone forming agents for 1-2 years then antiresorptive

Bone forming drugs

Teriparatide and Abaloparatide

- Teriparatide: PTH

- Abaloparatide: PTHrP

- SubQ; similar actions.

- Abaloparatide larger increases in BMD

- Treatment 18-24 months

- Abaloparatide: 86%⇩ vertebral, 43%⇩ nonvertebral fractures
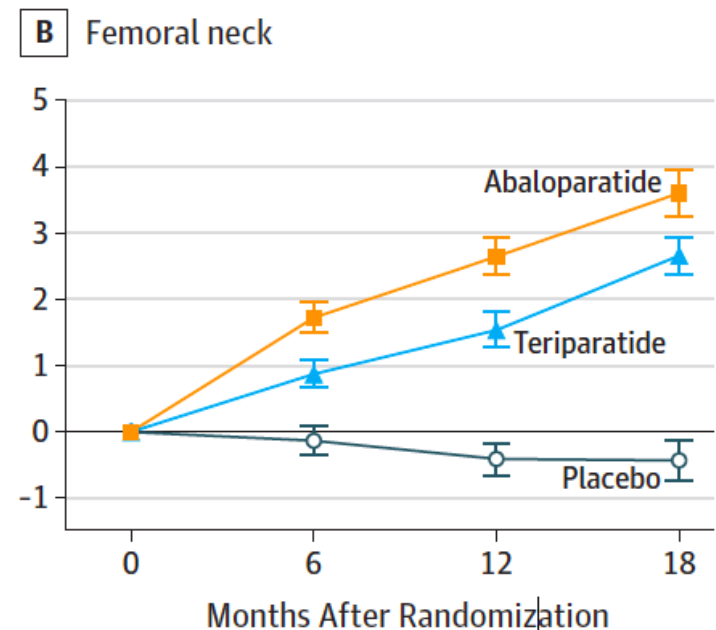
Cases reconsidered

Ms. O. Initial treatment

56 year old Japanese woman

- 3 years ago: wrist fracture while trail running

- FN BMD T-score -2.7

- Started alendronate

Ms. O. Initial treatment

56 year old Japanese woman

- 3 years ago: wrist fracture while trail running

- FN BMD T-score -2.7

- Started alendronate

Goal-directed Treatment

- Set a BMD goal above -2.5
- Low risk: 10% 10-yr risk of major fractures
- Alendronate: >50% chance of reaching goal in 5 years
- Measure height

Ms. O. Follow-up

- Annual visit. No subsequent fracture
- BMD FN T-score 'increased' from -2.7 to -2.4
- "Responding" to alendronate
- Continue until a holiday at 5 yrs

Ms. O. Follow-up

- Annual visit. No subsequent fracture

- BMD FN T-score 'increased' from -2.7 to -2.4

- "Responding" to alendronate

- Continue until a holiday at 5 yrs

Goal-directed Treatment
- Reports 100% adherence
- Measure height: no change
- OK to discontinue treatment now
- Repeat BMD and resume if T-score <-2.5

Mrs. S: Starting treatment

70 year old white woman
- Recent humerus fracture
- BMD: FN T-score = -3.5, Spine = -3.1
- $FRAX_{hip\ fx}$ = 9%, $FRAX_{major}$ = 25%
- Started alendronate

Mrs. S: Starting treatment

70 year old white woman
- Recent humerus fracture
- BMD: FN T-score = -3.5, Spine = -3.1
- $FRAX_{hip\ fx}$ = 9%, $FRAX_{major}$ = 25%
- Started alendronate

Goal-directed Treatment
- Goals: FN T-score > -2.5 and risks < 3% and 20%
- VFA or spine x-ray (no fracture); measure height.
- Low probability of reaching goal with alendronate
- Consider starting teriparatide or abaloparatide

Mrs. S: Follow-up

2 years of alendronate
- FN BMD improved 4%; T-score = -3.1
- Spine BMD improved 6%; T-score = -2.7
- She is 'responding to treatment.' Continue

Mrs. S: Follow-up

2 years of alendronate
- FN BMD improved 4%; T-score = -3.1
- Spine BMD improved 6%; T-score = -2.7
- She is 'responding to treatment.' Continue

Goal-directed Treatment
- Reports adhering to alendronate (has regular refills)
- Repeat height measurement (assume no change)
- No non-vertebral fracture
- 'Responding' but 0% chance of reaching T>-2.5 goal
- Consider abaloparatide, teriparatide, or denosumab

Limitations and issues

We need better evidence

- Better analyses comparing the chance of reaching BMD by starting alternative treatments

- Data about the chance of reaching goals by switching treatment

- For fracture goals: data about how treatment and achievement of BMD levels correlate with reduction in fracture risk
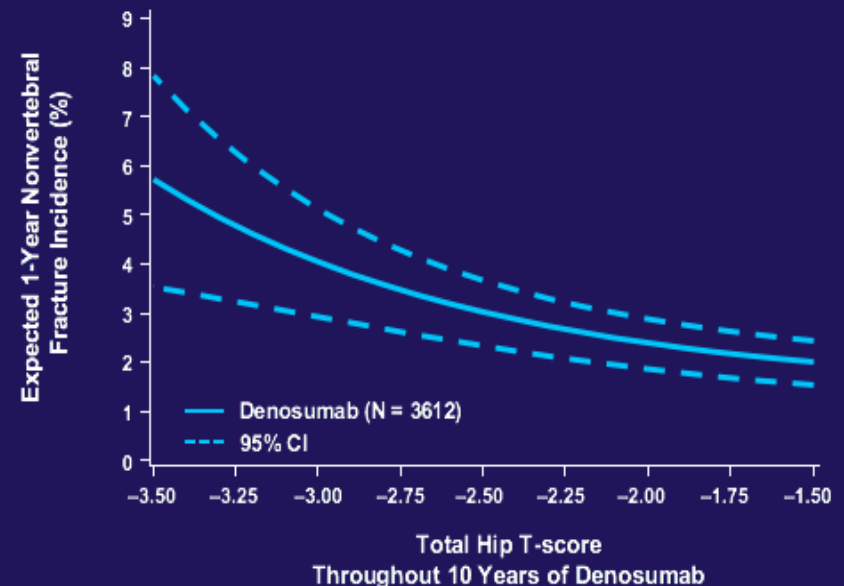
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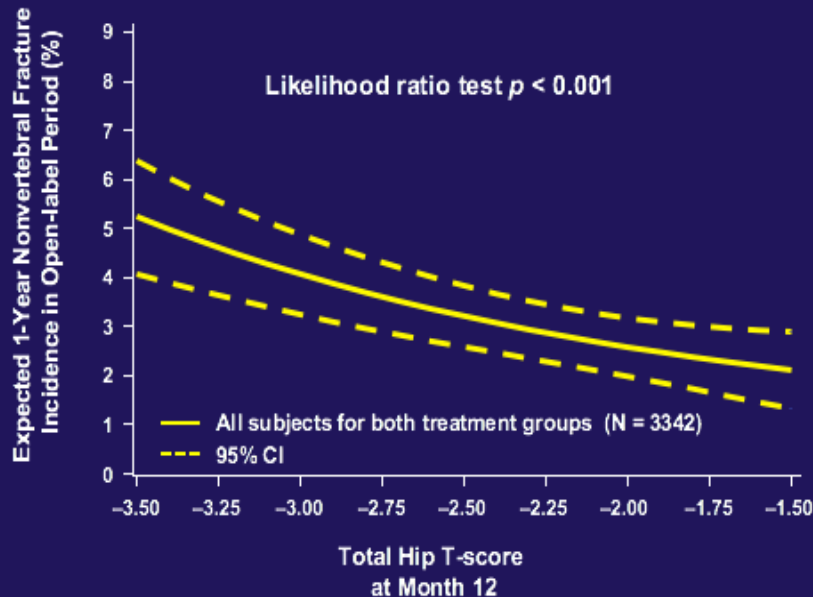
Limitation: Cost of more potent drugs

- More potent drugs are more expensive

|	Annual cost*
– Alendronate:	~$400
– Zoledronate:	~$1,200
– Denosumab:	~$3,600
– Abaloparatide	~$13,000
– Teriparatide:	~$21,000
– Romosozumab:	? (not approved)

  * Approximations from websites

Summary

- Set a goal with your patient
- Choose initial treatment based on the chance of reaching the goal
- Follow-up: check progress toward the goal
  - Adherence remains < 80%, consider zoledronate
  - Fracture history, height, spine imaging, BMD
  - Vertebral fracture: consider more potent drugs
  - Goal BMD T-score > -2.5, stop and maintain
  - Far from goal: switch to more potent treatment
- Goal-directed treatment is a work in progress

Summary

- Set a goal with your patient
- Choose initial treatment based on the chance of reaching the goal
- Follow-up: check progress toward the goal
  - Adherence remains < 80%, consider zoledronate
  - Fracture history, height, spine imaging, BMD
  - Vertebral fracture: consider more potent drugs
  - Goal BMD T-score > -2.5, stop and maintain
  - Far from goal: switch to more potent treatment
- Goal-directed treatment is a work in progress

Thank you

5-year risk of clinical vertebral fracture
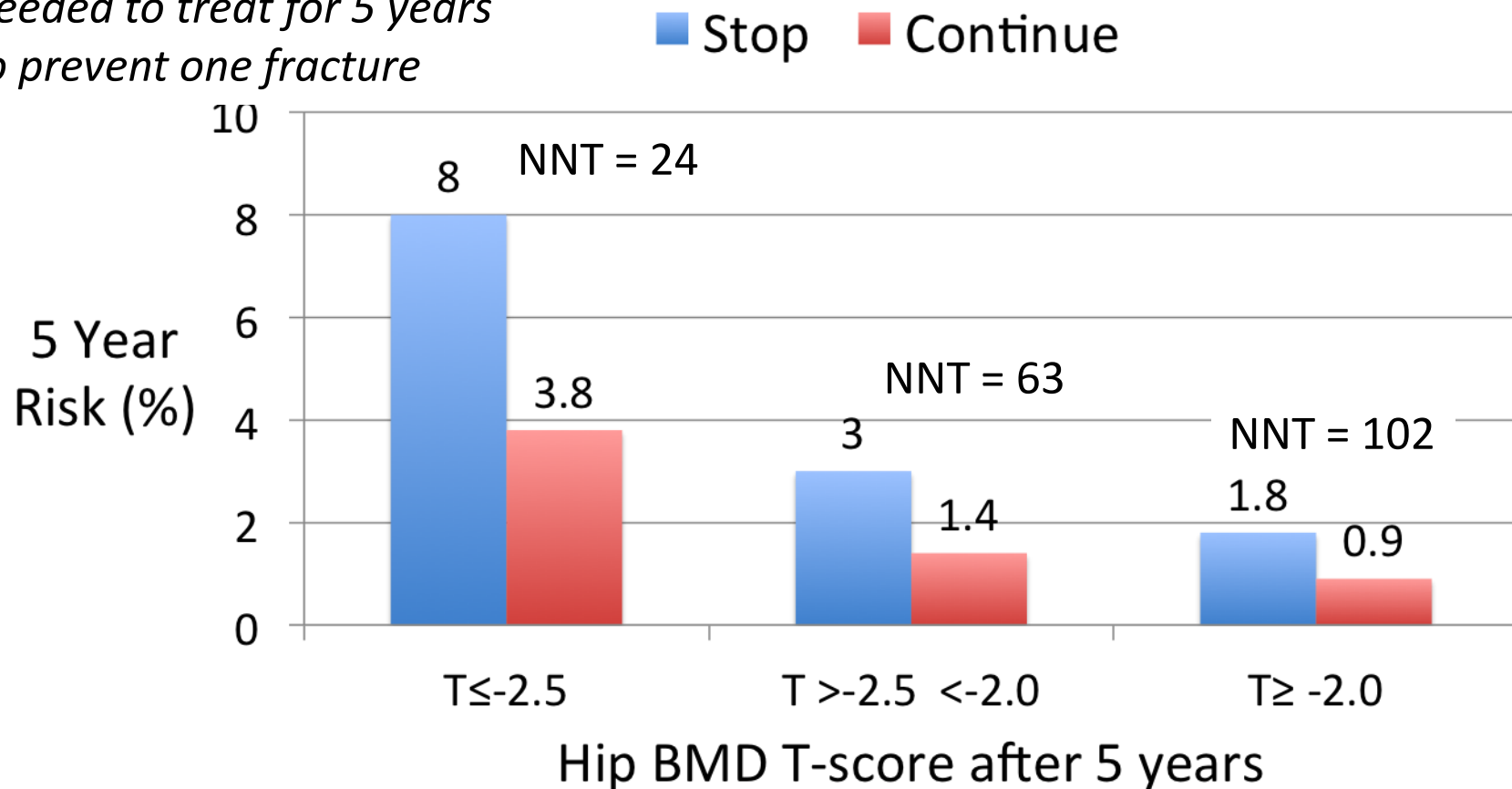# if you stop vs. continue alendronate after 5 years
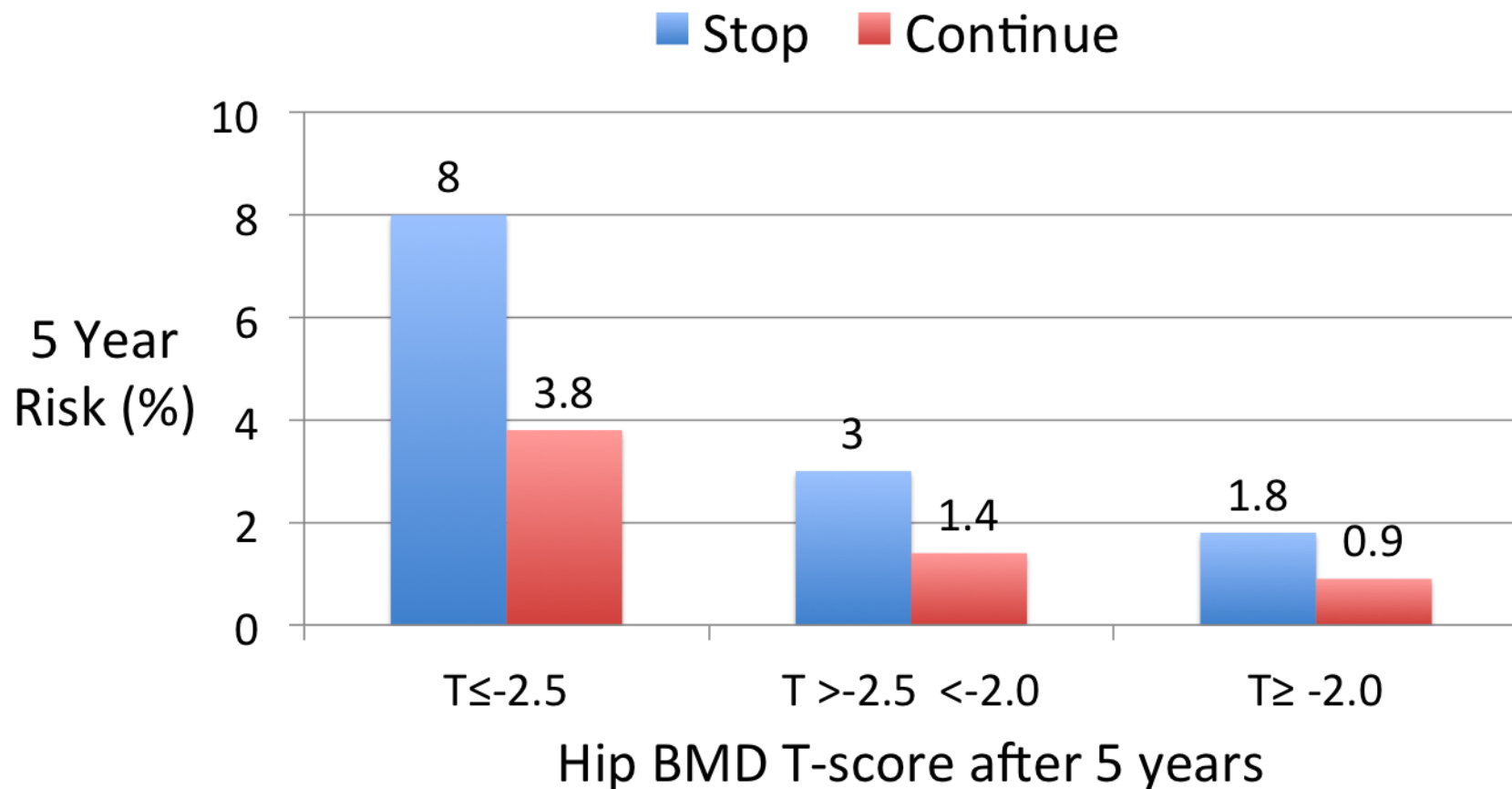
From the FLEX Trial
Black, Bauer, Schwartz, Cummings... NEJM 2012

5-year risk of clinical vertebral fracture
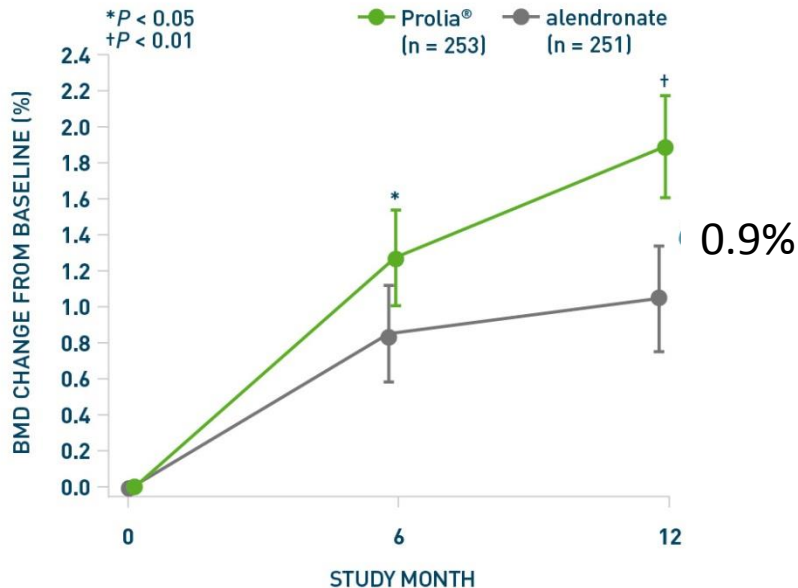# if you stop vs. continue alendronate after 5 years
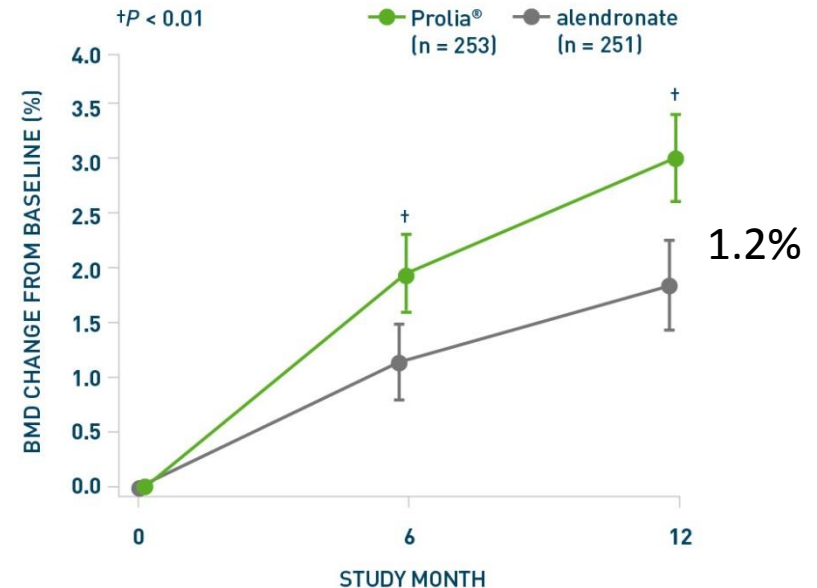

From the FLEX Trial
Black, Bauer, Schwartz, Cummings… NEJM 2012

Switching from alendronate to denosumab improves BMD

Total Hip

Lumbar Spine

No data about benefit for reducing fracture risk

Kendler, et al. JBMR 2010;25:72