IN THE NAME OF GOD

Management of patients at very high risk of osteoporotic fractures

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REVIEW

Management of patients at very high risk of osteoporotic fractures through sequential treatments

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AGENDA

- ✓**Introduction**
- ✓**Approaches to risk stratification**
- ✓What should be the duration of therapy
- ✓Approaches to sequential therapy
- ✓Bone turnover markers in treatment stratification
- ✓Long-term treatment

Case

68-year old lady is referred for management of her osteoporotic fracture.

She was on denosumab due to GI intolerance of BSP after low BMD from 18 mo ago

, What is the best treatment option for her now ?

Switching to zoledronate

Continuing with Teriparatide

Switching to romosozumab

Switching to Teriparatide

Continuing denosumab

Introduction

Table 6
2020 AACE Diagnosis of Osteoporosis in Postmenopausal Women

1. T-score −2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius
2. Low-trauma spine or hip fracture (*regardless of bone mineral density*)
3. T-score between −1.0 and −2.5 **and** a fragility fracture of proximal humerus, pelvis, or distal forearm
4. T-score between −1.0 and −2.5 **and** high FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds

Abbreviations: AACE = American Association of Clinical Endocrinologists; FRAX® = fracture risk assessment tool; TBS = trabecular bone score.

Introduction

the risk of a subsequent osteoporotic fracture is particularly acute immediately after an index fracture and wanes progressively with time

often termed “imminent risk” because of the temporal association

suggests that preventive treatment given as soon as possible after fracture would avoid a higher number of new fractures

This provides the rationale for very early intervention immediately after a sentinel fracture and necessitates treatment with agents that have the most rapid effect on fracture reduction.

A further recent development is the demonstration of a more rapid and greater fracture risk reduction of anabolic compared with antiresorptive treatments

fracture risk assessment

Thus, a fracture at any time in the past is associated with increased risk of an incident

fracture event, but an index fracture is associated with a marked excess fracture risk over and above this in the next 2 years

in the Iceland Reykjavik cohort Study have shown that, in individuals who sustained a recurrent fracture,

31 and 45% of fractures occurred within one year of the first (sentinel) fracture, depending on the fracture site

the currently available tool does not incorporate recency of fracture, or indeed a different risk associated with different fracture sites and therefore will underestimate 10-year fractur probability in the context of a prior fracture in the last 2 years.

the higher the fracture risk the more likely there will be a fracture in the next few years (i.e. the more imminent the risk)
and the more urgent is the need for treatment which
is highly effective and rapid acting.

Intervention Thresholds

T score threshold

Prior fracture threshold

Fixed fracture-risk thresholds across ages

Age specified intervention threshold using FRAX

Risk assessment

The IOF and ESCEO recommend that risk of fracture should be expressed as an absolute risk, i.e. probability of fracture over a ten-year interval

The resulting FRAX tool computes the 10-year probability of hip fracture or a major osteoporotic fracture, the latter comprising a clinical spine, hip, forearm or humerus fracture

In the European guidance, it is recommended that postmenopausal women with a prior fragility fracture should be treated without further assessment

Risk categories

- **low risk** includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above -1.0, a 10-year hip fracture risk < 3%, and 10-year risk of major osteoporotic fractures < 20%

- **Moderate** risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above -2.5, and 10-year hip fracture risk < 3% or risk of major osteoporotic fractures < 20%

- **High risk** includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of -2.5 or below, or 10-year hip fracture risk ≥ 3%, or risk of major osteoporotic fracture risk ≥ 20%

- **Very high risk** includes multiple spine fractures and a BMD T-score at the hip or spine of -2.5 or below

J Clin Endocrinol Metab, May 2019, 104(5):1595–1622

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/ AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS – 2020 UPDATE

High risk

T-scores between −1.0 and −2.5 and a history of fragility fracture of the hip or spine, and

T-scores between −1.0 and −2.5 and a FRAX® 10-year probability of major osteoporotic fracture ≥20% or 10-year probability of hip fracture ≥3% in the U.S. or above country-specific threshold in other countries or regions.

Very high risk

- A recent fracture (e.g., within the past 12 months),
- Fractures while on approved osteoporosis therapy,
- multiple fractures
- Fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids)

Very low T-score (e.g., less than −3.0),

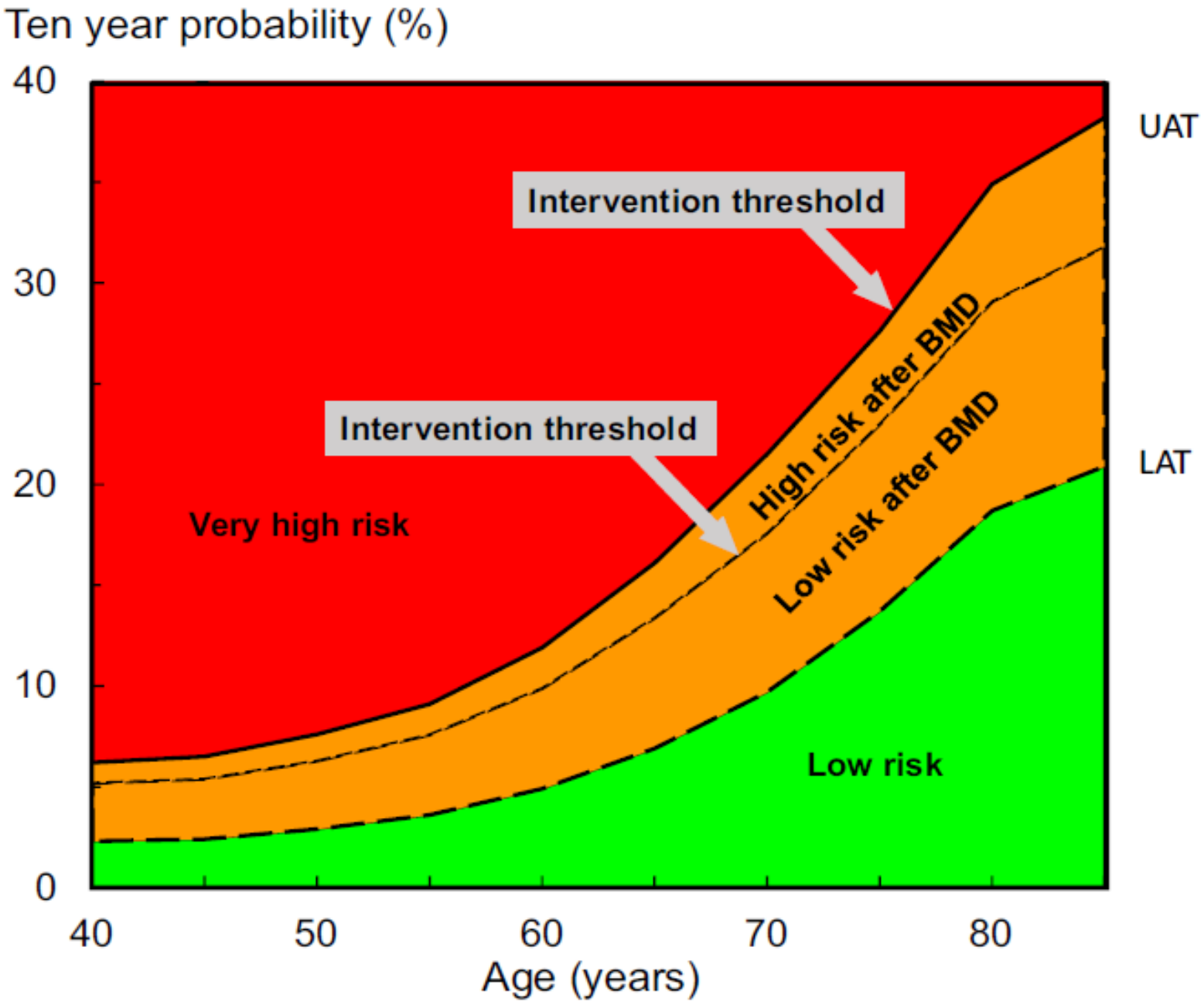
- High risk of falls or history of injurious falls
- major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm

Definitions

Intervention thresholds as set by FRAX-based 10-year probability (%) of a major osteoporotic fracture equivalent to women with a previous fracture (no other clinical risk factors, a body mass index of 24 kg/m2 and without BMD)

The lower assessment thresholds set by FRAX is based on the 10-year probability (%) of a major osteoporotic fracture equivalent to women without clinical risk factors (a body mass index of 24 kg/m2 and without BMD)

The upper assessment threshold is set at 1.2 times the intervention threshold


Ten year probability (%)
40
30
20
10
0
40
50
60
70
80
Age (years)
UAT
LAT
Intervention threshold
Intervention threshold
Very high risk
High risk after BMD
Low risk after BMD
Low risk

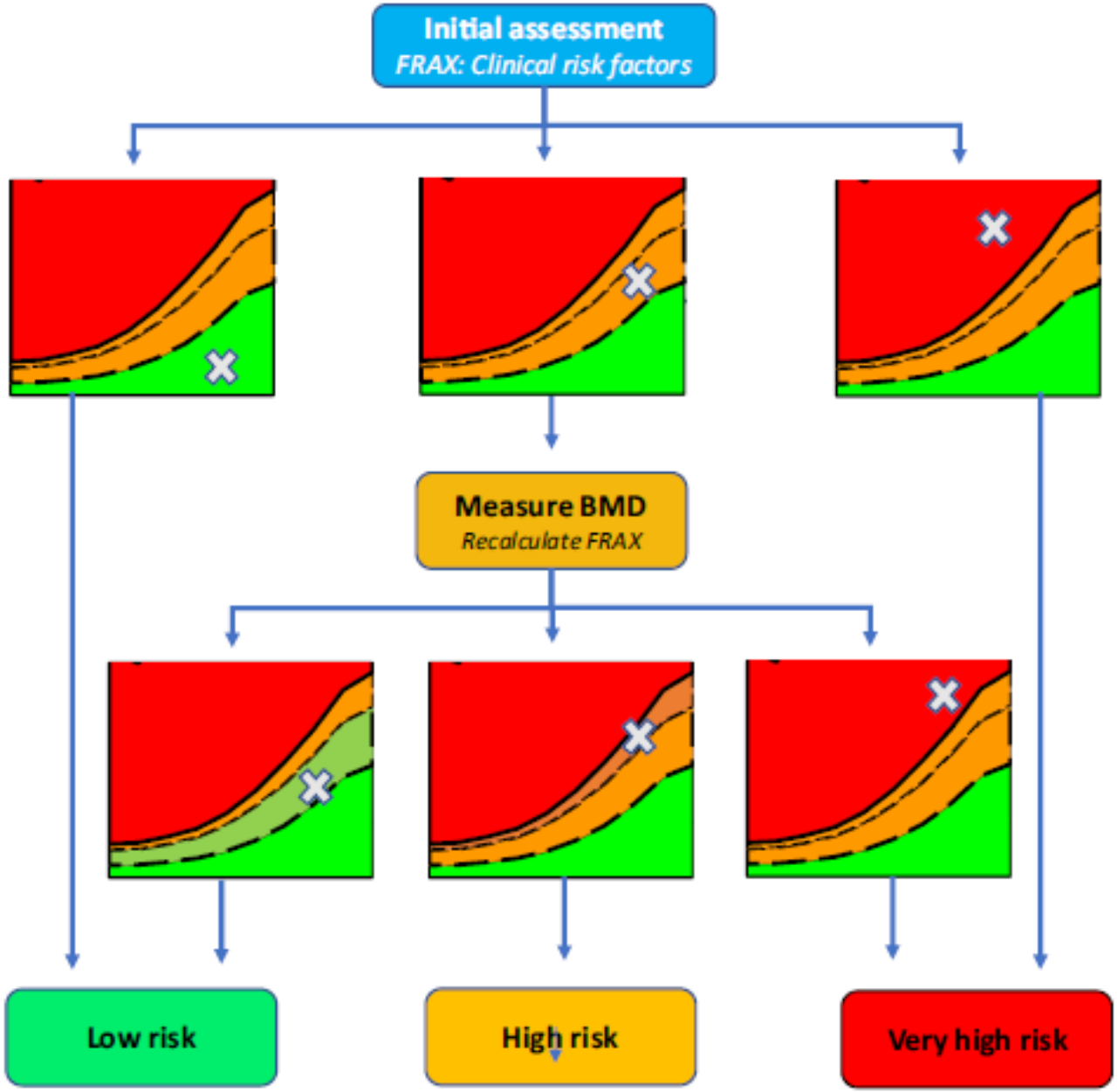
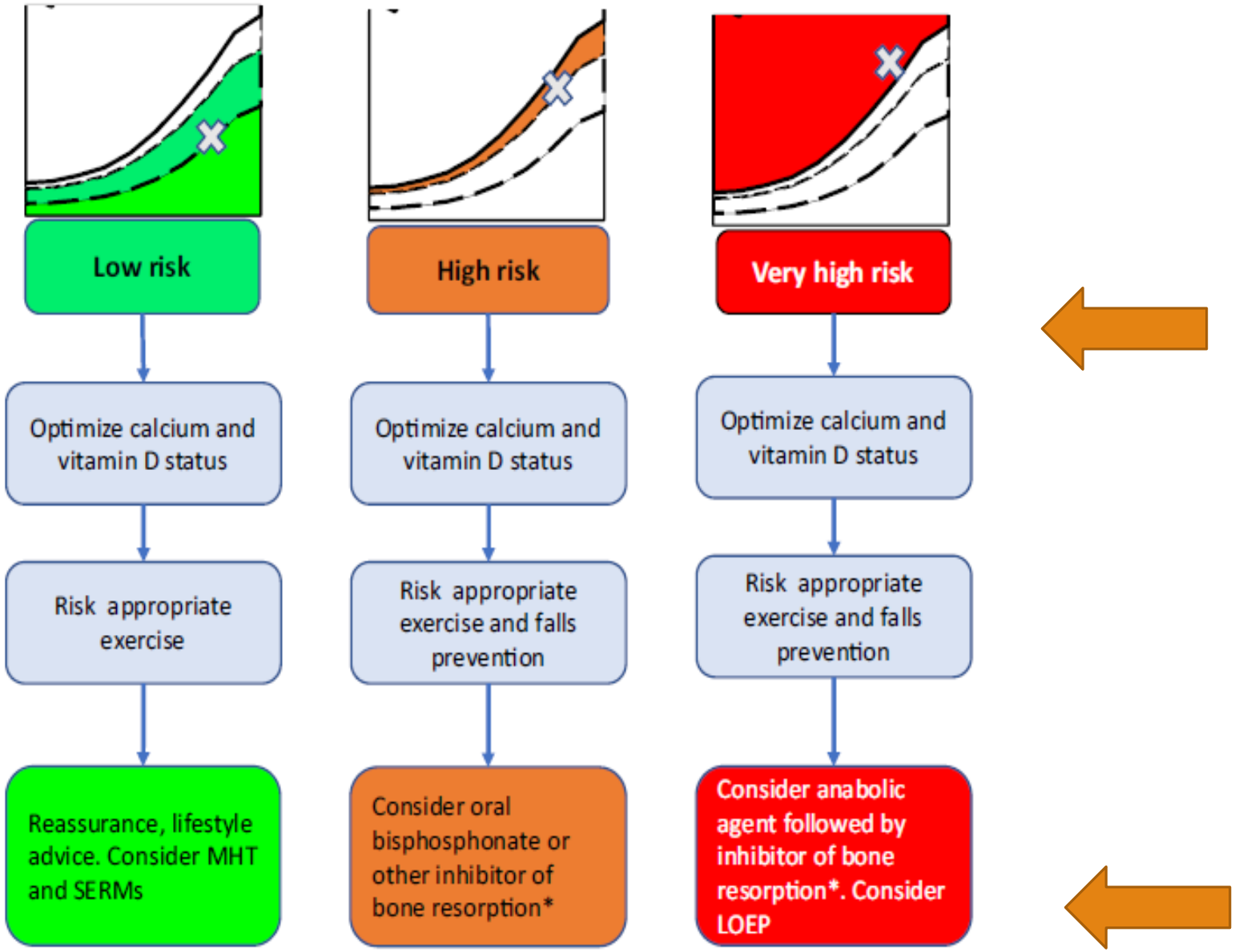

Initial assessment
FRAX: Clinical risk factors
Measure BMD
Recalculate FRAX
Low risk
High risk
Very high risk

Fig. 3 Treatment pathways according to the categorisation of fracture risk. For treatment modalities (inhibitors of bone resorption, anabolic agents, etc.), see Appendix, Table 6



anabolic agents efficacy

- It has been shown that BMD T-score improvements from baseline at the lumbar spine in patients treated with 1 year of romosozumab in FRAME are similar to that observed with 4.5 years of denosumab treatment in FREEDOM. One year of romosozumab followed by 1 year of denosumab treatment in FRAME led to BMD changes similar to 7 years of denosumab treatment

- If the initial BMD T-score is -2 or above, it is highly possible that the above target will be achieved with a bisphosphonate. On the other hand, if total hip BMD is below -2 , this attainment is unlikely with a bisphosphonate and therefore therapy might have to be initiated with a more potent medication or the bisphosphonate if already started may have to be replaced by a more potent one.

- Though antiresorptive agents decrease remodelling rates thereby attenuating the deficit in the mineralized bone matrix and prevent worsening of microarchitecture, the total bone matrix volume remains reduced as does the deterioration of microarchitecture that has already occurred

Paradigm shift

- Head to Head data suggest that anabolic agents have greater rapidity and efficacy for fracture risk reduction then any antiresorptive agent

- Recent evidence supports and **“anabolic first approach”** in patients at very high risk fracture followed by maintenance therapy using in antiresorptive agent

Aging Clinical and Experimental Research. 2022;34:695-714

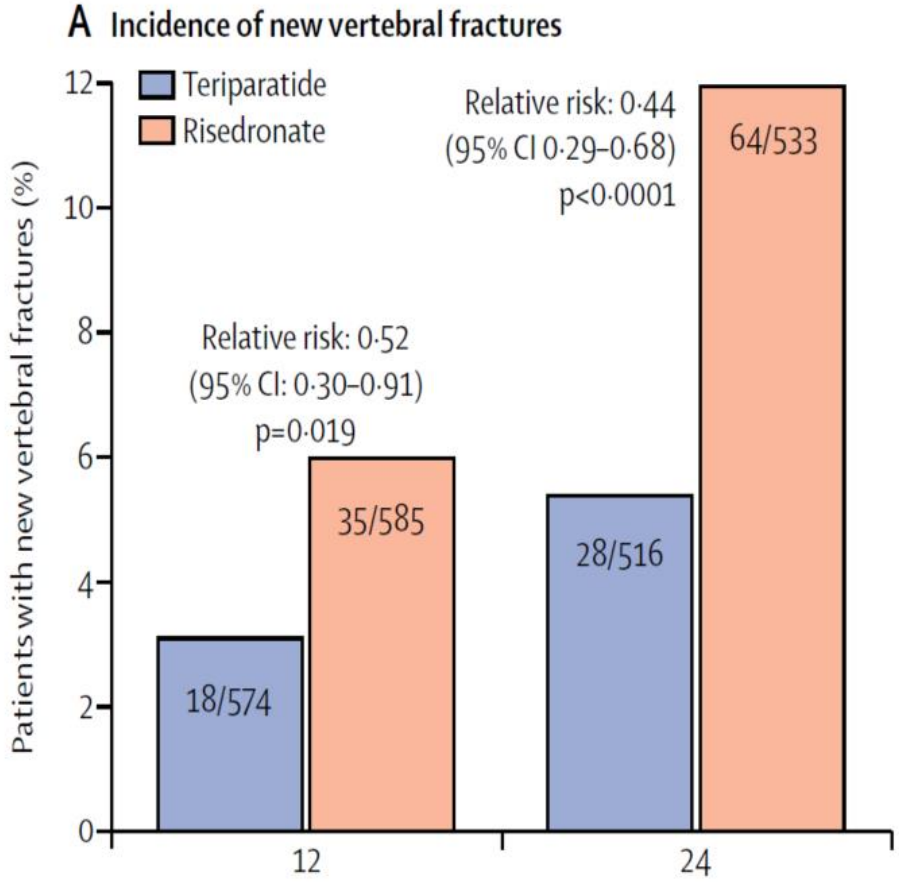
Approaches to sequential therapy

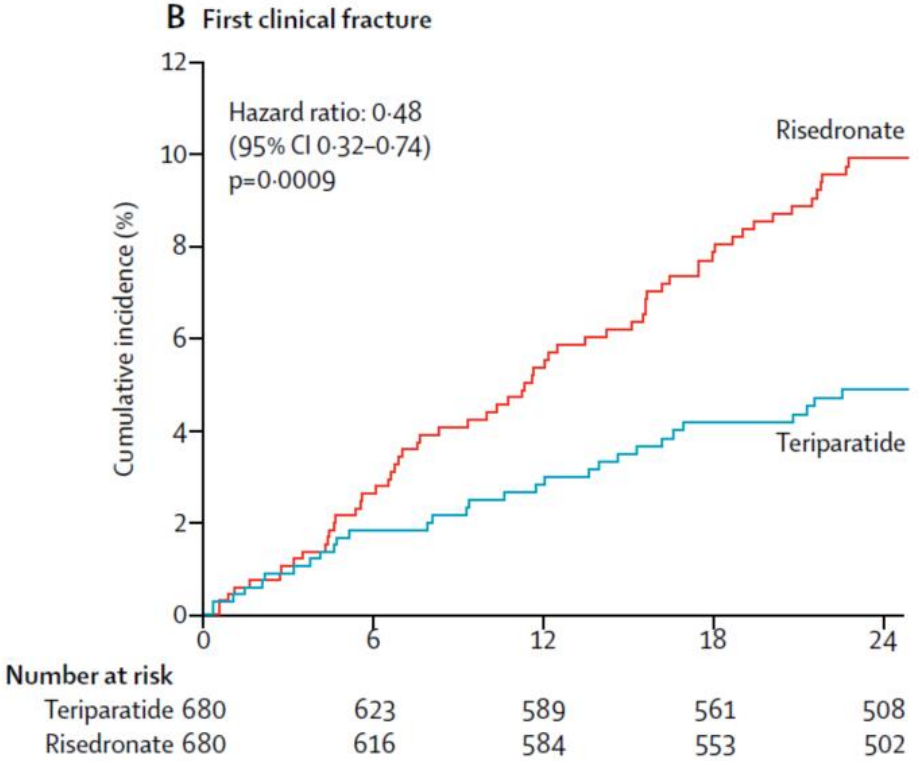
anabolic agent, given for 18 months, (relative risk reduction,RRR = 70%), then followed by an antiresorptive to maintain the effect for a total of 10 years, might be expected to save 33.8 hip fractures/1000 patient years in women aged 70 years with a recent fragility fracture

an antiresorptive that reduced the hip fracture risk by 40% (RRR = 40%) followed by an anabolic regimen for the last 18 months of a 10-year treatment would save only 20.0 hip fractures/1000 patient years

This alters the paradigm for the use of anabolic therapies, going beyond their current widespread use as “salvage therapy” when all other treatment has failed, to the notion of first-line anabolic treatment.

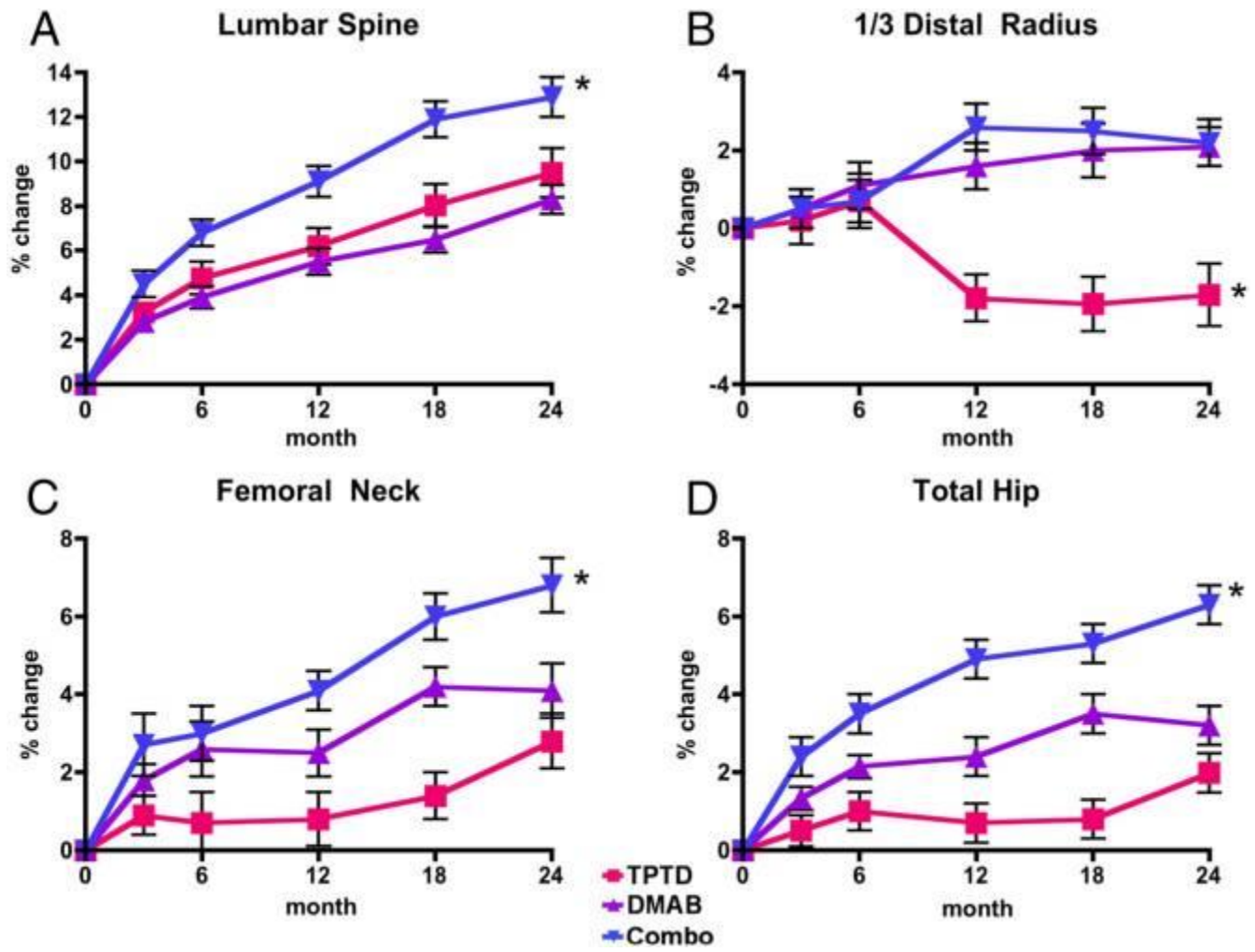
Risk of new vertebral and clinical fractures is significantly lower in patients receiving teriparatide than in those receiving risedronate

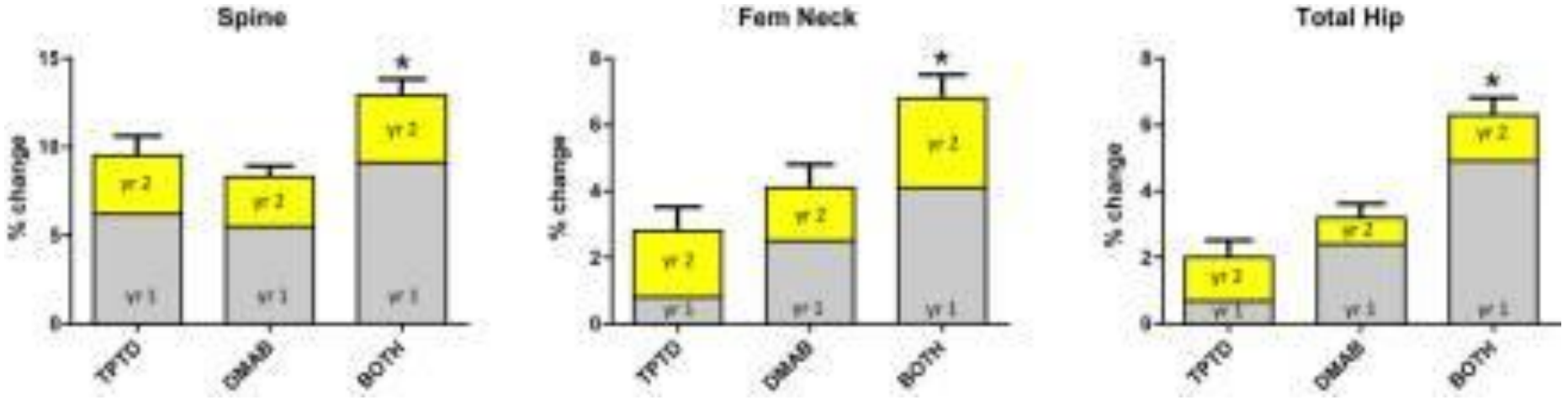




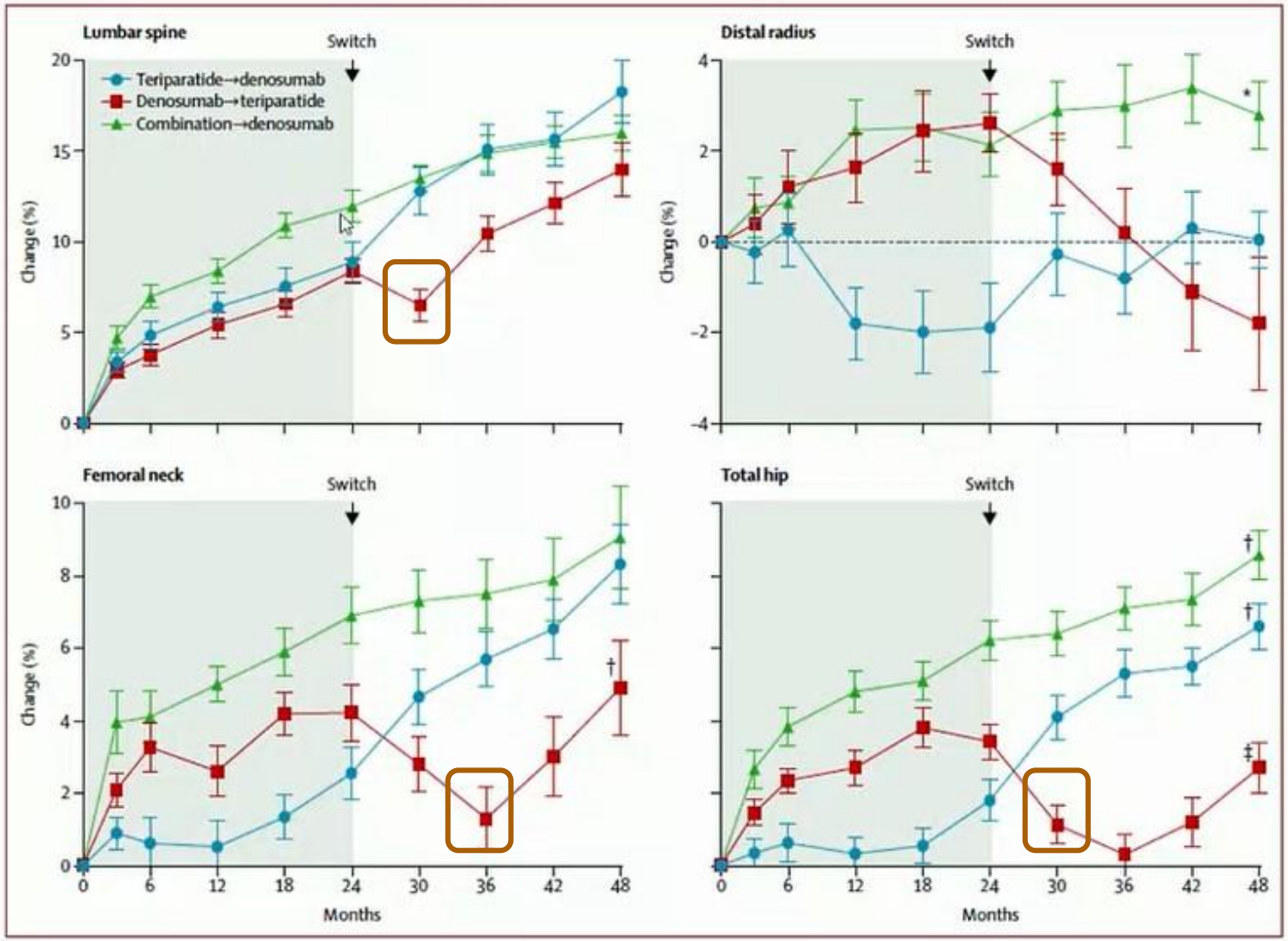
Teriparatide plus denosumab, and sequence of agents

- the DATA study
- combined teriparatide and denosumab for a 24-month period and observed increases in BMD greater than either agent alone
- switching from teriparatide to denosumab, bone mineral density continued to increase
- whereas switching from denosumab to teriparatide resulted in progressive or transient bone loss (no fracture data are available


A
Lumbar Spine
% change
month
*
B
1/3 Distal Radius
% change
month
*
C
Femoral Neck
% change
month
*
D
Total Hip
% change
month
*
TPTD
DMAB
Combo

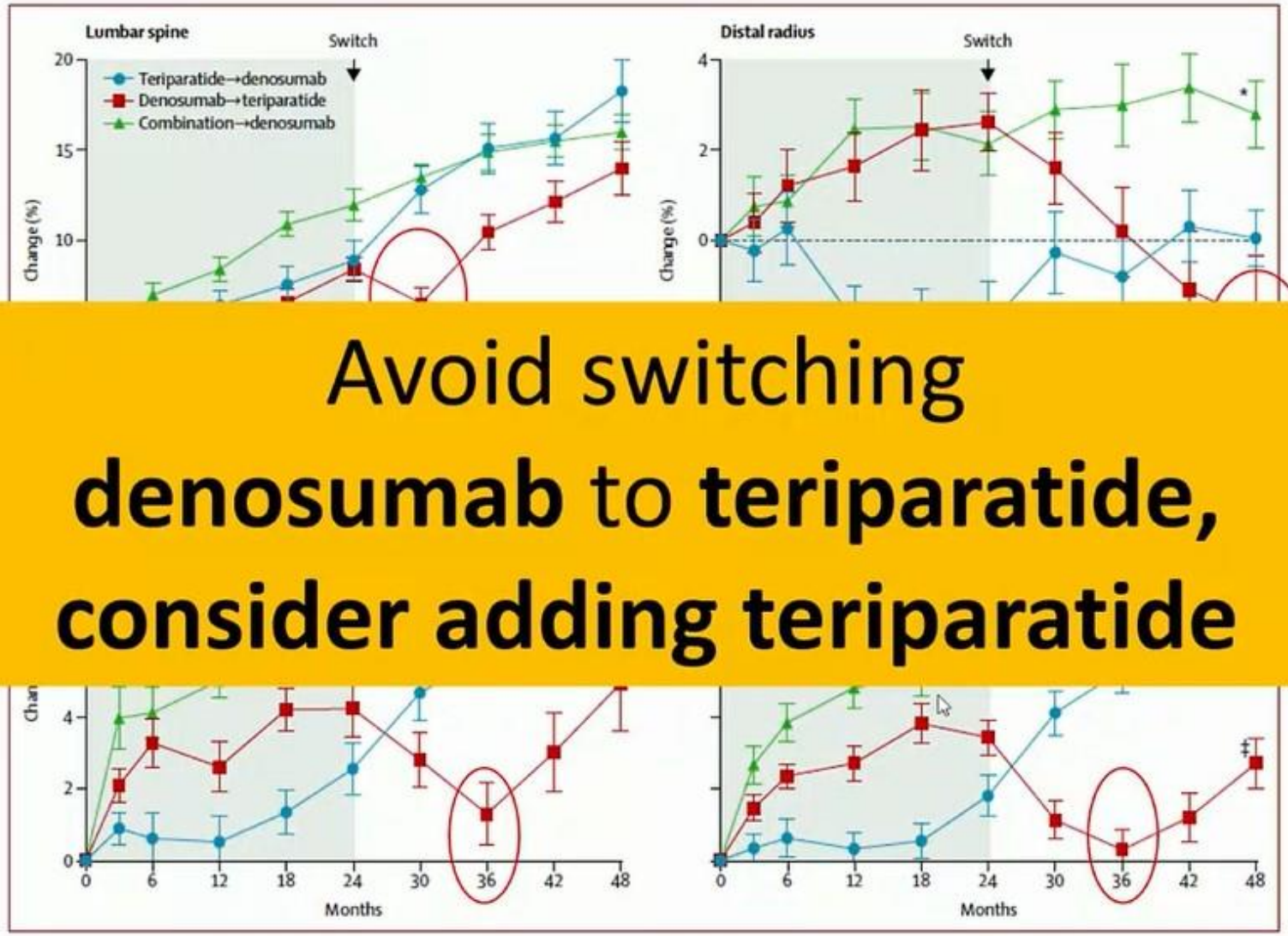

Spine
% change
15
10
5
0
yr 2
yr 1
*
TPTD
DMAB
BOTH
Fem Neck
% change
8
6
4
2
0
yr 2
yr 1
*
TPTD
DMAB
BOTH
Total Hip
% change
8
6
4
2
0
yr 2
yr 1
*
TPTD
DMAB
BOTH

Mean percent change in BMD from baseline to 48 months



Leder BZ et al. Lancet 2015; 386: 1147–55

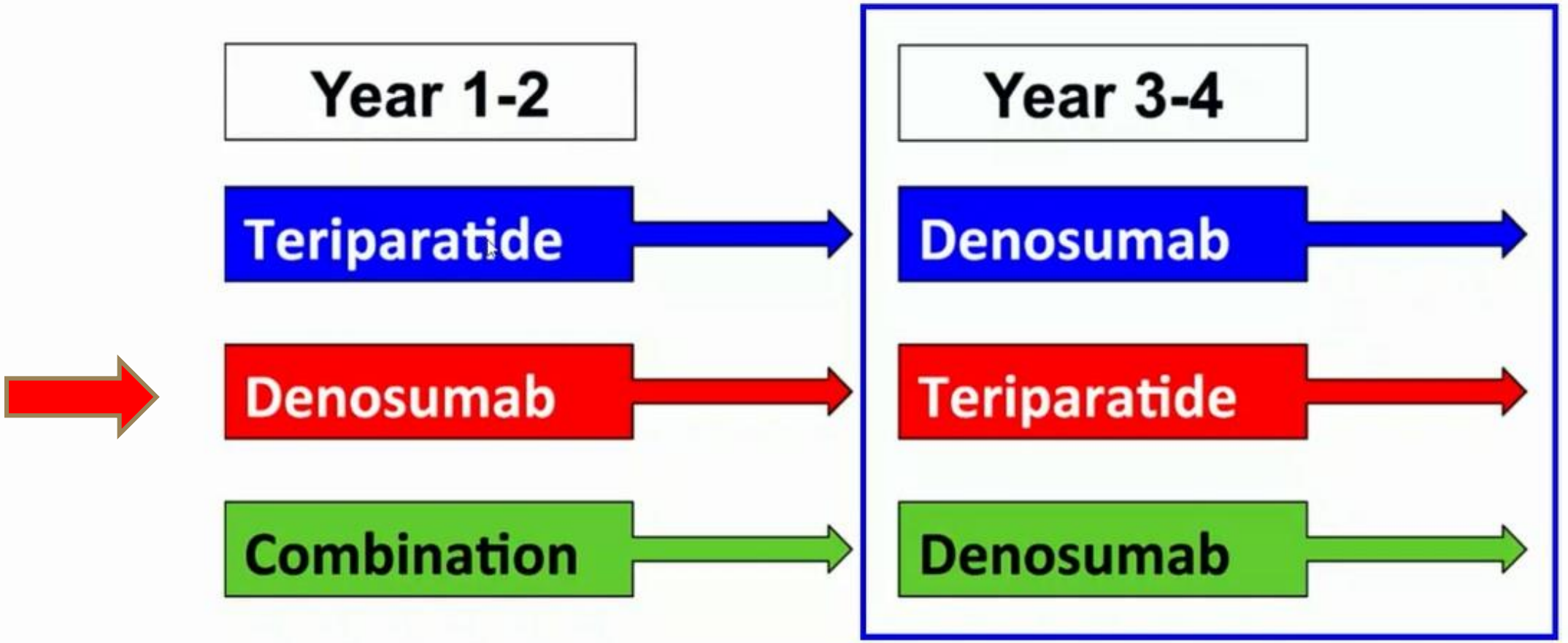
Mean percent change in BMD from baseline to 48 months



Avoid switching
denosumab to **teriparatide,**
consider adding teriparatide

Leder BZ et al. Lancet 2015; 386: 1147–55

DATA-Switch study design



Leder BZ et al. Lancet 2015; 386: 1147–55

Q9. What Is the Role of Concomitant Use of Therapeutic Agents?

R42. Until the effect of combination therapy on fracture risk is better understood, AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis (**Grade A; BEL 1**).

Abaloparatide

The ACTIVE trial

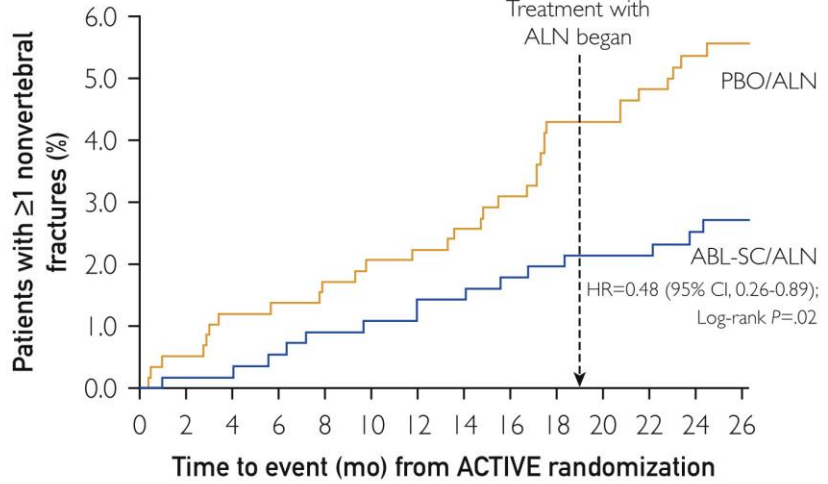
abaloparatide treatment for 18 months reduced new morphometric vertebral fractures by 86% and non-vertebral fractures by 43% in comparison with placebo

numbers needed to treat

In order to prevent one new vertebral fracture, 28 women would need to be treated with

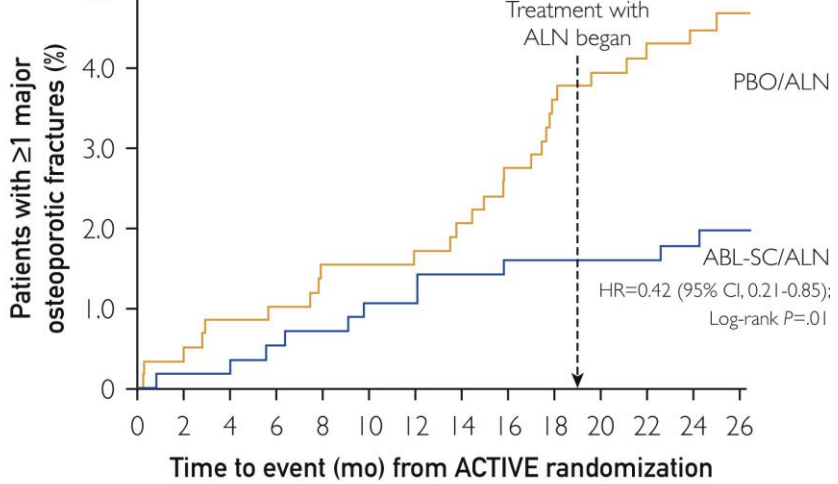
abaloparatide and 30 treated with teriparatide

To prevent one new non-vertebral fracture, 55 women would need to be treated with abaloparatide and 92 treated with teriparatide.



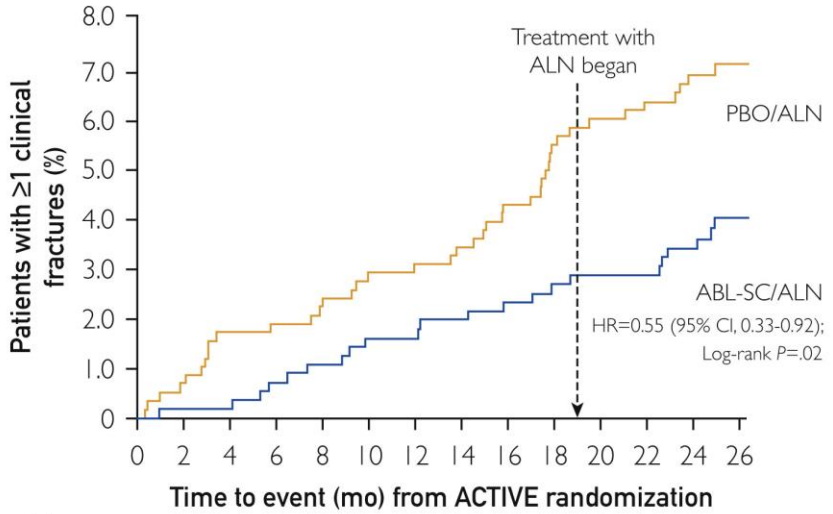
No. at risk					
PBO/ALN	581	573	568	556	529
ABL-SC/ALN	558	555	550	547	523

A



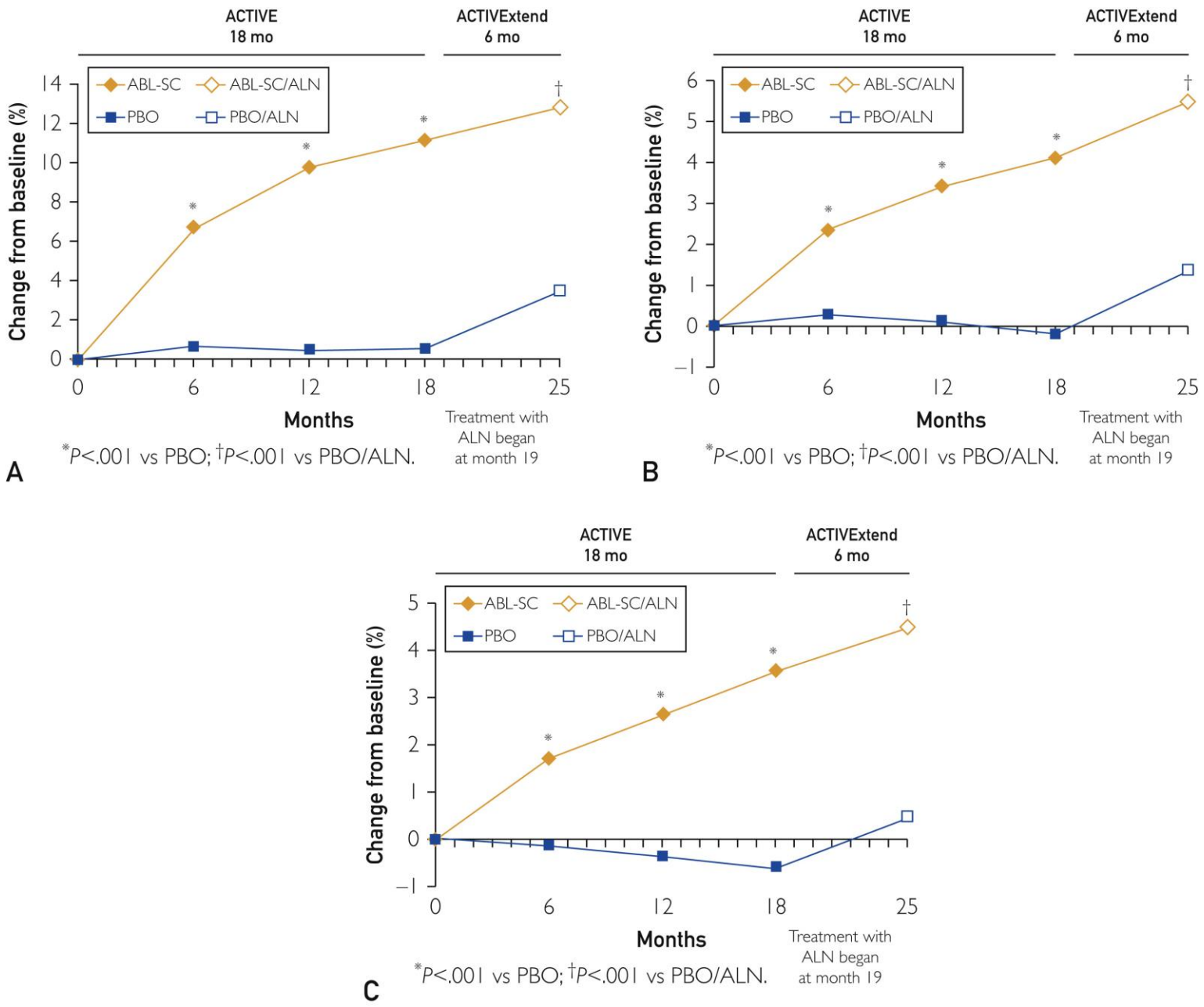
No. at risk					
PBO/ALN	581	575	571	559	533
ABL-SC/ALN	558	555	550	549	526

B



No. at risk					
PBO/ALN	581	570	563	548	521
ABL-SC/ALN	558	554	547	543	517

C



lumbar spine (A), total hip (B), and femoral neck (C

Romosozumab

is a humanised monoclonal antibody that binds and inhibits sclerostin, and has the dual effect of increasing bone formation and decreasing bone resorption

The FRAME extension study

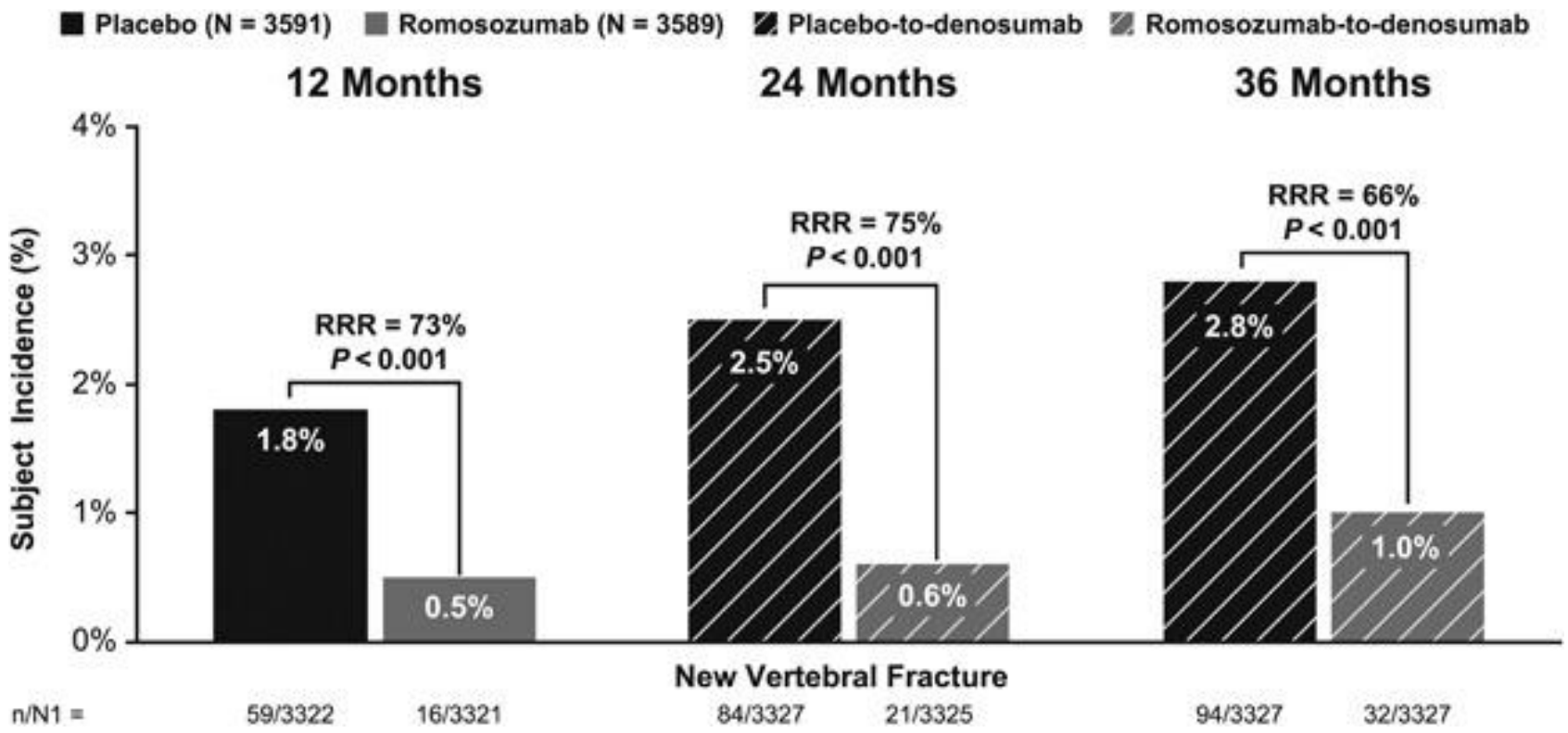
one year of romosozumab followed by 2 years of denosumab(compared placebo)

reductions in fracture risk

(new vertebral fracture (relative risk reduction [RRR], 66%;

clinical fracture (RRR, 27%; incidence, 4.0% versus 5.5%; p = 0.004), and

non-vertebral fracture (RRR, 21%; incidence, 3.9% versus 4.9%; p = 0.039)
and ongoing BMD gains.


Placebo (N = 3591)
Romosozumab (N = 3589)
Placebo-to-denosumab
Romosozumab-to-denosumab
12 Months
24 Months
36 Months
Subject Incidence (%)
4%
3%
2%
1%
0%
RRR = 73%
P < 0.001
RRR = 75%
P < 0.001
RRR = 66%
P < 0.001
1.8%
0.5%
2.5%
0.6%
2.8%
1.0%
New Vertebral Fracture
n/N1 =
59/3322
16/3321
84/3327
21/3325
94/3327
32/3327

Romosozumab

It is of interest that the effects of romosozumab are greater the higher the fracture probability at baseline

This makes romosozumab of particular relevance in patients at very high fracture risk.

An important and as yet not completely resolved consideration with the use of romosozumab is the apparent increased risk of cardiovascular adverse outcomes

Average percentage changes in total hip bone mineral density (BMD) achieved with osteoporosis therapy. Data compiled from multiple sources

Treatment	Total Duration (Mo)	Total Hip BMD Change from Baseline
Alendronate	120	6.7%
Denosumab	120	9.2%
Teriparatide for 24 mo followed by denosumab for 24 mo	48	6.6%
Abaloparatide for 18 mo followed by alendronate for 24 mo	42–43	6.4%
Romosozumab for 12 mo followed by alendronate for 24 mo	36	7.0%
Romosozumab for 12 mo followed by denosumab for 24 mo	36	9.4%

McClung MR, Clark AL. 2021 Osteoanabolic therapy for osteoporosis in women. Climacteric: 1–7

Approaches to sequential therapy

Bone mineral density increases with teriparatide after anti-resorptive treatment are blunted

The effect depends on the type of anti-resorptive treatment.

Studies have shown greater bone mineral density increases in patients pretreated with non - bisphosphonates and bisphosphonates with a lower affinity for hydroxyapatite than those with higher affinity

Approaches to sequential therapy

most studies suggest that anabolic therapies are likely to be more beneficial when administered to previously untreated patients. However, in real world practice, patients with severe osteoporosis are still likely to derive benefit from anabolics even if they are not treatment naïve and despite an element of blunting of the anabolic's effect with prior bisphosphonate therapy. Providing a treatment gap between antiresorptive therapy and subsequent anabolic treatment is unlikely to decrease this blunting.

Therefore, it is not necessary to provide this gap.

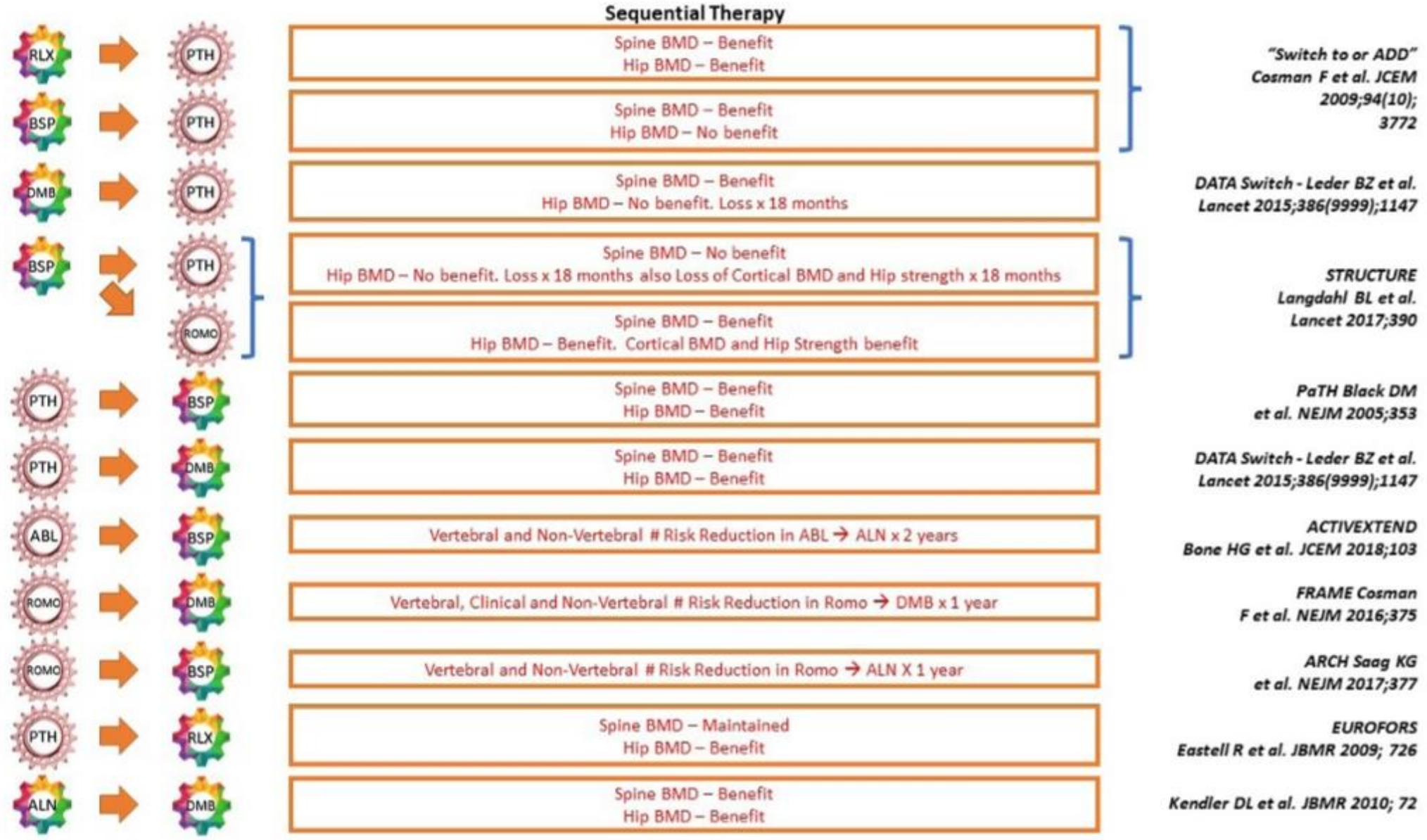


Figure 2. Sequential therapy.

Choice of anabolic agent

recommendations apply to anabolics as a class rather than as individual agents.

Duration of anabolic agent

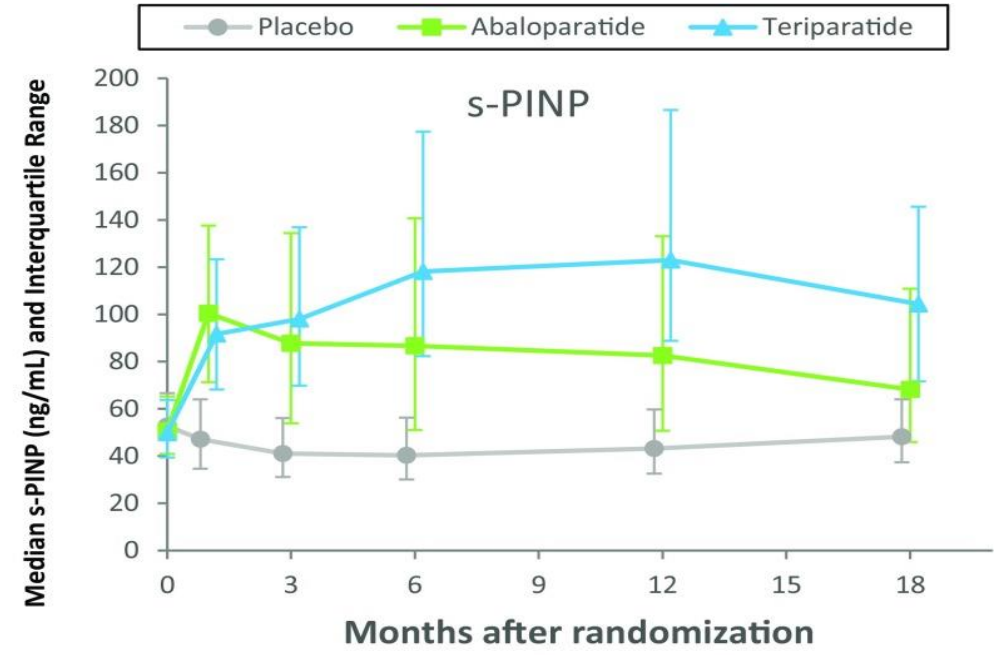
The current prescribing information recommends that lifetime treatment with teriparatide should be limited to a maximum duration of 2 years.

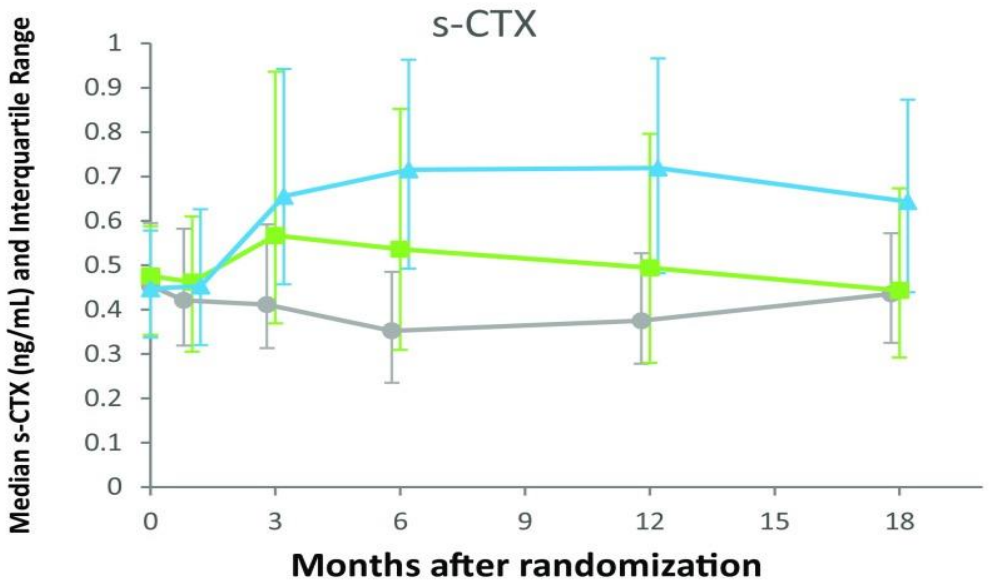
warning about a potential risk of osteosarcoma

during the 15-year surveillance period was no different than would be expected

An increase (PINP) and osteocalcin (bone formation markers) in the first six months of treatment, then there was a slight decrease over time

cross-linking telopeptide of type I collagen (CTX-I),indicating bone remodelling, also increased over six months and then decreased over time almost back to baseline by18 months.


Placebo
Abaloparatide
Teriparatide
s-PINP
Median s-PINP (ng/mL) and Interquartile Range
200
180
160
140
120
100
80
60
40
20
0
0
3
6
9
12
15
18
Months after randomization


s-CTX
Median s-CTX (ng/mL) and Interquartile Range
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
3
6
9
12
15
18
Months after randomization

Duration of anabolic agent

A strong association with the ratio of PINP at 3 months versus baseline with lumbar spine BMD

was observed in both drugs (slightly stronger in abaloparatide) indicating that the rapid

stimulation of bone formation with a high uncoupling index in the first few months of treatment

is particularly important, supporting short-term use of this bone-forming agent

Duration of anabolic agent

A rise in PINP (even steeper than observed with abaloparatide) followed by a fall back to baseline within the first 6 months of treatment is observed, alongside a sharp drop in bone resorption (CTX-I) on starting the agent, returning to baseline at 3–6 mo with both markers remaining below baseline at month 12

after 1 year, romosozumab is a moderate bone remodelling inhibitor, rather than a potent bone-forming

Bone turnover markers in treatment stratification

Studies have demonstrated that rapid bone loss is associated with increased levels of BTMs . It is

also well established that elevated BTMs are associated with increased fracture risk

patients with both low BMD and high BTMs are likely to be at very high risk of incident fracture

recent approaches have applied a “least significant change” approach to the use of BTM in monitoring treatment

Bone turnover markers in treatment stratification

High sensitivity CRP (hs-CRP)

an increased serum uric acid level associated with a lower risk of fracture

Higher cystatin C has been associated with higher risk of hip fractures in older women

periostin, cathepsin K, osteoprotegerin(OPG), RANKL, DKK-1, sclerostin, FGF-23, Klotho, and of course miRNAs ,high sphingosine-1-phosphate,

Bone turnover markers in treatment stratification

ESCEO and IOF algorithm, BTMs are recommended to be checked at baseline and 3 months after starting therapy, with responders to antiresorptive considered to be those who show changes in BTMs that exceed the least significant change (56% decrease for CTX-I and 38% decrease for PINP)

If at three months a decrease is not seen, it is recommended that adherence is discussed

with the patient, and if they are adhering well, a treatment change may be considered

Long-term treatment: cycling of anabolic/ antiresorptive therapies?

teriparatide for four 3-month cycles, each followed by 3 months off, and compared to daily teriparatide for 24 months, in both alendronate naive and women on alendronate. In the women on alendronate, cyclic teriparatide over 2 years improved BMD similarly to daily treatment in women who remained on alendronate (despite only 50% of the teriparatide dose), but in treatment naive women there did not appear to be a BMD advantage to cyclic administration

36-month cycles of 6 months of teriparatide followed by 6 months of denosumab>>>no benefit

cyclic approach could be useful in patients at the highest risk of imminent fracture>>>need further study

Long-term treatment

The decision-making process on when (and if ever) to stop antiresorptive therapy in a patient who has received a prior anabolic agent, is often complex

Alendronate and zoledronate-treated patients;>>>0.4% or lower decrease in femoral neck BMD>>>discontinuation of up to a year may be acceptable

The consensus of the group was that, if the patient remains at high risk or very high risk of fracture, it is likely that a patient will need prolonged antiresorptive therapy after anabolic treatment.

, if BMD no longer at high or very high risk >>> may be possible to stop treatment>>> maximum of a couple of years, though not if denosumab

In the case of denosumab,>>> infusion of 5 mg zoledronate helps to reduce the rebound loss in BMD on stopping denosumab,

Denosumab Discontinuation:

Recommendation

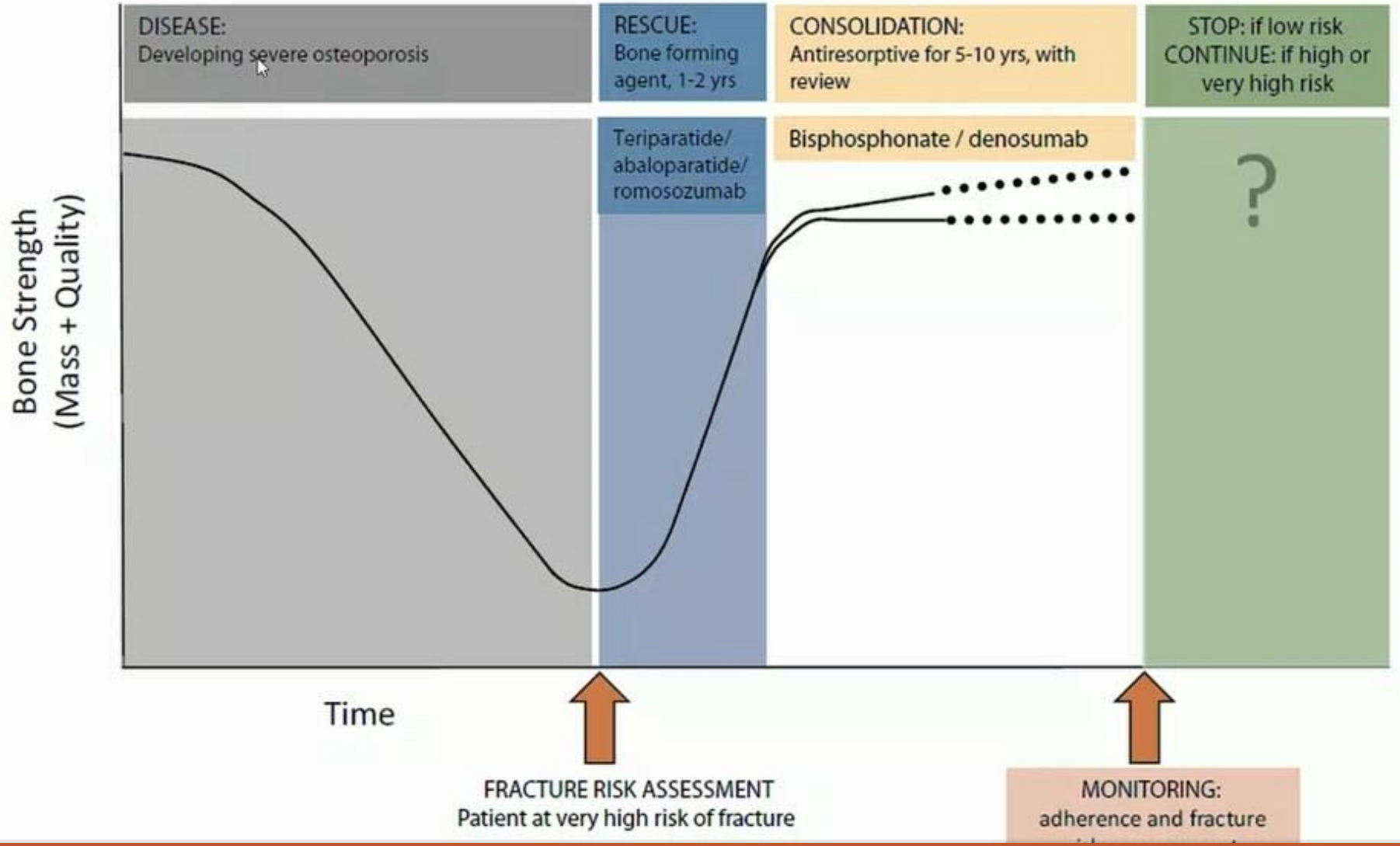
If the person has been only on short-term treatment with denosumab up to ~ 2.5 years, then upon discontinuation alendronate can be given for 1-2 years or a single dose of zoledronic acid can be administered 6 months after the last denosumab injection.

If on the other hand the person has been on denosumab for > 2.5 years, it is better to give a more potent bisphosphonate i.e., zoledronic acid 6 months after the last denosumab injection and to monitor the marker of bone resorption CTX at 3, 6 and 12 months and to readminister zoledronic acid if CTX values are above the premenopausal range.

If CTX levels are unable to be measured, the recommendation is to repeat the zoledronic acid infusion in 6 months

Outline of a recommended approach to sequential therapy

ESCEO position paper



Return To Case

68-year old lady is referred for management of her osteoporotic fracture.

She was on denosumab due to GI intolerance of BSP after low BMD from 18 mo ago

, What is the best treatment option for her now ?

Switching to zoledronate

Continuing with Teriparatide

Switching to romosozumab

Switching to Teriparatide

Continuing denosumab

Treatment failure

Two or more incident fragility fractures

One incident fracture and elevated serum βCTX or PINP at baseline with no significant reduction during treatment, a significant decrease in BMD, or both

Both no significant decrease in serum βCTX or PINP and a significant decrease in BMD

thanks for your attention