4° CONGRESSO NAZIONALE FRAGILITY FRACTURE NETWORK - ITALIA

Appropriatezza, Qualità e Sostenibilità delle Cure nel Percorso Ortogeriatrico

La cura dell'osteoporosi e la prevenzione secondaria delle fratture

Il ruolo del teriparatide e biosimilari

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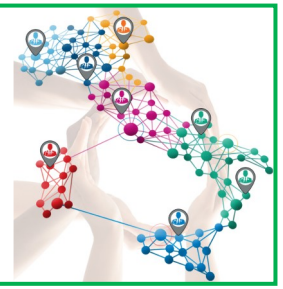
Università di Firenze

TERIPARATIDE IN FLS: SOME QUESTIONS TO BE ADDRESSED



- What about teriparatide, cortical bone and non vertebral/hip fracture prevention?
- Is teriparatide (and its biosimilars) a therapeutic chance in FLS?
- What about teriparatide in sequential treatments and possible combined treatments?
- What about teriparatide effect on fracture healing?

APPROVED ANABOLIC AND ANTIRESORPTIVE THERAPIES

- Increase BMD
- Reduce vertebral fractures in high-risk populations
- Reduce non-vertebral fractures modestly

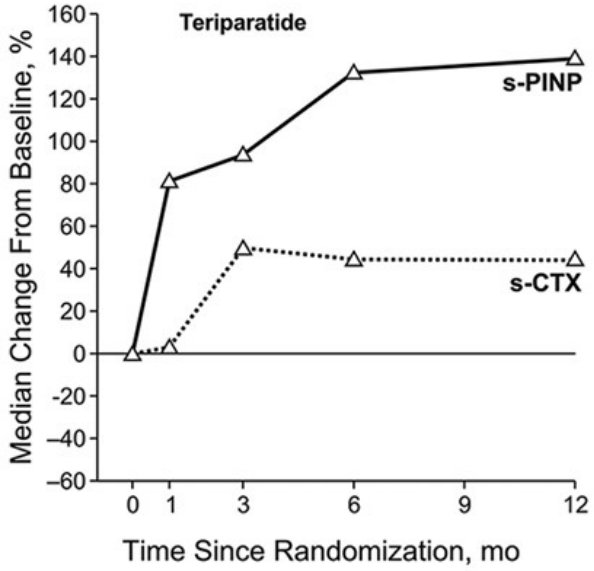
- intranasal calcitonin (antiresorptive): 1995
- alendronate (antiresorptive): 1996
- raloxifene (antiresorptive): 1997
- risedronate (antiresorptive): 1998
- teriparatide (anabolic): 2002
- ibandronate (antiresorptive): 2005
- zoledronic acid (antiresorptive): 2007
- denosumab (antiresorptive): 2010
- abaloparatide (anabolic): 2017
- romosozumab (anabolic/antiresorptive): 2019

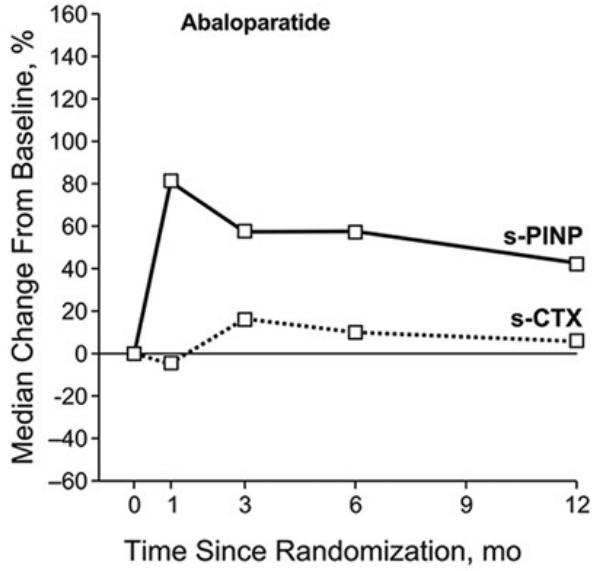
CURRENT ANABOLIC AND ANTIRESORPTIVE THERAPIES

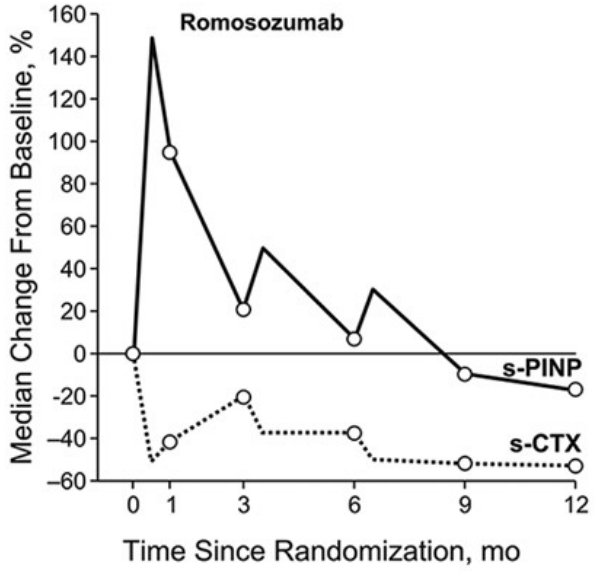
	mechanism of action	2-yr increase spine BMD	2-yr increase total hip BMD	RRR of spine fracture	RRR of non-spine fracture
Raloxifene	antiresorptive-SERM	2-3%	1%	50%	--
Oral BPs	antiresorptive-bisphosphonate	3-5%	2-3%	40-53%	0-20%
IV Zoledronic acid	antiresorptive-bisphosphonate	5-6%	3-4%	70%	25%
SC Denosumab	antiresorptive-RANKL-inhibitor	6-8%	3-4%	68%	20%
SC Teriparatide	anabolic-PTH analog	8-10%	1.5-2%	65-70%	35%
SC Abaloparatide	anabolic-PTH analog	10%	2-3%	70-80%	40%
Romosozumab	mixed anabolic/antiresorptive	11% (1 year)	4% (1 year)	48% vs. alendronate	20% vs. alendronate

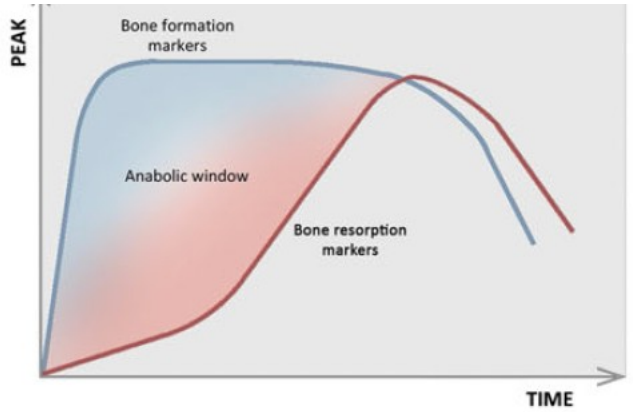
Black et al. Lancet. 1996, Black et al. NEJM. 2007, Cummings et al. NEJM. 2009, Neer et al. NEJM. 2001, Miller et al JAMA 2017, Saag et al NEJM 2017

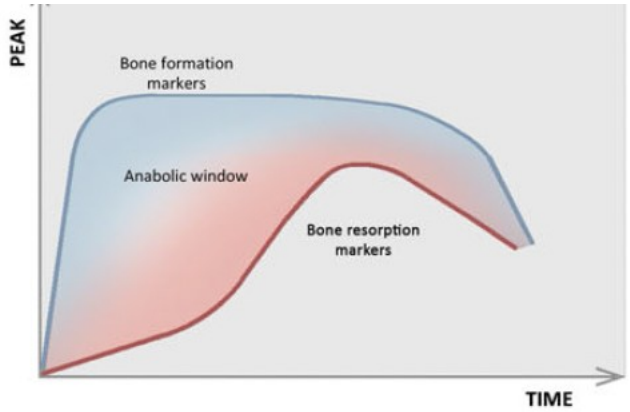
DIFFERENT ANABOLIC WINDOWS FOR DIFFERENT ANABOLICS

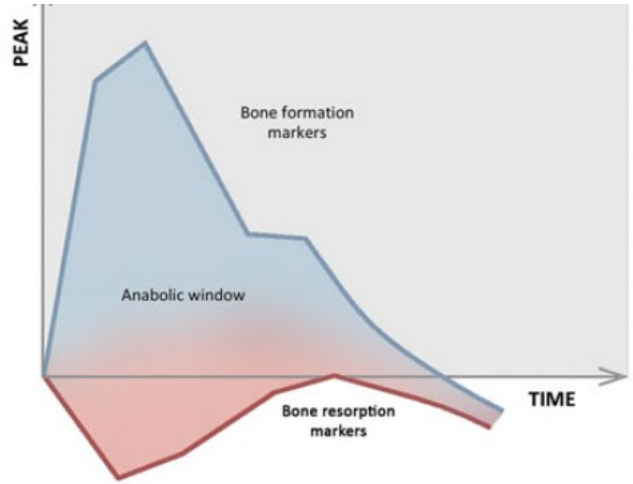










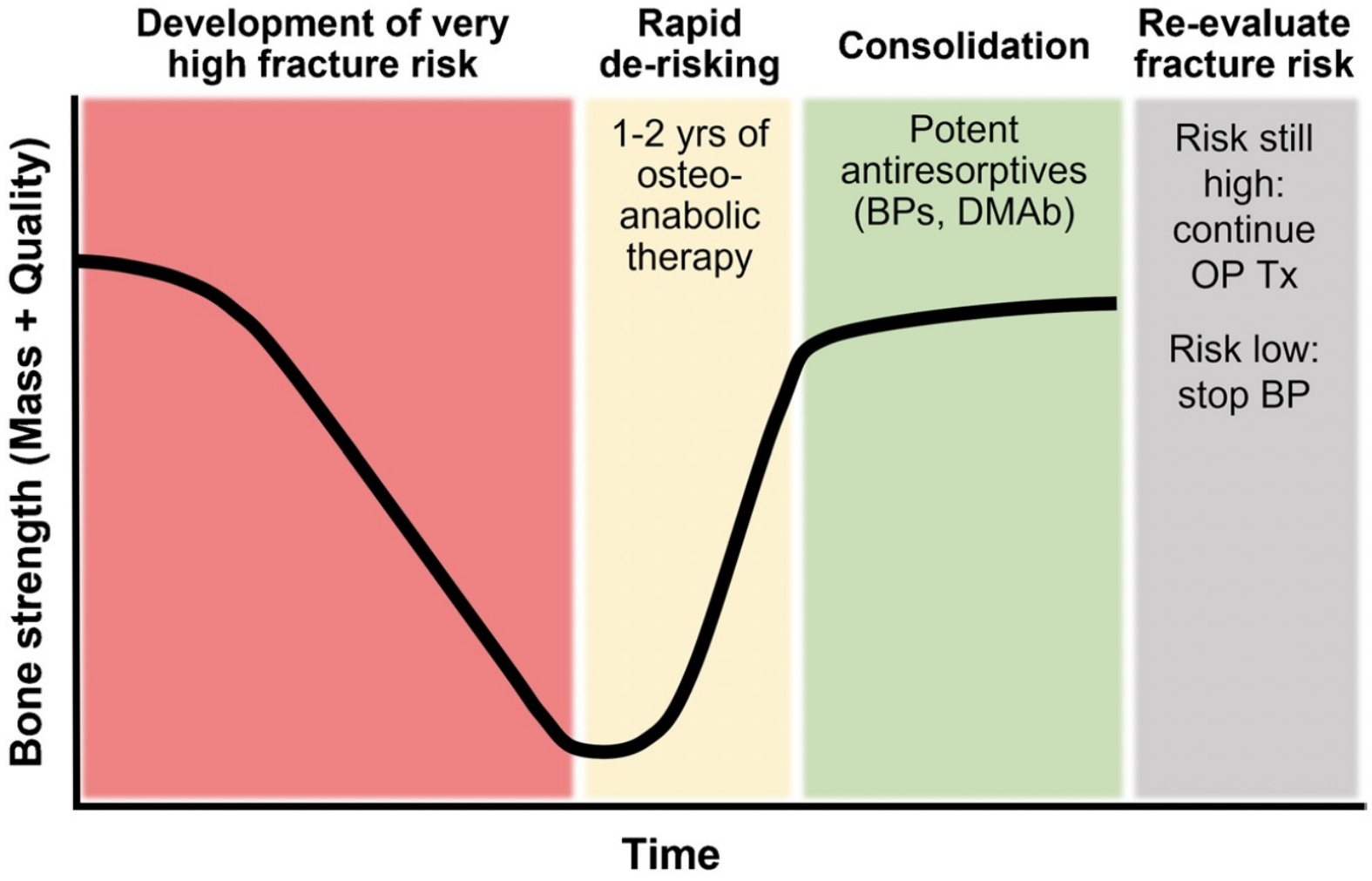


DIFFERENT BONE METABOLISM/RESPONSE FOR DIFFERENT ANABOLICS

Minisola et al. Ther Adv Musculosk Res 2019

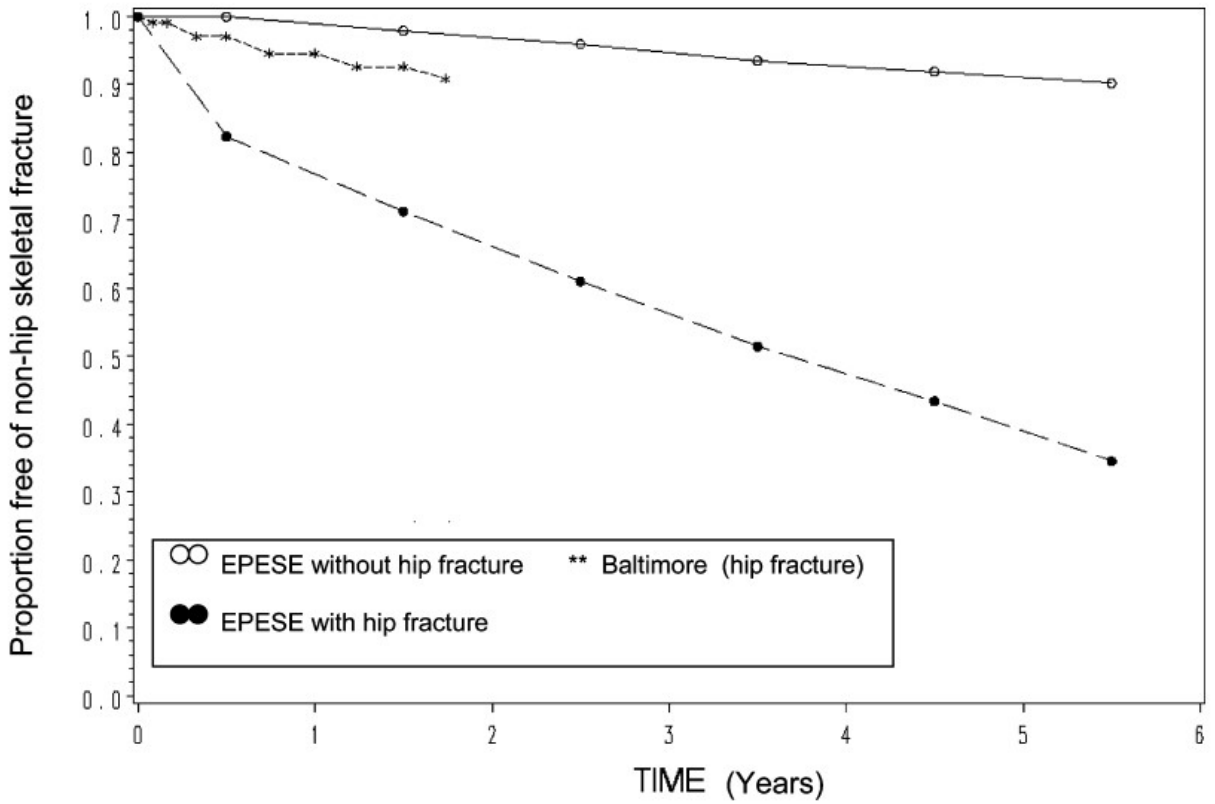
Tabacco & Bilezikian Brit J Clin Pharmacol 2019

ANABOLICS-TO-ANTIRESORPTIVES: THE BEST SEQUENCE TO DECREASE IMMINENT RISK OF FRACTURE



Kostenuik et al. Curr Osteoporos Rep 2023V

Subsequent fractures after hip fracture



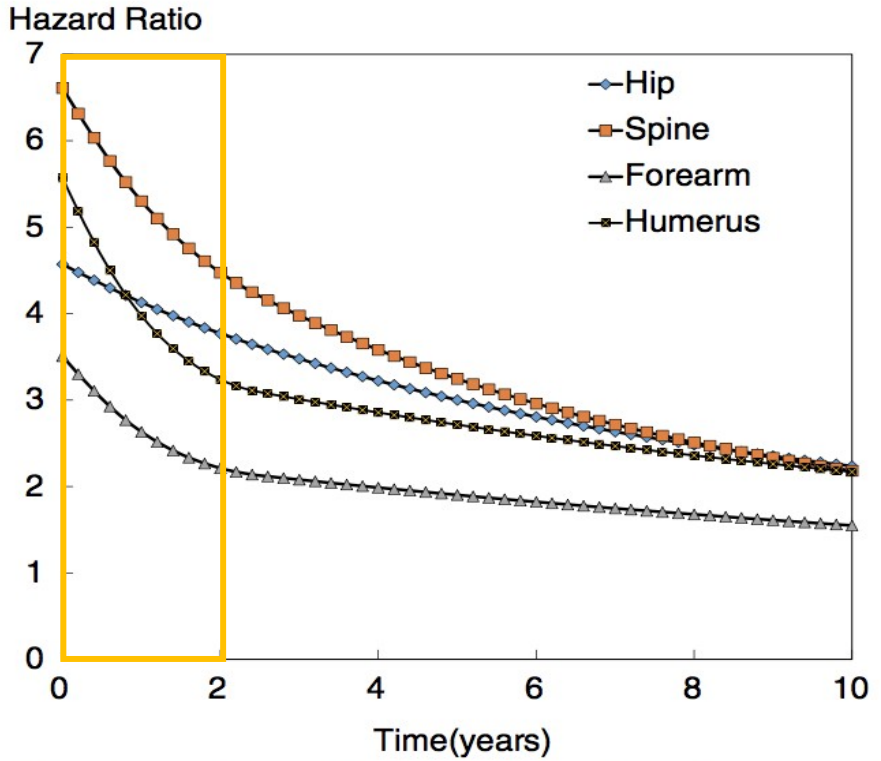
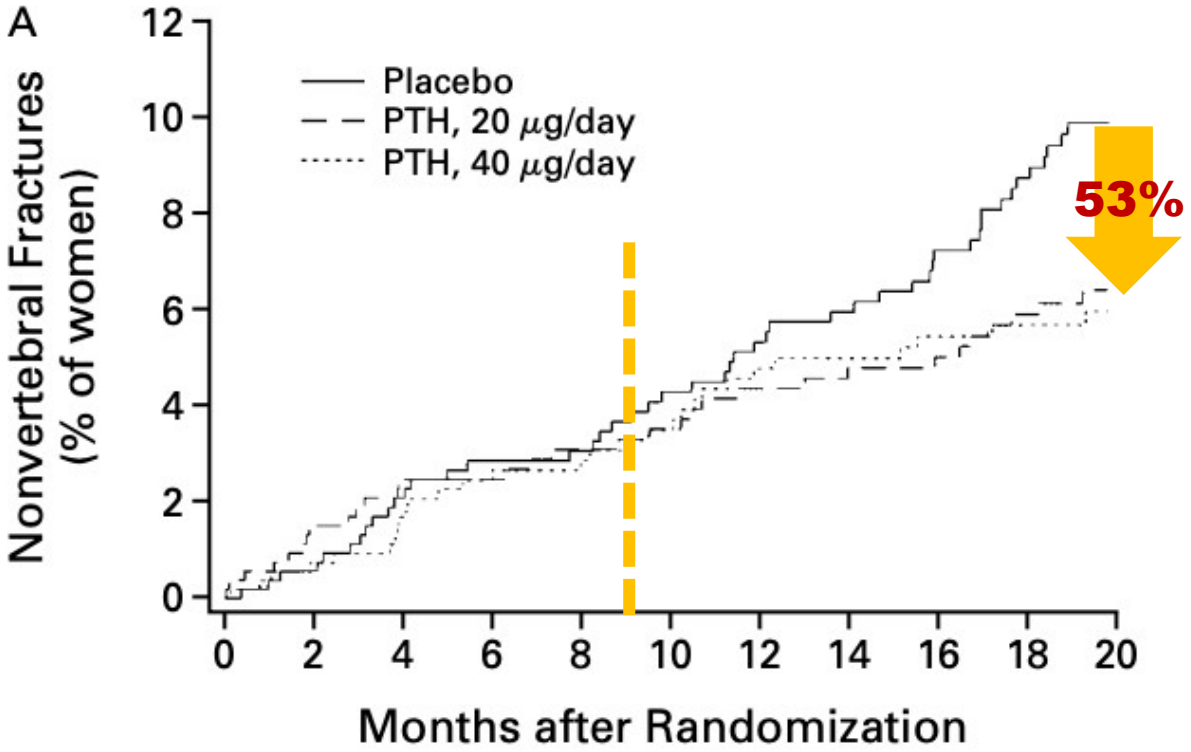


Fig. 2 Hazard ratio (sentinel fracture compared with the whole cohort) of osteoporotic fracture in women at the age of 70 years by time according to the site of sentinel fracture

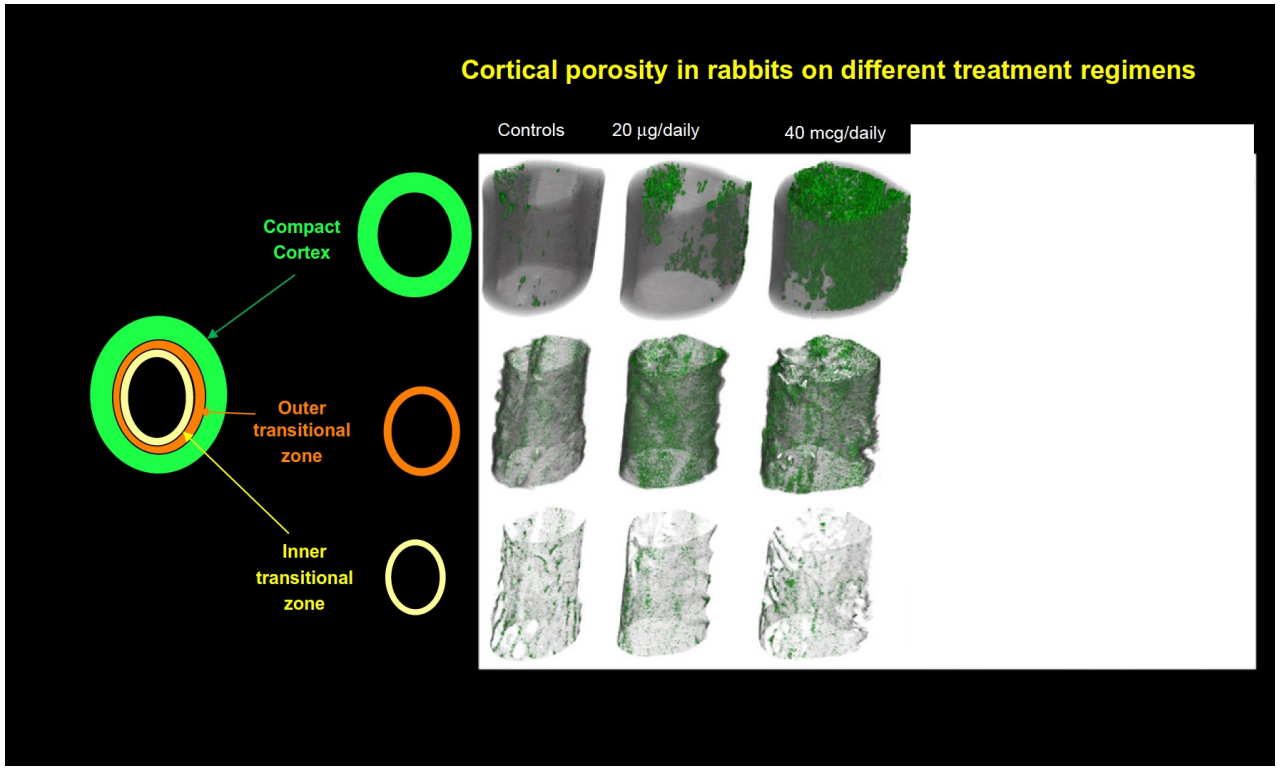
Coleman et al. 2003

Teriparatide: the beginning of the story (Fracure Prevention Trial)

1637 postmenopausal women with prior vertebral fractures

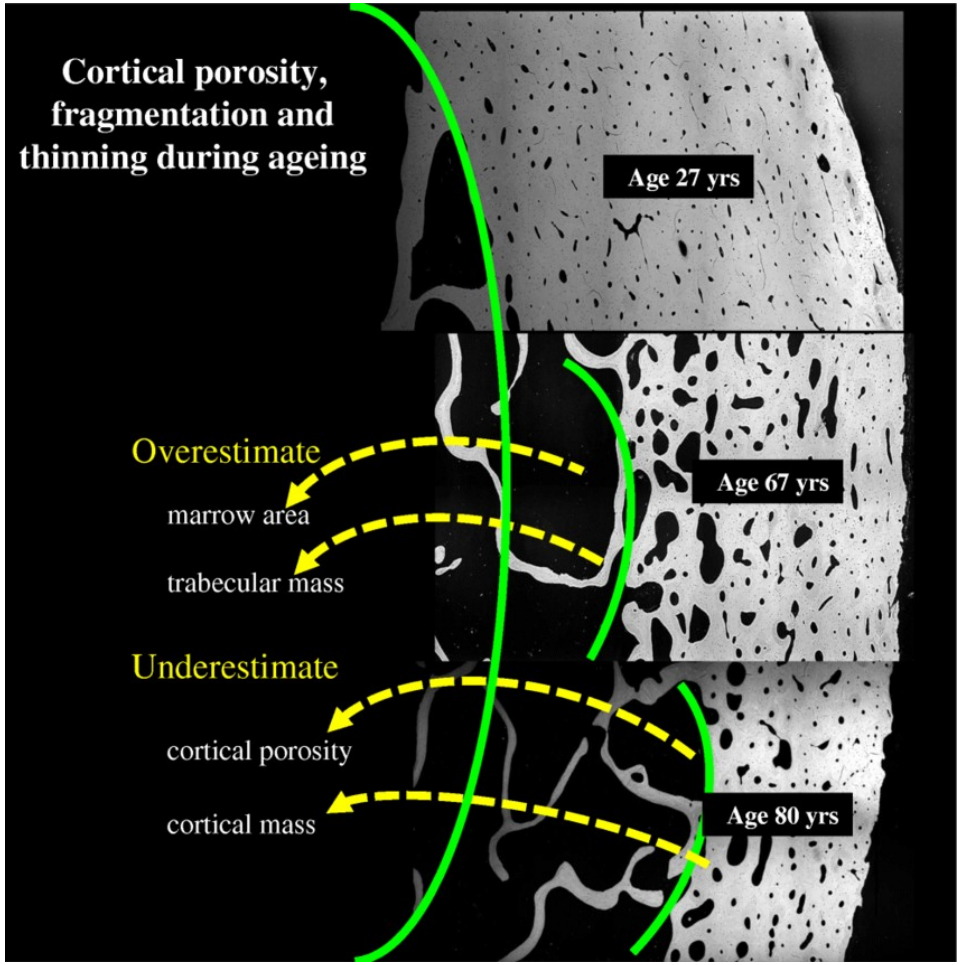


Neer et al. N Engl J Med 2001



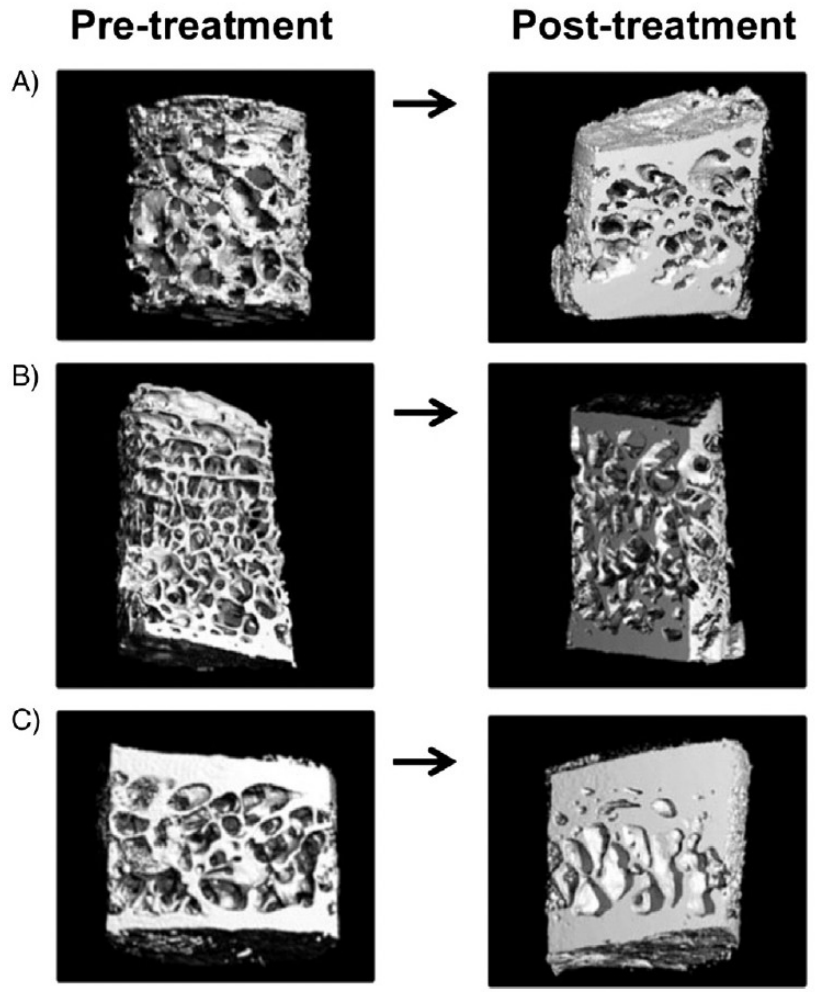
Zebaze et al. Bone 2017

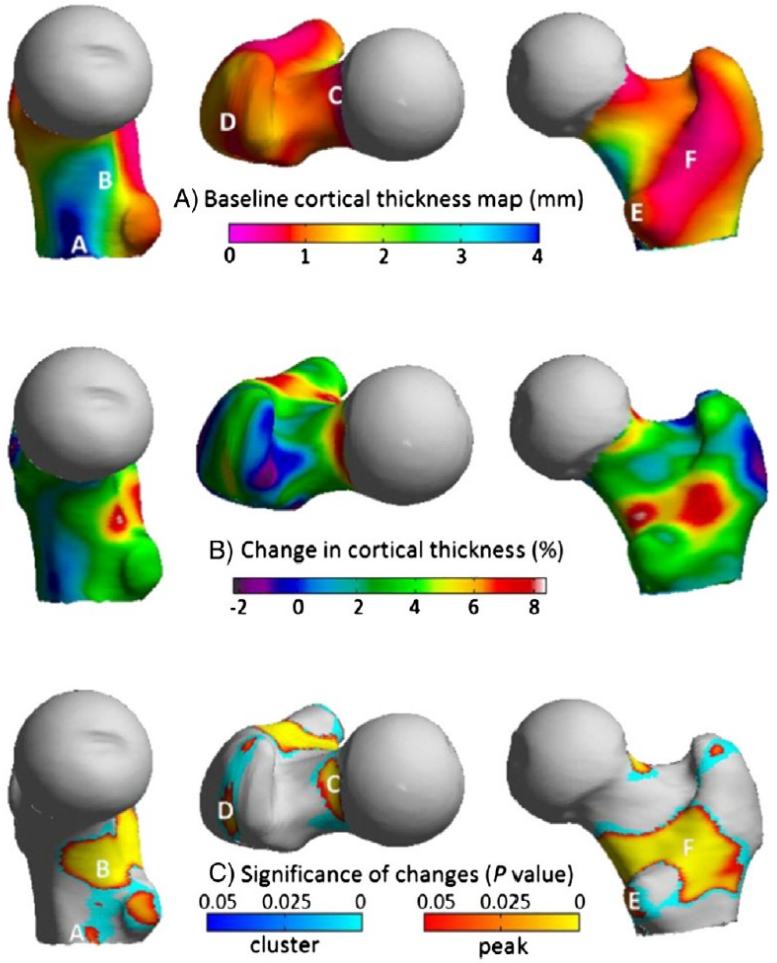
CORTICAL POROSITY AND BONE AGING



Ramchand & Seeman Curr Osteoporos Rep 2018

TERIPARATIDE: EFFECT AT THE HIP



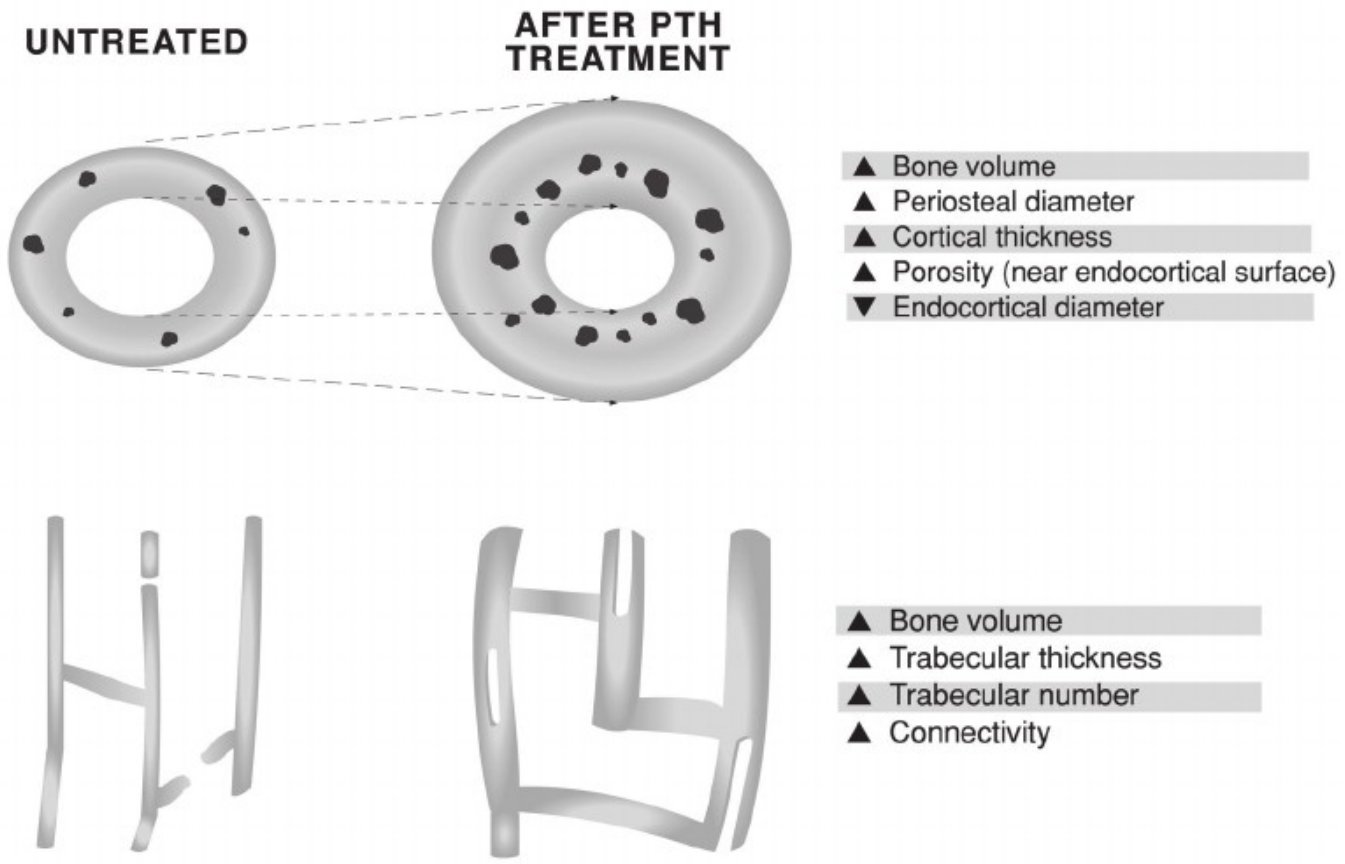


Increased (focal) cortical porosity and (diffuse) cortical thickness:
Increased cortical bone mass (especially at loading sites)

Increased cortical strength (FEA)

Eriksen et al. Bone 2014

PTH peptides and cortical porosity



TERIPARATIDE AND HIP FRACTURE PREVENTION

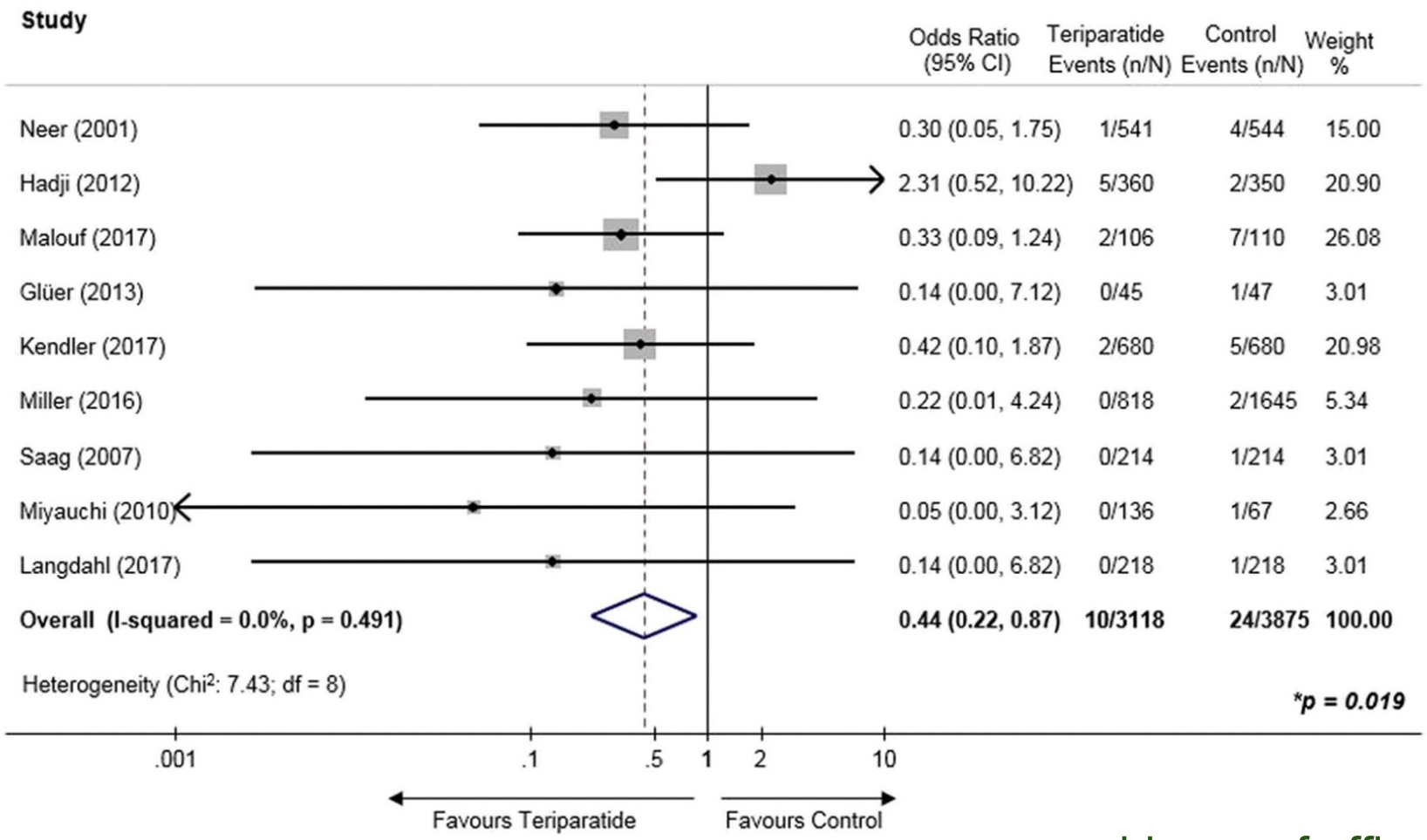


Fig. 2. Forest plot of hip fracture outcomes.

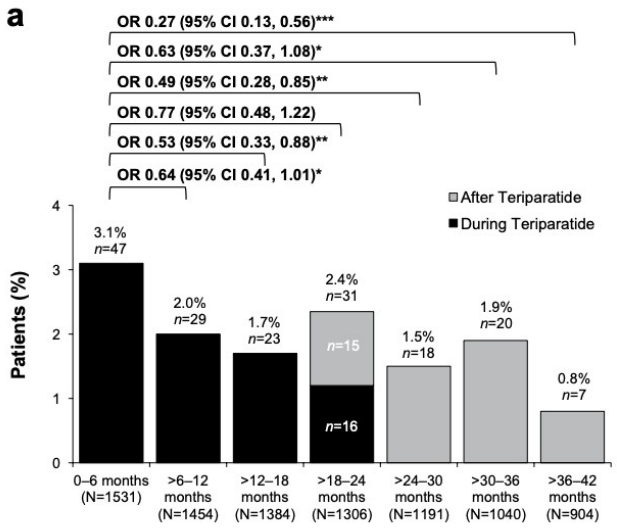
total number of 8644 patients

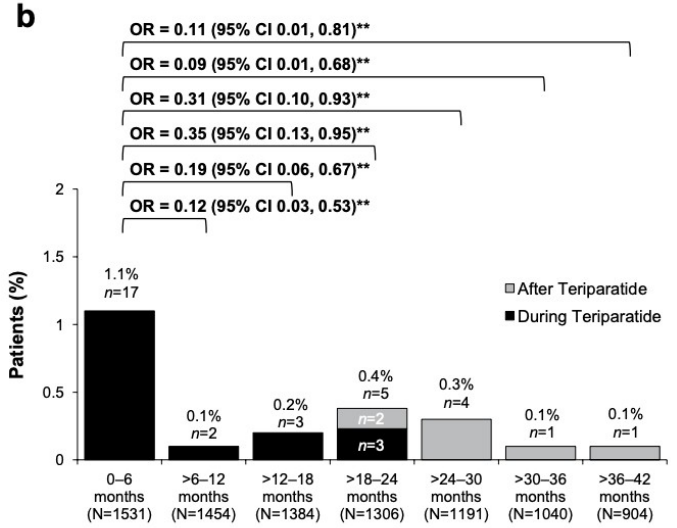
evidence of efficacy of teriparatide in reducing hip fractures by 56% in patients with osteoporosis

Diez-Perez et al. Bone 2019

FRACTURE RISK REDUCTION DURING AND AFTER TERIPARATIDE DISCONTINUATION IN REAL LIFE CLINICAL SETTING (ExFOS Study)

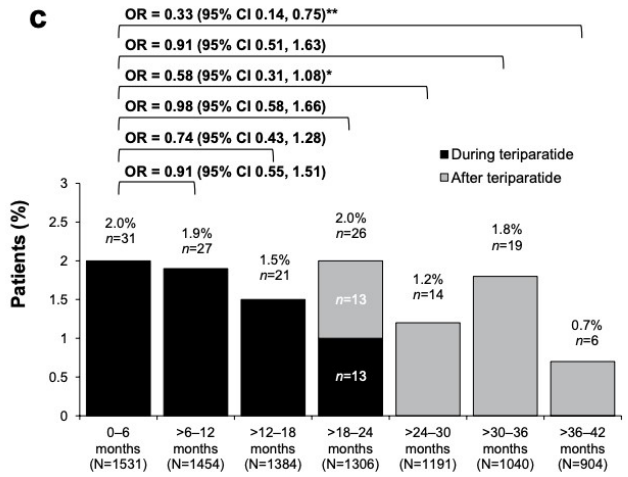
Clinical fractures

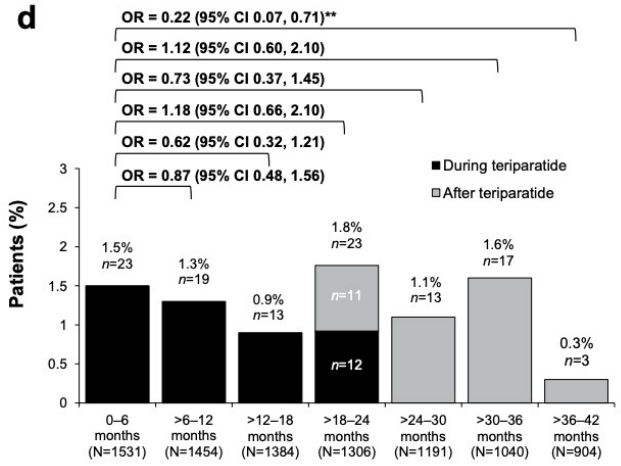




Clinical vertebral fractures

Non vertebral fractures





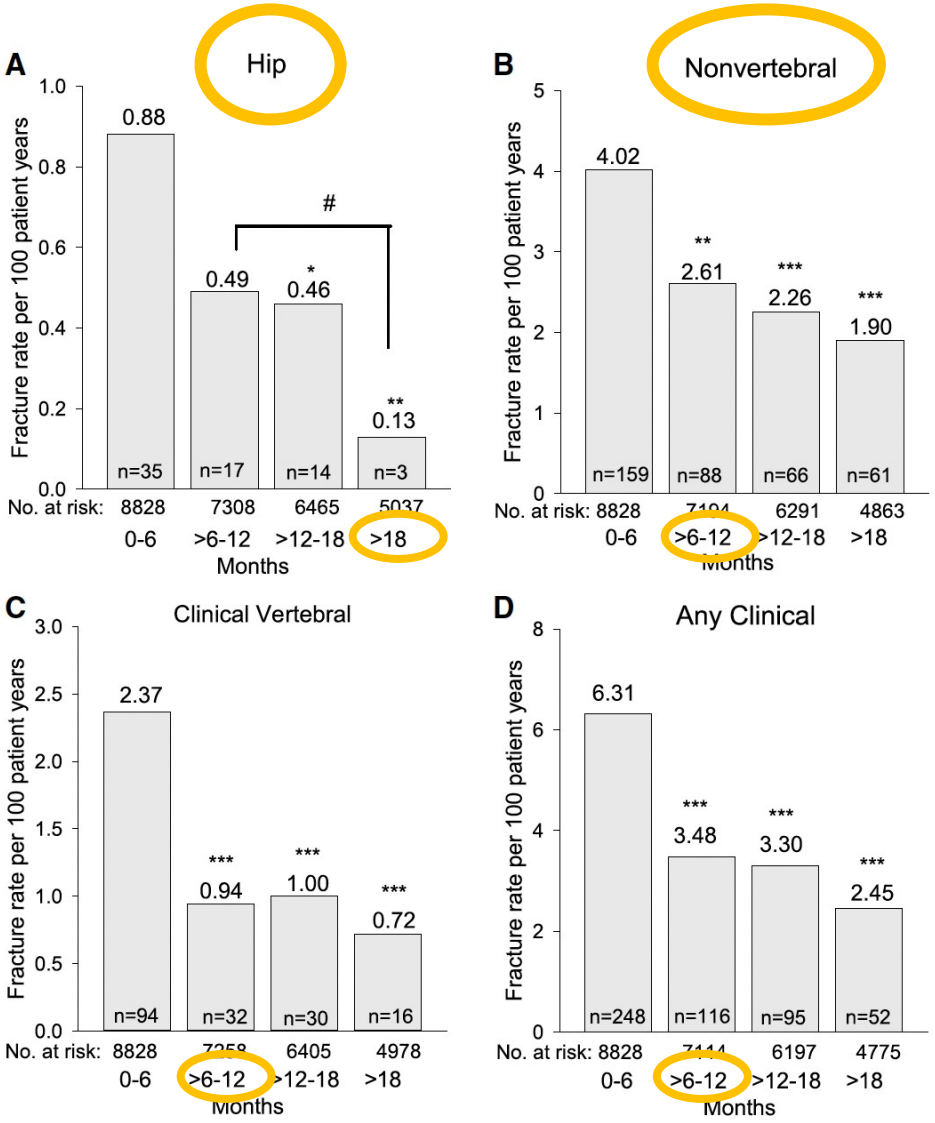
Main non-vertebral fracrtures (wrist/forearm, hip, humerus, leg or ribs)

Napoli et al. Calcif Tissue Int 2018

FRACTURE RISK REDUCTION BY TERIPARATIDE IN REAL LIFE CLINICAL SETTING

4 observational studies:

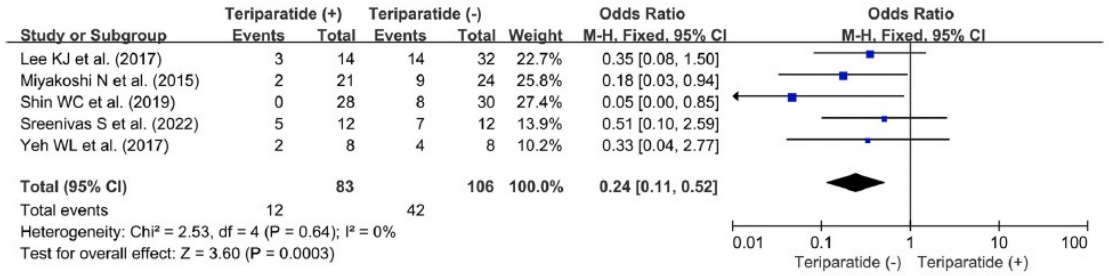
1. Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE, United States [US]
2. European Forsteo Observational Study (EFOS)
3. Extended Forsteo Observational Study (ExFOS, Europe)
4. Japan Fracture Observational Study (JFOS) [13]



Silverman et al. Calcif Tissue Int 2019

TERIPARATIDE AFTER ATYPICAL FEMUR FRACTURE

a

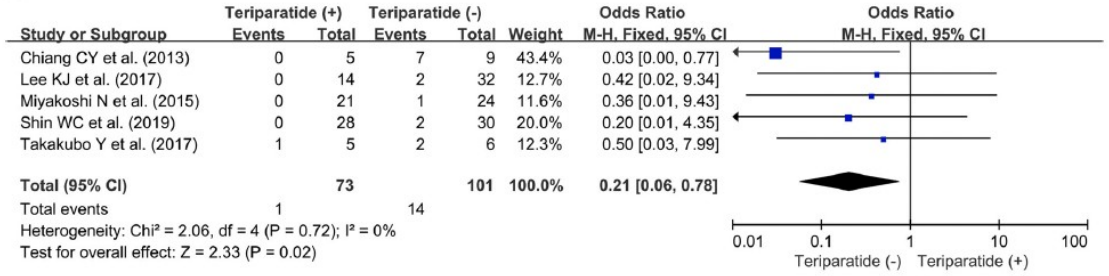


Study or Subgroup	Teriparatide (+) Events	Total	Teriparatide (-) Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lee KJ et al. (2017)	3	14	14	32	22.7%	0.35 [0.08, 1.50]
Miyakoshi N et al. (2015)	2	21	9	24	25.8%	0.18 [0.03, 0.94]
Shin WC et al. (2019)	0	28	8	30	27.4%	0.05 [0.00, 0.85]
Sreenivas S et al. (2022)	5	12	7	12	13.9%	0.51 [0.10, 2.59]
Yeh WL et al. (2017)	2	8	4	8	10.2%	0.33 [0.04, 2.77]
Total (95% CI)		**83**		**106**	**100.0%**	**0.24 [0.11, 0.52]**
Total events	12		42			

Heterogeneity: Chi² = 2.53, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 3.60 (P = 0.0003)

Rate of delayed union

b

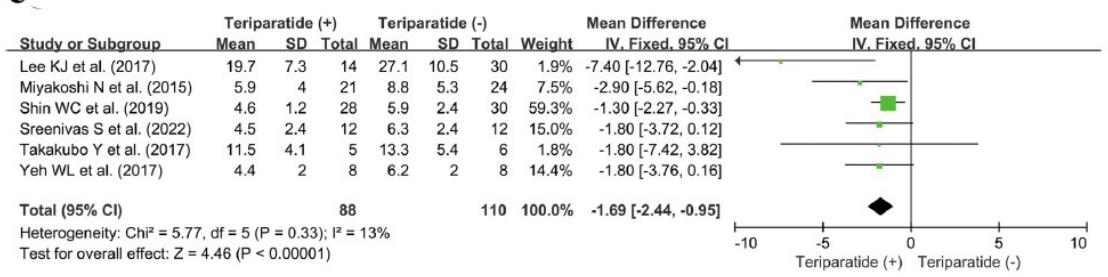


Study or Subgroup	Teriparatide (+) Events	Total	Teriparatide (-) Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chiang CY et al. (2013)	0	5	7	9	43.4%	0.03 [0.00, 0.77]
Lee KJ et al. (2017)	0	14	2	32	12.7%	0.42 [0.02, 9.34]
Miyakoshi N et al. (2015)	0	21	1	24	11.6%	0.36 [0.01, 9.43]
Shin WC et al. (2019)	0	28	2	30	20.0%	0.20 [0.01, 4.35]
Takakubo Y et al. (2017)	1	5	2	6	12.3%	0.50 [0.03, 7.99]
Total (95% CI)		**73**		**101**	**100.0%**	**0.21 [0.06, 0.78]**
Total events	1		14			

Heterogeneity: Chi² = 2.06, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.33 (P = 0.02)

Rate of non-union

c



Study or Subgroup	Teriparatide (+) Mean	SD	Total	Teriparatide (-) Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lee KJ et al. (2017)	19.7	7.3	14	27.1	10.5	30	1.9%	-7.40 [-12.76, -2.04]
Miyakoshi N et al. (2015)	5.9	4	21	8.8	5.3	24	7.5%	-2.90 [-5.62, -0.18]
Shin WC et al. (2019)	4.6	1.2	28	5.9	2.4	30	59.3%	-1.30 [-2.27, -0.33]
Sreenivas S et al. (2022)	4.5	2.4	12	6.3	2.4	12	15.0%	-1.80 [-3.72, 0.12]
Takakubo Y et al. (2017)	11.5	4.1	5	13.3	5.4	6	1.8%	-1.80 [-7.42, 3.82]
Yeh WL et al. (2017)	4.4	2	8	6.2	2	8	14.4%	-1.80 [-3.76, 0.16]
Total (95% CI)			**88**			**110**	**100.0%**	**-1.69 [-2.44, -0.95]**

Heterogeneity: Chi² = 5.77, df = 5 (P = 0.33); I² = 13%
Test for overall effect: Z = 4.46 (P < 0.00001)

Time required for fracture healing

Byun et al. Osteoporos Int 2023

THE HORIZON

- Osteoporosis is a chronic conditions which requires chronic therapy
- While current drug choices have greatly expanded, we are still unable to fully restore skeletal integrity in most patients with established disease.
- There are currently no new osteoporosis drugs that have proceeded beyond early-stage development
- For the near future, improvement in osteoporosis management will based on learning how to better use the drugs we have:
  - ✓**Combination therapy**
  - ✓**Sequential therapy**
  - ✓(Advances in mode of administration)

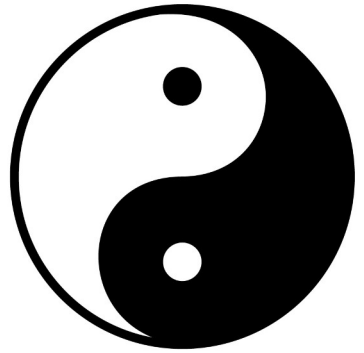
Combination therapy

- Osteoporosis is one of the few chronic conditions for which there is no accepted role for using more than one drug at a time.
- PTH/PTHrP Analogs: ↑↑ bone formation and ↑ bone resorption
- Bisphosphonates: ↓↓ bone resorption and ↓ bone formation

Positive bone balance (↑BMD)

Can osteoblast and osteoclast function be unlinked'

↑ bone formation and ↓ bone resorption



DENOSUMAB AND TERIPARATIDE ADMINISTRATION STUDY

(DATA & DATA EXTENSION STUDY)

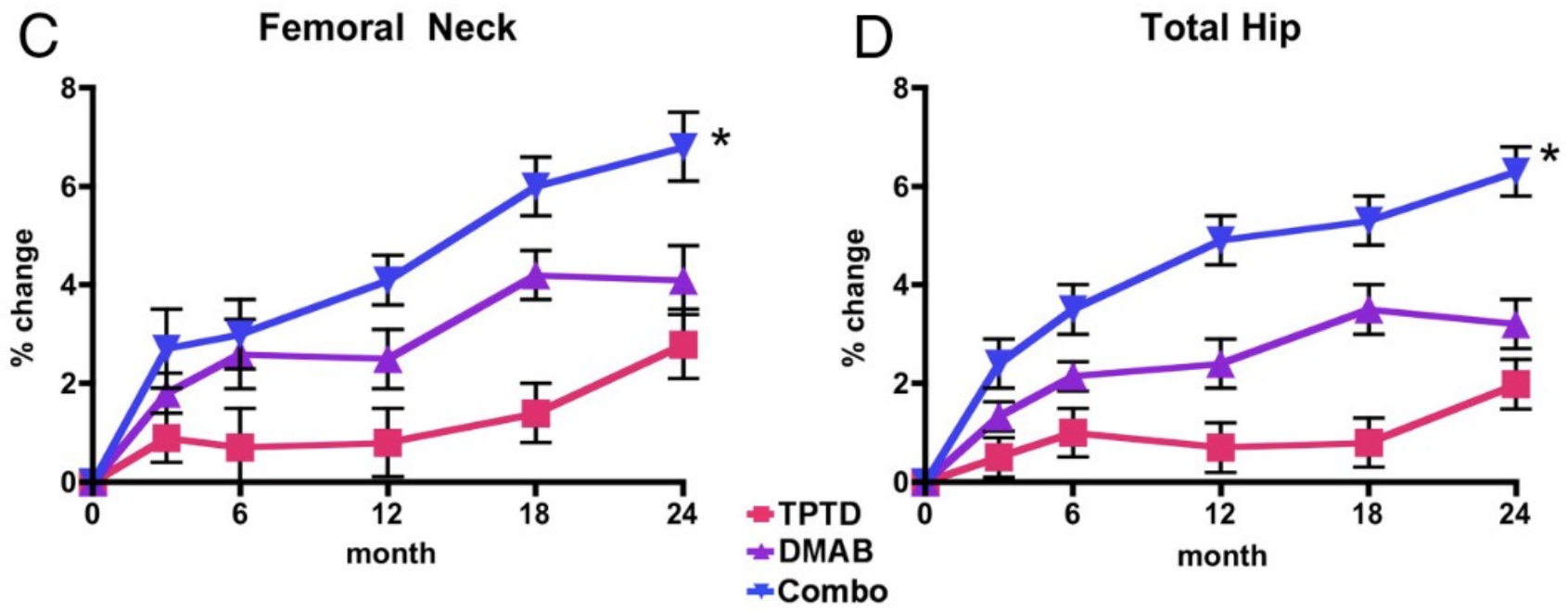
Years 1–2

Teriparatide	N=33
Denosumab	N=31
Combination	N=30

Tsai JN et al. Lancet 2013, Leder BZ et al. JCEM 2014

DENOSUMAB AND TERIPARATIDE ADMINISTRATION STUDY

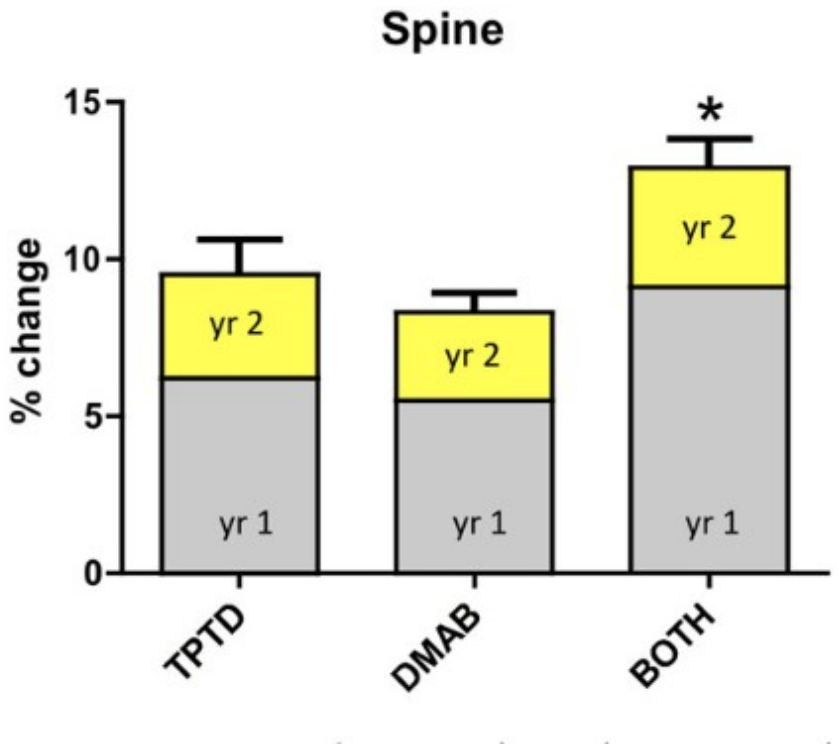
(DATA STUDY)

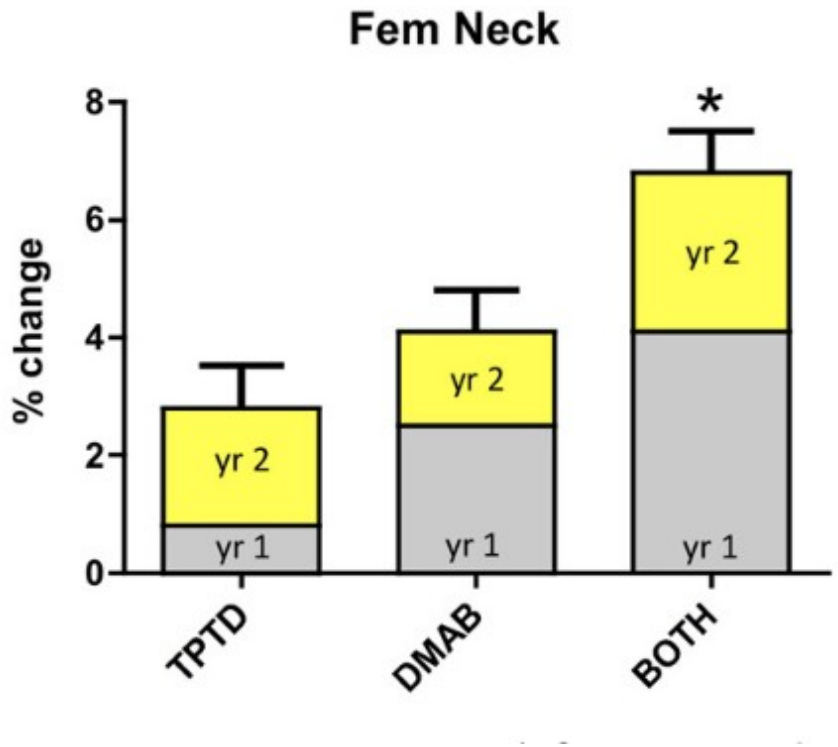


Tsai JN et al. Lancet 2013

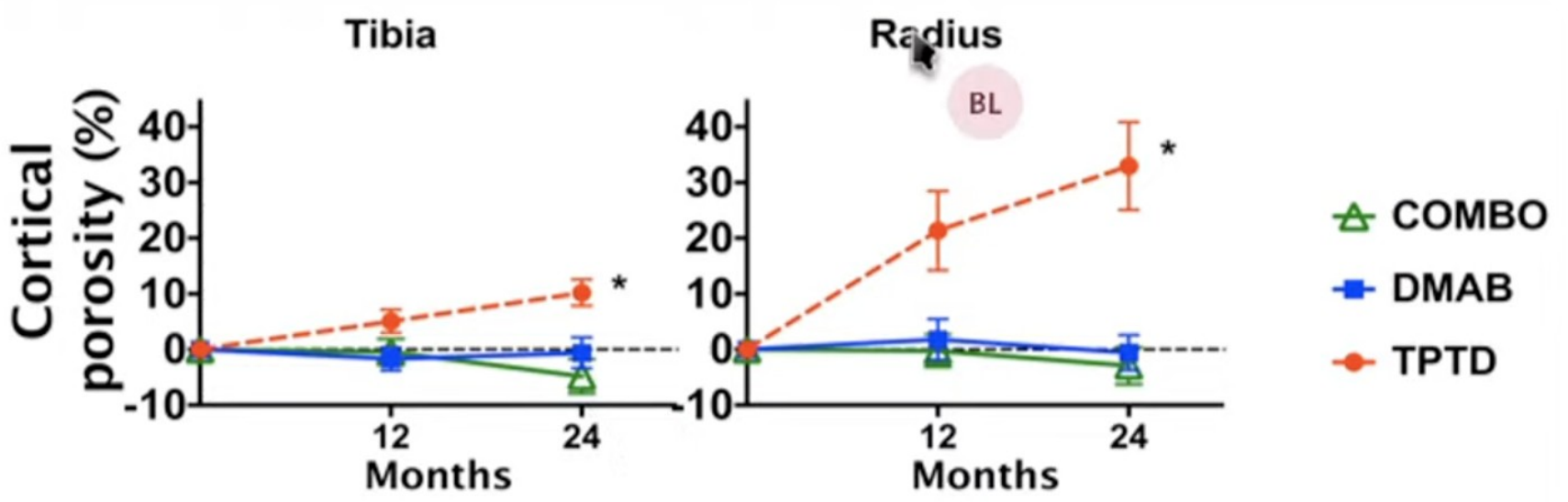
DENOSUMAB AND TERIPARATIDE ADMINISTRATION STUDY

(DATA STUDY)





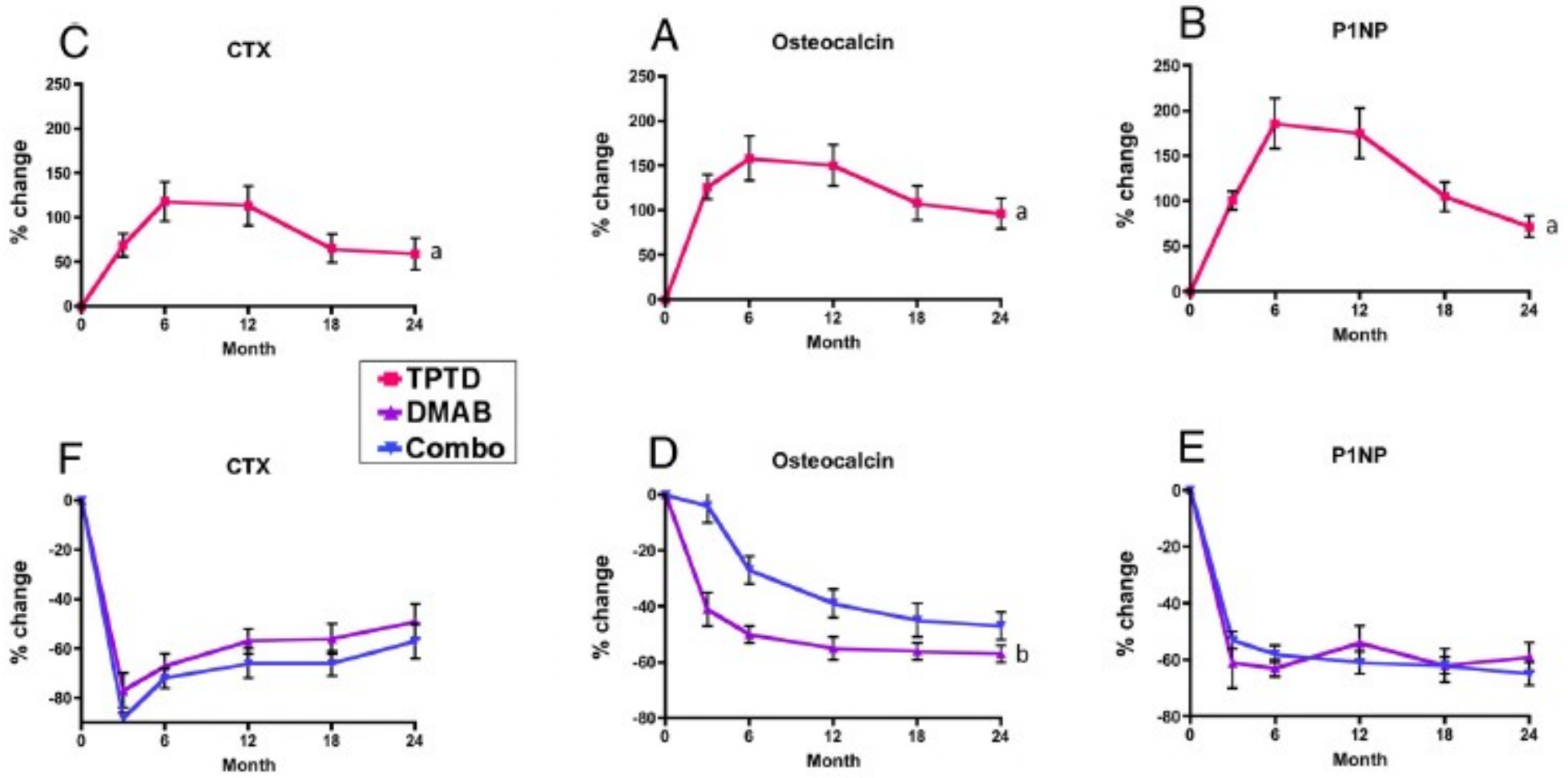
DENOSUMAB AND TERIPARATIDE ADMINISTRATION STUDY (DATA HR-pQCT STUDY)



* P-value <0.05 change from baseline

	Tibia P value	Radius P value
COMBO vs. TPTD	<0.001	<0.001
COMBO vs. DMAB	NS	NS
DMAB vs. TPTD	0.005	<0.001

DENOSUMAB AND TERIPARATIDE ADMINISTRATION STUDY (DATA STUDY)



Leder BZ et al. J Clin Endocrinol Metab 2014

Combination denosumab and high dose teriparatide for postmenopausal osteoporosis (DATA-HD): a randomised, controlled phase 4 trial

Joy N Tsai, Hang Lee, Natalie L David, Richard Eastell, Benjamin Z Leder

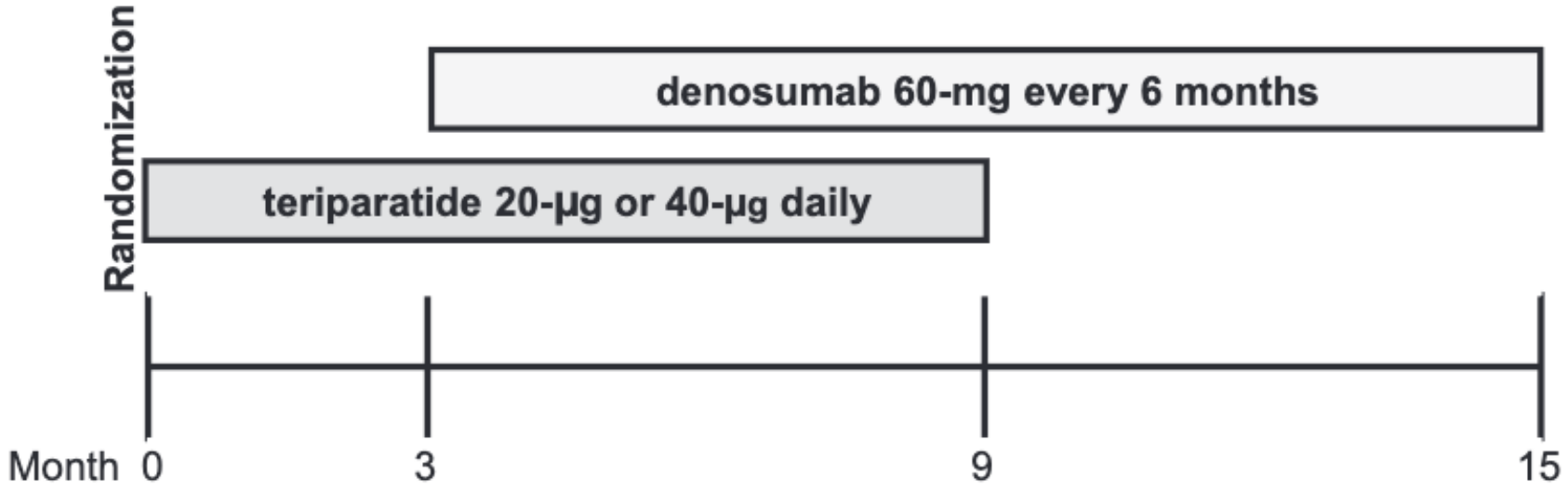
Hypothesis:

Combining denosumab with a larger anabolic stimulus would result in:

- an even greater separation between bone resorption and bone formation
- even larger and more rapid gains in bone mass than those observed in DATA

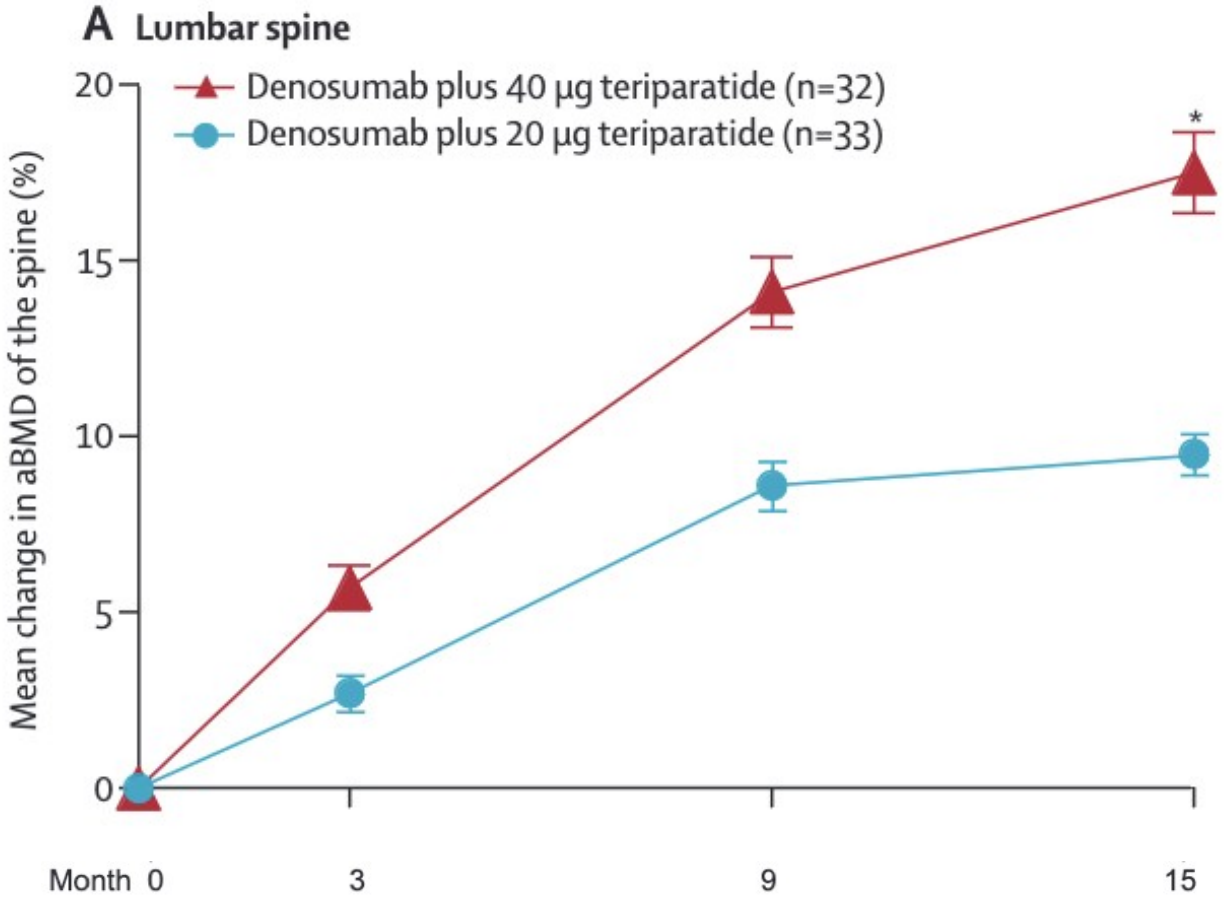
DATA HD

- 76 postmenopausal women aged 45+
- Entry criteria similar to DATA studies



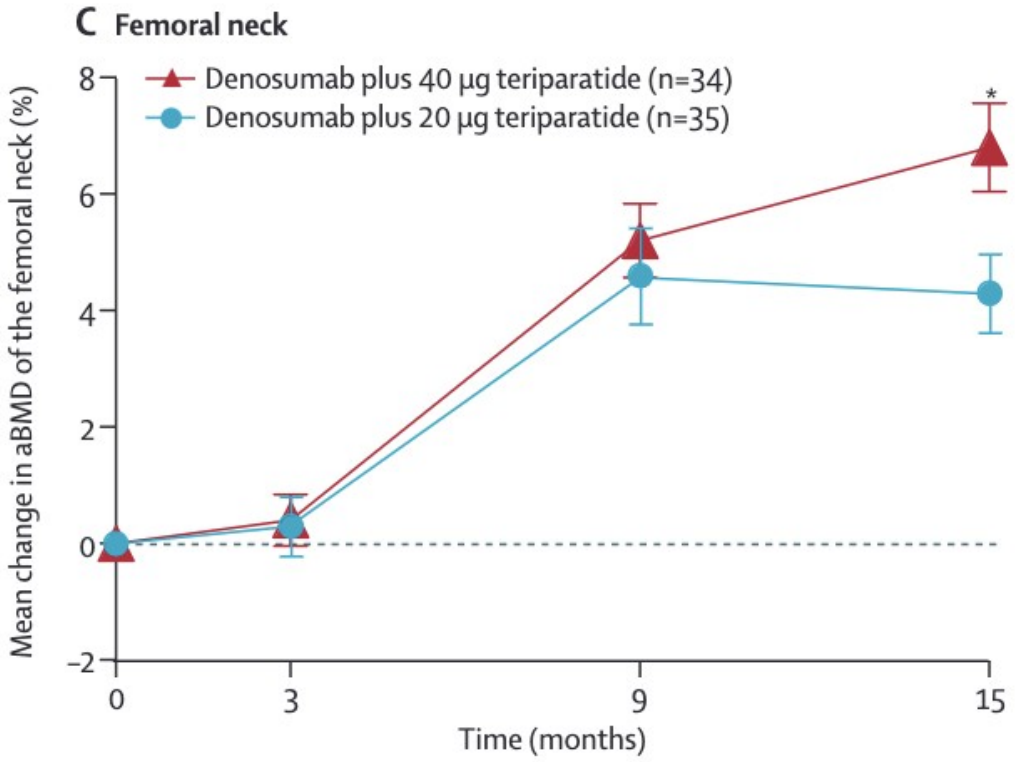
Tsai JN et al. Lancet Diab Endocrinol 2019

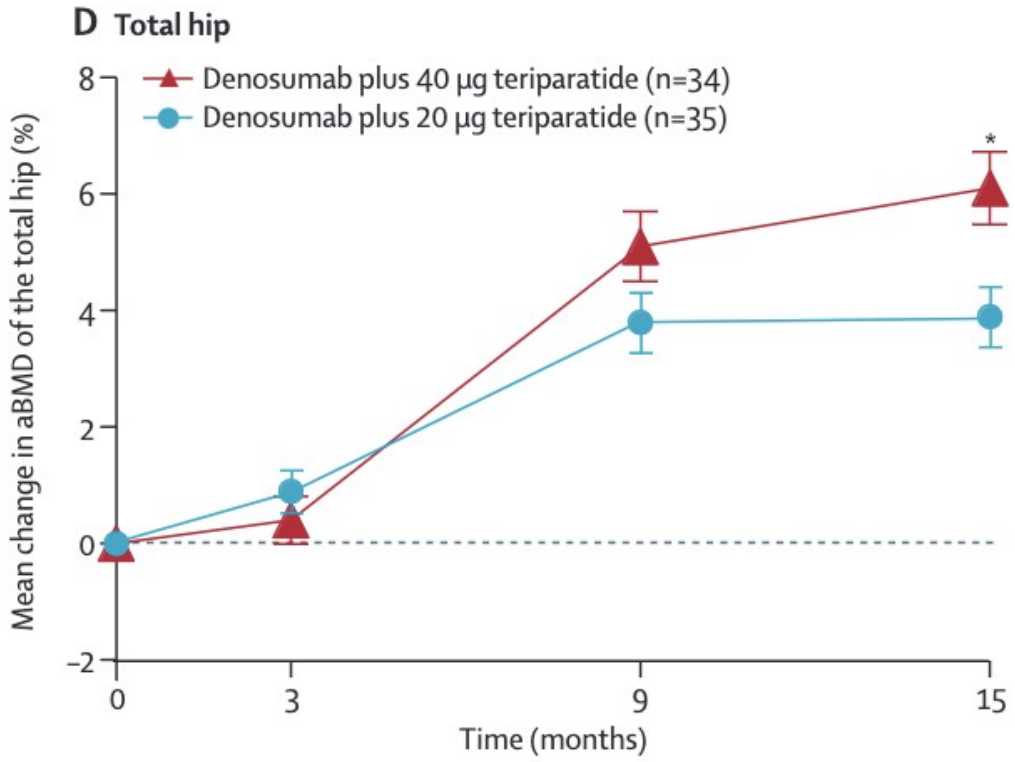
DATA HD: EFFECT ON LUMBAR SPINE BMD



Tsai JN et al. Lancet Diab Endocrinol 2019

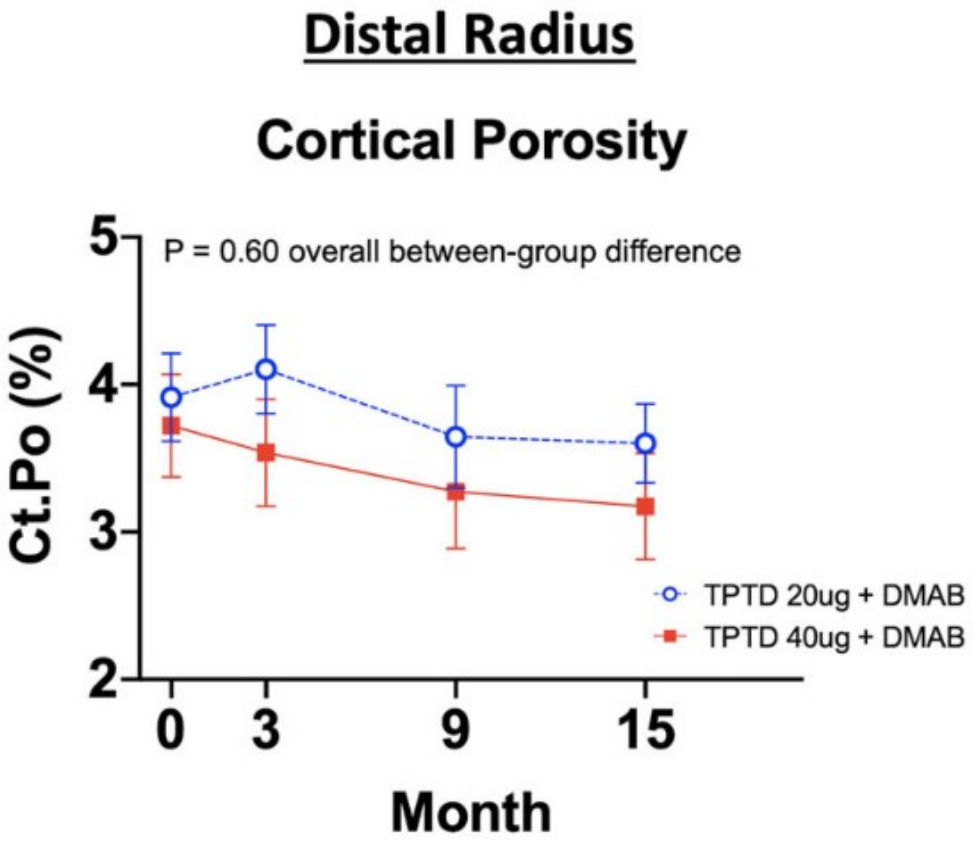
DATA HD: EFFECT ON HIP BMD

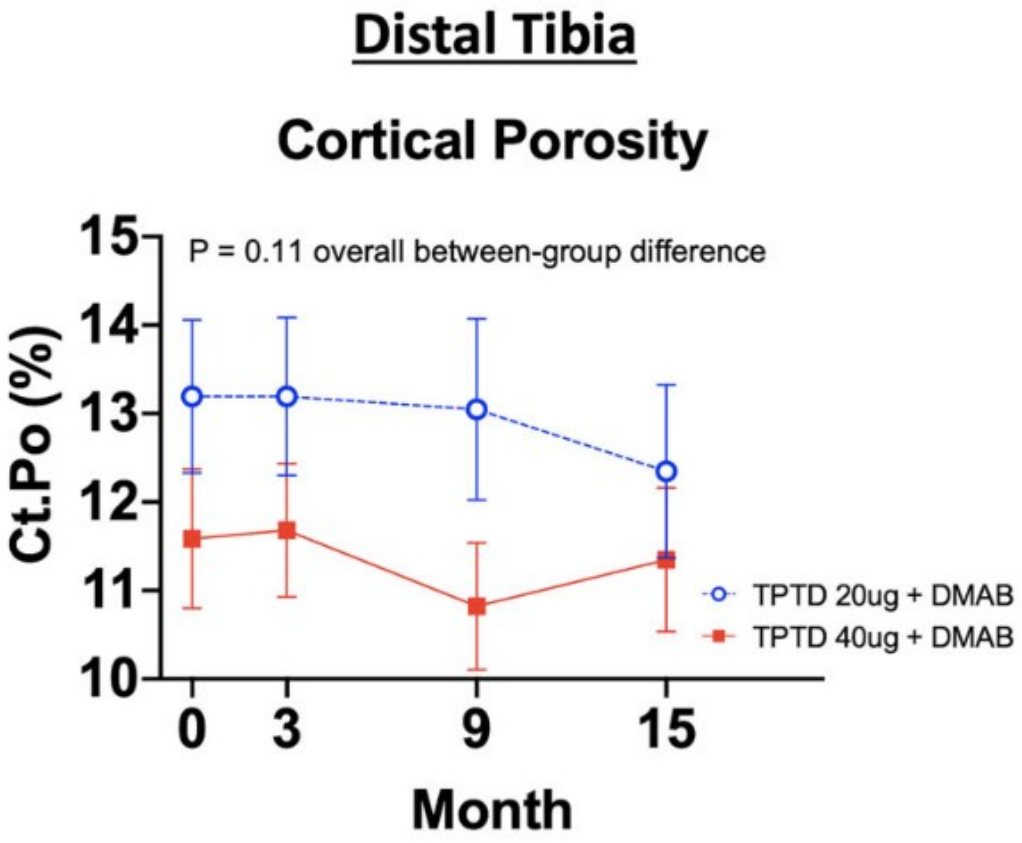




Tsai JN et al. Lancet Diab Endocrinol 2019

DATA-HD HR-pQCT

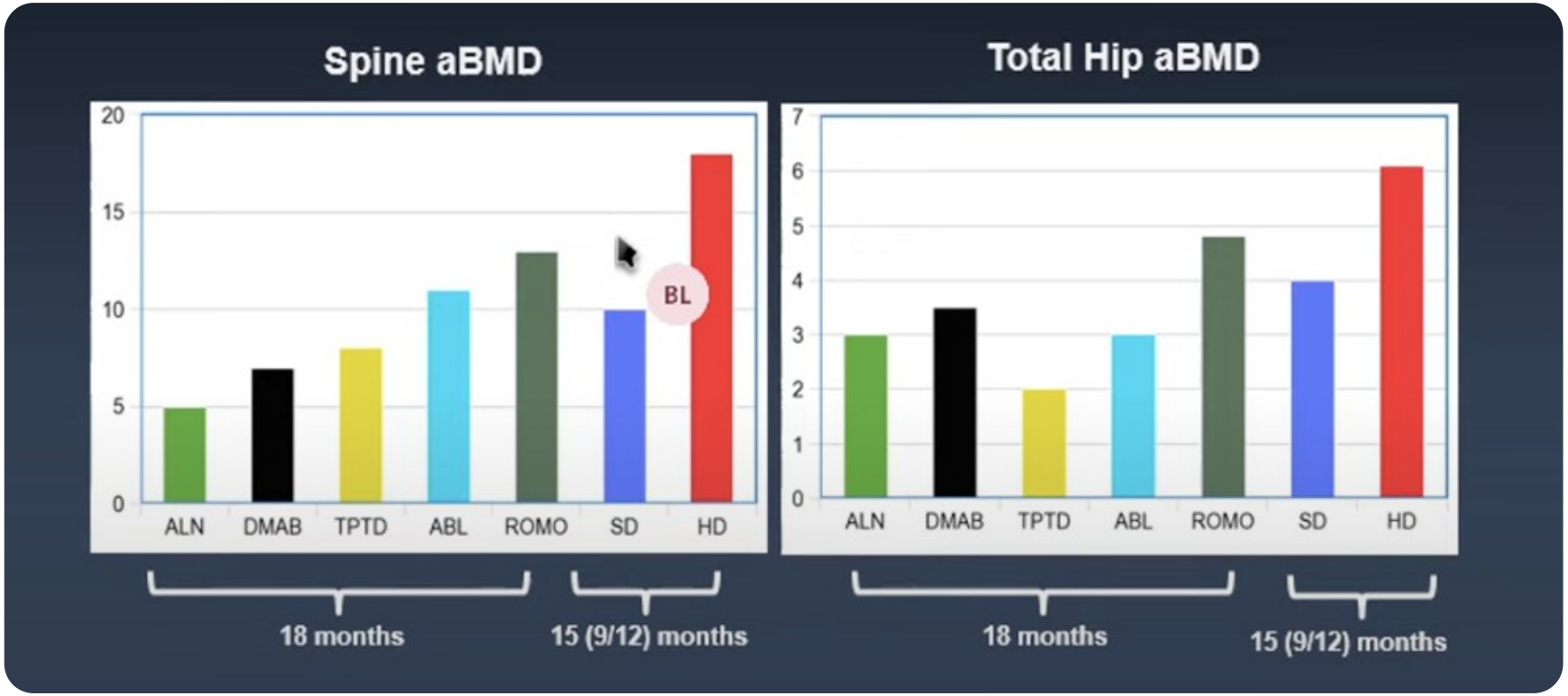




Ramchand SK et al. J Bone Miner Res 2021

Summary

9 months high-dose teriparatide, overlapping with 12 months of denosumab, increases hip and spine BMD more and more rapidly than SD combinations or any monotherapy.



ck et al. NEJM 2003, McClung et al. JCD 2013, Leder et al. JCEM 2014, McClung et al. JBMR 2018, Genant et al. JBMR

Summary

Medication	Time to 15% increase in spine BMD	Time to 6% increase in hip BMD
alendronate	Not achievable in 10 years	Not achievable in 10 years
zoledronic acid	Not achievable in 9 years	Not achievable in 9 years
denosumab	8 years	5 years
teriparatide	Not achievable in 2 years	Not achievable in 2 years
abaloparatide	Not achievable in 2 years	Not achievable in 2 years
DATA-HD regimen	12-15 months	12-15 months

ck et al. NEJM 2003, McClung et al. JCD 2013, Leder et al. JCEM 2014, McClung et al. JBMR 2018, Genant et al. JBMR

SEQUENTIAL THERAPIES: RATIONALE

• Given the limitations of current therapies, the sequential use of individual agents has become common in patients with established disease.

• Limitations of monotherapy:
  - Waning efficacy with prolonged use.
  - Greater risk of serious side effects with long term use.

• Designing the optimal drug sequence for individual patients requires understanding the long-term effects of each individual agent, the effects of discontinuing that agent, and the properties of specific drug transitions.

SEQUENTIAL OSTEOPOROSIS THERAPIES ANTIRESORPTIVE-TO-ANABOLIC: BP-TO-PTH

PERSPECTIVE

JBMR®

2021

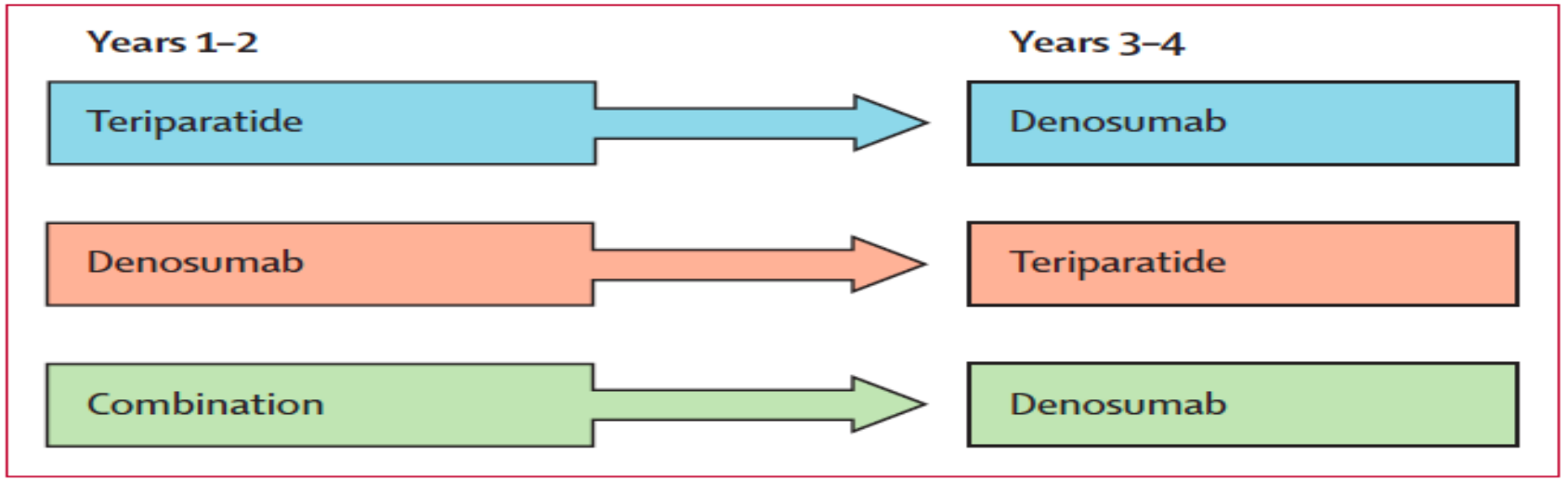
Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis

Felicia Cosman,[1,2] Jeri W Nieves,[1,3] and David W Dempster[1,4]

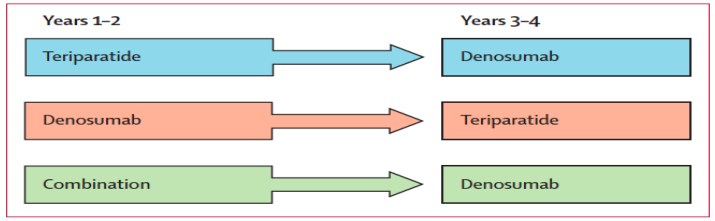
When switching from bisphosphonates to teriparatide, BMD increases are blunted compared to de novo teriparatide.

Study	Sample size	Treatment paradigm	% Change in total hip BMD during TPTD/PTH treatment			
			6 mo	12 mo	18 mo	24 mo
Ettinger et al.[27]	33	Alendronate (mean 29.3 mo) → TPTD (18 mo)	−1.8%	−1.0%	+0.3%	–
Boonen et al.[24]	107	Alendronate (median 29.2 mo) → TPTD (24 mo)	−1.2%	−0.6%	+0.6%	+2.1%
Boonen et al.[24]	59	Risedronate (median 23.4 mo) → TPTD (24 mo)	−1.6%	−0.4%	+0.9%	+2.9%
Miller et al.[30]	158	Risedronate (mean 37.2 mo) → TPTD (12 mo)	−1.2%	−0.3%	–	–
Miller et al.[30]	166	Alendronate (mean 38.0 mo) → TPTD (12 mo)	−1.9%	−1.7%	–	–
Cosman et al.[26]	50	Alendronate (mean 45.7 mo) → TPTD (18 mo)	−0.8%	–	+0.9%	–

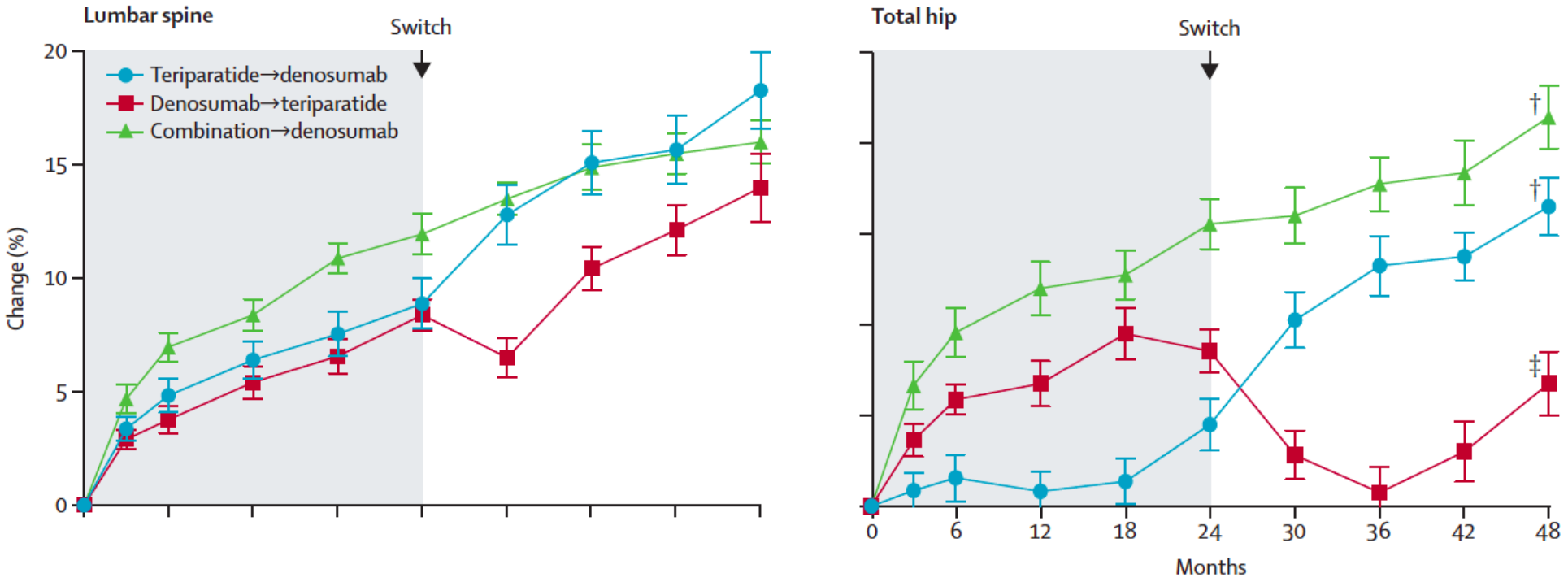
SEQUENTIAL OSTEOPOROSIS THERAPIES ANTIRESORPTIVE-TO-ANABOLIC: DENOSUMAB-TO-PTH



DATA-SWITCH STUDY

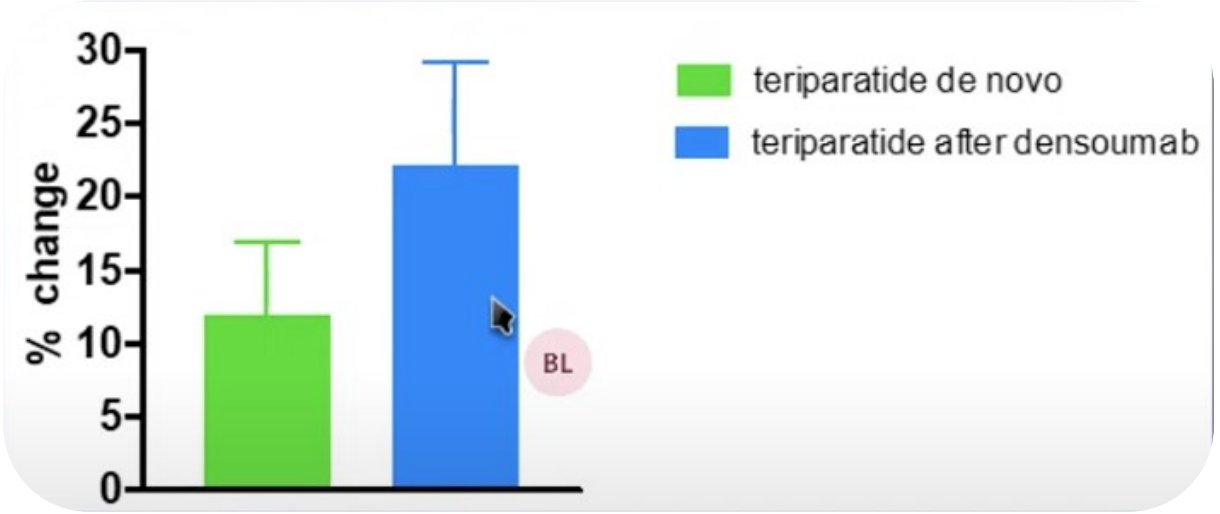


Denosumab increases BMD after stopping teriparatide

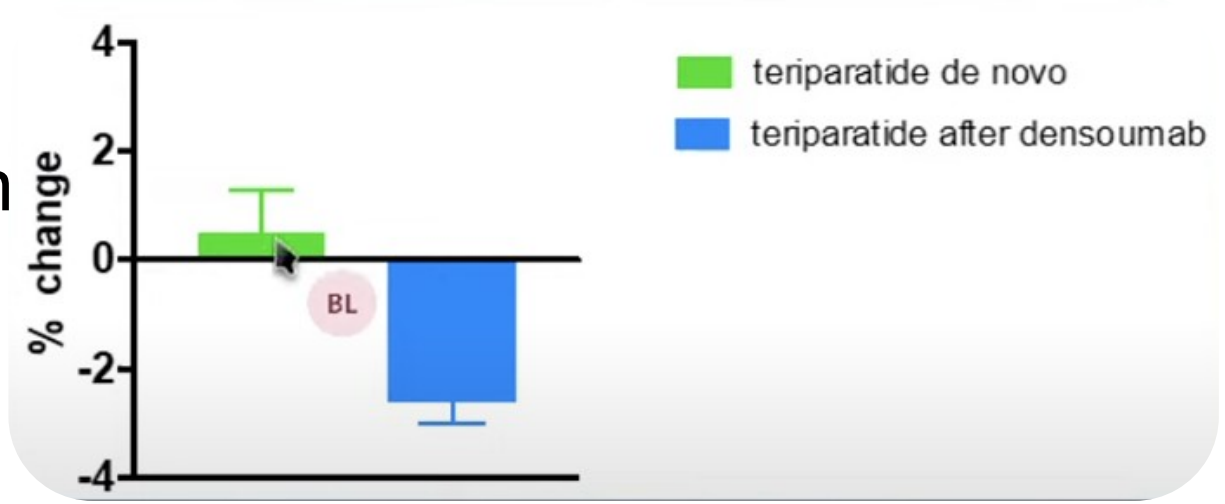


DATA-SWITCH STUDY HR-PQCT

Cortical porosity



Estimated strength by finite element analysis (FEA)



Tsai JN et al. J Bone Miner Res 2017

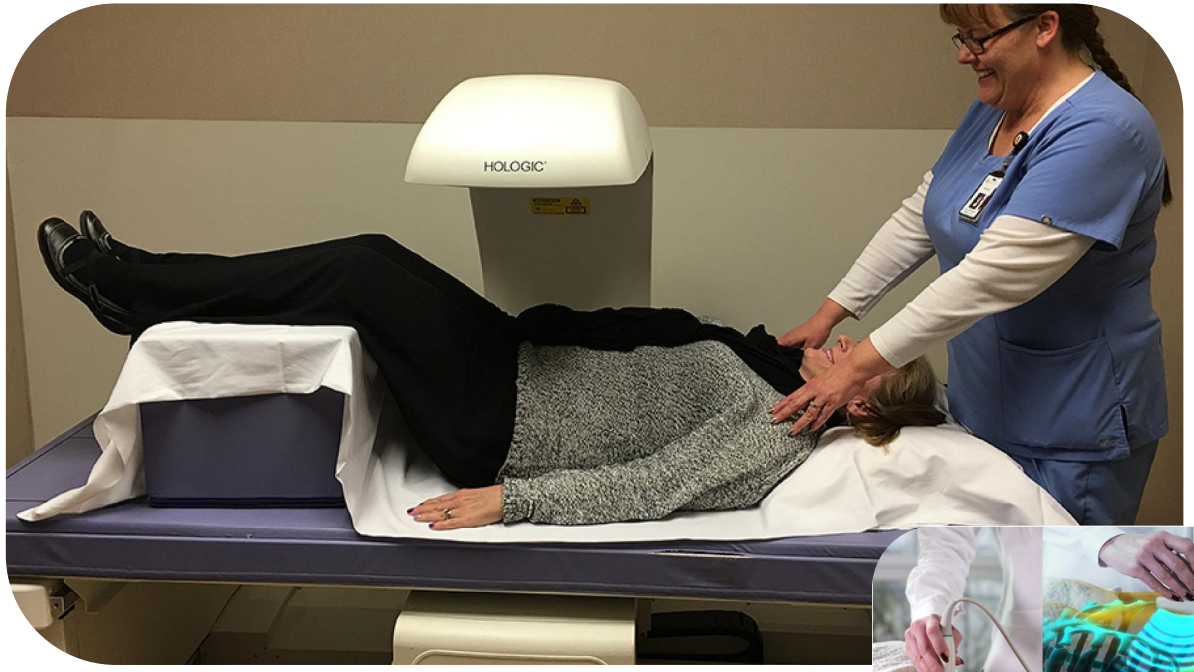
CONCLUSIONS I

- Teriparatide is a great anabolic option for fragile bones
- Teriparatide reduces the risk of fragility fractures at all sites (both trabecular and cortical)
- In FLS:
  - teriparatide is an optimal choice for drug-naïve patients (after a hip fracture) at very high/imminent fracture risk, obeying to the *anabolic-to-antiresorptive best practice* principle (not so quick effect, but still within 18 months)
  - in non-naïve patients pay attention to the antiresorptive-to-anabolic transition (warranted by reimbursement policies) avoiding denosumab-to-teriparatide shift (still bisphosphonate-to-teriparatide shift is acceptable, even if resulting in blunted response to teriparatide compared to de novo anabolic therapy)
- Combining teriparatide with other antiresorptive agents could increase and speed up its

CONCLUSIONS II

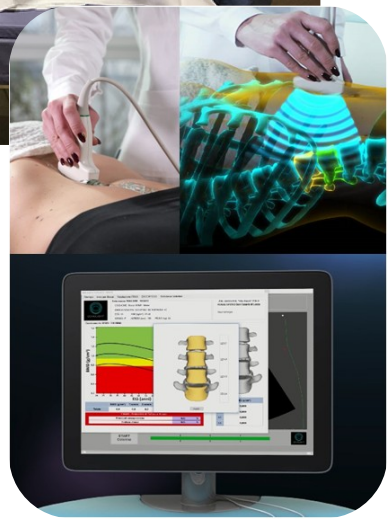
- Teriparatide is effective for fracture healing:
  - Do not stop teriparatide if incident/recurrent fracture
  - Good choice for atypical fractures
- Combining teriparatide with other antiresorptive agents could increase its «anabolic» properties (especially at cortical sites)

KEY MESSAGE: LOOK FOR SEVERE OSTEOPOROSIS AFTER HIP FRACTURE FOR ANABOLIC PRESCRIPTION & REIMBURSABILITY!

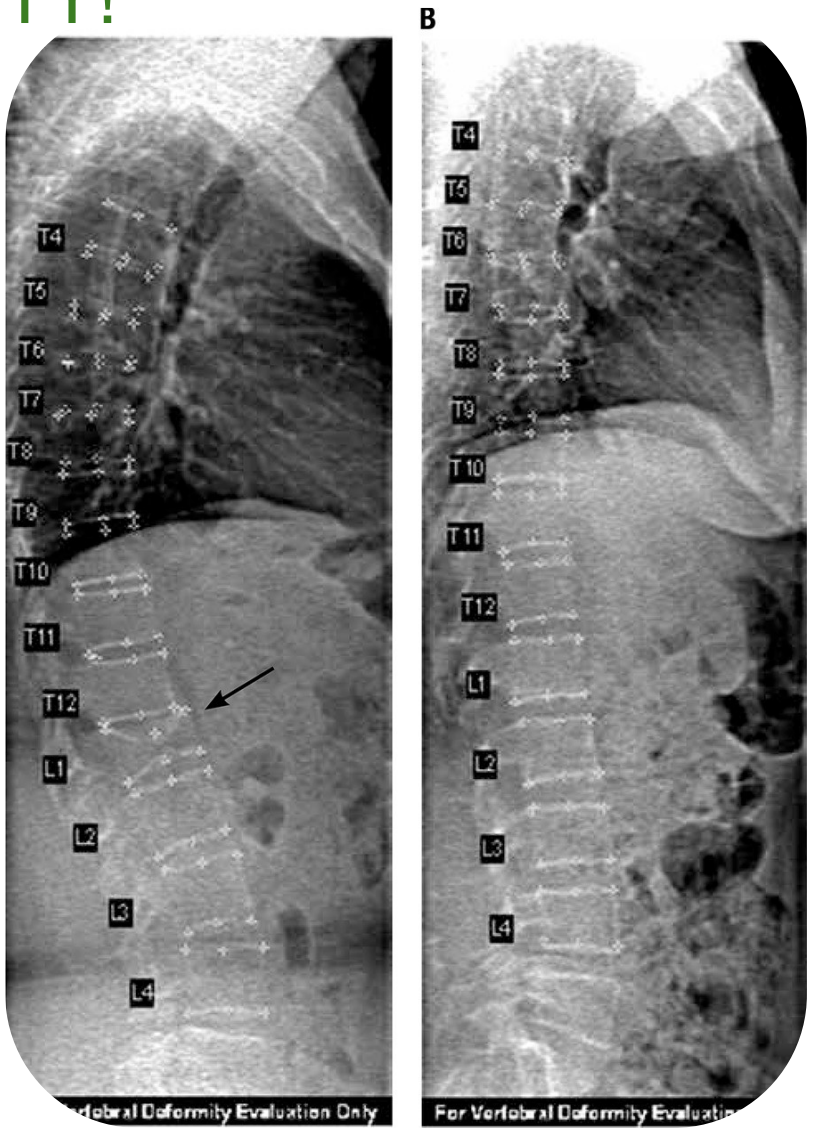


DXA

(T-score < -4)



(REMS)



Managing osteoporosis drugs

Eugène Isabey, 1841, Le cabinet de l'alchimiste, Lille

THANKS FOR YOUR ATTENTION AND THANKS TO FFN!