MALATTIE MUSCOLO-SCHELETRICHE

TERAPIA INTEGRATA, PERSONALIZZATA E QUALITÀ DI VITA

ROMA 6 - 7 ottobre 2023

IL CORRETTO UTILIZZO DEI FARMACI ANABOLICI

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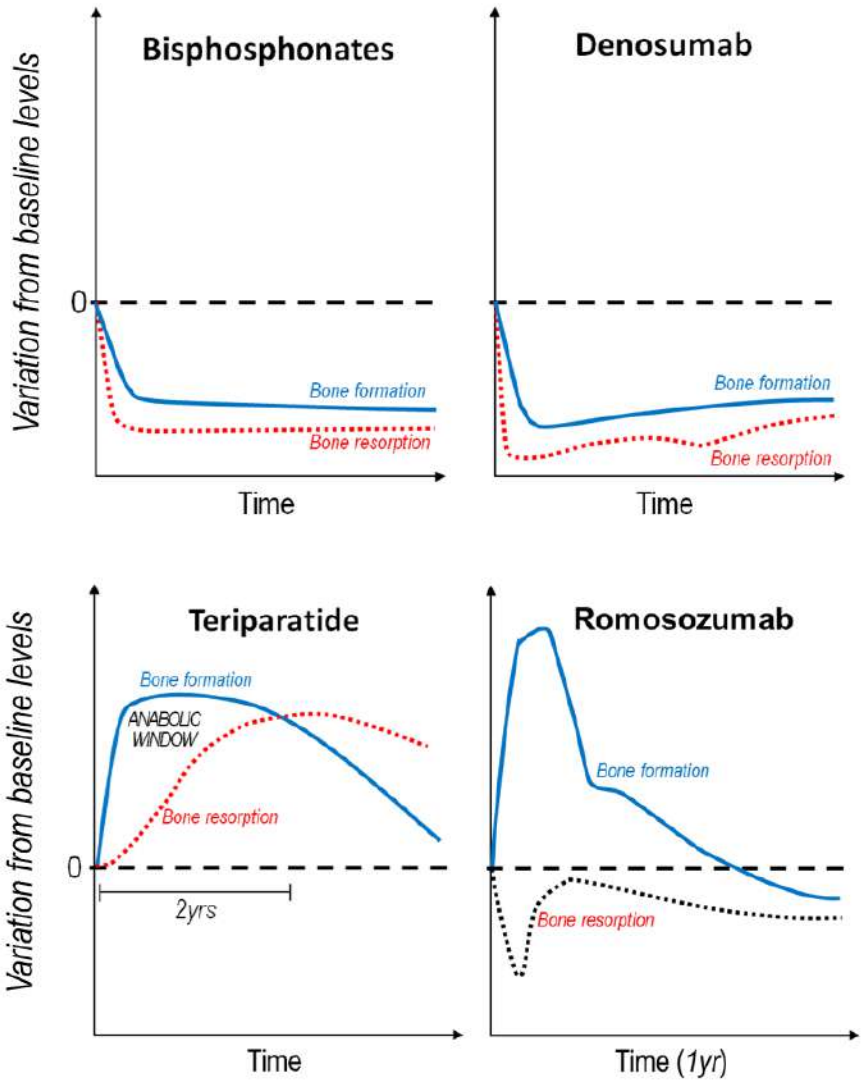
Established Treatments for Osteoporosis

Mechanism of Action	Compound(s)	Fracture risk reduction
Antiresorptive Drugs	**Bisphosphonates**	
	Alendronate *(oral)*	V, H, NV
	Risedronate *(oral)*	V, H, NV
	Ibandronate *(oral, i.v.)*	V, NV
	Zoledronate *(i.v.)*	V, H, NV
	Denosumab *(s.c.)*	V, H, NV
	ERT/HRT *(variable dosages)*	V, H, NV
	SERMs	
	Raloxifene *(oral)*	V
	Lasofoxifene *(oral)*	V, NV
	Bazedoxifene *(oral)*	V, NV
	Bazedoxifene+c.e. *(oral)*	*(not assessed)*
Anabolic Drugs	**Teriparatide** *(s.c.)*	V, H, NV
	[Abaloparatide *(s.c.)***]***	V, NV
Dual Action	**Romosozumab** *(s.c.)*	V, NV

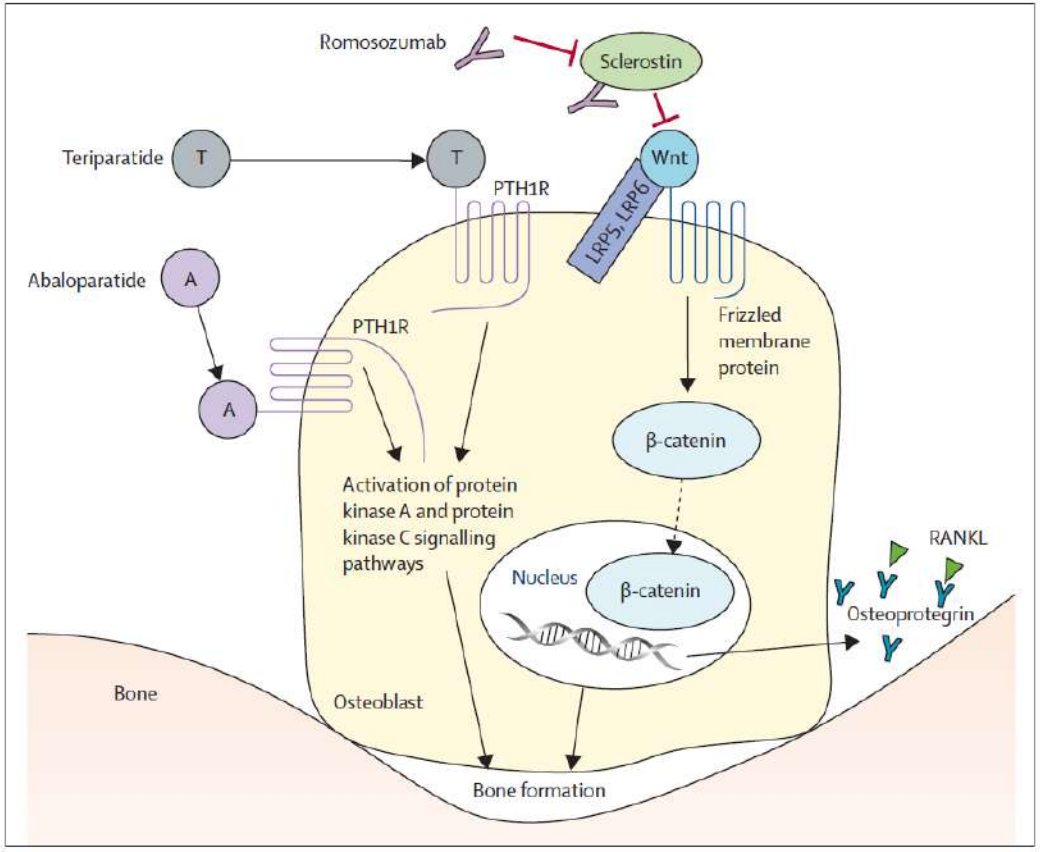


- The **ideal therapy for osteoporosis** would normalize bone strength by restoring the deficit in bone mass and by reconstructing the disordered skeletal architecture. Rebuilding bone structure requires the activation of osteoblastic bone formation

Adapted from Gennari L, et al. Expert Opin Pharmacother 2016

Osteoanabolic Agents

- **Teriparatide** *(PTH 1-34 analogue)* **2002** *(20 mcg/d) << biosimilar preparations*
- **Abaloparatide** *(modified PTHrP analogue)* **2017** *(80 mcg/d)*
- **Romosozumab** *(humanazed monoclonal antibody vs sclerostin)* **2019** *(210 mg/w)*



Reid IR, Billington EO. Lancet 2022; 399: 1080–92

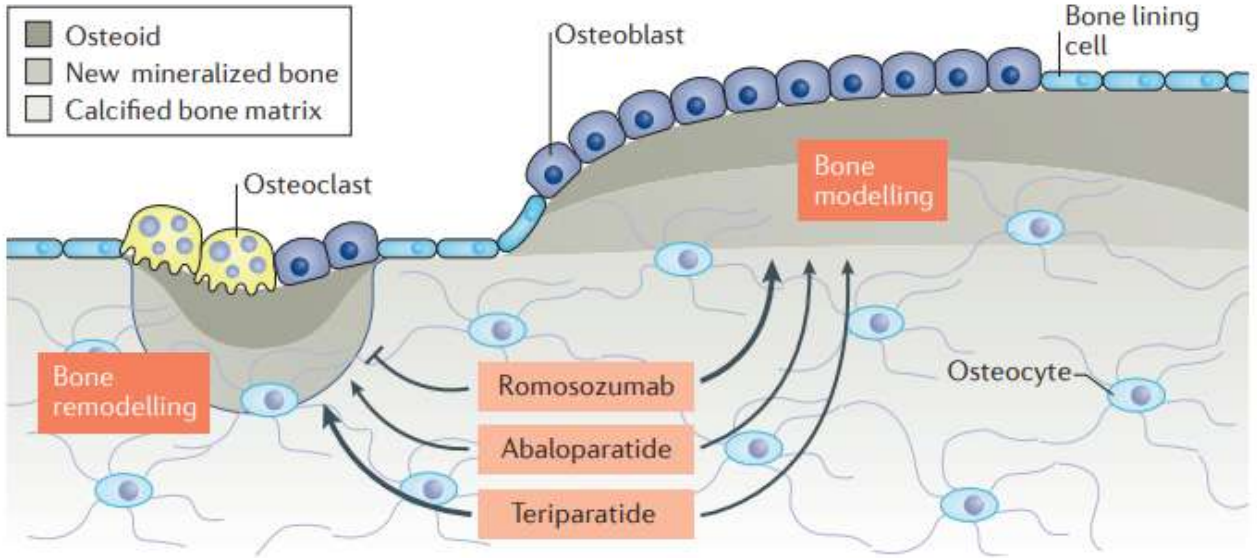
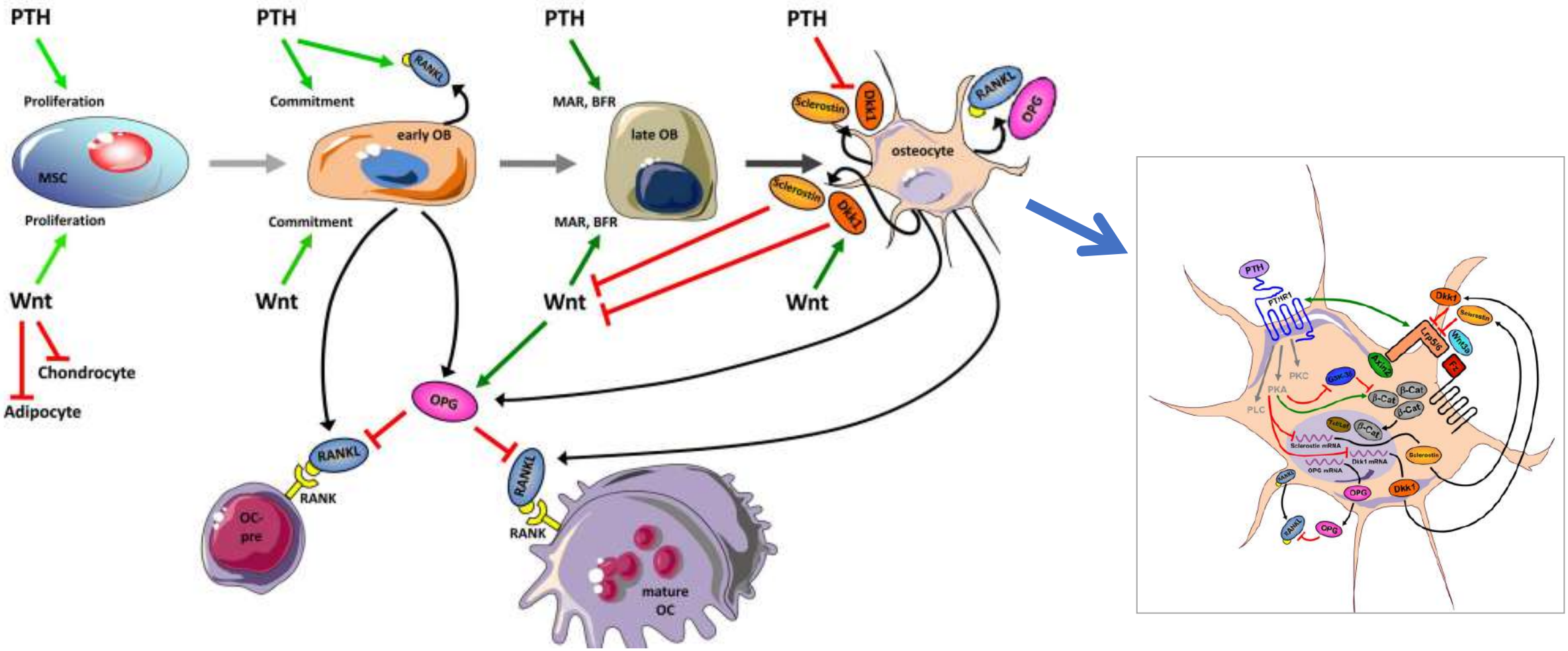


Fig. 1 | **Differential effects of bone-forming agents on bone surfaces.** Teriparatide and abaloparatide act primarily by activating bone formation coupled to bone resorption at remodelling surfaces, and to a lesser extent by activating quiescent bone-forming cells at modelling surfaces. Romosozumab acts primarily by activating modelling-based bone formation while inhibiting bone resorption at remodelling surfaces.

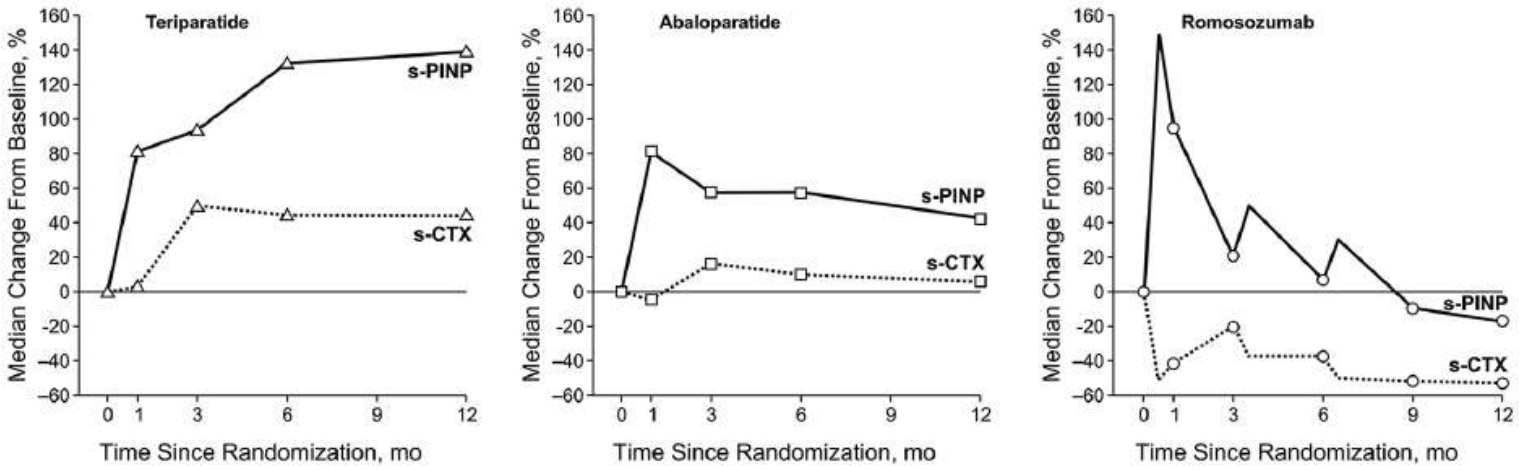
Ferrari S. Nature Reviews Rheumatology volume 14, page128(2018)

Effects of the two main anabolic pathways



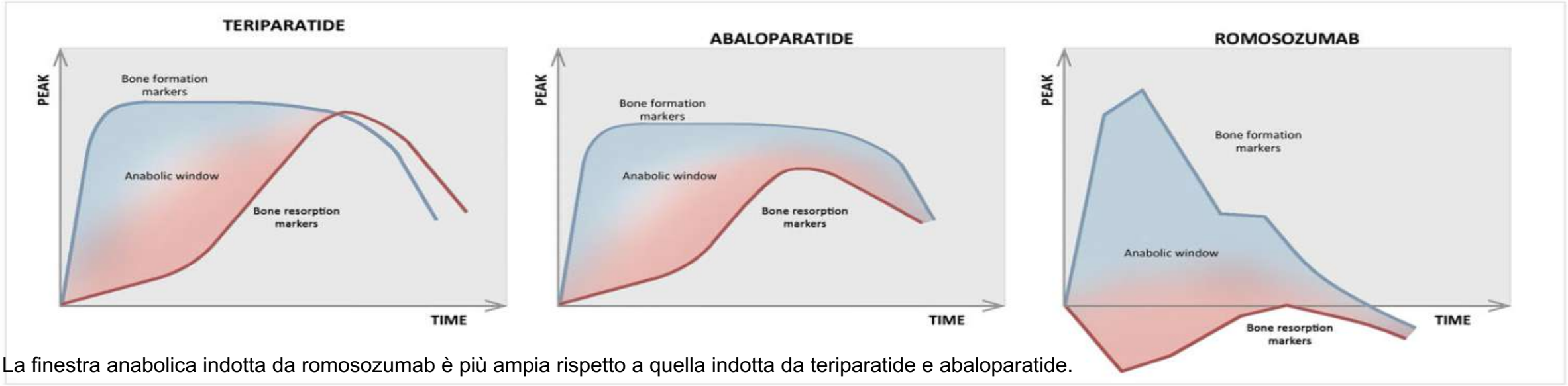
Baron R, 2012

Teriparatide, Abaloparatide e Romosozumab



Minisola et al 2019

La **finestra anabolica** rappresenta l'idea concettuale del **periodo di tempo in cui questi farmaci esercitano il loro massimo effetto osteoanabolico.**



La finestra anabolica indotta da romosozumab è più ampia rispetto a quella indotta da teriparatide e abaloparatide.

Tabacco G, Br J Clin Pharmacol (2019) 85 1084–1094

How and When to Use Osteoanabolic Therapy: Agenda

- Safety-Efficacy Profile
  - *Placebo-controlled studies*
  - *Comparative studies*

- Who are the **best candidates** for osteoanabolic agents?

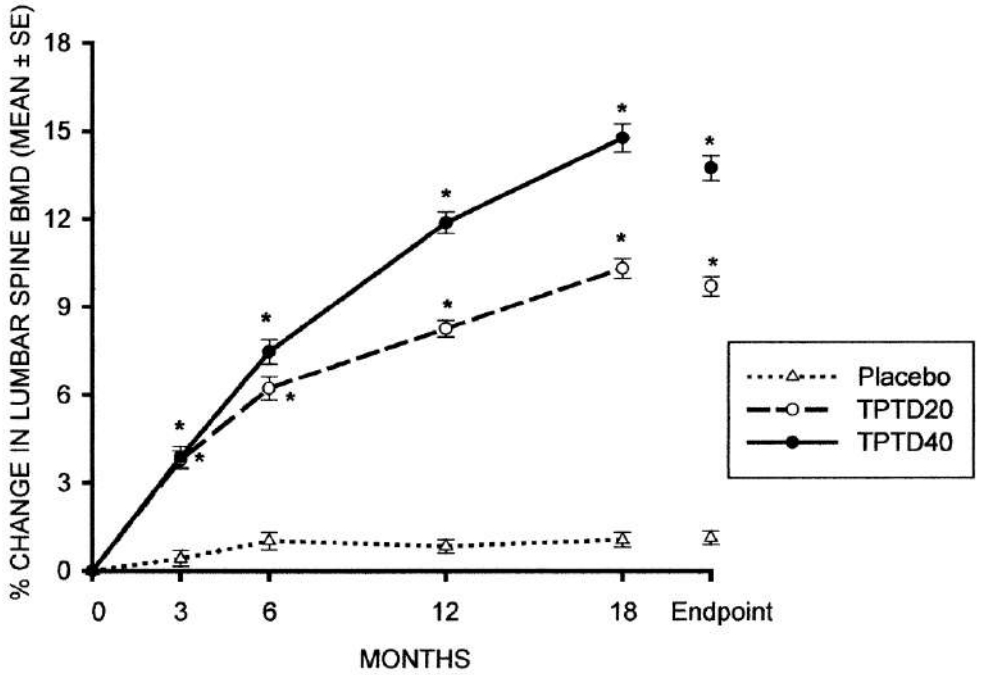
- What should be done at the **end of a treatment course** with osteoanabolic agents?

- Should osteoanabolic agents be used **before** or **after antiresorptive drugs**?

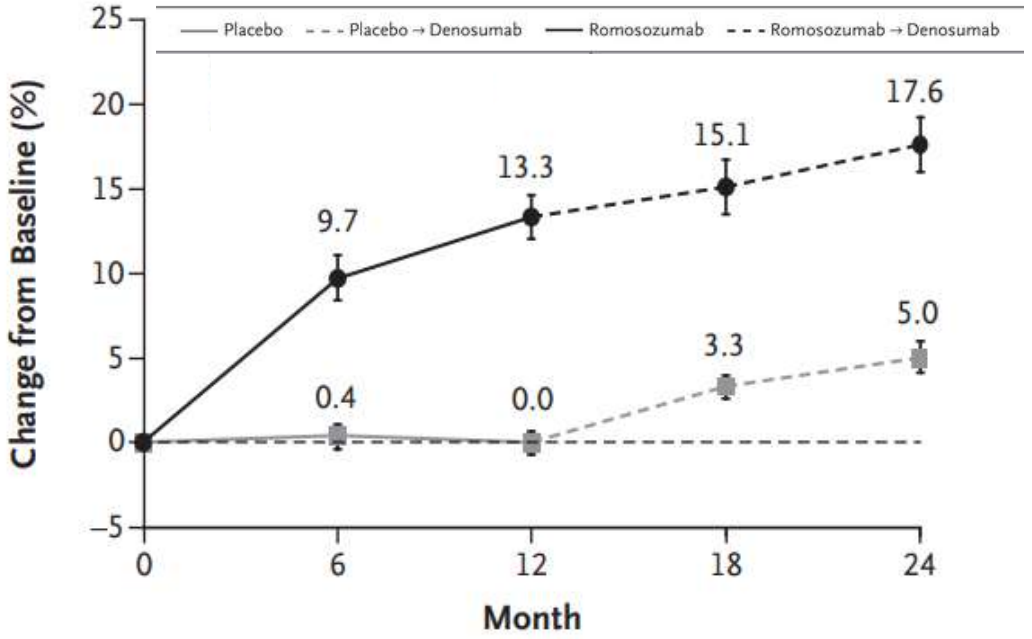
BMD changes with osteoanabolic drugs compared to placebo

Osteoanabolic drug	Study name and reference	Treatment interval	BMD Mean % difference from placebo		
			Lumbar spine	Total hip	Femoral neck
Teriparatide	PFT [22]	~18 months	8.6%	3.6%	3.5%
Abaloparatide	ACTIVE [18]	18 months	10.4%	4.3%	4.0%
Romosozumab	FRAME [23]	12 months	13.3%	6.9%	5.9%

McClung MR, et al. Postgrad Med 2022;30:1-11.

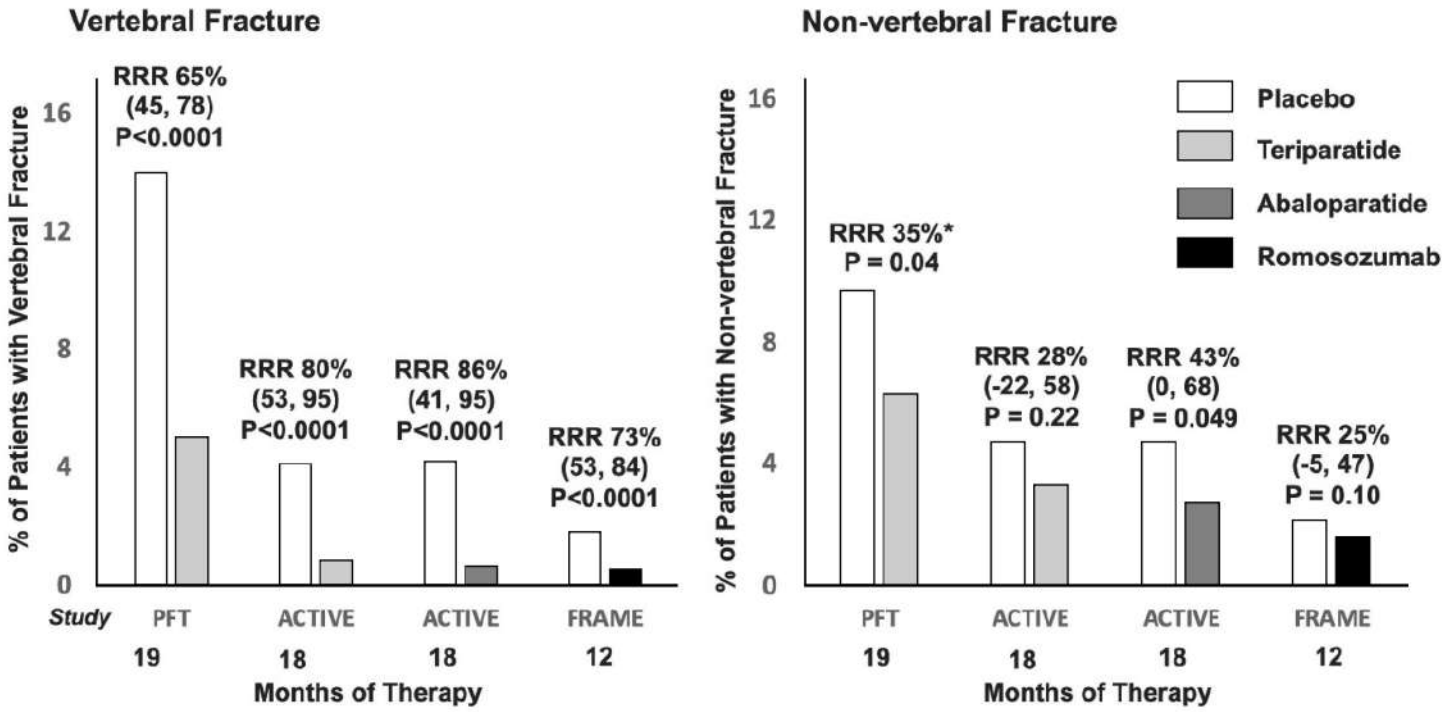


Neer RM, et al. N Engl J Med 344:1434–1441
Marcus R et al. J Bone Miner Res 2003;18:18–23



Cosman F et al. N Engl J Med 2016;375(16):1532-1543
doi: 10.1056/NEJMoa1607948

Vertebral and non-vertebral fracture incidence in separate pivotal trials with osteoanabolic agents in postmenopausal osteoporosis



NOTE: Because of different patient populations and the different length of follow-up among the studies presented, comparison between studies is not appropriate. * Confidence interval not provided. RRR = relative risk reduction (95% confidence interval).

PFT = Pivotal fracture trial *[Neer RM, et al. N Engl J Med 2001;344(19):1434–1441]*
ACTIVE = Abaloparatide comparator trial in vertebral endpoints trial *[Miller PD, et al. JAMA 2016;316(7):722–733]*
FRAME = Fracture study in postmenopausal women with osteoporosis study *[Cosman F, et al. N Engl J Med 2016;375(16):1532–1543]*

McClung MR, et al. The role of osteoanabolic agents in the management of patients with osteoporosis. Postgrad Med 2022;30:1-11. doi:10.1080/00325481.2022.2069582

Fracture risk reduction with osteoanabolic agents vs anti-remodeling drugs

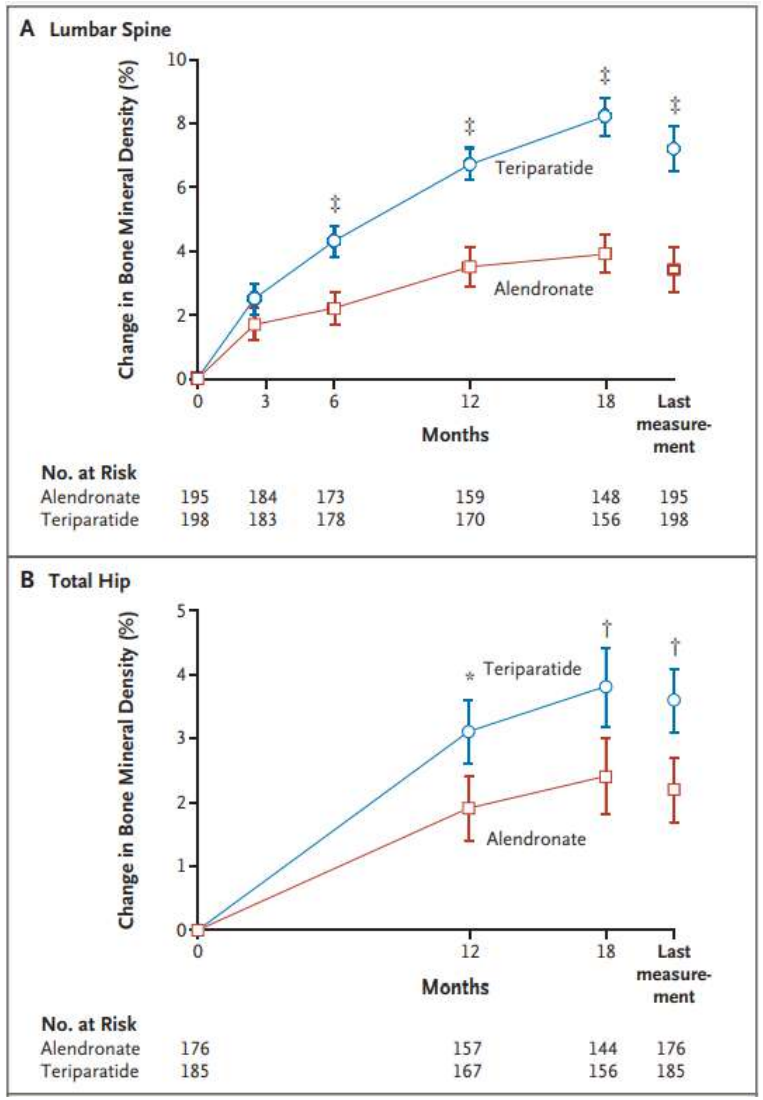
Drug	Teriparatide			Teriparatide			Teriparatide			Romosozumab		
Study (reference)	VERO [32]			Body [33]			Hadji [34]			ARCH [29]		
Treatment interval (months)	24			14			18			12		
	RIS	TPTD	RR (95% CI) P value	ALN	TPTD	RR (95% CI) P value	RIS	TPTD	RR (95% CI) P value	ALN	ROMO	RR (95% CI) P value
Vertebral fracture	12%	5.4%	56% (32, 71%) P = <0.0001	Not provided			9.4%	4.4%	53%* P = 0.01	6.3%	4.0%	37% (15–53%) P = 0.03
Non-vertebral fracture	6.1%	4.0%	34% (–10 to 61%) P = 0.10	13.7%	4.1%	70%* P = 0.042	8.3%	7.8%	6%* P = 0.89	4.6%	3.4%	26% (–1 to 46%) P = 0.057

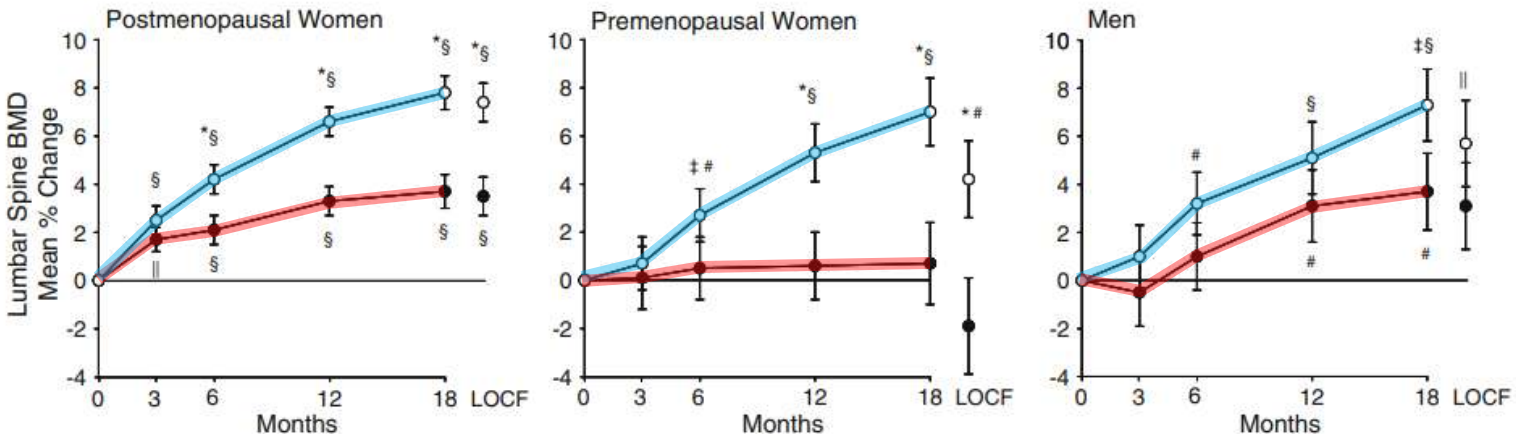
* Confidence interval not provided.

VERO = Vertebral Fracture Treatment Comparisons in Osteoporotic Women; ARCH = Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; RIS = risedronate; TPTD = teriparatide; ALN = alendronate; ROMO = romosozumab; RR = risk reduction; CI = confidence limits.

McClung MR, et al. The role of osteoanabolic agents in the management of patients with osteoporosis. Postgrad Med 2022;30:1-11. doi:10.1080/00325481.2022.2069582

Teriparatide or alendronate in glucocorticoid-induced osteoporosis





Variable	Alendronate (N=214)	Teriparatide (N=214)	P Value
Fractures			
Vertebral — no./total no. (%)*			
Radiographic evidence	10/165 (6.1)	1/171 (0.6)	0.004
Clinical evidence†	3/165 (1.8)	0	0.07
Nonvertebral — no. (%)‡			
Any	8 (3.7)	12 (5.6)	0.36
Nonvertebral fragility	3 (1.4)	5 (2.3)	0.46

Saag KG, et al. N Engl J Med 2007;357:2028-39. doi: 10.1056/NEJMoa071408

Langhdal, et al. Osteoporos Int 2009;20:2095–2104. doi: 10.1007/s00198-009-0917-y

➢Thus, osteoanabolic agents **could be considered as a first line option**, at least in those patients receiving high dosages of GCs over a long term

Indications and Safety Profile of Osteoanabolic Drugs

	Dose	Registered indications	Administration considerations	Adverse effects	Treatment duration and follow-up
(Continued from previous page)					
Anabolic agents					
Parathyroid hormone analogue					
Teriparatide	20 µg/day subcutaneously for 18–24 months	Treatment of postmenopausal, male, and glucocorticoid osteoporosis, and patients at high fracture risk	NA	Mild hypercalcemia in 6–11%, might require dose adjustment; FDA recommends considering >2 years of cumulative use during a patient's lifetime only if fracture risk remains high	Usually treat for up to 2 years and follow with anti-resorptive agent
PTHrP analogue					
Abaloparatide	80 µg/day subcutaneously for 18–24 months	Treatment of postmenopausal osteoporosis in patients at high fracture risk	Inject into the periumbilical region; administer initial doses where the patient can lie down if orthostatic hypotension occurs	Nausea, dizziness, and headache in up to 10% of patients; palpitations in 5%; mild hypercalcaemia in 3%; FDA recommends that cumulative use during a patient's lifetime is not >2 years	Treat for up to 2 years and follow with anti-resorptive agent
Monoclonal antibody against sclerostin					
Romosozumab*	210 mg/month subcutaneously for 12 months	Treatment of postmenopausal osteoporosis in patients at high fracture risk or those who have failed or are intolerant to other available osteoporosis therapy	Dose provided as two 105 mg syringes; should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year	Possible increased risk of serious cardiovascular events compared with alendronate treatment; cases of AFF and ONJ reported in pivotal registration trial; real-world incidence unknown	Treat for 12 months and follow with anti-resorptive agent

eGFR=estimated glomerular filtration rate. AFF=atypical femur fracture. ONJ=osteonecrosis of the jaw. FDA=US Food and Drug Administration. PTHrP=parathyroid hormone-related peptide. *Has both anabolic and antiresorptive effects.

Reid IR, Billington EO. Lancet 2022; 399: 1080–92

- Regulatory approvals of both **Teriparatide** and **Abaloparatide** originally included boxed warnings about the possible risk of osteosarcoma.
- **Romosozumab** carries a box warning stating that it is not recommended for patients at high risk for cardiovascular events and should not be given to anyone with a myocardial infarction or stroke within the last year

How and When to Use Osteoanabolic Therapy

- Safety-Efficacy Profile
  - *Placebo-controlled studies*
  - *Comparative studies*

- Who are the **best candidates for osteoanabolic agents**?

- What should be done at the **end of a treatment course** with osteoanabolic agents?

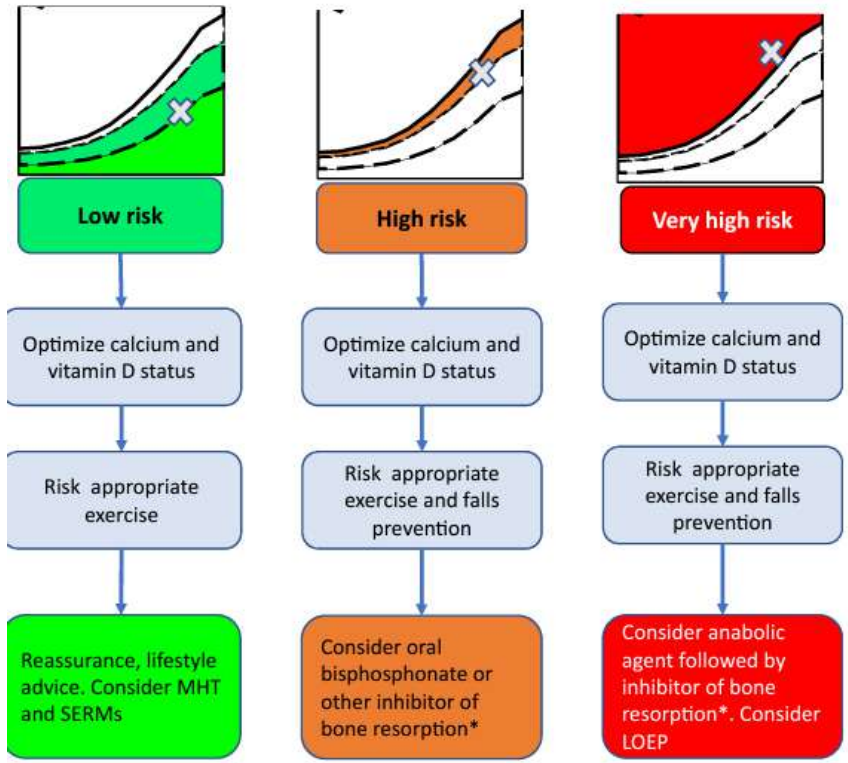
- Should osteoanabolic agents be used **before** or **after antiresorptive drugs**?

Who are the best candidates for osteoanabolic agents?

- Recent management guidelines suggest that the use of bone-forming drugs is most appropriate for **patients at very high risk of fracture**, where the absolute benefit and the cost-effectiveness are the greatest

- Examples of patients at very high fracture risk would include:
  - pts with **multiple or recent fractures** (within the past 12 m)
  - pts with **very low BMD** (e.g. a T-score of <-3.0)
  - pts with **very high estimates of fracture risk** using FRAX® *(e.g. 10 year probability of major osteoporosis fracture >30% or hip fracture >4.5%)* or other prediction tools.

- Because BMD increases are larger with osteoanabolic agents compared to anti-remodeling drugs, beginning therapy with an osteoanabolic agent is the best way to achieve a particular target BMD for **patients with very low BMD**



MHT, menopausal hormone therapy;
SERM, selective estrogen receptor modulator;
LOEP, local osteo-enhancement procedure
* See Appendix, table A2

Kanis JA, et al. Osteoporos Int. 2020;31(1):1–12. 8.

Lewiecki EM, et al. Am J Med. 2019;132(11):e771–e7
Camacho PM, et al. Endocr Pract. 2020;26 (Suppl 1):1–46. 5.
Shoback D, et al. J Clin Endocrinol Metab. 2020;105 (3):587–594.
Kanis JA, et al. Osteoporos Int. 2020;31(1):1–12. 8.
Kanis JA, et al. Osteoporos Int. 2021;32(10):1951–1960.
McClung MR, et al. Postgrad Med 2022;30:1-11.

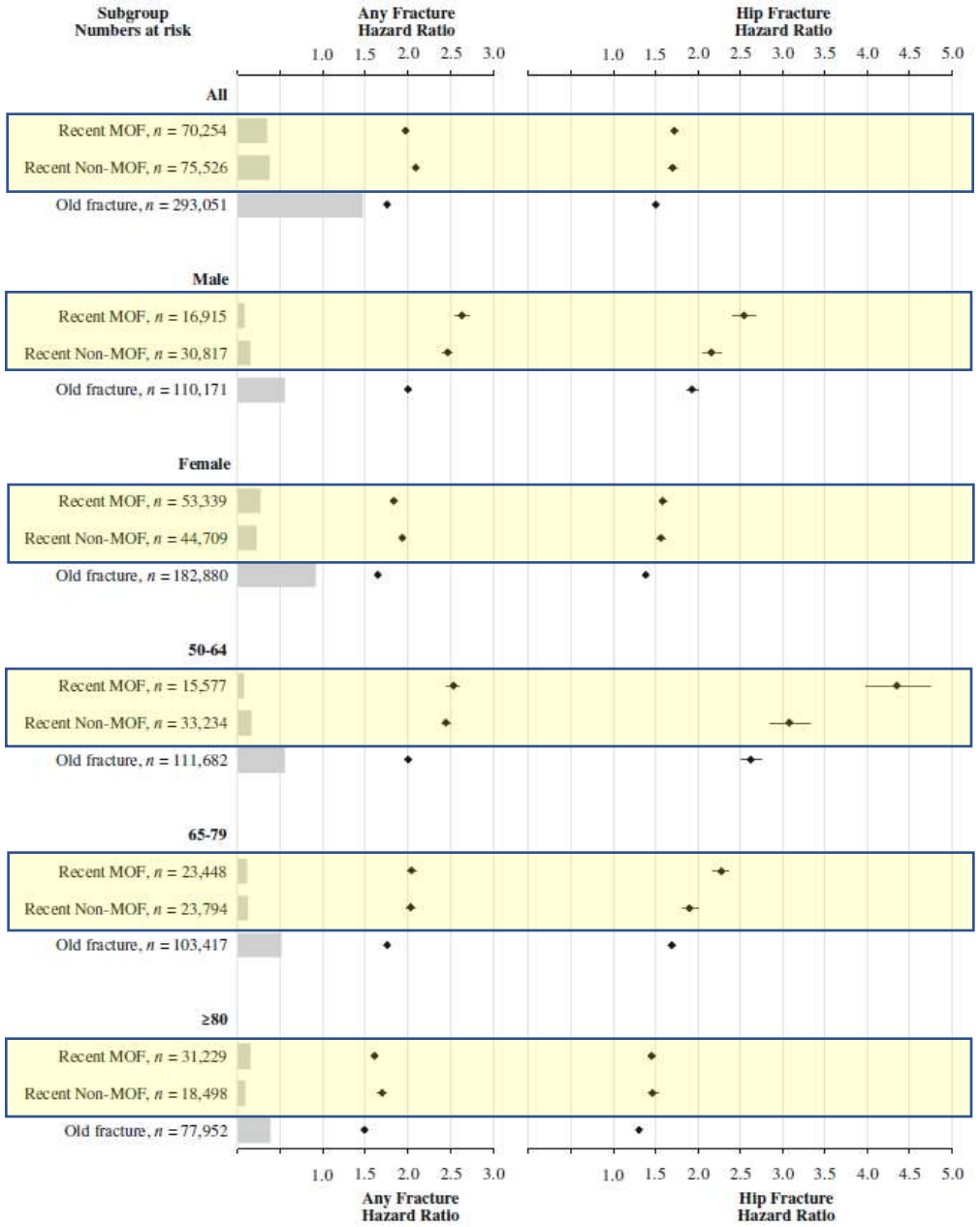
CONDITIONS AT HIGH RISK OF FRACTURE

- **Severe osteoporosis**

BMD **T-score<-2.5** SDS **+** one or more **fragility fractures**

- **Imminent risk of fracture**

highest fracture risk observed in the first **2 years following a fragility fracture**



The Importance of Recent Prevalent Fracture Site for Imminent Risk of Fracture – A Retrospective, Nationwide Cohort Study of Older Swedish Men and Women

Axelsson KF, et al. JBMR 2023

Registered Indications of Osteoanabolic Drugs

	Dose	Registered indications	Administration considerations	Adverse effects	Treatment duration and follow-up
(Continued from previous page)					
Anabolic agents					
Parathyroid hormone analogue					
Teriparatide	20 µg/day subcutaneously for 18–24 months	Treatment of postmenopausal, male, and glucocorticoid osteoporosis, and patients at high fracture risk	NA	Mild hypercalcemia in 6–11%, might require dose adjustment; FDA recommends considering >2 years of cumulative use during a patient's lifetime only if fracture risk remains high	Usually treat for up to 2 years and follow with anti-resorptive agent
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eGFR=estimated glomerular filtration rate. AFF=atypical femur fracture. ONJ=osteonecrosis of the jaw. FDA=US Food and Drug Administration. PTHrP=parathyroid hormone-related peptide. *Has both anabolic and antiresorptive effects.

Piano terapeutico web (nota 79 SSN)

Piano terapeutico web molto complesso (nota 79 SSN)*

*Link: https://www.cuore.iss.it/valutazione/carte

Reid IR, Billington EO. Lancet 2022; 399: 1080–92

Nota 79 (determina 05/08/2022 allegato 1):

La prescrizione a carico del SSN è limitata alle seguenti condizioni di rischio di frattura osteoporotica

- Prevenzione secondaria in soggetti con pregresse fratture osteoporotiche
  - *Fratture vertebrali o di femore*

Condizione	Trattamento I scelta[a]	II scelta	III scelta
1-2 fratture[b]	Alendronato (± vit.D), Risedronato, Zoledronato[d]	Denosumab[e] Ibandronato, Raloxifene, Bazedoxifene	
≥ 3 fratture	Teriparatide[g]	Denosumab[e] Zoledronato[d]	Alendronato (± vit.D) Risedronato, Ibandronato
≥ 1 frattura + T-score colonna o femore[c] ≤ -4			
≥ 1 frattura + trattamento > 12 mesi con prednisone o equivalenti ≥ 5 mg/die			
Nuova frattura vertebrale o femorale nonostante trattamento in Nota 79 da almeno 1 anno			
Pazienti di sesso femminile con T-score colonna o femore <-2,5 (<-2,0 se ≥2 fratture vertebrali moderate o gravi oppure se frattura femorale nei 2 anni precedenti) + anamnesi ≥1 fratture vertebrali moderate o gravi oppure ≥2 fratture vertebrali lievi oppure frattura femorale + rischio di frattura a 10 anni (determinato con calcolatore validato) elevato ≥20% + impossibilità a seguire altri trattamenti efficaci (intolleranza, inefficacia o scadenza del periodo di impiego autorizzato)	Romosozumab[f] per max 12 mesi, seguito da farmaci antiriassorbitivi (bisfosfonati o denosumab)		

PREVENZIONE SECONDARIA

[a] Il passaggio dalla prima scelta del trattamento alle successive richiede la presenza di intolleranza, incapacità di assunzione corretta, effetti collaterali o controindicazioni al farmaco della classe precedente o, nel caso del teriparatide, la fine del periodo di trattamento massimo consentito. Da valutarsi la modifica della scelta terapeutica anche in caso di frattura osteoporotica vertebrale o di femore nonostante trattamenti praticati per almeno un anno con i farmaci della classe precedente.

[b] Ai fini dell'applicazione della Nota la diagnosi di frattura vertebrale si basa sul criterio di Genant (riduzione di almeno una delle altezze vertebrali di almeno il 20%) mentre per il romosozumab – in aderenza alle caratteristiche della popolazione studiata - si attribuisce un valore decisionale diverso per le fratture lievi o per le fratture di severità moderata o grave.

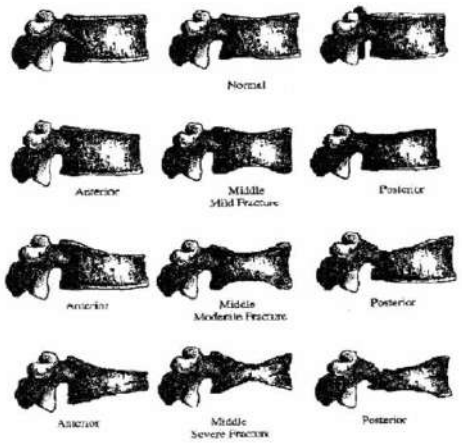
[c] Per l'applicazione della Nota 79, la valutazione densitometrica deve essere fatta a livello di colonna lombare e/o femore con tecnica DXA presso strutture pubbliche o convenzionate con il SSN.

[d] Lo zoledronato è prescrivibile e somministrabile solo in strutture ospedaliere pubbliche o convenzionate.

[e] Per il denosumab la Nota si applica su diagnosi e piano terapeutico della durata di 12 mesi, rinnovabile, da parte di medici specialisti (internista, reumatologo, geriatra, endocrinologo, ginecologo, ortopedico, nefrologo, oncologo e specialista in medicina fisica e riabilitativa), Universitari o delle Aziende Sanitarie.

[f] Per il romosozumab la Nota si applica (in soggetti di sesso femminile) su diagnosi e piano terapeutico fino alla durata massima di 12 mesi non rinnovabile, su prescrizione di centri ospedalieri o di medici specialisti (internista, reumatologo, endocrinologo, ginecologo, geriatra, ortopedico, fisiatra, nefrologo).

[g] Per il teriparatide la Nota si applica su diagnosi e piano terapeutico, della durata di 6 mesi prolungabile di ulteriori periodi di 6 mesi per non più di altre tre volte (per un totale complessivo di 24 mesi), di centri specializzati, Universitari o delle Aziende Sanitarie, individuate dalle Regioni e dalle Province autonome di Trento e Bolzano.



Classificazione fratture secondo Genant

Nota 79 (determina 05/08/2022 allegato 1):

La prescrizione a carico del SSN è limitata alle seguenti condizioni di rischio di frattura osteoporotica

- *Fratture non vertebrali e non femorali*

+ T-score colonna o femore ≤-3	Alendronato (± vit.D), Risedronato, Zoledronato[d]	Denosumab[e] Ibandronato, Raloxifene, Bazedoxifene	
Pazienti di sesso femminile con T-score colonna o femore <-2,5 + anamnesi ≥2 fratture non vertebrali + rischio di frattura a 10 anni (determinato con calcolatore validato) elevato ≥20% + impossibilità a seguire altri trattamenti efficaci (intolleranza, inefficacia o scadenza del periodo di impiego autorizzato)	Romosozumab[f] per max 12 mesi, seguito da farmaci antiriassorbitivi (bisfosfonati o denosumab)		
	Trattamento I scelta	Trattamento II scelta	

PREVENZIONE SECONDARIA

[e] Per il denosumab la Nota si applica su diagnosi e piano terapeutico della durata di 12 mesi, rinnovabile, da parte di medici specialisti (internista, reumatologo, geriatra, endocrinologo, ginecologo, ortopedico, nefrologo, oncologo e specialista in medicina fisica e riabilitativa), Universitari o delle Aziende Sanitarie.

[f] Per il romosozumab la Nota si applica (in soggetti di sesso femminile) su diagnosi e piano terapeutico fino alla durata massima di 12 mesi non rinnovabile, su prescrizione di centri ospedalieri o di medici specialisti (internista, reumatologo, endocrinologo, ginecologo, geriatra, ortopedico, fisiatra, nefrologo).

Indagine sul trattamento dell'osteoporosi in pazienti ambulatoriali specificamente rivolto alle categorie ad elevato rischio di frattura (studio SOS).

- **657 pazienti** in trattamento o precedentemente trattati con farmaci attivi sul metabolismo osseo

- **339 (52%)** con un quadro di **osteoporosi severa**

  → 88% in trattamento

- **217 (33%)** avevano riportato un evento fratturativo entro l'anno precedente, rientrando pertanto nella categoria "**a rischio imminente di frattura**"

  → 23% dei quali non risultava in terapia

Trattamenti nei soggetti con OP severa o imminente rischio di frattura

		Bisfosfonati orali	Zoledronato	Denosumab	Teriparatide	Altre Terapie*
OP Severa	SÌ	20%	4%	41%	32%	3%
	NO	39%	6%	29%	10%	16%
Imminente rischio di frattura	SÌ	24%	4%	31%	37%	4%
	NO	29%	6%	38%	15%	12%

(*): Farmaci non in Nota 79

Trattamenti nei soggetti nei quali era possibile l'utilizzo della terapia anabolica come prima scelta (secondo i criteri della nota 79)

Indicazione a terapia anabolica di prima scelta #	Bisfosfonati orali	Zoledronato	Denosumab	Teriparatide	Altre Terapie*
Nessuna	47%	9%	24%	1%	19%
≥3 fratture	7%	1%	52%	39%	1%
T-score<-4 + ≥1 frattura	19%	1%	35%	44%	1%
≥1 frattura + terapia CS	5%	14%	52%	29%	-
Nuova frattura durante terapia in Nota79 ≥12 mesi	20%	3%	32%	45%	-

(#): Prevenzione secondaria in pazienti con pregressa frattura vertebrale o femorale; (*): Farmaci non in Nota 79

GISMO
Gruppo Italiano Studio Malattie Metabolismo Osseo

How and When to Use Osteoanabolic Therapy

- Safety-Efficacy Profile
  - *Placebo-controlled studies*
  - *Comparative studies*

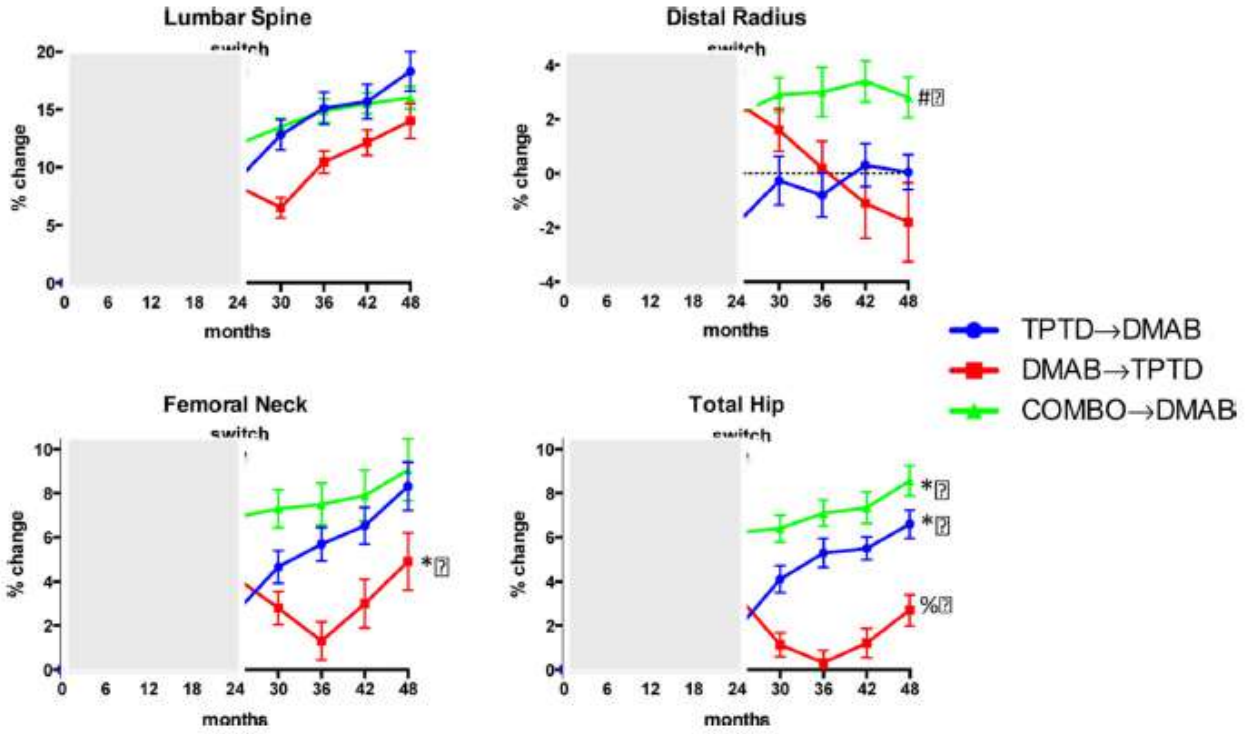
- Who are the best candidates for osteoanabolic agents?

- **What should be done at the end of a treatment course with osteoanabolic agents?**

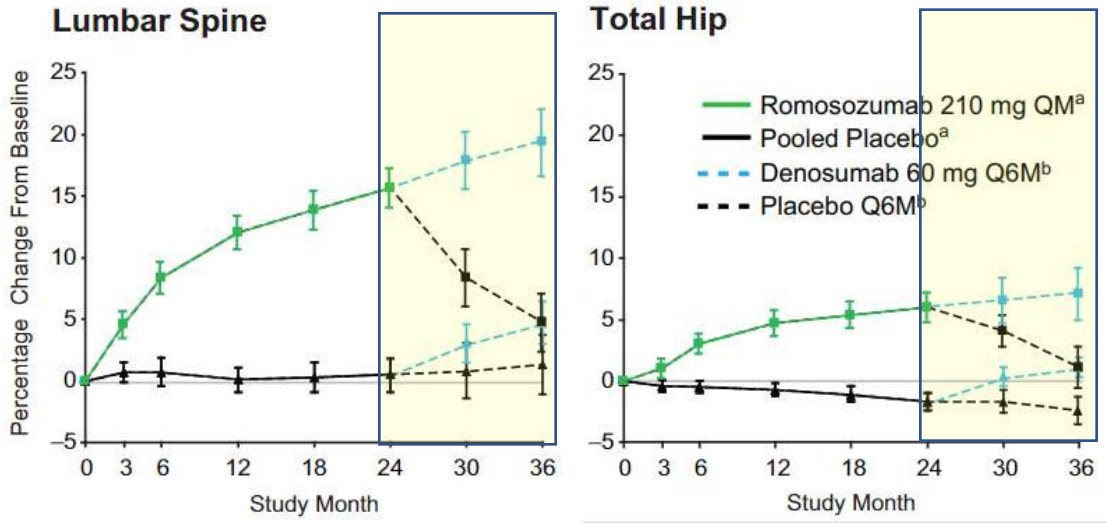
- Should osteoanabolic agents be used **before** or **after antiresorptive drugs**?

What should be done at the end of a treatment course with osteoanabolic agents?

➢ The **effects of osteoanabolic agents are lost when treatment is stopped**, and BMD values fall toward or to baseline within several months after discontinuation of teriparatide or romosozumab.



Leder B et al. Lancet 2015 (The DATA-Switch Study)



McClung MR, et al. J Bone Miner Res 2018;33(8):1397-1406 doi: 10.1002/jbmr.3452

➢ **A potent anti-remodeling drug**, either a bisphosphonate or denosumab, **should be used to maintain the skeletal benefits** of the bone-forming agent, even in patients whose BMD is no longer in the osteoporosis range.

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ANABOLIC THERAPY AND OPTIMAL TREATMENT SEQUENCES FOR PATIENTS WITH OSTEOPOROSIS AT HIGH RISK FOR FRACTURE

Felicia Cosman, MD

Professor of Medicine, Columbia University

Marzo 2020

Pazienti a più alto rischio in cui i farmaci anabolici dovrebbero essere considerati come trattamento iniziale

- Pazienti con fratture precedenti che hanno un alto rischio di altre fratture a breve termine (nei successivi 2 anni).
- Pazienti che presentano una BMD bassa (T-score ≤ a -3) anche in assenza di precedenti fratture in cui è improbabile che il trattamento con antiriassorbitivi permetta il raggiungimento del livello di BMD target in un periodo di trattamento di 3 anni.
- T-score total hip - 2.5: attualmente numerosi studi supportano anche la valutazione del T-score totale dell'anca come obiettivo per la terapia dell'osteoporosi essendo un marker di rischio di frattura successiva.

Massimizzare la densità minerale ossea dell'anca nei pazienti ad alto rischio di frattura a breve termine è un obiettivo importante del trattamento.

- La sequenza di trattamento anabolico-antiriassorbitivo massimizza la BMD dell'anca garantendo il raggiungimento degli obiettivi di trattamento*.
- Con **2 anni di teriparatide seguiti da 2 anni di denosumab**, la **BMD totale dell'anca è aumentata del 6,6%** durante uno studio della durata di 4 anni (DATA Study).
- Con **18 mesi di abaloparatide seguiti da 2 anni di alendronato**, il guadagno cumulativo totale di **BMD dell'anca** in 3,5 anni è stato del **6,5%.**
- Con **1 anno di romosozumab seguito da 2 anni di denosumab**, il guadagno cumulativo **BMD dell'anca** a 3 anni è stato del **9,4%.**

Should osteoanabolic agents be used before or after antiresorptive drugs?

➢**The optimal sequence of treatment is an osteoanabolic agent followed by a potent anti-remodeling drug, particularly for patients at very high risk of fracture**

➢ In fact, BMD responses to teriparatide and romosozumab are greater when given before an anti-remodeling drug compared to the opposite sequence

➢ However, osteoanabolic agents should also be considered for patients remaining at high risk of fracture after several years of bisphosphonate therapy:

Table 1. Key points

	For patients who discontinue denosumab, follow-on antiresorptive therapy is required to prevent the overshoot in bone remodeling and minimize subsequent bone loss.
	Transitioning from denosumab to teriparatide (and most likely abaloparatide) should be avoided as this leads to accelerated bone remodeling and rapid bone loss.
	Following bone-forming and dual-acting agents with an antiresorptive is required to maintain the achieved bone mineral density gains.
	In postmenopausal women who have not received any prior bone-targeted therapy, the greatest gains in bone mass are achieved with the initial use of a bone-forming/dual-acting drug followed by an antiresorptive.
	Initial therapy with a bisphosphonate may modestly diminish the bone effects of subsequent bone-forming or dual-acting drugs but prior antiresorptive use is not a contraindication to anabolic therapy.

Ramchand SK et al 2023

How and When to Use Osteoanabolic Therapy
CONCLUSIVE REMARKS

- By stimulating new bone formation, **osteoanabolic drugs address both of the major skeletal components of osteoporosis** by increasing BMD more quickly and usually to a greater extent than anti-remodeling drugs and by repairing and restoring the disordered trabecular and cortical bone microarchitecture.

- Who are the **best candidates** for osteoanabolic agents?

  *Recent management guidelines suggest that the use of bone-forming drugs is most appropriate for **patients at very high risk of fracture** (e.g. multiple or recent fractures, very low BMD, or very high estimates of fracture risk, high imminent risk of fracture), where the absolute benefit and the cost- effectiveness are the greatest*

- What should be done at the **end of a treatment course** with osteoanabolic agents?

  *At the end of a 12-to-24-month course of osteoanabolic therapy, transitioning to a potent **anti-remodeling agent** maintains and enhances the treatment benefit.*

- Should osteoanabolic agents be used **before** or **after antiresorptive drugs**?

  *The optimal sequence of treatment is an **osteoanabolic agent followed by a potent anti-remodeling drug**, particularly for patients at very high risk of fracture.*

Data from a national survey seem to indicate that in Italy patients with Severe OP do not often receive adequate anabolic treatment (teriparatide) and a consistent percentage of patients with "imminent risk of fracture" remains untreated or not adequate treated with anabolic drugs