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CLINICIAN NOTE

EVIDENCE SUMMARY

Sequential and combination therapy

Bones before they break · lecture preparation · 18 October 2026 · For discussion, not a prescription



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Bottom line: in women at very high fracture risk, start with a bone-building drug and follow it with a bisphosphonate or denosumab. Never stop denosumab without a follow-on drug, and avoid switching from denosumab to teriparatide. Combining teriparatide with denosumab or zoledronate raises bone density more, but no trial shows fewer fractures.

HOW TO READ THE GRADES

- **LoE** (level of evidence): I = large randomised trial or meta-analysis of trials; II = smaller, open-label or extension trial, or prospective cohort; III = post hoc or retrospective analysis; IV = case series; V = expert opinion or narrative review.
- **Certainty** (High, Moderate, Low, Very low) is our GRADE-style reading of the cited sources, unless a guideline grade is quoted.
- Most sequence and combination trials measure bone density (BMD), not fractures. BMD is a surrogate; a bigger BMD gain does not prove fewer fractures.

1. What changes practice — Anabolic first

FIVE POINTS FOR THE LECTURE

- Very high risk (recent or multiple fragility fractures, very low T-score): an anabolic drug first, then an antiresorptive. This order gives fewer fractures than a bisphosphonate alone in head-to-head trials [1,2] and bigger BMD gains than the reverse order [3,4].
- Every anabolic course must end with an antiresorptive, planned on the day the anabolic starts, so there is no gap [5].
- Denosumab must not be stopped without a bisphosphonate. Stopping raises the vertebral fracture rate to untreated levels, often as multiple fractures [6,7].
- Avoid denosumab followed by teriparatide. Hip and wrist density fall for up to two years [8,9].
- Teriparatide with alendronate adds nothing over teriparatide alone [10,11]. Teriparatide with denosumab or with zoledronate gives more BMD, but without fracture data [12,13].

CERTAINTY: MODERATE *High for anabolic-first fracture benefit versus a bisphosphonate; low for combination benefit (BMD only).*

2. What the guidelines say — Newest first

GUIDELINES AND POSITION STATEMENTS ON SEQUENCE

GROUP, YEAR	POSITION ON SEQUENCE AND COMBINATION
ECTS position statement, men, 2026 [14]	In men at very high fracture risk, consider an anabolic drug first, then an antiresorptive to keep the gain. Plan any stop carefully, above all after denosumab.
UK NOGG 2024, published 2025 [5]	Teriparatide or romosozumab is a first-line option in postmenopausal women at very high risk. Anyone stopping denosumab, romosozumab, teriparatide or abaloparatide needs a follow-on antiresorptive, planned at the start. No evidence yet supports one order among the anabolic drugs.
ACP 2023, US [15]	Bisphosphonate first for most (strong). Romosozumab (moderate certainty) or teriparatide (low certainty), then a bisphosphonate, only in women at very high risk (conditional).
BHOF 2022, US [16]	Bone loss resumes after any drug is stopped: sooner after non-bisphosphonates, later after bisphosphonates.
ISBMR 2021, India [17]	Bisphosphonates remain the first choice in most patients. Drug choice depends on whether there is a vertebral or hip fracture, or on clinical risk.

GROUP, YEAR	POSITION ON SEQUENCE AND COMBINATION
ECTS 2020, denosumab stop [7]	Start another antiresorptive 6 months after the last denosumab injection. Long-term denosumab is reasonable in high-risk patients already on it.
AACE 2020, US [18]	Adds a very-high-risk category and a section on moving between drugs.
Endocrine Society 2020 update [19]	Romosozumab is an option for very high risk; weigh heart and stroke risk first (boxed warning).

India: ISBMR 2021 is the only Indian society statement found. Its abstract does not set out a sequence; the full text is paywalled and was not read [17].

OUTSIDE INDIA *Outside India: UK, US and European guidance agrees on anabolic-first for very high risk and on a planned antiresorptive after any anabolic or denosumab [5,14,15]. Not Indian data; use as a guide.*

3. Why the order matters — Remodelling

THE BIOLOGY IN ONE PARAGRAPH

Teriparatide and abaloparatide build bone mostly on surfaces that are being remodelled. A potent antiresorptive given first switches remodelling off, so the anabolic drug has less to work on. At the hip, teriparatide also opens new remodelling spaces in cortical bone, so hip BMD falls below baseline for about 12 months after a bisphosphonate and almost 24 months after denosumab [9]. Anabolic effects also fade with time: within 12 to 18 months for PTH-type drugs and sooner for romosozumab. A following antiresorptive keeps the new bone [20].

CERTAINTY: MODERATE *Mechanism from trials, biopsies and expert review.*

4. Sequences that help — Anabolic → antiresorptive

FRACTURE AND BMD DATA

- **Romosozumab 12 months, then denosumab (FRAME).** New vertebral fractures 0.5% vs 1.8% at 12 months (73% lower), and 0.6% vs 2.5% at 24 months after both arms switched to denosumab (75% lower) [21]. Two years of this sequence gave T-score gains close to 7 years of denosumab [22].
- **Romosozumab 12 months, then alendronate (ARCH).** Against alendronate alone: new vertebral fractures 6.2% vs 11.9% (48% lower), hip fractures 2.0% vs 3.2% (38% lower). Serious heart and stroke events in year 1 were 2.5% vs 1.9% [1].
- **Abaloparatide 18 months, then alendronate (ACTIVE, ACTIVExtend).** Over 43 months, new vertebral fractures 0.9% vs 5.6% with placebo then alendronate (84% lower) [23,24].
- **Teriparatide first (VERO).** In severe osteoporosis, new vertebral fractures 5.4% vs 12.0% with risedronate (risk ratio 0.44) over 24 months [2].
- **Teriparatide, then denosumab (DATA-Switch).** Over 4 years, total hip BMD +6.6%, against +2.8% for the reverse order [8].
- **Pooled data.** A 2026 meta-analysis of 39 studies found the biggest BMD gains with romosozumab followed by denosumab or a bisphosphonate, and teriparatide followed by denosumab [4]. A 2026 meta-analysis of 6 RCTs (17,872 patients) found anabolic-first treatment cut vertebral fractures (pooled estimate 0.43), with considerable heterogeneity [25].

NO INDIAN DATA *No Indian trial of any drug sequence was found. An Indian systematic review (JAPI 2025) pooled 18 RCTs, none run in India, and found anabolic-then-antiresorptive superior to the reverse [26]; an Indian orthopaedic review reached the same view [27].*

OUTSIDE INDIA *Outside India: FRAME, ARCH, ACTIVE and VERO were large international trials; their fracture results are the evidence base for anabolic-first [1,2,21,23]. Not Indian data; use as a guide.*

CERTAINTY: HIGH *Fracture endpoints in large RCTs; ACTIVExtend was open-label.*

5. Sequences that do not help, or harm — Avoid

AND WHY

- **Denosumab, then teriparatide.** In DATA-Switch, hip BMD gained only 2.8% over 4 years (against 6.6% for the reverse order), and wrist BMD fell 1.8% [8]. Hip BMD stays below baseline for nearly 24 months after the switch [9]. Why: teriparatide opens remodelling spaces while denosumab's brake comes off [9].
- **Stopping denosumab with no follow-on drug.** After stopping, vertebral fractures rose from 1.2 to 7.1 per 100 patient-years, the rate in untreated women. 60.7% of those who fractured had more than one vertebral fracture, against 38.7% after placebo. A prior vertebral fracture raised the odds of multiple fractures 3.9 times [6]. Why: bone turnover rebounds above baseline within 6 months

of a missed dose [6].

- **Long bisphosphonate use, then teriparatide.** After 3 or more years of oral bisphosphonate, 12 months of teriparatide gave total hip BMD -0.6%, against +2.6% with romosozumab (STRUCTURE) [28]. Pooled data: spine gains after the switch, but no hip gain [4].
- **Antiresorptive, then romosozumab.** It works, but less. Total hip gain at 12 months was 6.0 to 6.2% with romosozumab first, 2.9% after alendronate and 0.9% after denosumab [3].

NO INDIAN DATA *No Indian study of these switches was found.*

OUTSIDE INDIA *Outside India: the switch data come from a small trial (DATA-Switch, 77 women) and an international trial in the Americas and Europe (STRUCTURE, 436 women) [8,28]. Not Indian data; use as a guide.*

CERTAINTY: MODERATE *BMD endpoints; denosumab-stop fracture data are post hoc [6].*

6. Stopping denosumab safely — 6 months

WHEN AND WITH WHAT

- Give zoledronic acid (or another bisphosphonate) 6 months after the last denosumab dose, and plan it before denosumab is started [5,7].
- Short denosumab courses: after about 2.2 years of denosumab, one zoledronic acid infusion kept spine BMD stable for 2 years; women given two more denosumab doses and then stopped lost 4.8% [29].
- Long denosumab courses: after about 4.6 years, zoledronic acid did not fully stop the loss. Spine BMD fell 4.8% within 12 months, whatever the timing of the infusion (6 months, 9 months or by turnover markers) [30].
- Dose count matters: with 6 or fewer injections, spine BMD stayed stable (+1.0%) after zoledronic acid; with more than 6, it fell 7.0% [31]. Check BMD and turnover markers after longer courses; a second dose may be needed.

NO INDIAN DATA *No Indian data on stopping denosumab were found.*

OUTSIDE INDIA *Outside India: the zoledronic acid studies above were small European studies of 47 to 61 patients each, none run in India [29,30,31]. Not Indian data; use as a guide.*

CERTAINTY: LOW *Small trials, BMD endpoints; fracture prevention after stopping is unproven [7].*

7. Combination therapy — Given together

WHICH PAIRS WORK AND WHICH DO NOT

COMBINATION	WHAT THE TRIAL SHOWED	VERDICT
Teriparatide + denosumab (DATA, RCT, n=94, 12 months) [12]	Spine BMD +9.1% vs +6.2% (teriparatide) and +5.5% (denosumab); total hip +4.9% vs +0.7% and +2.5%.	Beneficial for BMD. No fracture data; two injectable drugs, high cost.
Combination, then denosumab (DATA-Switch, 4 years) [8]	Total hip +8.6%, the largest gain of the three arms; wrist +2.8%.	Beneficial for BMD; small (23 women).
Teriparatide + zoledronic acid (RCT, n=412, 12 months) [13]	Spine +7.5% vs +7.0% (teriparatide) and +4.4% (zoledronic acid); hip +2.3% vs +1.1% and +2.2%. Faster early gains.	Beneficial for BMD. Not powered for fractures.
PTH(1-84) + alendronate (PaTH, RCT, n=238, women) [10]	No synergy; trabecular spine density rose about twice as much with PTH alone.	Not beneficial. Alendronate blunts PTH.
Teriparatide + alendronate (RCT, n=83, men) [11]	Spine and femoral-neck gains smaller with the combination than with PTH alone.	Not beneficial.
Adding teriparatide to ongoing alendronate, vs switching [9]	Hip BMD and hip strength better when teriparatide is added than when alendronate is stopped.	Option if a switch is needed; low certainty.

Note on the 16 October version: two claims there (a lower clinical fracture rate with teriparatide + zoledronic acid, and hip loss when teriparatide is added to long-term denosumab) could not be confirmed from the abstracts read and have been removed.

CERTAINTY: LOW *BMD only, small trials, mostly open-label; industry part-funded (DATA [12]).*

8. Indian context

Indian data

WHAT INDIAN STUDIES ADD

Biosimilar teriparatide: in an Indian phase 3 double-blind RCT (n=177 postmenopausal women, 48 weeks), Alkem's biosimilar was non-inferior to reference teriparatide, with spine BMD +8.58% vs +8.02% [32]. It tested teriparatide alone, not a sequence.

Indian reviews: a JAPI 2025 systematic review and an Indian Journal of Orthopaedics review both support anabolic-first, using non-Indian trials [26,27].

NO INDIAN DATA *No Indian cost-effectiveness study of any drug sequence was found.*

OUTSIDE INDIA *Outside India: US guidance (ACP 2023) also weighs cost and keeps anabolic-first for women at very high risk only [15]. Not Indian data; use as a guide.*

9. Practical points

FOR THE CLINIC AND THE LECTURE

PRACTICAL POINTS

- Sort the patient by risk first: very high risk gets anabolic-first; high risk usually starts with a bisphosphonate [5,15].
- Teriparatide course, then zoledronic acid or denosumab. Romosozumab 12 months, then denosumab or alendronate [1,8,21].
- Romosozumab: weigh heart attack and stroke risk before starting (boxed warning) [1,19].
- Before starting denosumab, plan the exit. If it is stopped, give zoledronic acid 6 months after the last dose, then follow BMD and turnover markers [7,31].
- Do not switch from denosumab to teriparatide. If an anabolic is needed after denosumab, romosozumab protects the hip better, but the gain is small [3,8].
- Do not combine teriparatide with oral alendronate [10,11].

10. Key studies, graded

LOE · DESIGN · N · FOLLOW-UP · KEY RESULT

STUDY	LOE, DESIGN	N, FOLLOW-UP	KEY RESULT
FRAME [21]	I, RCT	7,180; 24 mo	Vertebral fracture 73% lower at 12 mo, 75% at 24 mo
ARCH [1]	I, RCT	4,093; 24 mo + event-driven	Vertebral 48%, hip 38% lower vs alendronate
ACTIVExtend [24]	II, open-label extension	1,139; 43 mo	Vertebral 84% lower
VERO [2]	I, RCT	1,360; 24 mo	Vertebral RR 0.44 vs risedronate
DATA [12]	II, open-label RCT	94; 12 mo	Combination spine +9.1%
DATA-Switch [8]	II, RCT extension	77; 48 mo	Hip +6.6% vs +2.8% by order
STRUCTURE [28]	II, open-label RCT	436; 12 mo	Hip +2.6% (romo) vs -0.6% (teriparatide)
Cosman 2011 [13]	II, RCT	412; 12 mo	Combination fastest spine and hip gains
PaTH [10]	I, RCT	238; 12 mo	No synergy with alendronate
FREEDOM stop [6]	III, post hoc of RCT	1,001 stoppers	Vertebral fractures 1.2 → 7.1 per 100 patient-years
Anastasilakis 2019 [29]	II, RCT	57; 24 mo	Zoledronic acid kept spine BMD
Sølling 2020 [30]	II, RCT	61; 12 mo after ZOL	Spine -4.8% despite zoledronic acid
Makras 2021 [31]	II, prospective cohort	47; 12 mo	+1.0% (≤6 doses) vs -7.0% (>6)
Nayak 2026 [4]	I, SR/MA	39 studies	Anabolic-first gives biggest BMD gains
Cipolloni 2026 [25]	I-II, SR/MA (heterogeneous)	6 RCTs; 17,872	Vertebral pooled estimate 0.43

Where the evidence is weak

FLAGS

WEAK OR LIMITED EVIDENCE

- Combination therapy: BMD only, small open-label trials; no fracture trial [12,13].
- Denosumab exit: small trials of 47 to 61 patients; best drug, timing and duration after long courses unknown [30,31].
- Order among anabolic drugs (for example teriparatide then romosozumab) is not settled [5].
- Men and secondary osteoporosis: few trials; the 2026 ECTS statement relies mostly on BMD data [14].
- India: no Indian trial of any sequence or of stopping denosumab.
- Industry funding: ARCH, STRUCTURE and DATA were part- or fully funded by the drug makers [1,12,28].
- Corrections: published errata exist for ACP 2023, ACTIVE, VERO and BHOF 2022, and a correction for the 2026 sequential meta-analysis (its text could not be opened; figures here are from the original abstract) [4].

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VERIFIED BY PMID AND DOI · VANCOUVER STYLE

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