Θεραπεία οστεοπόρωσης – Νεότερα δεδομένα
Προεδρείο: Γ. Δήμου – Θ. Τεμεκονίδης

17.00 - 17.30	Αντικαταβολική αγωγή **Κ. Μαυρουδής**
17.30 - 18.00	Αναβολική αγωγή **Χρ. Κοσμίδης**
18.00 - 18.15	Ερωτήσεις - Συζήτηση

Θεραπεία οστεοπόρωσης
Νεότερα δεδομένα
Αντικαταβολική αγωγή

ΚΩΝΣΤΑΝΤΙΝΟΣ Ι. ΜΑΥΡΟΥΔΗΣ
ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ
τ. Συντονιστής Διευθυντής
Ενδοκρινολογίας, Διαβήτη & Μεταβολισμού
ΓΝΑ ¨Ασκληπιείο Βούλας ¨

Archives of Osteoporosis (2022) 17:58
https://doi.org/10.1007/s11657-022-01061-5

POSITION PAPER

UK clinical guideline for the prevention and treatment of osteoporosis

Celia L. Gregson[1,2] · David J. Armstrong[3] · Jean Bowden[1] · Cyrus Cooper[4,5,6] · John Edwards[7] · Neil J. L. Gittoes[8] · Nicholas Harvey[4,5] · John Kanis[9] · Sarah Leyland[10] · Rebecca Low[11] · Eugene McCloskey[12] · Katie Moss[13] · Jane Parker[1] · Zoe Paskins[14] · Kenneth Poole[15,16] · David M. Reid[17] · Mike Stone[18] · Julia Thomson[10] · Nic Vine[1] · Juliet Compston[19]

Received: 20 December 2021 / Accepted: 3 January 2022 / Published online: 5 April 2022

Abstract

Summary The National Osteoporosis Guideline Group (NOGG) has revised the UK guideline for the assessment and management of osteoporosis and the prevention of fragility fractures in postmenopausal women, and men age 50 years and older. Accredited by NICE, this guideline is relevant for all healthcare professionals involved in osteoporosis management.

Introduction The UK National Osteoporosis Guideline Group (NOGG) first produced a guideline on the prevention and treatment of osteoporosis in 2008, with updates in 2013 and 2017. This paper presents a major update of the guideline, the scope of which is to review the assessment and management of osteoporosis and the prevention of fragility fractures in postmenopausal women, and men age 50 years and older.

Osteoporosis: Anti-fracture efficacy of approved drug treatments for postmenopausal women, and men, when given with Ca & Vitamin D

Intervention	Vertebral fracture	Non-vertebral fracture	Hip fracture	Licenced for use in men
Romosozumab *	Ib	IIb	IIb	No
Teriparatide *	Ia	Ia	Ia	Yes
Alendronate	Ia	Ia	Ia	Yes
Ibandronate	Ib	Ib	NAE	No
Risedronate	Ia	Ia	Ia	Yes
Zoledronate	Ia	Ia	Ia	Yes
Calcitriol	IIa	NAE	NAE	Yes
Denosumab	Ia	Ia	Ia	Yes
HRT	Ia	Ia	Ia	No
Raloxifene	Ia	NAE	NAE	No
Strontium Ranelate	Ia	Ia	IIb	Yes

∗Evidence of superiority for vertebral fracture prevention in Postmen/women with very high fracture risk

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Pharmacological treatment options (I)

Recommendations

1. Fracture risk assessment, patient suitability and preference and cost-effectiveness should inform the choice of drug treatment. In most people at risk of fragility fracture, anti-resorptive therapy is the first-line option (*strong recommendation*).

Antiresorptive drug treatment

2. Offer oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate as the most cost-effective interventions. Alternative options include denosumab, ibandronate, hormone replacement therapy, raloxifene and strontium ranelate (*strong recommendation*).
3. Offer intravenous zoledronate as a first-line treatment option following a hip fracture (*strong recommendation*).

Pharmacological treatment options

4. Before starting denosumab, ensure a long-term personalised osteoporosis management plan is in place and that both the patient and the primary care practitioner are made aware that denosumab treatment should not be stopped or delayed without discussion with a healthcare professional (*strong recommendation*).
5. Avoid unplanned cessation of denosumab because it can lead to increased vertebral fracture risk, hence it must not be stopped without considering an alternative therapy (*strong recommendation*).
6. If denosumab therapy is stopped, intravenous infusion of zoledronate is recommended 6 months after the last injection of denosumab, with subsequent monitoring of serum CTX guiding the timing of further treatment (*strong recommendation*). Where monitoring of serum CTX is not possible, consider a further intravenous infusion of zoledronate 6 months after the first dose of zoledronate (*conditional recommendation*).
7. Limit the initiation of HRT for the treatment of postmenopausal osteoporosis to younger post-menopausal women (age ≤ 60 years) who have low baseline risk for adverse malignant and thromboembolic events (*strong recommendation*).
8. Discuss continued use of HRT after the age of 60 years with the patient, with treatment based on an individual risk–benefit analysis (*conditional recommendation*).

Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians

Recommendation 1a: ACP recommends that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis (strong recommendation; high-certainty evidence)

Recommendation 1b: ACP suggests that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in males diagnosed with primary osteoporosis (conditional recommendation; low-certainty evidence).

Recommendation 2a: ACP suggests that clinicians use Denosumab as a second-line treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; moderate-certainty evidence).

Ann Intern Med. 2023;176:224-238

Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians

Recommendation 2b: ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in males diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; low-certainty evidence).

Recommendation 3: ACP suggests that clinicians use the Romosozumab, moderate-certainty evidence) or Teriparatide, low-certainty evidence), followed by a bisphosphonate, to reduce the risk of fractures only in females with primary osteoporosis with very high risk of fracture (conditional recommendation).

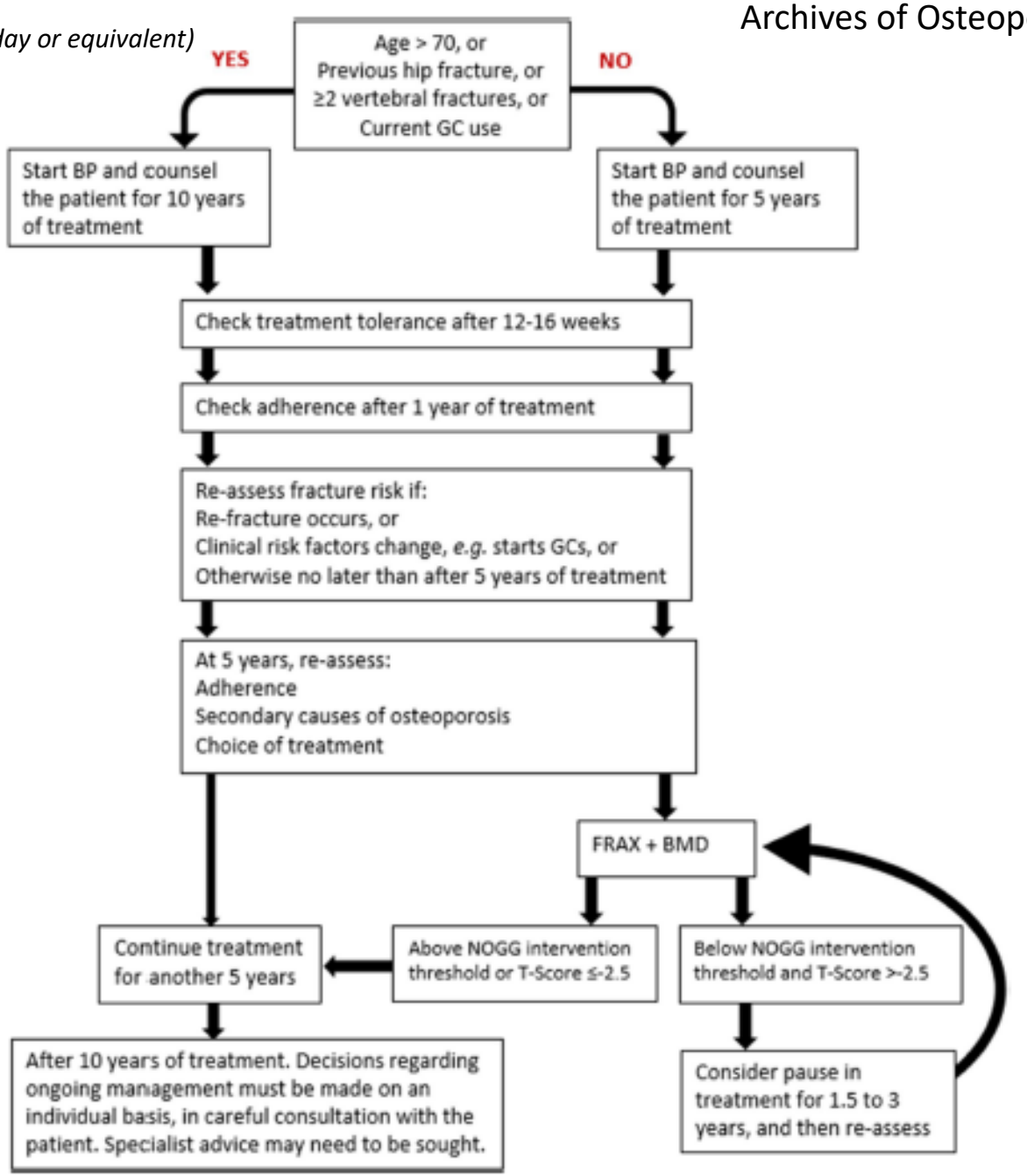
Recommendation 4: ACP suggests that clinicians take an individualized approach regarding whether to start pharmacologic treatment with a bisphosphonate in females over the age of 65 with low bone mass (osteopenia) to reduce the risk of fractures (conditional recommendation; low-certainty evidence).

Ann Intern Med. 2023;176:224-238

Oral Bisphosphonates: clinical flowchart for long-term treatment and monitoring

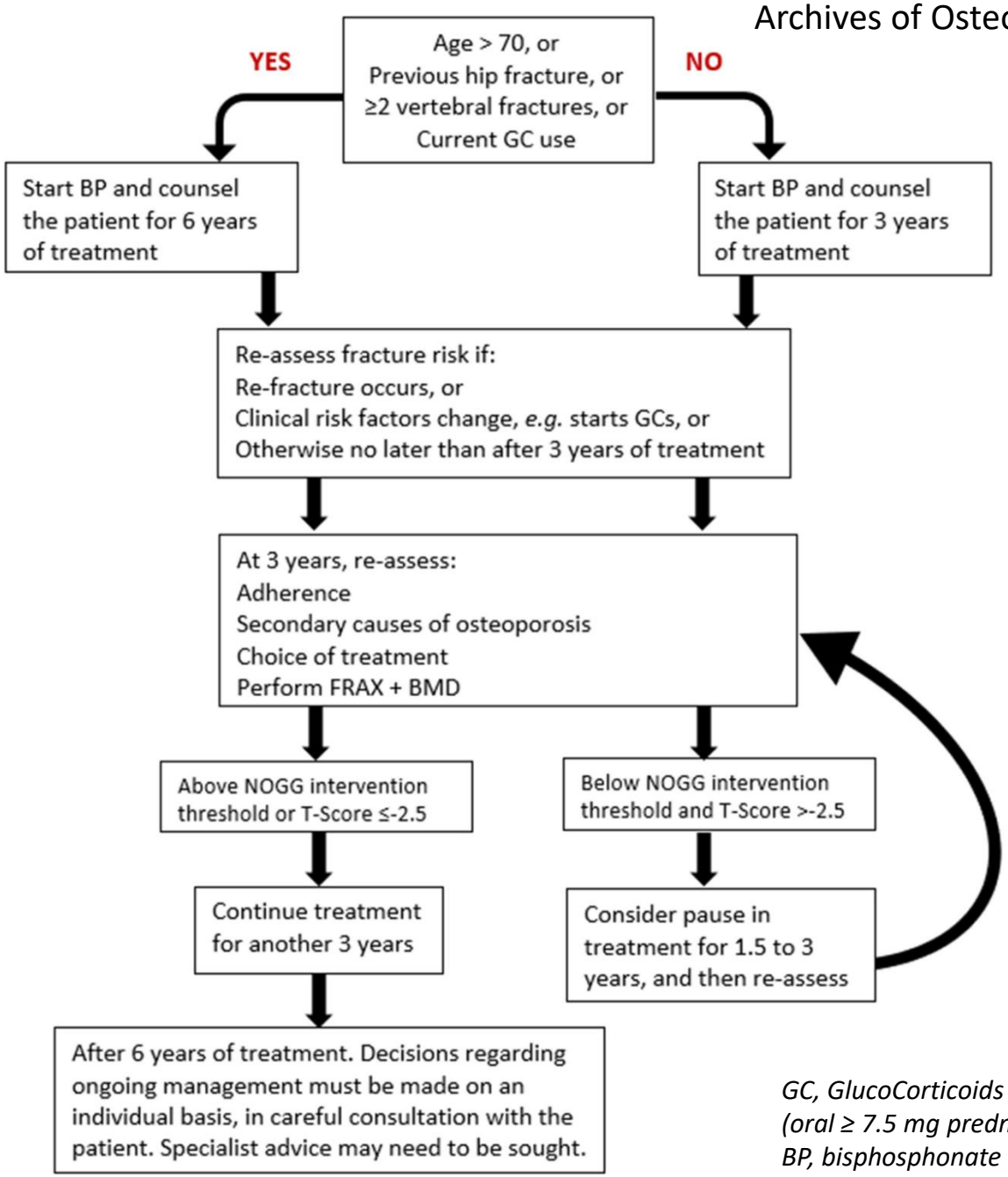
GC, GlucoCorticoids
(oral ≥ 7.5 mg prednisolone/day or equivalent)
BP, bisphosphonate

Archives of Osteoporosis (2022) 17:58



Intravenous Bisphosphonates: clinical flowchart for long-term treatment and monitoring

Archives of Osteoporosis (2022) 17:58



GC, GlucoCorticoids
(oral ≥ 7.5 mg prednisolone/day or equivalent).
BP, bisphosphonate

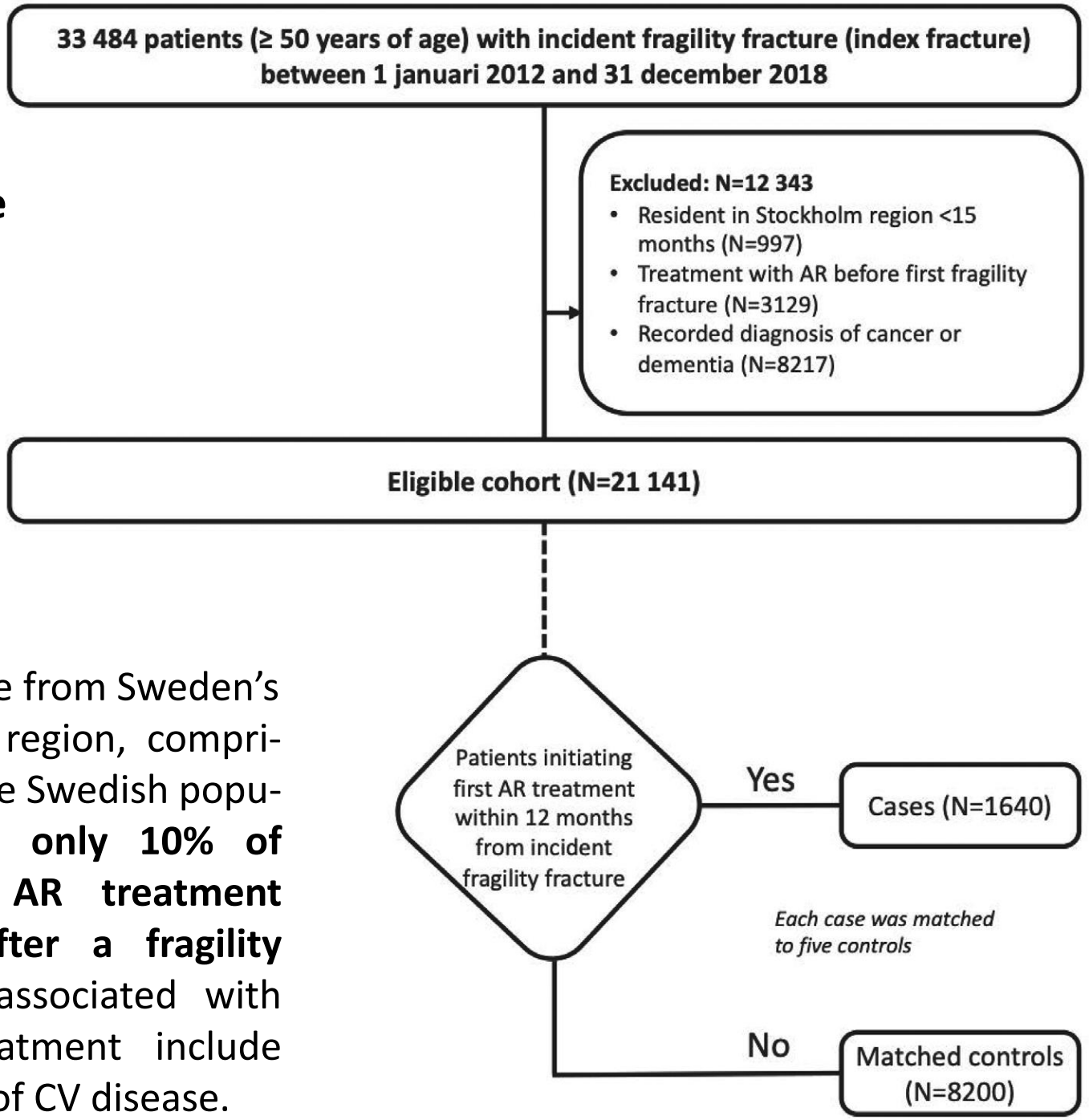
ORIGINAL ARTICLE

JBMR®

Real-World Effectiveness of Anti-Resorptive Treatment in Patients With Incident Fragility Fractures—The STORM Cohort—A Swedish Retrospective Observational Study

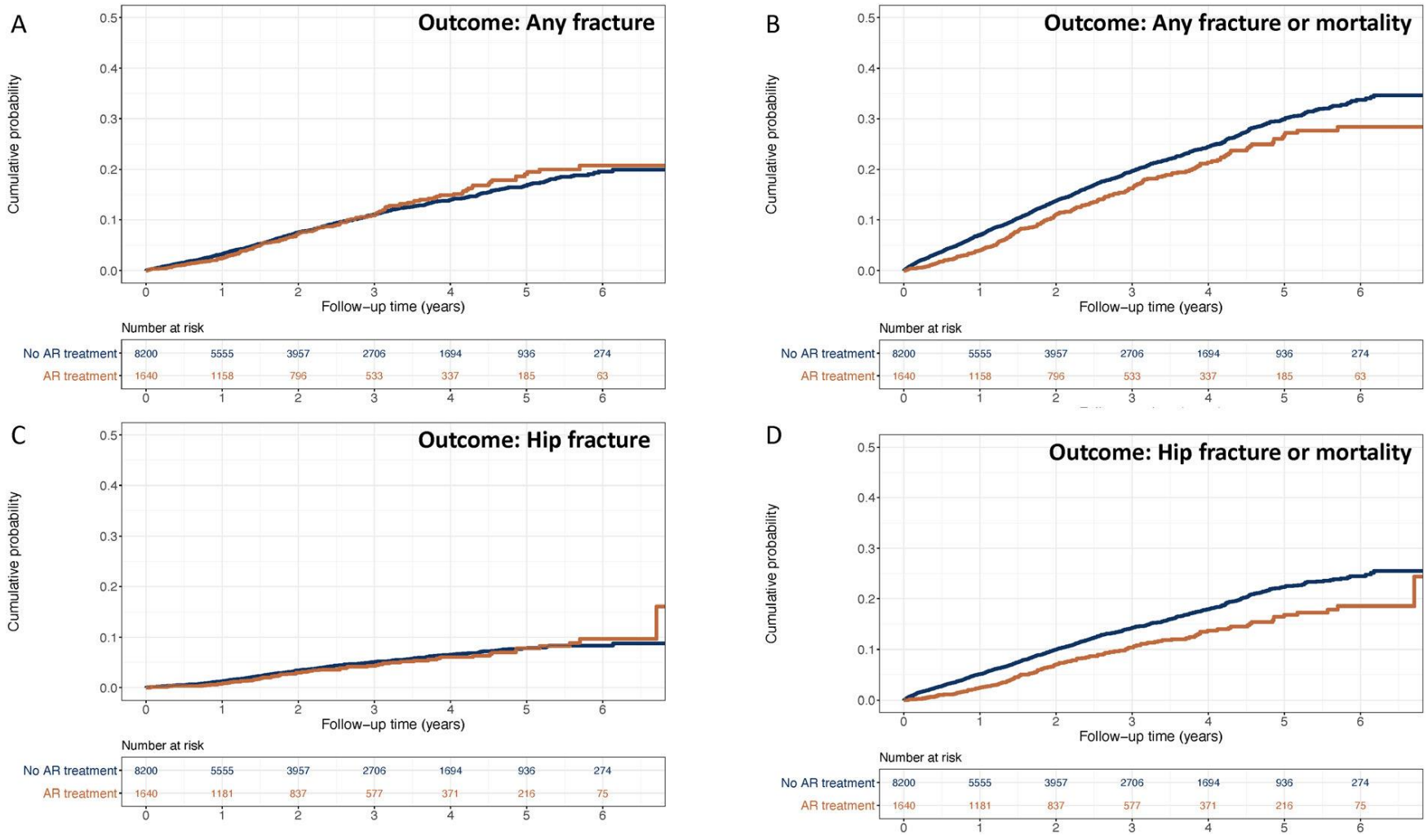
Results from real-world evidence (RWE) from the largest healthcare region in Sweden show low uptake of antiresorptive (AR) treatment, but beneficial effect in those receiving treatment, especially for the composite outcome of hip fracture or death. For RWE studies, Sweden is unique, with virtually complete coverage of electronic medical records (EMRs) and both regional and national registries, in a universal publicly funded healthcare system. To our knowledge, there is no previous RWE study evaluating the efficacy of AR treatment compared to no AR treatment after fragility fracture, including data on parenteral treatments administered in hospital settings. The Stockholm Real World Management (STORM) study cohort was established in the healthcare region of Stockholm to retrospectively assess the effectiveness of AR treatment after first fragility fracture using the regional EMR system for both hospital and primary care

Derivation of the study cohort



Real world evidence from Sweden's largest healthcare region, comprising a quarter of the Swedish population, show that **only 10% of patients receive AR treatment within 1 year after a fragility fracture.** Factors associated with not receiving treatment include having a diagnosis of CV disease.

Kaplan-Meier plots for the respective outcomes for the cumulative probability of



In those treated, AR have positive effects particularly on the composite of fracture and death (any fracture/death and hip fracture/death) in individuals matched for all major confounders

RESEARCH ARTICLE

JBMR®

Zoledronate Reduces Height Loss Independently of Vertebral Fracture Occurrence in a Randomized Trial in Osteopenic Older Women

Ian R Reid,[1,2] Sonja Bastin,[2] Anne M Horne,[1] Borislav Mihov,[1] Gregory D Gamble,[1] and Mark J Bolland[1,2]

[1]Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
[2]Auckland District Health Board, Auckland, New Zealand

ABSTRACT (I)

Vertebral fractures are associated with height loss, reduced quality of life, and increased mortality and are an important endpoint for osteoporosis trials. However, height loss is associated with quality of life and mortality independent of associations with fracture.

We have used data from a recent 6-year trial of zoledronate in 2000 osteopenic women aged > 65 years to assess the impact of the semi-quantitative and quantitative components of the definition of vertebral fracture on the outcome of that trial, to determine what factors impacted on height loss and to test whether height loss can be used as a surrogate for vertebral fracture incidence.

RESEARCH ARTICLE

JBMR®

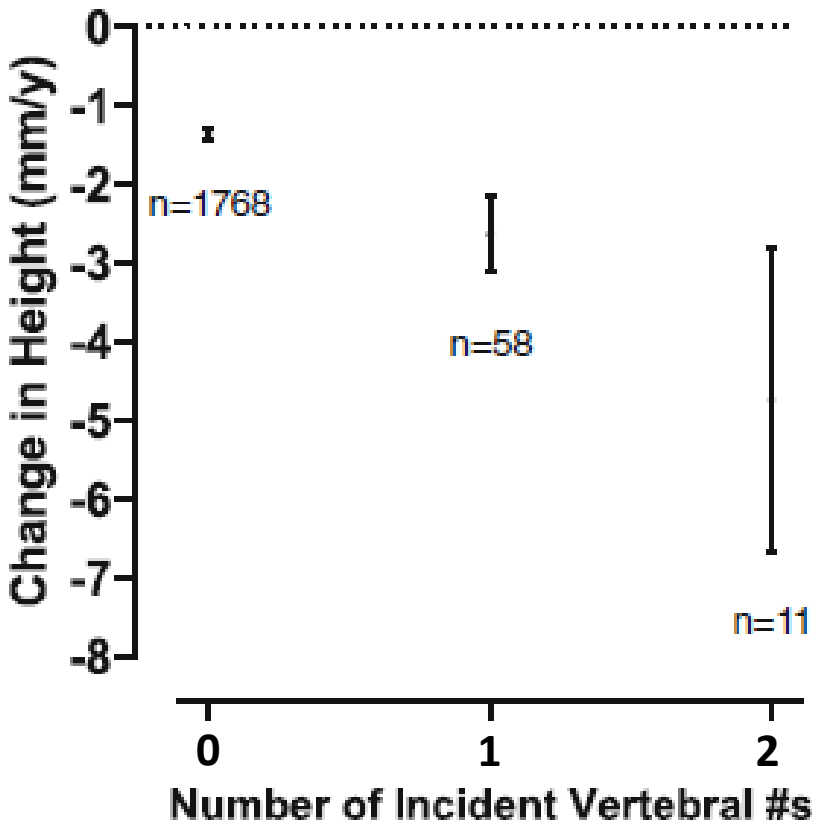
Zoledronate Reduces Height Loss Independently of Vertebral Fracture Occurrence in a Randomized Trial in Osteopenic Older Women

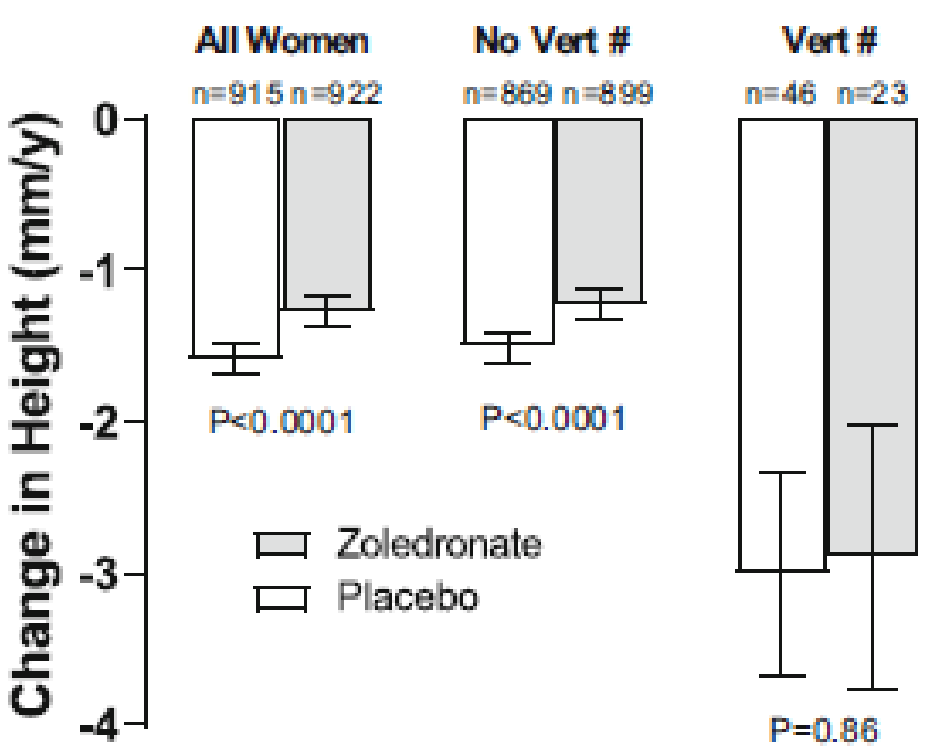
Ian R Reid,[1,2] Sonja Bastin,[2] Anne M Horne,[1] Borislav Mihov,[1] Gregory D Gamble,[1] and Mark J Bolland[1,2]

[1]Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
[2]Auckland District Health Board, Auckland, New Zealand

ABSTRACT (II)

In the trial protocol, an incident vertebral fracture was defined as a change in Genant grade plus both a 20% and 4 mm decrease in a vertebral height. The addition of the quantitative criteria reduced the number of fractures detected but did not change the size of the antifracture effect (odds ratios of 0.49 versus 0.45) nor the width of the confidence intervals for the odds ratios. Multivariate analysis of baseline predictors of height change showed that age accelerated height loss ($p < 0.0001$) and zoledronate reduced it ($p = 0.0001$). Incident vertebral fracture increased height loss ($p = 0.0005$) but accounted for only 0.7% of the variance in height change, so fracture could not be reliably inferred from height loss.. © 2022 American Society for Bone and Mineral Research (ASBMR).





In women without incident vertebral fractures, height loss was still reduced by zoledronate (height change: zoledronate, 1.23; placebo 1.51 mm/yr, $p < 0.0001$). This likely indicates that zoledronate prevents a subtle but widespread loss of vertebral body heights not detected by vertebral morphometry. Because height loss is associated with quality of life and mortality independent of associations with fracture, it is possible that zoledronate impacts on these endpoints via its effects on vertebral body integrity

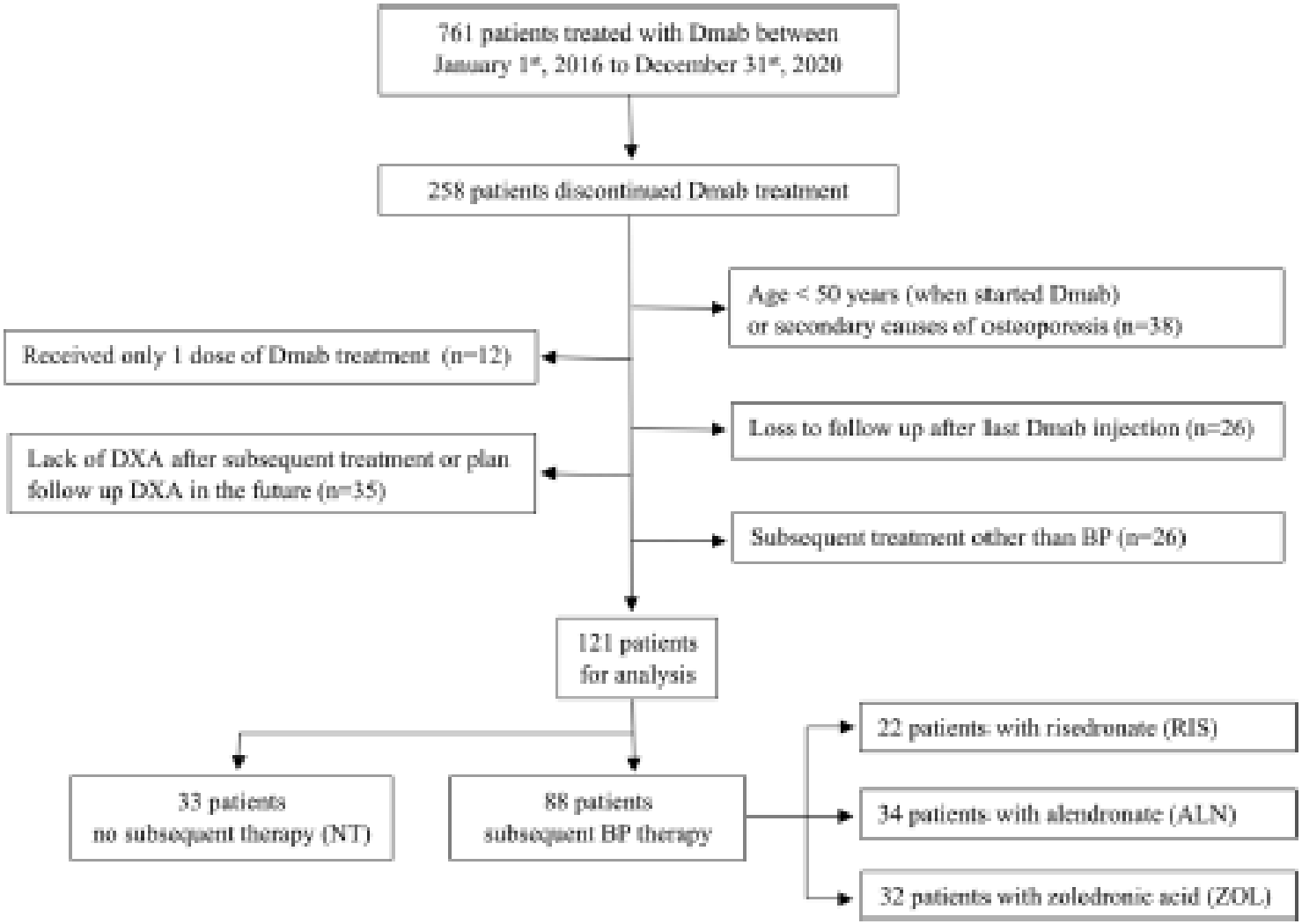
Osteoporosis International
https://doi.org/10.1007/s00198-022-06648-9

ORIGINAL ARTICLE

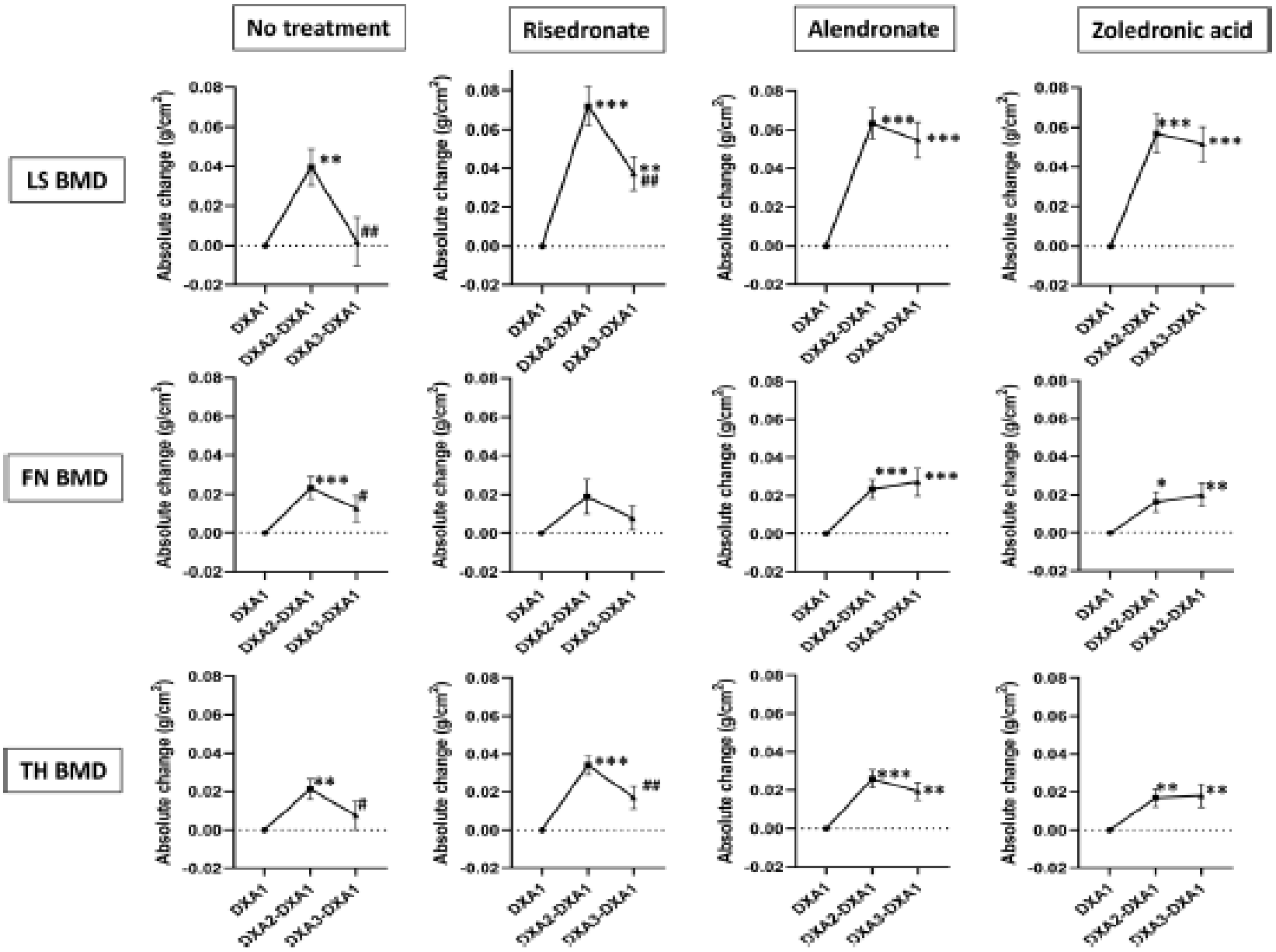
Bone loss after denosumab discontinuation is prevented by alendronate and zoledronic acid but not risedronate: a retrospective study

Teerapat Tutaworn[1,2] · Jeri W. Nieves[1,3] · Zhaorui Wang[4] · Justin E. Levin[1] · Jae E. Yoo[1] · Joseph M. Lane[1,4,5]

Received: 25 July 2022 / Accepted



Absolute change in LS, FN, and TH BMD during denosumab treatment and after receiving no therapy or received Risedronate, Alendronate, or Zoledronic acid



Osteoporosis International

Bone loss after denosumab discontinuation is prevented by alendronate and zoledronic acid but not risedronate: a retrospective study

Conclusion

Subsequent treatment with weekly alendronate or once yearly zoledronic acid mitigates BMD loss at the LS, FN, and TH after Dmab discontinuation. There is no significant difference between the two treatments at the LS, FN, and TH, even following long-term Dmab treatment. Patients receiving no treatment or those receiving risedronate post Dmab, both demonstrate significant bone loss with no significant differences between these groups. Data from a prospective study is needed to identify risk factors for BMD loss after Dmab discontinuation, even while being treated with a BP.

Osteoporos Int. 2023 Mar;34(3):573-584

Osteoporosis International (2023) 34:599–605
https://doi.org/10.1007/s00198-022-06651-0

SHORT COMMUNICATION

Changes in RANKL and TRAcP 5b after discontinuation of denosumab suggest RANKL mediated formation of osteoclasts results in the increased bone resorption

Anne Sophie Sølling[1,2] · Torben Harsløf[1] · Niklas Rye Jørgensen[3,4] · Bente Langdahl[1]

Received: 31 May 2022 / Accepted: 14 December 2022 / Published online: 22 December 2022

Purpose The rapid increase in bone turnover occurring when discontinuing long-term treatment with denosumab (DMAB), is not fully understood. We aimed to investigate the mechanisms underlying the rebound activation of bone resorption by measuring tartrate-resistant acid phosphatase 5b (TRAcP 5b), RANKL, osteoprotegerin (OPG), C-terminal collagen crosslinks (CTX), and procollagen type I N-propeptide (P1NP) in patients discontinuing long-term DMAB. Methods Sixty-one patients with BMD T-score > − 2.5 at the spine and hip discontinuing long-term DMAB were randomized to treatment with zoledronate (ZOL) 6 months (**6 M group**, *n* = 20), 9 months (**9 M group**, *n* = 20) or 12 months after the last DMAB injection or when bone turnover was high (**12 M group**, *n* = 21). Bone turnover markers were measured immediately before initiation of ZOL treatment.

Conclusion Following discontinuation of long-term DMAB, we find high levels of RANKL, which most likely result in an increase in the number of active osteoclasts (illustrated by TRAcP5b) causing an increased bone turnover

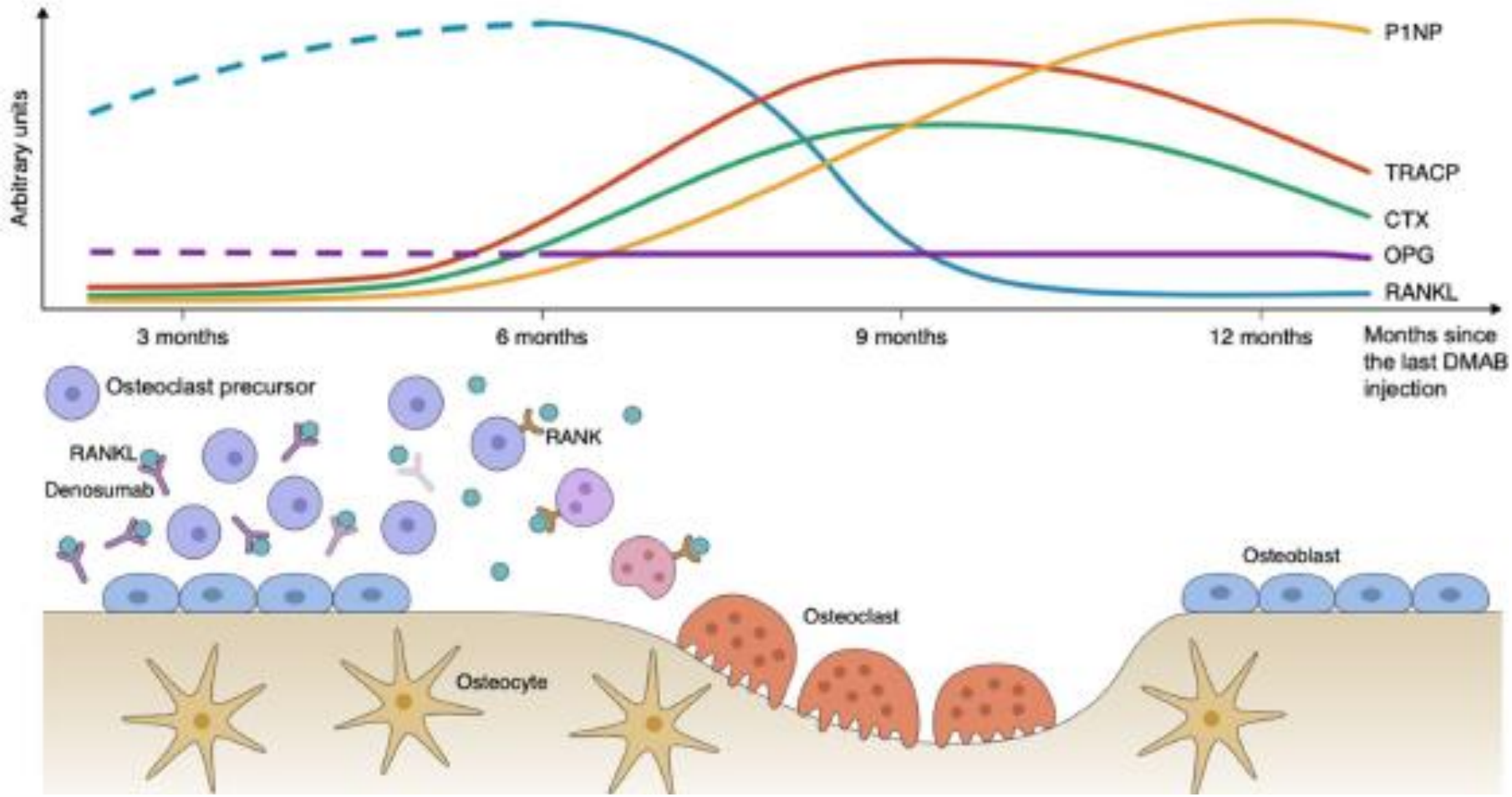
Bone turnover markers in the three groups

	CTX (ug/l)	PINP (ug/l)	TRAcP 5b (U/l)	RANKL (pg/ml)	OPG (pmol/l)
6-month group ($n=20$)	0.21 ± 0.20*	21 ± 10*	3.73 ± 1.9* ↓	368 ± 173* ↑	5.1 ± 2.0
9-month group ($n=18$)	0.80 ± 0.28	85 ± 42	6.56 ± 1.93	96 ± 48	5.1 ± 2.5
12-month group ($n=10$)	0.61 ± 0.16	107 ± 46	6.22 ± 1.22	71 ± 44	5.2 ± 0.3
Between-group differences (ANOVA)	*$p<0.001$*	*$p<0.001$*	*$p<0.001$*	*$p<0.001$*	*$p=0.98$*

Results We found
higher CTX and PINP in the 9 M and 12 M groups compared to the 6 M group ($p < 0.001$). In the 6 M group, TRAcP 5b was lower and RANKL higher than in the other two groups ($p < 0.001$). TRAcP 5b correlated negatively with RANKL ($R = -0.54$), and time since the last DMAB injection correlated positively with CTX ($R = 0.56$), PINP ($R = 0.72$), TRAcP 5b ($R = 0.51$) and negatively with RANKL ($R = -0.70$) ($p < 0.001$ for all). We found no difference in OPG between groups.

Summary In patients discontinuing long-term denosumab, RANKL levels are high 6 months after the last denosumab injection. Nine and 12 months after the last denosumab injection RANKL levels are lower, but TRAcP 5b levels are higher, suggesting that accumulated RANKL increases the number of active osteoclasts.

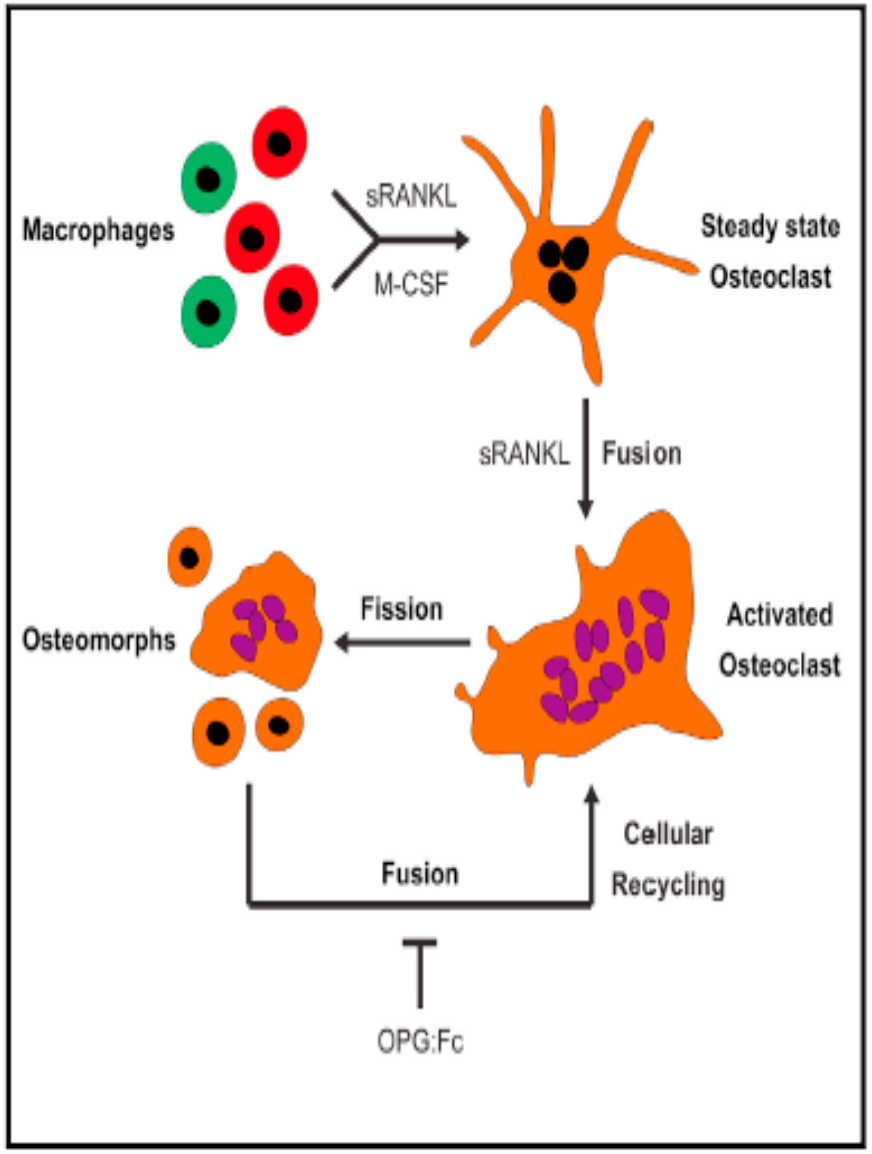
Suggestive mechanisms underlying the rebound activation of bone resorption after DMAB discontinuation



Conclusion: The underlining mechanism of the "rebound phenomenon" when long-term DMAB is discontinued is still not fully understood. Our results support the most accepted theory of an accumulation of inactive osteoclast precursor cells with increasingly higher levels of DMAB-bound RANKL. Once DMAB is discontinued, however, RANKL is released and quickly stimulates an increase in the number of active osteoclasts resulting in a rapid increase in bone turnover.

Cell

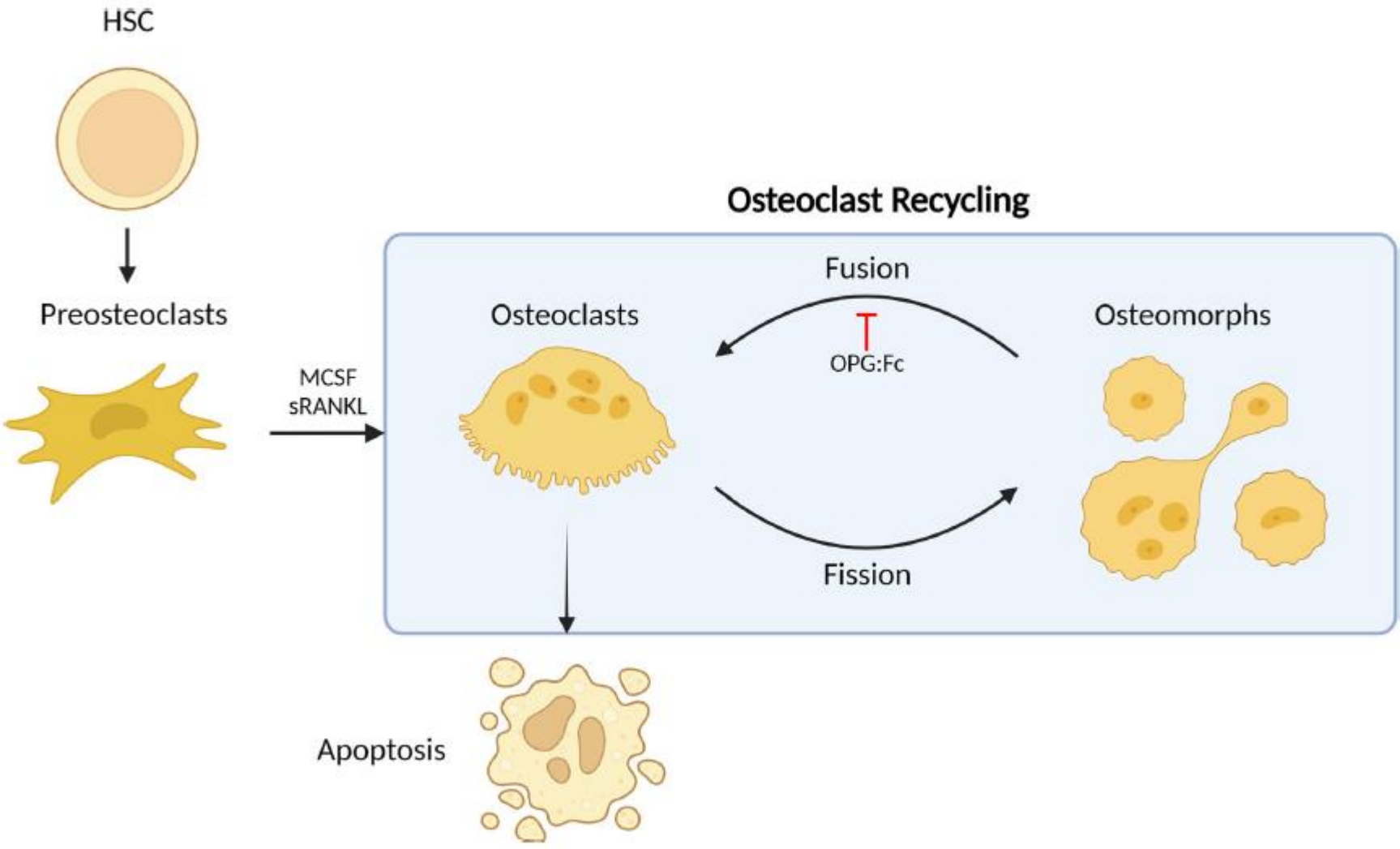
Osteoclasts recycle via osteomorphs during RANKL-stimulated bone resorption



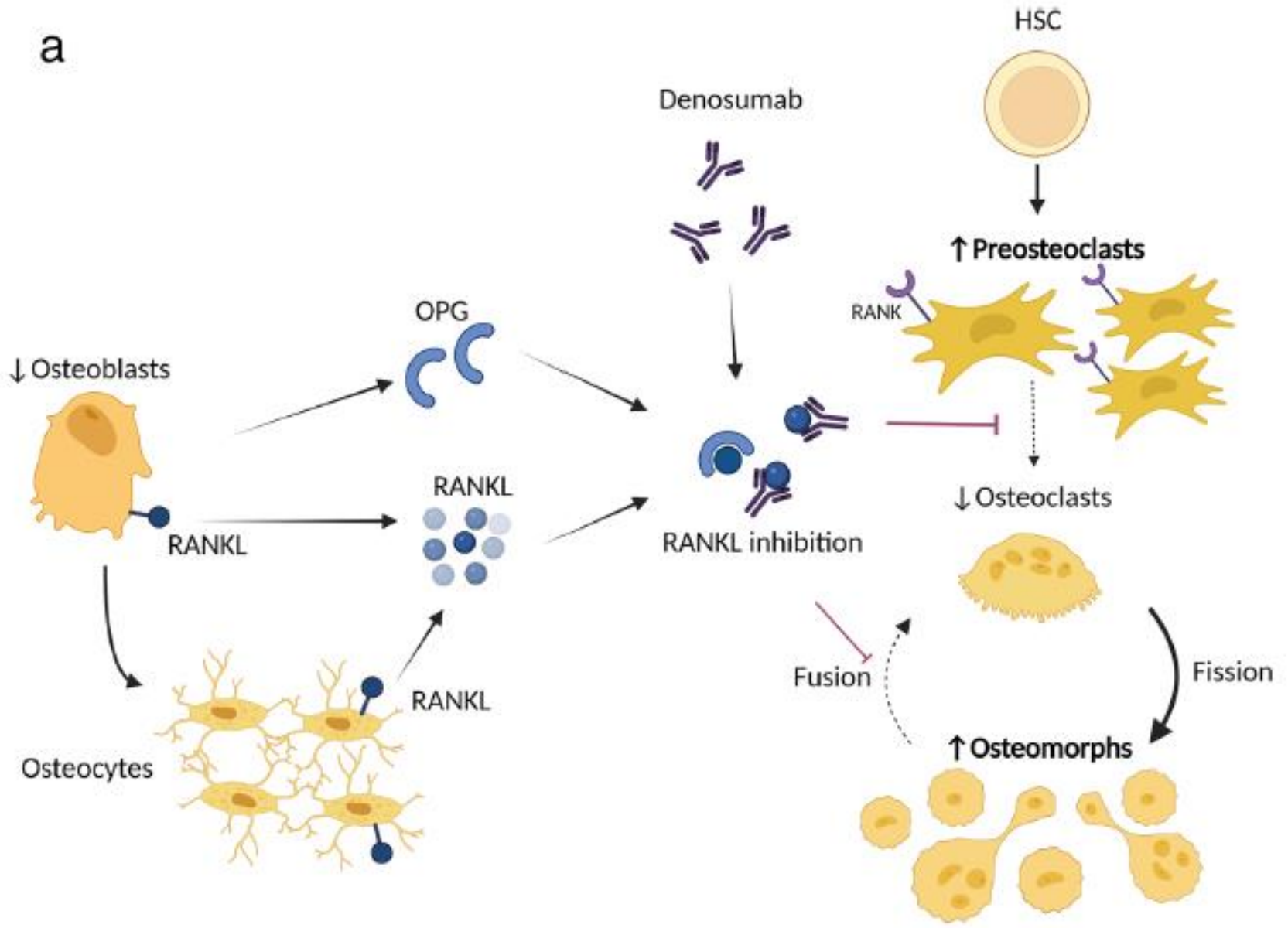
McDonald et al 2021, 184: : 1330-1347.e13

Current Osteoporosis Reports (2022) 20:505–515
https://doi.org/10.1007/s11914-022-00756-5

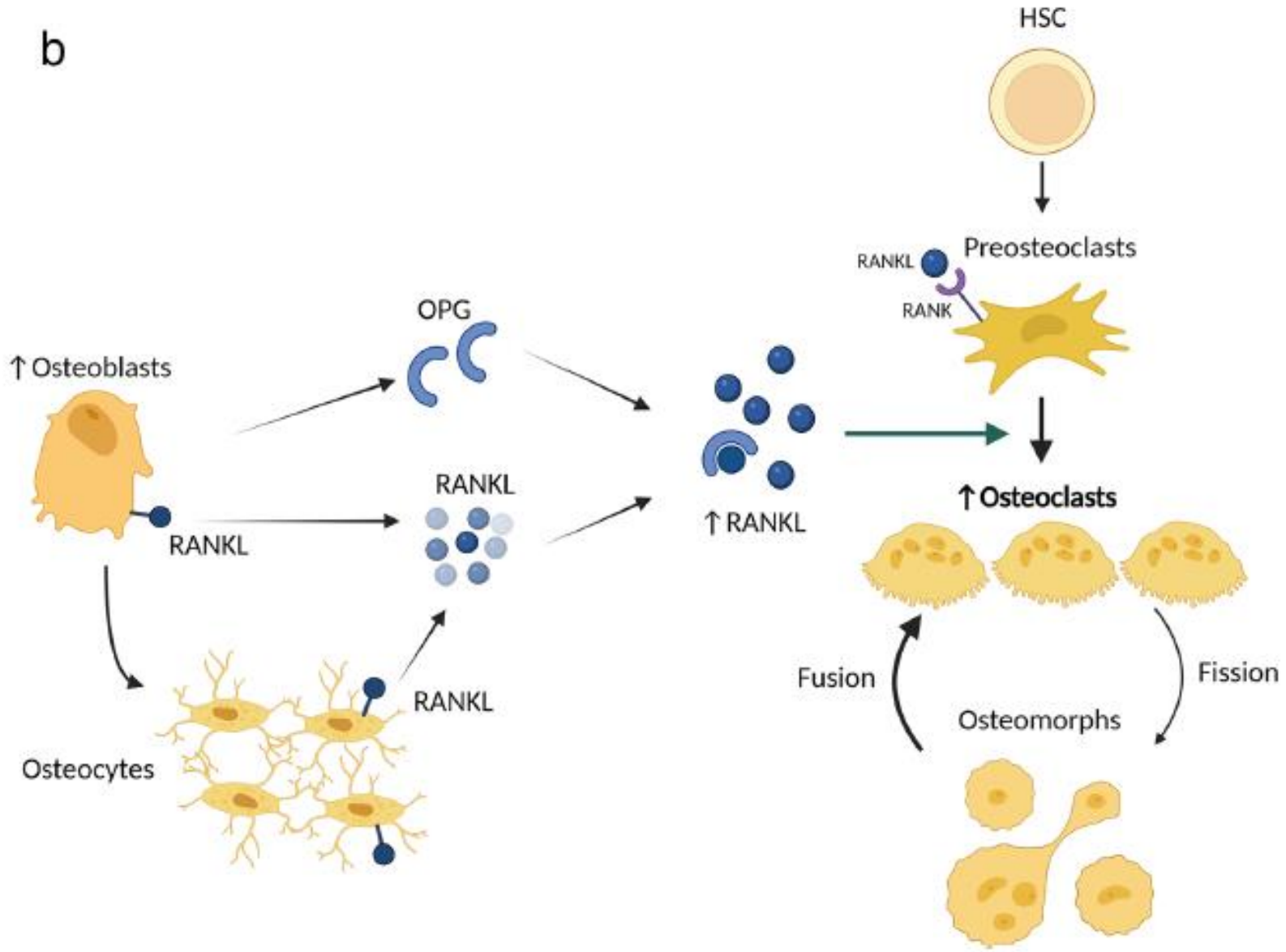
Osteoclast Recycling and the Rebound Phenomenon Following Denosumab Discontinuation



The effect of denosumab on osteoclast recycling.
a During denosumab treatment



The effect of denosumab on osteoclast recycling
b Denosumab discontinuation



Bone 163 (2022) 116498

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journal homepage: www.elsevier.com/locate/bone

Full Length Article

Effects of zoledronate on bone mineral density and bone turnover after long-term denosumab therapy: Observations in a real-world setting

Judith Everts-Graber [a,b,*], Stephan Reichenbach [b,c], Brigitta Gahl [d], HansJörg Häuselmann [e], Hans Rudolf Ziswiler [a], Ueli Studer [a], Thomas Lehmann [a]

Background: The rebound effect after denosumab discontinuation is lessened with subsequent zoledronate therapy. However, it is unclear whether this mitigation is sufficient after long-term denosumab treatment.

Objective: This retrospective observational study analysed bone mineral density (BMD) and bone turnover marker (BTM) changes after denosumab therapy according to treatment duration and subsequent zoledronate regimen.

Methods: We measured the outcomes of 282 women with postmenopausal osteoporosis who discontinued denosumab and received zoledronate 6 months later. In patients with longer denosumab therapy (≥5 years), BTMs were measured every 3 months and a second zoledronate infusion was administered if BTM levels increased by ≥2-fold. The BMD of all women was measured before denosumab therapy, at the last injection and 1 to 2 years after the first zoledronate.

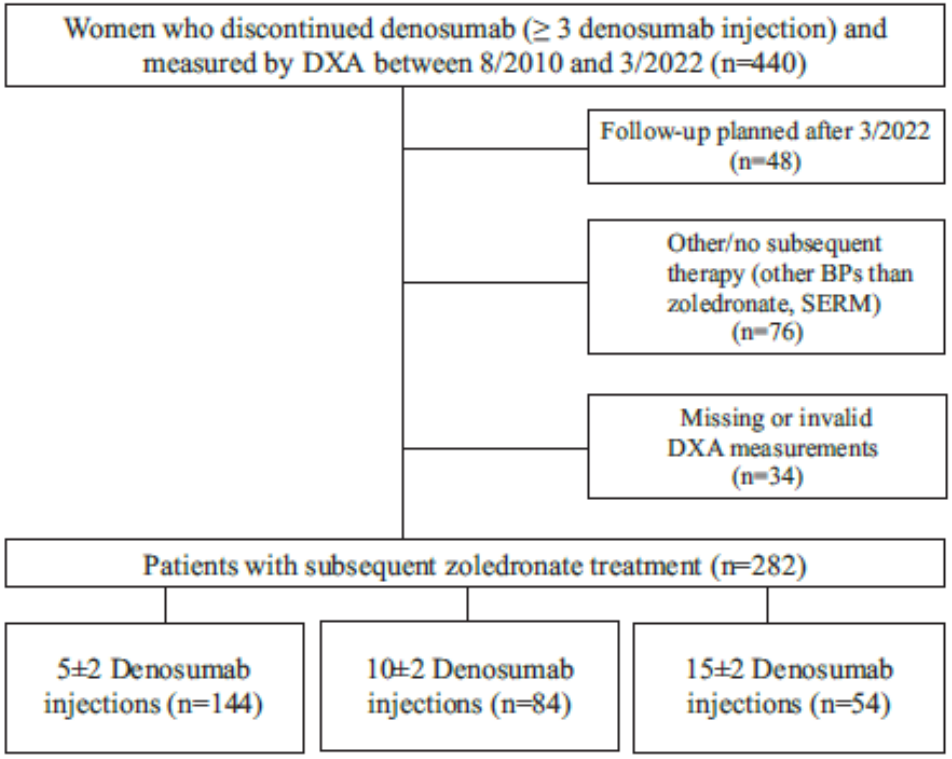
Conclusions: Rebound-associated bone loss reached a plateau after denosumab treatment durations of 4–6 years, irrespective of the frequency of subsequent zoledronate therapy.

We therefore aimed to describe BMD changes in patients who were:

- treated with denosumab for 2 to 9 years and who
- received subsequent treatment with zoledronate.

We evaluated:

- bone mass gains under therapy,
- bone mass changes after switching to zoledronate and the
- evolution of BMD and BTMs in relation to the number of zoledronate infusions given (one versus 2 within 12 months).



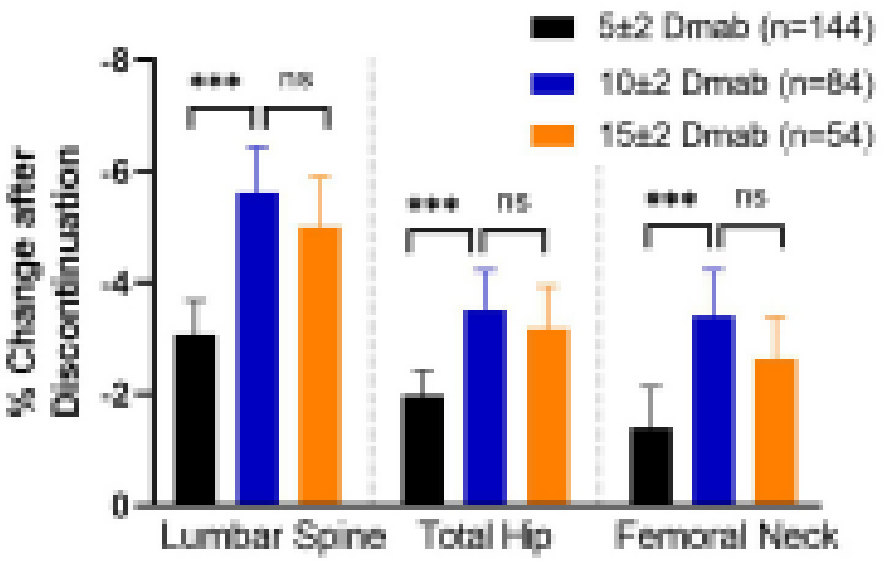
5±2 Dmab (n=144) **Short**

10±2 Dmab (n=84) **Medium**

15±2 Dmab (n=54) **Long**

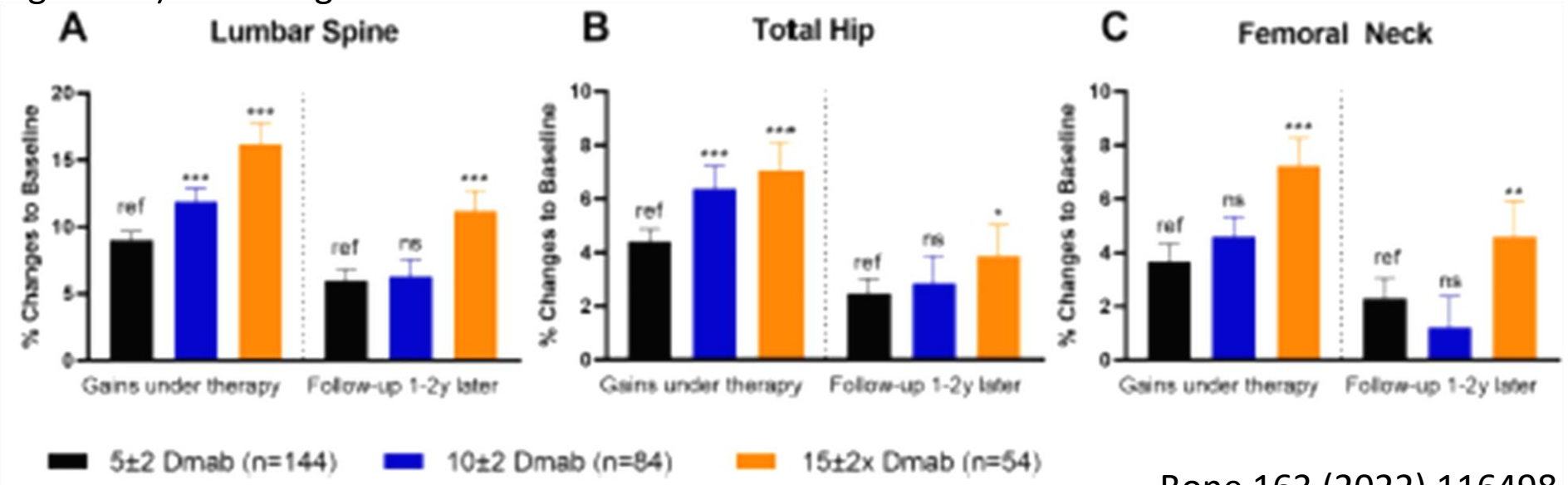
n=282

BMD changes after Dmab discontinuation according to Dmab treatment duration.
BMD changes (mean ± 95%CI) between the last Dmab injection with subsequent zoledronate and follow-Up DXA 18–30 months later, according to dmab duration



BMD changes compared to baseline during and after Dmab therapy

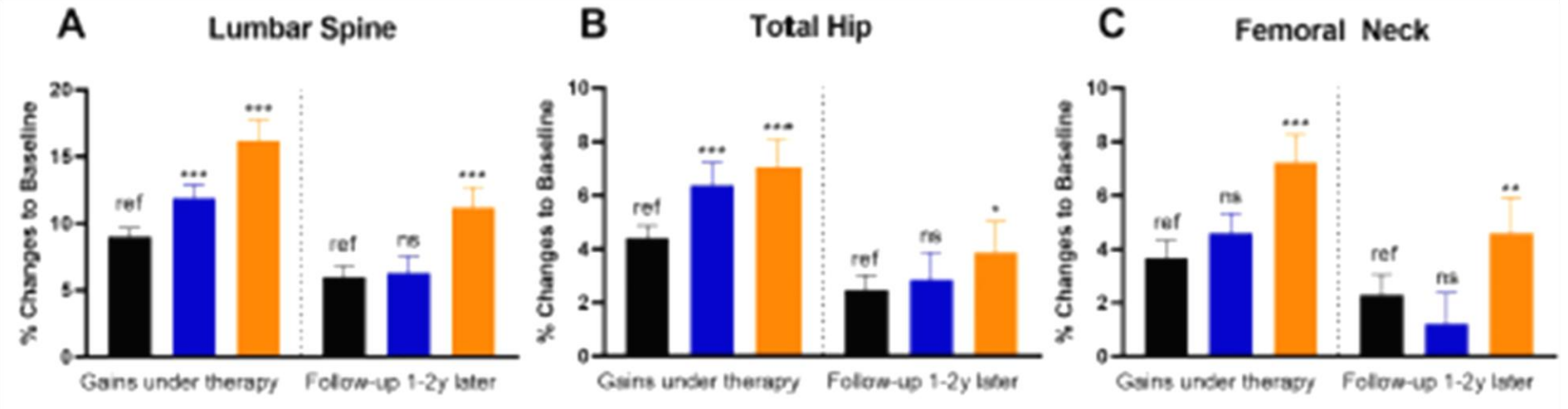
BMD gains under Dmab therapy and net BMD gains 18–30 months after the last Dmab injection and subsequent Zol ("Follow-up 1-2 y later", indicating BMD changes compared to baseline, right side) according to Dmab duration.



Bone 163 (2022) 116498

BMD changes compared to baseline during and after Dmab therapy

BMD gains under Dmab therapy and net BMD gains 18–30 months after the last Dmab injection and subsequent Zol ("Follow-up 1-2 y later", indicating BMD changes compared to baseline, right side) according to Dmab duration.



The net BMD changes compared to baseline were significantly different between the long and short Dmab durations at the LS ($p < 0.001$), TH ($p = 0.020$) and FN ($p = 0.003$).

The BMD changes from baseline showed no significant differences between the short and medium durations at the LS ($p = 0.69$), TH ($p = 0.49$) or FN ($p = 0.12$).

Comparing the BMD changes to baseline between patients with medium and long Dmab durations demonstrated significant increases in the long-term group at the LS and the FN ($p < 0.001$), but not at the TH ($p = 0.2$).

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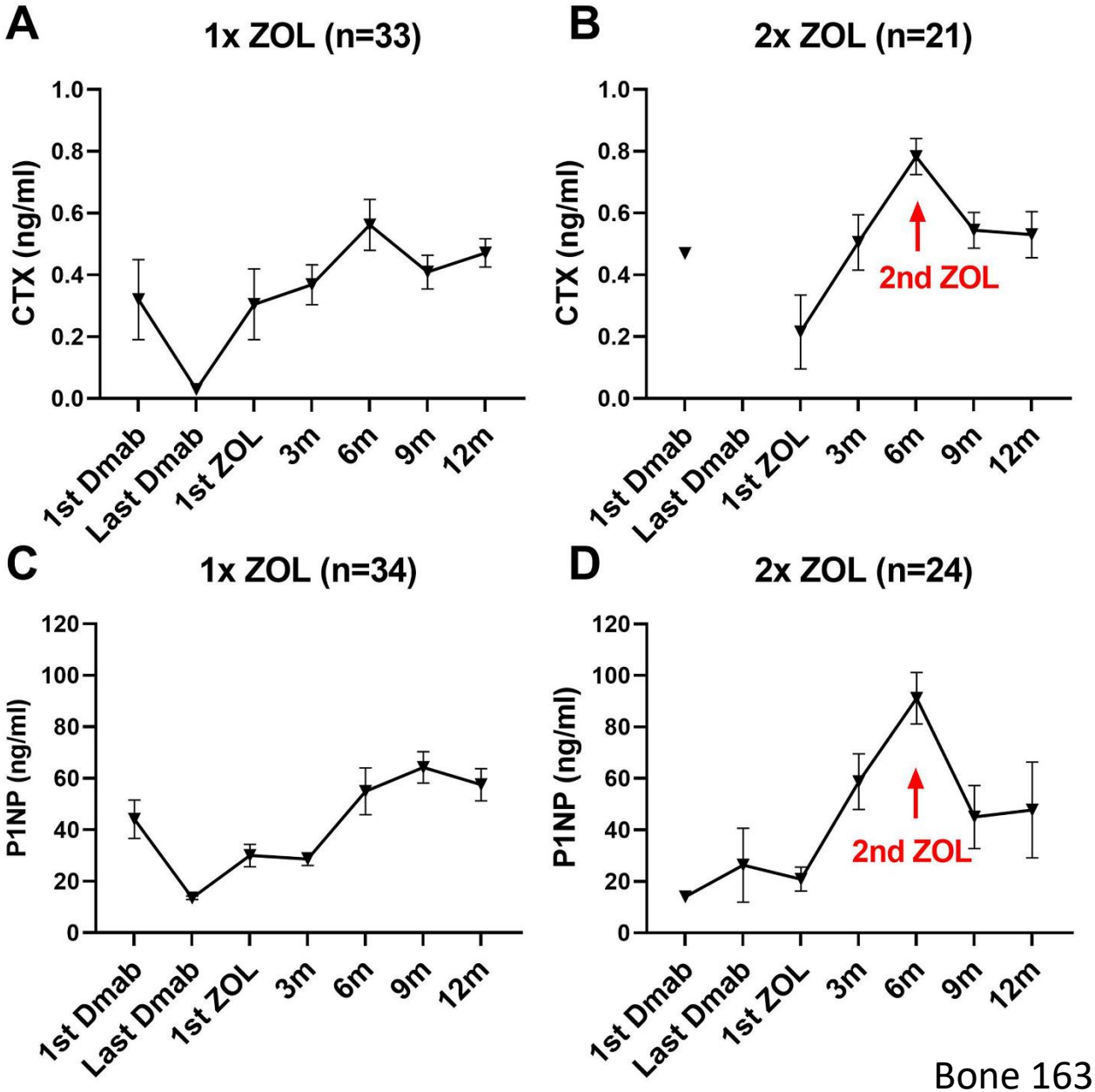
BTM evolution after Dmab discontinuation



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Effects of zoledronate on bone mineral density and bone turnover after long-term denosumab therapy: Observations in a real-world setting

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Conclusions

Our observations suggest that regarding BMD gains, denosumab treatment durations are ideally short (up to 3 years) or long (>7 years), but not medium (4–6 years). Our patients with medium duration treatment did not achieve the best possible BMD gains under denosumab, and experienced the maximal rebound-associated bone loss after its discontinuation. Because this is the first time that BMD changes after long-term denosumab treatment have been compared to medium- and short-duration therapy, this observation needs to be confirmed. In addition, the frequency and timing of (repeated) zoledronate infusions should be further investigated to optimise sequential therapy with denosumab and zoledronate and thereby maximise the preservation of BMD gains achieved under denosumab therapy.

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Commentary

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Short or Long-term Osteoporosis Therapy With Denosumab?

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So, to prevent post-denosumab bone loss, should we treat with denosumab for less than 3 years and then immediately transition to a BP, rather than keep some patients on long-term denosumab, as recently suggested by Everts-Graber et al. That in our view would be detrimental to those patients who have not yet sufficiently improved their BMD and therefore remain at high risk for fractures, since only denosumab continuously accrues BMD upon long-term exposure, and most reported cases of multiple vertebral fractures upon denosumab discontinuation occur in patients with severe osteoporosis. Nevertheless, the study by Makras et al, as well as other recent studies, provide some evidence to support more aggressive BP therapy using Zol infusions in patients exposed for more than 2 to 3 years to denosumab and for whom repeated dosing of Zol may sometimes be necessary within the first year postdenosumab to completely prevent bone loss. Alternatively, older subjects at high fracture risk should be maintained on denosumab, since the long-term benefits/risk of this therapy remain highly favorable. Finally, subjects at very high risk should be treated with shorter sequences starting with a bone-forming drug, such as romosozumab (a sclerostin neutralizing antibody), followed by denosumab or Zol.