

Malattie muscolo-scheletriche e pandemia da SARS-CoV-2

**CATANIA**

24 - 25 settembre 2021

GISMO

Gruppo Italiano Studio
Malattie Metabolismo Osseo
organizzazione di volontariato

- Osteoporosi
- Malattie Muscolo-Scheletriche
- Malattie Metaboliche
- Dolore
- Nutrizione

*Dieci anni di
esperienza con
Denosumab in Italia
...
compresa la pandemia*

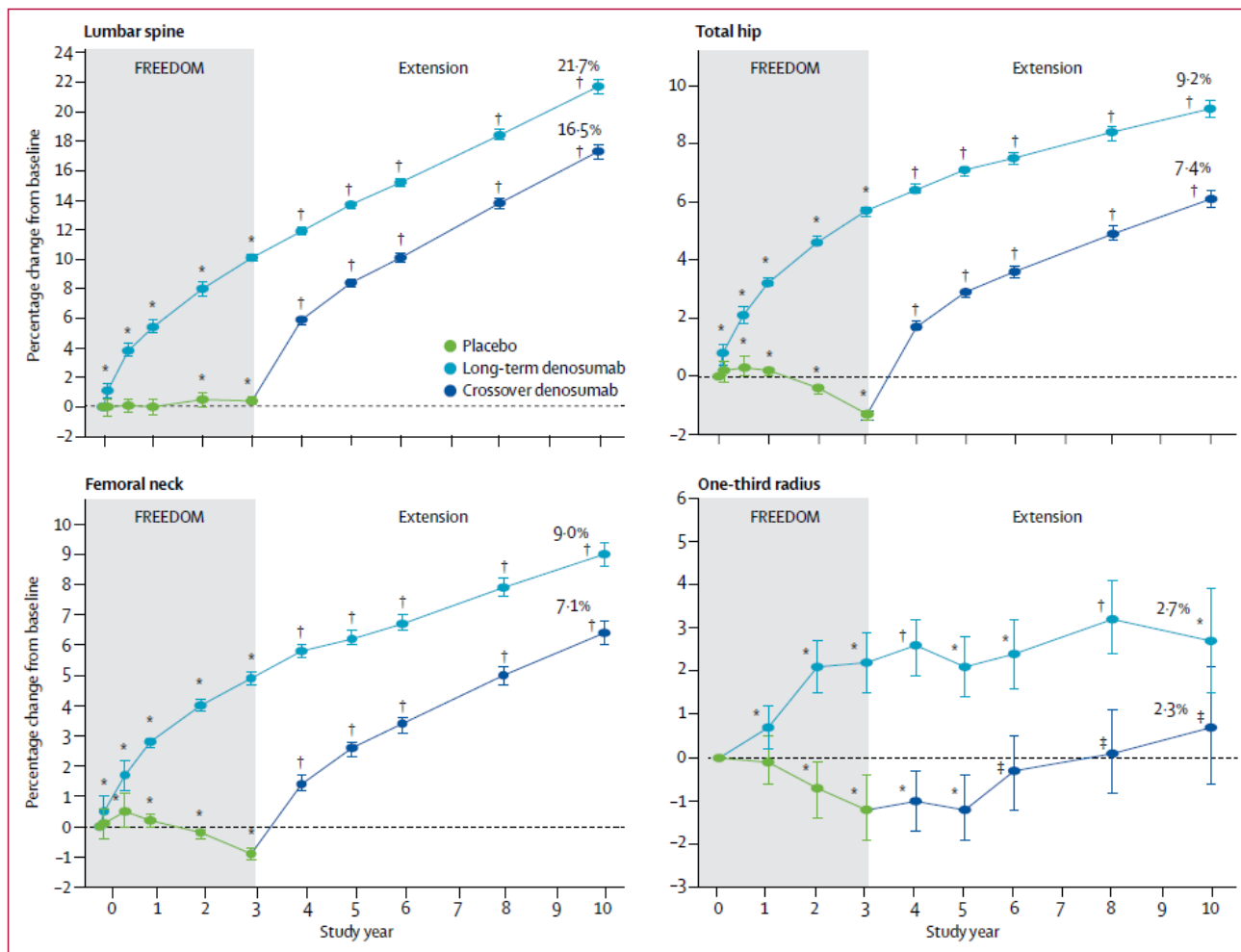
**Prof. Maurizio
Rossini
UOC Reumatologia
Università di Verona**



Disclosures

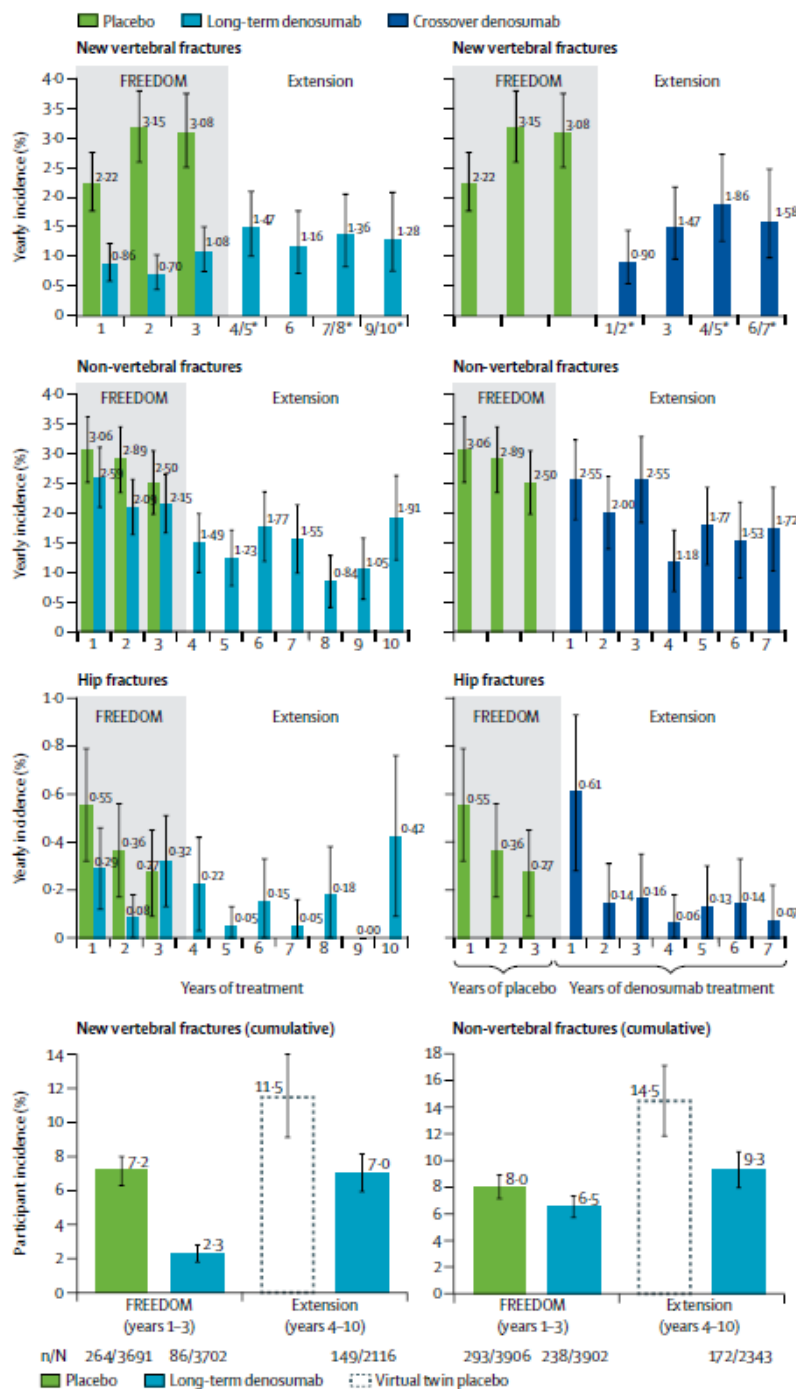
- *AMGEN*
- *ABBVIE*
- *ABIOMED*
- *BMS*
- *ELI LILLY*
- *GALAPAGOS*
- *NOVARTIS*
- *PFIZER*
- *SANDOZ*
- *THERAMEX*
- *UCB*

10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension



10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension

modif by Rossini



. BMD Changes in Studies Included in the Meta-Regression

modif by Rossini

Journal of Bone and Mineral Research, Vol. 34, No. 4, Month 2019, pp 632–642.
DOI: 10.1002/jbmr.3641

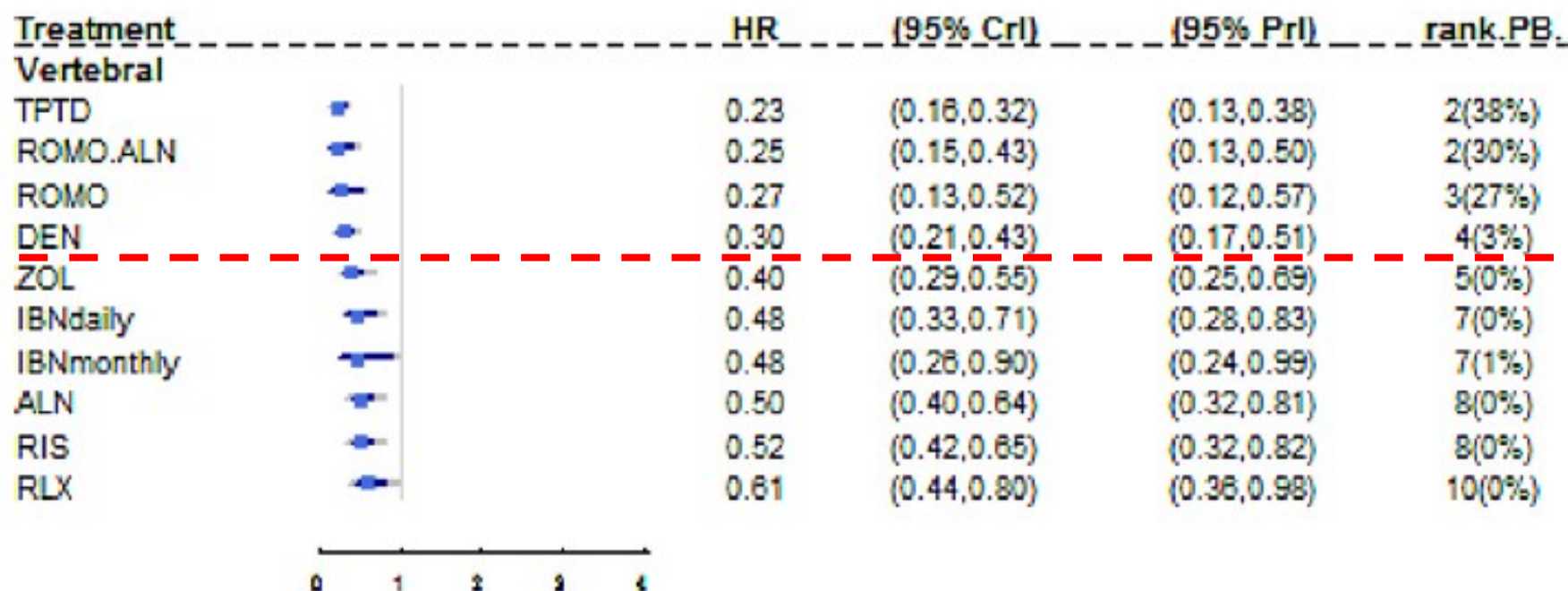
Table 2. BMD changes in studies included in the meta-regression.

Author (year)	Drug	Study duration (years)	Δ TH BMD (%)		Δ FN BMD (%)		Δ LS BMD (%)	
			Placebo	Active	Placebo	Active	Placebo	Active
Anti-sclerostin antibody								
Cosman (2016) ⁽¹⁶⁾	Romosozumab	1	0.00	6.80	−0.70	5.20	0.00	13.30
RANKL inhibitor								
Cummings (2009) ⁽⁶⁾	Denosumab	3	−1.00	5.00	NA	NA	0.05	9.25
Nakamura (2014) ⁽⁴⁸⁾	Denosumab	2	−1.10	4.60	−1.10	4.00	0.10	9.10
PTH(1-84) and PTH analogs								
Miller (2016) ⁽¹⁸⁾	Abaloparatide	1.5	−0.10	4.18	−0.43	3.60	0.63	11.20
Neer (2001) ⁽¹²⁾	PTH(1-34)	1.8	−1.00	3.10	−0.70	3.95	1.10	11.70
Nakamura (2012) ⁽¹³⁾	PTH(1-34)	1.4	0.10	3.10	−0.50	1.80	0.30	6.70
Fujita (2013) ⁽¹⁴⁾	PTH(1-34)	1.5	NA	NA	NA	NA	0.50	4.40
Greenspan (2007) ⁽¹⁵⁾	PTH(1-84)	1.4	−1.09	1.02	−0.69	1.78	−0.32	6.53
Bisphosphonate								
Liberman (1995) ⁽³³⁾	Alendronate	3	NA	NA	−1.30	3.53	−0.80	6.83
Black (1996) ⁽³⁴⁾	Alendronate	3	−1.50	3.20	−0.40	3.70	1.80	8.00
Cummings (1998) ⁽³⁵⁾	Alendronate	4	−1.60	3.40	−0.80	3.80	1.50	8.30
Hosking (1998) ⁽³⁶⁾	Alendronate	2	−1.40	1.45	NA	NA	−1.80	2.90
Pols (1999) ⁽³⁷⁾	Alendronate	1	0.10	3.10	−0.20	2.30	0.10	5.00
Greenspan (2002) ⁽³⁸⁾	Alendronate	2	NA	NA	−0.10	3.30	2.00	6.40
Black (2007) ⁽³⁹⁾	Zoledronic acid	3	−2.00	4.02	−1.00	4.06	0.20	6.90
Lyles (2007) ⁽⁴⁴⁾	Zoledronic acid	5	−0.90	5.50	−0.70	3.60	NA	NA
Boonen (2012) ⁽⁴⁵⁾	Zoledronic acid	2	0.20	2.30	0.10	3.40	1.60	7.70
Nakamura(2017) ⁽⁴⁶⁾	Zoledronic acid	2	−0.70	3.30	−0.50	3.50	0.30	7.90

Clinical effectiveness of denosumab, raloxifene, romosozumab, and teriparatide for the prevention of osteoporotic fragility fractures: A systematic review and network meta-analysis

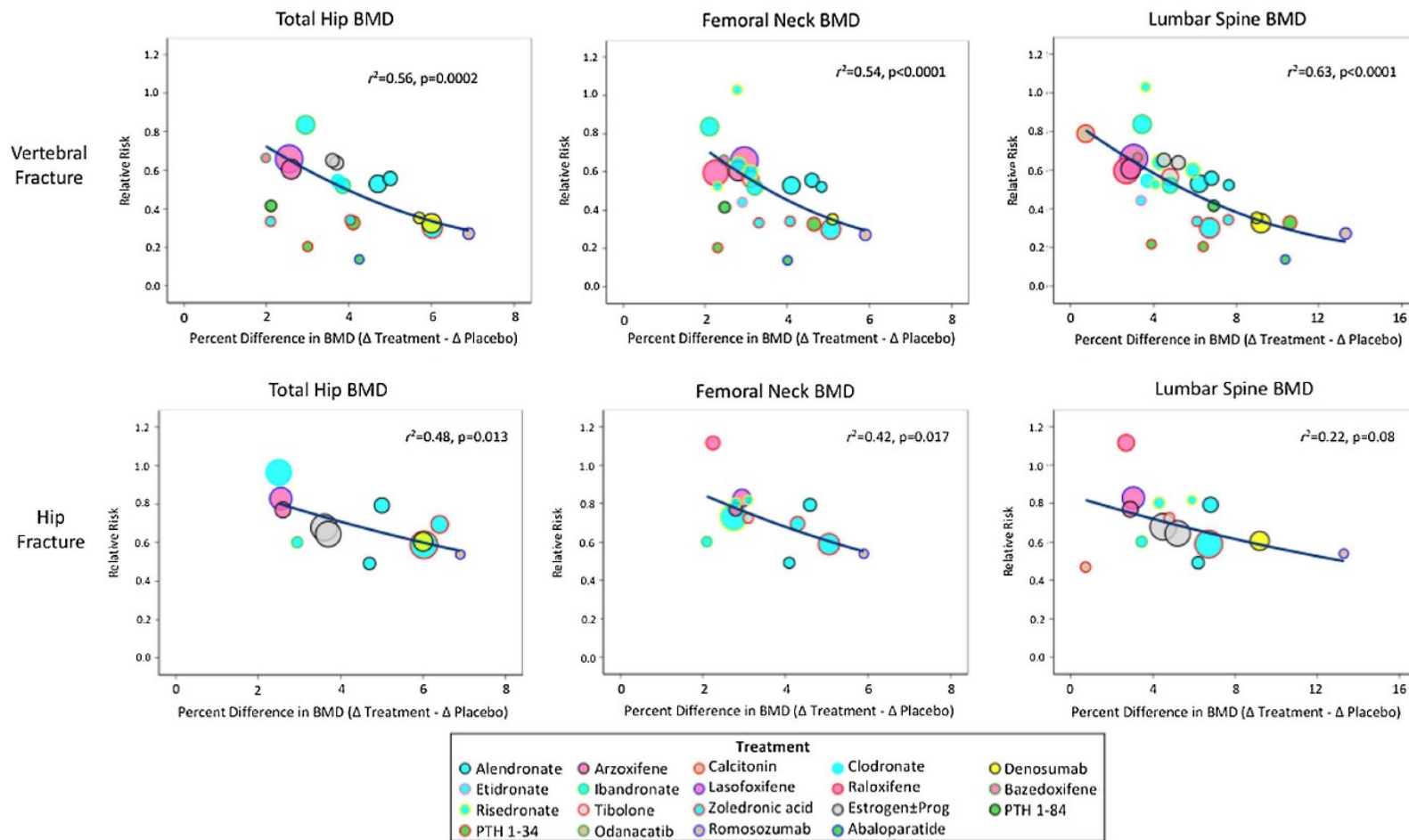
E.L. Simpson*, Marrissa Martyn-St James, Jean Hamilton, Ruth Wong, Neil Gittoes, Peter Selby, Sarah Davis

Effects of treatment on vertebral fractures relative to placebo.

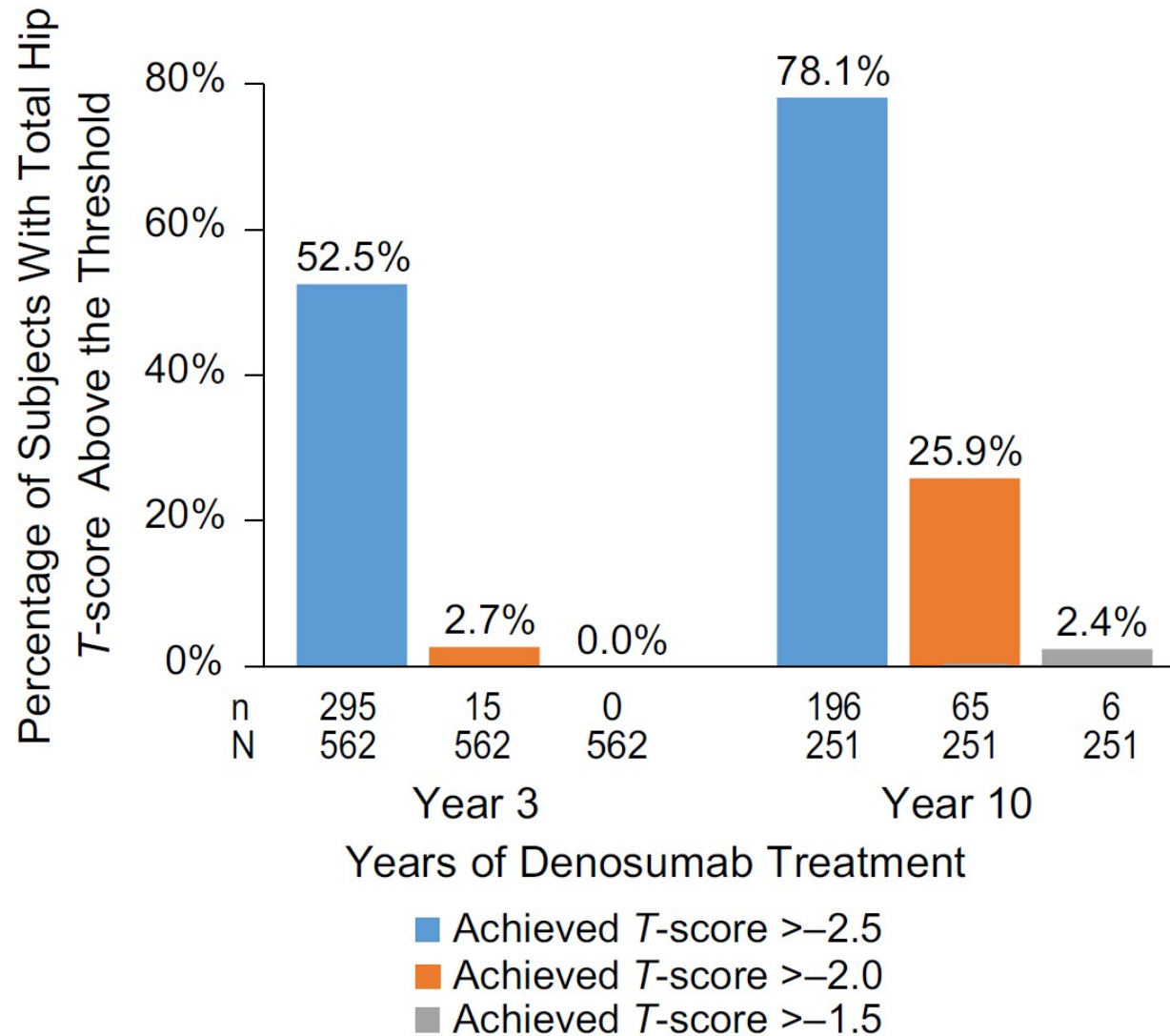


Change in Bone Density and Reduction in Fracture Risk: A Meta-Regression of Published Trials

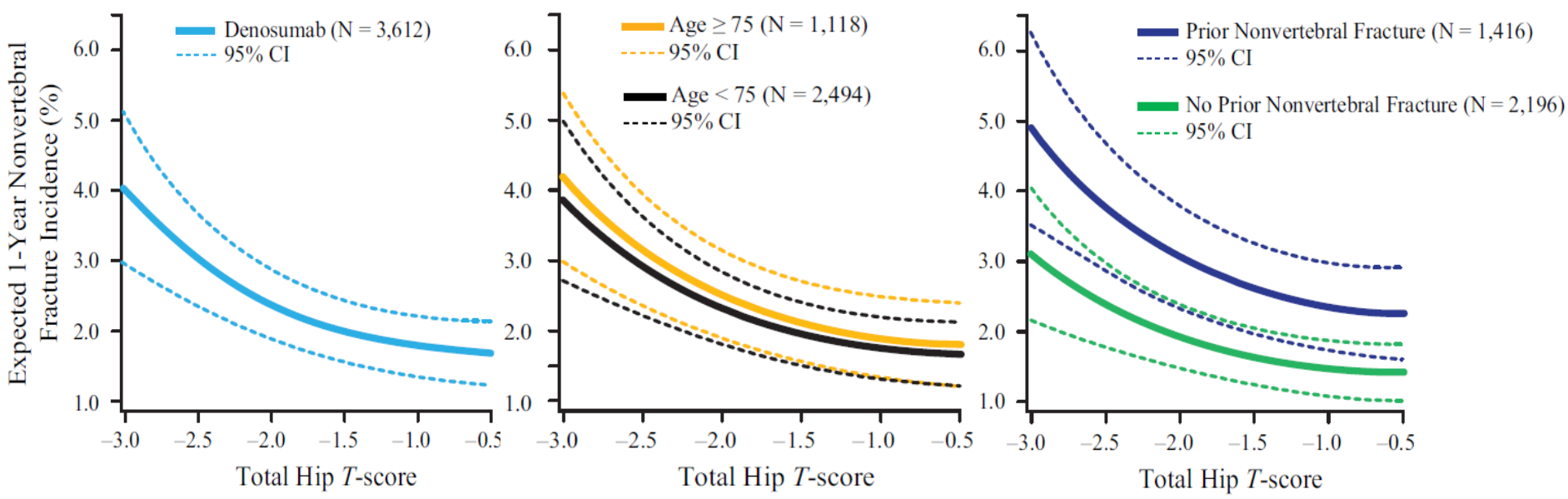
improvements in BMD with osteoporosis therapies may be useful surrogate endpoints for fracture



Percentage of subjects with a osteoporosis attaining T-scores of osteopenia with denosumab



Relationship Between Bone Mineral Density T-Score and Nonvertebral Fracture Risk Over 10 Years of Denosumab Treatment

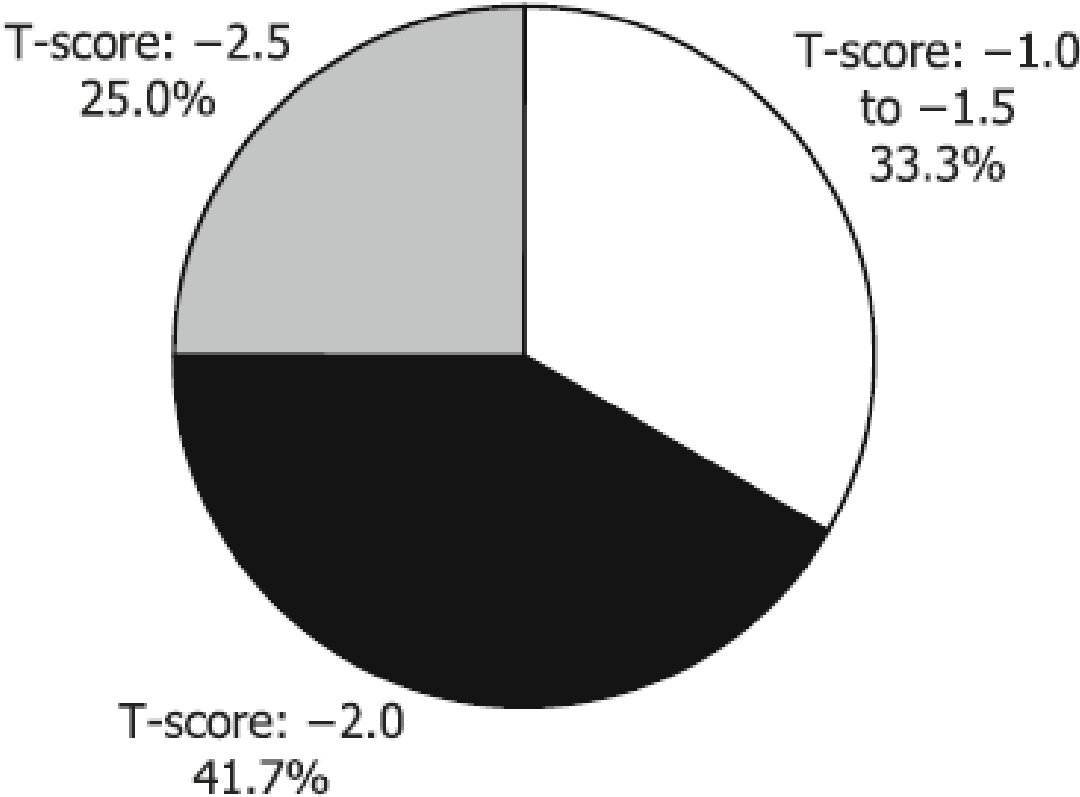


importance of follow-up BMD measurements in patients receiving denosumab therapy because BMD remains a robust indicator of fracture risk

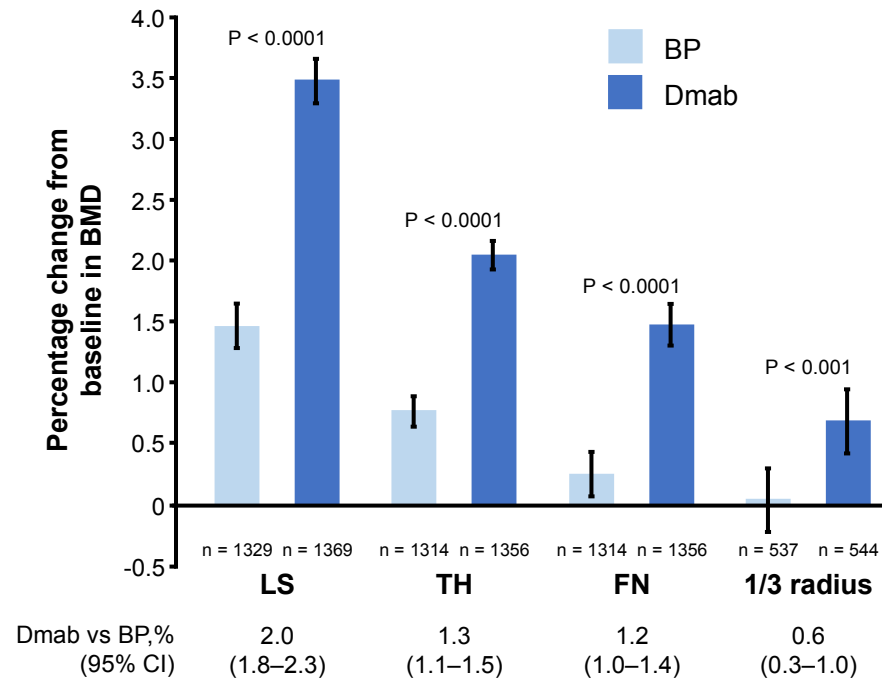


Is a treat-to-target strategy in osteoporosis applicable in clinical practice? Consensus among a panel of European experts

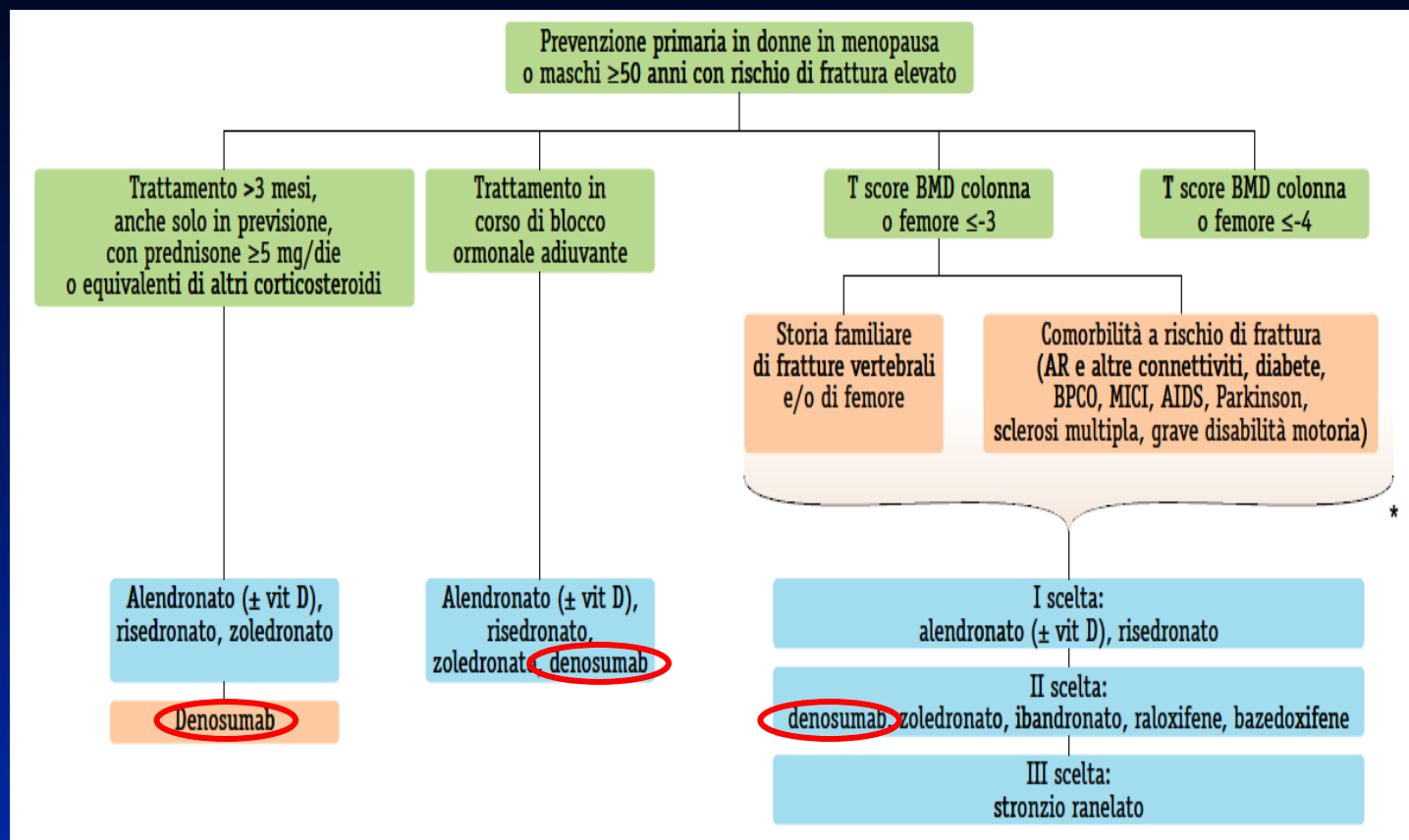
T. Thomas¹ • E. Casado² • P. Geusens^{3,4} • W. F. Lems⁵ • J. Timoshanko⁶ • D. Taylor⁷ • L. C. Hofbauer⁸



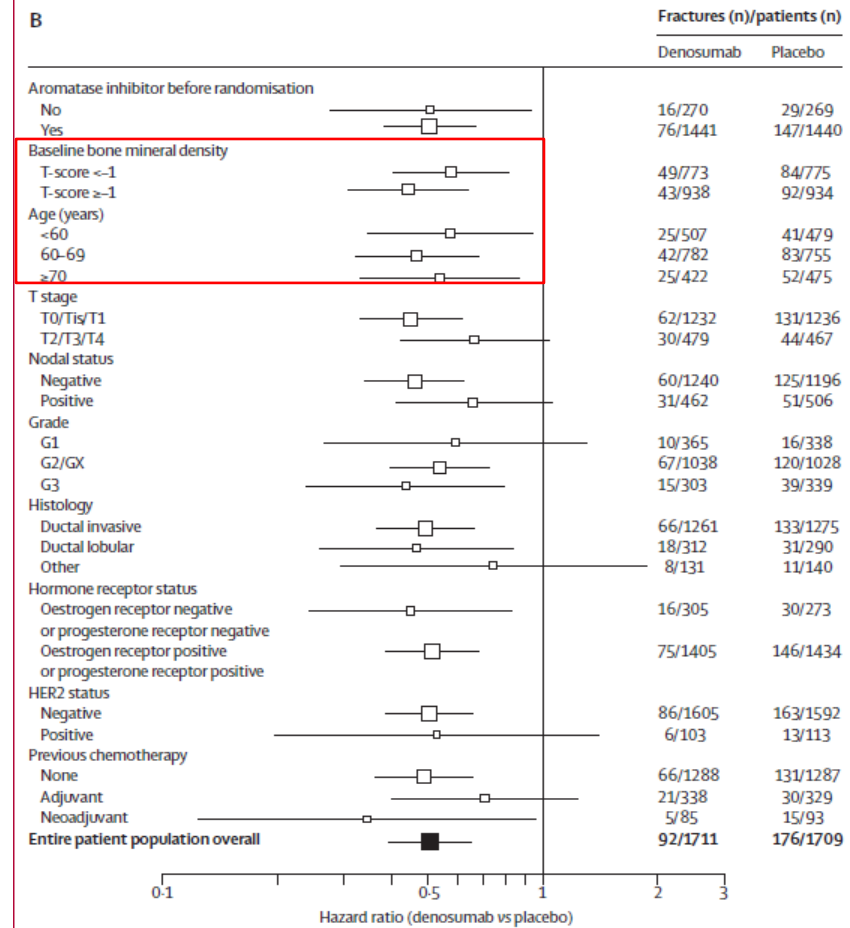
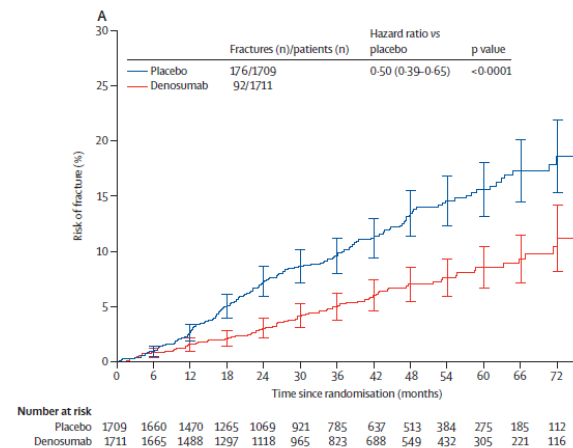
Transitioning from BPs to Dmab is more effective in increasing BMD at all sites than continuing treatment with BPs



Nota 79 AIFA per la Prevenzione Primaria



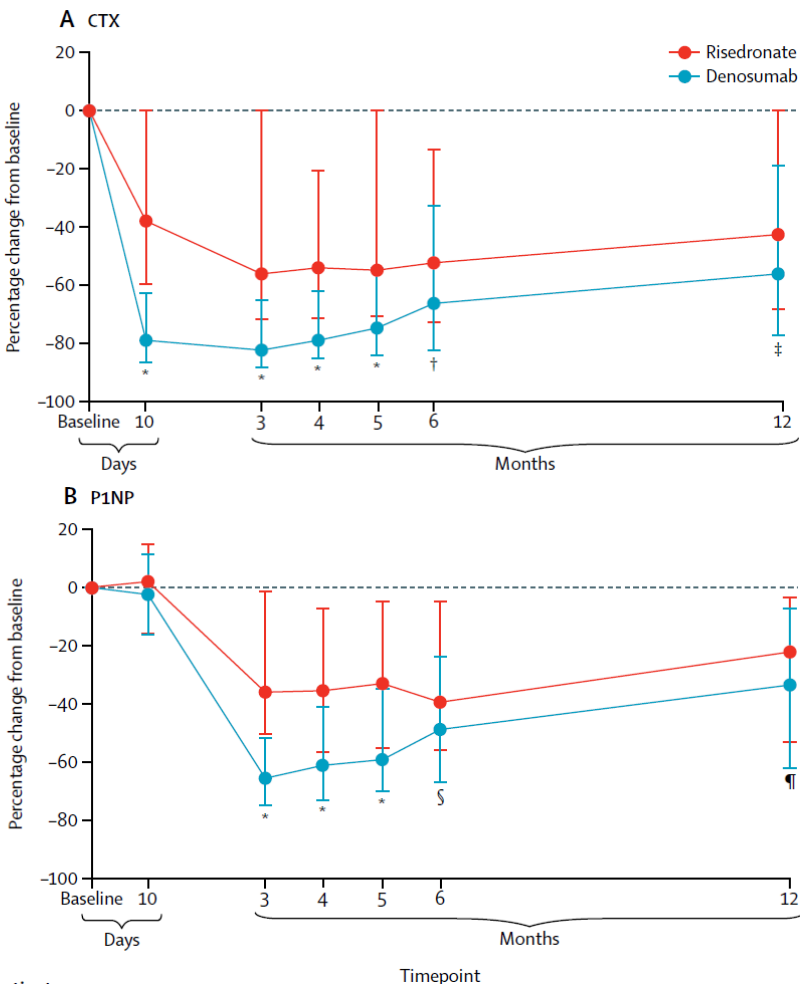
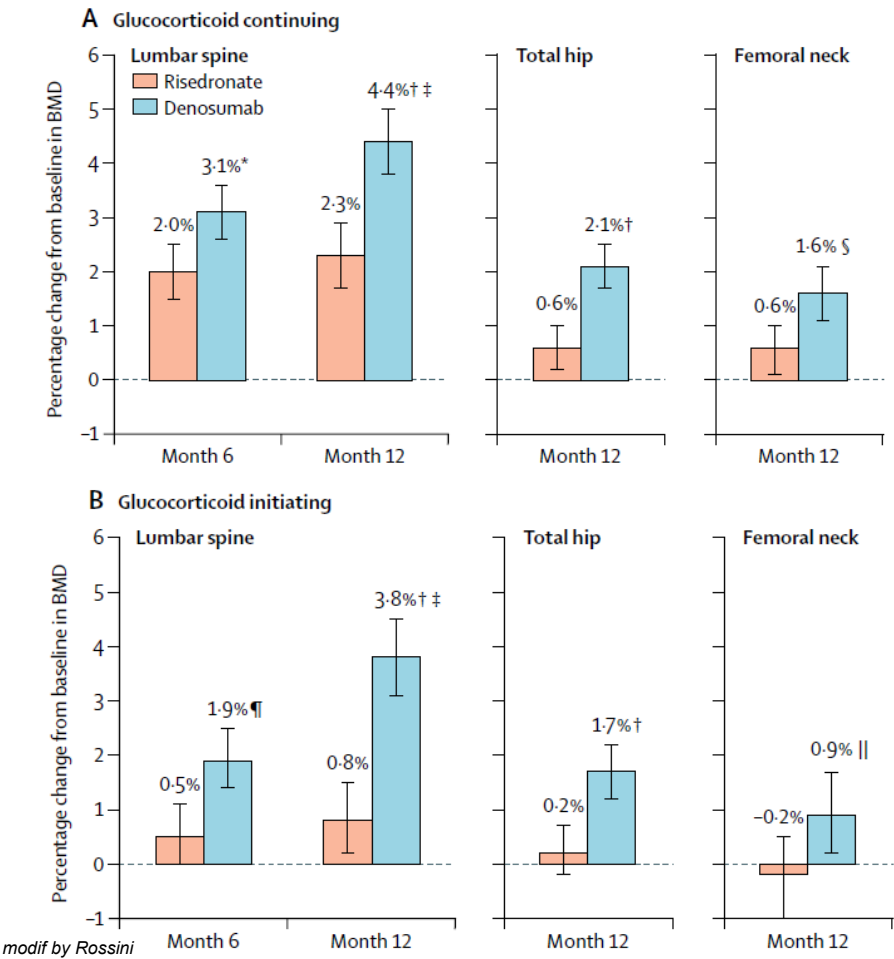
Adjuvant denosumab in breast cancer



modif by Rossini

Gnant et al, Lancet, 2015

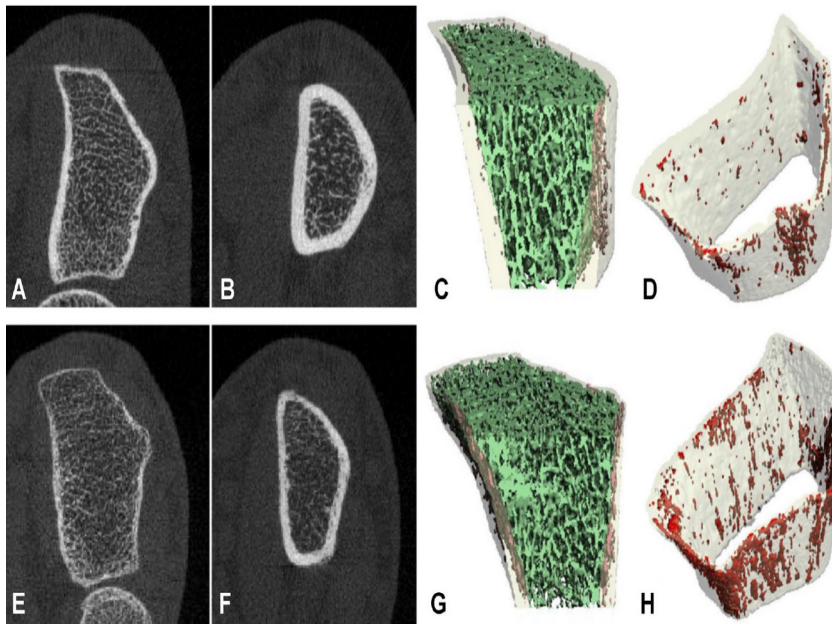
Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind



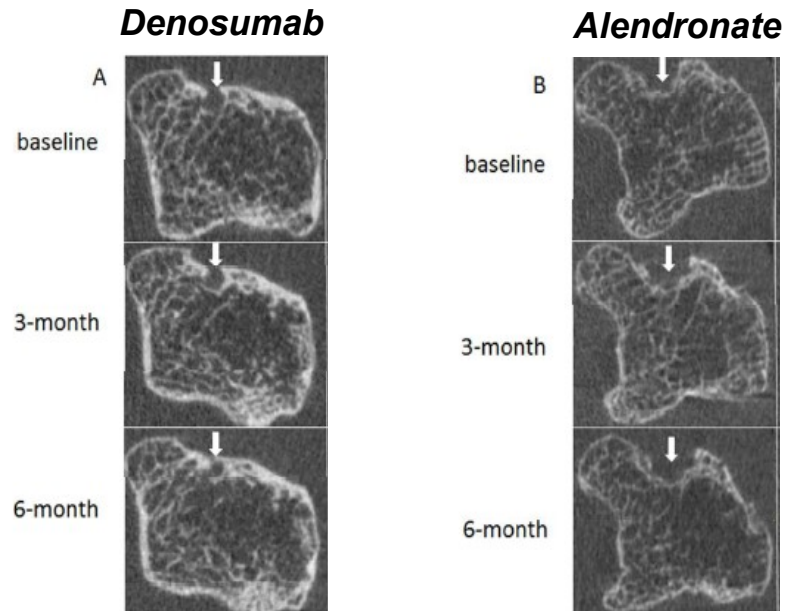
Off-label uses of denosumab in metabolic bone diseases

Expert opinion on off-label denosumab use in metabolic bone diseases based on current evidence and the pathogenesis of each disease.		
Disease	Suggestion based on preliminary results (Yes; Yes in specific conditions; No; Neither yes or not) ^a	Specific conditions to be considered
Dmab administered mainly for BMD and/or BTM improvement and/or fracture risk reduction		
Paget's disease of bone	Yes in specific conditions	Renal impairment; BP contraindication; giant cell tumor co-existence
Juvenile Paget disease	Yes	
Fibrous dysplasia	Yes	
Thalassemia bone disease	Yes	
CKD-associated bone disease	Yes in specific conditions	sHPT
Organ transplantation-associated bone disease	Yes in specific conditions	Renal impairment; contraindication or unresponsiveness to other treatment options
Osteogenesis imperfecta	Neither yes or not	Possible use: Cases with mutations in the <i>SERPINF1</i> gene; renal impairment; BP contraindication; unresponsiveness to BP
Mastocytosis	Neither yes or not	
Neurofibromatosis	Neither yes or not	
Osteoradionecrosis	Neither yes or not	
Multiple system atrophy	Neither yes or not	
Duchenne muscular dystrophy	Neither yes or not	
Spinal cord injury-associated bone loss	Neither yes or not	
Anorexia Nervosa	Neither yes or not	
Hypophosphatasia	No	
Pregnancy and lactation-associated osteoporosis	No	
Dmab administered mainly to manage symptoms and lesions		
Hajdu Cheney syndrome	Yes	
Langerhans cell histiocytosis	Yes	
Giant cell granuloma	Yes in specific conditions	Lesions recurrent, disfiguring and resistant to other treatment options
Aneurysmal bone cysts	Yes in specific conditions	Renal impairment; contraindication or unresponsiveness to other treatment options
Melorheostosis	Neither yes or not	Possible use: BP contraindication; unresponsiveness to BP
Diffuse sclerosing osteomyelitis	Neither yes or not	
Bone marrow edema syndrome	Neither yes or not	
Perthes' disease	Neither yes or not	
Low Back Pain and Modic Changes	Neither yes or not	
Gorham-Stout disease	Neither yes or not	
Charcot neuropathic osteoarthropathy	Neither yes or not	
Periprosthetic osteolysis	Human data still unpublished	
Dmab administered mainly to manage hypercalcemia		
Hyperparathyroidism	Yes in specific conditions	Renal impairment; resistant hypercalcemia; hypercalcemia before PTx; patients unable to undergo PTx (palliative treatment)
Immobilization hypercalcemia	Yes	
Tuberculosis-associated hypercalcemia	Yes in specific conditions	Renal impairment
Myelofibrosis	Neither yes or not	

Rheumatology Unit, Department of Medicine, University of Verona, Verona, Italy



Zhu TY et al, JBMR, 2014

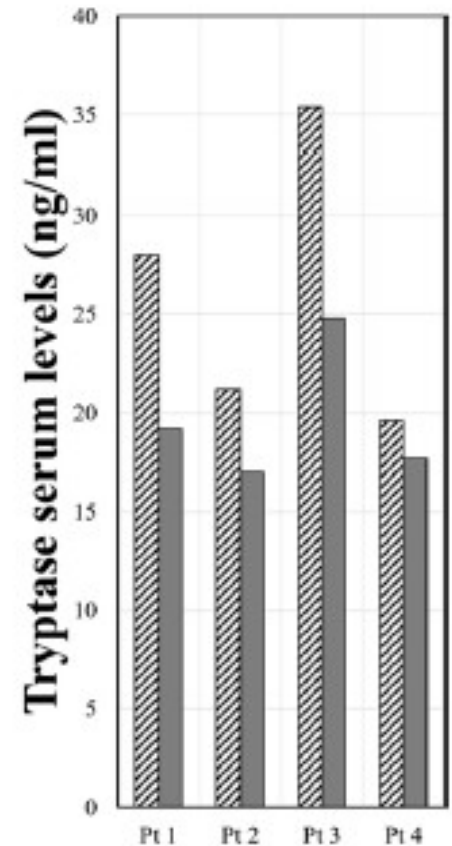
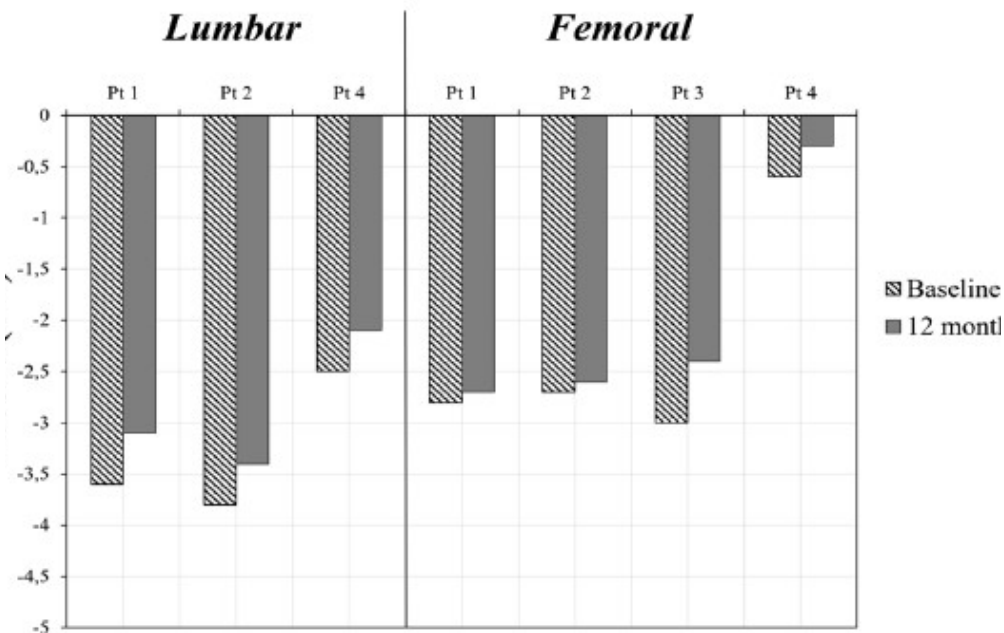


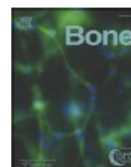
Yue et al, Arthritis Care Res, 2017

ORIGINAL RESEARCH

Denosumab for the Treatment of Mastocytosis-Related Osteoporosis: A Case Series

Giovanni Orsolini¹ · Irene Gavioli¹ · Gaia Tripi¹ · Ombretta Viapiana¹ · Davide Gatti¹ · Luca Idolazzi¹ · Roberta Zanotti² · Maurizio Rossini¹





Case Report

Hajdu Cheney Syndrome; report of a novel *NOTCH2* mutation and treatment with denosumab☆

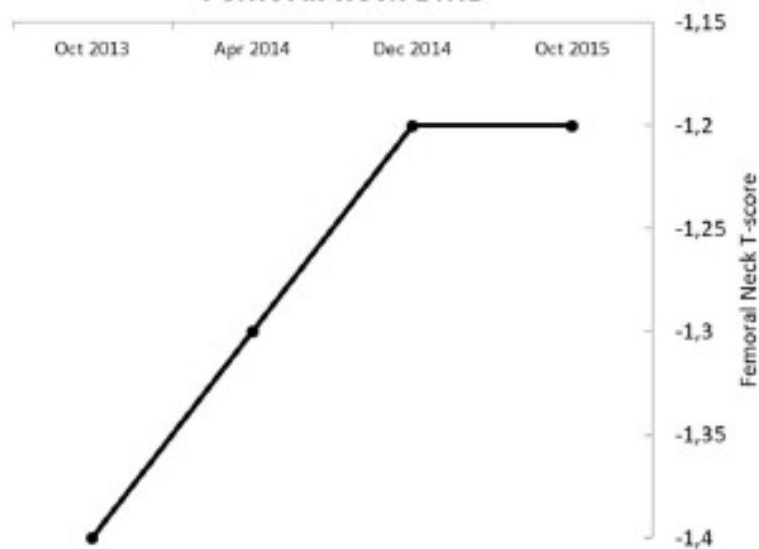
Giovanni Adami ^{a,*}, Maurizio Rossini ^a, Davide Gatti ^a, Giovanni Orsolini ^a, Luca Idolazzi ^a, Ombretta Viapiana ^a, Aldo Scarpa ^b, Ernesto Canalis ^c

^a Rheumatology Unit, Department of Medicine, University of Verona, Piazzale L. Scuro 2, 37134 Verona, Italy

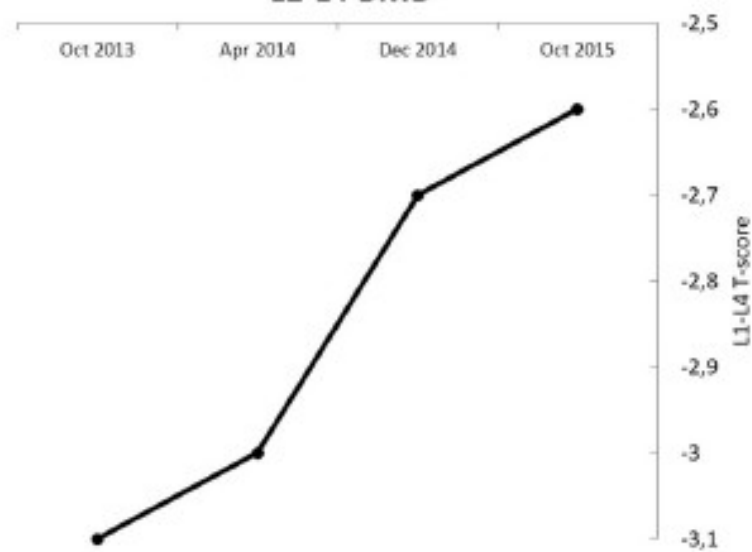
^b ARC-Net Research Centre, University and Hospital Trust of Verona, Piazzale L. Scuro 2, 37134 Verona, Italy

^c Department of Orthopaedic Surgery, the UConn Musculoskeletal Institute, UConn Health, Farmington, CT 06030, United States

Femoral neck BMD



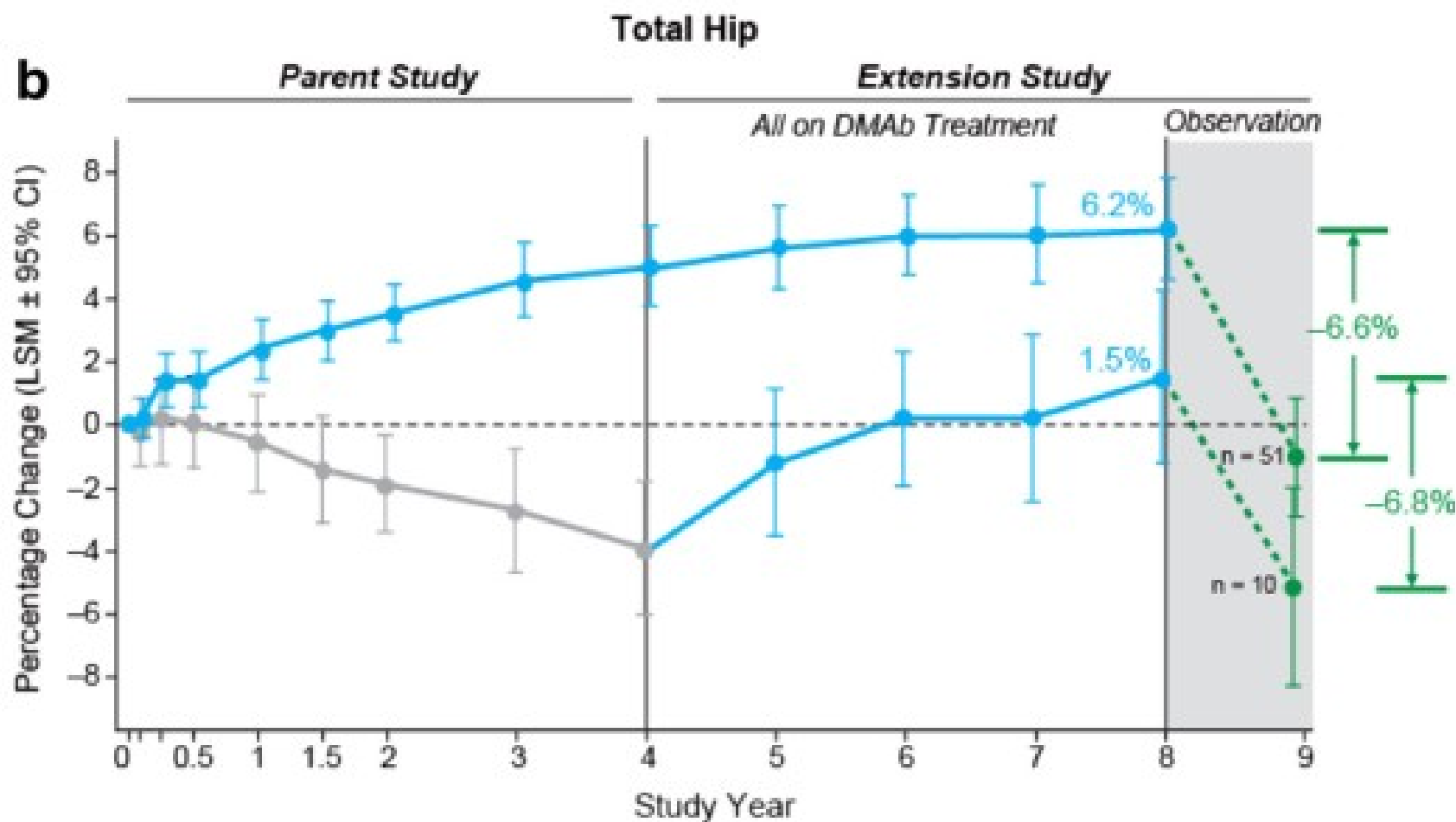
L1-L4 BMD



modif. by Rossini

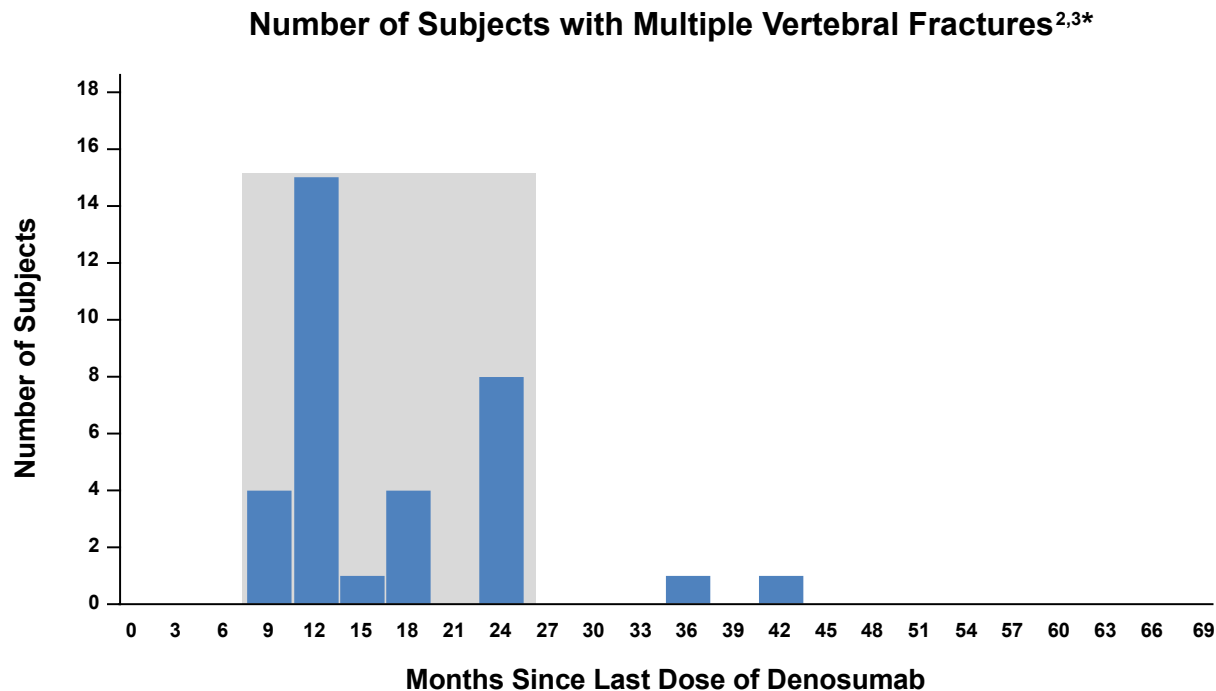
Observations following discontinuation of long-term denosumab therapy

M. R. McClung^{1,2} · R. B. Wagman³ · P. D. Miller⁴ · A. Wang³ · E. M. Lewiecki⁵



Multiple Vertebral Fractures after Denosumab Discontinuation Primarily Appear to Occur During a Period Associated with Transient Increases in Bone Resorption Markers Above Baseline Levels

In a Phase 3 postmenopausal osteoporosis prevention study, denosumab discontinuation led to transient increases in serum CTX that exceeded pre-treatment baseline levels from around the 8th month through the 24th month after the last denosumab dose¹



All content on this slide is currently a working hypothesis subject to change.

*Shaded box reflects period during which serum CTX levels were observed to transiently increase above baseline levels after denosumab discontinuation.

CTX=C-terminal telopeptide of type 1 collagen

1. Bone HG, et al. *J Clin Endocrinol Metab.* 2011;96:972-980. 2. Adapted from: Ferrari S, et al. *ENDO* 2017 Abstract OR08-3. 3. Data on File, Amgen.

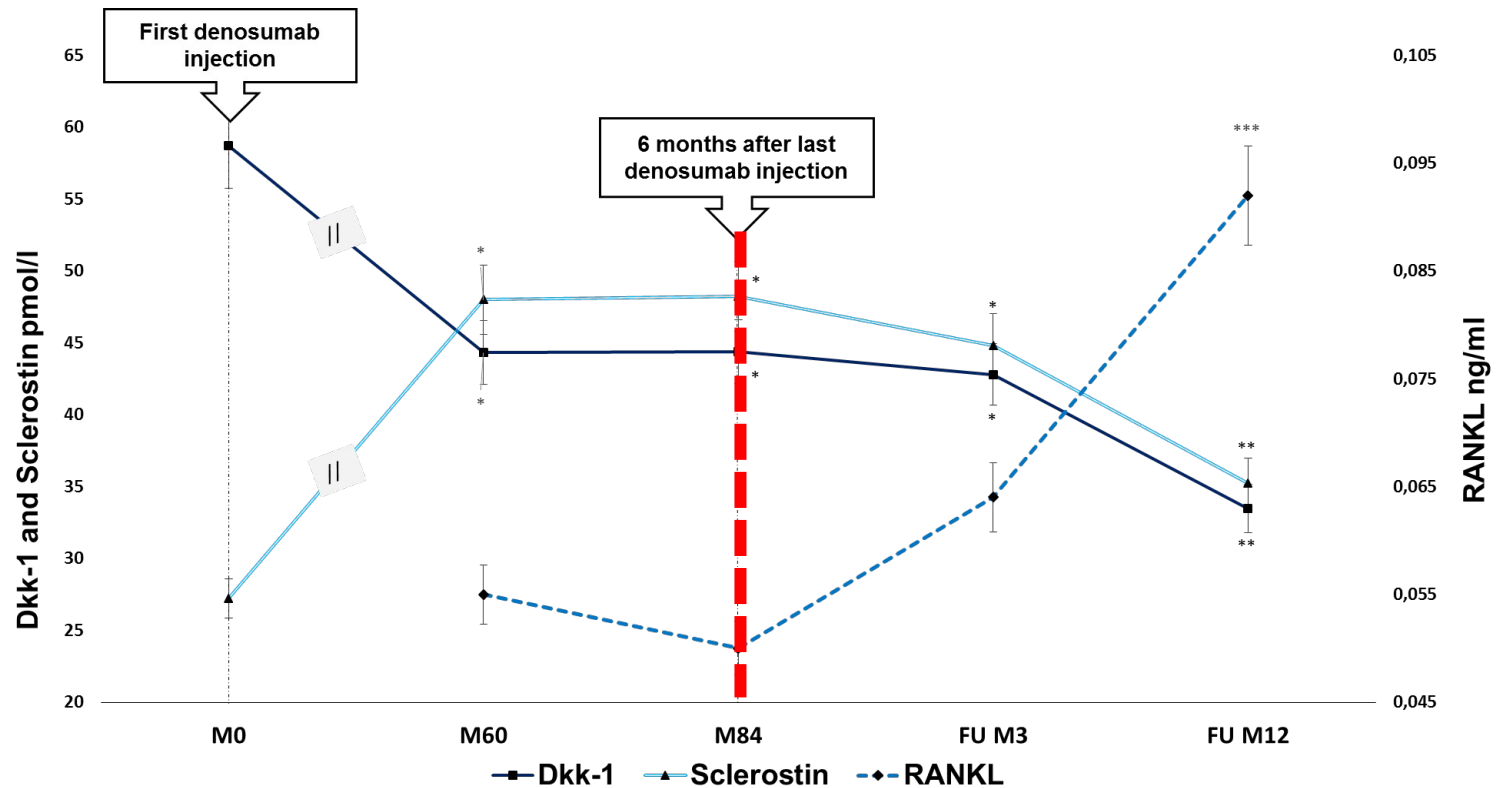


Full Length Article

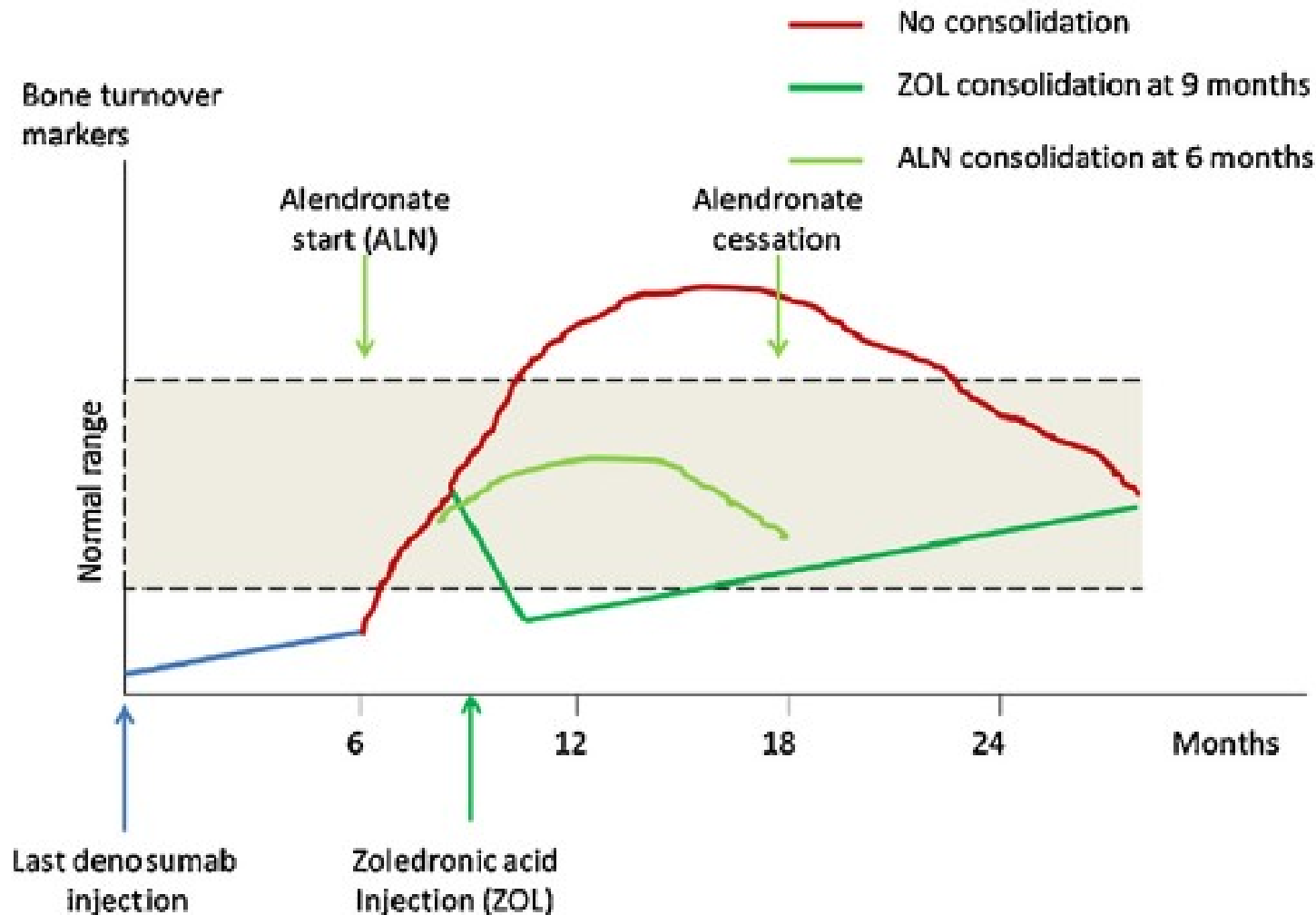
Changes in Dkk-1, sclerostin, and RANKL serum levels following discontinuation of long-term denosumab treatment in postmenopausal women[☆]



A. Fassio^{a,*}, G. Adami^{a,b}, C. Benini^a, E. Vantaggiato^a, K.G. Saag^b, A. Giollo^a, I. Lippolis^a, O. Viapiana^a, L. Idolazzi^a, G. Orsolini^a, M. Rossini^a, D. Gatti^a

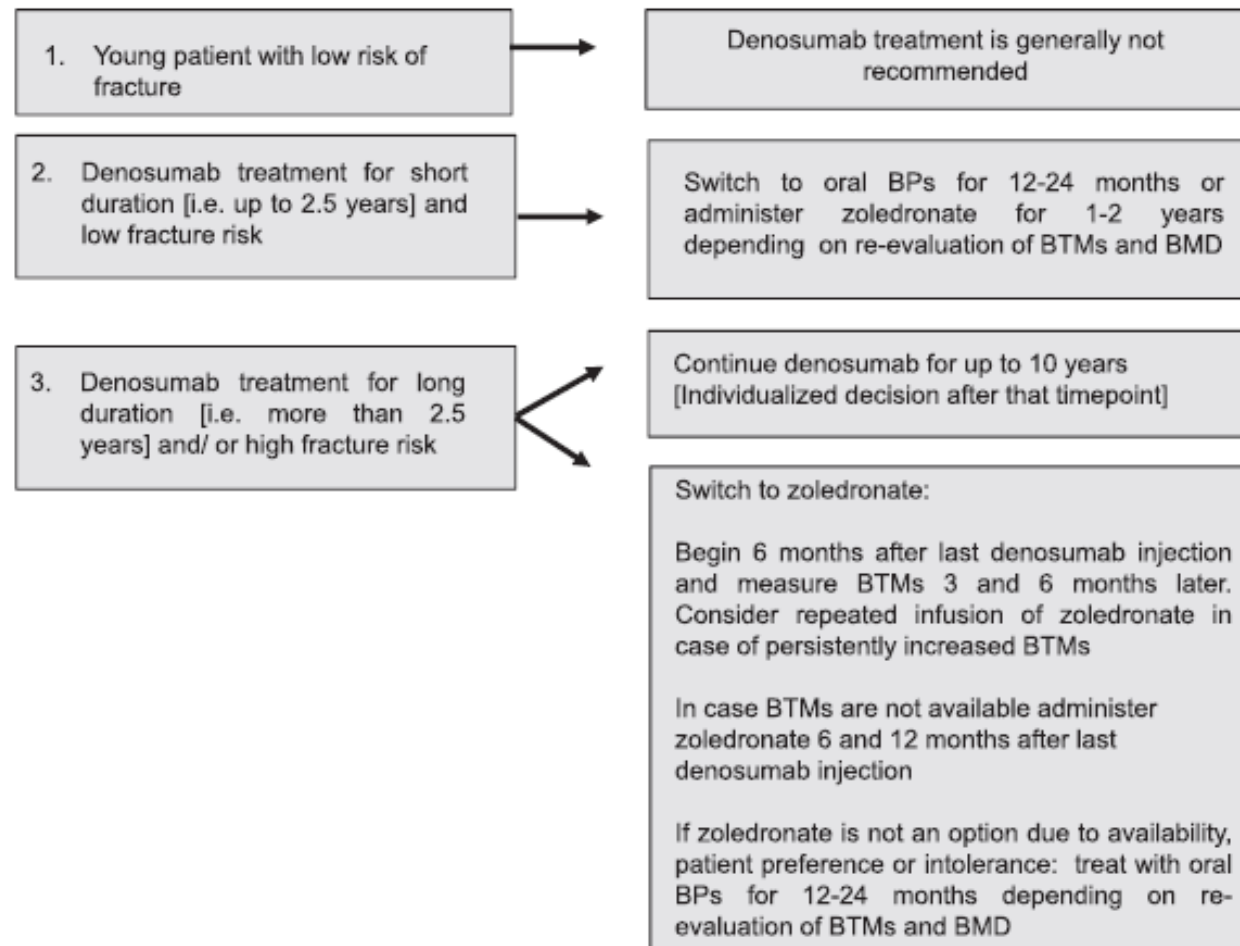


Effects and management of denosumab discontinuation



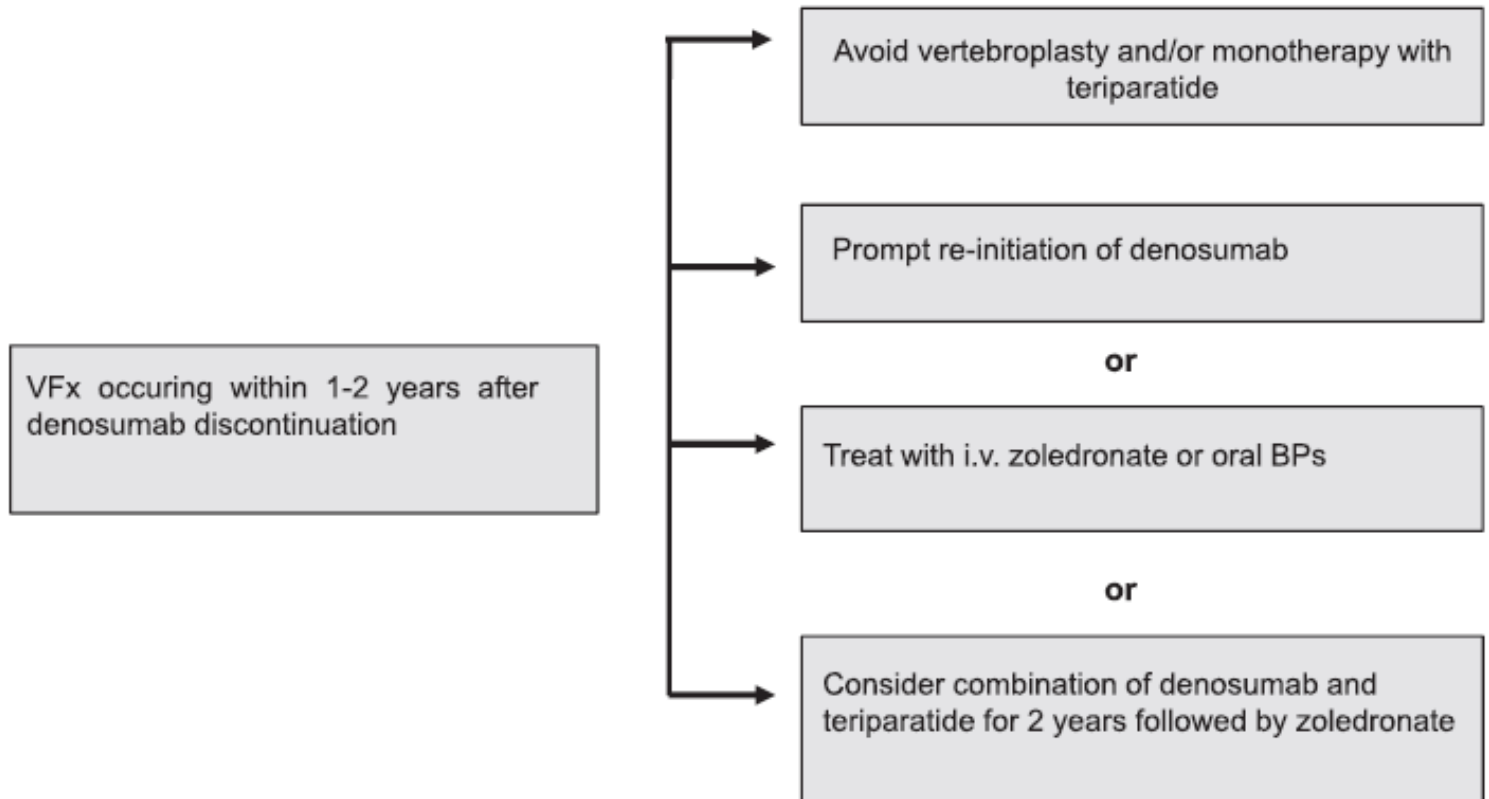
Reports and Recommendations

Fracture Risk and Management of Discontinuation of Denosumab Therapy: A Systematic Review and Position Statement by ECTS



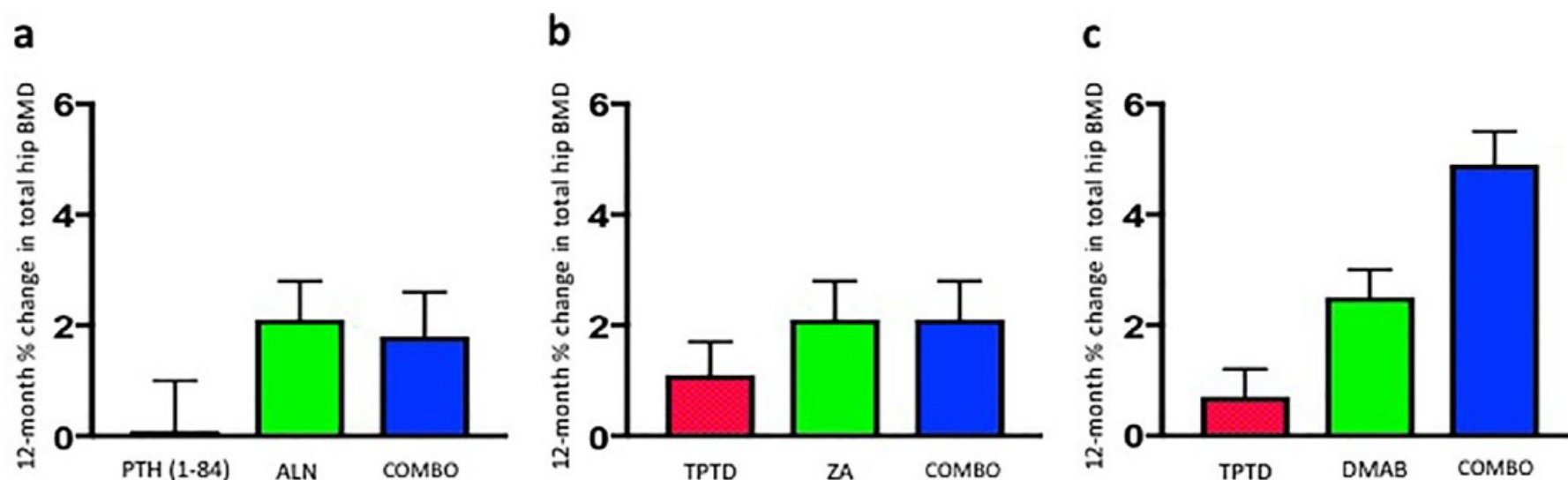
Reports and Recommendations

Fracture Risk and Management of Discontinuation of Denosumab Therapy: A Systematic Review and Position Statement by ECTS



Optimizing Sequential and Combined Anabolic and Antiresorptive Osteoporosis Therapy²⁰¹⁸

Benjamin Z Leder^{1,2}



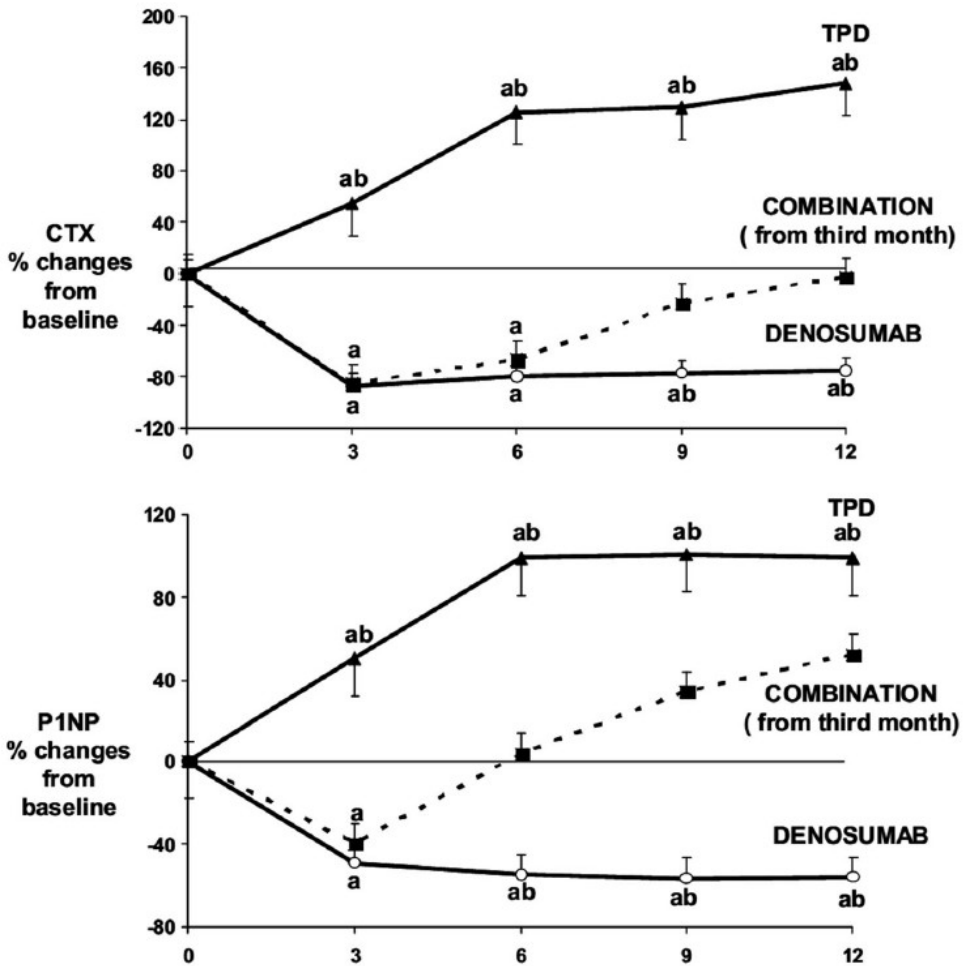
OSTEOPOROSIS

Teriparatide and denosumab: two drugs are better than one!

modif by Rossini

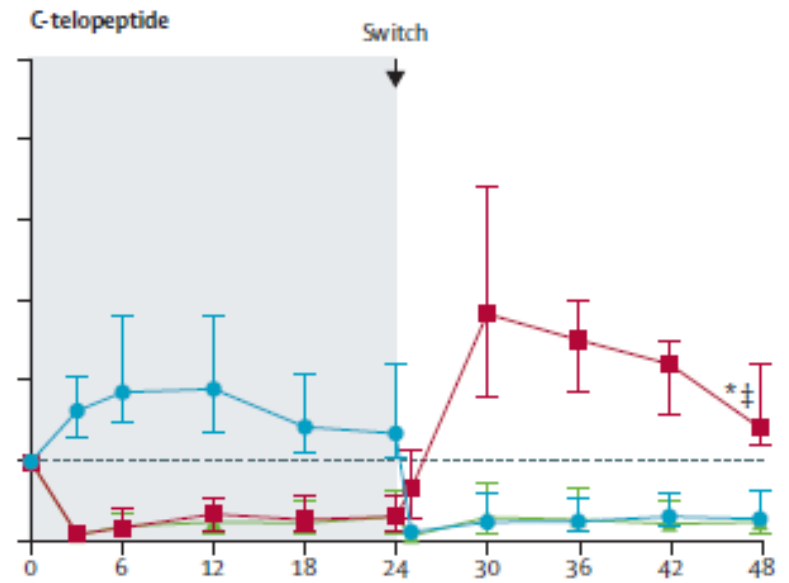
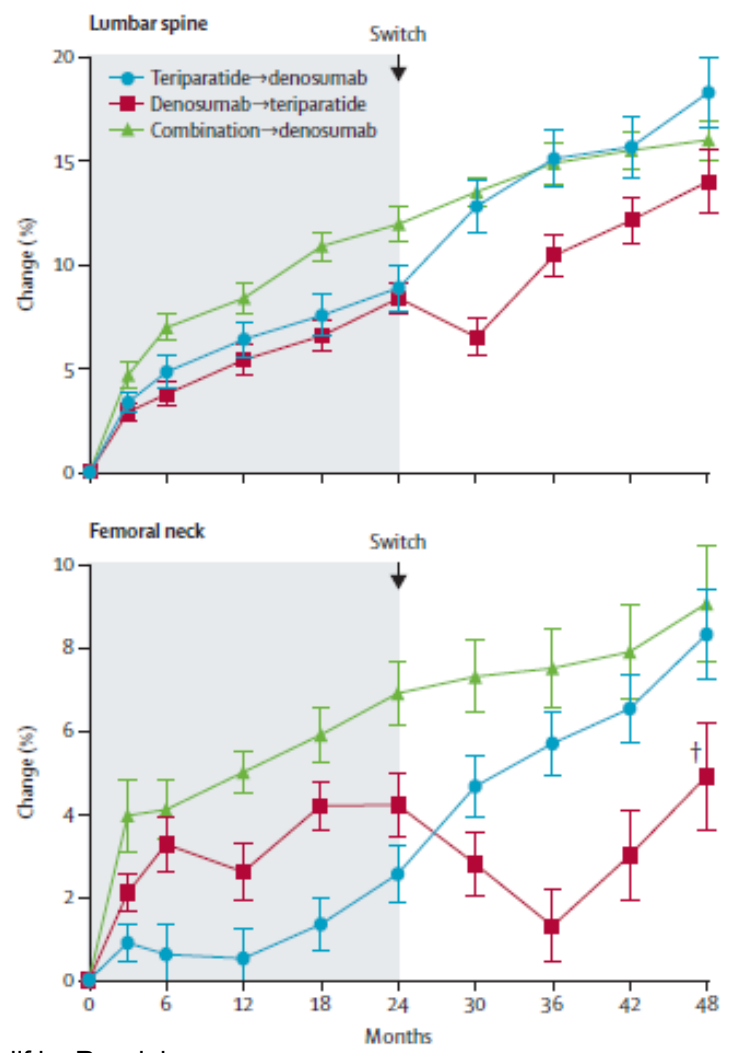
Teriparatide and denosumab combination therapy and skeletal metabolism

L. Idolazzi¹ · M. Rossini¹ · O. Viapiana¹ · V. Braga¹ · A. Fassio¹ · C. Benini¹ · V. Kunnathully¹ · S. Adami¹ · D. Gatti¹




Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial

Benjamin Z Leder, Joy N Tsai, Alexander V Uihlein, Paul M Wallace, Hang Lee, Robert M Neer, Sherri-Ann M Burnett-Bowie

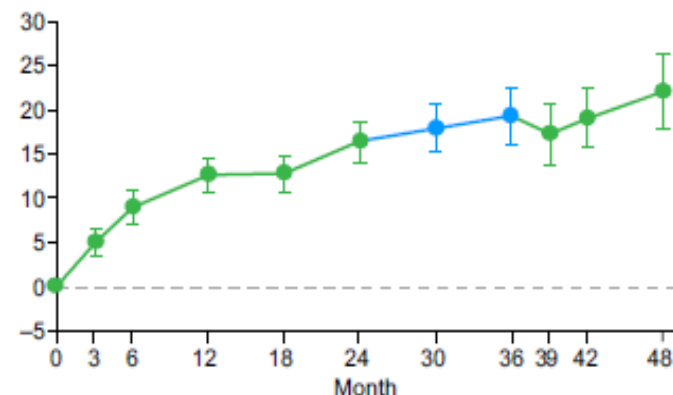
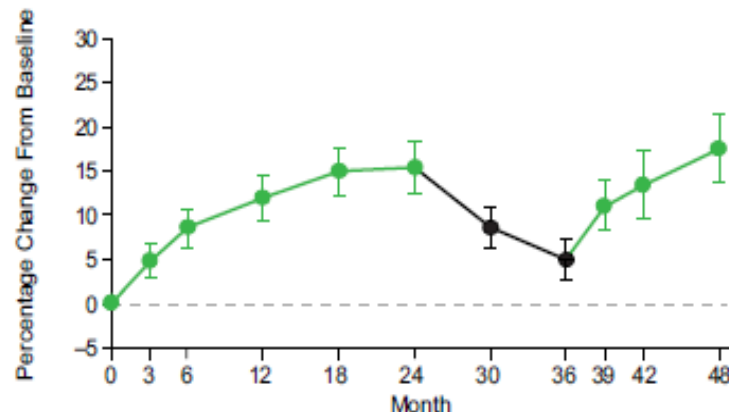


Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab

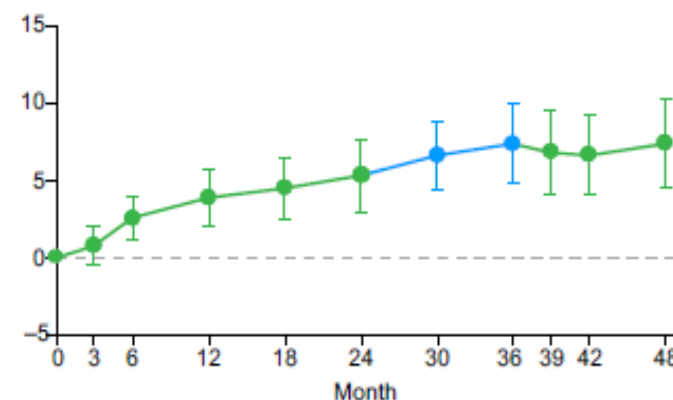
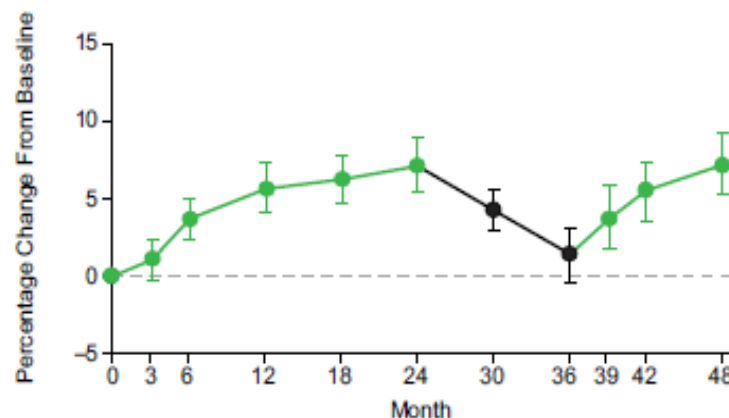
D.L. Kendler¹  • H.G. Bone² • F. Massari³ • E. Gielen⁴ • S. Palacios⁵ • J. Maddox⁶ • C. Yan^{7,8} • S. Yue^{6,9} • R.V. Dinavahi⁶ • C. Libanati¹⁰ • A. Grauer^{6,11}

● Romosozumab (210 mg QM) ● Placebo ● Denosumab (60 mg Q6M)

a. Lumbar Spine



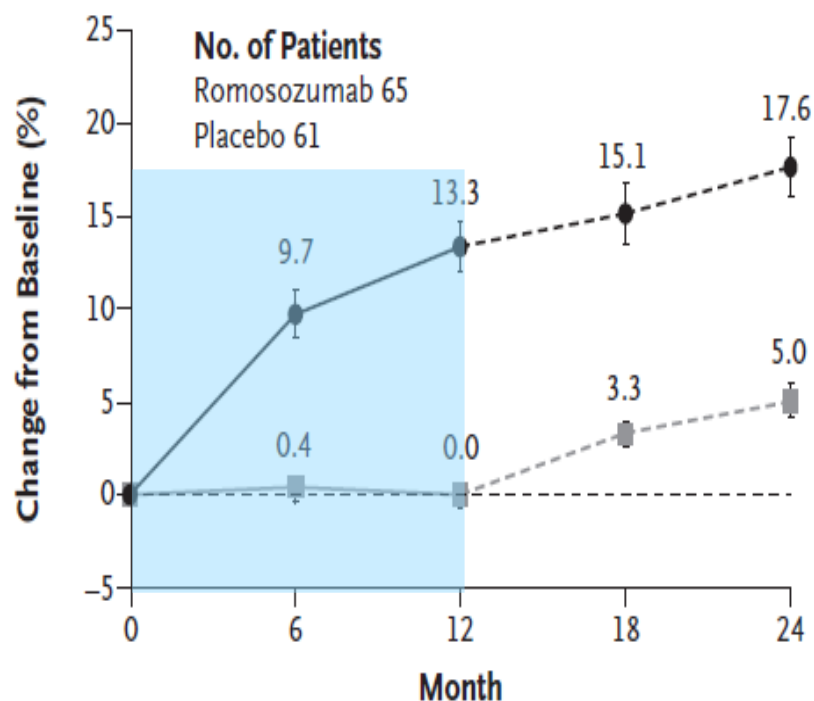
b. Total Hip



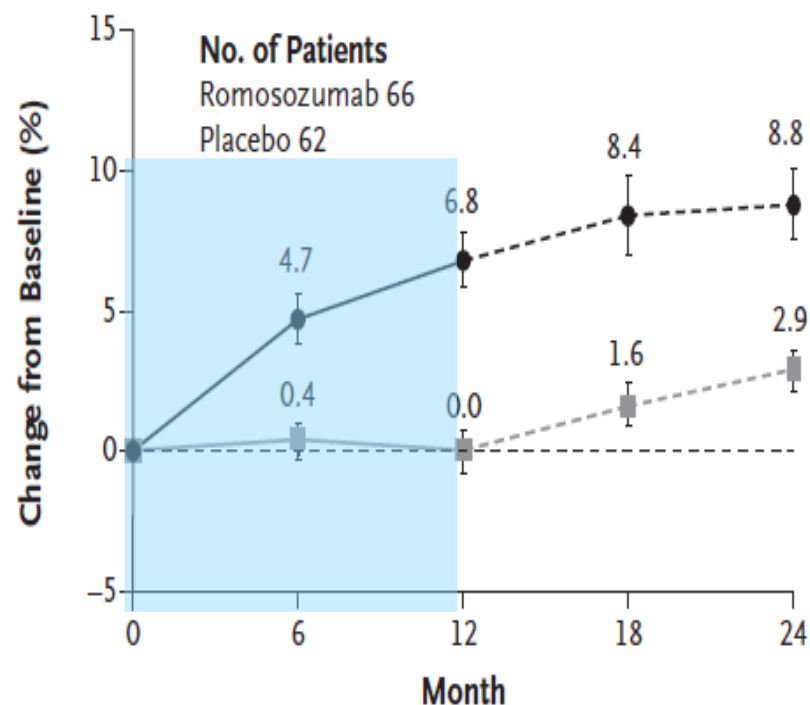
FRAME: Lumbar Spine and Total Hip BMD Through 12 and 24 Months

— Placebo - - - Placebo → Denosumab — Romosozumab - - - Romosozumab → Denosumab

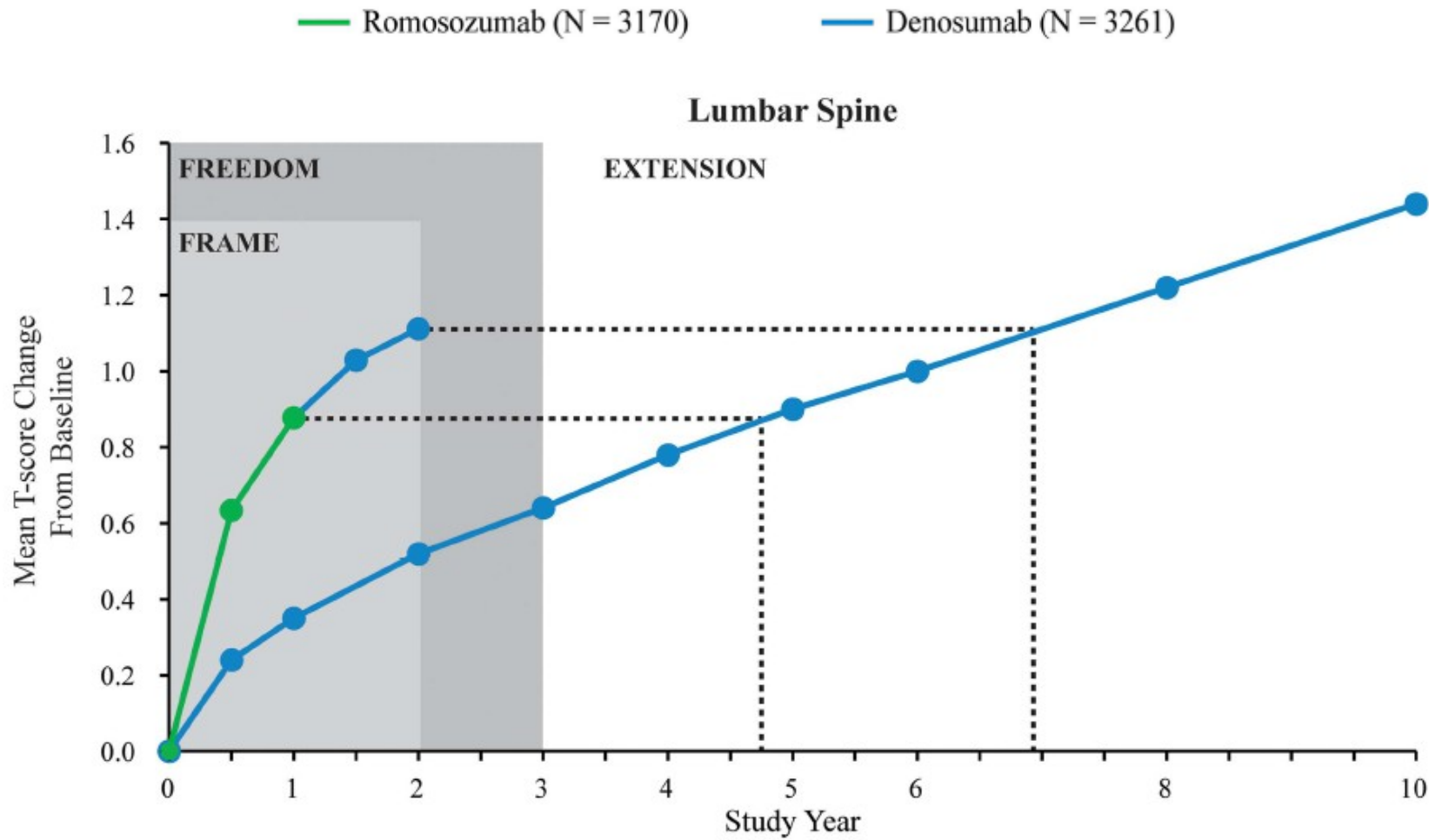
A Change in Bone Mineral Density at Lumbar Spine



B Change in Bone Mineral Density at Total Hip



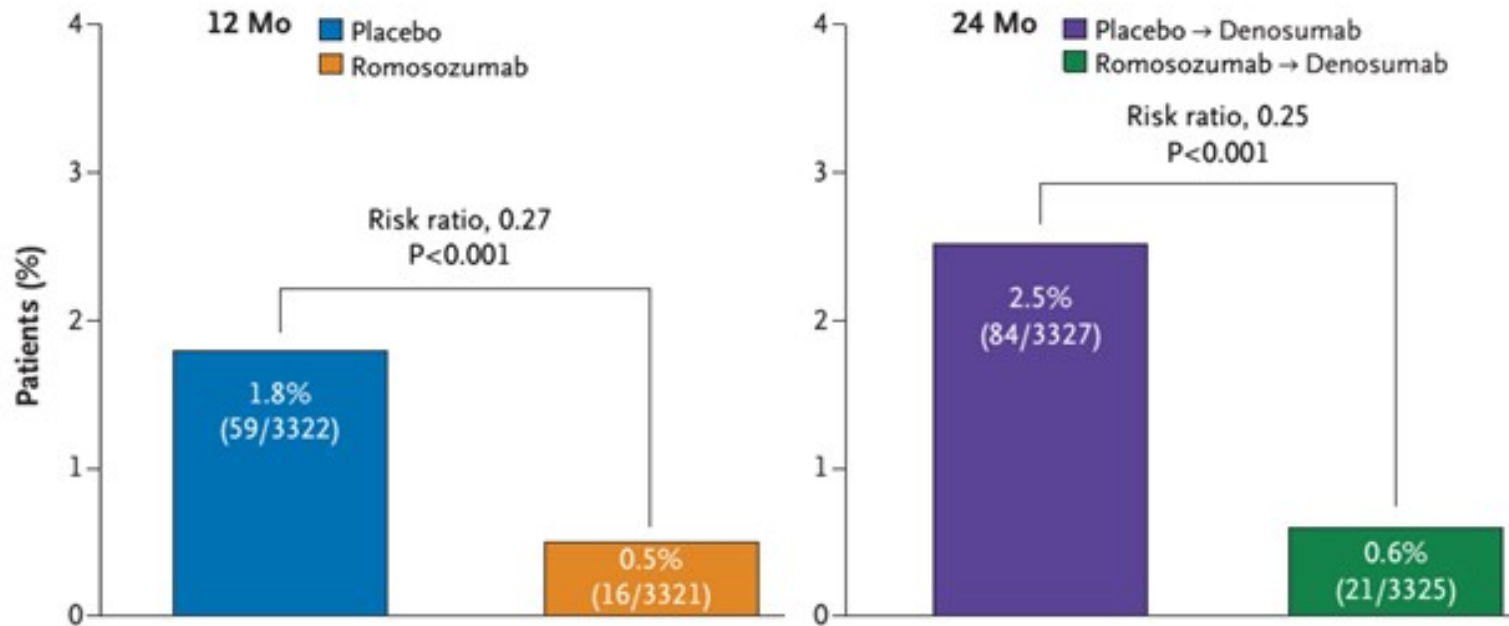
FRAME Study: The Foundation Effect of Building Bone With 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab



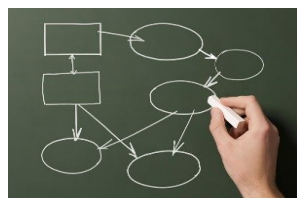
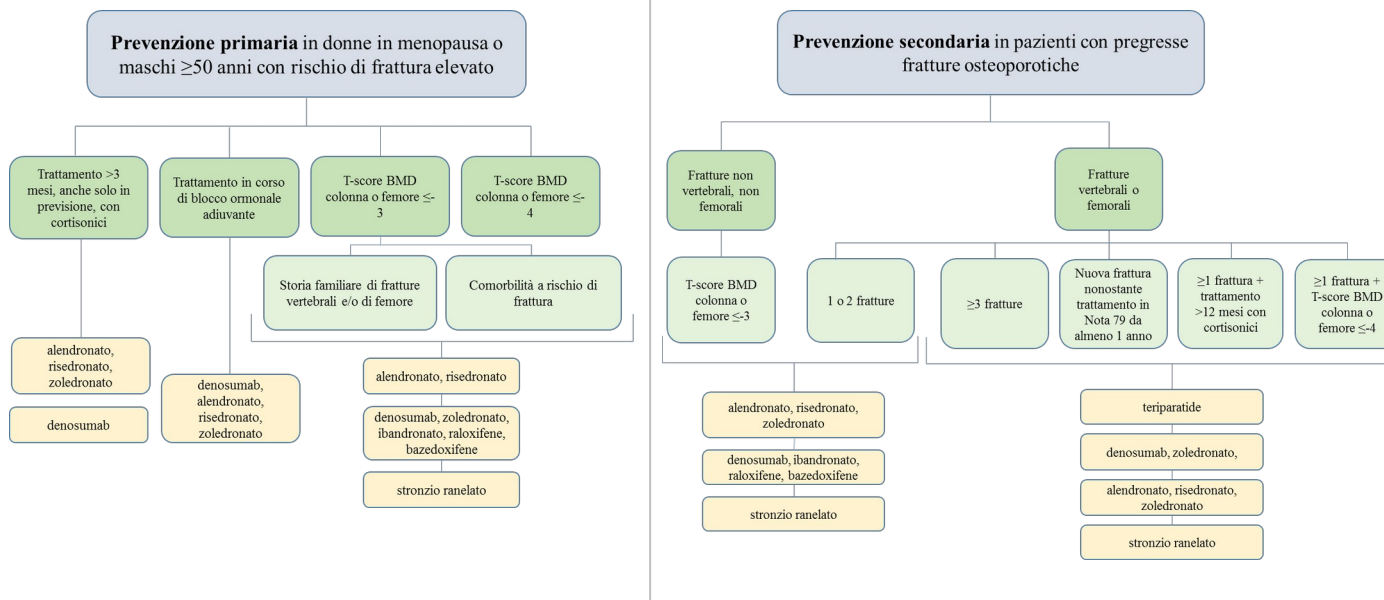
ORIGINAL ARTICLE

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Incidence of New Vertebral Fracture



La Nota 79: dal diagramma di flusso ad un algoritmo matematico informatizzato ?



DEFACALC 79

A cura della Sezione di Reumatologia, Dipartimento di Medicina,
Università di Verona con l'egida di SIOMMMS e SIR

SIOMMMS

Società Italiana dell'Osteoporosi
del Metabolismo Minerale
e delle Malattie dello Scheletro

SIR

Società Italiana
di Reumatologia

Different fracture risk profile in patients treated with anti-osteoporotic drugs in real-life

G. Adami, A. Giollo, M. Rossini, G. Orsolini, C. Benini, O. Viapiana,
D. Gatti, A. Fassio

Rheumatology Unit, University of Verona, Policlinico Borgo Roma, Verona, Italy

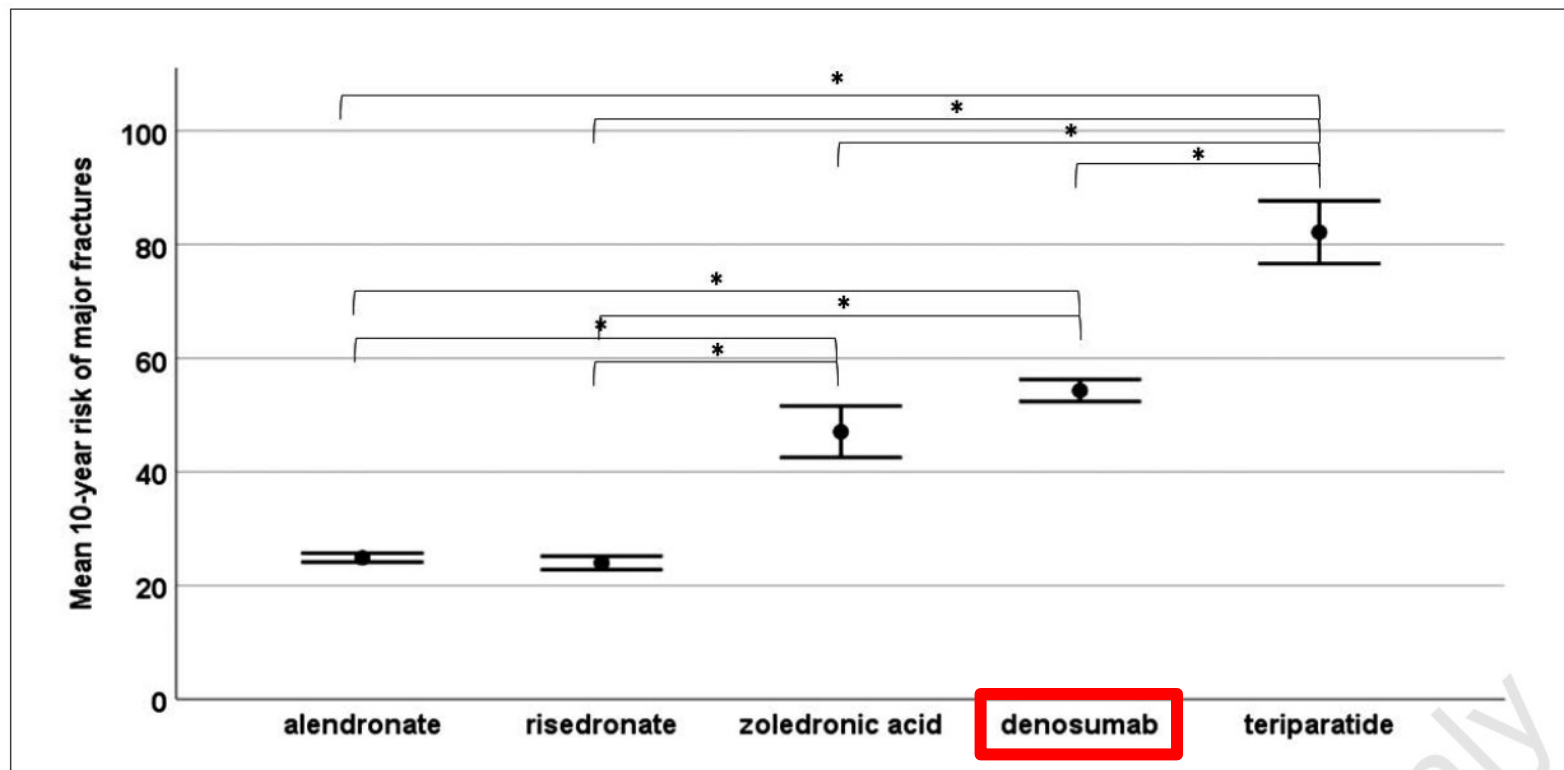
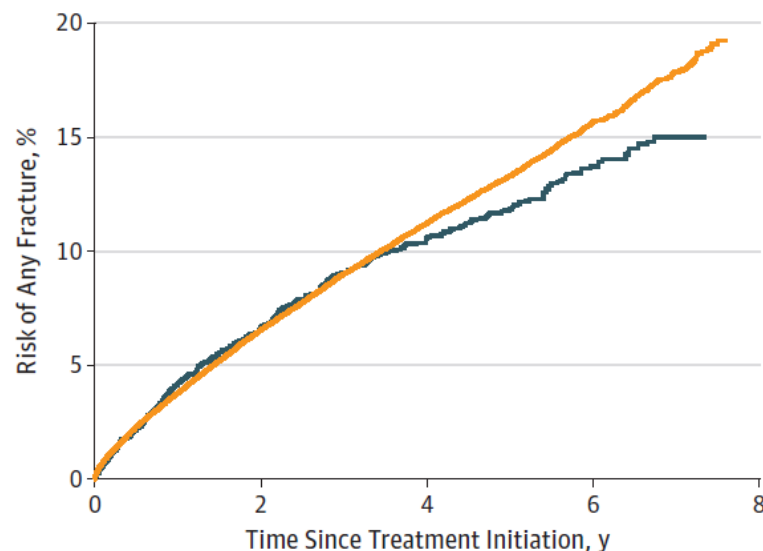
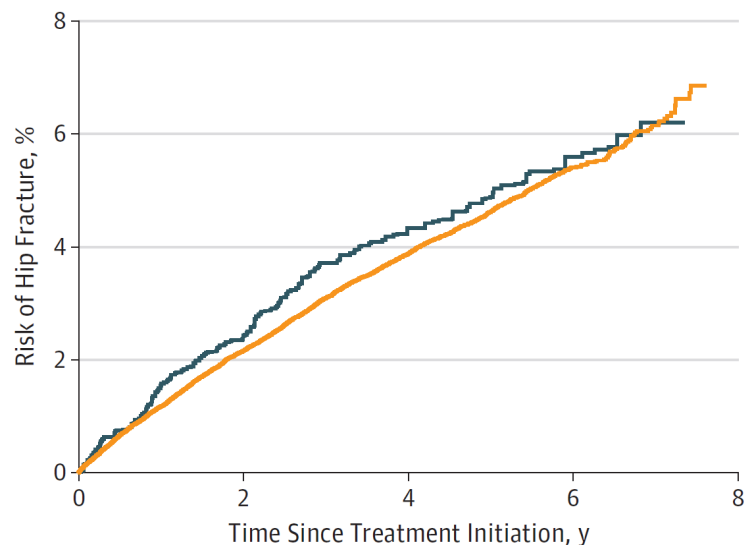


Figure 1 - Mean 10-year fracture risk estimated with DeFRA tool at the time of treatment initiation, *p<0.01.

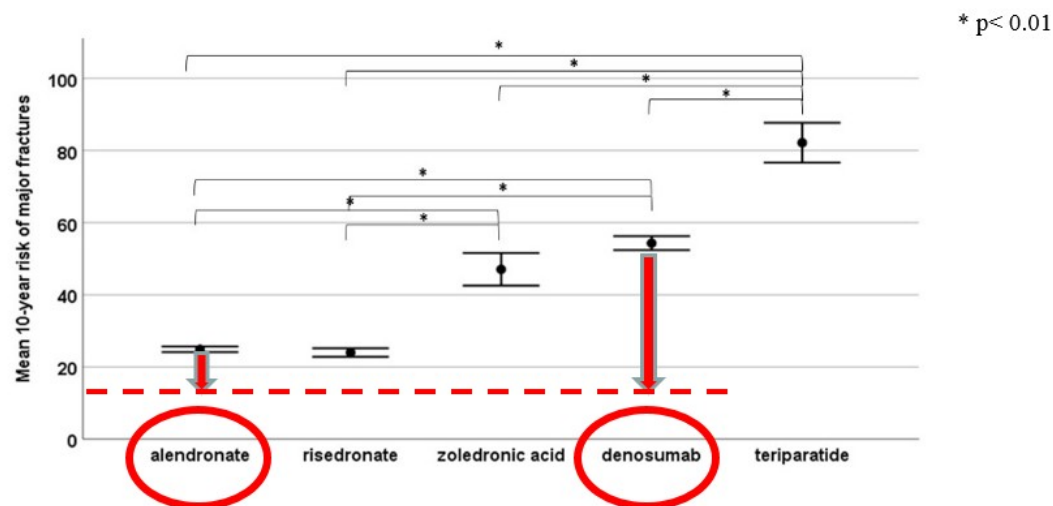
Comparison of Risk of Osteoporotic Fracture in Denosumab vs Alendronate Treatment Within 3 Years of Initiation



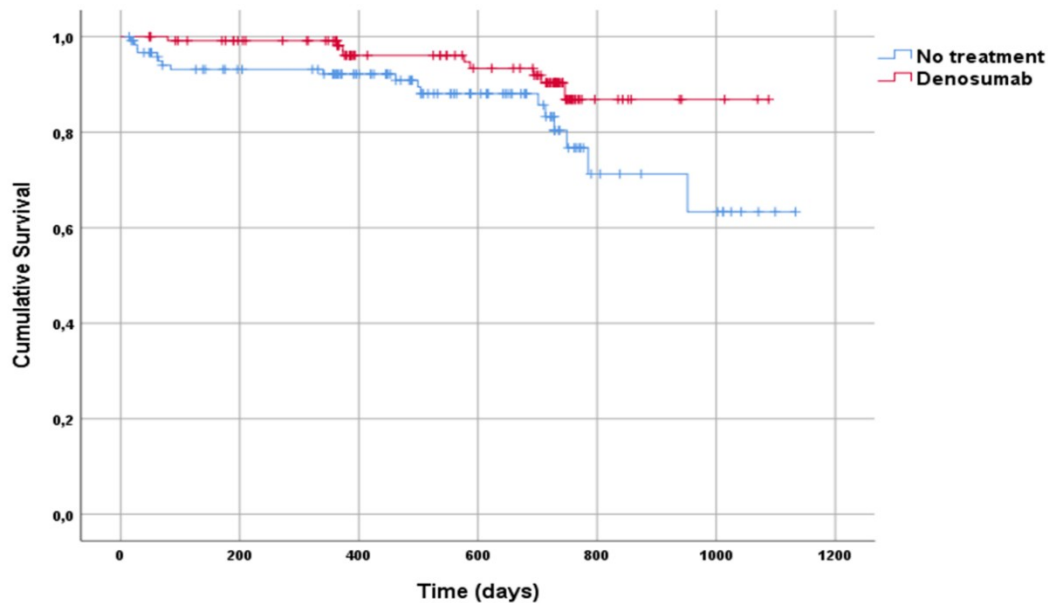
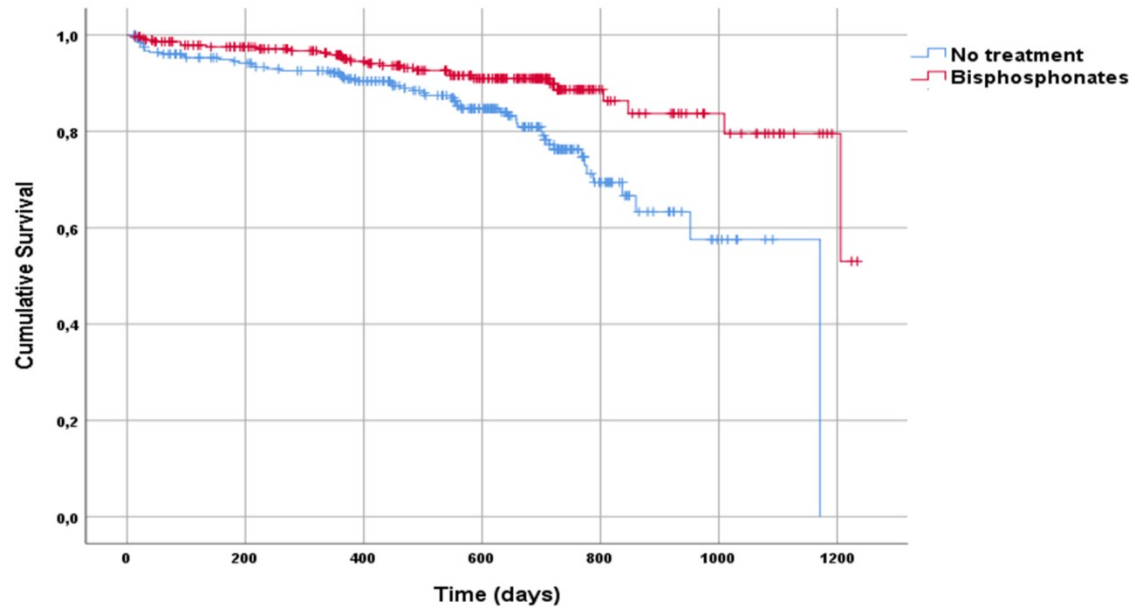
Conclusions

In this nationwide cohort study based on routinely collected data in Denmark, treatment with denosumab and alendronate were associated with similar risks of hip and any fracture over a 3-year Pedersen et al, JAMA Net Open, 2019

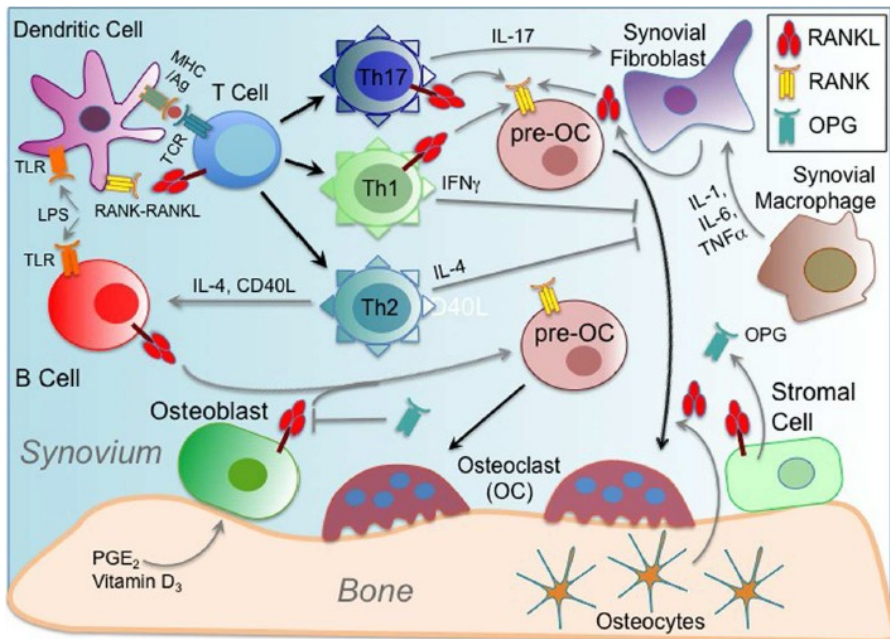
Limitations:no data on BMD... and 10-yea risk of fracture!!!!



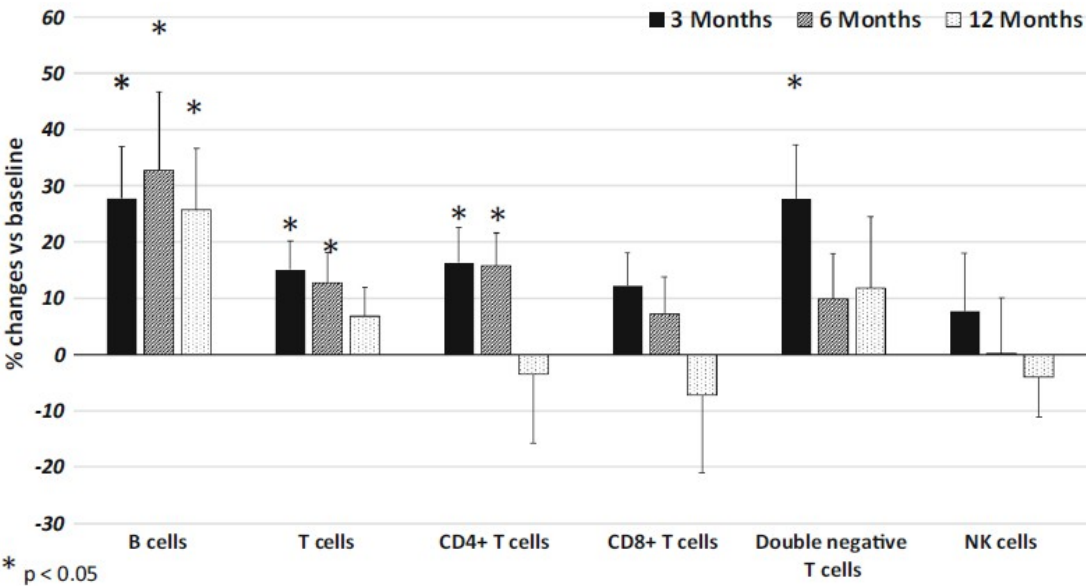
Real-life short-term effectiveness of anti-osteoporotic treatments: a longitudinal cohort study using a web-based fracture risk assessment tool



Osteoimmunology of RANKL-RANK-OPG



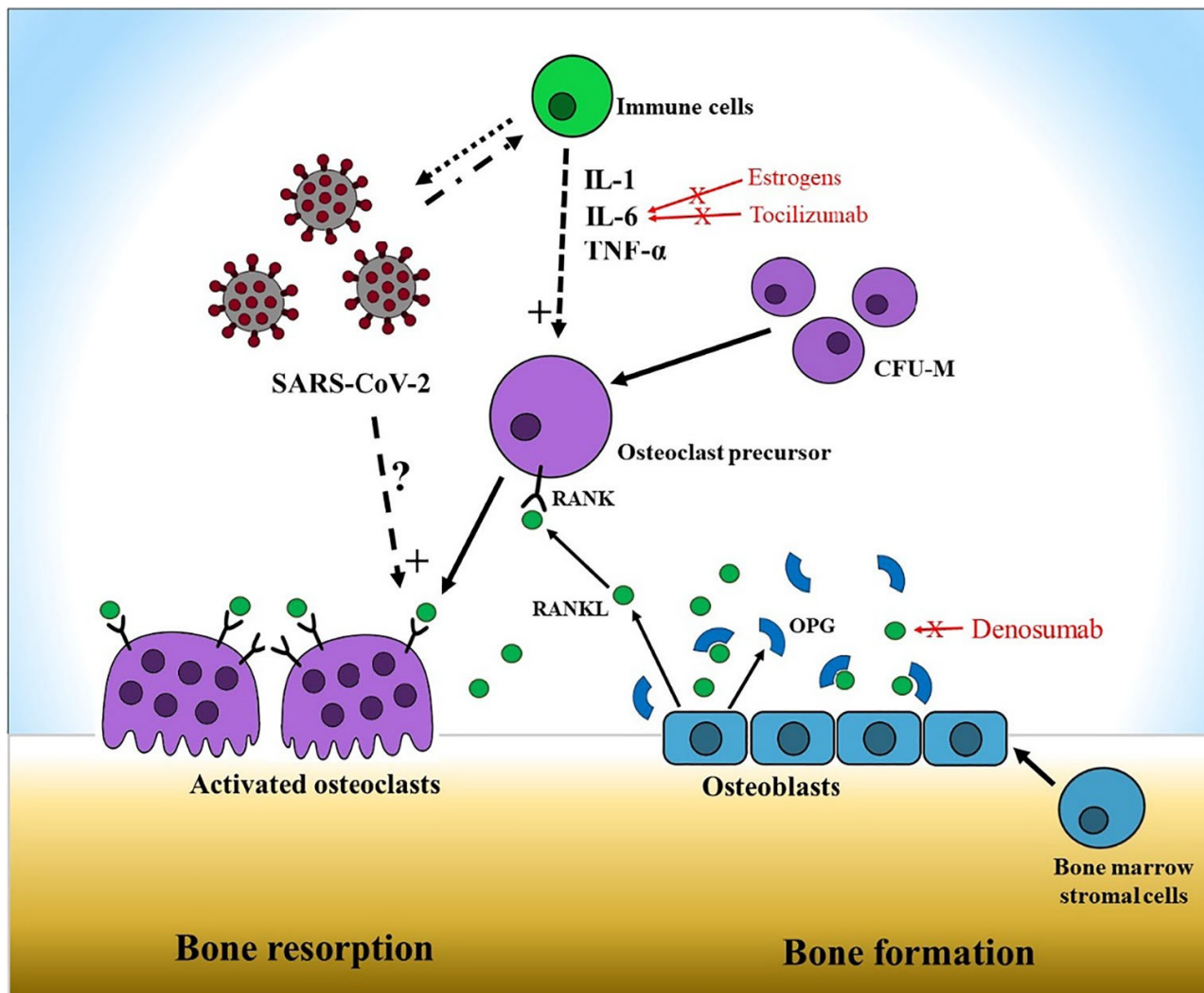
Walsh et al, Front Immunol 2014





Bone Metabolism in SARS-CoV-2 Disease: Possible Osteoimmunology and Gender Implications

Gianmaria Salvio¹ • Claudio Gianfelice¹ • Francesca Firmani¹ • Stefano Lunetti¹ • Giancarlo Balercia¹ •
 Gilberta Giacchetti¹

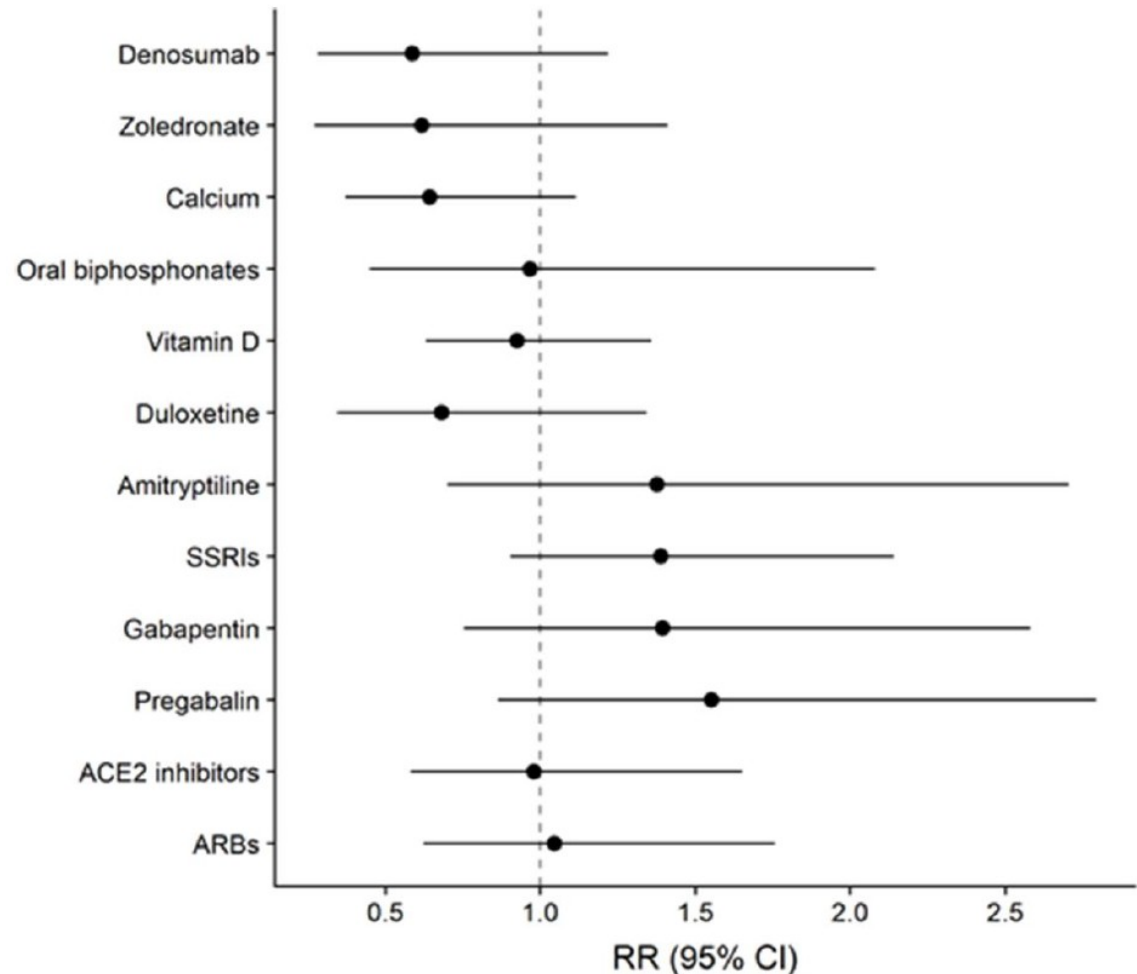


Influence of anti-osteoporosis treatments on the incidence of COVID-19 in patients with non-inflammatory rheumatic conditions

Josep Blanch-Rubió^{1,2,*}, Natalia Soldevila-Domenech^{3,7,*}, Laura Tío², Jone Llorente-Onaindia², Manuel Ciria-Recasens^{1,2}, Luciano Polino², Alba Gurt⁵, Rafael de la Torre^{3,6,7}, Rafael Maldonado^{2,4,§}, Jordi Monfort^{1,2,§}, and the Covidmar Study Group[#]

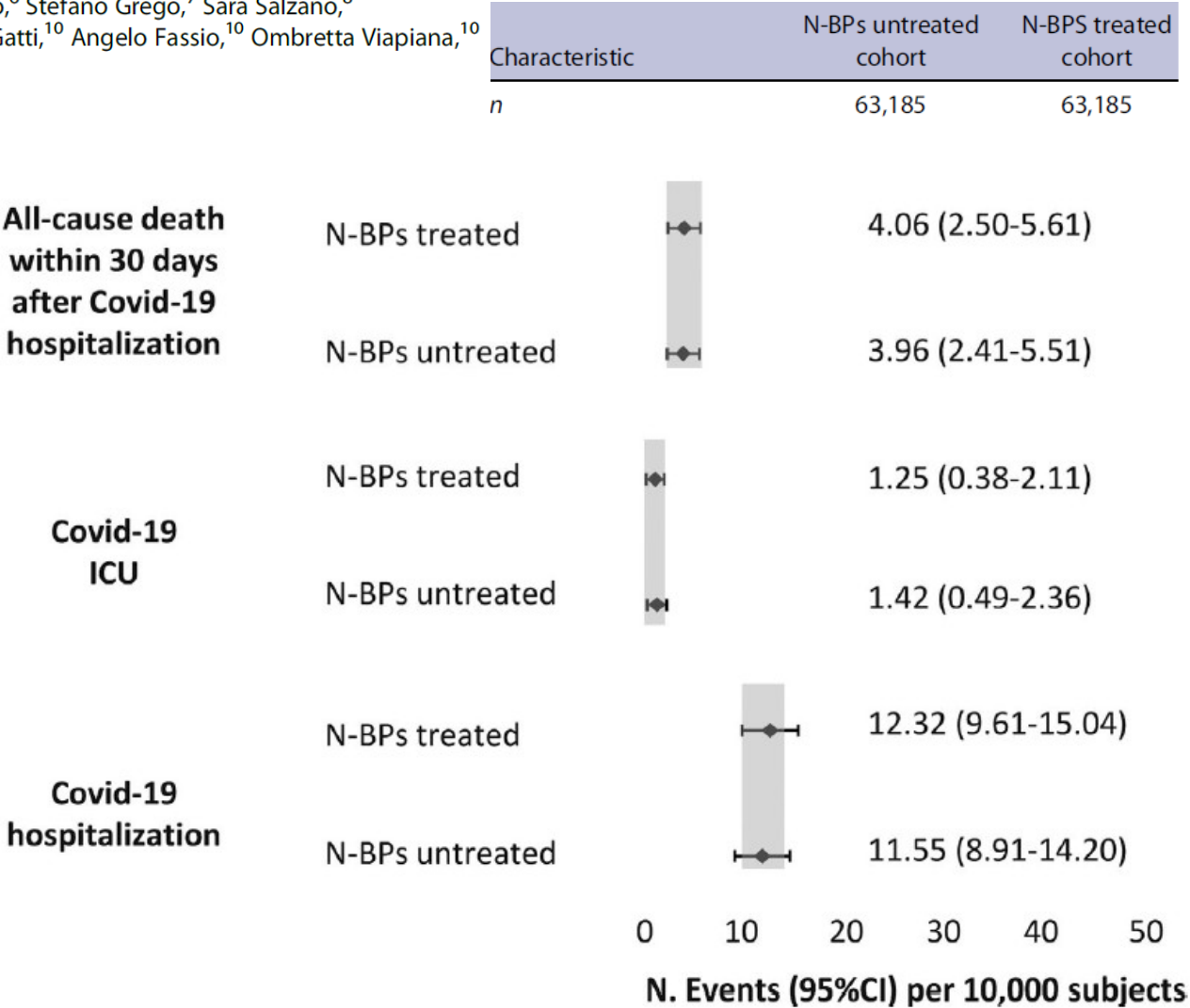
Treatments followed

Denosumab	264 (12.6%)
Intravenous Zoledronate	179 (8.52%)
Oral bisphosphonates	143 (6.80%)
Teriparatide	25 (1.19%)
Calcium	490 (23.3%)
Vitamin D	1303 (62.0%)
Thiazide diuretics	262 (12.5%)
SERMs	11 (0.52%)
Analgesics	1220 (58.0%)
Gabapentin	164 (7.80%)
Pregabalin	146 (6.95%)
Opioids	546 (26.0%)
Other Analgesics	959 (45.6%)
Antidepressants	657 (31.3%)
Tricyclic antidepressants	124 (5.90%)
Amitriptyline	102 (4.85%)
Others	22 (1.05%)
Dual-action antidepressants	277 (13.2%)
Duloxetine	207 (9.85%)
Venlafaxine	60 (2.85%)
Others	10 (0.48%)
SSRIs antidepressants	333 (15.8%)
Reboxetine	2 (0.10%)
Trazodone	33 (1.57%)
Glucocorticoids	60 (2.85%)
Inhaled Glucocorticoids	189 (8.99%)
Anti-hypertensive drugs	646 (30.7%)
ACE inhibitors	363 (17.3%)
ARBs	290 (13.8%)
Chronic NSAIDs	318 (15.1%)
Synthetic DMARDs	30 (1.43%)
Biologic DMARDs	1 (0.05%)



The Use of Oral Amino-Bisphosphonates and Coronavirus Disease 2019 (COVID-19) Outcomes

Luca Degli Esposti,¹ Valentina Perrone,¹ Diego Sangiorgi,¹ Margherita Andretta,² Fausto Bartolini,³ Arturo Cavaliere,⁴ Andrea Ciaccia,⁵ Stefania Dell’orco,⁶ Stefano Grego,⁷ Sara Salzano,⁸ Loredana Ubertazzo,⁸ Adriano Vercellone,⁹ Davide Gatti,¹⁰ Angelo Fassio,¹⁰ Ombretta Viapiana,¹⁰ Maurizio Rossini,¹⁰  and Giovanni Adami¹⁰ 



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Modifica Registro PROLIA

Si informano gli utenti dei Registri Farmaci sottoposti a Monitoraggio che, al fine di garantire una gestione del monitoraggio del medicinale più flessibile e maggiormente aderente alla pratica clinica, è stata apportata nel Piano terapeutico web-based PROLIA la seguente modifica:

- Prima Rivalutazione obbligatoria dopo il 5° ciclo, successive ogni 4 cicli

Si specifica che le modifiche sopra descritte hanno effetto retroattivo, pertanto anche i trattamenti già inseriti a sistema potranno proseguire utilizzando le nuove impostazioni.

Ufficio Registri di Monitoraggio

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Roma, 9 settembre 2021

Prof. Roberto Gerli
Presidente

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OGGETTO: riscontro a nota della Società Italiana di Reumatologia del 4 agosto 2021, recante in oggetto: “richiesta di annullamento delle modifiche apportata al registro Prolia, come da comunicato AIFA del 14/05/2021, in seguito a difficoltà oggettive riscontrate per il paziente e per il medico.”.

Egregio Prof. Gerli,

in relazione alla comunicazione della SIR di cui in oggetto si fornisce il seguente riscontro.

In particolare, ci preme chiarire che il disagio della prescrizione di un PT della durata di 6 mesi si verifica una sola volta per consentire la prima rivalutazione obbligatoria dopo 5 somministrazioni (come richiesto dalla Azienda Farmaceutica titolare del medicinale). Dopo la prima rivalutazione sarà possibile prescrivere sempre Piani Terapeutici della durata di 50 settimane.

Annullare questa impostazione informatica attualmente presente significherebbe incorrere di nuovo nel più grave problema dell'impossibilità di prescrivere il farmaco in caso di una discontinuità di trattamento. Problema che si è già evidenziato in passato dopo numerosissime segnalazioni di medici che chiedevano l'intervento di AIFA per sbloccare il trattamento.

Di conseguenza, per aderire alla richiesta della SIR si ritiene utile un comunicato di chiarimento sul sito istituzionale dell'AIFA che rassicuri i medici prescrittori, rispetto alla prescrizione di un PT della durata di 6 mesi, e di conseguenza la necessità del paziente di recarsi in ospedale due volte in un anno, avverrà una sola volta.



Società Italiana dell'Osteoporosi del Metabolismo
Minerale e delle Malattie dello Scheletro

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