Οστεοπόρωση: Προβλήματα σε ασθενείς που παίρνουν θεραπεία.

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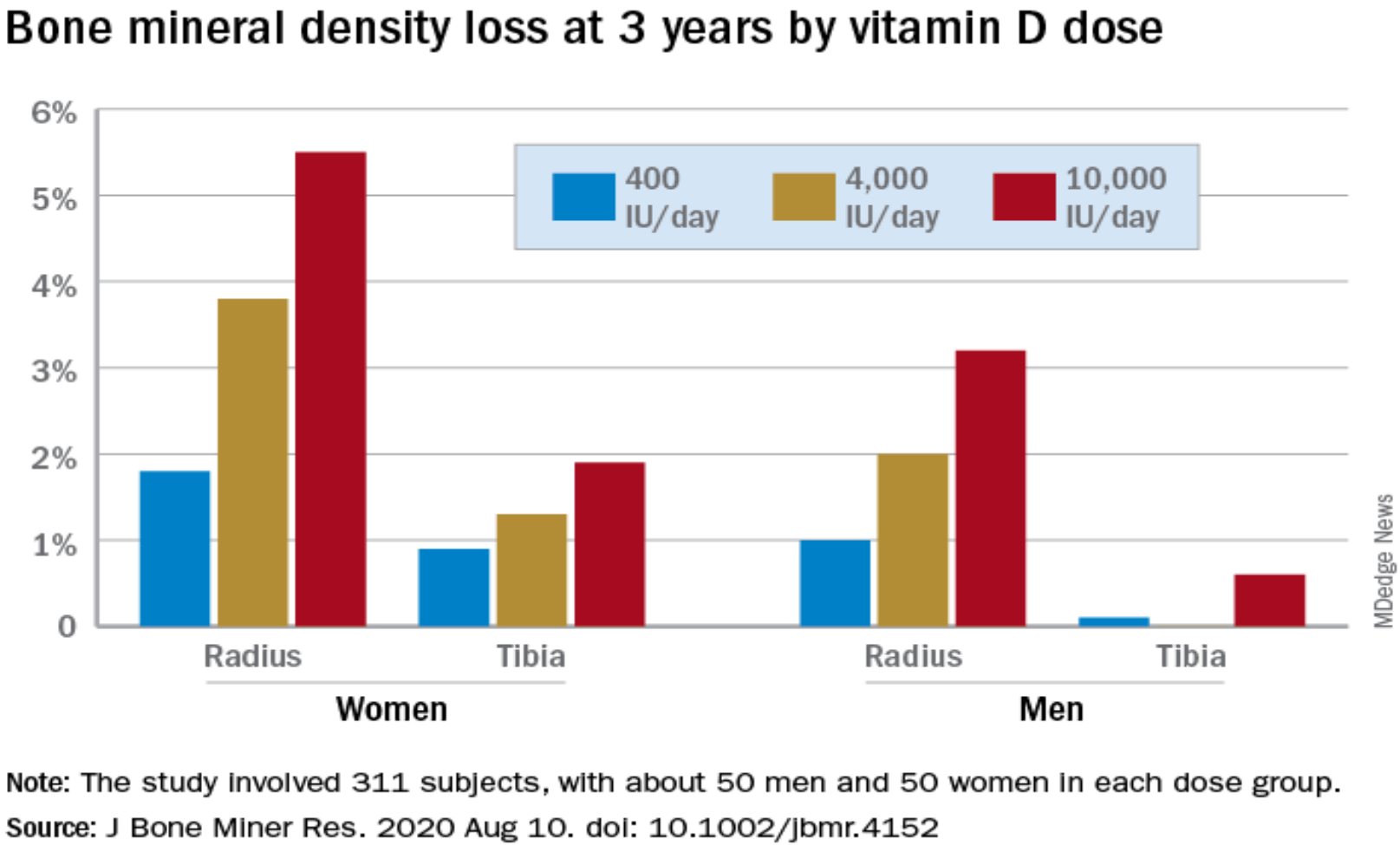
Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength
A Randomized Clinical Trial



Note: The study involved 311 subjects, with about 50 men and 50 women in each dose group.

Source: J Bone Miner Res. 2020 Aug 10. doi: 10.1002/jbmr.4152

In addition to total volumetric BMD, a similar dose-response relationship was found for cortical volumetric BMD.

Younger females, closer to menopause, lost larger amounts of total volumetric BMD than older females at both the radius and tibia.

25OHD3 ng/ml	0	3 ΜΗΝΕΣ	3 ΧΡΟΝΙΑ
400	30,52	30,68	30,96
4000	32,52	46,12	52,88
10000	31,36	75,2	57,76

Table 1. Participant characteristics for females and males at baseline.

	400 IU		4000 IU		10,000 IU	
Variable	Female	Male	Female	Male	Female	Male
Lumbar spine T-score [c]	-0.6 (1.1)	0.5 (1.5)	-0.2 (1.2)	0.6 (1.3)	-0.8 (1.0)	0.9 (1.4)
Total hip T-score [d]	-0.5 (0.8)	0.6 (1.0)	-0.3 (1.0)	0.7 (1.0)	-0.6 (0.8)	0.5 (1.1)

Table 1. Participant characteristics for females and males at baseline.

	400 IU		4000 IU		10,000 IU	
Variable	Female	Male	Female	Male	Female	Male
Plasma CTx (Beta-Crosslaps) (ng/L) [k]	371.2 (125.5)	308.7 (106.9)	372.8 (130.6)	307.9 (124.0)	390.1 (117.2)	303.8 (121.6)

The increase in bone resorption with higher doses of vitamin D, indicated by higher CTx in females, is not unexpected. High dose vitamin D3 supplementation results in increased conversion into the active vitamin D metabolite**, calcitriol**, and may also stimulate local (autocrine) synthesis of calcitriol within the bone cell environment. Calcitriol has been demonstrated to act directly on bone cells through the vitamin D receptor.

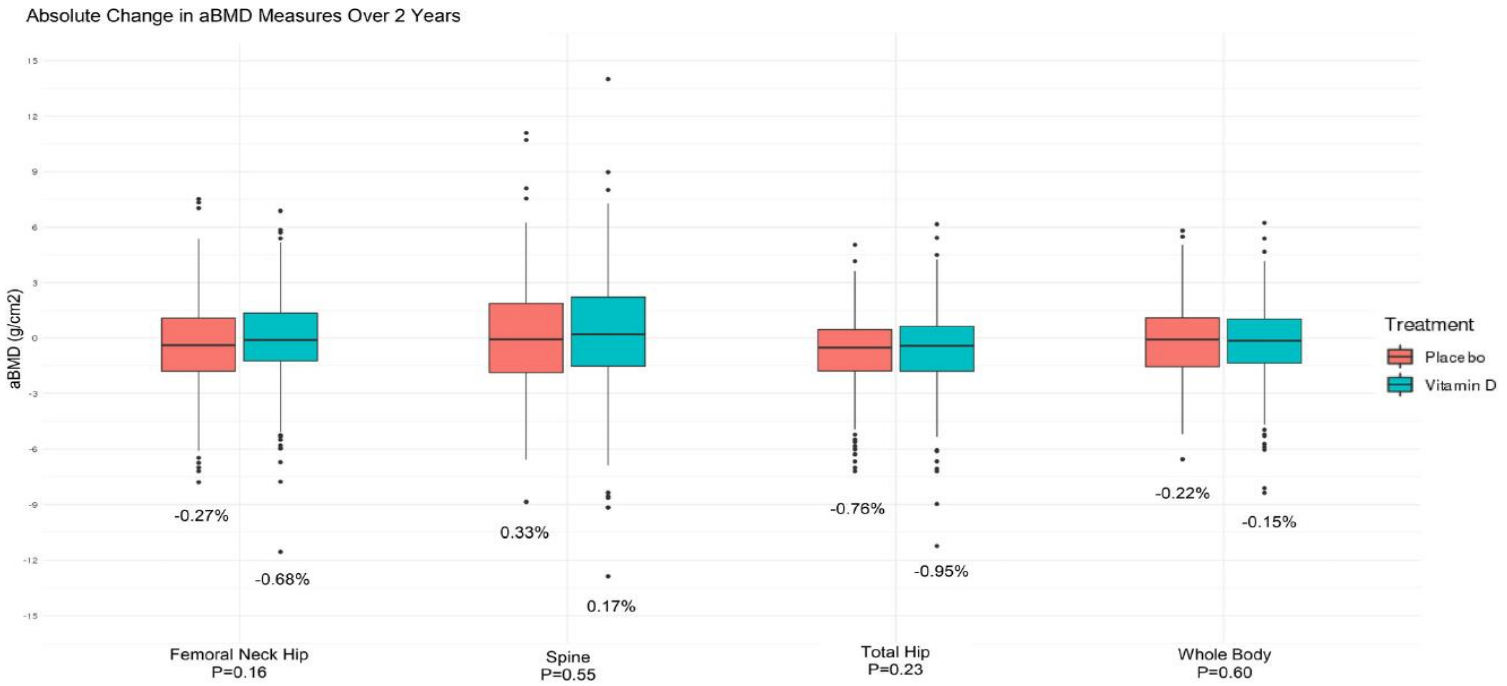
Although the vitamin D receptor is expressed in osteoblasts and osteoclasts, it appears calcitriol's main effect on bone resorption is primarily through stimulation of osteoblasts to facilitate recruitment of osteoclast precursors and activation of osteoclasts.

Effects of Supplemental Vitamin D on Bone Health Outcomes in Women and Men in the VITamin D and OmegA-3 TriaL (VITAL) (2000 IU/d)

Table 1. Characteristics of the Bone Health Subcohort at Baseline According to Randomized Assignment to Vitamin D_3 Versus Placebo Groups

Characteristic	Total (N = 771)	Vitamin D_3 group (n = 388)	Placebo group (n = 383)	p Value
Baseline total 25(OH)D (nmol/L),[4] mean (SD), N = 770	69.1 (22.7)	67.4 (22.2)	71.1 (23.2)	0.025

27,64ng/ml 26,96 ng/ml 28,44 ng/ml



There were no effects of daily supplemental vitamin D3 on pQCT outcomes at the radius or tibia

- Τα παραπάνω δεν ισχύουν για τα άτομα με έλλειψη βιταμίνης D η για ασθενείς με οστεοπόρωση.
- **ΤΟ ΠΟΛΎ ΔΕΝ ΕΊΝΑΙ ΑΠΑΡΑΙΤΗΤΑ ΚΑΛΟ**

A decade of FRAX: how has it changed the management of osteoporosis?

John A. Kanis,Nicholas C. Harvey, Helena Johansson,Enwu Liu, Liesbeth Vandenput
Mattias Lorentzon, William D. Leslie, Eugene V. McCloskey

Aging Clinical and Experimental Research (2020) 32:187–196

- Το Frax δημιουργήθηκε το 2008 και παρέχει ένα αλγόριθμο ειδικό για κάθε χώρα εκτίμησης της 10 πιθανότητας κατάγματος ισχίου η μειζόνων καταγμάτων (ισχίο, κλινικά σπονδυλικά, αντιβραχίου, βραχιονίου).
- Ο διαδικτυακός του τόπος δέχεται περίπου 3 εκατ. επισκέψεις το χρόνο.
- Το Frax έχει ενσωματωθεί σε πάνω από 80 κλινικές οδηγίες παγκόσμια

Screening with FRAX

- Η μελέτη SCOOP έγινε σε 5 κέντρα του Ηνωμένου Βασιλείου και είναι τυχαιοποιημένη ελεγχόμενη διάρκειας 5 ετών. Συμπεριέλαβε γυναίκες ηλικίας 70-85 ετών που τυχαιοποιήθηκαν να λάβουν θεραπεία βάσει FRAX (6233) η βάσει της στρατηγικής case finding (6250).
- Το screening βάσει frax συνοδεύτηκε από μείωση του κινδύνου των καταγμάτων του ισχίου (HR 0.72; 95% CI 0.59–0.89;*p* = 0.002),και η μείωση ήταν μεγαλύτερη όσο αυξάνονταν ο βασικός κίνδυνος. Δεν υπήρξε σημαντική μείωση όλων των καταγμάτων (HR 0.94; 95% CI 0.85–1.03).
- Η στρατηγική του screening συνοδεύτηκε από αύξηση της χρήσης αντιοστεοπορωτικών φαρμάκων και καλύτερη συμμόρφωση κατά τη διάρκεια της παρακολούθησης.
- Επιπρόσθετα ήταν cost-efffective

FRAX for connoisseurs

- relatively simple arithmetic procedures have been proposed which can be applied to the conventional FRAX estimates of probabilities of hip fracture and a major fracture to adjust the probability assessment with knowledge of:

- high, moderate, and low exposure to glucocorticoids
- concurrent data on lumbar spine BMD
- information on trabecular bone score (TBS)
- hip axis length
- falls history
- immigration status
- type 2 diabetes
- chronic kidney disease
- recency of vertebral fracture

Official Positions for FRAX Clinical Regarding **Falls and Frailty**: Can Falls and Frailty be Used in FRAX?

- **Option 1**
- Adding the number of falls in the previous year as a separate risk factor to the FRAX algorithm.
- the FRAX team should examine ways of incorporating information from other studies such as SOF or other large observational studies.
- **For example the SOF data suggests that each extra fall (up to 5 or more) in the previous year increases the 10-year hip fracture risk by 30%.**

- **Option 2**
- In the absence of incorporating falls history into the FRAX algorithm, the other option, in the shorter term would be to make the FRAX user aware of the current limitations of FRAX (i.e., lack of falls as a risk in this case, which is likely to underestimate 10 year risks in patients with falls, especially recurrent falls).

- **Option 3**
- The falls subgroup considered whether other parameters such as **sarcopenia, frailty and functional status** could also be incorporated in FRAX in trying to further improve 10 year fracture risks.
- Although there are studies suggesting this approach may have some utility, the view of the subcommittee was that a falls history incorporated these parameters.
- For a busy clinician, asking a falls history is straight forward and not time-consuming, whereas assessing sarcopenia,frailty or functional status are problematic, suffer from lack of universally accepted definitions and assessment tools, are time-consuming, and therefore will not be practical.

- **Option 4**
- The guidance given to clinicians in FRAX therefore should include statements about the importance of falls prevention.
- Options include developing a care pathway for falls assessment and management

Recency of vertebral fracture

Age	10-year probability of MOF		Ratio
	(A) Recent vertebral fracture	(B) Prior fracture in adult life	
50	29.0	11.7	2.47
60	36.1	19.4	1.86
70	41.9	27.6	1.52
80	42.5	34.2	1.·24
90	34.7	33.3	1.04

BMI set at 25 kg/m^2

The right-hand column provides the ratio by which to adjust FRAX probabilities by virtue of a recent clinical vertebral fracture. Probabilities and ratios are derived from the UK

POSITION PAPER

Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures

John A Kanis, Helena Johansson, Nicholas C Harvey, Vilmundur Gudnason, Gunnar Sigurdsson, Kristin Siggeirsdottir, Mattias Lorentzon, Enwu Liu,Liesbeth Vandenput Eugene V McCloskey

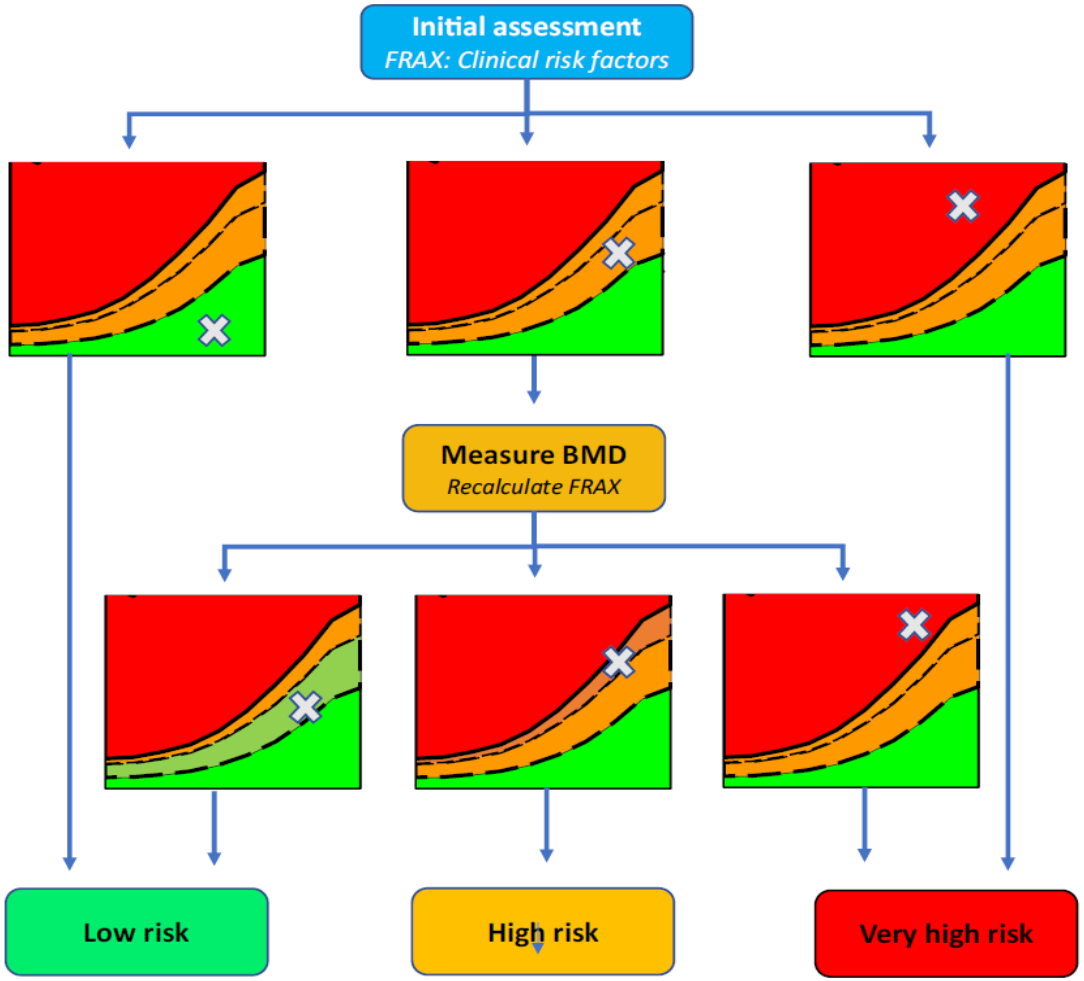
9th April 2020

AGE	50	60	70	80	90
ICELAND	2.62	1.84	1.50	1.23	1.01
UK	2.47	1.86	1.52	1.24	1.04

Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures

J. A. Kanis[1,2] · N. C. Harvey[3] · E. McCloskey[1,4] · O. Bruyère[5] · N. Veronese[6] · M. Lorentzon[2,7,8] · C. Cooper[3,9] · R. Rizzoli[10] · G. Adib[11] · N. Al-Daghri[12] · C. Campusano[13] · M. Chandran[14] · B. Dawson-Hughes[15] · K. Javaid[9] · F. Jiwa[16] · H. Johansson[1,2] · J. K. Lee[17] · E. Liu[2] · D. Messina[18] · O. Mkinsi[19] · D. Pinto[20,21] · D. Prieto-Alhambra[9,22] · K. Saag[23] · W. Xia[24] · L. Zakraoui[25] · J. -Y. Reginster[12,26]

Osteoporosis International (2020) 31:1–12



ΠΑΡΑΔΕΙΓΜΑΤΑ ΠΟΛΥ ΥΨΗΛΟΥ ΚΙΝΔΥΝΟΥ

Table 1 Examples of risk assessment in women from the UK (BMI set to 25 kg/m^2). Risk factors include prior fracture (of uncertain recency), prior clinical vertebral fracture within the past two years, family history of hip fracture, exposure to glucocorticoids, exposure to higher than average doses of glucocorticoids and bone mineral density (BMD) T-score at the femoral neck

Age (years)	Prior fracture	Recent spine fracture	Family history	GC	GC high dose	BMD (T-score)	10-year probability (%)	Category of risk
70	Yes					-	20	Low[1]
70			Yes			-	17	Low
70	Yes		Yes			-	30	Very high
70		Yes				-	30	Very high
60				Yes		−1.5	10	Low
60				Yes		−2.0	13	High
60				Yes	Yes	−2.0	15	Very high

[1] Qualifies for treatment by virtue of a prior fracture

VERY HIGH RISK*

If one or more of the below is true[†]:

- ❑ Fx within past 12 months[1,4]
- ❑ Multiple Fxs[1-3§]
- ❑ Fx while on OP Tx[1]
- ❑ Fx while on medication harmful to bone[1]
- ❑ Very low T-score <−3.0[1-3§]
- ❑ FRAX probability >30% MOF, >4.5% hip[1,4]

HIGH RISK*

If any of the below is true[†]:

Age: postmenopausal[1-4] **+**

- ❑ Prior Fx (>12 mos) **or**[1-3]
- ❑ T-score ≤−2.5 **or**[1-3]
- ❑ T-score −1.0 to − 2.5 **and** FRAX probability ≥20% MOF **or** ≥3% hip[1-3]

LOW RISK*

If all of the below are true[†‡]:

- ❑ Age: postmenopausal[2,3]
- ❑ No prior Fx[2,3]
- ❑ T-score > − 1.0 **and** FRAX probability <20% MOF **and** <3% hip[2,3]

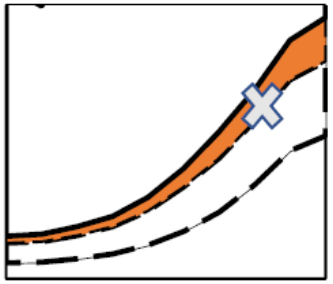
1.Camacho PM, et al. Endocr Pract. 2020;26:564-570. 2. Shoback D, et al. J Clin Endocrinol Metab. 2020;105(3):1-8. 3. Eastell R, et al. J Clin Endocrinol Metab. 2019;104:1595-1622.4. Kanis JA, et al. Osteoporos Int. 2020;31:1-12.

Low risk

Optimize calcium and vitamin D status

Risk appropriate exercise

Reassurance, lifestyle advice. Consider MHT and SERMs

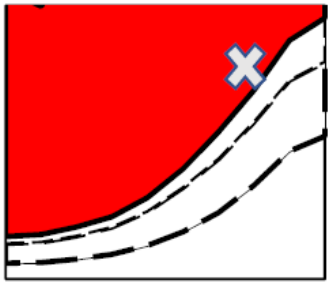


High risk

Optimize calcium and vitamin D status

Risk appropriate exercise and falls prevention

Consider oral bisphosphonate or other inhibitor of bone resorption*



Very high risk

Optimize calcium and vitamin D status

Risk appropriate exercise and falls prevention

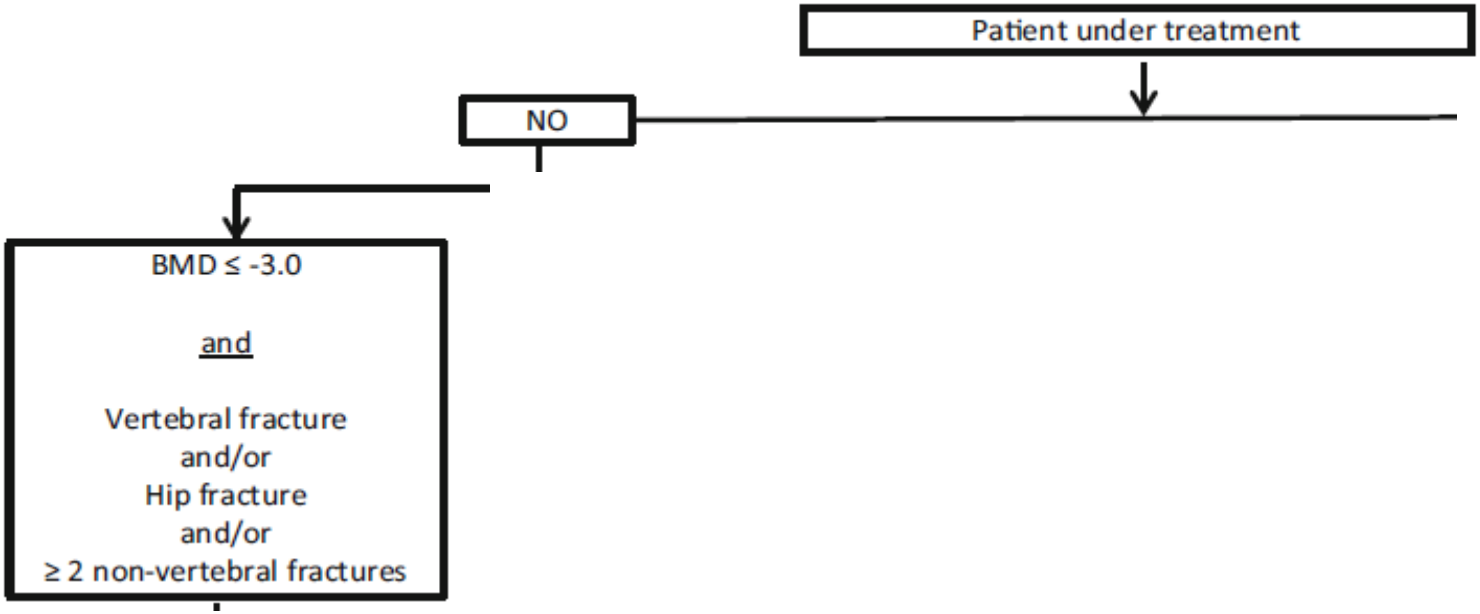
Consider anabolic agent followed by inhibitor of bone resorption*. Consider LOEP

MHT, menopausal hormone therapy;
SERM, selective estrogen receptor modulator;
LOEP, local osteo-enhancement procedure

The 2018 Guidelines for the diagnosis and treatment of osteoporosis in Greece

Polyzois Makras[1,2] · Athanasios D. Anastasilakis[2,3] · George Antypas[2,4] · Efstathios Chronopoulos[2,5] · Evangelia G. Kaskani[2,6] · Aikaterini Matsouka[2] · Dimos K. Patrikos[2,7] · Konstantinos D. Stathopoulos[2,8] · Symeon Tournis[2,9] · George Trovas[9] · Christos Kosmidis[2,10]

ALGORITHM FOR THE TREATMENT OF OSTEOPOROSIS



Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials

Dennis M Black, Douglas C Bauer, Eric Vittinghoff, Li-Yung Lui, Andreas Grauer, Fernando Marin, Sundeep Khosla, Anne de Papp, Bruce Mitlak, Jane A Cauley, Charles E McCulloch, Richard Eastell, Mary L Bouxsein*, for the Foundation for the National Institutes of Health Bone Quality Project*

	Study drug	N	Mean baseline age, years	Median (IQR) follow-up, months	Mean baseline femoral neck T-score	Prevalence of vertebral fracture at baseline	Fracture outcomes, vertebral/hip/non-vertebral, N
ALN phase 3* (1995)[51]	Alendronate	994	63·5 (7·0)	36·2 (35·4–36·6)	−2·15 (0·72)	233 (23·4%)	··/4/68
FIT vertebral fracture (1996)[52]	Alendronate	2027	70·3 (5·6)	36·0 (33·8–36·7)	−2·44 (0·57)	2027 (100%)	223/33/245
FIT clinical fracture (1998)[53]	Alendronate	4432	67·1 (6·1)	50·7 (48·9–55·0)	−2·21 (0·50)	0	121/41/494
FOSIT† (1999)[31]	Alendronate	1908	62·7 (7·6)	12·2 (12·0–12·3)	−1·97 (0·73)	..	··/4/52
Men's study‡ (2000)[54]	Alendronate	241	62·7 (12·5)	24·3 (24·1–24·5)	−2·15 (0·57)	121 (50·2%)	11/··/··
BONE* (2004)[55]	Ibandronate	2929	68·7 (6·2)	36·1 (31·1–36·5)	−2·10 (0·72)	2743 (93·6%)	167/21/229
IBAN IV* (2004)[56]	Ibandronate (intravenous)	2860	67·0 (5·1)	36·4 (36·1–36·7)	−2·14 (0·69)	2814 (98·4%)	274/26/243
HIP* (2001)[57]	Risedronate	9331	78·0 (5·4)	35·7 (10·9–36·6)	−2·75 (0·59)	2890 (31·0%)	497/205/913
VERT—North America (1999)[28]	Risedronate	1628	68·4 (7·5)	36·1 (17·5–36·6)	−2·21 (0·88)	1272 (78·1%)	180/15/157
VERT—multi-national (2000)[27]	Risedronate	814	70·8 (7·0)	36·2 (23·3–36·6)	−2·40 (0·80)	766 (94·1%)	166/17/100
Horizon 2301 (2007)[58]	Zoledronic acid (intravenous)	7736	73·1 (5·4)	36·1 (35·7–36·4)	−2·71 (0·53)	4893 (63·2%)	535/140/679
Horizon 2310‡ (2007)[59]	Zoledronic acid (intravenous)	2127	74·5 (9·7)	23·3 (16·4–30·9)	−2·39 (0·91)	..	··/56/186
LOFT (2019)[60]	Odanacatib	16 071	72·8 (5·3)	48·4 (36·0–60·9)	−2·66 (0·52)	7330 (45·6%)	891/216/1084
Women's health initiative—E only† (2003)[33]	Hormone therapy	10 739	63·6 (7·3)	99·5 (90·4–111·1)	−1·05 (1·05)	..	··/139/1331
Women's health initiative—E plus P† (2006)[34]	Hormone therapy	16 608	63·3 (7·1)	100·0 (91·0–110·9)	−1·24 (1·01)	..	··/241/2113
ACTIVE†§ (2016)[30]	Abaloparatide	1645	68·8 (6·5)	18·9 (18·5–19·1)	−2·15 (0·65)	365 (22·2%)	36/2/55
FRX prevention trial*¶ (2001)[21]	PTH(1–34) (subcutaneous)	1637	68·9 (7·0)	19·2 (17·6–20·8)	−2·23 (0·80)	1412 (86·3%)	105/9/119
TOP† (2007)[32]	PTH(1–84) (subcutaneous)	2532	64·4 (7·7)	18·2 (13·1–18·4)	−2·23 (0·64)	471 (18·6%)	59/6/79
FREEDOM (2009)[61]	Denosumab (subcutaneous)	7808	72·3 (5·2)	36·5 (36·0–36·9)	−2·20 (0·63)	1844 (23·6%)	350/69/556
GENERATIONS (2011)[62]	Arzoxifene	9354	67·4 (5·6)	56·0 (52·5–57·4)	−1·87 (0·71)	1423 (15·2%)	294/46/687
BZA phase 3*§ (2008)[29]	Bazedoxifene	5643	66·4 (6·7)	36·0 (22·4–36·0)	−1·82 (0·77)	3164 (56·1%)	141/18/258
PEARL* (2010)[63]	Lasofoxifene	8556	67·4 (5·2)	60·5 (59·7–61·0)	−2·19 (0·64)	2416 (28·2%)	607/90/760
MORE* (1999)[64]	Raloxifene	7705	66·0 (7·1)	35·8 (35·3–36·2)	−2·30 (0·56)	2875 (37·3%)	503/58/677

Dashes indicate that no data were available. All medications delivered orally, except where noted. E=oestrogen. P=progestogen. *Multiple dose groups combined. †Studies not included in the meta-regression analysis, because 24-month BMD change data were not available. ‡Study with male participants: Men's study with 100% male participants and Horizon 2310 with 23·9% male participants. §Active comparator group from initial trial excluded. ¶All non-vertebral fractures were included from this study as the percentage with major trauma (49%) was much higher than for other studies (usually <10%).

Table 1: Characteristics of randomised, placebo-controlled fracture outcome trials included in the Bone Quality database

TOTAL 67853 participants

Lancet Diabetes Endocrinol
2020; 8: 672–82

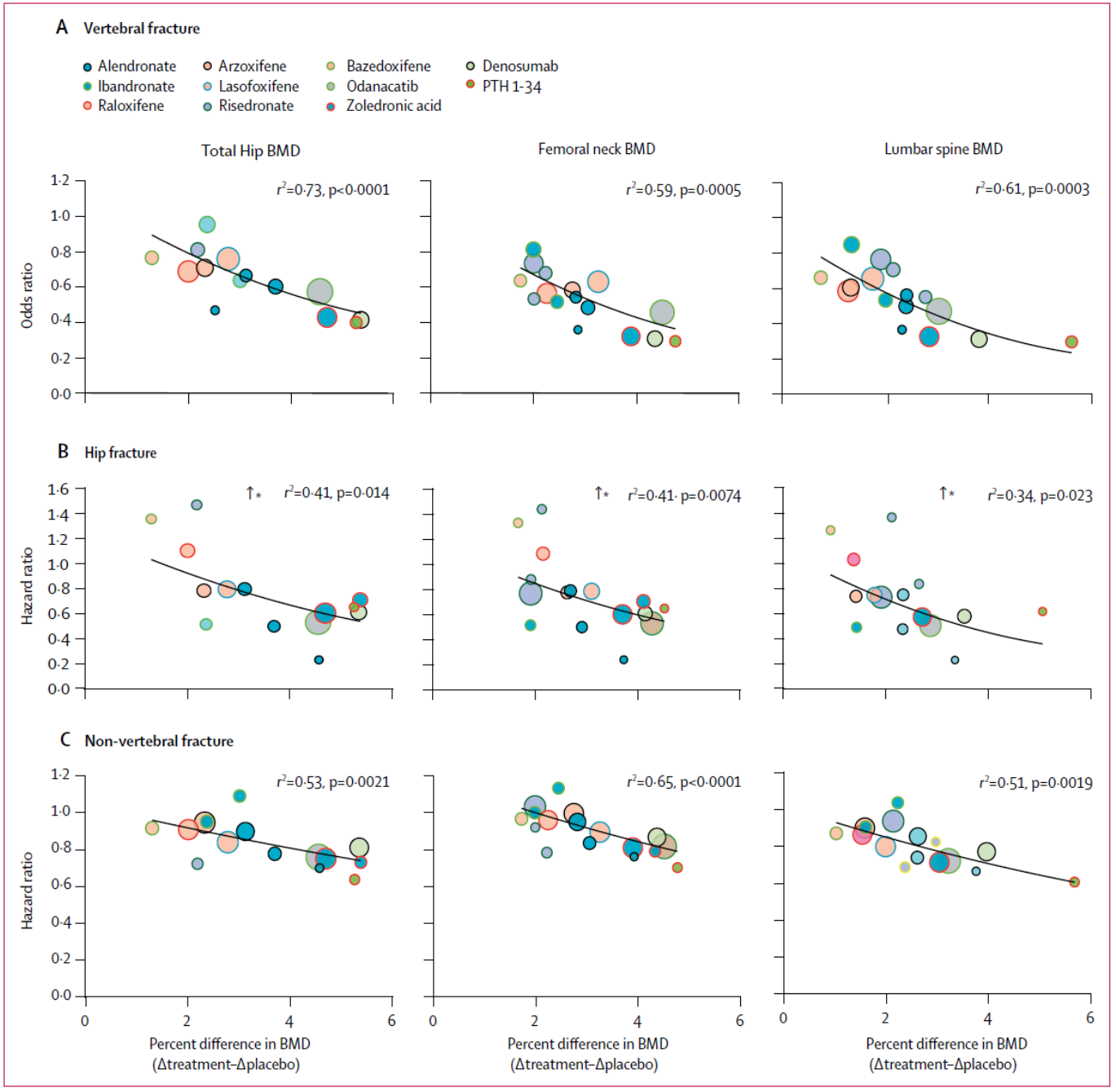


Figure 2: **Association between 24-month treatment-related differences in bone mineral density (active-placebo, in %) and reduction in fracture risk**
(A) Vertebral fracture risk. (B) Hip fracture risk. (C) Non-vertebral fracture risk. Individual trials are represented by circles with areas that are approximately proportional to the number of fractures in the trial. Drugs of the same class are represented by the symbols of the same colour. *BONE study (ibandronate) hazard ratio 2·08.

No more fracture trials in osteoporosis?

Comment -Ian R Reid

- **Added value of this study**
- We compiled individual patient data from all major osteoporosis trials including more than 90 000 participants with bone mineral density measurements from 23 placebo controlled fracture outcome trials.
- We conducted rigorous analyses to show that treatment-related bone mineral density changes are strongly related to fracture risk reductions.
- **These results show that change in bone mineral density could substitute for fracture reductions in future trials of new osteoporosis medications**, greatly reducing the size of required trials and the associated cost of new drug development.

Bisphosphonates and lower mortality risk: when it sounds to be good to be true …

W. D. Leslie

Osteoporosis International (2019) 30:2365–2367

- HORIZON Recurrent Fracture Trial παρατηρήθηκε μια μείωση κατά 28% της συνολικής θνησιμότητας μετά την χορήγηση του Ζολενδρονικού οξέος σε ασθενείς που υπέστησαν κάταγμα ισχίου.(Safety analysis όχι planned outcome)
- Η επισκόπηση των καμπυλών δείχνει ότι διαχωρίζονται μετά τον 16 μήνα χορήγησης.
- Αντίθετα στην HORIZON Pivotal Fracture Trial σε μετεμμηνοπαυσιακές γυναίκες με οστεοπόρωση δεν παρατηρήθηκε διαφορά στη θνησιμότητα (2.9% placebo-3.4%zoledronic acid P=0.27).
- Και επίσης εάν γίνει pooling των 2 μελετών δεν υπάρχει σημαντική διαφορά στη θνησιμότητα.

- Υπάρχουν αρκετές μετά-αναλύσεις που αναφέρουν ότι η χορήγηση των διφωσφονικών σχετίζεται με μειωμένη θνησιμότητα αλλά τα αποτελέσματα είναι ετερογενή με μια να αναφέρει ότι η δράση τους αρχίζει μετά από 6 μέρες χορήγησης και άλλη να υποστηρίζει μείωση της θνησιμότητας κατά 8% για κάθε μήνα χορήγησης τους.
- Το μεγαλύτερο βέβαια πρόβλημα είναι ότι πρόκειται για μετά-αναλύσεις μελετών παρατήρησης που δεν μπορούν ποτέ να εξαλείψουν υπολειπόμενους η μη μετρούμενους συγχητικούς παράγοντες (residual or unmeasured confounding) με αποτέλεσμα να μην ξέρουμε εάν η παρατηρούμενη διαφορά (στη συγκεκριμένη περίπτωση η θνησιμότητα) είναι πραγματική. (μπορεί και να είναι αλλά θέλει άλλες κατάλληλες μελέτες).
- Ο Leslie είναι απαισιόδοξος ότι μπορεί να γίνουν τέτοιες μελέτες στον μέλλον γιατί τα γενόσημα διφωσφονικά άλλαξαν το οικονομικό τοπίο με αποτέλεσμα να μην υπάρχουν διαθέσιμα χρήματα για χορηγίες τόσο μεγάλων μελετών και επιπρόσθετα υπάρχουν ηθικά προβλήματα στο να αφήνεις υψηλού κινδύνου ασθενείς χωρίς θεραπεία αρκετά χρόνια.

- Η τελευταία μετά –ανάλυση τυχαιοποιημένων ελεγχόμενων κλινικών μελετών από τον Cummings et.al JAMA Intern Med 2019 δεν έδειξε κάποια σημαντική διαφορά στην θνησιμότητα για όλα τα αντιοστεοπορωτικά φάρμακα ,τα διφωσφονικά συνολικά η το ζολενδρονικό οξύ από μόνο του.

2020 AACE/ACE Diagnostic Criteria for Osteoporosis

1	T-score −2.5 or below	→	Lumbar spine, femoral neck, total proximal femur, or 1/3 radius
2	Low-trauma spine or hip fracture	→	Regardless of bone mineral density
3	T-score between −1.0 and −2.5	+	Fragility fracture of proximal humerus, pelvis, or distal forearm
4	T-score between −1.0 and −2.5	+	High FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds

Camacho PM, et al. *Endocrine Practice*. 2020;5:1-37.

JAMA Original Investigation

Effect of Intravenous Zoledronic Acid on Tibiofemoral Cartilage Volume Among Patients With Knee Osteoarthritis With Bone Marrow Lesions

A Randomized Clinical Trial

JAMA. 2020;323(15):1456-1466

Key Points

Question Is zoledronic acid effective for reducing knee cartilage loss in patients with symptomatic knee osteoarthritis and bone marrow lesions?

Findings In this randomized clinical trial that included 223 adults, the mean change in tibiofemoral cartilage volume over 24 months was −878 mm^3 in the zoledronic acid group and −919 mm^3 in the placebo group, a difference that was not statistically significant.

Meaning The findings do not support the use of zoledronic acid for slowing cartilage volume loss in patients with knee osteoarthritis.

Table 3. Adverse Events

	No. (%)	
	Zoledronic acid (n = 113)	Placebo (n = 110)
Adverse events		
Any	108 (96)	91 (83)
Any serious[a]	23 (20)	24 (22)
Any acute reactions[b]	98 (87)	61 (56)
Acute reaction after first infusion	97 (86)	50 (46)
Acute reaction after second infusion	41 (36)	28 (26)

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