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ΕΚΔΗΛΩΣΗ



Β

ΜΕΤΑΒΟΛΙΚΑ ΝΟΣΗΜΑΤΑ ΤΩΝ ΟΣΤΩΝ

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ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΑΠΘ

ΑΡΙΣΤΟΤΕΛΕΙΟ
ΠΑΝΕΠΙΣΤΗΜΙΟ
ΘΕΣΣΑΛΟΝΙΚΗΣ



Φάρμακα και σκελετός

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Reader, Έδρα Πειραματικής Φυσιολογίας, Α.Π.Θ.

Hormonal therapy

- Glucocorticoids

- Thyroid hormone

- Aromatase inhibitors

- Ovarian suppressing agents

- Androgen deprivation therapy

- Thiazolidinediones

Psychotropic and anticonvulsant therapy

- Selective serotonin reuptake inhibitors

- Anticonvulsants

Drugs used for cardiovascular diseases

- Heparins

- Oral anticoagulants

- Loop diuretics

Drugs targeting the immune system

- Calcineurin inhibitors

- Anti-retroviral therapy

Drugs used for gastrointestinal diseases

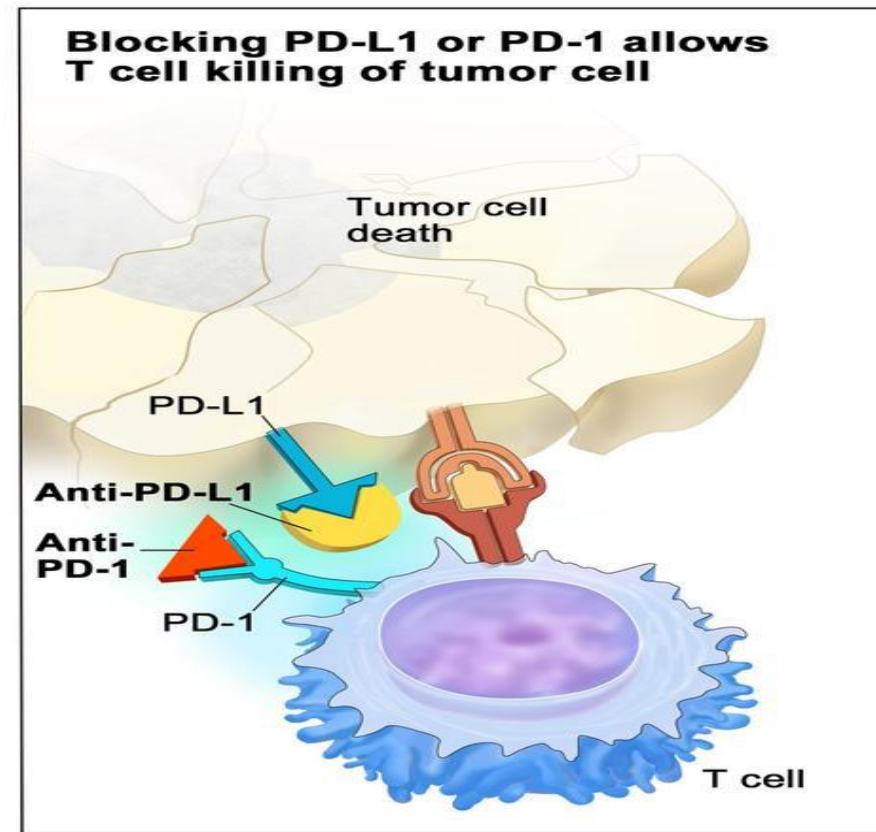
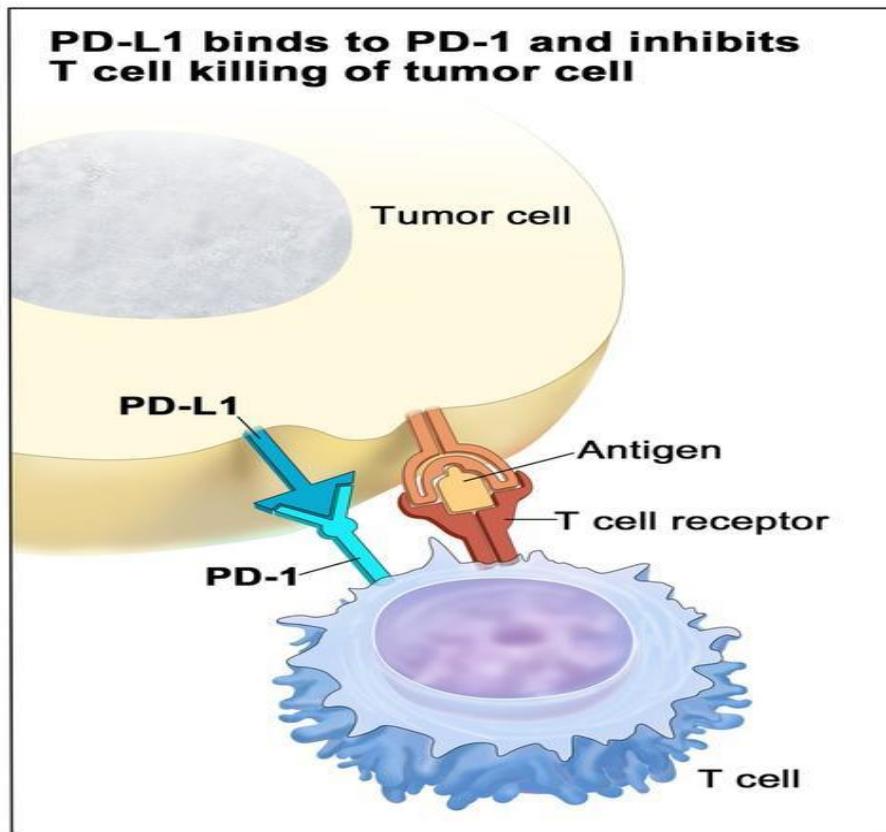
- Proton pump inhibitors

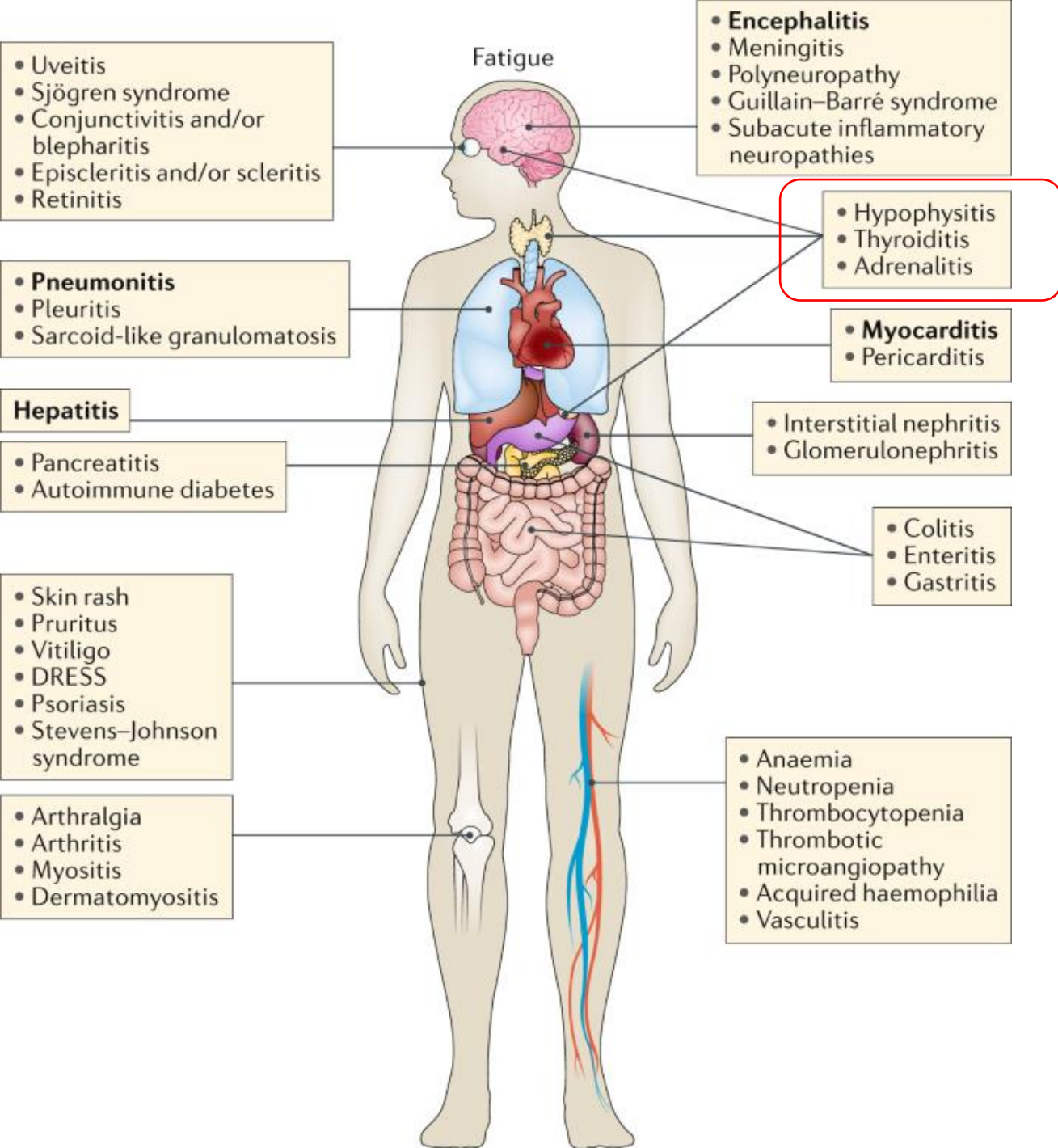
**Ας ξεκινήσουμε με μια κατηγορία
φαρμάκων που δεν
περιλαμβάνεται στους πίνακες.**

Τουλάχιστον μέχρι σήμερα!

Fracture rate increases after immune checkpoint inhibitor treatment: a potential new immune related adverse event

Carrie Ye ¹, Kevin Lee ², William D Leslie ³, Mu Lin ⁴, John Walker ⁵, Michael Kolinsky ⁵





Τι γίνεται με τα οστά;

- ❖ Background: several case reports linking ICIs with fracture risk
- ❖ BUT no population level studies

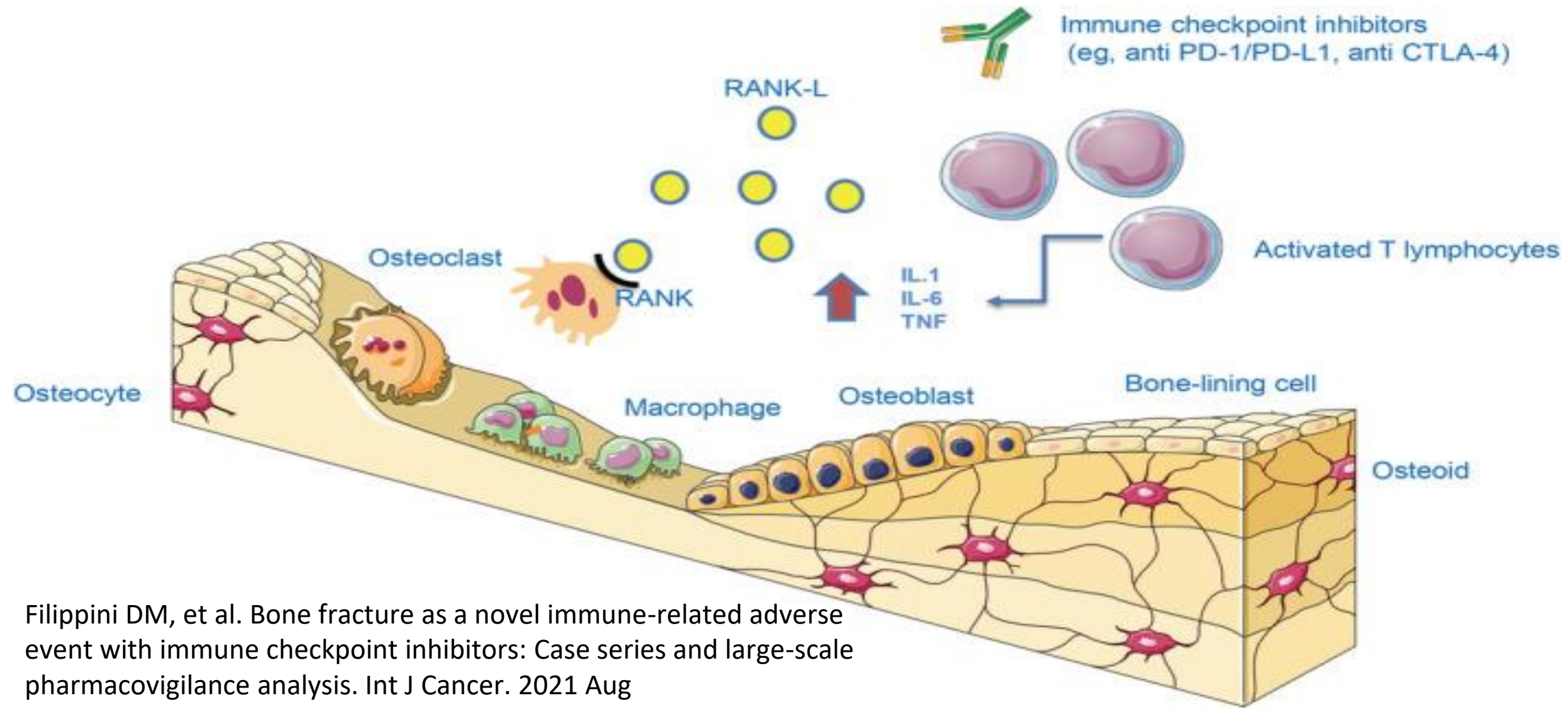
The study

- Immune check point inhibitors
- Population, retrospective study
- Individuals treated with ICI for cancer between September 29, 2010 and March 31, 2019
- At least 40 years old
- Presence of fracture diagnostic codes in the year prior to and up to 2 y after ICI initiation
- Three groups: the year prior to ICI initiation (-1 to 0), the year after ICI initiation (0 to +1) and the second year after ICI initiation (+1 to +2).

The results

- The study cohort consisted of 1600 ICI users (mean age 65.7 y, 59% male)
- Most patients were treated with an anti-PD-1 agent (73.9%), followed by anti-CTLA-4 agent (9.8%), anti-PD-L1 agent (9.8%), and combination ICI (6.4%).
- ICIs were initiated on average 707.8 d after cancer diagnosis.
- The fracture rate:
 - ❖ in the year prior to ICI initiation was 11.3 per 1000 patient years.
 - ❖ in the year after ICI initiation was significantly higher at 27.3 per 1000 patient years ($p < 0.01$)
 - ❖ with a rate of 17.6 per 1000 patient years in the second year after ICI initiation ($p = 0.28$).
- ***The relative risk of sustaining a major fracture in the year after compared to the year prior to ICI initiation was 2.39 (95%CI 1.34-4.27, $p < 0.01$).***

Emerging evidence suggests that systemic activation of T cells in vivo leads to an osteoprotegerin ligand-mediated increase in osteoclastogenesis and bone loss. In fact, ICIs can enhance bone resorption by activating T cells, which in turn causes bone loss with bone fragility, increasing the risk of fractures.



Filippini DM, et al. Bone fracture as a novel immune-related adverse event with immune checkpoint inhibitors: Case series and large-scale pharmacovigilance analysis. *Int J Cancer*. 2021 Aug

Bad to the bones: prescribing of drugs for the prevention and treatment of osteoporosis in patients on chronic glucocorticoids

[Sarah J. Billups](#),^{✉1} [Vinh K Thai](#),¹ [Jacob Denkins](#),¹ [Ian C. Dettman](#),¹ and [Micol S. Rothman](#)²

This study **aimed** to

- a) Identify a cohort of patients at risk for glucocorticoid-induced osteoporosis based on their prescribed glucocorticoid regimens and to quantify the proportion who were also prescribed osteoporosis pharmacologic treatment
- b) The secondary objective was to recognize patient characteristics associated with receiving such treatment.

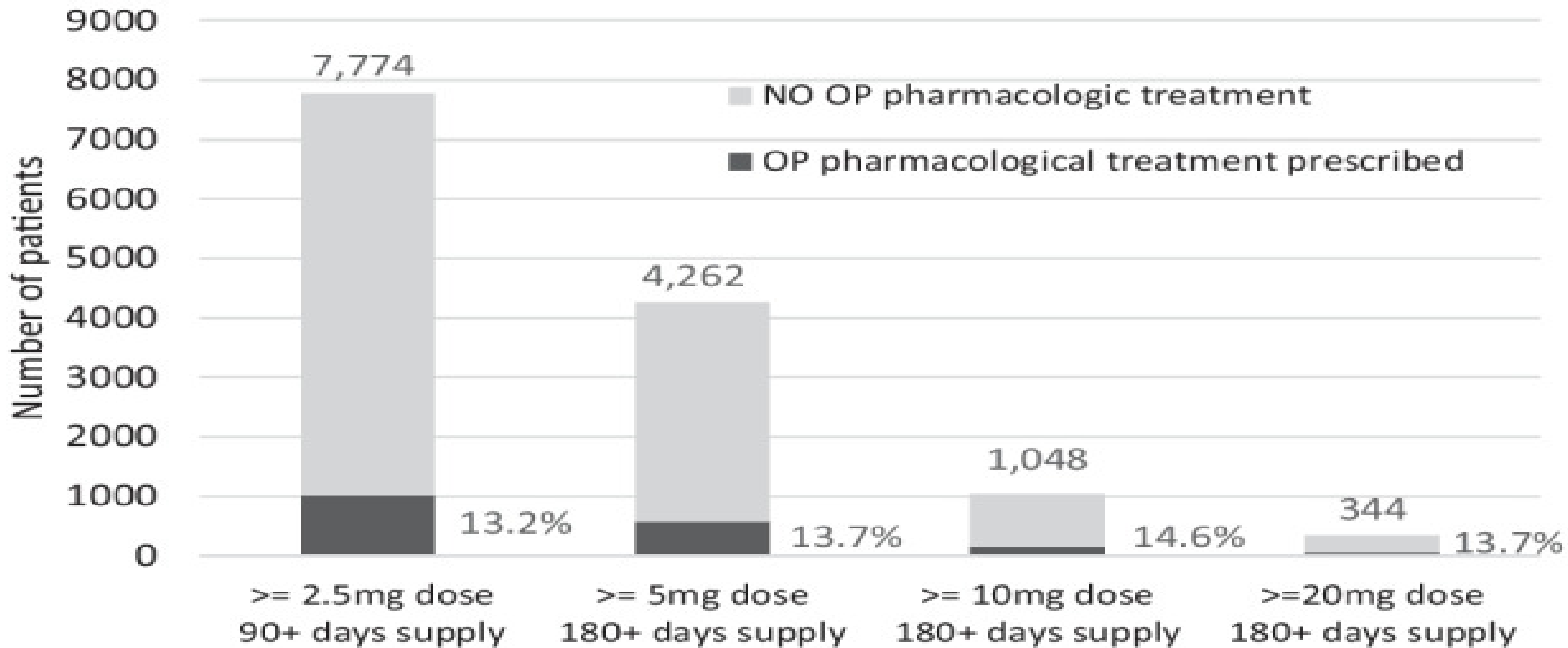
Method

A retrospective single-site cohort study used prescription order data to identify 7774 adults prescribed chronic glucocorticoids and measure the proportion also prescribed osteoporosis pharmacologic treatment.

Table 2

FRAX scores for a random sample of patients with data available for calculation

	Met this criteria n, (%)	Treatment ordered n, (%)
Major OP fracture risk \geq 20%	186/536 (34.0)	74/186 (39.8)
Hip fracture risk \geq 3%	302/536 (56.0)	109/302 (36.1)
Either score above threshold	311/536 (58.0)	110/311 (35.4)





Conclusions

The rate of prescribing osteoporosis pharmacologic treatment in patients prescribed systemic glucocorticoids is **less than 1 in 5 patients**, even at doses of 10 or more mg per day.

Review Article

The safety of long-term use of inhaled corticosteroids in patients with asthma: A systematic review and meta-analysis

Wenli Shang^{a 1}, Guizuo Wang^{a 1}, Yan Wang^{b 1}, Dong Han^a  

Purpose

This systematic review and meta-analysis was performed to determine the safety of long-term use of ICS in patients with asthma including osteoporosis.

Methods – results

Eighty-six RCTs (enrolling 51,538 participants) met the inclusion criteria.

Ερώτημα 1ο: Επίδραση στην ΜΟΠ της ΟΜΣΣ

- 5 RCTs
- 941 ασθενείς που έπαιρναν ICS – 958 placebo

Ερώτημα 2ο: Επίδραση στον ολικό καταγματικό κίνδυνο

- 11 RCTs
- 11.557 ασθενείς που έπαιρναν ICS – 6.129 placebo

Αποτέλεσμα

There was no statistically significant difference in the risk of decline in bone mineral density and fractures between the two groups.

CONCOMITANT PPI USE NEGATES ORAL BISPHOSPHONATE ANTI-FRACTURE EFFICACY: A POST HOC ANALYSIS FROM A RANDOMIZED CONTROLLED TRIAL OF CLODRONATE – JBMR, ahead of printing

E. McCloskey, N. C. Harvey, M. Lorentzon, L. Vandenput, E. Liu, J. A. Kanis, H. Johansson

- ❖ Oral bisphosphonates are frequently co-prescribed with antacid drugs that may interact with bisphosphonate anti-fracture efficacy. We explored the relationship between antacid use and clodronate efficacy on osteoporotic fracture risk within a well-documented, randomised, placebo-controlled study.
- ❖ Material and Methods: Concurrent medication use at baseline was used to identify those prescribed proton pump inhibitors (PPI), histamine 2 receptor antagonists (H2RA) or other antacids (OAA).

Methods

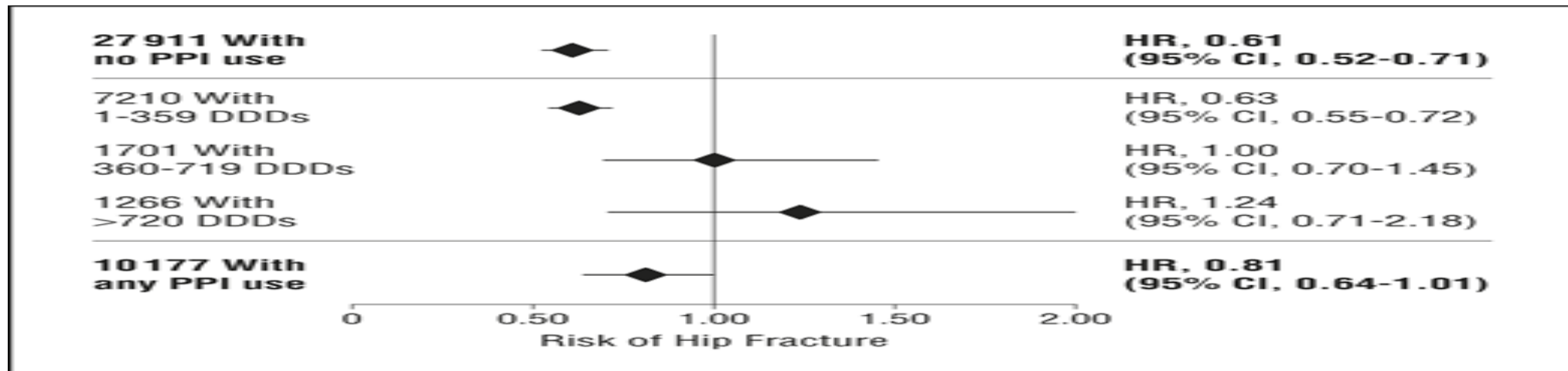
- 5212 women recruited to the trial:
 - ✓ 1339 (25.7%) were taking at least one antacid at entry, of whom
 - 451 took H2RA (8.7%),
 - 436 took PPI (8.4%) and
 - 652 took OAA (12.5%, predominantly [89%] sodium alginate-based products).
 - ✓ There was no significant difference in baseline antacid exposure between the clodronate and placebo groups and, as previously reported, clodronate was associated with a 23% reduction in osteoporotic fractures (HR 0.77, 0.63-0.93, p=0.002).

Results

- In the placebo group, none of the antacid classes were significantly associated with future osteoporotic fracture risk over the three year intervention study.
- **In contrast**, in the clodronate arm, while OAA and H2RA had no statistically significant effect on fracture risk, **PPI was associated with a 2.13-fold increase (95%CI 1.44-3.16, p=0.001)**
- Thus, the antifracture efficacy of clodronate in women not using PPI was substantial (HR 0.72, 95%CI 0.59-0.88, p=0.002) but with no apparent fracture reduction in women using PPI (HR 1.16, 0.69-1.97, NS). The p-value for interaction between PPI use and clodronate efficacy was 0.09.

Conclusion

- In this post hoc analysis, the efficacy of oral clodronate to reduce fracture risk was inhibited in the presence of concomitant PPI use, consistent with the observation by Abrahamsen and colleagues (2011)



- While the mechanism is unclear, this potentially clinically significant observation requires further exploration in studies of commonly used bisphosphonates.

Τι να κάνουμε στην κλινική πράξη;

- In the interim, because [omeprazole](#) was shown to reduce the fractional absorption of [calcium carbonate](#) in fasting postmenopausal women in some studies, we advise that postmenopausal women taking long-term PPI or H2 blocker therapy increase dietary calcium and, when necessary, use calcium supplements that do not require acid for absorption, such as [calcium citrate](#).

(H. Rosen, uptodate.com)

[J Bone Miner Res.](#) 2022 Jun; 37(6): 1117–1124.

PMCID: PMC9487988

Published online 2022 Apr 20. doi: [10.1002/jbmr.4548](https://doi.org/10.1002/jbmr.4548)

PMID: [35441396](https://pubmed.ncbi.nlm.nih.gov/35441396/)

Potential Adverse Effect of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) on Bisphosphonate Efficacy: An Exploratory Post Hoc Analysis From a Randomized Controlled Trial of Clodronate

[Zhangang Zheng](#),^{1,2} [Helena Johansson](#),^{3,4} [Nicholas C. Harvey](#),⁵ [Mattias Lorentzon](#),^{3,4} [Liesbeth Vandenput](#),^{3,4}
[Enwu Liu](#),⁴ [John A. Kanis](#),^{4,6} and [Eugene V. McCloskey](#)^{✉1,6}

Background – υπόθεση

- Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to have weak but beneficial effects on bone health, including fracture risk, but many epidemiological studies are likely confounded.
- We explored the relationship between NSAIDs and fracture risk in a post hoc analysis of a well-documented, randomized, placebo-controlled study of the bisphosphonate, clodronate, in which treatment reduced osteoporotic fracture risk by 23%.

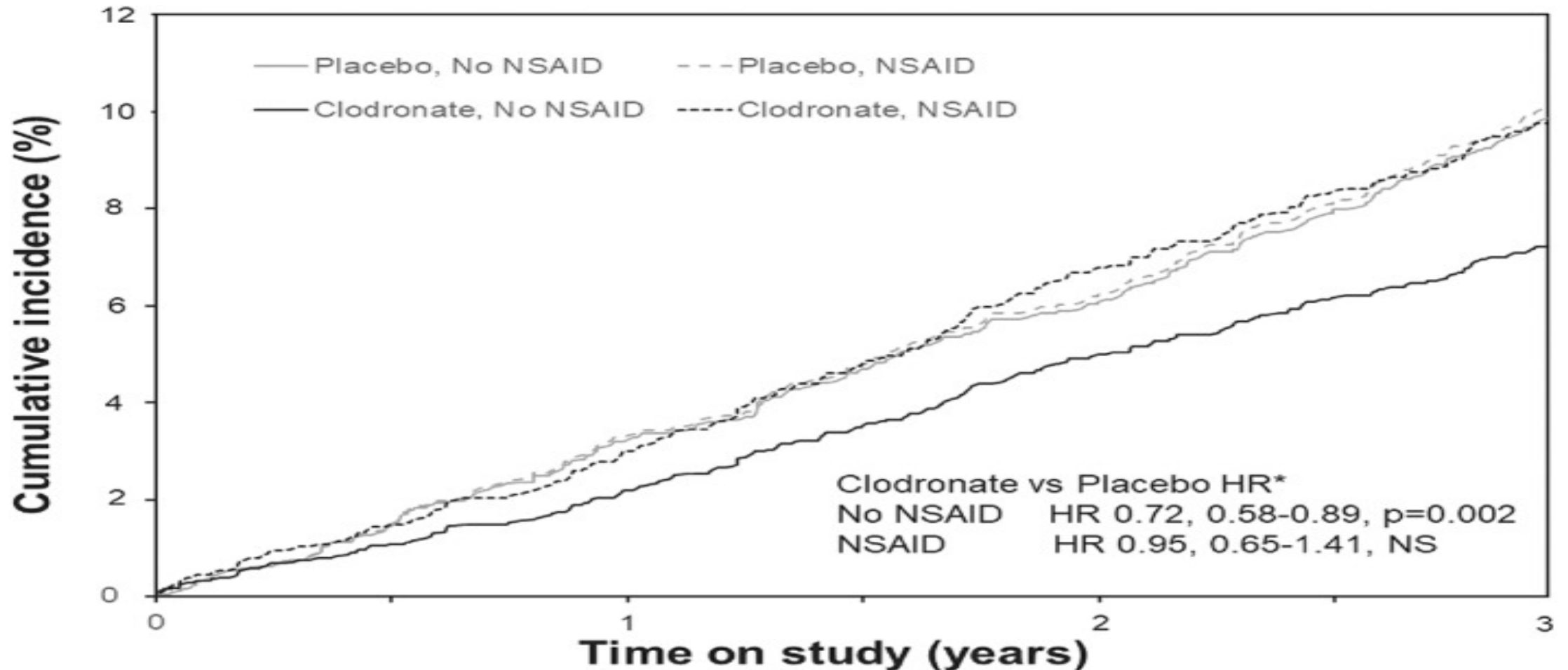
Μέθοδος - υλικό

- A total of 1082 (20.8%) women reported use of NSAIDs at baseline. They were slightly, but significantly, younger (mean 79 versus 80 years, $p = 0.004$), heavier (mean 66.7 versus 64.7 kg, $p < 0.001$) than nonusers, with slightly higher femoral neck bone mineral density (FN-BMD, 0.66 versus 0.64 g/cm², $p < 0.001$).

No NSAID ($n = 4130$)

NSAID ($n = 1082$)

Ερώτημα 1: *Relationship between NSAID use and osteoporotic fracture risk*

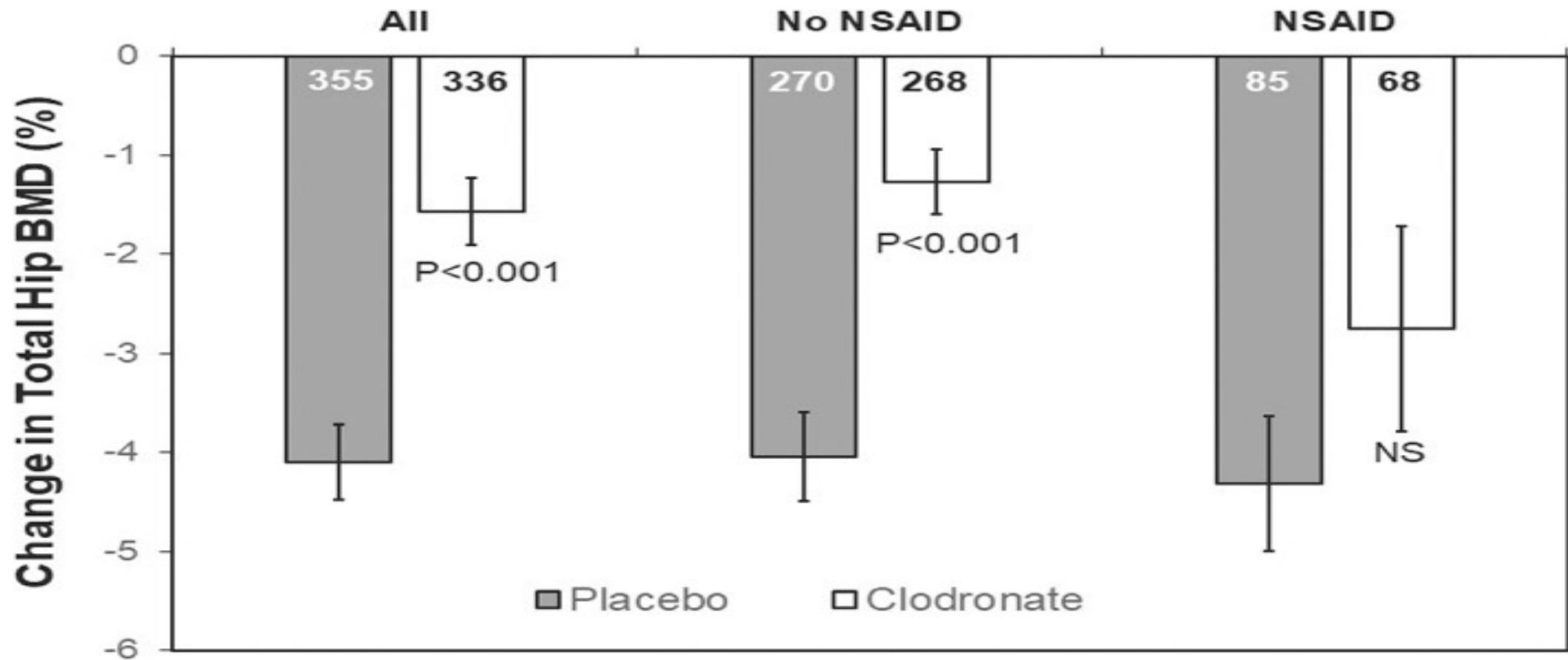


Ευρήματα:

1. In the placebo group, the rates of osteoporotic and hip fractures did **not** differ in women receiving NSAIDs compared to those not treated with NSAIDs; eg, the proportion sustaining osteoporotic fractures was 9.5% and 9.7%, respectively
2. In contrast, in the women receiving clodronate, NSAID use was associated with a 37% higher osteoporotic fracture risk, which was of borderline statistical significance; the increase was greater (49%) and statistically significant in the adjusted model
3. Of note, the incidence of osteoporotic fracture in those women on clodronate but also exposed to NSAIDs was similar to that observed in the placebo group (9.2%)

Ερώτημα 2: NSAID exposure, clodronate, and BMD changes over 3 years

- A total of 691 women had repeated measurement of hip and subregional BMD at the end of the 3-year treatment period.



Συμπεράσματα - σχόλια

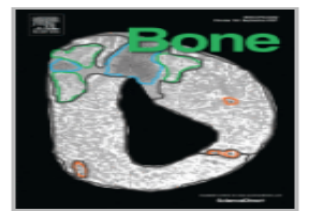
- Based on a well-documented clinical study that allows identification and adjustment for multiple confounders
- Suggests that there is little evidence of a direct effect of NSAIDs on fracture risk.
- Perhaps the most unexpected, but potentially most important finding from a clinical perspective, is the association between NSAID use and apparent complete negation of the protective effect of the oral bisphosphonate, clodronate, on osteoporotic fracture risk.
- We believe this is the first report of such an interaction

Μειονεκτήματα



- This was a post hoc analysis of a study not designed to address this particular question
- Our study population comprised elderly, community-dwelling women, and the findings might not be translatable into men or younger individuals of either sex, though biological reasons for potential differences are hard to identify
- Our analysis was based on self-reported NSAID use at entry to the study, though this was verified against GP prescriptions where available

Μηχανισμός;

- Μόνο εικασίες
- Μειωμένη συμμόρφωση ή/και απορρόφηση διφωσφονικού σε όσους παίρνουν ΜΣΑΦ;
- ❖ Oral clodronate has generally higher bioavailability (1% to 2% intestinal absorption) compared to that of oral nitrogen-containing bisphosphonates such as alendronate (<1%), but the absorption is still very low.
- Μειωμένη συμμόρφωση ή/και απορρόφηση συγχορηγούμενου ασβεστίου σε όσους παίρνουν ΜΣΑΦ;



Bone density and quality in patients treated with direct-acting oral anticoagulants versus warfarin

Jeferson Zanovelli Nalevaiko^a, Júlia Vieira Oberger Marques^b,
Matheus Felipe Oliveira^c, Arthur William Passos Raetsch^c, Gustavo Lenci Marques^a,
Ricardo Rasmussen Petterle^d, Carolina Aguiar Moreira^b,
Victória Zeghbi Cochenski Borba^b  

**Οστική ποιότητα σε ασθενείς υπό αντιπηκτική αγωγή:
Νεότερα αντιπηκτικά versus βαρφαρίνης**

Υπόθεση

- Direct-acting oral anticoagulants (DOACs) are therapeutic alternatives to warfarin that act independently of vitamin K, thus not affecting bone matrix formation.
- Most cross-sectional studies have found that mean bone density in warfarin-treated patients was lower than in control patients and a retrospective cohort study found that long-term exposure to warfarin was associated with an increased risk of vertebral and rib fractures.
- Very few studies have evaluated the effects of DOACs on bone mass, while no studies to date have compared the bone mineral density (BMD) and bone quality by trabecular bone score (TBS) in patients using warfarin and DOACs.

ΣΚΟΠΟΣ

- The main aim of this study was to determine bone density and quality using BMD measurement and bone microarchitecture using TBS measurement in patients treated with DOACs or warfarin compared with controls.

Μέθοδος

- Cross-sectional and observational study

Αποτελέσματα

- 150 patients were included: 50 patients in each group: a) warfarin, b) DOAC, c) placebo
- The mean age was 60.49 ± 7.48 years, and most participants were men (64%).
- Low bone mass was diagnosed in 42%, 50%, and 66% of the patients in the CG, DOACG, and WG, respectively ($p = 0.012$).
- The mean TBS decreased progressively from the CG to the DOACG and WG (1.328 ± 0.112 , 1.264 ± 0.138 , and 1.203 ± 0.112 , respectively, $p < 0.001$)
- On multivariate linear regression, the strongest negative predictor of TBS included warfarin use (-0.06 , 95%CI -0.11 to -0.02 , $p = 0.006$),

Συμπέρασμα

- Patients using anticoagulants have lower BMD and TBS values compared with controls. This negative effect on bone was more pronounced with warfarin, but was also seen with DOACs.

Σχόλια

- Μικρή έρευνα
- ? Είναι αληθής αυτή η μείωση BMD and TBS
- Αν ναι, ποιος ο μηχανισμός; Αντανακλούν μια κακή γενικότερη κατάσταση υγείας των ασθενών αυτών;
- Καλύτερες μελέτες είναι απαραίτητες
- Συνολικά, όταν επιλέγεται αντιθρομβωτική αγωγή η επίδραση στα οστά και ο καταγματικός κίνδυνος δεν αποτελεί κριτήριο απόφασης