Praxisrelevante Highlights aus dem Osteoporose-Register Schweiz

PD Dr. med. Judith Everts-Graber

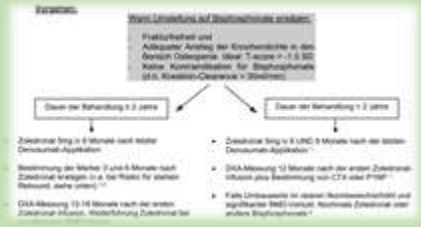
St. Urban Symposium

3. Mai 2025

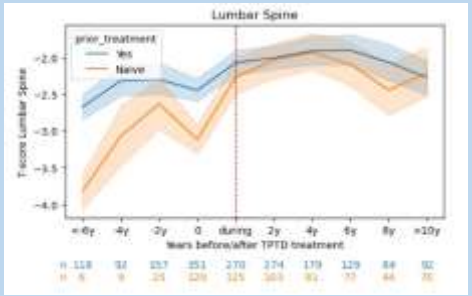
Swiss Osteoporosis Registry Group

Heutige Agenda

- **Denosumab** – Neues zur Sicherheit und Wirksamkeit

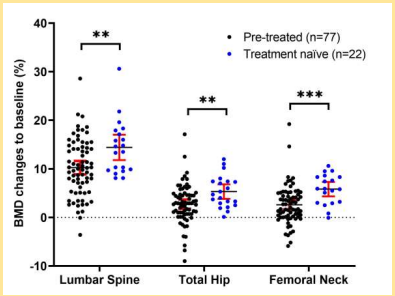


- **Teriparatide** – Langzeitverläufe bei firstline versus secondline

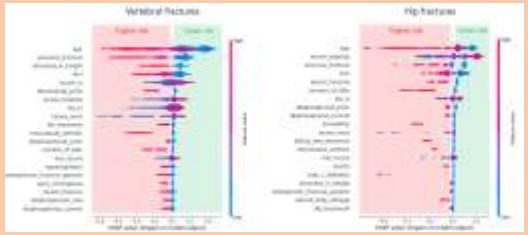


- **Romosozumab**

Erste Erfahrungen im klinischen Alltag



- **Frakturprädiktion** und **TOP-Tool**



Warum ein Register?

- Langzeiteffekte bei sequentiellen Therapien
- On/off-treatment Phänomene
  - zB Rebound nach Denosumab
- Wirksamkeit und Sicherheit bei multimorbiden Pat. (50% unserer Pat. sind bei RCTs nicht repräsentiert…) [1]
- Neue Medikamente: Erste «Real-World» Erfahrungen

1. C. Reyes et al., “Real-Life and RCT Participants: Alendronate Users Versus FITs’ Trial Eligibility Criterion,” Calcif Tissue Int, vol. 99, no. 3, 2016, doi: 10.1007/s00223-016-0141-7.

Osteoporose-Register werden **weltweit wichtiger** werden!

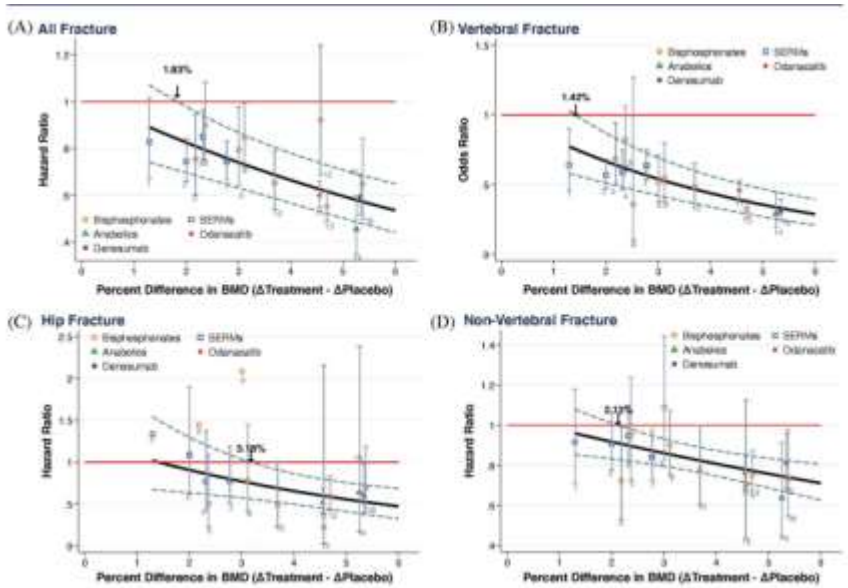
FDA Issues Timeline for Determination on FNIH-ASBMR-SABRE Application to Qualify BMD as a Surrogate Endpoint in Future Trials of Anti-Osteoporosis Drugs

Mar 25, 2024

SABRE

The FNIH-ASBMR-SABRE Project

Study to Advance BMD as a Regulatory Endpoint

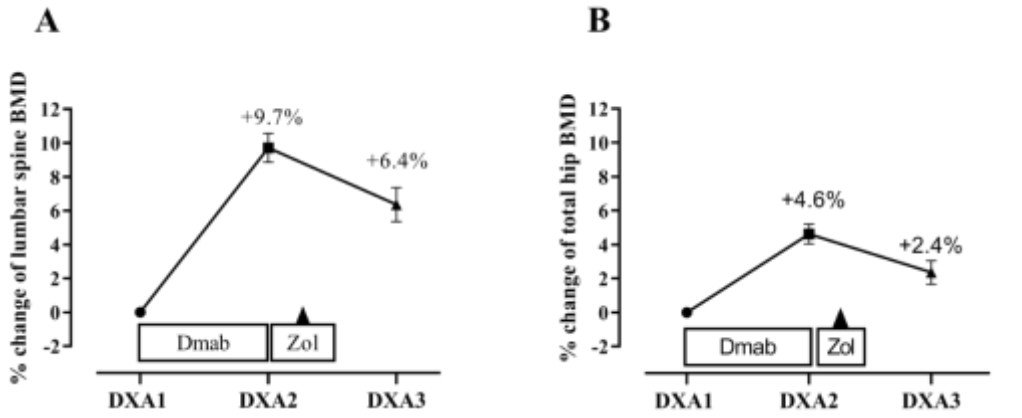


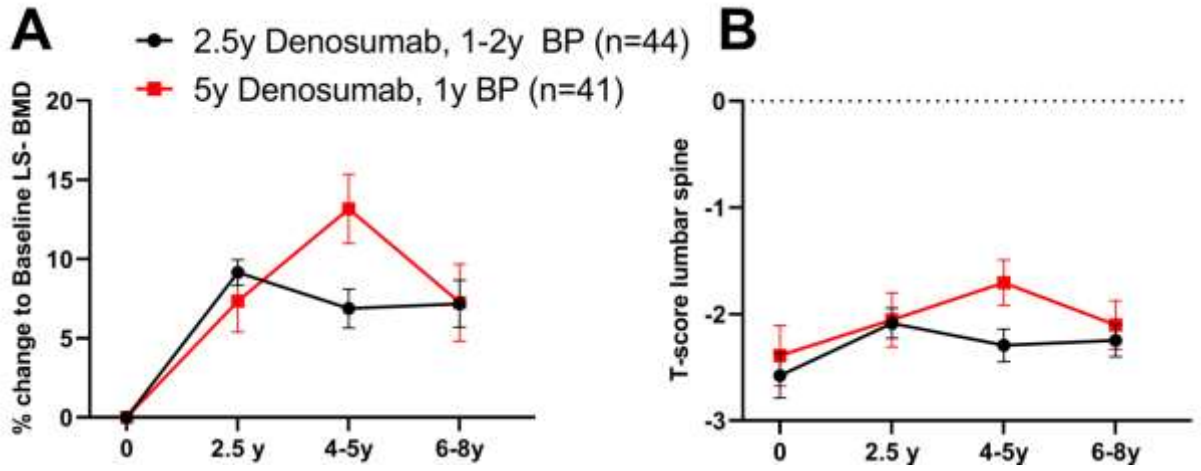
- In zukünftigen Trials wird ggf. Fraktur mit **Δ Total Hip BMD als Endpunkt** «ersetzt».
- Für zukünftige Medikamente bräuchte es nur noch **250/250 Probanden** über einen Zeitraum von **24 Monaten**
- **Sicherheit** wäre nicht mehr in Phase III angeschaut, sondern nur noch **Post-marketing surveillance**

Denosumab Rebound-Effekt

Erkenntnisse aus dem OP Register Schweiz

1. Einmalige Zoledronatinfusion 6 Monate post-Dmab
2. Rebound stärker bei längerer Behandlung
3. BMD Verlust trotz ZOL….

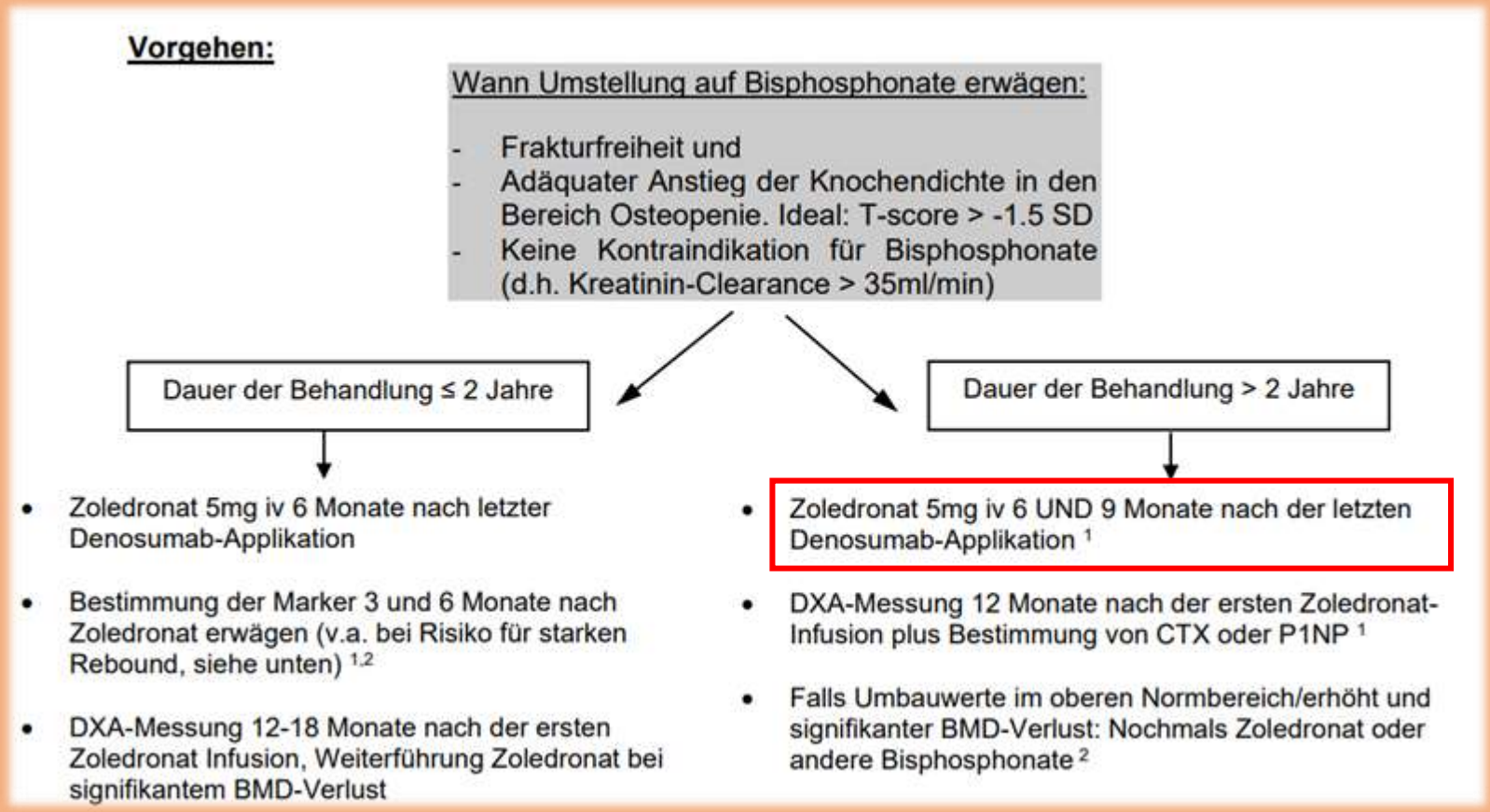




1. Everts-Graber et al., JBMR 2020, 2. Everts-Graber et al Bone 2021, 3. Everts-Graber et al Bone 2023

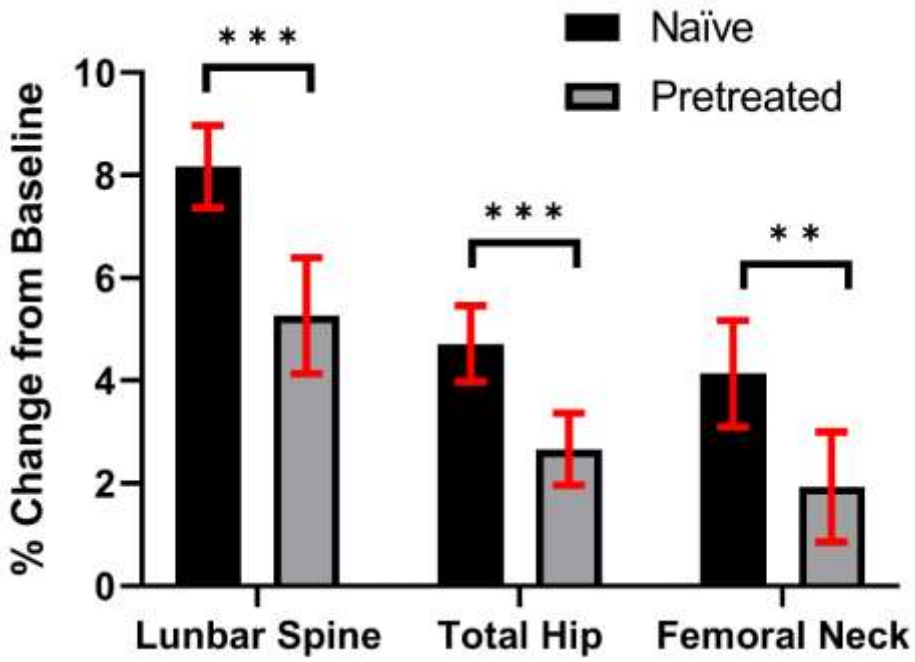
Denosumab – was gibt es Neues zum Rebound?

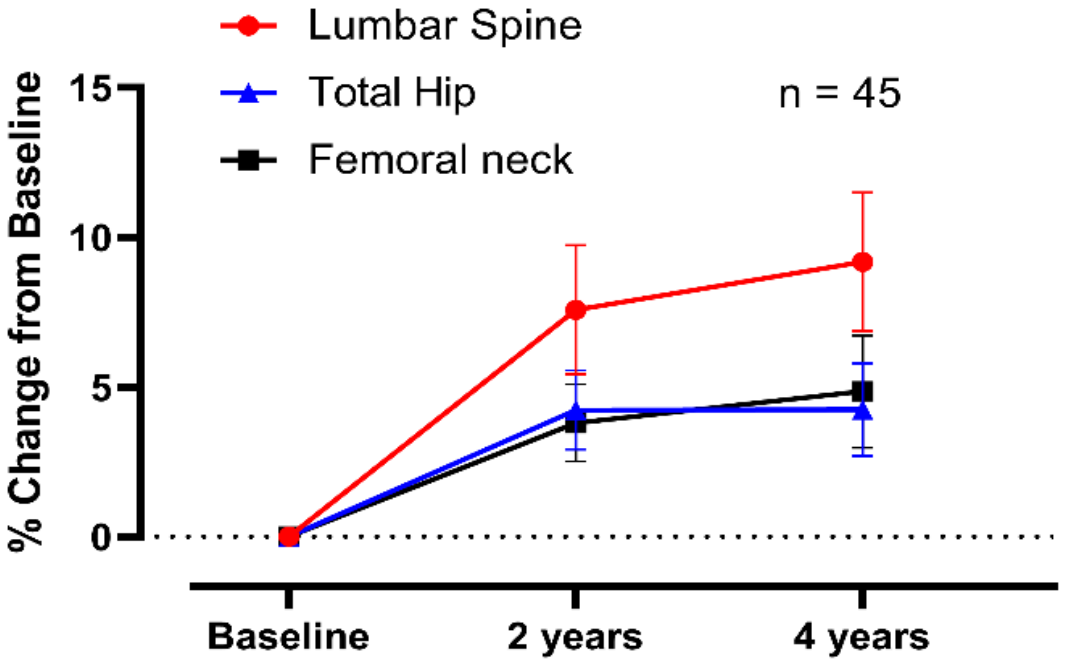
- Neue SGR-Guideline: www.rheuma-net.ch/
  - Unter «Behandlungsempfehlung»: Weiterbehandlung nach Denosumab



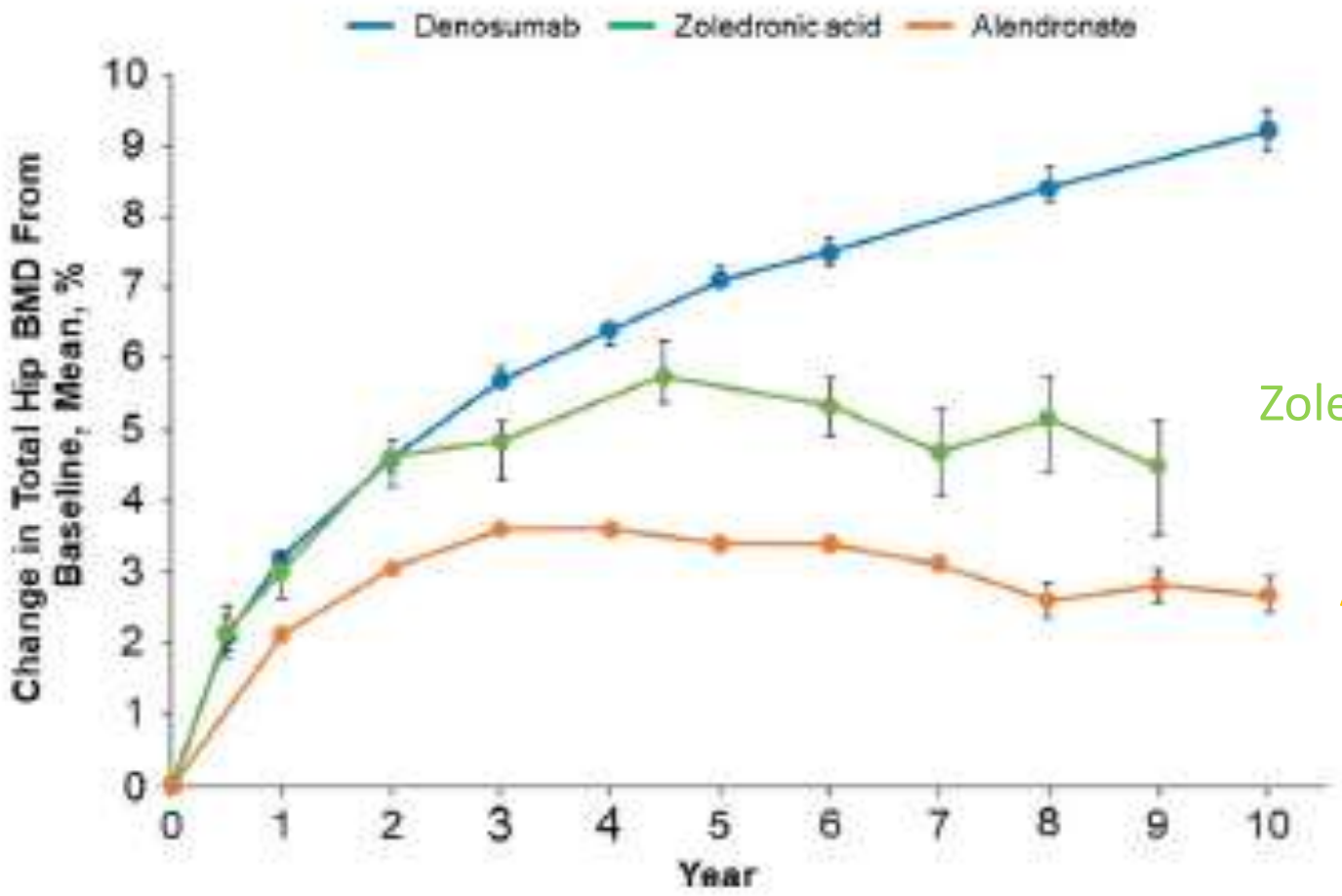
1x Denosumab, dann Zoledronat?

- 234 Pat., 90% weiblich, im Schnitt 66 Jahre alt, 40% vorbehandelt
- **1x Prolia, 6 Monate später 1 Zoledronat Infusion, ggf. 2. Infusion**
- **BMD Zunahme innert 24 Monaten:**





Demosumab – *besser* als Bisphosphonate?



Denosumab

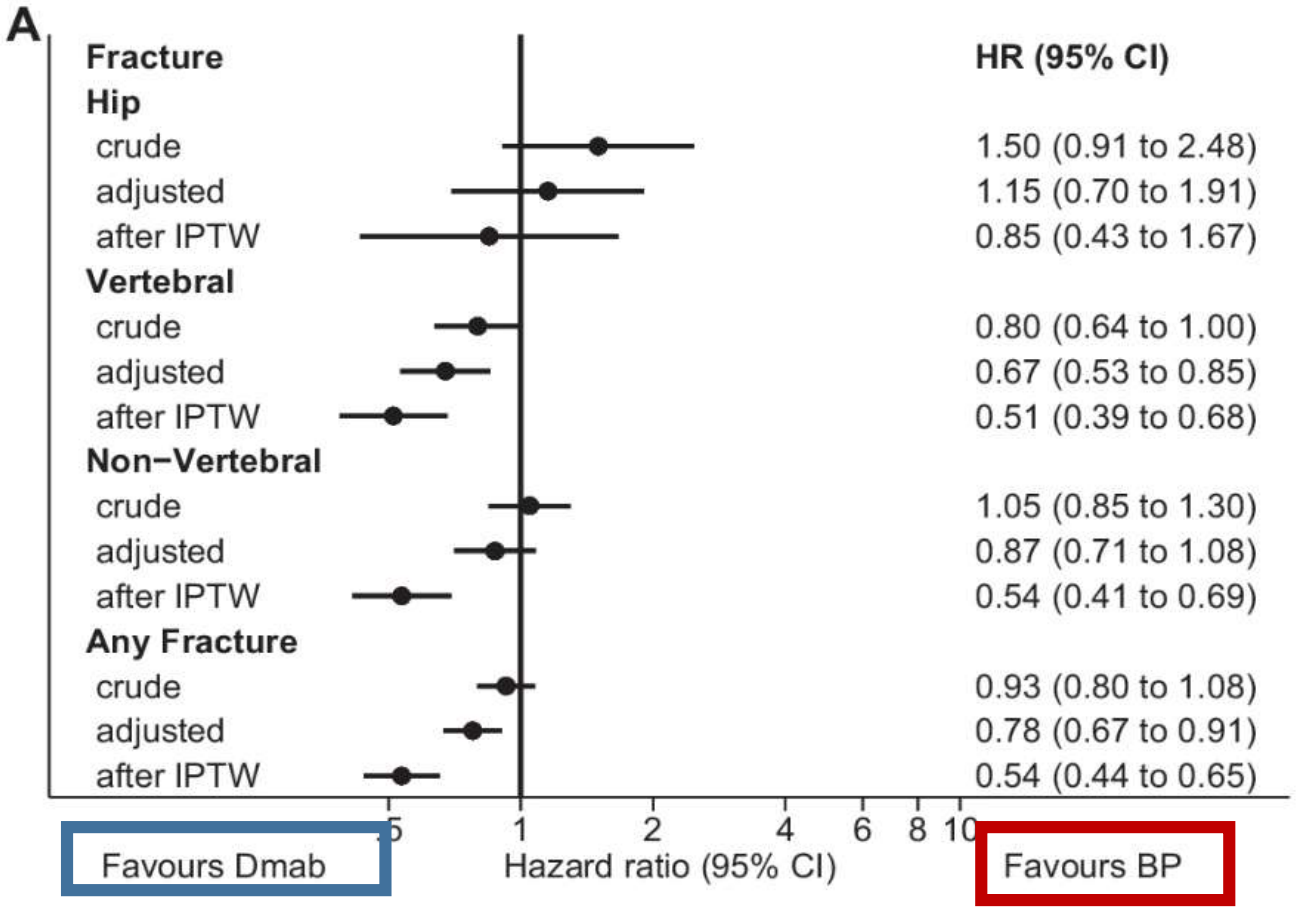
Zoledronate (Bisphosphonate iv)

Alendronate (Bisphosphonate po)

Kendler et al, "Denosumab in the Treatment of Osteoporosis: 10 Years Later: A Narrative Review", Adv Ther. 2022 Jan;39(1):58-74.

Bisphosphonate versus Denosumab

Frakturreduktion «Real-World»



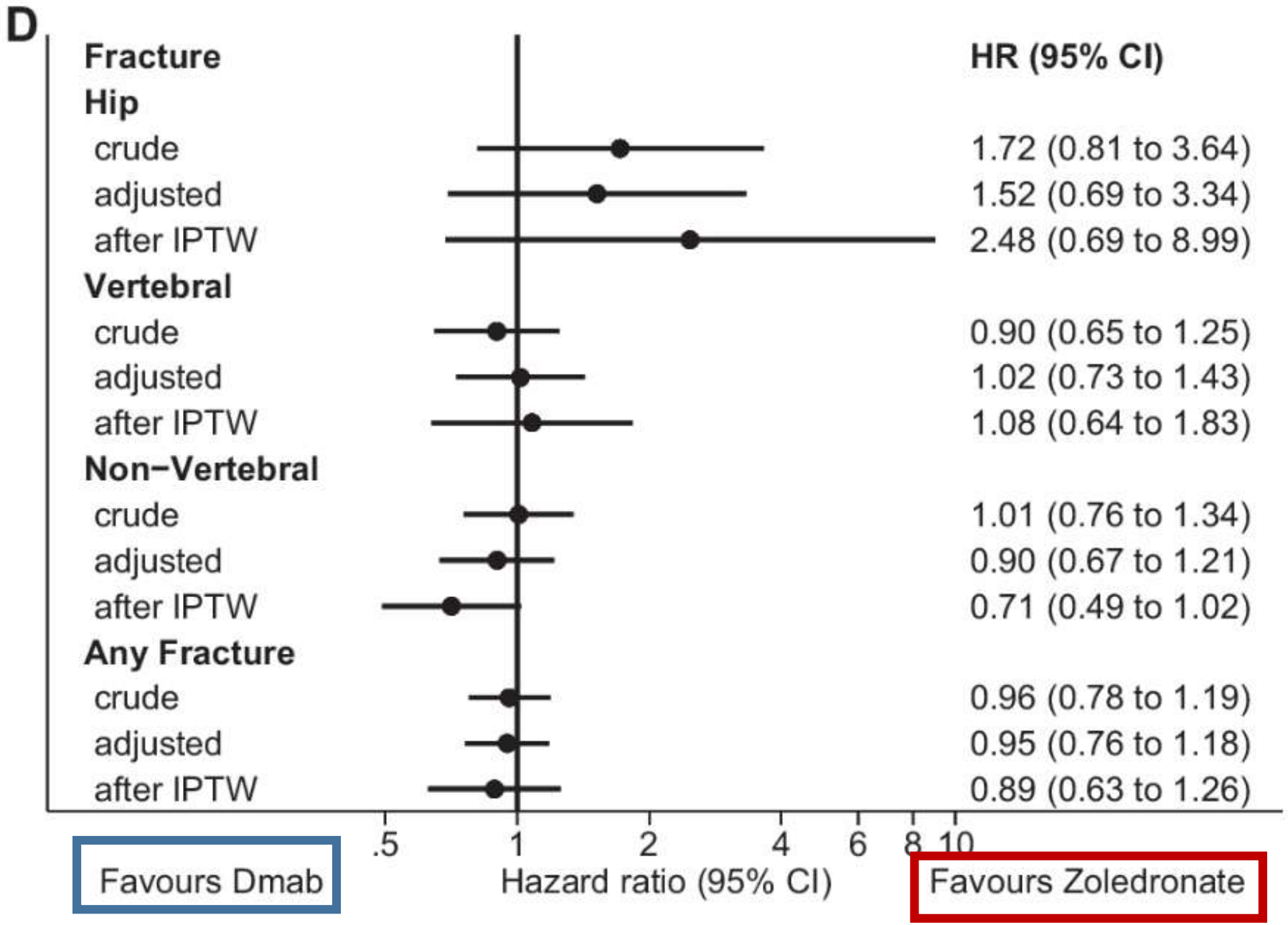
Osteoporosis International (2023) 34:1961–1973
https://doi.org/10.1007/s00198-023-06863-y

ORIGINAL ARTICLE

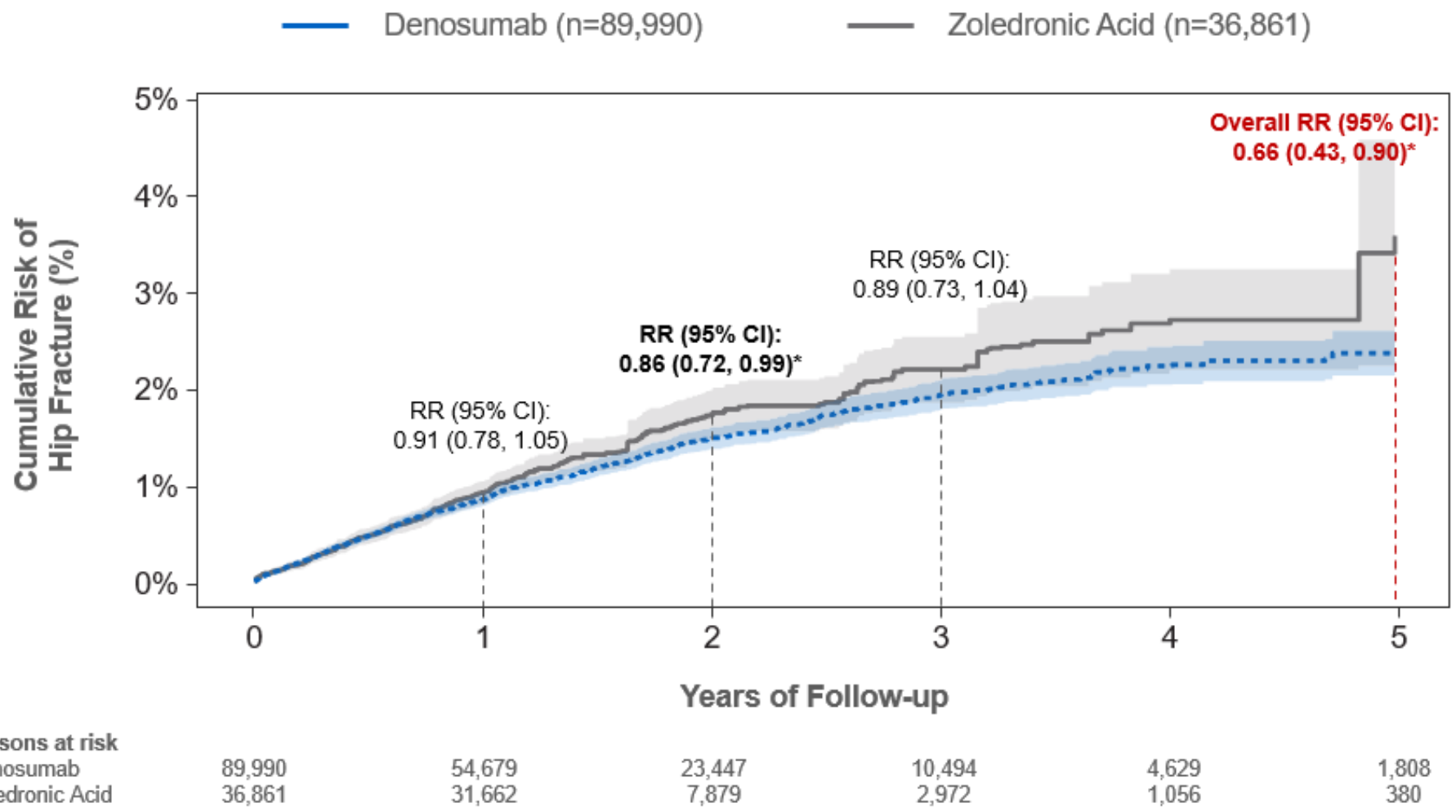
Comparison of anti-fracture effectiveness of zoledronate, ibandronate and alendronate versus denosumab in a registry-based cohort study

Judith Everts-Graber[1,2] · Harald Bonel[3,4,5] · Daniel Lehmann[6] · Brigitta Gahl[7] · HansJörg Häuselmann[8] · Ueli Studer[1] · Hans-Rudolf Ziswiler[1] · Stephan Reichenbach[2,9] · Thomas Lehmann[1]

- Denosumab leicht überlegen, v.a. bezüglich Wirbelfraktur
- **Kein** Unterschied Zoledronat und Denosumab


D
Fracture
HR (95% CI)
Hip
crude
1.72 (0.81 to 3.64)
adjusted
1.52 (0.69 to 3.34)
after IPTW
2.48 (0.69 to 8.99)
Vertebral
crude
0.90 (0.65 to 1.25)
adjusted
1.02 (0.73 to 1.43)
after IPTW
1.08 (0.64 to 1.83)
Non−Vertebral
crude
1.01 (0.76 to 1.34)
adjusted
0.90 (0.67 to 1.21)
after IPTW
0.71 (0.49 to 1.02)
Any Fracture
crude
0.96 (0.78 to 1.19)
adjusted
0.95 (0.76 to 1.18)
after IPTW
0.89 (0.63 to 1.26)
.5
1
2
4
6
8
10
Favours Dmab
Hazard ratio (95% CI)
Favours Zoledronate

“Denosumab reduced the risk of hip fracture by 34% compared with zoledronic acid by the end of study follow-up (5y)”

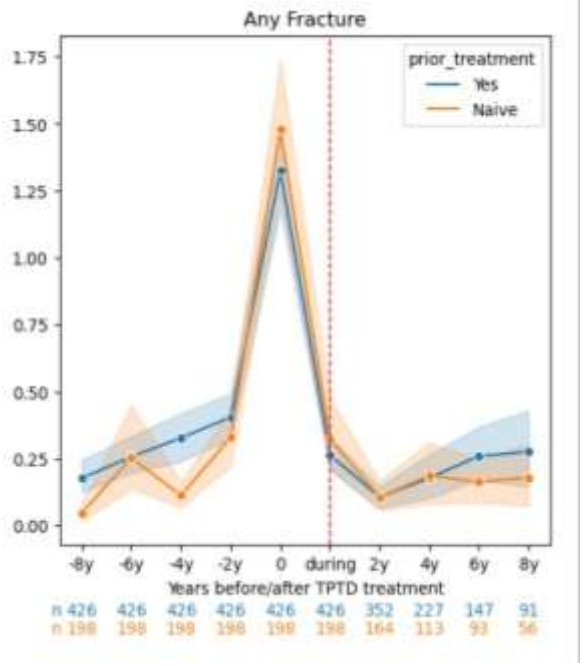


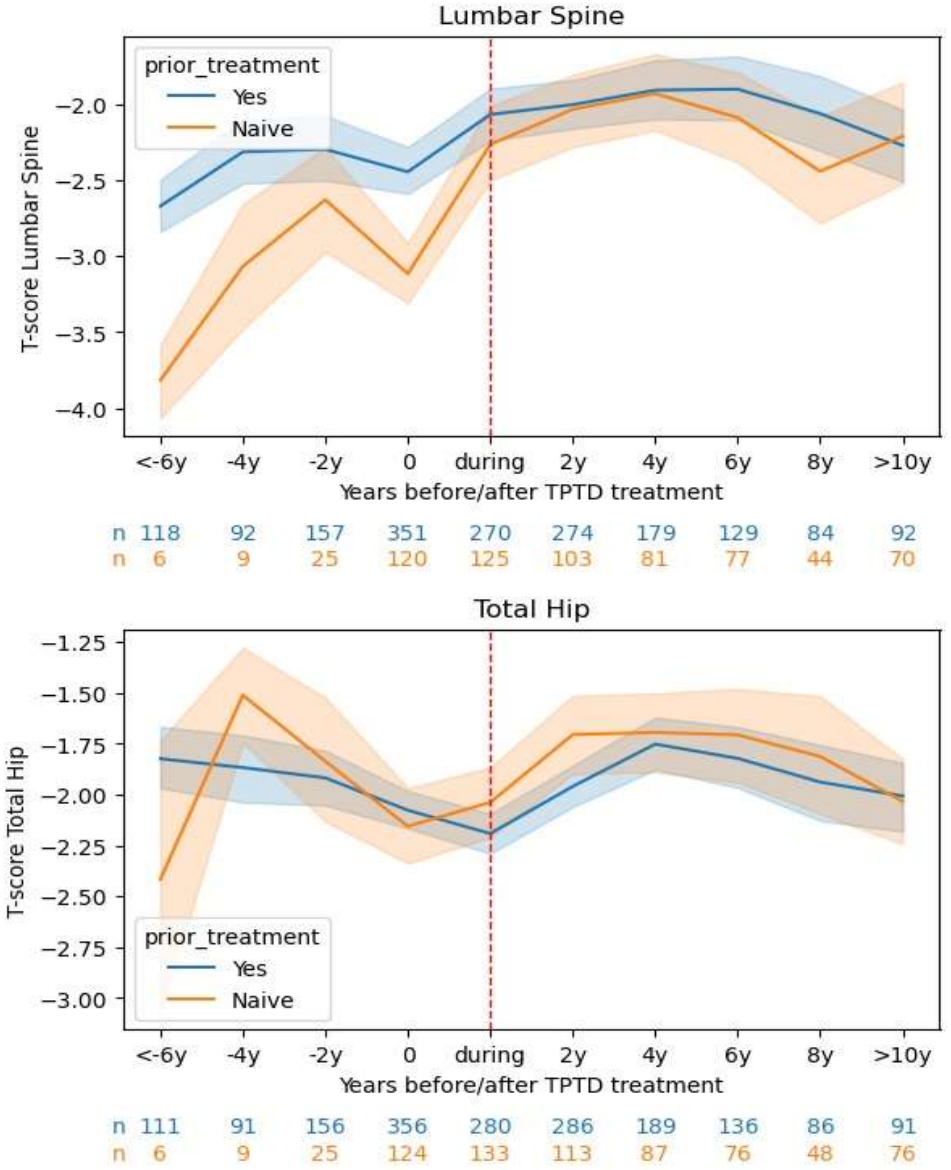
Abstract from the ASBMR 2023 ANNUAL MEETING, Vancouver

Teriparatide – what's new?

- 624 patients (87% female, age 67± 13 years)
- 198 (32%) received teriparatide first-line

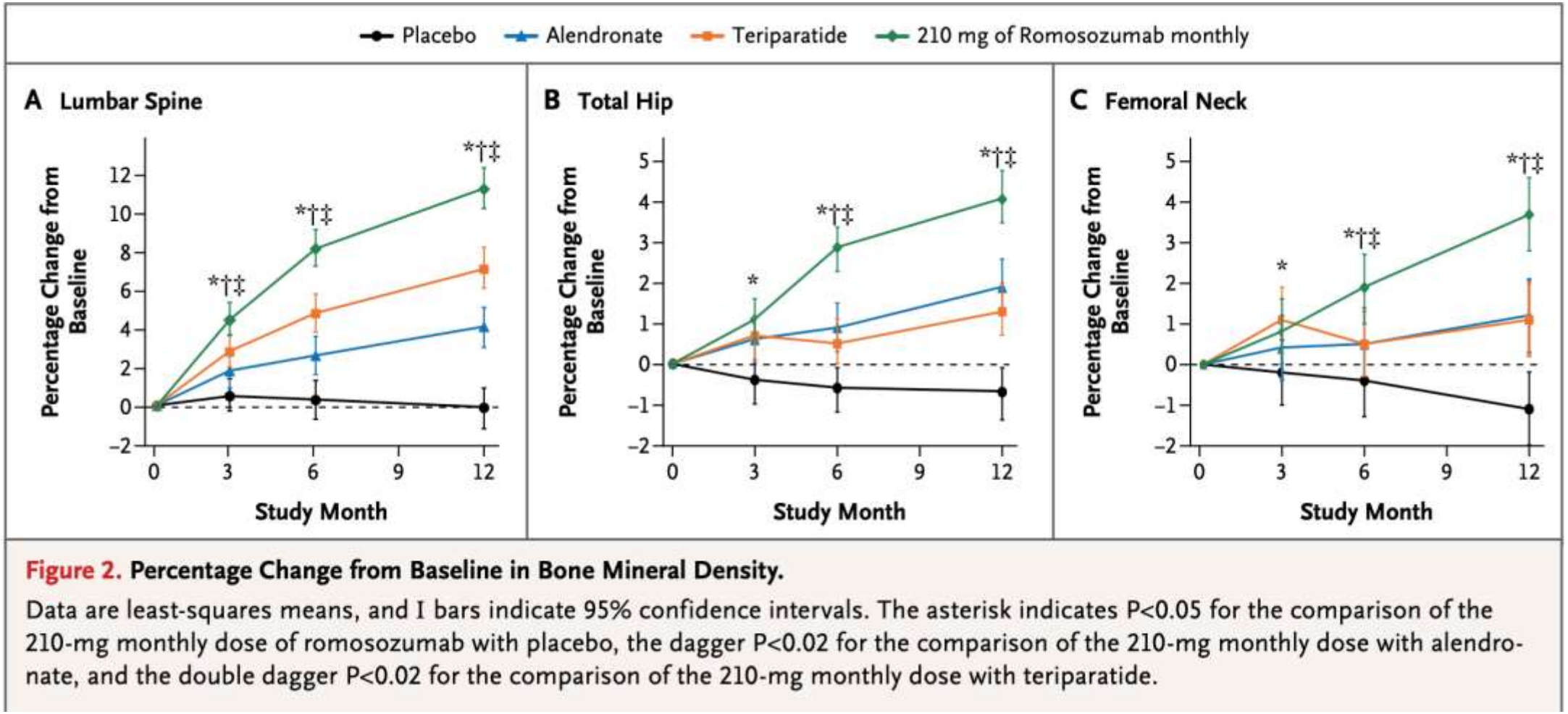
Teriparatide, as first or second-line therapy, sustained **reduced fracture incidences** and increased BMD and TBS for **up to 8 years** post-transition to antiresorptives.





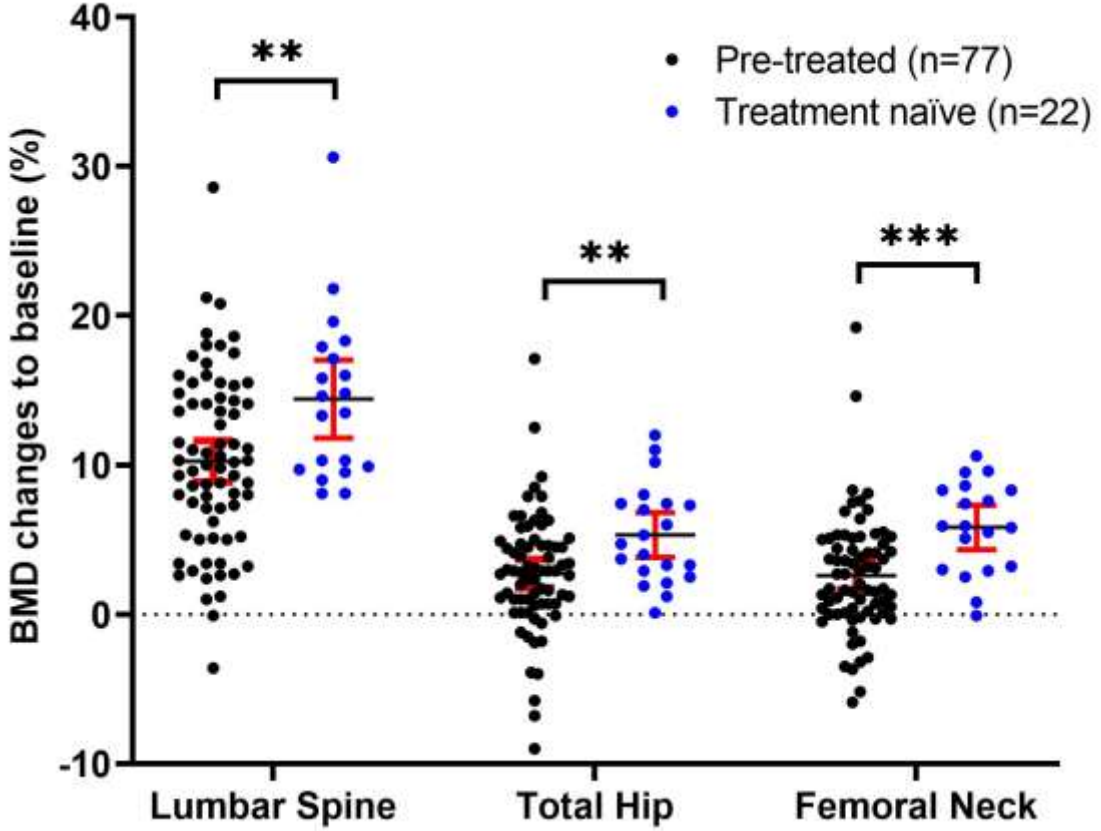
Guyer et al, "Long-term impact of teriparatide on bone mineral density, trabecular bone score, and fracture risk relative to total hip T-score: A two-decade, registry-based cohort study", Bone 2025 Mar 5:117445. doi: 10.1016/j.bone.2025.117445.

Romosozumab (Evenity®)



MClung. et al, N Engl J Med, 2014 Jan 30;370(5):412-20. doi: 10.1056/NEJMoa1305224.

Prior Treatment – BMD Response

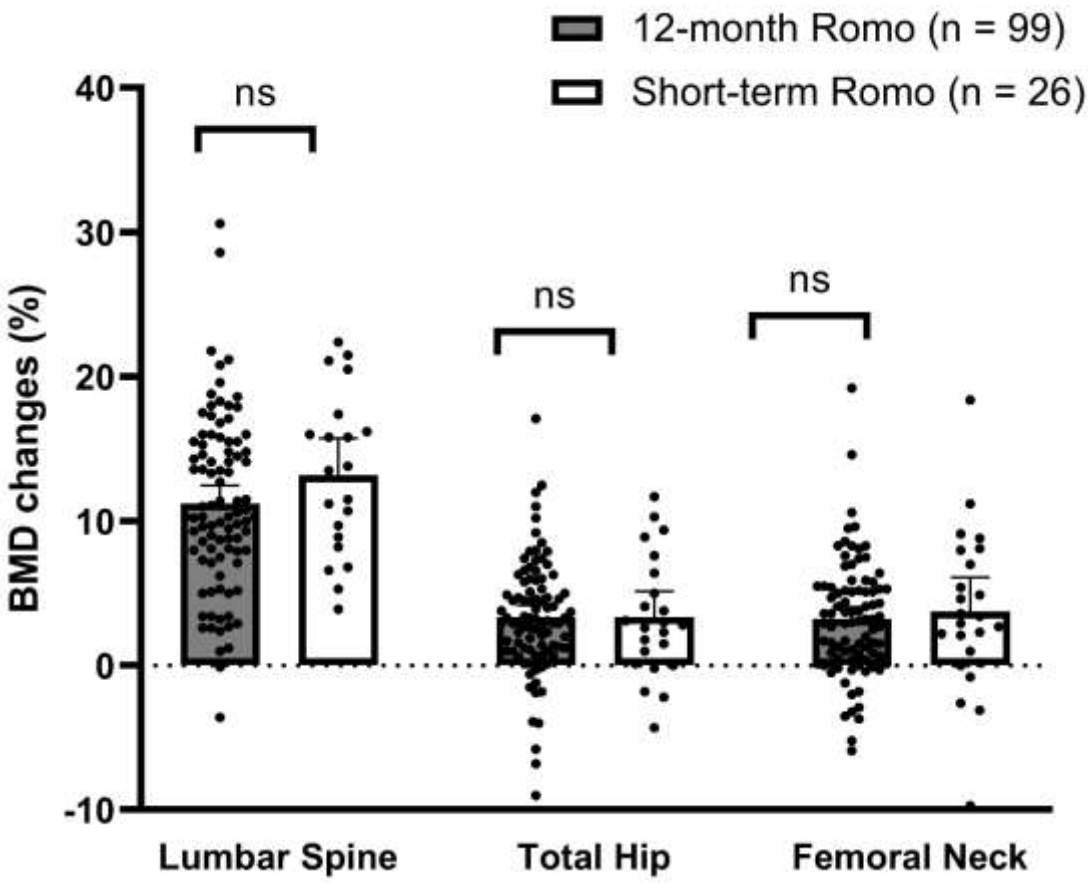


- 99 Patientinnen, mehrheitlich vorbehandelt
- **Bei allen sehr schöner Effekt an der LWS (+ 10-15%)**
- **An der Hüfte schwächer (+2%)** bei den vorbehandelten Pat., v.a. bei langer Vorbehandlung mit Bisphosphonaten

J. Everts-Graber *et al.*, “The effect of romosozumab on bone mineral density depending on prior treatment: a prospective, multicentre cohort study in Switzerland,” *Osteoporos Int. 2024 Sep;35(9):1605-1613. doi: 10.1007/s00198-024-07155-9*

Romosozumab nur 3-6 Monate?

- 26 Patientinnen mit 3-9 Monate Romosozumab (median: 6 Monate)
- **Gleiche BMD-Zunahme wie bei 1 Jahr Romosozumab**
- Romo ggf. frühzeitig auf antiresorptiv Therapie umstellen?



MS under review

Journal of Bone and Mineral Research, 2024, **00**, 1–10
https://doi.org/10.1093/jbmr/zjae089
Advance access publication: June 5, 2024
Research Article

Fracture risk prediction in postmenopausal women with traditional and machine learning models in a nationwide, prospective cohort study in Switzerland with validation in the UK Biobank

Oliver Lehmann[1], Olga Mineeva[2], Dinara Veshchezerova[2], HansJörg Häuselmann[3], Laura Guyer[4], Stephan Reichenbach[5,6], Thomas Lehmann[7], Olga Demler[2,8], Judith Everts-Graber[6,7,9,*], The Swiss Osteoporosis Registry Study Group[†]

[†]Mathias Wenger, Sven Oser, Martin Toniolo, Gernot Schmid, Ueli Studer, Hans-Rudolf Ziswiler, Christian Steiner, Ferdinand Krappel, Piero Pancaldi, Maki Kashiwagi, Diana Frey, René Zäch, and Heinz Weber

- Registry-based cohort study (training/test dataset: Swiss OP registry, validation cohort: UK Biobank)
- Analysis of traditional fracture prediction models (TOP-Tool, FRAX®) and machine-learning models (XG-Boost ± AFT, Random Survival Forest)

Fracture Prediction

The Swiss Approach

TOP

OSTEOPOROSE PLATTFORM

- 19,889 patients
- 15,383 postmenopausal women
- 6,175 with follow-up
- **5,944 women with BMD data**
- 1,190 fractures

Swiss OP registry: Development cohort

UKB

biobank uk

Improving the health of future generations

- 502,384 individuals
- 28,036 pm women with image data
- 8,397 with follow-up
- **5,474 women with BMD data**
- 290 fractures

UK biobank: Validation cohort

Performance (C-index/AUC)

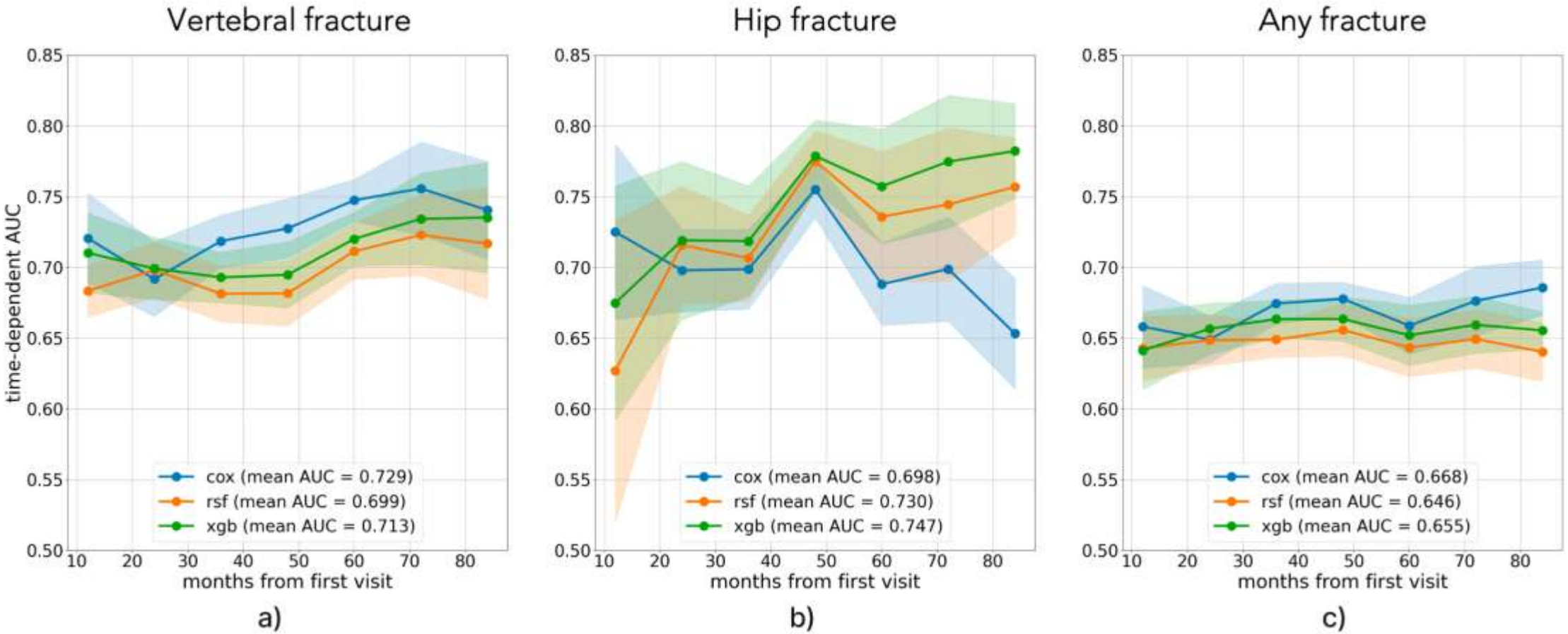
AUC values	Test quality
0.9–1.0	Excellent
0.8–0.9	Very good
0.7–0.8	Good
0.6–0.7	Satisfactory
0.5–0.6	Unsatisfactory

C-index (95%CI)	MOF/any	Hip	MOF FRAX	Hip FRAX
Swiss OP Registry	**0.69** [0.64, 0.73]	**0.72** [0.65, 0.79]	**0.60** [0.55, 0.64]	**0.62** [0.49, 0.74]
UK Biobank	**0.63** [0.58, 0.69]	**0.83** [0.7, 0.94]	na	na

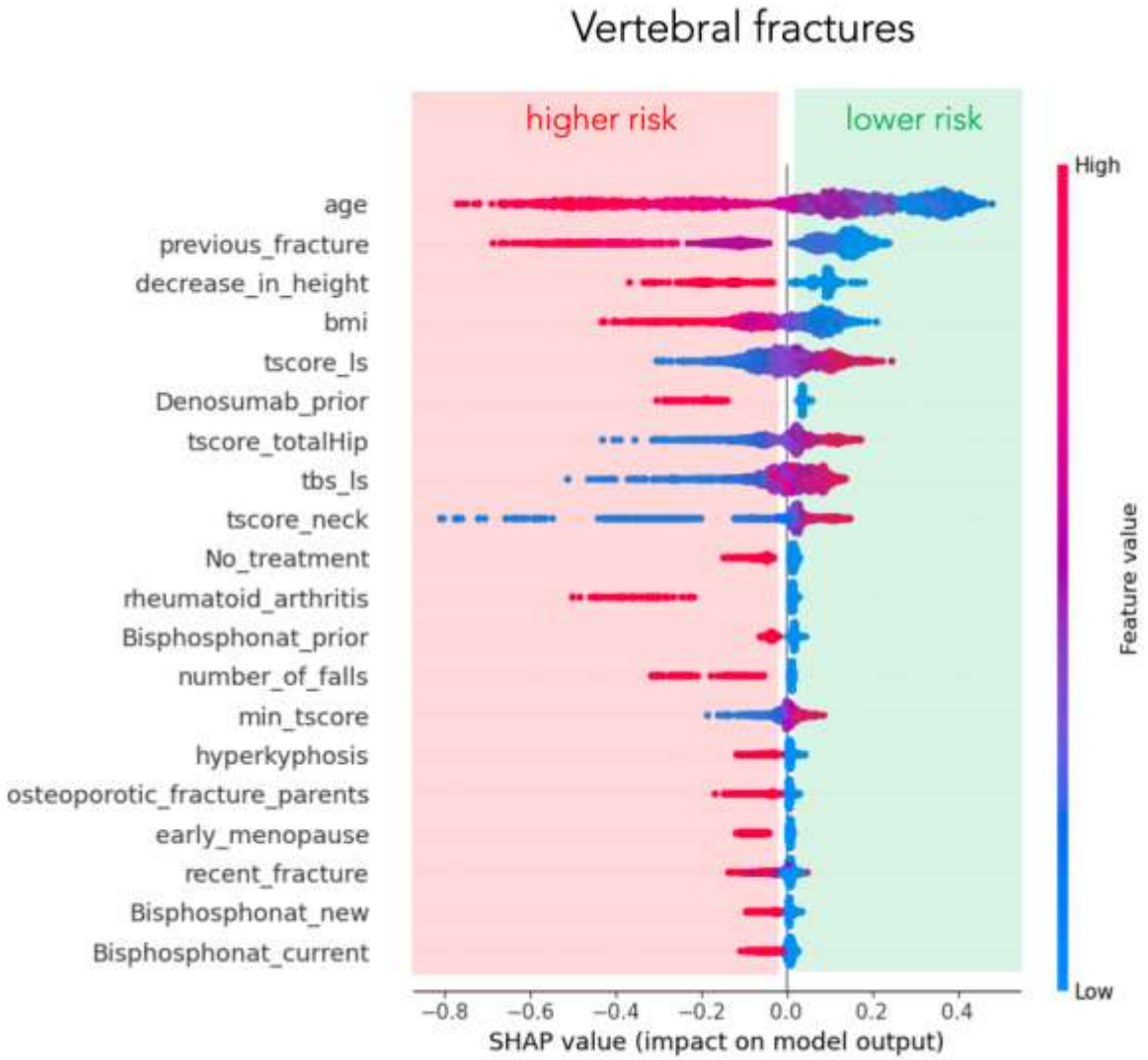
- Both our traditional and machine learning models performed **significantly better than FRAX** (p>0.001).
- Differences between traditional and ML models were moderate.

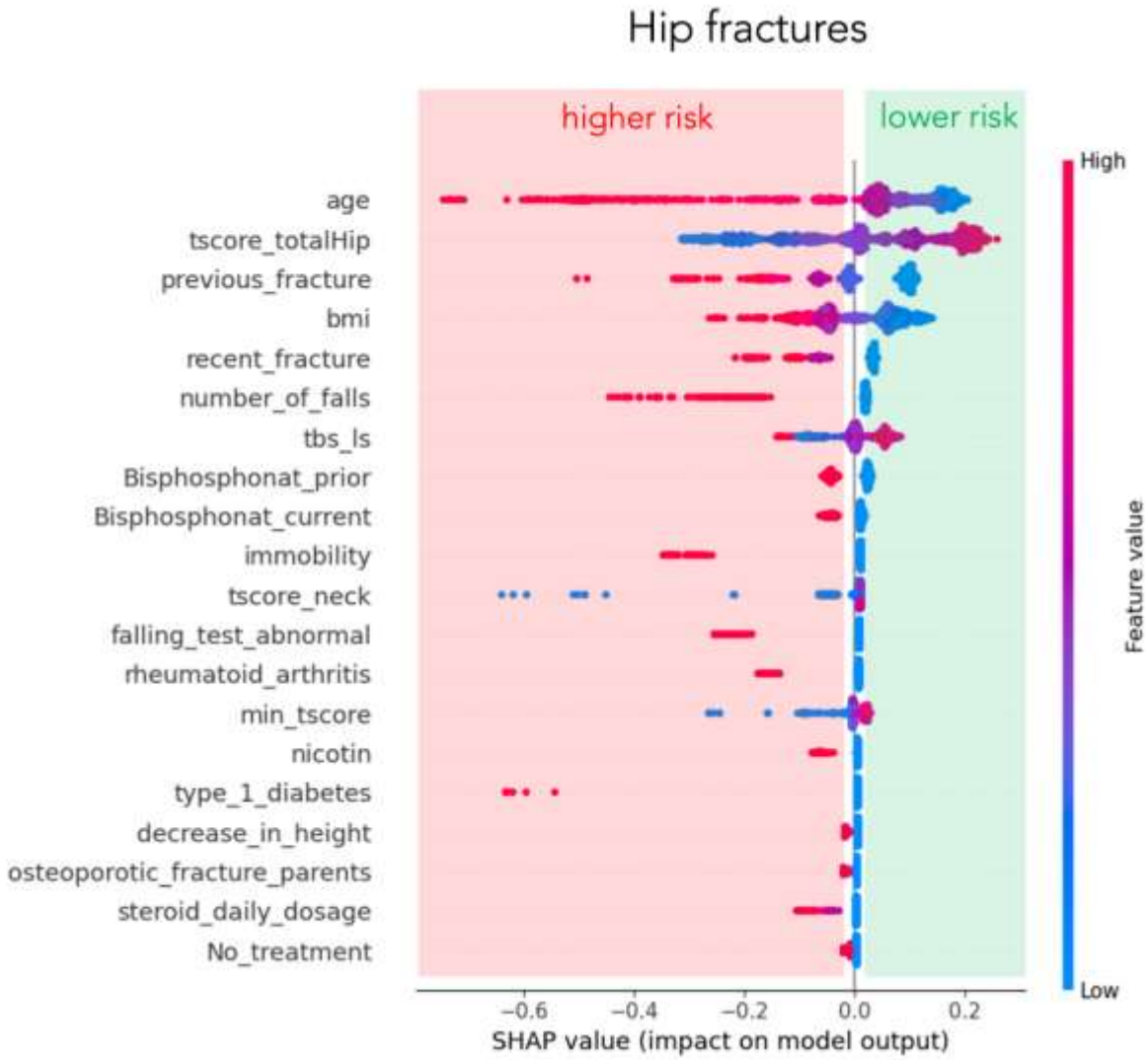
Fracture Prediction

The Swiss Approach

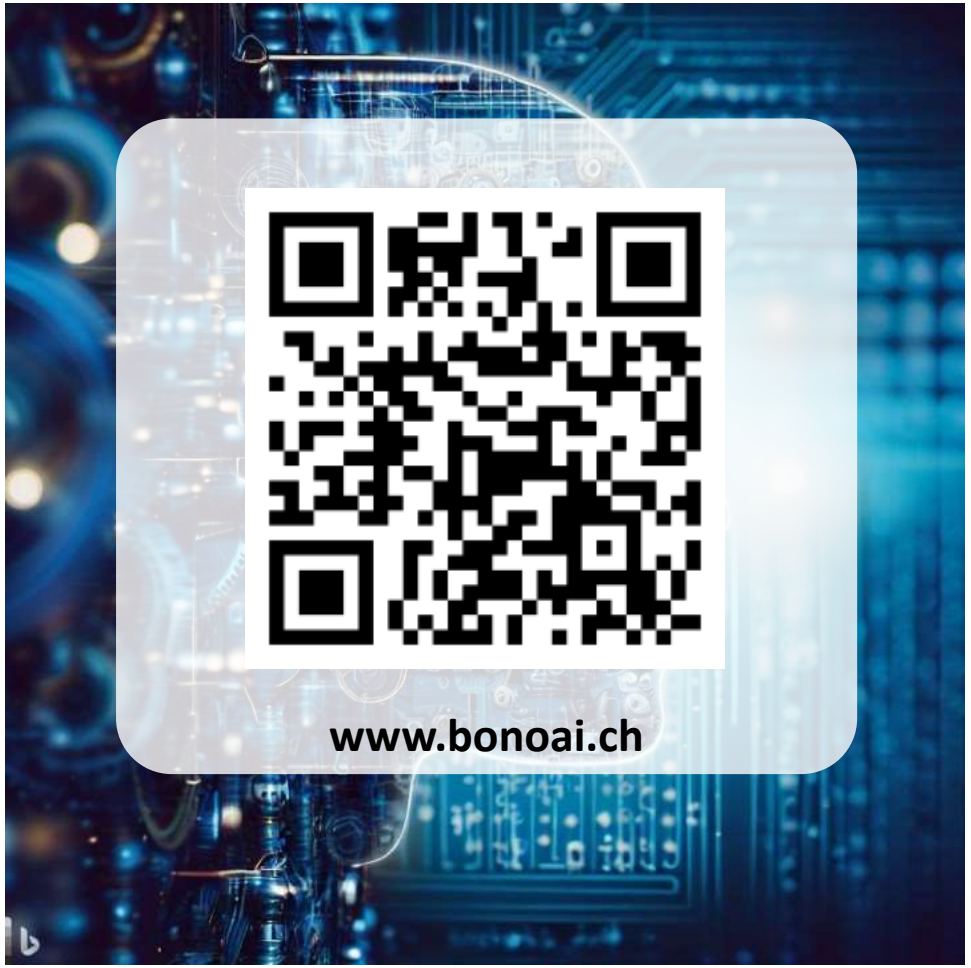


Welche Variablen wie wichtig?





Fracture prediction: the Swiss Approach



Fracture prediction can be enhanced by considering additional risk factors such as **lumbar spine T-score**, history of **falls**, glucocorticoid dosage, and the recency of fractures.

Machine learning methods enable both global and individualized risk predictions, representing a significant step toward **personalized medicine.**

https://bonoai.ch

Bono AI

Home

- Type 1 Diabetes
- COPD
- Gastrointestinal Disease
- Early Menopause
- Hyperpara
- Falling Test: abnormal
- Alcohol
- Nicotin
- Decrease in Height
- Low Back Pain
- Hyperkyphosis

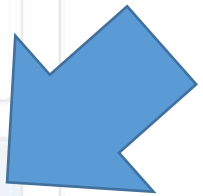
Prior	Current	New

Teriparatide

Prior	Current	New

HRT

Prior	Current	New



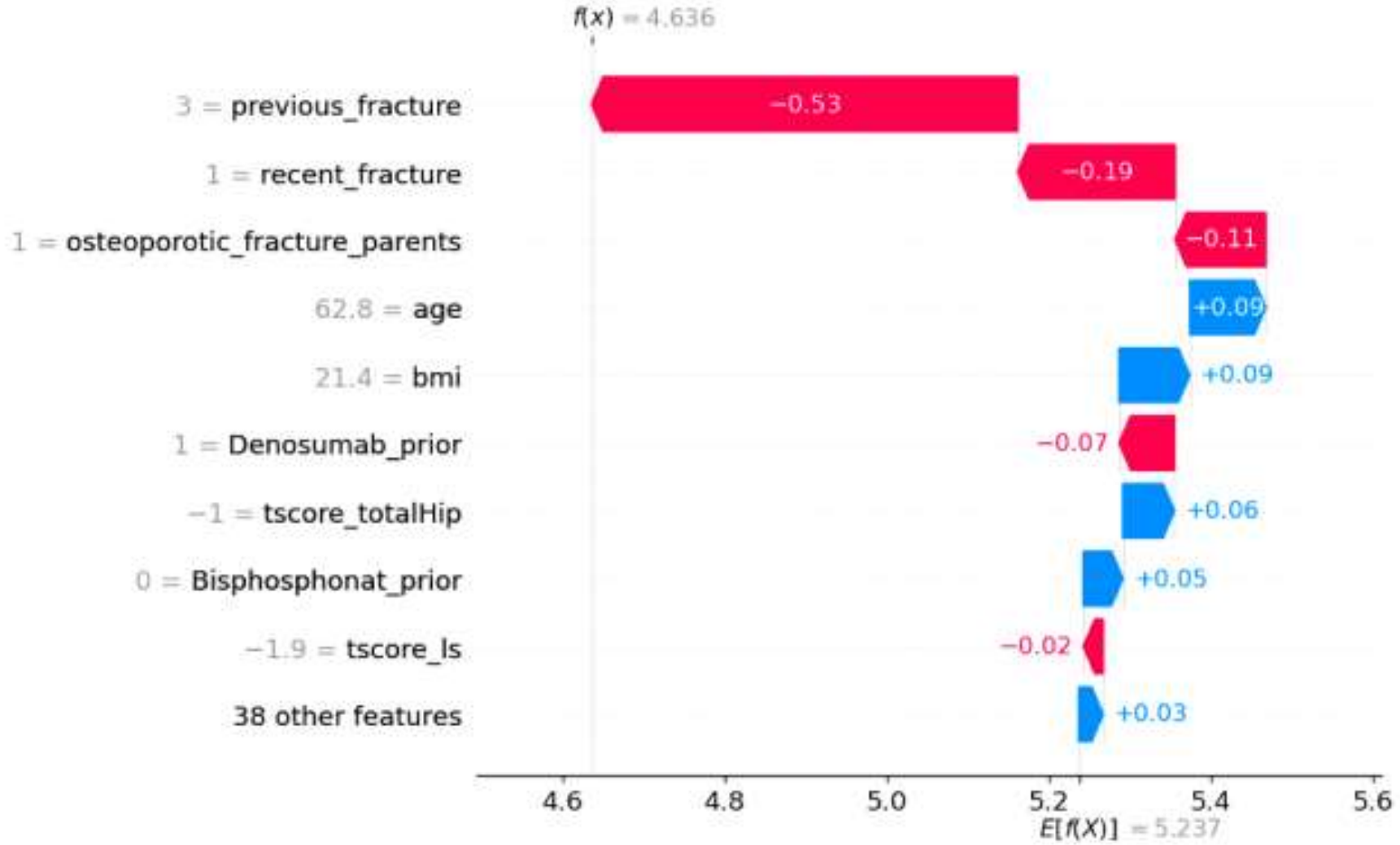
Risk Score

3-year fracture risk score at different sites.

Vertebral	Hip	Any
13.46%	5.62%	37.66%

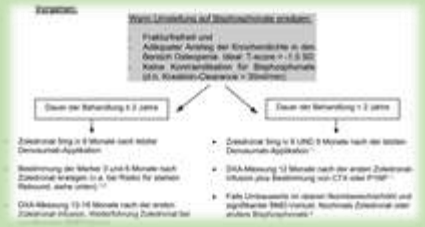
Fracture Risk of an Individual Patient

The SHAP waterfall plots



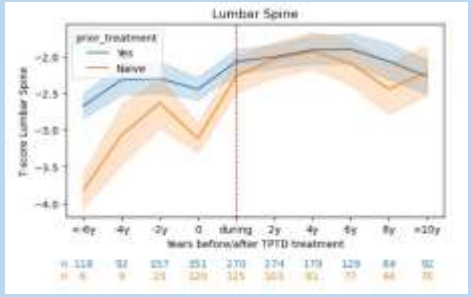
Dmab

- Neue SGR Guideline zur Nachbehandlung nach Dmab
- **Cave long-term Dmab – stärkerer Rebound**
- Wirksamkeit aber klar ersichtlich



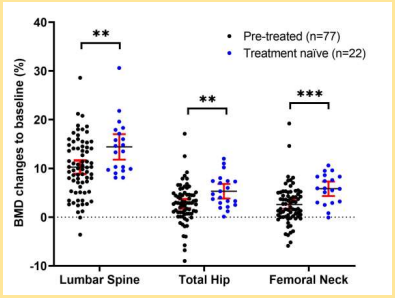
Teriparatide

- Gute Langzeitwirkung bei Hochrisikopat.
- **BMD und TBS bleiben bis 5 Jahre post-Teriparatie erhöht**
- **Frakturen ↓**



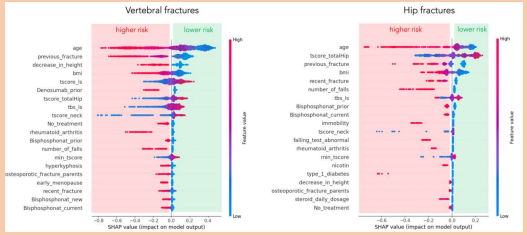
Romo

- Bessere Wirkung bei Therapie-naïven Personen
- **Bei allen sehr schöner Effekt an der LWS**
- **Evtl. kürzere Dauer**



TOP-Tool

- Validiert, zeigt sehr gute Prädiktion
- **T-score LWS, Stürze, Anzahl/Alter Frakturen und Steroiddosis sind relevant**



Ausblick

Kosteneffektivität einer koordinierten Osteoporoseabklärung und –therapie (gemeinsam mit HELSANA)

FRAXplus (mit Sheffield, UK) – was ändert sich, wie gut ist es?

Methotrexat-Osteopathie – erste Kohortenstudie!