# No Bones About It: Three High-Impact Topics for Frontline Clinicians

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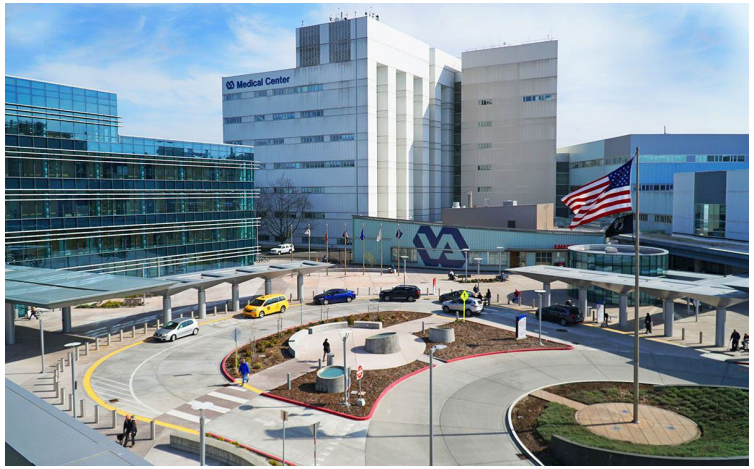
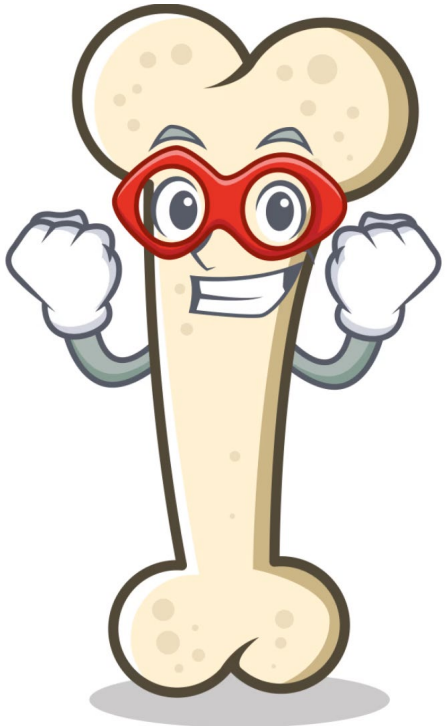


# Learning Objectives: A State of our Bones

1. IV Zoledronic Management and Key Clinical Pearls
2. When to Consider Anabolics and refer to Osteoporosis Clinics – Risk Stratification
3. GLP-1RAs and Bone - Update



I am part of ACP MKSAP Core Committee

# Question

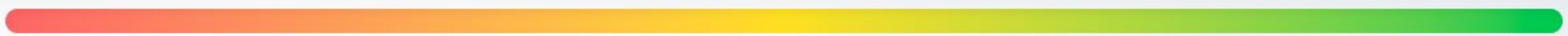
- Bisphosphonates soon after Fragility Fracture in the Inpatient Setting?
- A. Yes
- B. No
- C. Controversial

# Bisphosphonates Soon After a Fracture — Good or Bad?

## IV Zoledronic Acid Post-Fracture

Is it safe and effective to administer bisphosphonates soon after a fracture while inpatient?

*Explore timing, outcomes, and healing implications.*



Delayed Healing | Balance Point | Fracture Prevention

⚠ Would early inhibition of bone remodeling delay healing — or prevent fractures?

# Delayed Hip fracture Union

- Defined as 1 or more clinical symptoms (pain, inability to ambulate, and gait disorder) at least 6 weeks after surgical repair + any one of the following radiographic findings:
- Radiographic criteria at least 6 weeks after surgical repair (any one)
  - Persistence of fracture line without change from initial radiograph
  - Appearance of a fracture line not initially seen on radiograph in a fracture identified by MRI, CT, or bone scan
  - Displacement of a fracture not consistent with type of internal fixation
  - Lack of callus formation or consolidation of the fracture over at least 2 cortices.

# No delay in fracture healing or increased nonunion rates when bisphosphonates

- In an osteoporotic rat model, zoledronic acid given at 1 day, 1 week, or 2 weeks post-fracture **did not impair fracture healing;** instead, it increased callus size and strength.
- The HORIZON Recurrent Fracture Trial specifically examined zoledronic acid given at various intervals (including within 2 weeks) after hip fracture repair and found **no association between timing of infusion and delayed fracture healing or nonunion**.

Colón-Emeric C et al. HORIZON Recurrent Fracture Trial. Association between timing of zoledronic acid infusion and hip fracture healing. Osteoporos Int. 2011

# Safety of Inpatient Zoledronic Acid in the Immediate Post fracture Setting, JCEM 2023

- Aim: address the concerns of fever, hypocalcemia, and renal dysfunction associated with IV Zol in a real-world acute postfracture inpatient setting
- Acute phase reaction after ZA: occurs most commonly after the first infusion.
- Acute phase response includes symptoms of fever, myalgia, arthralgia, and bony pain

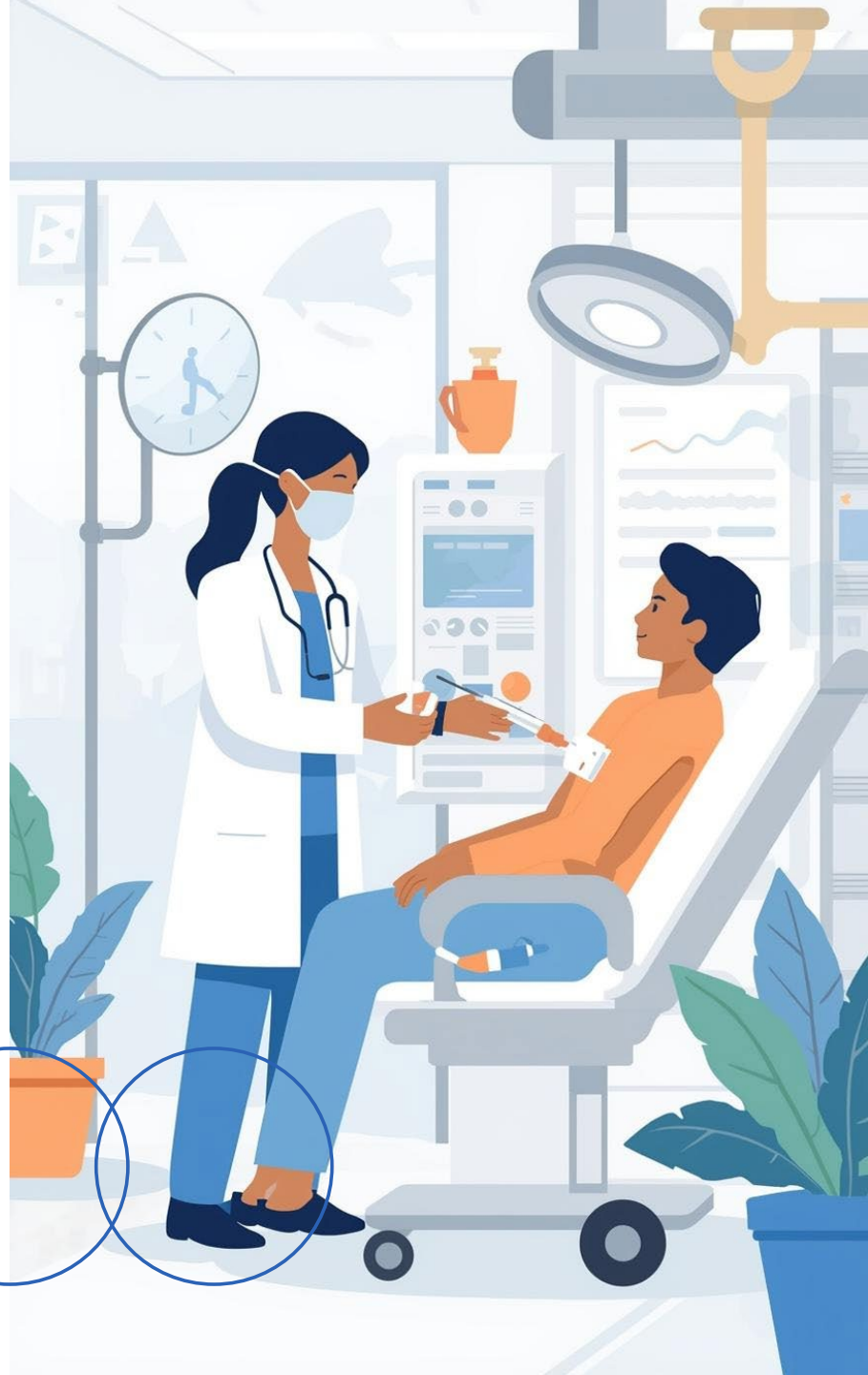
WuQiang Fan, Benjamin Z Leder, Michael Mannstadt, Thuan V Ly, Esteban Franco-Garcia, Marcy B Bolster

# Inpatient Zoledronic Acid (IP_ZA) Administration

Patients considered IP-ZA eligible if:

- ❑ (25-hydroxyvitamin D (25OHD) ≥ 20 ng/mL
- ❑ Creatinine clearance ≥ 35 mL/min
- ❑ lack of postoperative acute kidney injury (creatinine increase by 0.3 mg/dL or 50% above baseline)
- ❑ lack of postoperative new hypocalcemia (calcium < 7.5 mg/dL).

Periprosthetic fracture, ankle fracture, or facial or digital fracture per se are not considered as fragility fractures. Patients with febrile illness/infection excluded.



# Study Flow

**Patient Evaluation**

Fragility fracture patients evaluated for treatment eligibility.

All pts: Vitamin D 1000–2500 IU/day + Calcium 650–1000 mg/day

**Control Arm**

Comparator group received standard care without IP-ZA.

**Intervention Arm**

Patients who received IP-ZA were treated with

1. Single oral dose of acetaminophen 650 mg immediately before ZA infusion (Single-APAP group), OR
2. Standing acetaminophen 650 mg dose Q 6 hrs initiated immediately before IV ZA & for at least 48 hours (Multiple-APAP)

# Key Points of Study Design

## Overview

Focused on **secondary fracture prevention** methods

## Population

Involved **204 patients**

## Treatment

Administered **5 mg IV Zoledronic Acid over 45 min**

## Monitoring

Evaluated **temperature, creatinine, calcium levels**

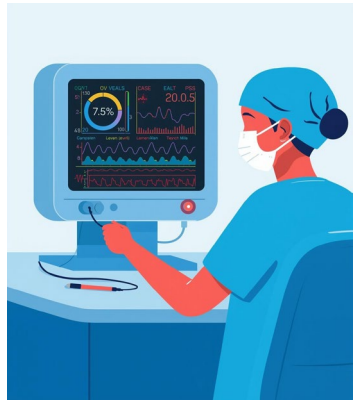


**Table 3.**

Number of patients with maximum body temperatures (Tmax in Celsius) >38 °C

| | | D1-B | D1-A | D2 | D3 | D4 |
|---|---|---|---|---|---|---|
| Non-IP-ZA | Pt w/Tmax > 38 °C (N) | 0 | | 3 | 0 | 0 |
| | Pt w/valid data (N) | 81 | | 80 | 80 | 71 |
| | % | 0 | | 3.75 | 0 | 0 |
| Single-APAP | Pt w/Tmax > 38 °C (N) | 0 | 1 | 10 | 2 | 0 |
| | Pt w/valid data (N) | 69 | 68 | 66 | 62 | 51 |
| | % | 0 | 1.47 | 15.15[a,b] | 3.22 | 0 |
| Multiple-APAP | Pt w/Tmax > 38 °C (N) | 0 | 1 | 5 | 2 | 0 |
| | Pt w/valid data (N) | 131 | 130 | 130 | 116 | 117 |
| | % | 0 | 0.77 | 3.85 | 1.72 | 0 |

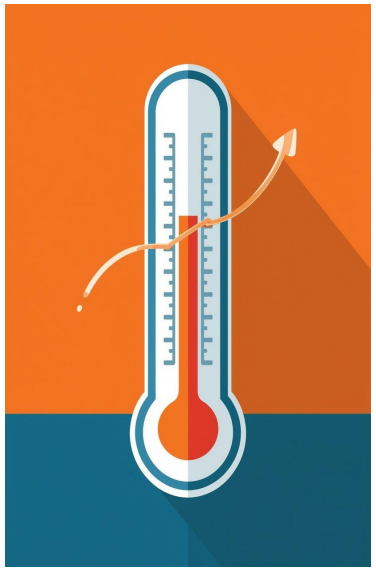
- The body temperatures were higher among the 204 ZA-treated patients as compared to those of the non-IP-ZA patients ($P = 0.008$).
- Among the ZA-treated patients, there was a statistically significant difference in temperatures between Single-APAP & Multiple-APAP subgroups ($P = .017$).
- A significant rise of Tmax on D2 (by 0.48 °C from D1-B, $P < .001$) in the Single-APAP group.
- The Multiple-APAP group did not experience a mean increase in Tmax.

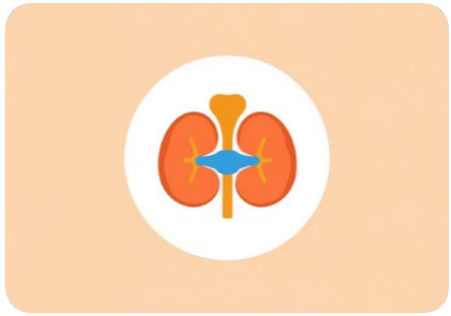
# Serum Calcium Levels

**Table 5. Serum calcium levels (mg/dL)**

| | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 |
|---|---|---|---|---|---|---|---|---|---|
| Non-IP-ZA T-SCa (81) | 8.96 ± 0.59 | 8.71 ± 0.54[a] | 8.79 ± 0.54 | 8.89 ± 0.57 | | | | | |
| ZA T-SCa (204) | 8.93 ± 0.64 | 8.85 ± 0.63 | 8.66 ± 0.65[a] | 8.58 ± 0.60[a] | 8.39 ± 0.65[a] | 8.52 ± 0.67[a] | 8.59 ± 0.69[a] | 8.60 ± 0.68[a] | 8.86 ± 0.60 |
| ZA C-SCa (63) | 9.47 ± 0.58 | 9.52 ± 0.45 | 9.23 ± 0.34[b] | 9.25 ± 0.48 | 9.07 ± 0.55[a] | 9.21 ± 0.60 | 9.36 ± 0.82 | 9.47 ± 0.76 | 9.94 ± 0.79 |

Data are described as mean ± SD. Nadir levels were underlined.
Abbreviations: D1–D9, Day 1 through Day 9; C-SCa, albumin-corrected serum calcium levels in mg/dL; T-SCa, total serum calcium levels in mg/dL; non-IP-ZA, non-inpatient-zoledronic-acid; ZA, zoledronic acid.
[a] $P < .01$ when compared to baseline (D1).
[b] $P < .05$ when compared to baseline (D1).





## Safety

IP-ZA is well tolerated in patients.

## Fever

Standing acetaminophen eliminates acute responses.

## Renal

No kidney injury was observed during study.

## Calcium

Mild transient drops noted in levels.

## Impact

No cases of symptomatic hypocalcemia, no delays in discharge, and no increase in 30-day readmission rates were reported.

# Takeaways from the Study

# IV Zoledronic acid – Clinical Domain

- Direct comparative data between 3 days, 1 week, and 2 weeks post-fracture are limited, but available evidence supports administration at any point during the initial hospitalization or within 2 weeks, **as long as renal function and vitamin D status are appropriate**

# Should Everyone Post Fracture Get IV Zol?

Not exactly!

# Question

A 57-year-old woman (She/her) with postmenopausal osteoporosis has sustained multiple vertebral fractures, s/p ground level falls. No Fam history of osteoporosis or fractures. Menopause was at age 49 years, never took Hrt. Secondary causes of osteoporosis are ruled out.

DXA demonstrates a left femoral neck T-score of –2.3 and left total hip T-score of –2.7.

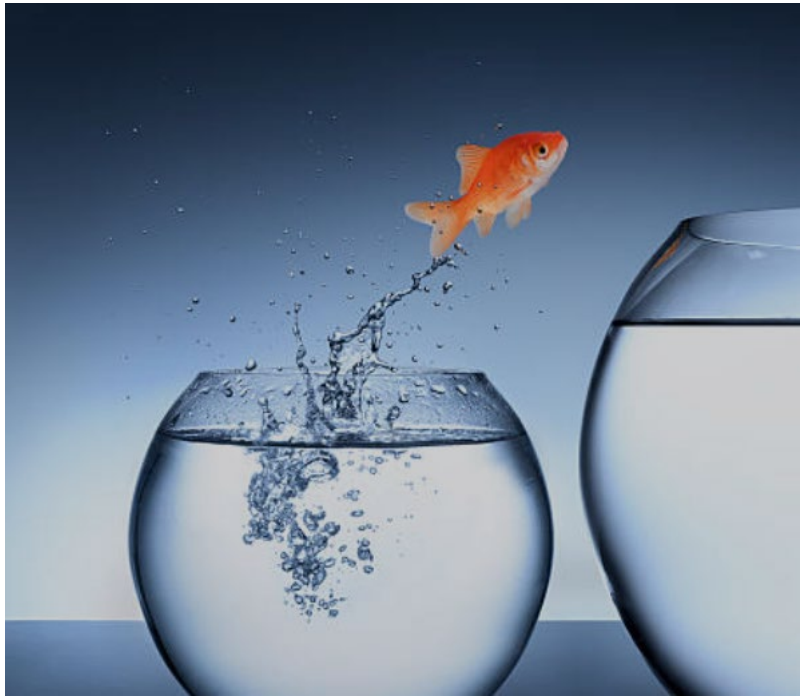
Given this patient's findings, which treatment sequence is most appropriate to optimize her bone mineral density?

- A. Alendronate > abaloparatide > drug holiday
- B. Denosumab > abaloparatide
- C. Romosozumab > zoledronate > drug holiday
- D. Denosumab > drug holiday

No Dmab Drug Holidays!

# Everyone First Gets Bisphosphonate

1. Imminent Risk
2. Order Matters



# Key Findings — Imminent Risk

The imminent risk of a fracture-existing worldwide data: a systematic review and meta-analysis.

Global incidence of "imminent" fractures—those occurring within 2 years after an initial fragility fracture—and highlights the high short-term risk of re-fracture, especially in older adults.

Wong et al 2022, Osteo International

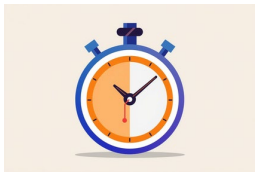
# Global Imminent Fracture Risk

## 1-Year Risk

The **global imminent fracture risk** is 7.6% within one year following a fragility fracture, indicating significant concern for patients.

## 2-Year Risk

The risk increases to **11.6%** within two years, emphasizing the importance of monitoring and preventive measures during this period.



## Gender Comparison

Women have a higher risk compared to men- > Hazard Ratio of 1.18

## Geographic Differences

Fracture risk varies significantly by region, with Asia at 7.3% compared to Europe & North America's 13.2%, indicating diverse healthcare needs.

## Re-fracture Incidence

Approximately **50% of all re-fractures occur within the first 2 years,** underscoring the **critical need** for immediate therapeutic action in patients.

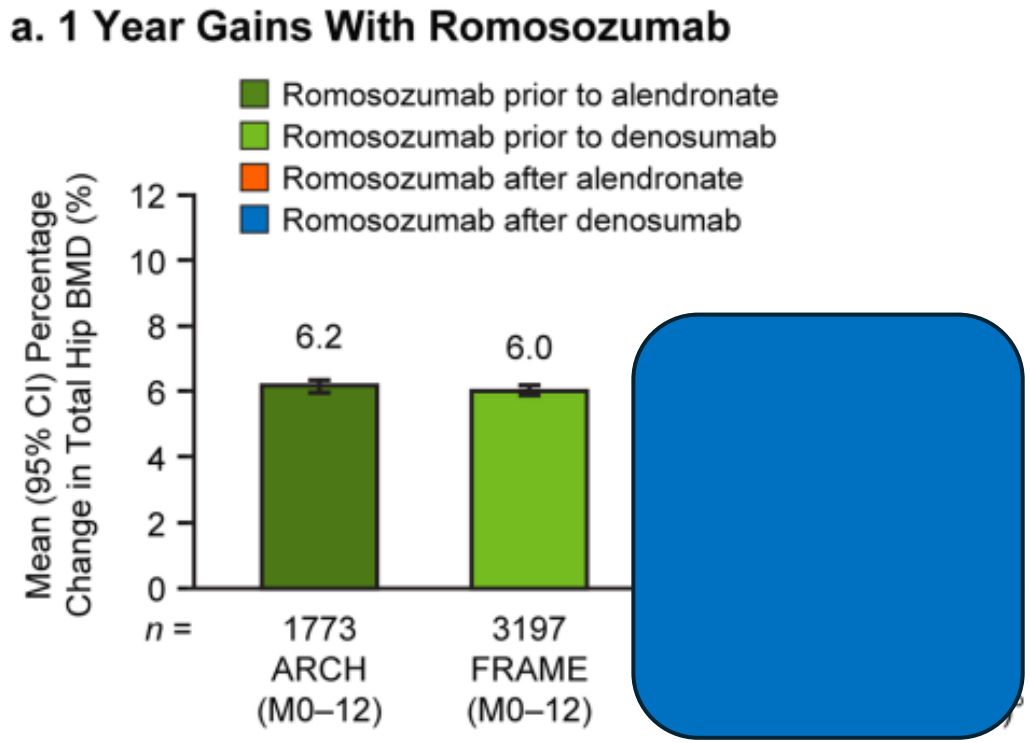
# Care and Prevention

**Prompt treatment** for older patients after fragility fractures is crucial to prevent further injuries and promote healing.

Age as a risk factor of imminent fracture

Gibson-Smith et al. studied the risk of sustaining the major (non-hip) fragility fractures in the first year after an index hip fracture was high at patients aged 70–79 years (HR of 1.60 (95% CI 1.04 to 2.49) compared w/ aged 50–59 years))

# Does Order Matter?




- Cosman et al. Osteoporosis Int (2022)

Costs: High variation

Generic: VISN 20 and ACP 2023

# PTH analogues in Clinic

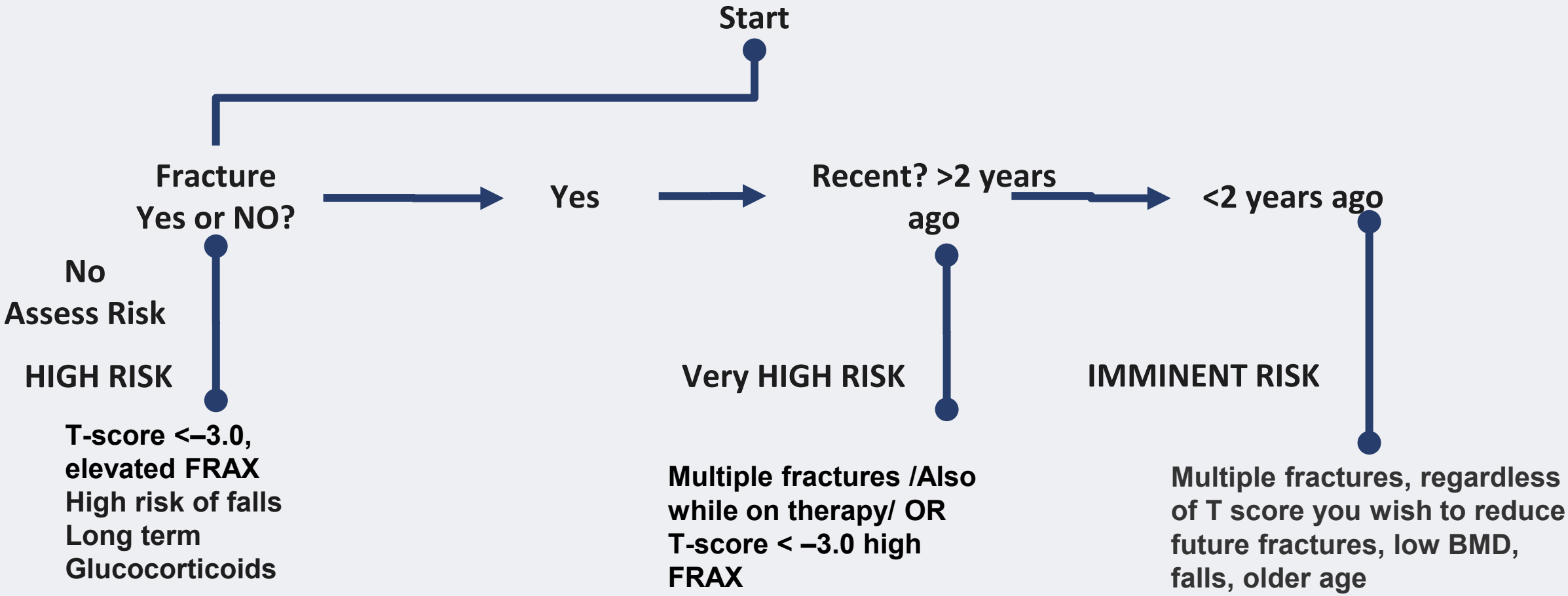
- Concerns: Kidney stones, Hypercalcemia, radiation exposure, bone mets/cancer
- Only if patient remains or at again high risk, could consider recourse (black box warning of osteosarcoma removed)
  - Individualized decision, judicious repeat courses
- Cost:
  - Teriparatide $1,010.06- 1,846 per month
  - Abaloparatide $1671.08 - $2,818
- Need for Daily Injections
  - Teriparatide 24 months vs. Abaloparatide 18 months duration
- Teriparatide needs refrigeration (Abaloparatide doesn't)
- No AFF or ONJ risks

# Romozosumab in Clinic

- Approved for 1 year
- Cost:  ~$5,574/year
- Injections but in Clinical Settings, Once a month
- Possible MI-CVA risk:
    - Black Box Warning: Not used if had MI or Stroke in past year

# Who are candidates for Anabolics?

## New Goal-directed Osteoporosis Treatment: ASBMR/BHOF task force position statement 2024




Anabolic vs Antiresorptive | Anabolic 1st | Anabolic 1st

# Key Principles – Risk Stratification

- Individualize treatment based on fracture history (recency, site, number, severity)
- Assess Risk Factors:
  - Bone Mineral Density (BMD)
  - Clinical risk factors (age, falls, medications-steriods)

→ Move away from “one-size-fits-all” bisphosphonate strategy; prioritize rapid fracture risk reduction for those at very high/imminent risk.

# Choosing Agents

- “We advocate for the clinician to risk stratify & encourage shared decision-making with patients when choosing the appropriate osteoporosis agent for fracture prevention”

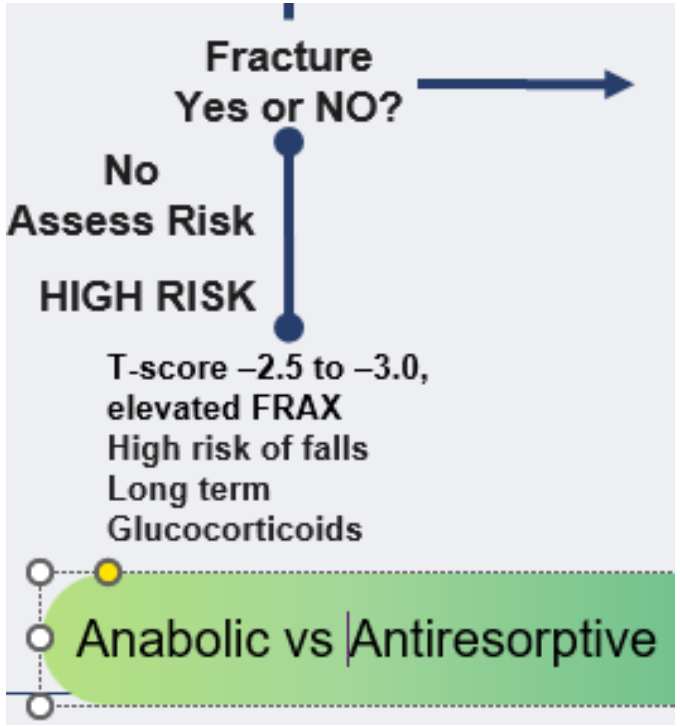
Wysham, Baker, Narla. Osteoporosis evaluation and treatment recommendations in rheumatoid arthritis

# Theory to Clinical Application….

- 61 yo Male (he/him) with ongoing tobacco use, found to have ‘low bone density’ on lung cancer CT screening
- DXA done: lowest T score -3.1 L Spine

- Risk factors; hx of osteomalacia – now improved, ongoing tobacco use
- Risk factors for falls: Gait issues – undergoing workup. “Professional faller”

- Initiated Secondary Osteo work up: checking Testosterone levels (only lab not done)



# Summary So Far…

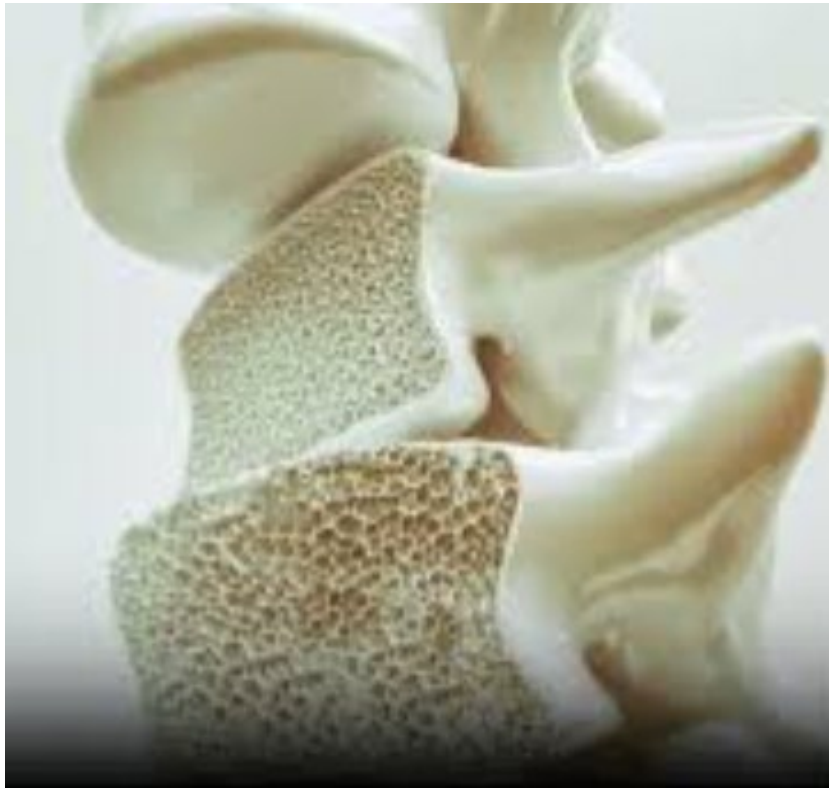
- Initial therapy with a Bip may modestly diminish subsequent bone-forming agents but prior antiresorptive *use is not a contraindication to anabolic therapy*
- This highlights the need to identify & treat patients that may benefit from anabolics before antiresorptives (*where all of you come in!)*
- If you strongly suspect that patients may risk stratify to Higher Risk Categories– refer to Osteoporosis Clinicians (pending insurance etc).

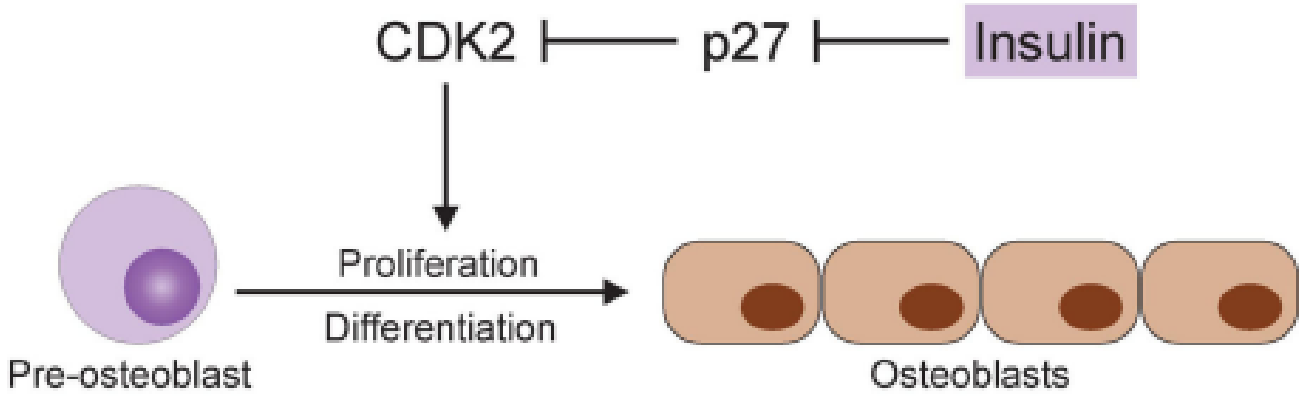
# Question

- Which diabetes medications are safest for bone health and least likely to increase fracture risk in a 71 yo patient w/T2DM & osteoporosis?

- A. Thiazolidinediones (TZDs) and sulfonylureas
- B. Thiazolidinediones (TZDs) and metformin
- C. Metformin and GLP-1s
- D. Sulfonylureas and GLP-1s

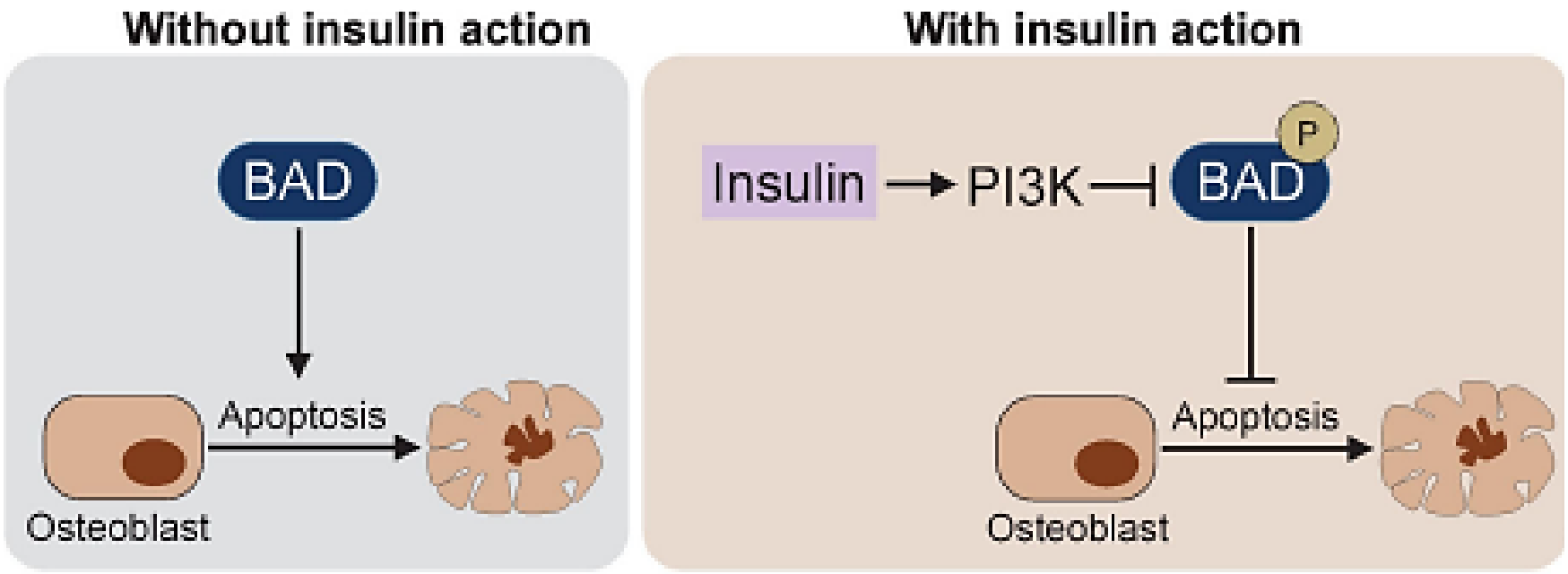
# Diabetes (GLP-1 RA) and Bone






Insulin enhances differentiation from osteoblast precursors to mature osteoblasts

Camila Romero-Dıaz et al. Diabetes Ther (2021)




**Type 1 diabetes:** Insulin deficiency leads to reduced osteoblast activity & decreased bone formation

Camila Romero-Dıaz et al. Diabetes Ther (2021)

**Type 2 diabetes:** chronic insulin resistance, hyperglycemia & associated metabolic disturbances ultimately impair bone quality.

Despite normal or increased BMD, bone turnover is reduced, & bone microarchitecture is altered, increasing fragility.

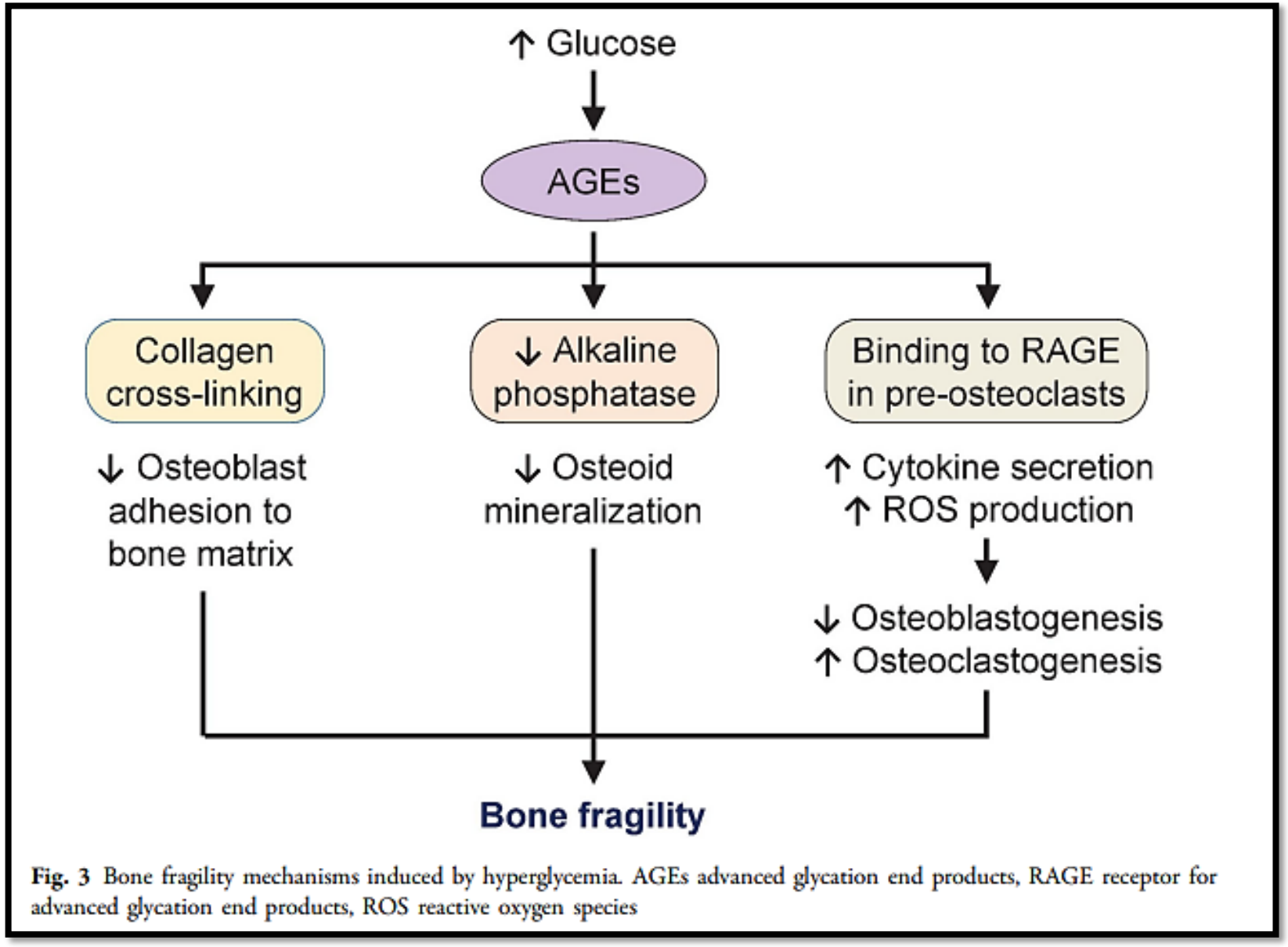



**Fig. 3** Bone fragility mechanisms induced by hyperglycemia. AGEs advanced glycation end products, RAGE receptor for advanced glycation end products, ROS reactive oxygen species

Camila Romero-Dıaz et al. Diabetes Ther (2021)

- GLP-1RAs are incretins that stimulate insulin release and suppress glucagon

- Zebrafish models treated with GLP-1 RAs (liraglutide) have increased bone formation

# Do GLP-1RAs have a protective effect on the bone?

- Chaudry et al
- Fracture Risk in Women Over 55 with Type 2 Diabetes Mellitus: A Comparative Analysis of GLP-1 Receptor Agonist

- American Society for Bone and Mineral Research (ASBMR) Annual Meeting. Oral presentation 1033.

# Study Flow

Retrospective Cohort using TriNetX Global Collaborative Network

**Population:** Women aged **55–89 years** with **Type 2 Diabetes Mellitus (T2DM)**
**Exposure:** Prescription of a **GLP-1 receptor agonist (GLP-1 RA)**

*Lixisenatide, Liraglutide, Exenatide, Tirzepatide, Semaglutide, Dulaglutide*

**Control Arm**

**Comparison Group:**
Matched controls not prescribed GLP-1 RAs (Alternative therapies)

**Other Notes:**

**Matching Variables:**
Age, race, BMI, HbA1c Osteoporosis diagnosis, Tobacco use, Corticosteroid use and other confounders
**Follow-Up:**
**2-year** and **5-year** fracture outcomes

# Key Points of Study Design

## Fractures

GLP-1 RA users had **significantly lower rates** of:

- •Subtrochanteric & intertrochanteric fractures
- •Femoral neck fractures
- •Vertebral wedge compression fractures
- •Distal radius fractures

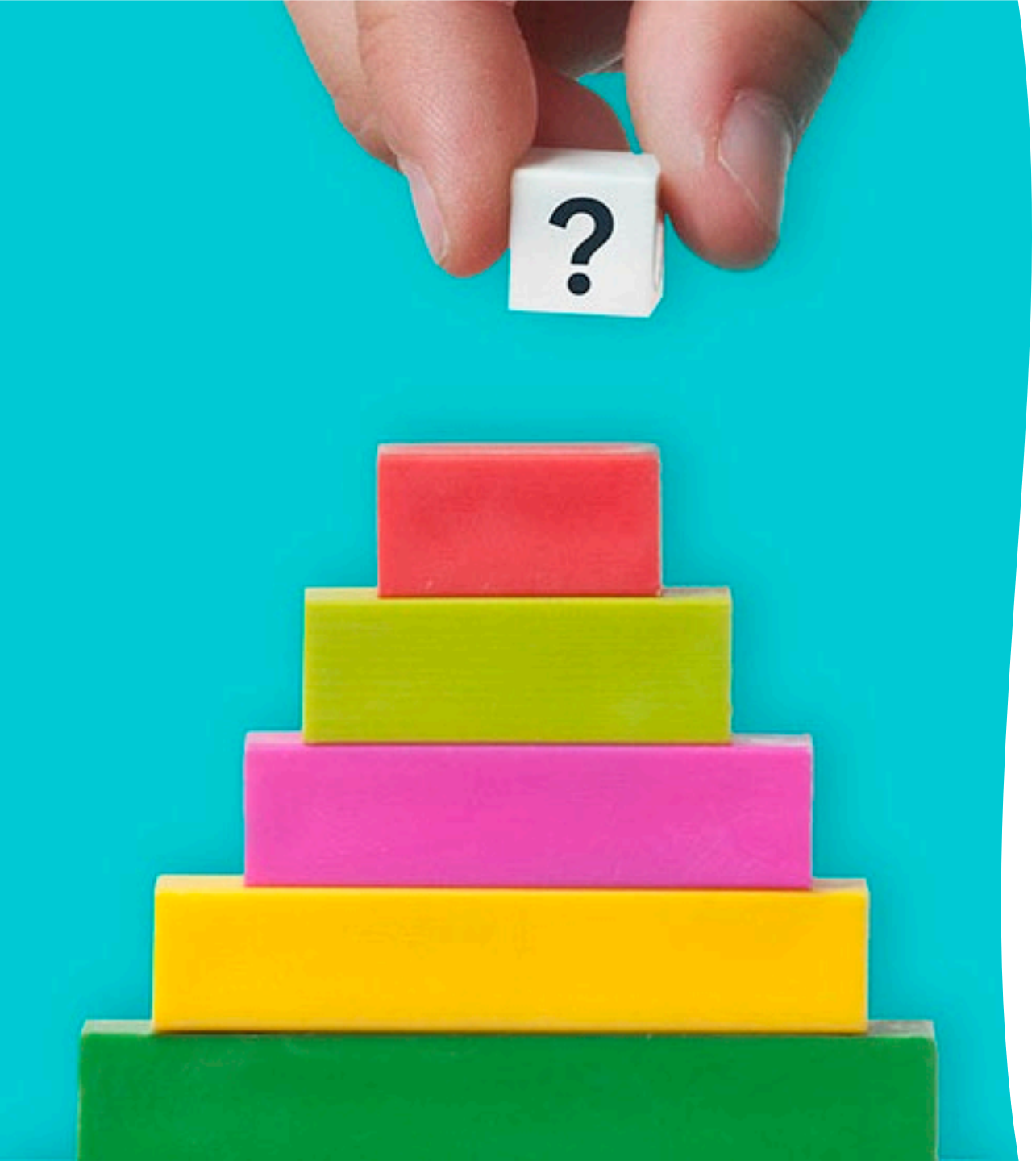
**p < 0.0001** across fracture types

## Long Term

Benefits of GLP-1 RAs persisted through a **5-year follow-up**

## Future Research

Mechanism remains unclear → **further research warranted** to understand GLP-1's role in bone metabolism.

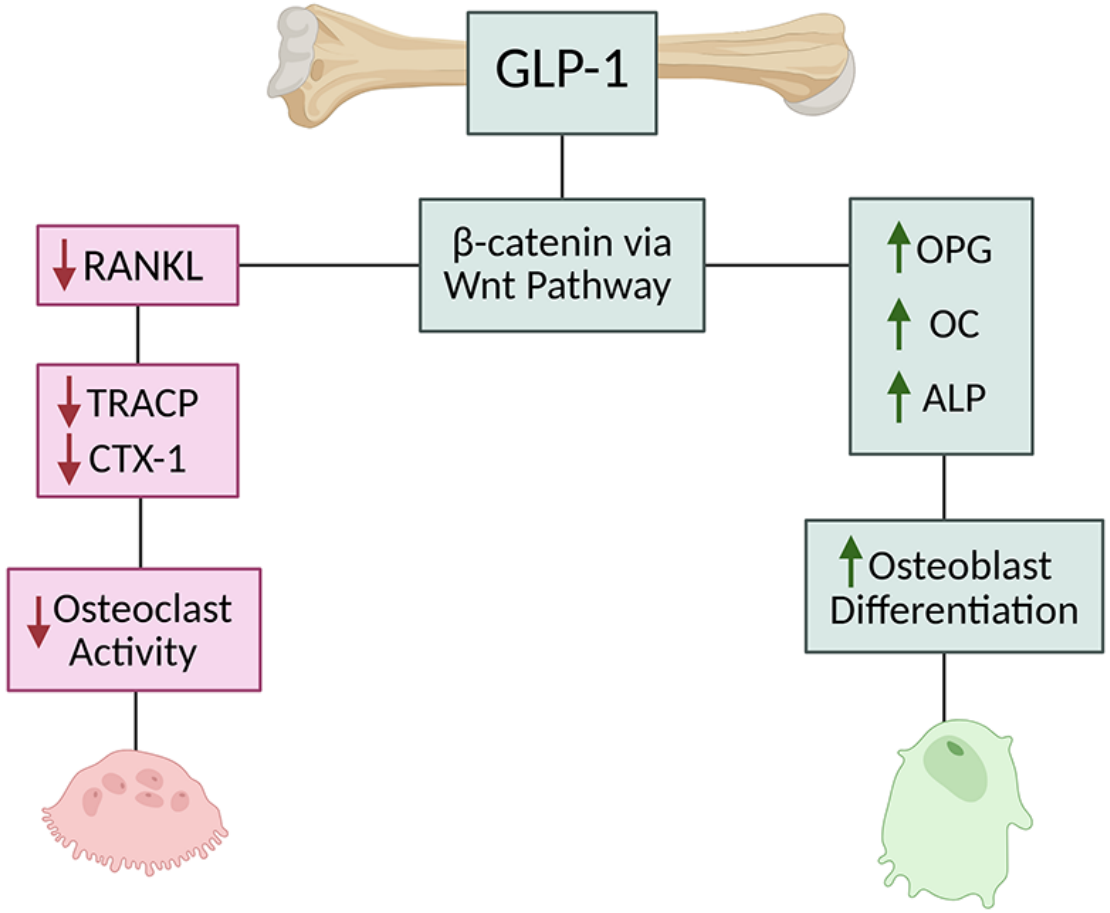



# Limitations

- Dose dependance? Dose duration?
- How do we know its due to GLP-1? Association vs weight loss?
- Didn’t include humerus fractures
- Control Group – on any Non GLP-1 agents – no stratification based on DM class --? Subgroup analysis?

# Impact on Bone

- GLP-1 RAs are associated with improvements in BMD at LS, femoral neck, and total hip & favorably affect bone turnover markers by reducing bone resorption (e.g. CTX) & increasing formation markers (P1NP, osteocalcin, bone alkaline phosphatase).




Marielle Renae De Baun, OMS 2026; Glynnis Page, OMS 2026

# Summary

- Initial therapy w/ Bip may modestly subsequent bone-forming agents but prior antiresorptive *use is not a contraindication to anabolic therapy*.
- GLP-1 receptor agonists are considered to have a neutral or safer bone profile for now – Further studies are needed.
- Inpt IV Zol after a recent fracture is evidence-based, guideline-supported, and safe, provided contraindications are excluded.

Thank you!
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Radhika Narla Views