Management of Osteoporosis in CKD

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CKD mineral and bone disease (CKD-MBD)

- CKD-MBD is a common complication of CKD that arises early in the course of the disease.
- It is associated with high morbidity and mortality.
- The term CKD-MBD is used broadly to describe abnormalities in mineral metabolism, skeletal health, and soft tissue calcifications.
- The skeletal derangements associated with CKD-MBD are associated with bone loss and fractures.

Fracture risk

- Compared with the general population, fracture incidence rates are more than **fourfold** higher.
- They are associated with greater morbidity and mortality.

Definitions in CKD-Associated Osteoporosis

Term	Definition
Primary osteoporosis	Chronic, progressive disease characterized by low bone mass, microarchitecture deterioration of bone tissue, bone fragility, and a consequent increase in fracture risk (51)
Postmenopausal	Caused by estrogen deficiency in postmenopausal women
Age related	Associated with aging in both men and women
Secondary osteoporosis	Osteoporosis secondary to medical conditions, nutritional deficiencies, and medication side effects (52)
CKD-MBD	A systemic disorder of mineral and bone metabolism due to CKD manifested by abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; abnormalities of bone turnover, mineralization, volume, linear growth, or strength; and vascular or other soft tissue calcification
Renal osteodystrophy	A disorder of bone quality and strength secondary to CKD; the bone component of CKD-MBD
Adynamic bone disease	Low or absent bone formation and turnover (53)

Diagnosis of CKD-Associated Osteoporosis

- The World Health Organization defines osteoporosis as a T score ≤ −2.5.
- Osteoporosis can also be defined clinically as the presence of a low trauma fracture with or without bone mineral density (BMD) in the osteoporotic range.

Bone density and quality

- Bone strength is the integration of bone density and quality.
- Clinically, **bone density** is measured by assessment of BMD by dual energy x-ray absorptiometry (DXA).
- **Bone quality** reflects bone material properties and includes bone microarchitecture, turnover, micro-damage, mineralization, and collagen structure.

Bone quality

- Disorders in bone quality help explain the finding that **one half** of all osteoporotic fractures occur in patients with T scores > −2.5.
- Cortical and trabecular microarchitecture can be measured noninvasively using high-resolution bone imaging methods; however, other components of bone quality are assessed by bone biopsy.
- **Renal osteodystrophy**, a complex heterogeneous disorder of bone quality and density, is a form of osteoporosis.

Fracture risk classification

- Fracture risk classification can be on the basis of the World Health Organization T score, because the four longitudinal studies that influenced the update reported **that T scores** performed **similarly** in patients with and without CKD.

Epidemiology of CKD-Associated Osteoporosis and Fractures in CKD

- Osteoporosis was **twice** as common in those with an eGFR<60 ml/min compared with those with an eGFR>60 ml/min.
- Among women and men with osteoporosis, >80% and 50%, respectively, had a Cockcroft–Gault creatinine clearance <35 ml/min.
- In predialysis-CKD, a history of osteoporosis was associated with a greater than **twofold** odds of hip fracture compared with the general population.

Epidemiology

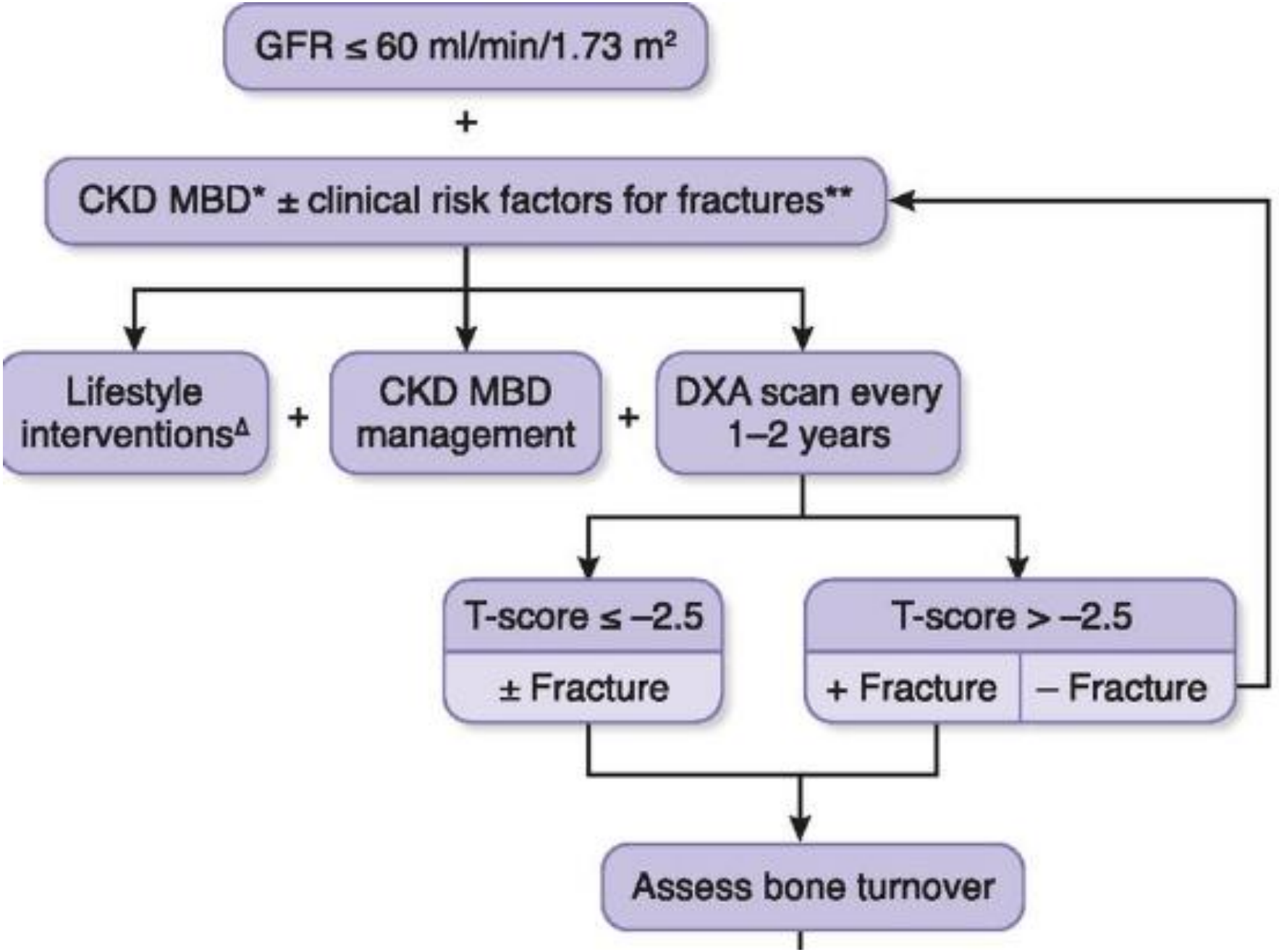
- In general, **fractures** were reported to be greater than **two- to 100-fold** more common than in age-matched individuals without CKD.
- **Mortality** rates after fracture were greater than **threefold** greater for patients with than without CKD.

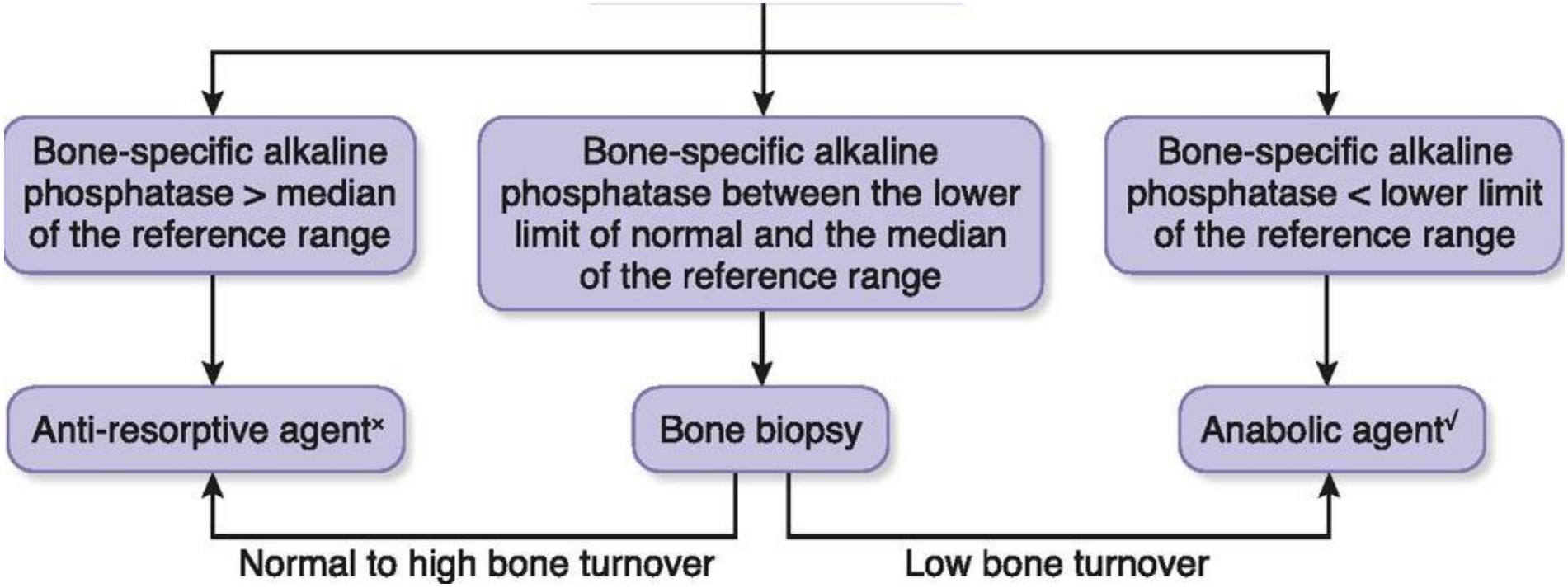
The Changing Paradigm of Managing CKD-Associated Osteoporosis

- Current treatment paradigm for renal osteodystrophy:
  - Suppressing high turnover with active vitamin D and/or calcimimetics
  - While simultaneously avoiding the development of adynamic bone disease through excessive use of these same agents.
- No data to suggest that this approach has been successful in decreasing all-type fracture rates
  - (In contrast: epidemiologic data suggest the opposite).

The Changing Paradigm of Managing CKD-Associated Osteoporosis…

- The update no longer mandates that a bone biopsy be obtained before starting osteoporosis treatment because of
  - Growing evidence suggesting that antiresorptive therapies have efficacy at preventing fractures in creatinine clearance of **15–59 ml/min/1.73 m²**
  - Lack of evidence that these medications induce adynamic bone disease.


GFR ≤ 60 ml/min/1.73 m²
+
CKD MBD* ± clinical risk factors for fractures**
Lifestyle interventions^Δ
+
CKD MBD management
+
DXA scan every 1–2 years
T-score ≤ –2.5
± Fracture
T-score > –2.5
+ Fracture
– Fracture
Assess bone turnover


Bone-specific alkaline phosphatase > median of the reference range
Bone-specific alkaline phosphatase between the lower limit of normal and the median of the reference range
Bone-specific alkaline phosphatase < lower limit of the reference range
Anti-resorptive agent×
Bone biopsy
Anabolic agent√
Normal to high bone turnover
Low bone turnover

Bone biopsy

- Gold standard for the diagnosis of renal osteodystrophy type and can inform treatment decisions.
- But important limitations:
  - Cost, availability at only a few centers worldwide, time-consuming, its ability to determine bone disease type at only a single time point, its invasiveness and discomfort to the patient, and the fact that it has never been shown to predict fracture risk.

Bone biopsy…

- The update acknowledges these limitations and suggests that circulating levels of parathyroid hormone (PTH) and bone-specific alkaline phosphatase can be used in the clinic to evaluate underlying bone turnover.
- So, bone biopsy may be used when diagnosis of turnover is not clear.

Managing CKD-MBD

Overview of available therapies for kidney-associated osteoporosis

Drugs	Dosage	FDA-Approved eGFR Cutoffs	Effect on Mineral Metabolism
Alendronate	70 mg PO once weekly	eGFR≥35 ml/min	Hypocalcemia, hypophosphatemia
Ibandronate	150 mg PO once monthly or 3 mg iv every 3 mo	eGFR>30 ml/min	–
Risendronate	5 mg PO daily or 35 mg PO weekly	eGFR>30 ml/min	Hypocalcemia, hypophosphatemia, increased PTH levels
Abaloparatide	80 µg Subcutaneously once daily	Any eGFR, not studied in ESKD	Hypercalcemia, hypercalciuria
Teriparatide	20-40 µg Subcutaneous daily	eGFR>30 ml/min	Hypercalcemia, hypocalcemia, hypercalciuria
Denosumab	60 mg Subcutaneous every 6 mo	Any eGFR	Hypocalcemia, hypophosphatemia
Romosozumab	210 mg Subcutaneous monthly	Not studied in CKD	–

Early management

- Before initiating an antiresorptive or anabolic agent to treat CKD-associated osteoporosis, we stress the importance of managing CKD-MBD through control of:
  - ✓ Vitamin D deficiency
  - ✓ Hyperphosphatemia
  - ✓ Hyperparathyroidism

Secondary hyperparathyroidism

- It is a major feature of CKD-MBD and begins early in the course of CKD, and its prevalence increases as kidney function declines.
- Despite the seemingly beneficial adaptive increase in PTH secretion to increase calcium levels, decrease phosphate levels, and increase vitamin D levels:
  - Hyperparathyroidism becomes **maladaptive over the long term.**

Vitamin D

- Correction of 25-hydroxyvitamin D deficiency can partially correct elevated PTH levels in patients with mild to severe CKD.
- Furthermore, data in ESRD suggest that levels of 25-hydroxyvitamin D >30 ng/ml optimize bone mineralization.

Plasma phosphate

- Lowering the plasma phosphate concentration with oral phosphate binders can partially reverse hypocalcemia and hyperparathyroidism.
- A meta-analysis of trials of phosphate binders:
  - Sevelamer compared with calcium-based binders
  - No significant decrease in mortality, hospitalization, or end of treatment level of calcium-phosphorus product
- Other studies:
  - Higher mortality with calcium-based binders compared with noncalcium-based binders.

Plasma phosphate…

- Calcium-based binders are thought to increase vascular calcification and cardiovascular mortality.
- In addition to vitamin D analogs, the use of the calcimimetic cinacalcet can reduce risk of fractures in patients with CKD and secondary hyperparathyroidism.

Cinacalcet

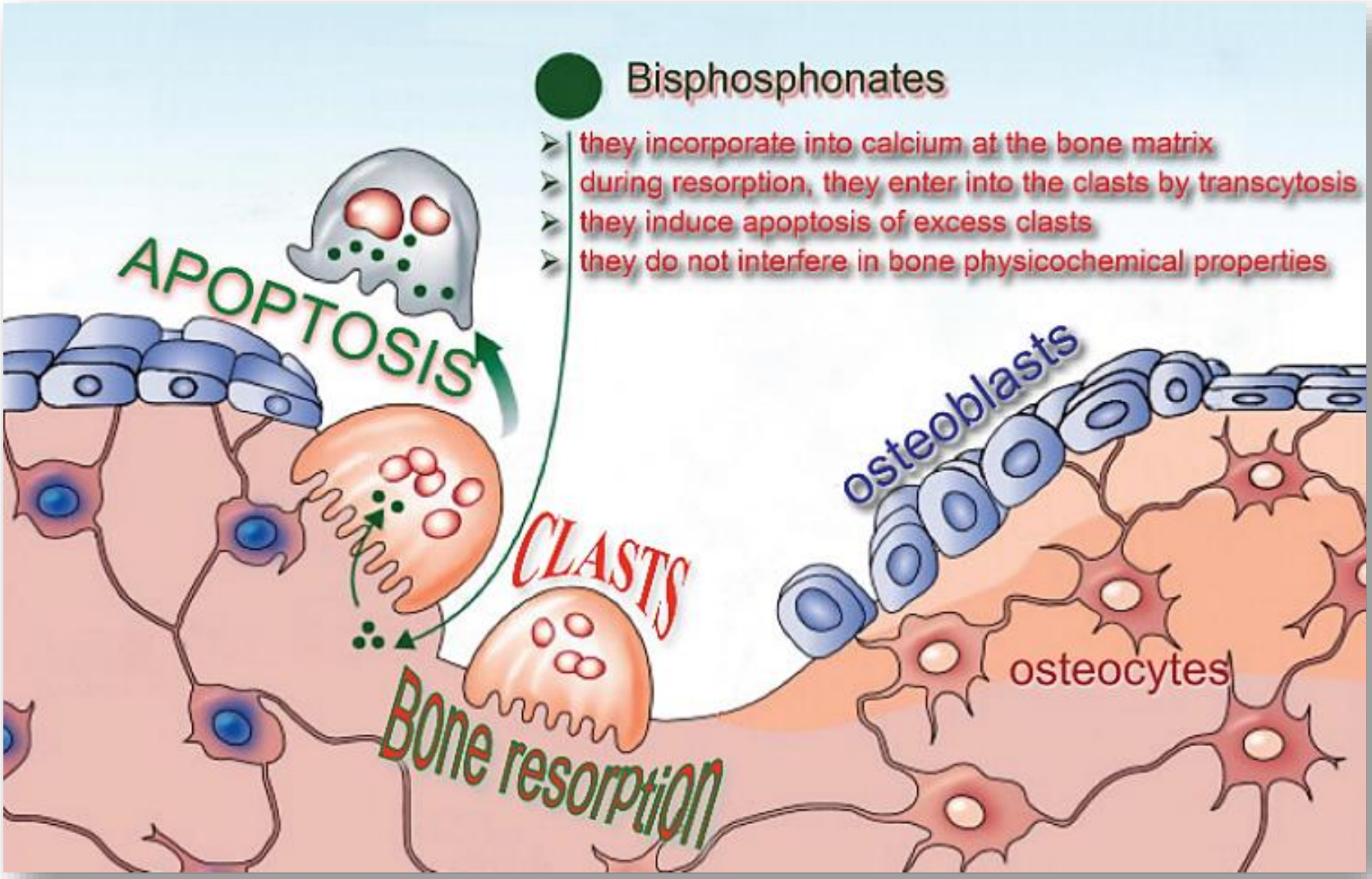
- One year of treatment with cinacalcet increased BMD of the femoral neck
  - 7.3% (with cinacalcet) vs 6.2% (without cinacalcet)
- BONAFIDE Study:
  - Bone Biopsy Study for Dialysis Patients with Secondary Hyperparathyroidism of ESRD
  - Investigated bone-tissue level effects of cinacalcet in ESRD and PTH≥300 pg/ml:
    - ✓ Cinacalcet induced a 48.3% median decrease in PTH levels ($P<0.001$)
    - ✓ Significant reduction ($P<0.001$) in the bone formation rate

Nonpharmacologic strategies

- Nonpharmacologic strategies with proven antifracture efficacy should be used in all patients.
- 60% of the observed reduction in fracture incidence in general population attributed to lifestyle interventions:
  - Calcium and vitamin D supplementation
  - Smoking cessation,
  - Weight-bearing exercise,
  - Fall prevention
  - Improved nutrition
  - Moderating alcohol intake

Antiresorptive Agents

Bisphosphonates



Bisphosphonates

- Bisphosphonates are taken up by osteoclasts and inhibit farnesyl pyrophosphate synthase
- Farnesyl pyrophosphate synthase: a crucial enzyme in synthesis of isoprenoid compounds that are essential for osteoclast function
- Except for the nitrogen-containing bisphosphonates: they induce osteoclast apoptosis

Bisphosphonates…

- Bisphosphonates are not taken up by other organs, and residual drug that is not absorbed by osteoclasts is cleared by the kidney.
- So, not recommended in eGFR<30 ml/min
  - Due to concern of excessive accumulation of bisphosphonate in the skeleton, thus resulting in oversuppression of bone remodeling.

Bisphosphonates…

- Over the past decade, data suggest:
  - ✓ Safe in patients with an eGFR of 15–59 ml/min per 1.73 m^2 due to age-related declines in kidney function and without CKD-MBD.

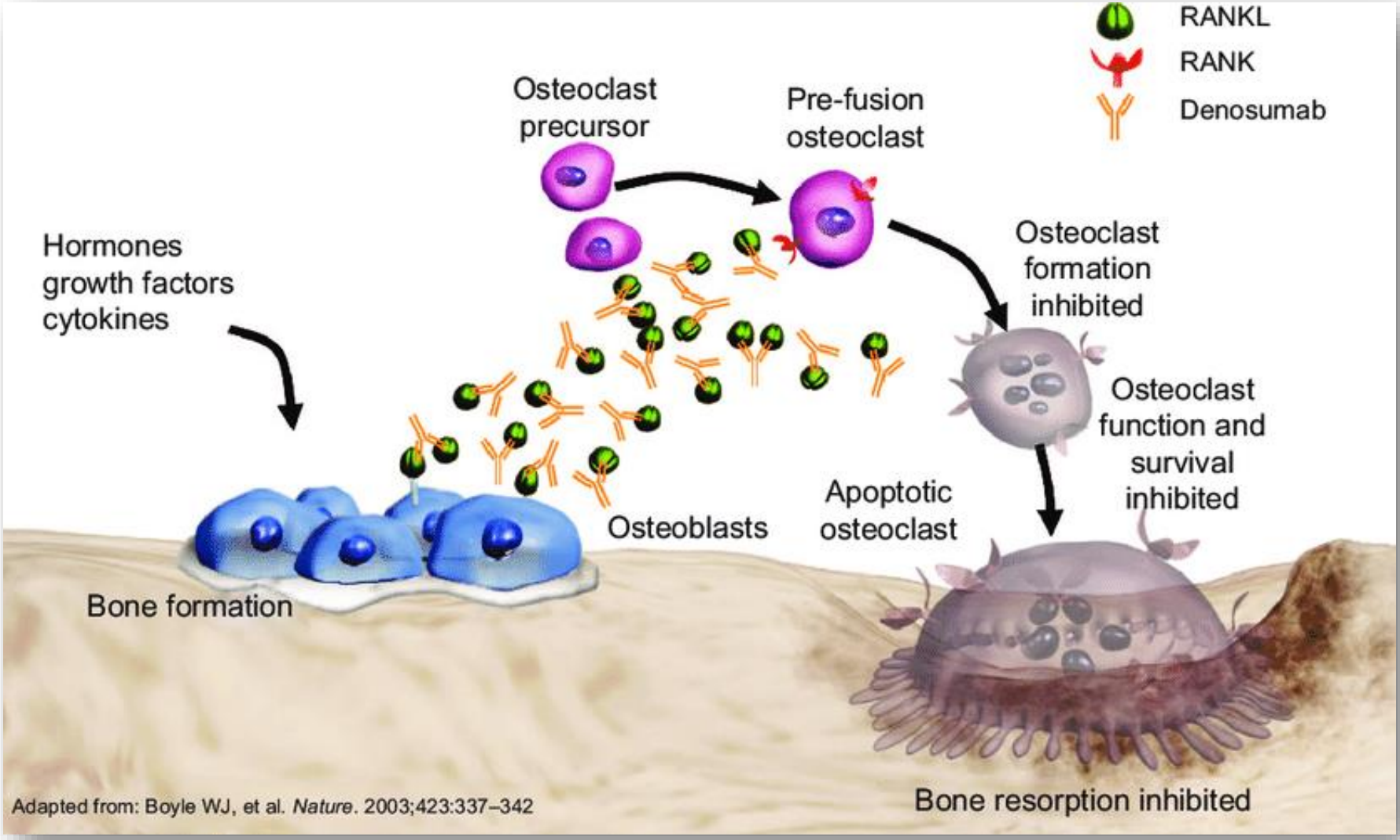
Risedronate in CKD

- In a post hoc analysis of nine double-blinded, controlled trials:
  - Women with lower GFR treated with risedronate had a significant increase in BMD and reduction in vertebral fractures compared with placebo.
  - Risedronate did not have adverse effects on kidney function.
  - Trans-iliac crest bone biopsies did not reveal adynamic bone disease or mineralization defects
  - Risendronate administration did not result in a significant change in eGFR.

Alendronate

- Treatment with alendronate similarly increased BMD at spine and hip and reduced risk of clinical and spine fractures in subjects:
  - With and without an eGFR<45 ml/min

Denosumab


RANKL
RANK
Denosumab
Osteoclast precursor
Pre-fusion osteoclast
Hormones growth factors cytokines
Osteoclast formation inhibited
Osteoclast function and survival inhibited
Osteoblasts
Apoptotic osteoclast
Bone formation
Bone resorption inhibited
Adapted from: Boyle WJ, et al. Nature. 2003;423:337–342

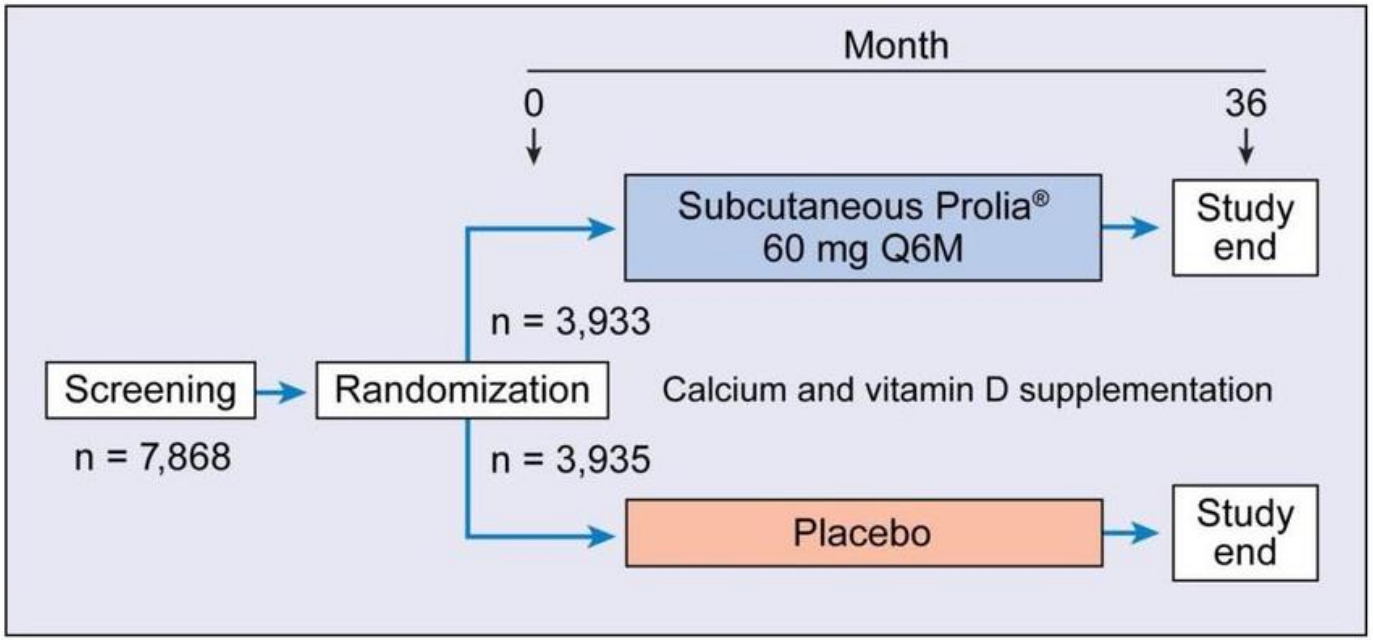
Denosumab

- A potent antiresorptive agent
- It is an mAb against the receptor activator of NF-κB ligand, and inhibits osteoclast proliferation and development.
- In contrast to bisphosphonates
  - Denosumab is not cleared by the kidney
  - So, there is no risk of over-suppressing bone turnover due to drug accumulation in CKD.

Denosumab

Denosumab
FREEDOM STUDY (PHASE 3)

- Multinational, randomised, double-blinded trial of 7,868 po stmenopausal women



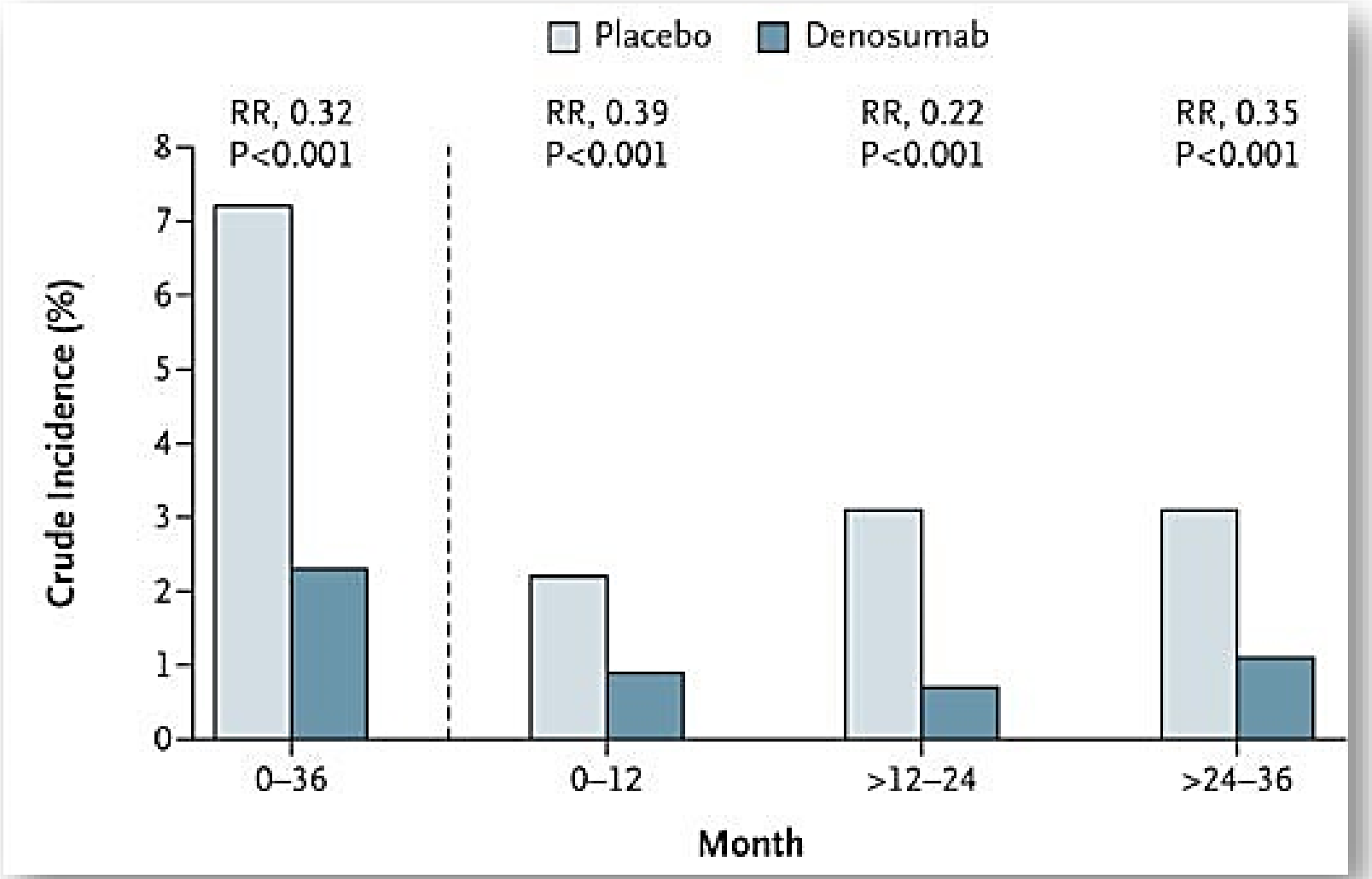
Cummings SR, et al. *N Engl J Med.* 2009;361:1-10.

Denosumab, Key efficacy results

	Denosumab, n (%)	Placebo, n (%)	Relative Risk or Hazard Ratio (95% CI)	*P*
New vertebral fracture (primary end point)	86 (2.3)	264 (7.2)	0.32 (0.26-0.41)	<.001
Nonvertebral fracture[a] (secondary end point)	238 (6.5)	293 (8.0)	0.80 (0.67-0.95)	.01
Hip fracture (secondary end point)	26 (0.7)	43 (1.2)	0.60 (0.37-0.97)	.04

[a]Patients who experienced nonvertebral fractures associated with severe trauma (13 in the denosumab group and 15 in the placebo group) were not included in the analysis.

New vertebral fracture incidence
Denosumab vs. placebo



Denosumab

- The registration trial included 7868 postmenopausal women
- ➢ Treatment with denosumab for 36 months reduced vertebral (40%), hip (68%), and nonvertebral (20%) fracture risks.
- ➢ There was no interaction between treatment effect and kidney function, and adverse events did not differ by GFR.
- ➢ Denosumab increased BMD at spine and hip, resulted in a 68% lower odds of vertebral fracture in subjects with eGFR of 30–59 ml/min per 1.73 m^2.

Denosumab…

- Denosumab can be safely administered to patients with CKD-associated osteoporosis as long as patients are supplemented with vitamin D, have adequate calcium intake, and are monitored for hypocalcemia.
- Hypocalcemia was the most common adverse event.

Osteoanabolic Agents

Osteoanabolic Agents

- Recombinant PTH or PTH-related peptides
- Use in CKD is controversial
- Studies indicate that, although teriparatide increased cortical thickness, cortical porosity increased, and density decreased, while bone strength was maintained.
- In CKD, high baseline levels of PTH drive cortical losses through increases in cortical porosity and thinning due to endocortical trabecularization.

Osteoanabolic Agents…

- Osteoanabolic agents should not be used to treat high-turnover bone disease due to hyperparathyroidism.
- In patients with low-turnover or adynamic bone disease, these agents may increase bone turnover and result in increased BMD.

Osteoanabolic Agents…

- The current body of literature suggests that teriparatide is safe
  - In patients fitting the criteria of the Fracture Prevention Trial and patients with CKD and low-turnover bone disease (after parathyroidectomy) with high risk for fracture on the basis of BMD and clinical history.

Teriparatide

- Teriparatide is a recombinant peptide of the first 34 amino-terminal residues of PTH.
- It was the first FDA approved osteoanabolic agent to treat osteoporosis and prevent fractures in both age-related and glucocorticoid-induced osteoporosis.

Teriparatide…

- Increased BMD at spine and femoral neck in all kidney function groups
- Had similar efficacy in preventing vertebral and nonvertebral fracture in GFR <80 ml/min compared with >80 ml/min.
- Had adverse events (hypercalcemia, hyperuricemia)
  - More common in lowest levels of GFR

Teriparatide…

- Data on the use of teriparatide in patients with **moderate to severe CKD-MBD** are available from small observational studies.

Abaloparatide

- A novel osteoanabolic agent recently approved by FDA for treatment of osteoporosis and prevention of fractures.
- An analog of PTH-related peptide
- It was designed to have relatively greater affinity for the transient state of PTH/PTH1 receptor, thus being **more purely anabolic.**

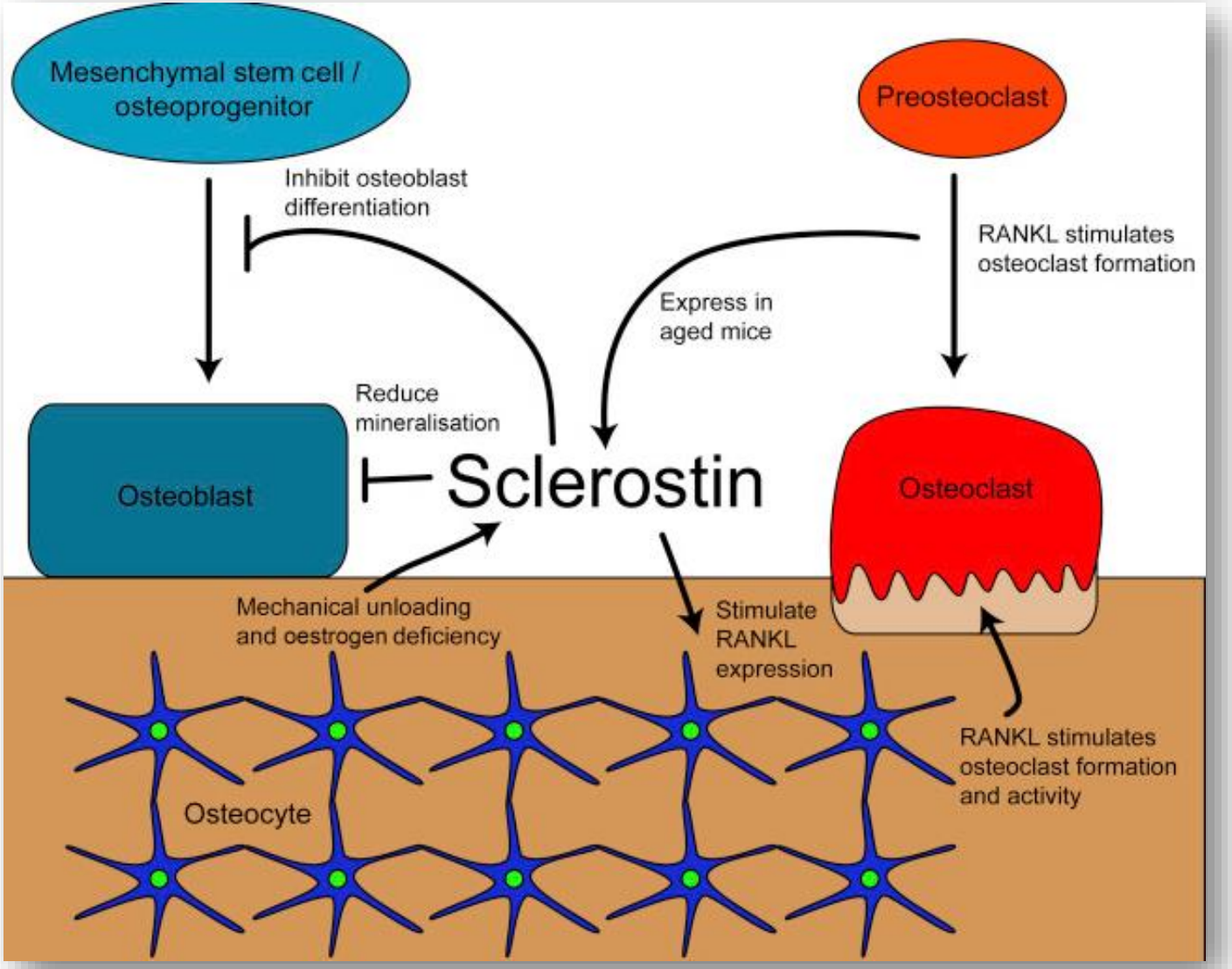
Abaloparatide…

- In human clinical trials, abaloparatide increased BMD at spine and hip and decreased risk of spine and nonspine fractures
  - With approximately 50% lower risk of hypercalcemia than teriparatide.
- In postmenopausal women treated with 12–18 months of abaloparatide
  - Bone histomorphometry showed no evidence of excessive osteoid, marrow fibrosis, or abnormalities in mineralization

Abaloparatide…

- On the basis of the ability of abaloparatide to increase bone mass and formation with less risk of hypercalcemia:
  - It may be an ideal agent to treat patients with CKD-MBD and low to normal bone turnover with high fracture risk.
- However, there are no data in patients with CKD-MBD.

Sclerostin


Mesenchymal stem cell / osteoprogenitor
Preosteoclast
Inhibit osteoblast differentiation
RANKL stimulates osteoclast formation
Express in aged mice
Reduce mineralisation
Osteoblast
Sclerostin
Osteoclast
Mechanical unloading and oestrogen deficiency
Stimulate RANKL expression
RANKL stimulates osteoclast formation and activity
Osteocyte

Sclerostin

- A glycoprotein product of the SOST gene, and it is secreted almost exclusively by osteocytes.
- Inhibits Wnt signaling, which is a key negative regulator of bone formation.
- Loss of function SOST mutations result in high-bone mass phenotypes through uncoupling formation and resorption in favor of formation.

Sclerostin…

- Since inhibition of sclerostin favors bone formation over resorption
- It could provide great utility in treating CKD-associated osteoporosis
- As its use is not associated with induction of low turnover bone disease (a theoretical risk of using antiresorptive agents).

Romosozumab

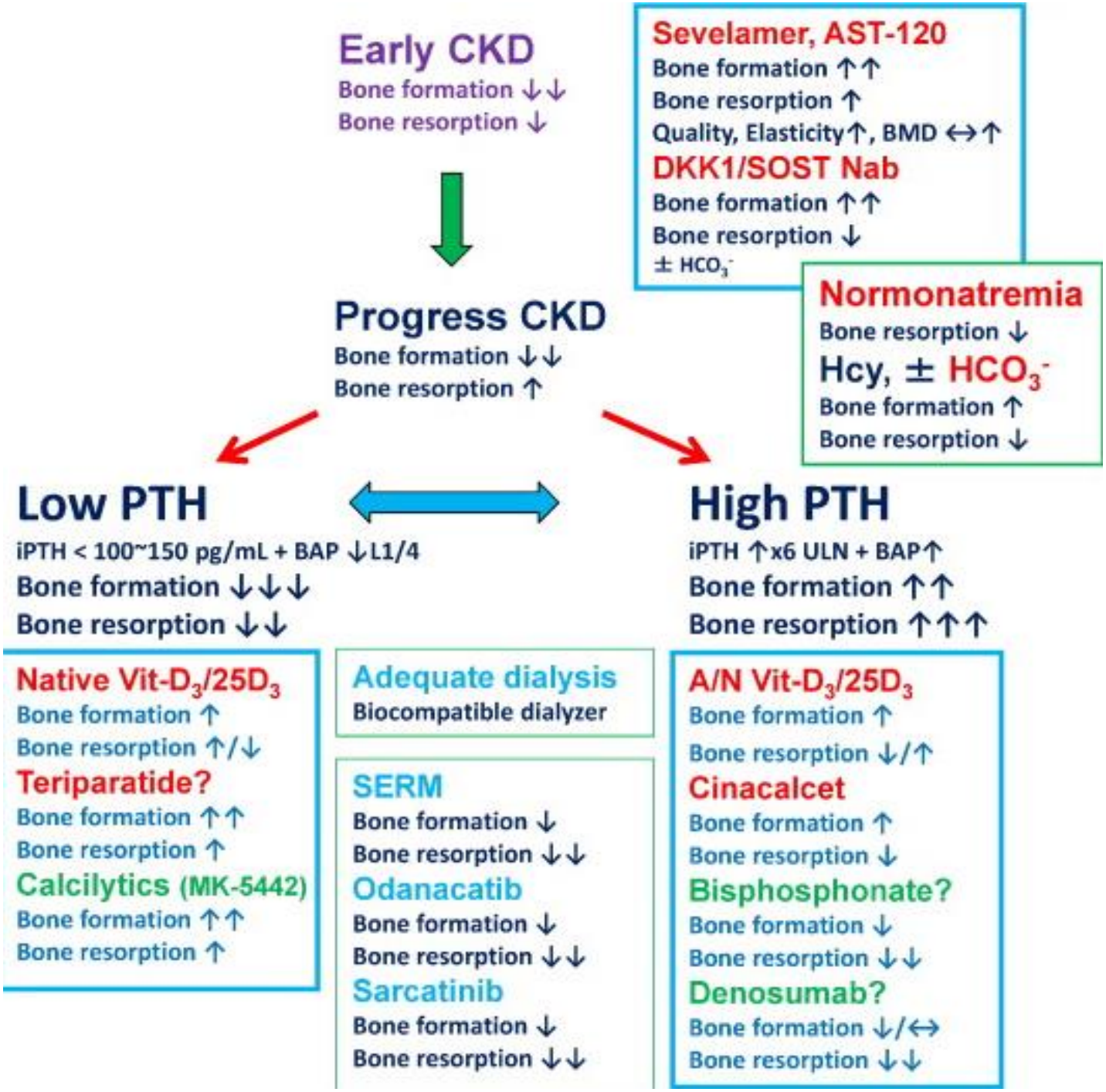
- In clinical trials, romosozumab, a humanized mAb that targets sclerostin, resulted in
  - Increase in BMD to a greater extent than alendronate and teriparatide
  - Decrease in risk of vertebral and nonvertebral fractures in postmenopausal women

Inhibition of sclerostin

- Since inhibition of sclerostin favors bone formation over resorption
  - ➢ It could provide great utility in treating CKD-associated osteoporosis
  - ➢ Also, its use is not associated with induction of low turnover bone disease (a theoretical risk of using antiresorptive agents)

Romosozumab and CVD

- In a recent study by Saag et al:
  - Two groups
  1) Patients given 12 months of **romosozumab** followed by 12 months of alendronate
  2) 24 continuous months of alendronate
  - Increase in serious CVD in **romosozumab group.**
- It is important to note that CVD have not been reported in other studies.
- So, wheter these results indicate that romosozumab increases cardiac risk or alendronate is cardioprotective???
  - Not known


Early CKD
Bone formation ↓↓
Bone resorption ↓
Sevelamer, AST-120
Bone formation ↑↑
Bone resorption ↑
Quality, Elasticity↑, BMD ↔↑
DKK1/SOST Nab
Bone formation ↑↑
Bone resorption ↓
± HCO3-
Progress CKD
Bone formation ↓↓
Bone resorption ↑
Normonatremia
Bone resorption ↓
Hcy, ± HCO3-
Bone formation ↑
Bone resorption ↓
Low PTH
iPTH < 100~150 pg/mL + BAP ↓L1/4
Bone formation ↓↓↓
Bone resorption ↓↓
High PTH
iPTH ↑x6 ULN + BAP↑
Bone formation ↑↑
Bone resorption ↑↑↑
Native Vit-D3/25D3
Bone formation ↑
Bone resorption ↑/↓
Teriparatide?
Bone formation ↑↑
Bone resorption ↑
Calcilytics (MK-5442)
Bone formation ↑↑
Bone resorption ↑
Adequate dialysis
Biocompatible dialyzer
SERM
Bone formation ↓
Bone resorption ↓↓
Odanacatib
Bone formation ↓
Bone resorption ↓↓
Sarcatinib
Bone formation ↓
Bone resorption ↓↓
A/N Vit-D3/25D3
Bone formation ↑
Bone resorption ↓/↑
Cinacalcet
Bone formation ↑
Bone resorption ↓
Bisphosphonate?
Bone formation ↓
Bone resorption ↓↓
Denosumab?
Bone formation ↓/↔
Bone resorption ↓↓