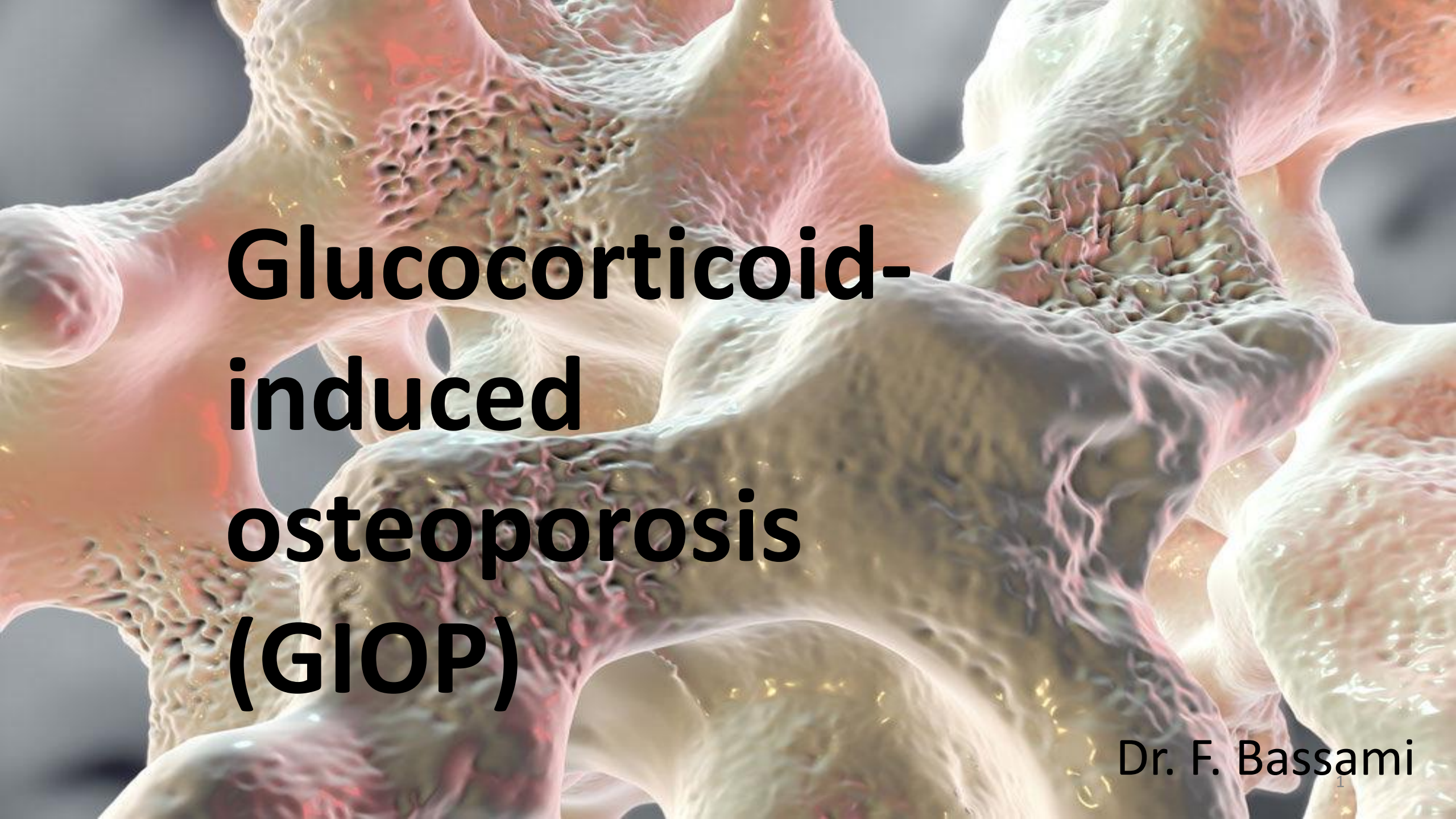


Glucocorticoid-induced osteoporosis (GIOP)

Dr. F. Bassami

Introduction

Glucocorticoids are widely used in the treatment of many diseases across a broad range of medical specialities.

Their adverse effects on the skeleton, first recognised by Harvey Cushing in 1932, result in substantial morbidity and mortality.

However, despite the significant advances that have since been made in our understanding of the epidemiology, pathophysiology, and management of glucocorticoid-induced osteoporosis, it remains relatively neglected and under-treated.

Effects of glucocorticoids on bone loss and fracture risk

The characteristics of glucocorticoid-induced bone loss and associated increase in fracture risk are well documented.

Rapid bone loss occurs soon after the initiation of glucocorticoid therapy and an increase in fracture risk is seen within 3-6 months.

These effects are dose-dependent and the increase in fracture risk is maintained throughout the duration of therapy. Following discontinuation of glucocorticoids, fracture risk declines but may not revert to baseline levels.

Effects of glucocorticoids on bone loss and fracture risk

The threshold dose of prednisolone at which adverse skeletal effects occur is debated.

Recent evidence suggests that harmful effects may be seen at daily doses as low as 2.5 mg.

In a prospective observational cohort study of 884 women with a spectrum of inflammatory rheumatic musculoskeletal diseases treated with oral prednisolone, doses as low as ≤2.5 mg daily were associated with loss of BMD and a higher fracture incidence than in the propensity score-matched healthy control group.

Effects of glucocorticoids on bone loss and fracture risk

Although an increase in fracture risk is seen at all sites, vertebral fractures are particularly characteristic.

Using data from placebo-treated patients in clinical trials of glucocorticoid-induced osteoporosis, Amiche et al. reported an annual incidence of vertebral fracture of 5.1% and of non-vertebral fracture, 2.5% within the first 6 months of glucocorticoid therapy; with longer term duration the figures were 3.2% and 3.0% respectively.

Effects of glucocorticoids on bone loss and fracture risk

The majority of studies have focused on oral glucocorticoid therapy and the skeletal effects of intravenous, inhaled, intra-articular, or topical glucocorticoid therapy are less well established.

High doses of inhaled glucocorticoids have been reported in some studies to increase fracture risk but concomitant use of oral glucocorticoids is often a confounding factor.

High doses of intravenous glucocorticoids, for example following solid organ transplantation, have been associated with increased fracture risk but are often used with other immunosuppressive drugs that also have adverse effects on bone.

Effects of glucocorticoids on bone loss and fracture risk

Intra-articular and topical therapy are generally not associated with adverse skeletal effects.

However, potent cytochrome P450 3A4 inhibitors such as ritanovir, which is used as a booster in anti-retroviral therapy, significantly increase the bioavailability of glucocorticoids and there have been several case reports of PLHIV developing iatrogenic Cushing's syndrome after treatment with small amounts of topical or intra-articular steroids.

Pathophysiology

Direct effects of glucocorticoids on bone

Glucocorticoids have wide-ranging effects on all bone cell types, mostly mediated via the glucocorticoid receptor.

Glucocorticoid-induced bone loss:

- Transient and rapid increase in bone resorption
- Reduction in bone formation (maintained for the duration of glucocorticoid exposure)

- Early increase in bone remodelling rate
- Reduction in bone formation

- Rapid bone loss
- Increase in fracture risk

Pathophysiology

Osteoblasts

Effects on osteoblasts are mediated through changes in their formation, lifespan, and function.

1.Up-regulation:
- PPARgamma
- CCAAT-enhancer-binding-protein alpha

- Diversion of stromal precursors towards adipogenesis and away from osteoblastogenesis
- Inhibition of osteogenic transcription factors (RUNX2)

Pathophysiology

Osteoblasts

2.Inhibit the proliferation of committed osteoblast precursors and suppress their differentiation:

- inhibition of Wnt proteins and bone morphogenetic proteins (BMPs)
- Stimulation of sclerostin and dickkopf1

3.Reduced formation of bone matrix proteins:

- Osteocalcin
- Collagen

4.Increased apoptosis reduces the lifespan of osteoblasts.

Pathophysiology

Osteocytes

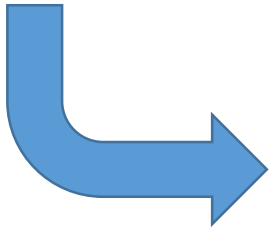
1.Glucocorticoid therapy → Osteocytes → ↑ Sclerostin, ↑ dickkopf1 → Reduced bone formation

3. Pro-apoptotic effects on osteocytes → ↓ lifespan

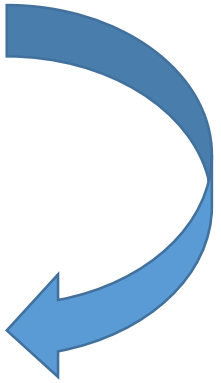
Pathophysiology

Osteoclasts

1.
   - ➢ Increased production of RANKL by osteocytes and osteoblasts
   - ➢ Reduced production of osteoprotegerin (OPG)



- reduced osteoclast apoptosis
- stimulation of osteoclastogenesis
- ⬆ Osteoclast activity



Early and transient increase in osteoclastic bone resorption

Pathophysiology

Osteoclasts

2.Increased production of macrophage colony stimulating factor (M-CSF) by osteoblasts

Stimulates the differentiation of osteoclast precursors

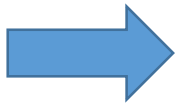
Progressive decrease in generation and lifespan of osteocytes and osteoblasts with continued glucocorticoid administration

Transient nature of increased bone resorption

Pathophysiology

Indirect effects of glucocorticoids on bone

- ❑Hypogonadism
- ❑Reduced intestinal calcium absorption
- ❑Reduced renal tubular calcium reabsorption
- ❑Decreased production of insulin growth factor-1 (IGF1) and its binding protein IGF1-BP
- ❑Muscle weakness and wasting



Decreased mechanical loading of the skeleton and increased risk of falls

Pathophysiology

Effect of glucocorticoids on bone microarchitecture and strength

Fractures occur at a higher BMD in glucocorticoid-treated individuals than in other forms of osteoporosis (partial independence of fracture risk from BMD):

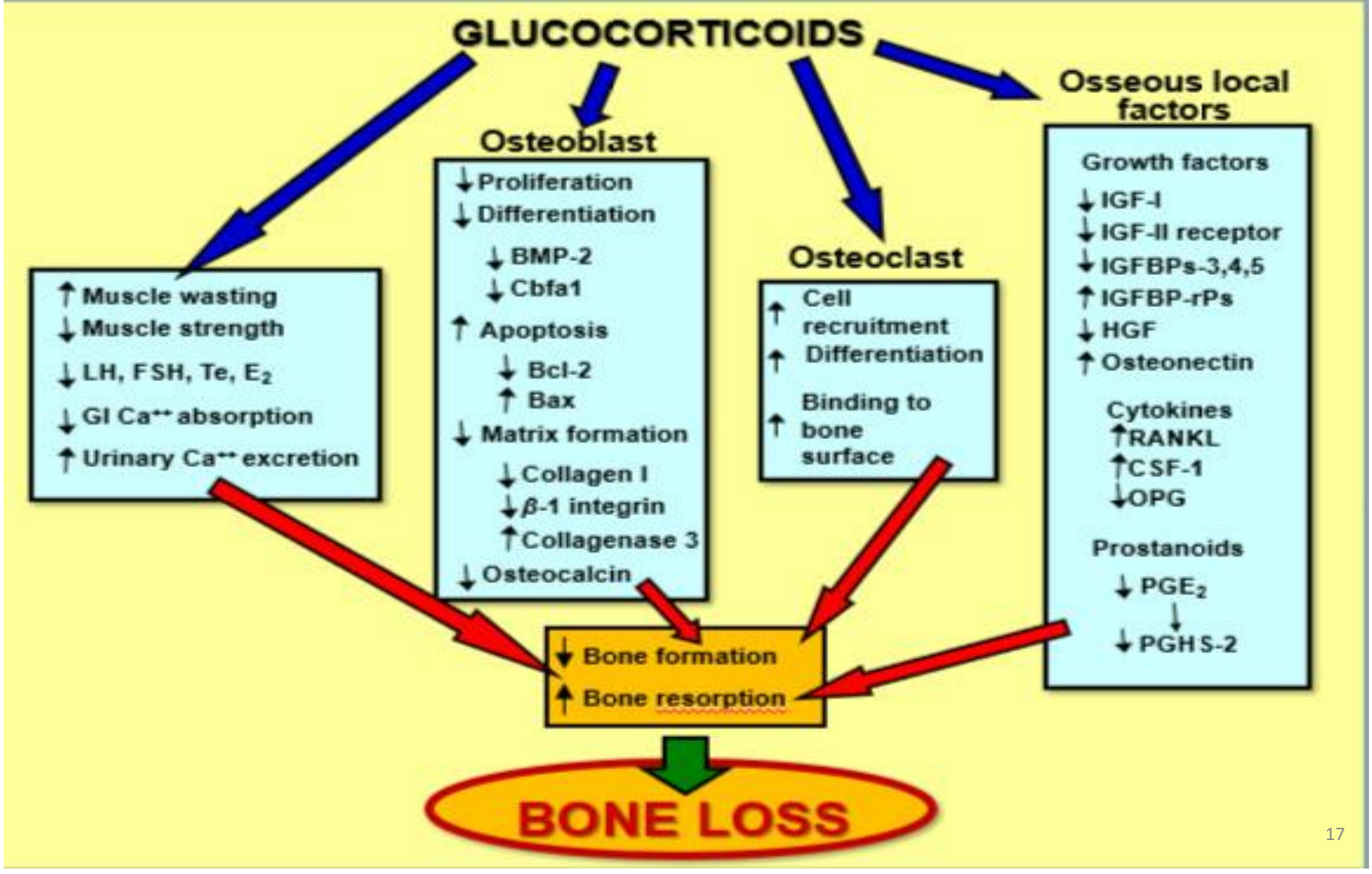
- Changes in bone microarchitecture (trabecular and cortical) ,bone quality and bone strength

Trabecular bone score (TBS):

Indirect index of trabecular bone architecture in the lumbar spine and has been shown to predict fracture independently of BMD.

High TBS values (note that TBS is unitless) correlate with homogeneous (i.e., normal) bone texture, while low values are indicative of more variable (i.e., weaker) bone texture.

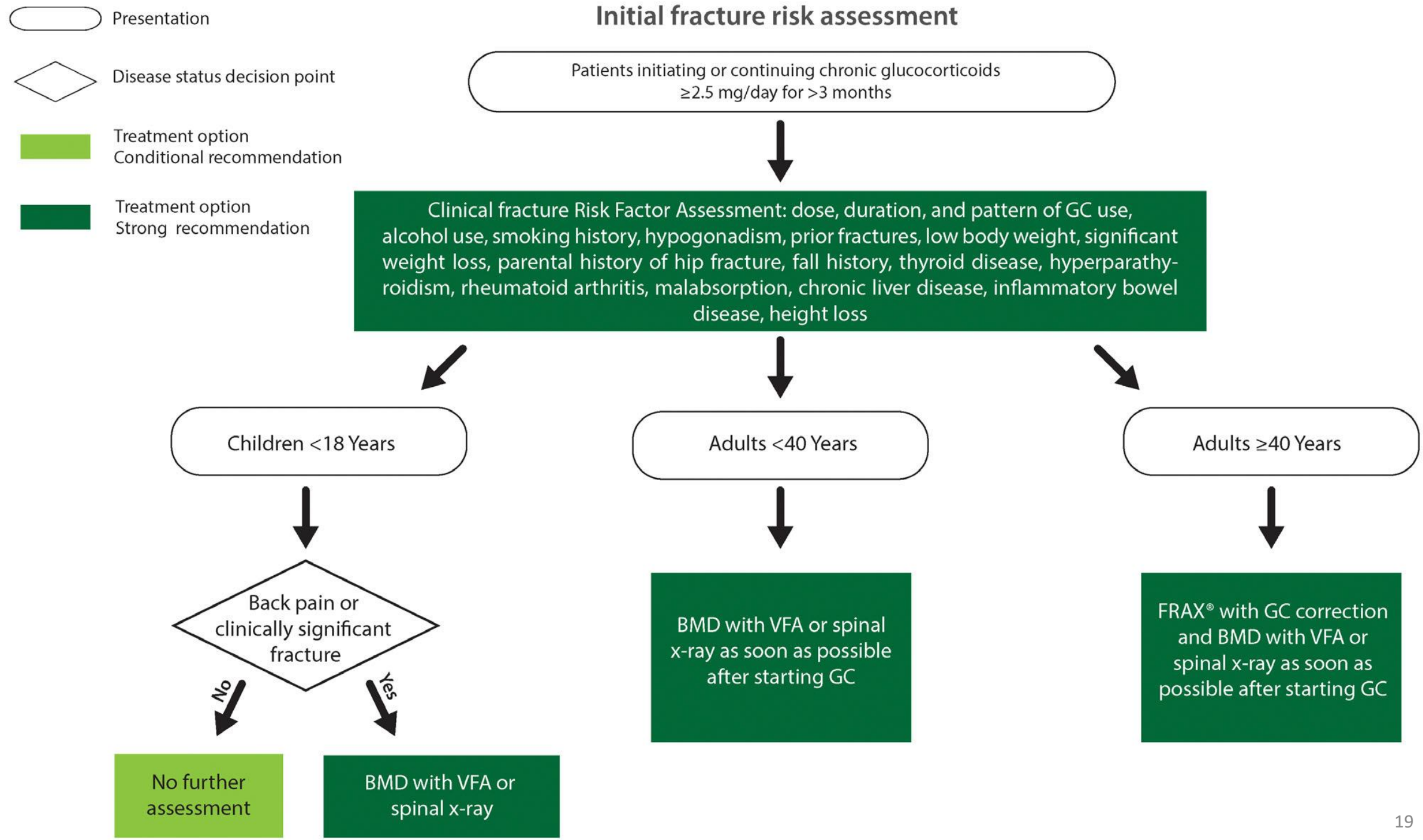
It has been reported to be significantly lower in individuals treated with long-term glucocorticoids compared to non-treated controls, despite similar lumbar spine BMD in the treated and non-treated groups.


GLUCOCORTICOIDS
↑ Muscle wasting
↓ Muscle strength
↓ LH, FSH, Te, E_2
↓ GI Ca^{++} absorption
↑ Urinary Ca^{++} excretion
Osteoblast
↓ Proliferation
↓ Differentiation
↓ BMP-2
↓ Cbfa1
↑ Apoptosis
↓ Bcl-2
↑ Bax
↓ Matrix formation
↓ Collagen I
↓ β-1 integrin
↑ Collagenase 3
↓ Osteocalcin
Osteoclast
↑ Cell recruitment
↑ Differentiation
↑ Binding to bone surface
Osseous local factors
Growth factors
↓ IGF-I
↓ IGF-II receptor
↓ IGFBPs-3,4,5
↑ IGFBP-rPs
↓ HGF
↑ Osteonectin
Cytokines
↑ RANKL
↑ CSF-1
↓ OPG
Prostanoids
↓ PGE_2
↓ PGHS-2
↓ Bone formation
↑ Bone resorption
BONE LOSS

Assessment of fracture risk in glucocorticoid users

As soon as possible (within 6 months) after initiation of ≥2.5 mg/day GC treatment for >3 months, for all adults (≥18 years old) we strongly recommended initial clinical fracture risk assessment including :

1) symptomatic and asymptomatic fracture history
2) FRAX (age ≥40 only)
3) BMD
4) VFA or spine x-rays


Initial fracture risk assessment
Presentation
Disease status decision point
Treatment option
Conditional recommendation
Treatment option
Strong recommendation
Patients initiating or continuing chronic glucocorticoids
≥2.5 mg/day for >3 months
Clinical fracture Risk Factor Assessment: dose, duration, and pattern of GC use, alcohol use, smoking history, hypogonadism, prior fractures, low body weight, significant weight loss, parental history of hip fracture, fall history, thyroid disease, hyperparathyroidism, rheumatoid arthritis, malabsorption, chronic liver disease, inflammatory bowel disease, height loss
Children <18 Years
Adults <40 Years
Adults ≥40 Years
Back pain or clinically significant fracture
No
Yes
No further assessment
BMD with VFA or spinal x-ray
BMD with VFA or spinal x-ray as soon as possible after starting GC
FRAX® with GC correction and BMD with VFA or spinal x-ray as soon as possible after starting GC

FRAX

Nontraumatic or pathological fractures of the spine, hip, wrist, or humerus

FRAX GC correction:

If GC dose is >7.5 mg/day, multiply the 10-year risk of MOF by 1.15 and the hip fracture risk by 1.2.

If hip fracture risk is 2.0% multiply by 1.2 for adjusted risk = 2.4%.

FRAX

Adjustments for 10-year FRAX-estimated fracture probability in individuals with positive VFA:

For MOF, the proposed multipliers are 1.15 and 1.53 in individuals without or with a history of clinical fracture respectively, with corresponding figures of 1.31 and 1.76 for hip fracture probability.

FRAX limitations:

- FRAX does not take account of the dose or duration of glucocorticoid therapy and therefore underestimates risk in individuals receiving high doses, this adjustment may not correct for very high doses of GC (≥30 mg/day).
- FRAX does not incorporate falls, site, number or timing of fractures, or frailty that may put a person at higher risk of fracture.
- Use of total hip BMD in FRAX may lead to underestimation of fracture risk if spine BMD is differentially affected.

Country : UK Name / ID : About the risk factors

Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age: Date of birth: Y: M: D:

2. Sex Male Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture No Yes

6. Parent fractured hip No Yes

7. Current smoking No Yes

8. Glucocorticoids No Yes

9. Rheumatoid arthritis No Yes

10. Secondary osteoporosis No Yes

11. Alcohol 3 more units per day No Yes

12. Femoral neck BMD

Select

Clear Calculate

BMI

The ten year probability of fracture (%)

without BMD

Major osteoporotic	
Hip fracture	

View NOGG Guidance

Definitions

Very high fracture risk:

- ❑ Adults ≥40 years of age

  - Prior OP fracture(s) OR
  - BMD t-score ≤−3.5 OR
  - FRAX (GC-Adjusted) 10-year risk of MOF ≥30% or hip ≥4.5% OR
  - High GC ≥30 mg/day for >30 days OR
  - Cumulative doses ≥5 g/y

- ❑ Adults <40 years of age

  - Prior fracture(s) OR
  - GC ≥30 mg/day OR
  - Cumulative doses ≥5 g/y

Definitions

High fracture risk:

❑Adults ≥40 years of age

- BMD t-score ≤−2.5 but >−3.5 OR
- FRAX (GC Adjusted) 10-year risk of MOF ≥20% but <30% or hip ≥3% but <4.5%

Moderate fracture risk:

❑Adults ≥40 years of age

- FRAX (GC-Adjusted) 10-year risk of MOF ≥10 and <20%, hip >1 and <3% OR
- BMD t-score between −1 and −2.4

❑Adults <40 years of age

- Continuing GC treatment ≥7.5 mg/day for ≥6 months and BMD z-score < −3 OR
- Significant BMD loss (more than the least significant change of DXA)

Definitions

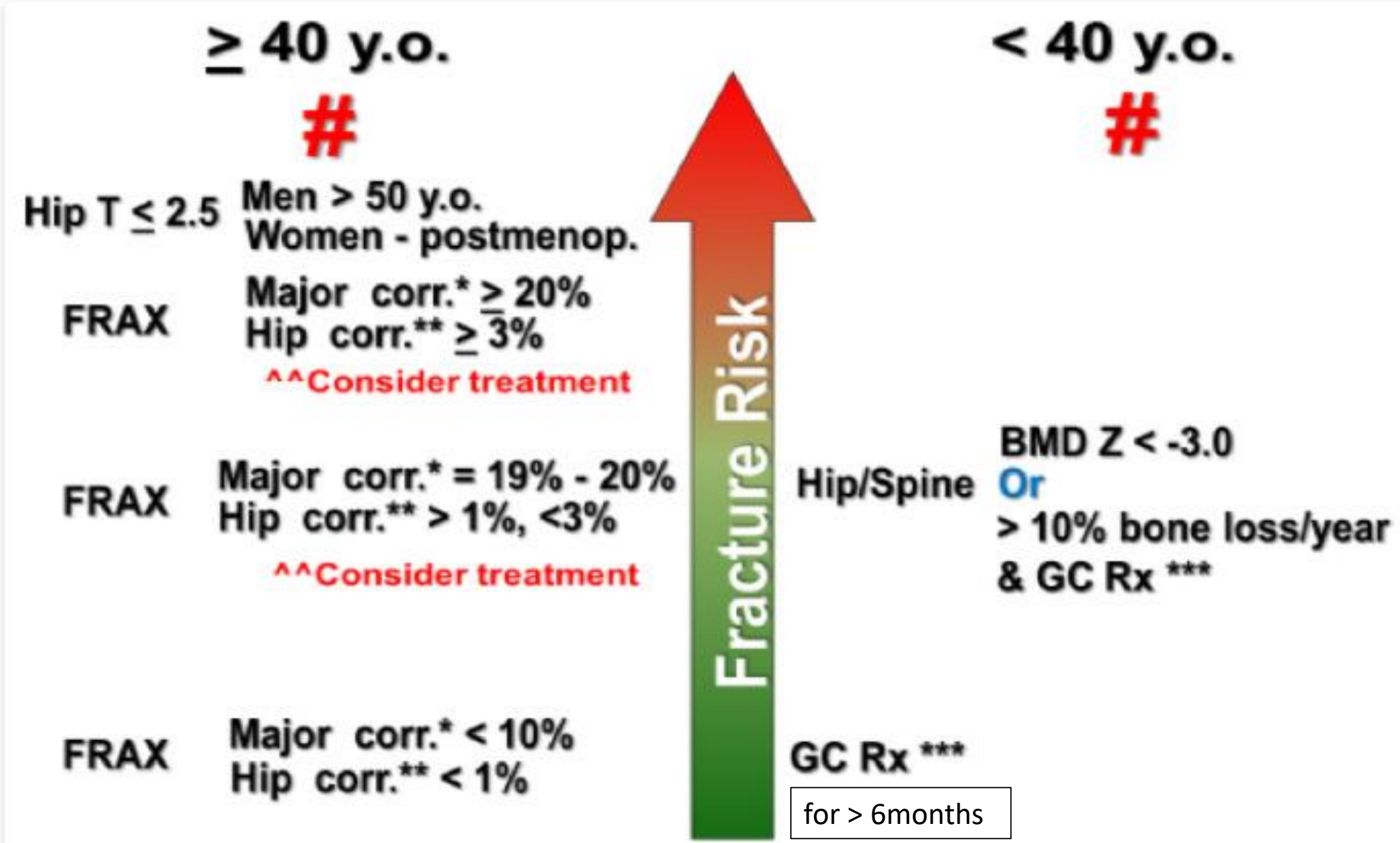
Low fracture risk:

❑Adults ≥40 years of age

- FRAX (GC-Adjusted) 10-year risk of MOF <10%, hip <1 %
- BMD t-score >−1.0

❑Adults <40 years of age

None of the above risk factors other than GC treatment


≥ 40 y.o.
#
< 40 y.o.
#
Hip T ≤ 2.5
Men > 50 y.o.
Women - postmenop.
FRAX
Major corr.* ≥ 20%
Hip corr.** ≥ 3%
^^Consider treatment
FRAX
Major corr.* = 19% - 20%
Hip corr.** > 1%, <3%
^^Consider treatment
FRAX
Major corr.* < 10%
Hip corr.** < 1%
Fracture Risk
Hip/Spine
BMD Z < -3.0
Or
> 10% bone loss/year
& GC Rx ***
GC Rx ***
for > 6months

Reassessment of fracture risk in glucocorticoid users

- For adults continuing chronic GC ≥2.5 mg/day but <7.5mg/day and assessed as **low fracture risk**, who were not recommended to start therapy, or **moderate fracture risk** who chose not to start OP therapy (except calcium and vitamin D), we strongly recommend fracture risk reassessment every 1 to 2 years:

- Clinical fracture risk history
- New symptomatic fractures
- FRAX
- BMD
- VFA and/or spine x-rays

Repeating DXA assessment every 1 to 2 years allows providers to detect the least significant BMD change according to their DXA machine, triggering the need to start OP therapy.

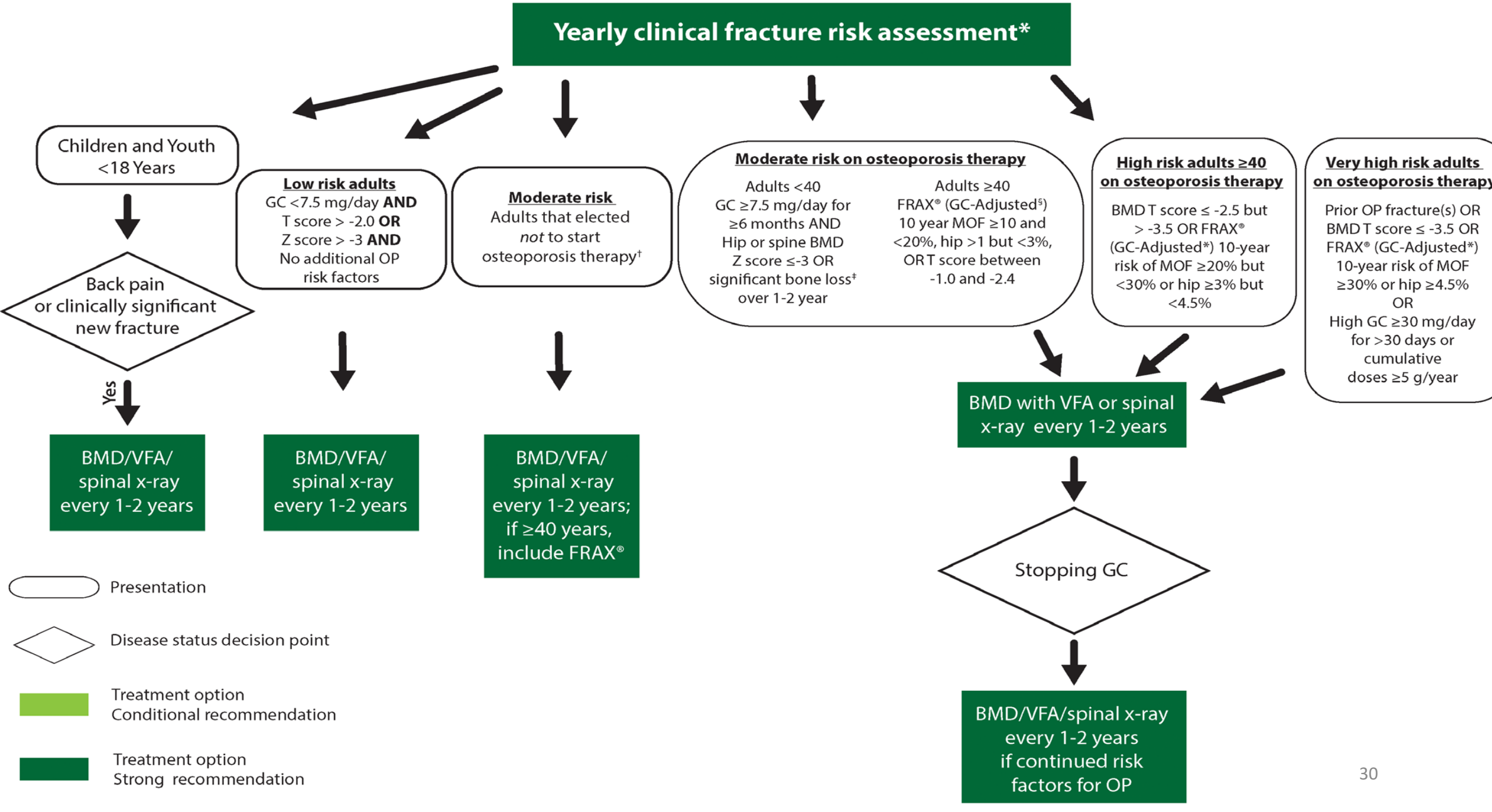
Reassessment of fracture risk in glucocorticoid users

- For adults continuing chronic GC ≥2.5 mg/day and assessed as moderate, high, or very high fracture risk who are continuing OP therapy ≥1 year, we strongly recommend fracture risk re-assessment every 1 to 2 years

  - ✓ Reassessment allows providers to determine if patients continuing GC and OP therapy are maintaining, gaining, or losing BMD, warranting possible changes in OP therapy.
  - ✓ Yearly BMD assessment until a stable BMD is reached may be preferred in very high fracture risk patients.

- For adults stopping GC and remaining at moderate, high, or very high fracture risk, we strongly recommend continuing OP therapy

Fracture risk re-assessment for patients continuing chronic GC ≥ 2.5 mg/day for >3 months



Management: general considerations

Although the adverse effects of excess glucocorticoids on bone are well documented, management of glucocorticoid-induced osteoporosis remains suboptimal with low rates both of BMD testing and treatment, and poor adherence to treatment.

The rapid onset of bone loss and increased fracture risk following initiation of glucocorticoid therapy emphasises the need for early intervention in high-risk individuals.

Management: general considerations

If access to bone densitometry is limited, bone protective medication should not be delayed in the presence of strong risk factors, for example advanced age, high dose of glucocorticoids, or previous history of fracture.

However, DXA including VFA should be performed as soon as is possible, to provide a baseline for monitoring and to confirm that treatment is indicated.

Management: general considerations

The dose of glucocorticoid prescribed should be regularly reviewed and kept to a minimum, and consideration given to use of glucocorticoid-sparing alternative therapies or formulations with lower systemic absorption.

However, since the underlying disease itself is often associated with factors that increase fracture risk, for example inflammation, malabsorption, reduced mobility, and falls, there is a balance to be struck between the harmful skeletal effects of inadequately suppressed disease and those of glucocorticoid excess.

Initial treatment in GC induced osteoporosis

- For all adults and children beginning or continuing chronic GC at a dose of ≥2.5 mg/day for >3 months, we conditionally recommended optimizing age appropriate dietary and supplemental calcium and vitamin D, in addition to lifestyle modifications

  - ✓ Dietary and supplemented elemental calcium:

    - adults :up to 1,000 to 1,200 mg daily
    - Children: between 1,000 and 1,300 mg daily based on age.

Recommended Dietary Allowance for Calcium		
Age	**Sex**	**Recommended dietary allowance (mg/day)**
0-6 months	M + F	200
6-12 months	M + F	260
1-3 years	M + F	700
4-8 years	M + F	1,000
9-18 years	M + F	1,300
19-50 years	M + F	1,000
51-70 years	M	1,000
51-70 years	F	1,200
71+ years	M + F	1,200

Initial treatment in GC induced osteoporosis

✓vitamin D supplemented

- vitamin D supplemented to maintain serum 25(OH)D levels ≥30 to 50 ng/mL
- 600 to 800 IU daily or more is typically require

✓Lifestyle modifications

- Smoking cessation
- Limiting alcohol to ≤2 servings a day
- Eating a balanced diet
- Maintaining weight in the recommended range
- Performing regular weight-bearing or resistance training exercises

Initial treatment in GC induced osteoporosis

- For adults ≥40 years with high or very high fracture risk, we strongly recommended treatment with OP therapy over treatment with calcium and vitamin D alone.
- For adults ≥40 years with high or very high fracture risk, we strongly recommended oral BP over no treatment

  - ✓ A strong recommendation for oral BP is based on studies showing a reduction in total and vertebral fractures at 24 months and increased hip and lumbar spine BMD compared to calcium and vitamin D alone in GIOP.

Initial treatment in GC induced osteoporosis

- For adults ≥40 years with very high fracture risk, we conditionally recommend PTH/PTHrP over anti-resorptives (BP or DEN)

  - ✓ Compared to oral BP, PTH is superior at increasing BMD 24 and 36 months and prevented vertebral fractures at 36 months.
  - ✓ In the very high risk group, providers may recommend PTH/PTHrP as initial treatment because anabolism is blunted in patients previously treated with BP.

Initial treatment in GC induced osteoporosis

- For adults ≥40 years with high fracture risk, we conditionally recommend PTH/PTHrP or DEN over BP.

  - ✓ DEN and PTH show superior BMD gains in GIOP compared to BP and may be preferred in patients with high risk.

Initial treatment in GC induced osteoporosis

- For adults ≥40 years with high fracture risk, we conditionally recommend IV or oral BP, PTH/PTHrP, or DEN over Raloxifene (RAL) or Romosozumab.

  - ✓ Due to RAL harms of venous thrombotic embolism events (pulmonary embolism/deep vein thrombosis [PE/DVT]) and fatal stroke and association of ROM with increased myocardial infarction, stroke, and death, these therapies should be reserved for those unable to tolerate other agents.

Initial treatment in GC induced osteoporosis

- ✓~~ROM~~ should not be started in patients with a myocardial infarction or stroke within 12 months.
- ✓Shared decision-making between patients and clinicians is needed to determine if benefits outweigh the risks in patients with other cardiovascular risk factors that may be untreated including hyperlipidemia, hypertension, and smoking.

Initial treatment in GC induced osteoporosis

- ✓Compared to BP and RAL, PTH/PTHrP, DEN, and ROM require sequential therapy with an anti-resorptive agent to prevent bone losses.
- ✓Discontinuation of DEN after two or more doses can be associated with rapid loss of BMD and development of new vertebral compression fractures as soon as 7 to 9 months after the last DEN dose. As such, 6 to 7 months after the last dose of DEN, BP or ROM therapy is recommended.
- ✓If ROM is used after DEN, then it must be followed with a course of BP.

Initial treatment in GC induced osteoporosis

- ✓The precise timing, dose, and duration of BP or ROM use after DEN cessation is still under study, but treatment for at least 1 year with an oral BP or 1 to 2 years of IV BP seems prudent, until additional research is available.

Initial treatment in GC induced osteoporosis

- ✓Discontinuation of PTH/PTHrP medication may lead to gradual loss of bone gained over 12 to 18 months (anti-fracture efficacy may persist for 18 months), which can be prevented by treatment with anti-resorptive therapy (BP or DEN) .
- ✓ If DEN is used sequentially after discontinuation of PTH/PTHrP, then a BP should be started at the completion of DEN therapy. Therefore, BP therapy is recommended after discontinuation of PTH/PTHrP.
- ✓ROM can be followed by DEN or BP.

Initial treatment in GC induced osteoporosis

- ✓BP, DEN, and ROM have increased risk of atypical femur fractures and osteonecrosis of the jaw compared to oral BP.
- ✓The panel recommends initial treatment choice be informed by patient co-morbidities and preferences regarding costs, burden of injections, and the need for sequential therapy.

Initial treatment in GC induced osteoporosis

- In adults ≥40 years with high and very high fracture risk, we conditionally recommend against using multiple OP therapies at the same time

  - ✓ In patients with postmenopausal OP, studies have shown synergistic increases in BMD with combination of PTH with IV BP , PTH with RAL , and PTH and DEN.
  - ✓ However, based on the added cost, the possibility of greater side effects, and the lack of fracture evidence, combination therapy is not currently recommended.

Initial treatment in GC induced osteoporosis

- For all adults with moderate fracture risk, we conditionally recommend oral or IV BP, PTH/PTHrP, or DEN over no treatment.
- In all adults with moderate fracture risk, we conditionally recommend against ~~ROM~~ and ~~RAL~~ therapies except in those intolerant of other OP medications, due to possible lifethreatening harms, including thrombosis, fatal stroke, major cardiovascular events, and death.

Initial treatment in GC induced osteoporosis (GIOP)

- In adults with low fracture risk, we strongly recommend against adding oral or IV BP, PTH/PTHrP, RAL, DEN, or ROM.

  - ✓ Adults <40 years have low fracture risk and have significant capacity to rebuild BMD losses induced by chronic GC therapy, OP therapy should not be started in this low-risk group.
  - ✓ Adults >40 years on low-dose steroids that meet low risk criteria have uncertain benefit from osteoporosis therapy.

Initial pharmacological treatment for adults

Presentation

Disease status decision point

Treatment option
Conditional recommendation

Treatment option
Strong recommendation

Optimize dietary and supplemental calcium (1000-1200 mg/day) and vitamin D (600-800 IU/day) to maintain serum vitamin D level >30-50 ng/ml

Clinical fracture risk assessment, BMD with VFA or spinal x-ray, FRAX® (if age ≥40)

Low Risk

Adults <40 Years
GC <7.5 mg/day AND Z score > -3 AND no other OP risk factors

Adults ≥40 Years
GC <7.5mg/day AND FRAX® (GC-Adjusted) 10-year risk of MOF <10%, hip <1%, BMD T score > -1.5

Strongly recommend no further treatment, clinical fracture risk assessment with BMD with VFA or spinal x-ray every 1-2 years

Adults <40 Years **Adults ≥40 Years**

Moderate Risk

BMD Z score ≤ -3 OR significant bone loss over 1-2 years AND GC ≥7.5mg/day for ≥6 months

FRAX® (GC-Adjusted*) 10-year risk MOF ≥10 and <20%, or hip ≥1 but <3%, OR BMD T score between -1 and -2.4

Conditionally recommend oral BP, IV BP, DEN[‡¶], PTH/PTHrP[¶]

Conditionally recommend *against* RAL and ROM[‡] due to potential harms[§] except for those intolerant to other agents

Adults ≥40 Years

High Risk

BMD T score ≤ -2.5 but > -3.5 OR FRAX® (GC-Adjusted*) 10-year risk of MOF ≥20% but <30% or hip ≥3% but <4.5%

Conditionally recommend DEN[‡] or PTH/PTHrP over BP

Conditionally recommend IV BP, RAL or ROM over no treatment

Strongly recommend oral BP over no treatment[†]

Adults

Very High Risk

Prior OP fracture(s) OR BMD T score ≤ -3.5 OR FRAX® (GC-Adjusted*) 10-year risk of MOF ≥30% or hip ≥4.5%
OR
High GC ≥30 mg/day for >30 days or cumulative doses ≥5 g/year

Conditionally recommend PTH/PTHrP over anti-resorptive (BP, DEN)
Conditionally recommend DEN[‡], IV BP, RAL or ROM over no treatment

Strongly recommend oral BP over no treatment[†]

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- For adults ≥40 years at very high fracture risk due to treatment with one or more courses of high-dose GC therapy (mean dose prednisone equivalent ≥30 mg daily for ≥30 days) or cumulative GC dose ≥5 g over 1 year, we conditionally recommend treating with PTH/PTHrP over anti-resorptive agents regardless of FRAX score or BMD. We strongly recommend oral BP over no treatment and conditionally recommend an IV BP, DEN, RAL or ROM over no treatment.

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- For adults <40 years receiving one or more courses of high-dose GC therapy (mean dose prednisone equivalent ≥30 mg daily for ≥30 days) or cumulative GC dose ≥5 g over 1 year, we conditionally recommend oral or IV BP, PTH/PTHrP, DEN. We conditionally recommended against ~~RAL/ROM~~.

  - ✓ In this younger population, PTH/ PTHrP and ROM should only be used in adults with closed growth plates.
  - ✓ DEN should be used with caution in patients with open growth plates.

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- For patients who can become pregnant at moderate or high risk of fracture, we conditionally recommend treating with oral or IV BP, DEN, or PTH/PTHrP

  - ✓ OP therapy is not contraindicated in patients who can become pregnant but should be used with effective birth control if sexually active.
  - ✓ BP are avidly taken up by the fetal skeleton as shown in animal models and have a long half-life of BP in adult bones with unclear side effects for the fetal skeleton.

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- ✓ Risedronate and ibandronate have shorter skeletal halflives among BP and may be preferred in this setting.
- ✓ DEN may cause fetal harm and is contraindicated in pregnancy.
- ✓ Avoid pregnancy for 5 months after the last dose of DEN.

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- For adults with solid organ transplants and an estimated glomerular filtration rate (eGFR) ≥35 mL/min who are continuing chronic GC treatment, we conditionally recommend treatment with BP, DEN, PTH/PTHrP, or RAL, based on individual patient factors over no treatment.
  - ✓ This group of patients is typically considered at increased risk of fracture regardless of BMD, due to the known risk of OP associated with solid organ transplantation and anti-rejection medications.

- In this solid organ transplant population, we conditionally recommend against using ~~ROM~~ due to potential harms in this population.

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- For adult renal transplant recipients on chronic GC treatment, we conditionally recommend metabolic bone disease expert evaluation for chronic kidney disease–mineral and bone disorder (CKD-MBD).
  - ✓ In patients with stage IV and V CKD, renal osteodystrophy, including adynamic bone disease, osteomalacia, osteitis fibrosa cystica, and mixed uremic osteodystrophy, is nearly universal.
  - ✓ Bone-specific alkaline phosphatase, intact PTH, and bone biopsy may exclude renal osteodystrophy.
  - ✓ ~~BP~~ should generally not be used if eGFR <35 mL/min.

<30 mL/min for risedronate and ibandronate
<35 mL/min for alendronate and zoledronate

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- ✓ Once renal osteodystrophy and hyperparathyroidism is excluded, no dose adjustment is needed when prescribing DEN, PTH/PTHrP, or ROM.
- ✓ However, if eGFR is <30 mL/min, DEN is not contraindicated but induces prolonged and more severe hypocalcemia.
- ✓ The panel recommended that patients without hyperparathyroidism and eGFR ≥30 mL/min could use vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol) instead of biologically active forms of vitamin D (calcitriol, paricalticol, or doxercalciferol).
- ✓ Patients with GFR <30 mL/min might require biologically active VitD to maintain neutral calcium balance.

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- For children and youth ages 4 to 17 years treated with GCs for >3 months who are at low or moderate risk for fracture, optimization of age-appropriate dietary and supplemental calcium and vitamin D to fulfill the Recommended Daily Allowance is conditionally recommended in addition to an exercise program. We conditionally recommend against starting OP therapy due to the low risk of osteoporotic fractures in children and youth ages 4 to 17 years.

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- For children and youth ages 4 to 17 years with an osteoporotic fracture who are continuing treatment with chronic GC at a dose of ≥0.1 mg/kg/day for >3 months, treating with an oral or IV BP is conditionally recommended over no treatment.

  - ✓ Other OP therapies are understudied in this young age group with open growth plates.
  - ✓ Depending on the specific disease or cause of pediatric OP, there is uncertainty about when and how to screen, and depending on the guidelines, it requires a history of clinically significant fracture(s), defined as ≥1 vertebral fractures, ≥2 long bone fractures prior to age 10 years, or ≥3 long bone fractures up to age 19 years.

Special populations of patients beginning long-term GC therapy at very high risk for fracture

- ✓ 12% of children with rheumatic conditions on chronic GC averaging doses of 0.94 ± 0.84 mg/kg/ day for 6 months who then tapered to 0.06 ± 0.12 mg/kg/day between 30 months and 36 months had vertebral fracture in the three years following GC initiation.
- ✓ The same study found that every 0.5 mg/kg increase in average daily GC dose was associated with a two-fold increased fracture risk (HR 2.0, 95% CI 1.1–3.5).

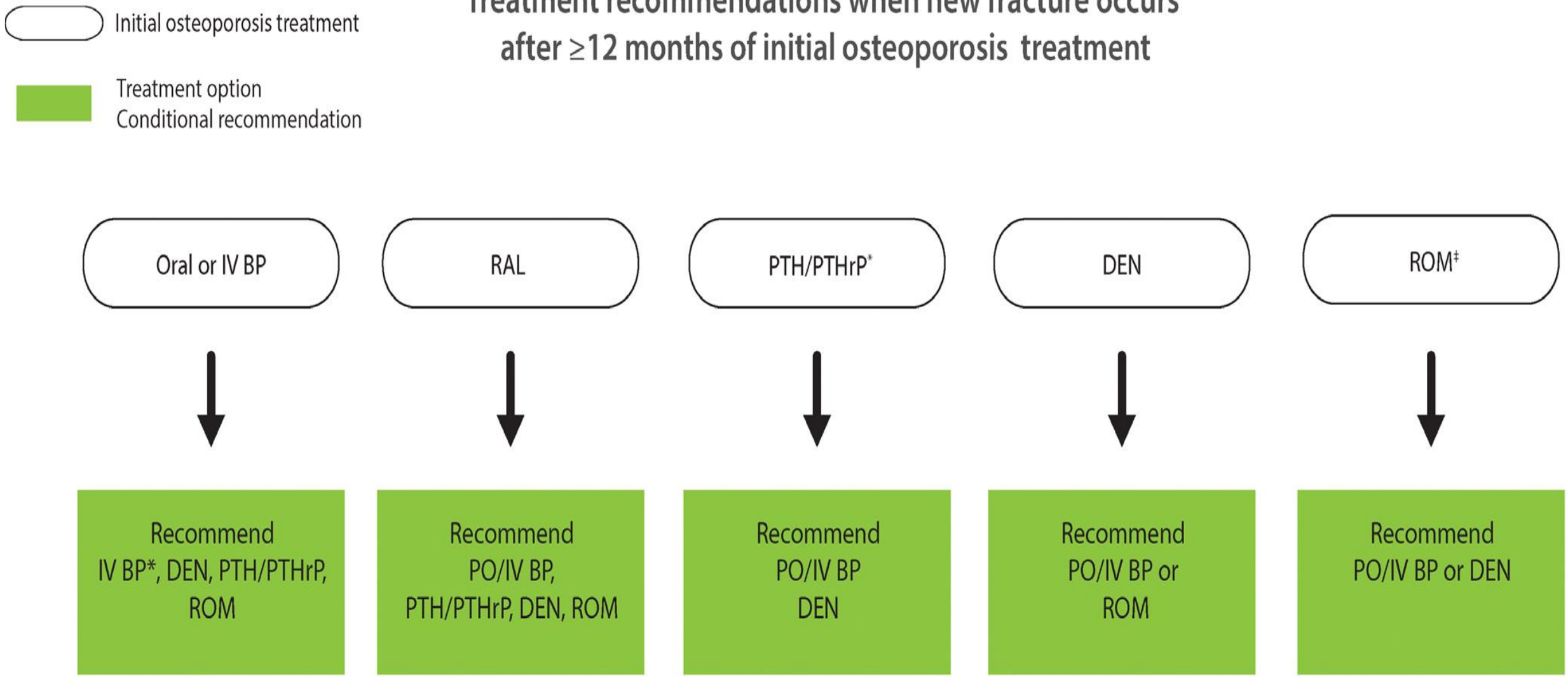
Initial treatment failure

- For adults continuing GC treatment who have had an osteoporotic fracture ≥12 months after starting OP therapy, or who have had a significant loss of BMD (eg, greater than the least significant change per their DXA machine) after 1 to 2 years of OP treatment, we conditionally recommend changing to another class of OP medication over not switching the class of OP medication.

Initial treatment failure

- ✓If oral BP is the first OP therapy and suboptimal adherence or poor absorption is suspected, based on low certainty evidence, we conditionally recommend treatment with IV BP, DEN, ROM, or PTH/PTHrP.
- ✓Of note, use of PTH/PTHrP after long-term BP treatment has blunted anabolic response but still increases BMD.
- ✓If DEN is the first agent, switching to PTH/PTHrP may lead to transient bone losses in the hip and spine and is not recommended; however, PTH/PTHrP followed by DEN leads to continued BMD increases

Treatment recommendations when new fracture occurs after ≥12 months of initial osteoporosis treatment



BP = bisphosphonate, IV = intravenous, PO = oral, DEN = denosumab, ROM = romosozumab, PTH = parathyroid hormone, PTHrP = PTH related peptide, RAL = raloxifene, OP = osteoporosis. BMD = bone mineral density, *If oral BP absorption or adherence a concern, †Bone loss may be gradual and anti-fracture efficacy may last 18 months but should be followed by anti-resorptive, ‡ROM is used for 12 months only

Treatments when GC are discontinued

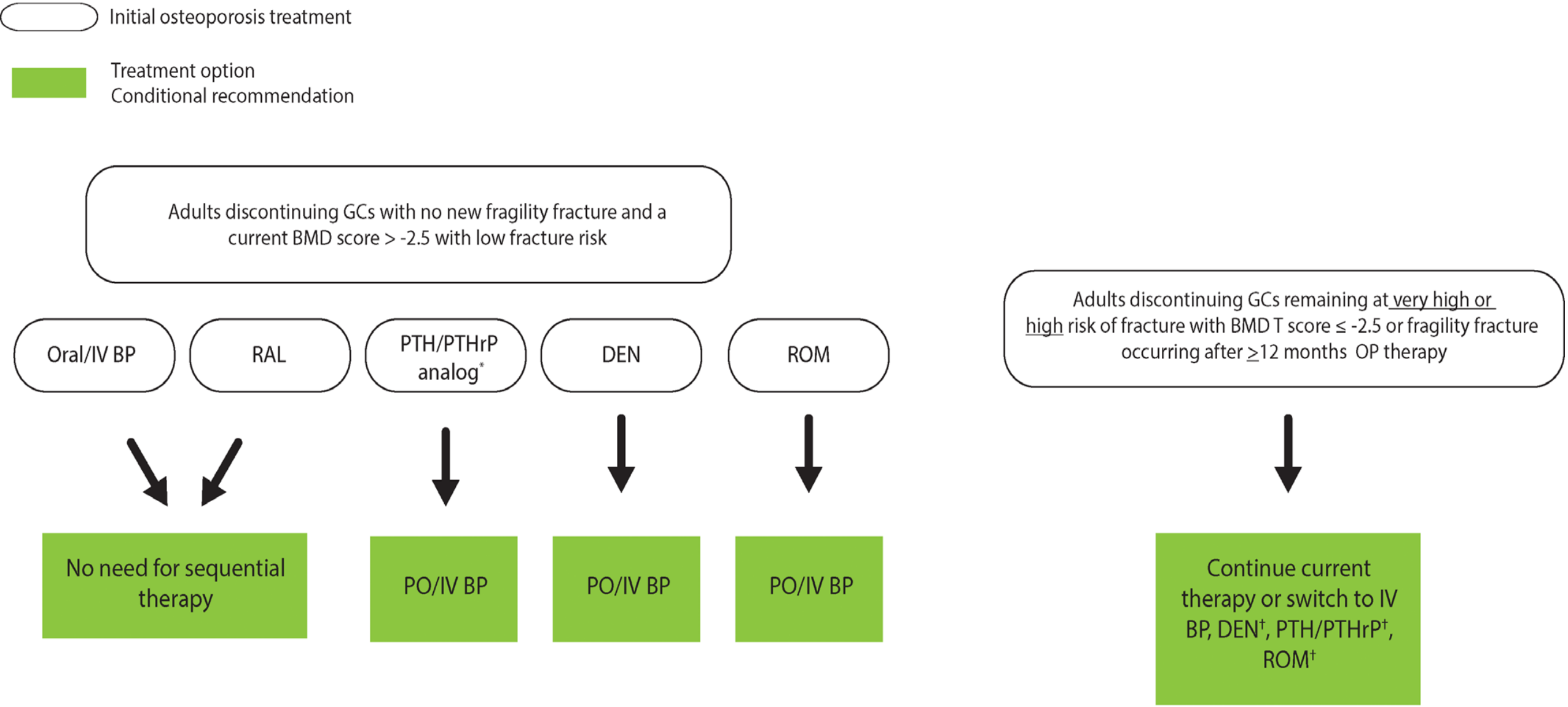
- For adults taking OP therapy and discontinuing GC therapy, with no new fragility fracture and a current BMD t-score ≥−2.5, we strongly recommended stopping current OP therapy and continuing calcium and vitamin D. However, sequential therapy is strongly recommended after stopping DEN, PTH/PTHrP, and ROM.

  - ✓BP and RAL can be discontinued without need for sequential therapy.
  - ✓DEN, PTH/PTHrP, and ROM should be transitioned to anti-resorptive therapy, but the best formulation and duration of treatment is unclear at this time.

Treatments when GC are discontinued

- For adults ≥40 years discontinuing GC therapy and continuing to be at high risk of fracture (BMD t-score ≤−2.5, or history of a fragility fracture occurring after ≥12 months of therapy), we conditionally recommend continuing current OP therapy or switching to another class of OP medication.

Sequential osteoporosis treatment recommendation when initial therapy and GC are discontinued



BP = bisphosphonate, IV = intravenous, PO = oral, DEN = denosumab, ROM = romosozumab, PTH = parathyroid hormone, PTHrP = PTH related peptide, RAL = raloxifene, OP = osteoporosis; *Bone loss may be gradual and anti-fracture efficacy maintained 18 months but antiresorptive is recommended; †Will require sequential therapy with BP

GONADAL HORMONE THERAPY

Sex hormone treatment should be considered whenever a patient with GC excess develops hypogonadism.

A retrospective study in postmenopausal women taking GCs found an increased BMD in those who were taking estrogens, compared to increasing bone loss in those who were not.

Moreover, in a randomized controlled clinical trial of postmenopausal women taking GCs for rheumatoid arthritis, a significant increase in lumbar spine BMD was observed in those receiving hormone replacement therapy (HT) compared to those receiving placebo.

GONADAL HORMONE THERAPY

However, a large randomized clinical trial in postmenopausal women treated with a combination of estrogen and progestin planned to last 8.5 years was interrupted after 5 years, because the overall risks exceeded the benefits of the treatment.

GONADAL HORMONE THERAPY

Similarly, adult men with GC excess who develop hypogonadism benefit from testosterone replacement.

In GC-treated asthmatic men with testosterone deficiency, i.m. testosterone injections increased lumbar spine but not hip BMD.

However, since most studies have shown an increase in prostate size and prostate-specific antigen levels in older men on testosterone supplementation/therapy, testosterone administration should be monitored with yearly digital examinations and prostate-specific antigen measurements.

Bisphosphonate Holidays

Because bisphosphonates accumulate and may have a prolonged residence time in bone (and residual therapeutic effect after stopping), "bisphosphonate holidays" may be considered.

AACE recommends that patients who are initially at very high risk and remain at high risk receive a treatment duration of 10 years for an oral bisphosphonate or 6 years for IV zoledronate.

For patients at very high fracture risk, a non-bisphosphonate treatment (teriparatide) may be offered during the holiday from the bisphosphonate.

For patients at "high fracture risk," a drug holiday can be considered after 5 years of stability on oral bisphosphonates or 3 years of IV zoledronate.

Bisphosphonate Holidays

The optimal duration of a bisphosphonate holiday has not been established.

The rank order for binding affinity for bone is zoledronate > alendronate > risedronate; logic suggests that the holiday might be longest after treatment with zoledronate, shortest after treatment with risedronate, and intermediate after treatment with alendronate.

Monitoring during bisphosphonate holidays are important.

Two recent retrospective studies have suggested that the risk of new clinical fractures is higher in patients on a bisphosphonate holiday, especially if their T-scores ≤ −2.5.

Bisphosphonate Holidays

Consider resuming therapy in patients who experience fracture or show significant BMD loss.

Some experts feel that a rise in bone resorption markers (e.g., CTX or N-terminal telopeptide type-I collagen) to pretreatment levels might be a signal that the holiday should be over, but this is debatable and may not apply to patients with osteoporosis who had low bone resorption markers before treatment was started.

Table 17
Drugs Approved by the U.S. Food and Drug Administration for Prevention and Treatment of Postmenopausal Osteoporosis[a]

	Postmenopausal Osteoporosis	
Drug	**Prevention**	**Treatment**
Abaloparatide (Tymlos)	—	80 µg SQ daily
Alendronate (Fosamax)	5 mg PO daily 35 mg PO weekly	10 mg PO daily 70 mg PO weekly[b] 70 mg + D[c]
Calcitonin (Miacalcin, Fortical)	—	200 IU intranasally once daily, or 100 IU SQ qod
Denosumab (Prolia)	—	60 mg SQ every 6 months
Estrogen (multiple formulations; estrogen-bazodoxifene)	Multiple regimens	—
Ibandronate (Boniva, generic form)	2.5 mg PO daily 150 mg PO monthly	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 months
Raloxifene (Evista)	60 mg PO daily	60 mg PO daily
Risedronate (Actonel, Atelvia, generic form)[d]	5 mg PO daily 35 mg PO weekly 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 150 mg PO monthly
Romosozumab (Evenity) Teriparatide (Forteo)	— —	210 mg SQ monthly 20 µg SQ daily
Zoledronate (Reclast, generic infusion form)	5 mg IV every 2nd year	5 mg IV once yearly

Abbreviations: IV = intravenously; PO = orally; qod = every other day; SQ = subcutaneously.
[a]Please review the package inserts for specific prescribing information.
[b]Fosamax 70 mg is available as both a tablet and a unit dose liquid. Alendronate (generic Fosamax) is available.
[c]Fosamax Plus D is a tablet containing 70 mg of alendronate and 2,800 IU or 5,600 IU of vitamin D for weekly administration.
[d]Risedronate 150 mg once monthly tablet is available.

References:

1. Juliet E. Compston. Extensive expertise in endocrinology: advances in the management of glucocorticoid-induced osteoporosis. European Journal of Endocrinology, 2023, 188, R46–R55.
2. Mary Beth Humphrey, Linda Russell, Maria I. Danila, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. 2023 American College of Rheumatology. Arthritis & Rheumatology Vol. 75, No. 12, December 2023, pp 2088–2102.
3. Pauline M. Camacho, MD, FACE; Steven M. Petak, MD, JD, FACP, FCLM, MACE, CCD; Neil Binkley, MD; et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/ AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS— 2020 UPDATE. ENDOCRINE PRACTICE Vol 26 (Suppl 1) May 2020.
4. Feingold KR, Anawalt B, Blackman MR, et al. An Overview of Glucocorticoid-Induced Osteoporosis. Endotext, March 19, 2022

THANK YOU
FOR
YOUR ATTENTION

Abbreviations:

MOF = major osteoporotic fracture

BMD = bone mineral density

FRAX = Fracture Risk Assessment Tool

TBS = Trabecular bone score

VFA = Vertebral Fracture Assessment

BP = bisphosphonate

DEN = Denosumab

PTH = parathyroid hormone

PTHrP = PTH-related protein

TER = Teriparatide

ABL = Abaloparatide

ROM = Romosozumab

RAL = Raloxifene