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2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

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Objective. The objective is to update recommendations for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP) for patients with rheumatic or nonrheumatic conditions receiving >3 months treatment with glucocorticoids (GCs) ≥2.5 mg daily.

Methods. An updated systematic literature review was performed for clinical questions on nonpharmacologic, pharmacologic treatments, discontinuation of medications, and sequential therapy. Grading of Recommendations Assessment, Development and Evaluation approach was used to rate the certainty of evidence. A Voting Panel achieved ≥70% consensus on the direction (for or against) and strength (strong or conditional) of recommendations.

Results. For adults beginning or continuing >3 months of GC treatment, we strongly recommend as soon as possible after initiation of GCs, initial assessment of fracture risks with clinical fracture assessment, bone mineral density with vertebral fracture assessment or spinal x-ray, and Fracture Risk Assessment Tool if ≥40 years old. For adults at medium, high, or very high fracture risk, we strongly recommend pharmacologic treatment. Choice of oral or intravenous bisphosphonates, denosumab, or parathyroid hormone analogs should be made by shared decision-making. Anabolic agents are conditionally recommended as initial therapy for those with high and very high fracture risk. Recommendations are made for special populations, including children, people with organ transplants, people who may become pregnant, and people receiving very high-dose GC treatment. New recommendations for both discontinuation of osteoporosis therapy and sequential therapies are included.

Conclusion. This guideline provides direction for clinicians and patients making treatment decisions for management of GIOP. These recommendations should not be used to limit or deny access to therapies.

INTRODUCTION

Glucocorticoids (GCs) remain a common therapeutic modality for patients with a variety of diseases. Prevention of GC-induced bone loss and fractures has been a focus of the American College of Rheumatology (ACR) for many years because patients with osteoporotic fractures have increased risk of morbidity and mortality (1–4). It is estimated that 1% of the US population is treated with long-term GCs (5). GC doses ≥2.5 mg/day increase fracture at both the spine and hip, and GC <2.5 mg/day increase the risk of spinal fractures (6). Both high daily (≥30 mg/day) and high cumulative (≥5 g/year) doses of GCs further increase the risk of fragility fractures, with peak incidence at 12 months (7–11). The highest rate of bone loss occurs within the first 3 to 6 months of GC treatment, due to early osteoclast activation followed by decreased osteoblast proliferation and increased apoptosis of osteoblasts and osteocytes (12). In children, GCs adversely affect bone strength, growth, and peak bone mass, with increased fracture risk (11,13–15). However, children (16) and young adults often regain lost bone when GCs are discontinued (17).

Despite increasing treatment options to prevent and treat glucocorticoid-induced osteoporosis (GIOP), many GC-treated patients are not evaluated or treated, resulting in preventable fractures (18,19). Risk calculators provide estimates of the 10-year risk of major osteoporotic fractures (MOFs) and hip fractures among individuals ≥40 years of age, with adjustment for GC doses >7.5 mg/day or <2.5 mg/day in some calculators (20–22). Of note, the Fracture Risk Assessment Tool (FRAX) is not validated for adults <40 years. These calculators underestimate fracture risk for patients on very high doses of GC therapy (eg, ≥ 30 mg/day) and do not adequately include frailty, multiple fractures, or fall history.

The ACR first published recommendations for prevention and treatment of GIOP in 1996 (23). ACR updated these guidelines in 2001, 2010, and 2017 as new techniques for assessing fracture risk, risk factors, and therapies became available (23–26). This guideline updated the literature search from April 23, 2016, through January 24, 2022, and it includes two medications newly US Food and Drug Administration (FDA)-approved for OP treatment since the 2017 guideline.

METHODS

This guideline follows the ACR guideline development process and ACR policy guiding management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), including use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (27,28) and adherence to Appraisal of Guidelines for Research and Evaluation (AGREE) criteria (29). Supplementary Appendix 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42646/abstract, includes a detailed description of the methods. Briefly, the Core Leadership Team (MBH, LR, MID, HAF, GG, SU) reviewed the 2017 ACR GIOP guideline clinical Patient/Intervention/Comparator/Outcomes (PICO) questions, modified and drafted new PICO questions in topic areas not covered previously (eg, abaloparatide, romosozumab, combination and sequential therapy) (see Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/art.42646/abstract). The Literature Review Team updated the systematic literature reviews for each of the previous PICO questions and/or performed new ones for new questions, graded the quality of evidence (high, moderate, low, very low), and produced the evidence report (see Supplementary Appendix 3, http://onlinelibrary.wiley.com/doi/10.1002/art.42646/abstract). The resulting evidence was reviewed, and recommendations were formulated and voted on by an expert Voting Panel. A virtual Patient Panel of three patients with GIOP and one parent of a child treated with GCs reviewed the evidence with a co-principal investigator (LR) and provided patient perspectives and preferences for consideration by the Voting Panel. Voting Panel consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) of each recommendation. Rosters of the Core Leadership

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Team, Literature Review Team, Voting Panel, and Patient Panel are included in Supplementary Appendix 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42646/abstract. This study did not involve human subjects and, therefore, approval from Human Studies Committees was not required.

RECOMMENDATIONS

How to interpret the recommendations

According to GRADE, a strong recommendation is usually supported by moderate- to high-certainty evidence, including randomized control trials, the recommended course of action would apply to all or almost all patients, and there is high confidence that the benefits of the intervention clearly outweigh the harms (or vice versa). In rare instances, a strong recommendation or best practices may be made with very-low certainty evidence if the recommendation is considered benign, low cost, and without harms.

A conditional recommendation is supported by lower certainty evidence, has uncertainty regarding the balance of benefits and harms, is sensitive to individual patient preferences, or has costs expected to impact the decision. Thus, conditional recommendations warrant shared decision-making with the patient. Notably, most evidence reviewed in this guideline is downgraded for indirectness because 1) identified studies in GIOP rely on a surrogate fracture risk marker, bone mineral density (BMD), because they were not powered for fracture outcomes and 2) available fracture data were exclusively or predominantly from general osteoporosis (OP) studies.

Key recommendations

1. As soon as possible after initiation of ≥2.5 mg/day GC treatment for >3 months, screening for fracture risk in patients ≥40 years of age should be assessed by using FRAX and by performing BMD using dual-energy x-ray absorptiometry (DXA) with vertebral fracture assessment (VFA) testing or spinal x-rays. BMD with VFA testing or spinal x-ray is advised in patients <40 years, as FRAX is not validated in this population.
2. Adequate age-appropriate dietary and supplemental intake of calcium and vitamin D, weight-bearing exercise, and avoidance of smoking and excessive alcohol intake is encouraged for all patients receiving GCs.
3. All adult patients with medium, high, or very high fracture risk should be offered OP therapy.
4. Oral bisphosphonates (BP) are strongly recommended over no treatment in high or very high fracture risk adults.
5. For adults with very high fracture risk, anabolic agents (parathyroid hormone [PTH] and PTH-related protein [PTHrP]) are conditionally recommended over antiresorptive agents (BP or denosumab [DEN]).
6. In adults ≥40 years of age at high risk of fracture, DEN or PTH/PTHrP are conditionally recommended over BP.
7. In adults at moderate risk of fracture, oral or intravenous (IV) BP, DEN, and PTH/PTHrP are conditionally recommended.
8. Include in decision-making that sequential OP treatment is recommended to prevent rebound bone loss and vertebral fractures after discontinuation of DEN, romosozumab, and PTH/PTHrP.

Table 1 presents the definitions of terms used in the recommendations and a synopsis of the age-based recommendations for fracture risk assessment and treatments.

Recommendations for fracture risk assessment (Figure 1)

For all adults (≥18 years old) initiating or continuing GC therapy ≥2.5 mg/day for >3 months, we strongly recommended initial clinical fracture risk assessment including symptomatic and asymptomatic fracture history, FRAX (age ≥40 only), and BMD with VFA or spine x-rays over no assessment (PICO 8.1–8.4).

These strong recommendations are based on good clinical practice and the need for clinicians to risk stratify patients beginning or continuing GC therapy, despite the low certainty of the evidence. Initial assessment should occur as soon as possible within 6 months of GC therapy initiation. Clinical fracture risk assessment includes dose, duration, and pattern of GC use, alcohol use, smoking history, hypogonadism, history of prior fractures (traumatic, fragility, asymptomatic), low body weight, significant weight loss, parental history of hip fracture, fall history, thyroid disease, hyperparathyroidism, rheumatoid arthritis, malabsorption, chronic liver disease, and inflammatory bowel disease (Figure 1). BMD with VFA or spinal x-rays are strongly recommended, and, for adults ≥40 years old, FRAX analysis is also recommended. (Figure 1). If prednisone dose is >7.5 mg daily, FRAX GC correction is recommended (Table 1, Figure 1) (21); however, even this adjustment may not correct for very high doses of GC (≥30 mg/day) (30). Additionally, FRAX does not incorporate falls, number or timing of fractures, or frailty that may put a person at higher risk of fracture. BMD assessment provides a strong predictor of fracture risk and serves as a baseline for reassessment because FRAX analysis is not validated for fracture risk reassessment during OP therapy. Trabecular bone score (TBS) provides a more sensitive measure of therapeutic responses to OP treatment (31). BMD measurement is strongly recommended for patients <40 years on GCs ≥2.5 mg/day with one or more osteoporotic risk factors. In this age group, z-scores ≤ –2.0 indicates low bone mass for age. Unlike *t*-scores, z-scores do not provide an

Table 1. Definitions of selected terms used in the recommendations and upgraded position statements for GIOP*

Term	Adults ≥40 years of age	Adults <40 years of age
MOF	Nontraumatic or pathological fractures of the spine, hip, wrist, or humerus	Nontraumatic or pathological fractures of the spine, hip, wrist, or humerus
Clinical fracture risk assessment	History of GC use, evaluation for falls, fractures, frailty, secondary causes of OP, FRAX with GC adjustment, BMD with VFA or spinal x-ray	History of GC use, evaluation for falls, fractures, frailty, secondary causes of OP, BMD with VFA or spinal x-ray (FRAX not validated at age <40 years)
Follow-up risk assessment during GC treatment	BMD with VFA or spinal x-ray every 1–2 years during OP therapy; BMD with VFA or spinal x-ray every 1–2 years after OP therapy is discontinued	BMD with VFA or spinal x-ray every 1–2 years during treatment; BMD with VFA or spinal x-ray every 1–2 years after OP therapy is discontinued
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[†]	Not applicable as FRAX is not validated in this age group
Very high fracture 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/y	Prior fracture(s) OR GC ≥30 mg/day OR cumulative ≥5 g/y
High fracture 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%	–
Moderate fracture risk	FRAX (GC-Adjusted) 10-year risk of MOF ≥10 and <20%, hip >1 and <3% OR BMD *t*-score between −1 and −2.4	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)
Low fracture risk	FRAX (GC-Adjusted) 10-year risk of MOF <10%, hip <1 %, BMD >−1.0	None of the above risk factors other than GC treatment
Recommended treatment strategy	**Adults ≥40 years at moderate, high, or very high risk of fracture**	**Adults <40 years at moderate or very high risk of fracture**
Calcium and vitamin D	Optimized intake of dietary and supplemental calcium and vitamin D based on age-appropriate US Recommended Dietary Allowances	
BP (Alendronate [oral], Risedronate [oral]; Ibandronate [oral/ IV], Zoledronic acid [IV])	We strongly recommend OP treatment for those at moderate, high, or very high risk of fracture. We **s**trongly recommend oral BP over no treatment in high and very high fracture risk due to fracture reduction in GIOP. We conditionally recommend IV BP, ROM, RAL over no treatment in high and very high risk of fracture. In moderate risk, we conditionally recommend BP, DEN, or PTH/PTHrP in no preferred order among these agents.	We conditionally recommend treatment for those at moderate or very high risk of fracture with oral or IV BP,[‡] PTH/PTHrP,[§] or DEN[§#]
PTH/PTHrP Agonists (TER, ABL, Anti-RANKL, DEN)	We conditionally recommend PTH/PTHrP over anti-resorptives in patients at very high risk of fracture. We conditionally recommend DEN[§#] or PTH/PTHrP over oral and IV BP in high risk of fracture. In moderate risk, we conditionally recommend BP, DEN, or PTH/PTHrP in no preferred order among these agents.	–
Selective estrogen receptor modifier (RAL), Anti-sclerostin (ROM)	We conditionally recommend IV BP, ROM, RAL over no treatment in high and very high risk of fracture. Except in patients intolerant of other agents, we conditionally recommend against RAL due to harms of VTE and fatal stroke or ROM due to uncertain harms with increased myocardial infarction, stroke and death.	We conditionally recommended against RAL due to harms of VTE and fatal stroke or ROM due to uncertain harms including increased myocardial infarction, stroke and death

* ABL = Abaloparatide; BMD = bone mineral density; BP = bisphosphonate; DEN = Denosumab; FRAX = Fracture Risk Assessment Tool; GC = glucocorticoid; MOF = major osteoporotic fracture; PTH = parathyroid hormone; PTHrP = PTH-related protein; RAL = Raloxifene; RANKL = Receptor activator of NF-κβ-Ligand; ROM = Romosozumab; TER = Teriparatide; VTE = venous thromboembolism.
† FRAX GC correction example: if hip fracture risk is 2.0% multiply by 1.2 for adjusted risk = 2.4%.
‡ Use with caution in patients who may become pregnant due higher potency and longer half-life in fetal bones.
§ Avoid in young adults with open growth plates.
# Use with caution in patients of child-bearing potential due to potential fetal harm. Avoid pregnancy for 5 months after last dose.

estimate of fracture risk because adults <40 years have low fracture risk at baseline.

This guideline did not include specific PICO questions concerning DXA or spinal imaging in children beginning or continuing chronic GC therapy, but the Voting Panel discussed this population. Despite uncertainty about initial DXA or screening spine radiographs, we recommend spine x-ray in children with back pain (32). However, the totality of a child's clinical presentation

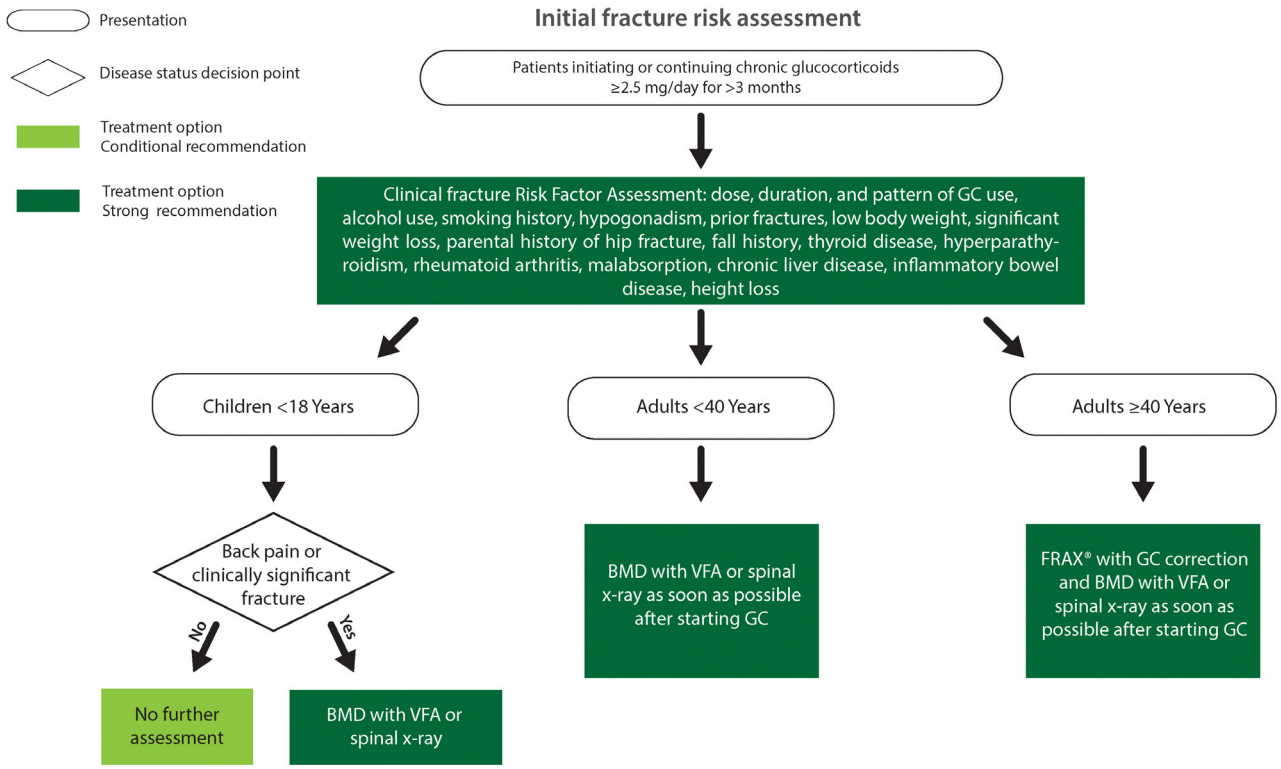


Figure 1. Initial fracture risk assessment. GC = glucocorticoid; MOF = major osteoporotic fracture; VFA = vertebral fracture assessment.

(eg, age at diagnosis, growth, body mass index [BMI], disease severity, GC dosing, BMD, symptomatic or asymptomatic vertebral compression fractures) should be taken into account when considering assessment for OP therapy (16).

As in prior guidelines, we used risk categories of low, moderate, and high using DXA and/or FRAX assessments (see Table 1). Similar to other recent OP guidelines (33-35) (United Kingdom National Osteoporosis Guideline Group [NOGG], American Association of Clinical Endocrinologists [AACE], Brazilian Society of Endocrinology and Metabolism [SBEM]), we further identified a very high risk group with prior osteoporotic fractures, very low BMDs, very high FRAX risks, or high daily dose or high cumulative doses of glucocorticoids.

Recommendations for reassessment of fracture risk (Figure 2)

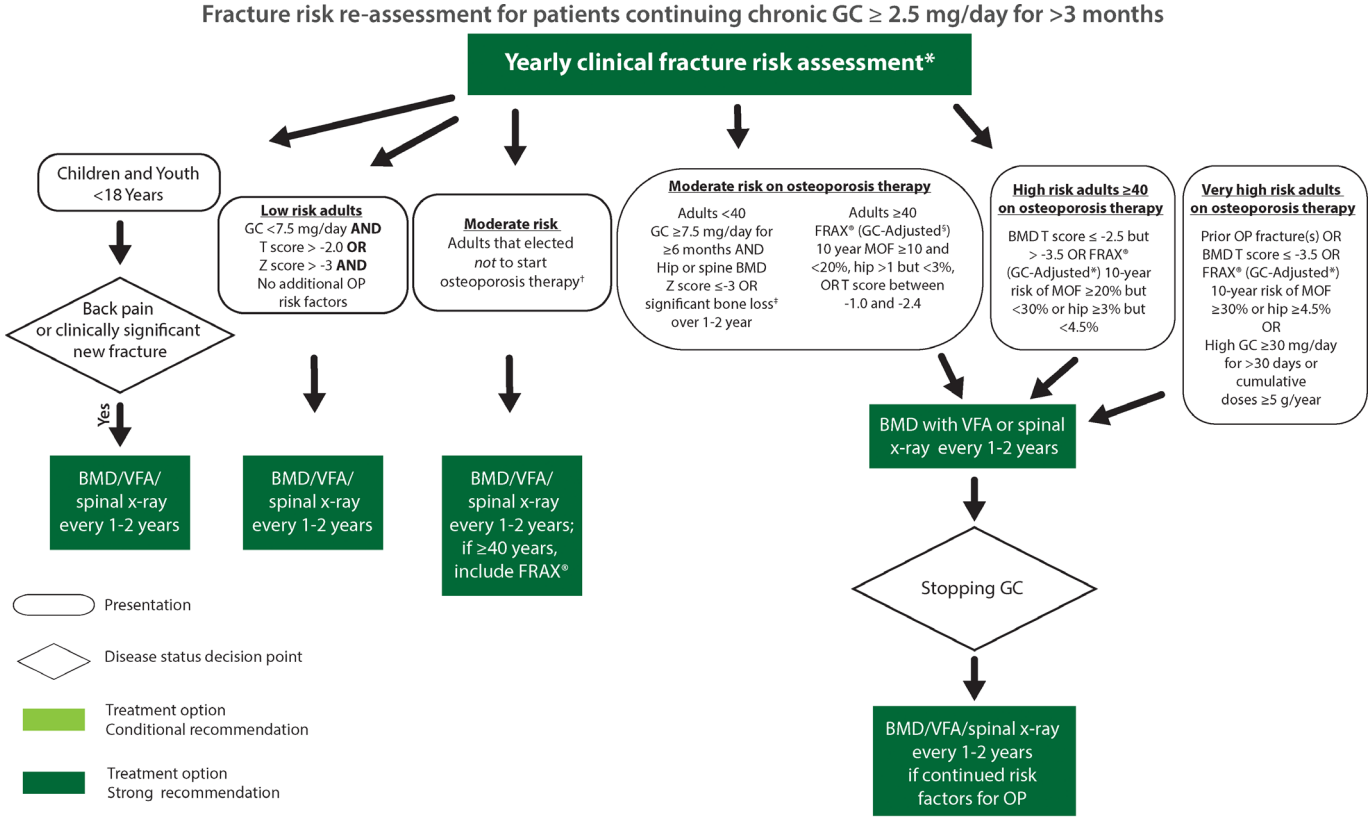
For adults continuing chronic GC ≥2.5 mg/day but <7.5 mg/day and assessed as low fracture risk, who were not recommended to start therapy, or moderate fracture risk who chose not to start OP therapy (except calcium and vitamin D), we strongly recommend fracture risk reassessment every 1 to 2 years (PICO 9.1–9.4).

Despite the low certainty of the evidence, this is a strong recommendation as good clinical practice. Fracture risk reassessment includes 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.

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 over no risk reassessment (PICO 9.5–9.12).

Despite the low certainty of the evidence, this is a strong recommendation as good clinical practice. 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 (PICO 12.1–12.6).



OP = osteoporosis; GC = glucocorticoids; FRAX® = Fracture risk assessment tool can only be used in adults ≥40 years; BMD = bone mineral density testing; *Clinical fracture risk 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; †Moderate risk adults should be offered therapy but may choose not to be treated; ‡ > least significant decline according to DXA machine (typically 3-5%); §FRAX® GC correction for GC ≥7.5 mg/day example: if hip fracture risk is 2.0% multiply by 1.2 for adjusted risk = 2.4%

Figure 2. Fracture risk re-assessment for patients continuing chronic GC ≥2.5 mg/day for >3 months. DXA = dual-energy x-ray absorptiometry; MOF = major osteoporotic fracture; VFA = vertebral fracture assessment.

Recommendations for initial treatment (Table 2, Figure 3)

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 (PICO 1.1–1.3, 2.1–2.3, 3.1–3.3, 4.1–4.3, 5.1–5.3, 6.1–6.3, 7.1–7.4).

The evidence for calcium and vitamin D supplementation for fracture reduction in GIOP is low to very low. Dietary and supplemented elemental calcium intake of up to 1,000 to 1,200 mg daily is recommended for adults (36) and between 1,000 and 1,300 mg daily based on age of the child. Serum vitamin D levels should be monitored, and vitamin D supplemented to maintain serum vitamin D 25(OH)D levels ≥30 to 50 ng/mL; 600 to 800 IU daily or more is typically required. Lifestyle modifications include smoking cessation, limiting alcohol to ≤2 servings a day, eating a balanced diet, maintaining weight in the recommended range, and performing regular weight-bearing or resistance training exercises. All subsequent recommendations refer to adults and children beginning or continuing chronic GCs at a dose of ≥2.5 mg/day for >3 months and assume the use of calcium, vitamin D, and lifestyle modifications.

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 (PICO 1).

For adults ≥40 years with very high fracture risk, we conditionally recommend PTH/PTHrP over anti-resorptives (BP or DEN) (PICO 1.13c, 1.14c, 1.15c, 1.18c, 1.19c, 1.20c).

Compared to alendronate, teriparatide increased lumbar and hip BMD and decreased vertebral but not nonvertebral fractures at 36 months in GIOP (37,38). Bone anabolic effect is blunted when treatment follows anti-resorptive therapy.

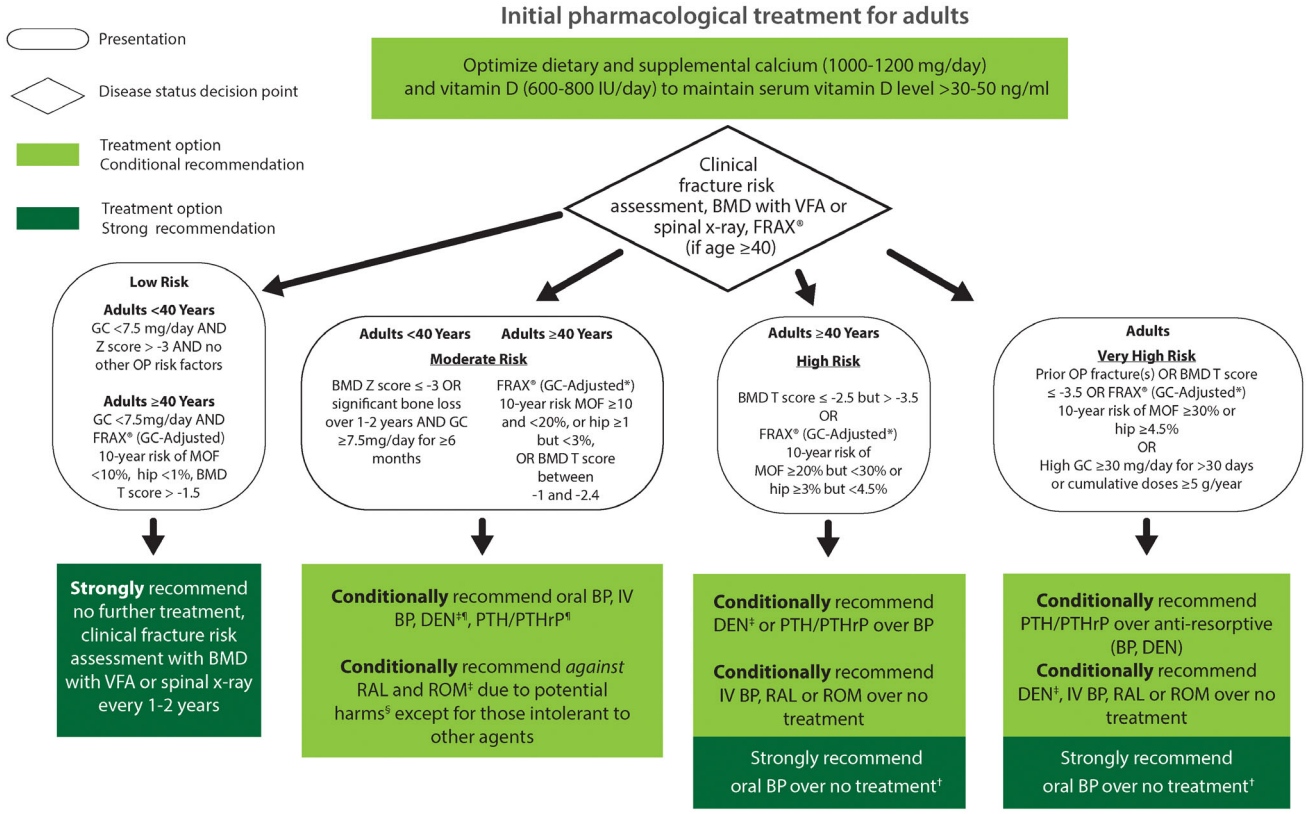
For adults ≥40 years with high or very high fracture risk, we strongly recommended oral BP (16) over no treatment (PICO 1).

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

Table 2. Recommendations for initial treatment for prevention of GIOP in adults beginning long-term GC therapy*

Recommendations for patients taking prednisone ≥2.5 mg/day for >3 months	Certainty of evidence	PICO evidence report basis	Evidence Report, pp
For adults and children beginning or continuing chronic GC treatment at low, moderate, high, or very high risk of fracture, we conditionally recommend optimizing dietary and supplemental calcium and vitamin D in addition to lifestyle modifications	Low or very low	1.1a,b,c–1.3a,b,c, 2.1–2.3, 7.16–7.26	6–8, 47–48, 63–65, 141–144,148–151
In adults ≥40 years†			
For adults ≥40 years with high or very high fracture risk, we strongly recommend OP therapy over no treatment. Agents to use include oral BP,‡ IV BP,§ PTH/PTHrP,§ DEN,§ RAL, or ROM.	Low or very low	1.4c–1.28c	6–50
For adults ≥40 years with very high fracture risk, we conditionally recommend PTH/PTHrP over anti-resorptive (DEN, BP) treatment.	Low	1.13c–1.20c	49–50
For adults ≥40 years with high fracture risk, we conditionally recommend PTH/PTHrP or DEN over BP treatment.	Low	1.13c–1.20c	49–50
For adults ≥40 years with high or very high fracture risk, we strongly recommend oral BP over no treatment.	Low	1.4c	8–18
For adults ≥40 years with high or very high fracture risk, we conditionally recommend using ROM or RAL in patients intolerant of other agents.	Very low	1.16c, 1.21c, 1.28c	50
For adults ≥40 years with high or very high fracture risk, we conditionally recommend against using two different OP medications.	Very low	1.29–1.35	53–62
For adults ≥40 years with moderate fracture risk, we conditionally recommend against ROM except for in patients intolerant of other agents, due to risk of myocardial infarction, stroke, or death.	Very low	1.12b, 1.16b, 1.17b, 1.21b–1.25b, 1.28b	40–41, 44–47
For adults ≥40 years with low fracture risk, we strongly recommend against OP medications due to known risk of harms and no evidence of benefit.	Very low	4.4a–4.13a	91–101
Adults receiving high-dose GC (initial dose ≥30 mg/day for >30 days or cumulative dose ≥5 g in 1 year)			
We conditionally recommend treating with PTH/PTHrP over anti-resorptives.	Low	6.1b–6.19a	120–141
Oral BP are strongly recommended over no treatment.	Low	6.1b–6.19a	120–141
IV BP and DEN are conditionally recommended over no treatment.	Low	6.1b–6.19a	120–141
RAL and ROM are conditionally recommended in those intolerant of other agents.	Low	6.1b–6.19a	120–141
In adults <40 years†			
Adults <40 years with moderate fracture risk, we conditionally recommend oral or IV BP,¶ DEN,¶ or PTH/PTHrP therapy.	Low or very low	2.4–2.22, 3.4–3.17	65–76, 79–84
Adults <40 years with moderate fracture risk, we conditionally recommend against using ROM due to risk of myocardial infarction, stroke, or death.	Very low	2.9, 3.9	70, 87
For adults with solid organ transplants, glomerular filtration rate ≥35 mL/min, and no evidence of CKD-MBD# or hyperparathyroidism			
We conditionally recommend expert evaluation for CKD-MBD in renal transplant recipients.	Low	5.1–5.26	103–118
We conditionally recommend treatment with oral or IV BP, DEN, PTH/PTHrP, or RAL based on individual patient factors.	Low	5.1–5.26	103–118
We conditionally recommend against using ROM due to risk of myocardial infarction, stroke, or death.	Very low	5.9	112
Children ages 4–17 years treated with GCs for >3 months (low and moderate risk)			
We conditionally recommend optimization of dietary and supplementation of calcium and vitamin D as recommended by the US RDA depending on the age of the child.	Very low	7.1a–7.4a	141–144
We conditionally recommend against starting oral or IV BP due to low risk of OP fractures in this age group.	Very low	7.5a	144
Children ages 4-17 years with an osteoporotic fracture who are continuing treatment with GCs at a dose of ≥0.1 mg/kg/day for >3 months (high risk)			
We conditionally recommend treating with an oral or IV BP.	Very low	7.1b–7.2b	148–153

* BP = bisphosphonate; CKD-MBD = chronic kidney disease–mineral and bone disorder; DEN = denosumab; GC = glucocorticoid; GIOP = GC-induced OP; IV = intravenous; OP = osteoporosis; PICO = Patients, Intervention, Comparison, Outcome; PTH/PTHrP = parathyroid hormone/parathyroid hormone–related protein; RAL = raloxifene; RDA = Recommended Dietary Allowances; ROM = romosozumab.
† In addition to calcium, vitamin D, and lifestyle modifications.
‡ Strong recommendation based on fracture data.
§ Conditional due to a lack of fracture data.
¶ Only for patients who are not planning on pregnancy during the OP treatment period or are using effective birth control if sexually active.
# Includes osteomalacia, adynamic bone disease, osteitis fibrosa cystica, mixed uremic osteodystrophy.



FRAX® = https//www.shef.ac.uk/FRAX/Tool.jsp; MOF= major osteoporotic fracture; *FRAX® GC correction for GC ≥7.5 mg/day example: if hip fracture risk is 2.0% multiply by 1.2 for adjusted risk = 2.4%, BP = bisphosphonate, IV = intravenous, PO = oral, PTH/PTHrP = parathyroid hormone/ parathyroid hormone related protein, DEN = denosumab, RAL = raloxifene, ROM = romosozumab, †Based on fracture data in GIOP, ‡Women who may become pregnant need birth control and avoid pregnancy until >5 months after last dose; §RAL(PE, DVT, fatal stroke); ROM (myocardial infarction, stroke and death; conditionally recommend RAL/ROM use in the highest risk patients unable to tolerate other agents; ¶Use with caution in persons with open growth plates

Figure 3. Initial pharmacological treatment for adults. BMD = bone mineral density; DVT = deep vein thrombosis; GC = glucocorticoid; GIOP = GC-induced OP; PE = pulmonary embolism; VFA = vertebral fracture assessment.

and vitamin D alone in GIOP (evidence report, Appendix S3, page 16).

For adults ≥40 years with high fracture risk, we conditionally recommend PTH/PTHrP or DEN over BP (PICO 1.4c–1.28.c).

For adults ≥40 years with high fracture risk, we conditionally recommend IV or oral BP, PTH/PTHrP, or DEN over Raloxifene (RAL) or Romosozumab (ROM) (PICO 1.4c–1.28.c).

High-certainty evidence indicates that oral BP prevents vertebral fractures in GIOP (39) and warrants a strong recommendation for use here. Compared to oral BP, PTH is superior at increasing BMD 24 and 36 months and prevented vertebral fractures at 36 months (37). In the very high risk group, providers may recommend PTH/PTHrP as initial treatment because anabolism is blunted in patients previously treated with BP (40). IV BP and DEN GIOP trials have not been powered to detect reductions of GIOP fractures and instead use a surrogate endpoint of BMD changes (41–43). However, the relationship between increases in BMD and a decrease in vertebral fractures is inconsistent and may account for only 25% of overall reduction in fracture risk (44). Evidence for fracture reduction of PTHrP, DEN, RAL, and ROM therapies have been demonstrated in general OP but not GIOP, leading to downgrading the evidence to low or very low certainty evidence. However, DEN and PTH show superior BMD gains in GIOP compared to BP and may be preferred in patients with high risk.

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 must be followed by a BP beginning at 6 to 7 months after the last DEN dose to prevent rapidly progressive vertebral fractures. Additionally, IV BP, DEN, and ROM have increased risk of atypical femur fractures and osteonecrosis of the jaw compared to oral BP (45). 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 (46,47). 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 (48).

In adults ≥40 years with high and very high fracture risk, we conditionally recommend against using multiple OP therapies at the same time (PICO 1.29–1.35).

Very low level evidence does not support using combination therapy (eg, PTH/PTHrP and DEN, PTH/PTHrP and BP) in GIOP. In patients with postmenopausal OP, studies have shown synergistic increases in BMD with combination of PTH with IV BP (49), PTH with RAL (50), and PTH and DEN (51). However, based on the added cost, the possibility of greater side effects, and the lack of fracture evidence, combination therapy is not currently recommended.

For all adults with moderate fracture risk, we conditionally recommend oral or IV BP, PTH/PTHrP, or DEN over no treatment (PICO 1.4b–1.28.b, 2.4b,c–2.17b,c).

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 life-threatening harms, including thrombosis, fatal stroke, major cardiovascular events, and death (PICO 1.6b, 1.10b, 1.12b, 1.16b, 1.17b, 1.21b, 1.22b, 1.23b, 1.24b, 1.25b, 1.28b, 2.9, 2.14, 2.18, 2.21).

Multiple studies have shown that 12 months of ROM followed by an anti-resorptive agent (BP or DEN) for 12 month prevents fractures in patients with postmenopausal OP when compared to anti-resorptive agent only (52–54). There is uncertainty concerning the cardiovascular risk, including myocardial infarction, stroke, and death related to ROM (47,55). However, until longer-term pharmacovigilance data become available, 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. For RAL, a meta-analysis of nine trials (24,523 postmenopausal women) found that raloxifene was associated with an increased risk of DVT and PE (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.1–2.1 and OR 1.9, 95% CI 1.0–3.5, respectively) (56). In the Raloxifene use for the heart (RUTH) trial, RAL were not associated with overall stroke risk but was associated with fatal stroke (59 vs 39 events, hazard ratio [HR] 1.49, 95% CI 1.0–2.2, absolute risk increase of 0.7 per 1000 woman-years) compared with placebo (46).

In adults with low fracture risk, we strongly recommend against adding oral or IV BP, PTH/PTHrP, RAL, DEN, or ROM (PICO 1.4a–1.28a).

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 (17,57). This strong recommendation is based on low certainty evidence of anti-fracture benefit in this low fracture risk group, coupled with clear potential harms such as osteonecrosis of the jaw (BP, DEN, ROM), atypical femur fractures (BP, DEN, ROM), PE, DVT, and fatal stroke (RAL), myocardial infarction, stroke, and death (ROM), or requirements for sequential therapy (PTH/PTHrP, DEN, ROM). Adults >40 years on low-dose steroids that meet low risk criteria have uncertain benefit from osteoporosis therapy.

Recommendations for special populations of patients beginning long-term GC therapy at very high risk for fracture (Table 2)

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.

The relative risk for vertebral fracture was 14 and for hip fractures was 3 with a dose of ≥30 mg per day and ≥ 5 g of cumulative use (10).

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 (PICO 6.4a,b–6.24a,b).

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.

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 (PICO 2).

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 (58). Risedronate and ibandronate have shorter skeletal half-lives among BP and may be preferred in this setting. DEN and PTH/PTHrP may also be used if growth plates have closed. However, DEN may cause fetal harm and is contraindicated in pregnancy. Avoid pregnancy for 5 months after the last dose of DEN.

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 (PICO 5.4-5.26).

In this solid organ transplant population, we conditionally recommend against using ROM due to potential harms in this population (PICO 5.9, 5.21, 5.16).

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. The overall certainty of evidence for treatment in this population is low, and numerous potentially influential individual patient factors need to be weighed when selecting treatment.

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 (59). Bone-specific alkaline phosphatase, intact PTH, and bone biopsy may exclude renal osteodystrophy. BP should generally not be used if eGFR <35 mL/min. 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 (60).

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.

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 (PICO 7.1a–7.5a).

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. (PICO 7.1b-7.2.b)

This conditional recommendation to treat with oral or IV BP to prevent recurrent fractures is based on low-certainty evidence. 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 (61,62). Twelve percent 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 (14). 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). Other OP therapies are understudied in this young age group with open growth plates.

Recommendations for 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 (PICO 10.1–10.9).

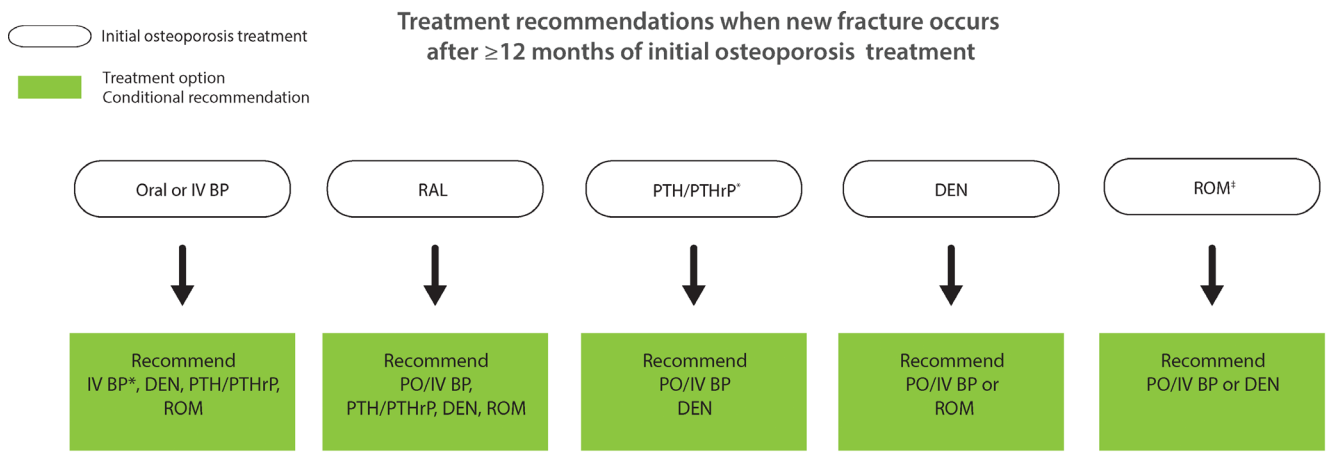
If oral BP is the first OP therapy and suboptimal adherence or poor absorption is suspected, based on low certainty evidence, we conditionally recommend treatment with IV BP, DEN, ROM, or PTH/PTHrP. Of note, use of PTH/PTHrP after long-term BP treatment has blunted anabolic response but still increases 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 (63–65); however, PTH/PTHrP followed by DEN leads to continued BMD increases (66,67) (Figure 4).

Recommendations for treatment when GC are discontinued (Figure 5)

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 (Figure 5**) (PICO 11.1, 13.1–13.4).**

This recommendation is based on low-certainty evidence and on the balance of benefits and harms of continued treatment with OP medication. 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 (68–70). Discontinuation of DEN can be associated with vertebral fractures that may be averted if a BP is started 6 to 7 months after the last DEN administration (41,42). Significant bone loss may occur after discontinuation of PTH/PTHrP, although anti-fracture efficacy may persist for 18 months; therefore, anti-resorptive therapy is recommended. ROM can be followed by DEN or BP (71).

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 (PICO 13.5–13.6).

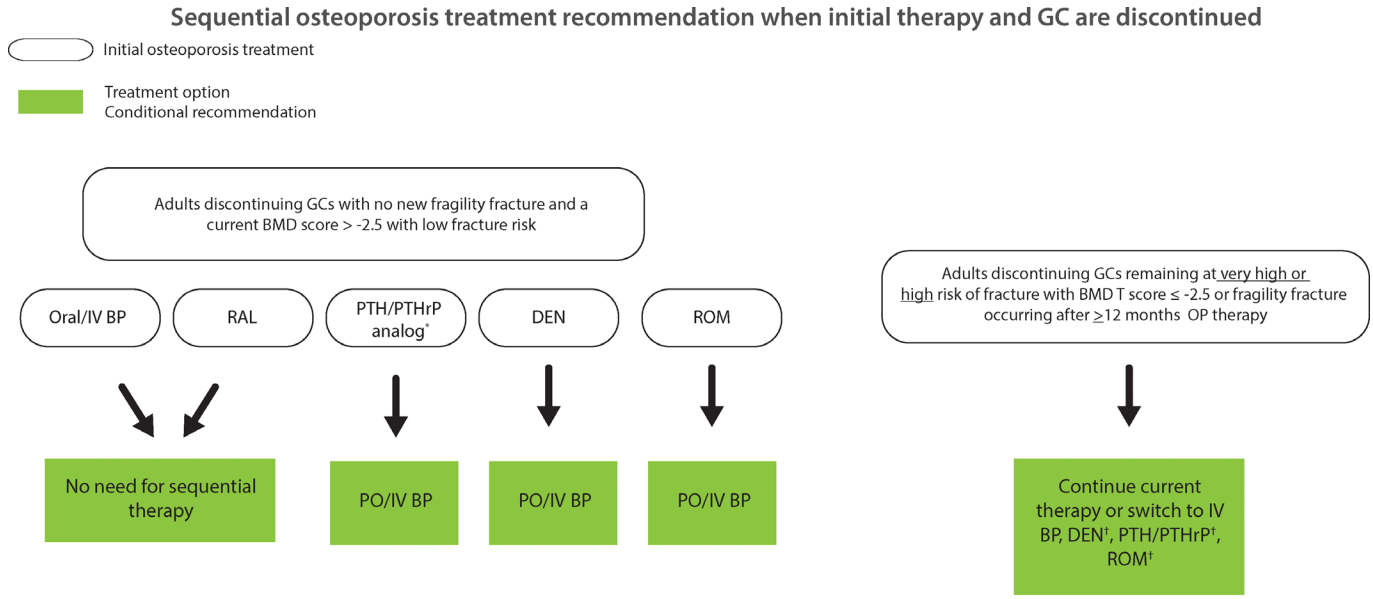


BP = bisphosphonate, IV = intravenous, PO = oral, DEN = denosumab, ROM = romosozumab, PTH = parathyroid hormone, PTHrP = PTH related peptide, RAL = raloxifene, OP = osteoporosis. BMD = bone mineral density, *If oral BP absorption or adherence a concern, †Bone loss may be gradual and anti-fracture efficacy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

Figure 4. Treatment recommendations when new fracture occurs after ≥12 months of initial osteoporosis treatment.

For adults ≥40 years continuing chronic GC who discontinue DEN, we strongly recommend starting an anti-resorptive over not starting OP medication (PICO 13.1, 13.3, 13.5).

DEN remains effective at longer than 10 years in patients with postmenopausal OP. However, discontinuation of DEN after two or more doses has been 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 9 months after the last dose of DEN, BP or ROM therapy is recommended (41,42). 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



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

Figure 5. Sequential osteoporosis treatment recommendation when initial therapy and glucocorticoids (GCs) are discontinued. BMD = bone mineral density.

(69,71,72). If ROM is used after DEN, then it must be followed with a course of BP.

For adults ≥40 years discontinuing chronic GC treatment who have completed a course of a PTH/PTHrP, we conditionally recommend starting BP over not starting an OP medication (PICO 13.4, 13.6).

Discontinuation of PTH/PTHrP medication may lead to gradual loss of bone gained over 12 to 18 months, which can be prevented by treatment with BP or DEN (73). If DEN is used sequentially after discontinuation of PTH/PTHrP, then a BP should be started at the completion of DEN therapy (Figure 4). Therefore, BP therapy is recommended after discontinuation of PTH/PTHrP.

DISCUSSION

The objective of this updated ACR guideline for the prevention and treatment of GIOP (25) is to aid clinicians who prescribe GC, across all specialties, to best identify GC-treated patients who would benefit from prevention and treatment of GIOP. The overall goal is to reduce the number of fractures and their adverse consequences in this patient population, while minimizing harm due to medications. Fractures, especially hip and vertebral fractures, are associated with increased mortality, and patients frequently do not return to their baseline mobility (2,4,74). This guideline now addresses several new areas compared to the 2017 guideline: 1) Previously only fracture data were considered; with this guideline, both fracture reduction and BMD outcomes were considered because most GIOP studies are not powered for fracture outcomes (however, if fracture outcomes were not available, BMD data were evaluated and evidence downgraded to very low certainty); 2) a very high fracture risk category was added; 3) a preference for anabolic agent as initial OP therapy in very high fracture risk was made; 4) a need for sequential therapy after DEN, ROM, and PTH/PTHrP was made; and 5) we recommended the choice of therapies be based on clinician and patient preferences and comorbidities, rather than rank ordering the available OP therapies.

We risk stratified patients as low, moderate, high or very high risk of fracture based on FRAX 10-year probability and DXA *t*- or z-scores (Table 1). Similar to other organizational postmenopausal OP guidelines (AACE, SBEM, UK, and National Osteoporosis Foundation (NOF)) (33–35), we have now included a very high fracture risk category (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) (Figures 2, 3, and5). These cut points were used to stratify PICO questions and weigh potential benefits versus harms of OP therapy. For prednisone-equivalent doses >7.5 mg/day, a FRAX GC correction is recommended and is achieved by multiplying the risk of MOF by 1.15 and the risk of hip fractures by 1.2. Fracture risk is considered highest for patients treated with very high (≥30 mg/day) or large cumulative GC doses (≥5 g/year) (75).

Risk assessment in children, youths, and adults <40 years is not as clear because these populations have substantially lower fracture risk than older adults. BP treatment for children was recommended only after a diagnosis of pediatric OP, which requires a clinically significant history of vertebral or long bone fractures. For children with a GC-associated fracture who continue to take high-dose GC therapy (>0.1 mg/kg/day), BP therapy is warranted.

For adults ≥40 years, the panel voted to give clinicians the ability to select an OP therapy based on the patient's specific comorbidities and preferences, BMD values, fracture history, and other characteristics, rather than rank ordering the medication recommendations. Fracture prevention data in GIOP is currently limited to oral BP and PTH. Anabolic agents may be the preferred initial therapy for those at very high risk for fracture based on BMD and vertebral fracture prevention superiority compared to anti-resorptives in patients with very high risk postmenopausal OP. Of note, abaloparatide and ROM are not approved in GIOP, and we recognize it may be difficult to access these medications for GIOP.

The panel specifically noted that the potential harms of RAL (venous thromboembolism [VTE] and fatal stroke) and ROM (major myocardial infarction, stroke, and death) would often favor the other available options when possible.

The panel emphasized the need for shared decision-making with patients to ensure they understand that some OP therapies (DEN, PTH/PTHrP, ROM) require another course of anti-resorptive OP therapy to prevent rapid bone loss and vertebral fractures (76,77). Discontinuation of DEN without the addition of anti-resorptive therapy is associated with vertebral fractures occurring as soon as 7 to 9 months after the last dose (76,77). Until the optimal therapy strategy is determined, many experts favor starting BP therapy 6 to 7 months after discontinuation of DEN for at least 1 year (78). Although the use of PTH after DEN causes transient loss of hip BMD, these drugs have been successfully cycled with increases in BMD (41,67). It is important that clinicians, patients, and/or their care partners understand and discuss the need for additional OP therapy after completing DEN, PTH/PTHrP, or ROM therapy.

The use of OP medications in patients after kidney transplant and with CKD was addressed in this guideline. When eGFR <35 mL/min, the risk of **r**enal osteodystrophy is significantly increased, including adynamic bone disease, osteomalacia, osteitis fibrosa cystica, and mixed uremic osteodystrophy. As such, MBD expert evaluation for CKD-MBD is conditionally recommended to exclude these conditions. Once excluded, no dose adjustment is needed when prescribing DEN, PTH/PTHrP, or ROM, but BP should be avoided. Use of DEN in this group may lead to prolonged and more severe hypocalcemia (60).

A limitation of this guideline is the lack of fracture data in GIOP-specific clinical trials and population studies. As such,

general OP population clinical trials data were reviewed when GIOP data were not available. This introduced indirectness into the certainty of the evidence and imprecision in the estimate of benefits for treatment in the GIOP population. Because of these limitations, most of the recommendations in this guideline are conditional.

Future studies in the treatment of GIOP should be powered to assess fracture risk reduction. Studies should focus on children and patients with CKD stage 4 and 5. As part of risk assessment, studies should explore the use of quantitative computed tomography (CT), bone finite element analysis from CT scans, and BMD measurements from CT colonography. It would be helpful to have validated fracture prediction scores for patients aged <40 years. More studies are needed to better identify the patient populations that might benefit from combination therapy and sequential therapy in GIOP. Additional studies are required to determine the best treatment options and duration of therapy after discontinuation of DEN. In conclusion, GIOP remains a common and challenging clinical scenario that is frequently unrecognized and undertreated. By systematically synthesizing the current knowledge and available clinical trials, we have provided an updated guideline to help clinicians best care for patients requiring long-term GC use.

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All authors were involved in drafting the article or revising it critically for important intellectual content. All authors approved of the final version to be published. Drs. Humphrey and Russell had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Humphrey, Russell, Danila, Fink, Uhl, Guyatt, Turner

Acquisition of data. Uhl, Abdulhadi, Charles, Cheah, Chou, Goyal, Haseltine, Jackson, Mirza, Moledina, Punni, Rinden, Turgunbaev, Wysham

Analysis and interpretation of data. Humphrey, Russell, Danila, Fink, Uhl, Guyatt, Turner, Uhl, Abdulhadi, Charles, Cheah, Chou, Goyal, Haseltine, Jackson, Mirza, Moledina, Punni, Rinden, Turgunbaev, Wysham, Cannon, Caplan, Grossman, Hansen, Lane, Ma, Magrey, McAlindon, Robinson, Saha, Gore, Womack

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