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

Guideline Summary

Revised July 9, 2023

A panel of adult and pediatric rheumatologists and endocrinologists updated the systematic literature review and included currently available medications for the prevention and treatment of glucocorticoid (GC)-induced osteoporosis. A patient panel was included in this update.

Similar to the 2017 guideline, we recommend risk stratifying patients as being at low, moderate, or high risk of fracture (Adults ≥40 years, FRAX® 10-year probability of major osteoporotic fracture <10%, 10-19%, or ≥20% respectively). We added a **very high risk category** (prior osteoporotic fracture(s) or bone mineral density (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. These cut points were used to stratify PICO questions and weigh potential benefits versus harms, when considering osteoporosis (OP) therapy. For all adults initiating or continuing GC therapy ≥2.5mg/day for >3 months, who have never had fracture risk assessment or been treated with OP therapy, initial clinical fracture risk assessment is strongly recommended over no assessment. Clinical fracture risk factor assessment includes the dose, duration, and pattern of GC use, alcohol use, smoking history, hypogonadism, history of 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, and height loss. If available, BMD testing with VFA or spinal x-ray is recommended as soon as possible after starting GC therapy for adults and every 1-2 years thereafter while continuing GC therapy.

A strong recommendation was made to use oral bisphosphonates (BPs) over no treatment for adults ≥40 years receiving long-term GCs, at high and very high risk for fracture, based on available fracture data in GIOP populations. Other agents including intravenous BPs, PTH/PTHrP, and denosumab (DEN) are also options and are conditionally recommended given lack of fracture prevention data in GIOP populations. For adults at high risk, we conditionally recommended DEN or PTH/PTHrP over BP. For adults at very high risk, we conditionally recommended PTH/PTHrP over antiresorptives (BP, DEN). Raloxifene (RAL) and romosozumab (ROM) may be used in selected patients, after careful consideration of potential harms including thrombosis, stroke, and cardiovascular events.

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
Major osteoporotic fracture (MOF)	Non-traumatic or pathological fractures of the spine, hip, wrist, or humerus	Non-traumatic or pathological fractures of the spine, hip, wrist, or humerus
Clinical fracture risk assessment	History of GC use, evaluation for falls, fractures, frailty, secondary	History of GC use, evaluation for falls, fractures, frailty, secondary

	causes of OP, FRAX® with GC adjustment, BMD with VFA or spinal x-ray	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 major osteoporotic fracture by 1.15 and the hip fracture risk by 1.2 *	Not applicable as FRAX® is not validate 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/year	Prior fracture(s) **OR** GC ≥30mg/day **OR** cumulative ≥5grams/year
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 ≥7.5mg/day for ≥6 months **AND** BMD Z score < -3 **OR** significant BMD loss (> 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 or high risk of fracture**	**Adults <40 years at moderate or high risk of fracture**
Calcium and Vitamin D	Optimized intake of dietary and supplemental calcium and vitamin D based on age-appropriate U.S. Recommended Dietary Allowances.	

Bisphosphonates (BP) Alendronate (oral) Risedronate (oral) Ibandronate (oral/ IV) Zoledronic acid (IV) **PTH & PTHrP Agonists** Teriparatide (TER) Abaloparatide (ABL) **Anti-RANKL** Denosumab (DEN) **Selective Estrogen Receptor Modulator** Raloxifene (RAL) **Anti-sclerostin** Romosozumab (ROM)	We **strongly** recommend OP treatment for those at moderate, high or very high risk of fracture. We **strongly** recommend oral BP over no treatment in high and very high fracture risk due to fracture reduction in GIOP. We **conditionally** recommend PTH/PTHrP over anti-resorptives in patients at very high risk of fracture. We **conditionally** recommend DEN[$&] or PTH/PTHrP over oral and IV BP in high risk of fracture. We **conditionally** recommend IV BP, ROM, RAL over no treatment in high and very high risk of fracture. In moderate risk, we **conditionally** recommend BP, DEN, or PTH/PTHrP in no preferred order among these agents. Except in patients intolerant of other agents, we **conditionally** recommend *against* RAL due to harms of VTE and fatal stroke or ROM due to uncertain harms with increased myocardial infarction, stroke and death	We **conditionally** recommend treatment for those at moderate or very high risk of fracture with oral or IV BP[$], PTH/PTHrP[%] or DEN[%&] 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

BP = bisphosphonate; PTH = parathyroid hormone; PTHrP = PTH-related protein; RANKL = Receptor activator of NF-κβ-Ligand; BMD = bone mineral density; GC= glucocorticoid; FRAX® = https//www.shef.ac.uk/FRAX/Tool.jsp; MOF = major osteoporotic fracture; * FRAX® GC correction example: if hip fracture risk is 2.0% multiply by 1.2 for adjusted risk = 2.4%; $ = Use with caution in women 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 women of child bearing potential due to potential fetal harm. Avoid pregnancy for 5 months after last dose.

Osteoporosis Medications for Patients with Chronic Kidney Disease or Following Renal Transplant

Bisphosphonates should generally not be used in patients with an eGFR < 35 ml/min. When eGFR is < 35 ml/min, the risk of renal osteodystrophy, including adynamic bone disease, osteomalacia, osteitis fibrosa

cystica and mixed uremic osteodystrophy, is increased. As such, metabolic bone disease expert evaluation for chronic kidney disease-mineral and bone disorder (CKD-MBD) is conditionally recommended to exclude these conditions. Hyperparathyroidism should also be assessed. Once excluded, no dose adjustment is needed when prescribing DEN, PTH/PTHrP, or romosozumab (ROM).

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

Recommendations for patients taking prednisone ≥2.5mg/day for >3months	Certainty of evidence	PICO evidence report basis	Page no(s). of evidence tables
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 (CAL/VIT D/LM)	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 (All additional recommendations are in addition to CAL/VIT D/LM.)			
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 in addition to CAL/VIT D/ LM 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 gm 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 (All additional recommendations are in addition to CAL/VIT D/LM.)			
Adults <40 years with MODERATE fracture risk, we **conditionally** recommended 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** recommended *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/minute, and no evidence of chronic kidney disease-mineral and bone disorder (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** recommended *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** recommended optimization of dietary and supplementation of CAL and VIT D as recommended by U.S. RDA depending on the age of the child.	Very low	7.1a-7.4a	141-144
We conditionally recommended *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

GIOP = Glucocorticoid-induced OP, BMP = Bone mineral density, GC = glucocorticoids, BP = bisphosphonate, IV = intravenous, DEN = denosumab, PTH/PTHrP = parathyroid hormone/ parathyroid hormone related protein, RAL = raloxifene, ROM = romosozumab, OP = OP; PICO = Patients, intervention, comparison, outcome; CAL/VIT D/LM = calcium/ vitamin D/ lifestyle modifications; # strong recommendation based on fracture data, $ conditional due to lack of fracture data, % who are not planning on pregnancy during the OP treatment period or are using effective birth control if sexually active; CAL = calcium; CVD = cardiovascular disease; OP = osteoporosis; PICO = Patients, intervention, comparison, outcome; GIOP = Glucocorticoid-induced OP; U.S. RDA = United States Recommended Dietary Allowances; CKD-MBD = chronic kidney disease-mineral and bone disorder; *includes osteomalacia, adynamic bone disease, osteitis fibrosa cystica, mixed uremic osteodystrophy

This updated guideline includes recommendations on abaloparatide (PTHrP) and romosozumab (ROM), which are newly available since the 2017 guideline. It also addresses sequential therapy, which was not addressed in the past. Patients should know that osteoporosis therapy with denosumab (DEN), teriparatide (PTH), PTHrP, or ROM will need sequential osteoporosis therapy to prevent bone loss after these drugs are discontinued. Recommendations for sequential therapies are based in part on initial study designs, long term follow-up studies, and new clinical trials. Patients completing a course of DEN should transition to 1-2 years of a BP. Patients completing a course of PTH, PTHrP, or ROM need to transition to a BP or DEN. Discontinuation of DEN after two or more doses has been associated with rapid bone loss and development of new vertebral compression fractures as soon as 7-9 months after the last dose. As such, BP therapy is recommended beginning at 6-7 months after the last dose of DEN. The precise timing, dose and duration of BP use after DEN cessation is under study, but treatment for at least 1 year seems prudent, until additional research is available. Stopping PTH/PTHrP without transition to another therapy can also result in bone loss, which can be prevented by institution of oral or IV BP or DEN. Stopping ROM without transition to another therapy can result in bone loss, which can be prevented by the institution of oral or IV BP.

Sequential Treatments Recommended When Initial OP Therapy and GC are Discontinued and at Low or Moderate Risk

Initial OP therapy	**Subsequent OP therapy options**
Oral/IV Bisphosphonate	No subsequent OP therapy needed
RAL	No subsequent OP therapy needed
PTH/PTHrP	Oral or IV Bisphosphonate
Denosumab	Oral or IV Bisphosphonate
Romosozumab	Oral or IV Bisphosphonate

Sequential treatments when a new fracture occurs after ≥12 months of initial OP therapy.

Initial OP therapy	**Subsequent OP therapy options**
Oral/IV Bisphosphonate	DEN, PTH/PTHrP, ROM
RAL	Oral or intravenous BP, PTH/PTHrP, DEN, ROM
PTH/PTHrP	Oral or intravenous BP, DEN
Denosumab	Oral or IV Bisphosphonate, ROM
Romosozumab	Oral or IV Bisphosphonate, DEN

Sequential Treatments Recommended When Initial OP Therapy and GC are Discontinued and Patient Remains High or Very High Risk

Continue current therapy or switch to IV Bisphosphonate, DEN, PTH/PTHrP, or romosozumab

*This summary was initially approved by the ACR Board of Directors on August 13, 2022 and updated on November 9, 2022 and July 9, 2023. These recommendations are included in a full manuscript, which was published in Arthritis & Rheumatology and Arthritis Care and Research October 16, 2023.**

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