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Clinical Practice Guideline

Prevention and treatment of glucocorticoid-induced osteoporosis in adults: recommendations from the European Calcified Tissue Society

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Abstract

Introduction: This report presents the recommendations of the European Calcified Tissue Society (ECTS) for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP) in adults. Our starting point was that the recommendations be evidence based, focused on non-bone specialists who treat patients with glucocorticoid (GC) and broadly supported by ECTS.

Methods: The recommendations were developed by global experts. After a comprehensive review of the literature, 25 recommendations were formulated, based on quality evidence. For stratifying fracture risk and the most appropriate first line of treatment, we have classified patients into 3 categories: those at medium risk of fractures, ie, adults without a recent (in the last 2 years) history of fracture; those at high risk of fractures, ie, adults with recent history of fracture, and/or at least one vertebral fracture (grade ≥ 2 according to Genant classification); and those at very high risk of fractures, ie, adults aged ≥70 years with a recent hip fracture, pelvis fracture, and/or at least one vertebral fracture (grade ≥ 2 according to Genant classification). The subtopics in the recommendations include who to assess, how to assess, who to treat, how to treat, and follow-up and monitoring.

Results: General measures are recommended for all patients who are being prescribed GCs for ≥3 months, ie, calcium and protein intake should be normalized, a 25(OH) vitamin D concentration of 50-125 nmol/L should be attained, and the risk of falls be minimized. (1) Who to assess? (R1-2) A preliminary assessment of fracture risk should be routinely performed in patients likely to receive oral GCs for ≥3 months: (i) women and men ≥ 50 years and (ii) patients at increased risk of fracture (history of fragility fracture *and/or* have comorbidities or are on medications that are frequently associated with osteoporosis. (2) How to assess (fracture risk)? (R3-6) Clinical risk factors include history of fragility fracture, systematic vertebral imaging, and GC dose-adjusted FRAX, measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA), fall risk, and biochemical testing. (3) Who to treat? (R7-12) Anti-osteoporosis treatment is indicated for women and men ≥ 50 years with (i) the presence of a recent history of vertebral and/or non-vertebral fracture (less than 2 years), (ii) *and/or* a GC dosage ≥ 7.5 mg/day, (iii) *and/or* age ≥ 70 years, (iv) *and/or* a *T*-score ≤ −1.5, (v) *and/or* 10-year probability risk above the country specific GC dose-adjusted FRAX® thresholds. In premenopausal women and men < 50 years with a *Z*-score ≤ −2 and/or a history of fragility fracture, it is recommended to refer the patient to a bone specialist. (4) How to treat? (R13-18) In women and men ≥ 50 years, (i) alendronate or risedronate is preferred as the first line of treatment in patients at medium risk of fractures, (ii) zoledronic acid or denosumab in patients at high risk of fractures, and (iii) teriparatide in patients at very high risk of fractures. It is imperative that sequential therapy be implemented in individuals receiving denosumab or teriparatide as their first-line treatment regimen. (5) Follow-up and monitoring (R19-25): in patients receiving anti-osteoporosis treatment, monitoring of clinical risk factors (eg, history of fragility fracture), systematic vertebral imaging, fall risk, BMD measurement using DXA, and biochemical testing should be performed regularly during follow-up.

Conclusions: The new, evidence-based recommendations by the ECTS for the prevention and treatment of GIOP provide clear and pragmatic advice to all health practitioners especially those who are not bone specialists.

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Keywords: glucocorticoids, glucocorticoid-induced osteoporosis, bone mineral density, osteoporosis, fractures, fracture risk

Significance

In formulating these guidelines, several novel practice concepts were introduced: (1) systematic recommendation of vertebral imaging for fracture risk assessment, along with routine use of vertebral fracture assessment during dual-energy X-ray absorptiometry (DXA) scans; (2) advising against delaying treatment while awaiting DXA results in specific cases and recommending alendronate or risedronate for postmenopausal women and men aged 50 or older initiating oral glucocorticoids at ≥7.5 mg/day without recent fracture history; and (3) suggesting oral bisphosphonates as the primary treatment for glucocorticoid-induced osteoporosis prevention and management in patients with medium fracture risk, while prioritizing teriparatide, zoledronic acid, or denosumab over oral bisphosphonates for patients at (very) high fracture risk.

Introduction

Oral glucocorticoids (GCs) are widely used by approximately 1%-2% of the adult population for many chronic conditions including rheumatoid arthritis (RA), asthma/chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, multiple sclerosis, lupus, polymyalgia rheumatica, and sarcoidosis.[1-3] Data from the 1999-2008 National health and Nutrition Examination survey indicate that oral GC users in the United States represent 1.2% (95% CI, 1.1-1.4) of the general population. The greatest use was reported in men ages ≥80 years (3.5%; 95% CI, 2.3-4.7) and women ages 70-79 years (2.7%; 95% CI, 1.7-3.7).[2]

Chronic GC excess increases the risk of skeletal adverse effects, with up to 30%-50% of GC-treated patients developing osteoporosis and/or fractures.[3,4] The risk of fracture increases rapidly, within the first 3 months of treatment even at low doses of GCs, remains stable under treatment for years and declines toward baseline rapidly after cessation of GCs.[3,5]

Glucocorticoid-induced osteoporosis (GIOP) is the most common cause of secondary osteoporosis.[1] In a landmark study using the General Practice Research Database in the United Kingdom,[5] an increased fracture risk with GC exposure was documented, with a dose-response relationship noted for vertebral, hip, forearm, and non-vertebral fractures. This risk was increased even at daily doses as low as 2.5 mg prednisolone or equivalent daily.[5,6] The risk for those taking higher doses continuously and a long duration has been reported as high as 7-fold for hip fracture and 17 for vertebral fracture.[7] This risk is partially independent of bone mineral density (BMD).[8] Clinical trials for the management of GIOP show that up to 1/3 of those initiating GC have baseline fractures despite normal BMD.[9-11] This is especially so among prevalent GC users who have baseline low BMD with baseline fractures present in over half of these patients.[9,12,13]

The pathophysiology of GIOP is complex.[14] Glucocorticoids affect the bone through direct actions on bone cells such as osteoblasts, osteocytes, and osteoclasts through modulation of intracellular signaling pathways, including Wnt/sclerostin and RANKL/OPG.[15] Besides their direct effects on bone, GCs induce mild secondary hyperparathyroidism by decreasing intestinal calcium absorption and renal tubular calcium reabsorption.[4] Glucocorticoids also suppress gonadotropin and growth hormone release, which likely contribute to further bone loss. Excessive and prolonged exposure to GCs also leads to loss of lean mass and reduced muscle strength, potentially leading to sarcopenia, which is an independent risk factor for falls and fractures.[16]

The effect of GCs on bone microarchitecture and strength has been evaluated using high-resolution peripheral quantitative computed tomography (HRpQCT), revealing alterations in cortical and trabecular volumetric BMD (vBMD), microarchitecture, and strength at both the distal radius and tibia.[17,18]

Despite the proven deleterious effects of GCs on bone health, and though anti-osteoporosis medications have been shown to be safe and effective in the management of GIOP, it remains underdiagnosed and undertreated, with less than 30% of GC-treated patients at high risk for fracture receiving anti-osteoporotic treatments.[19-22]

Our new guidelines, using a formal process for guideline development, provide up-to-date evidence-based recommendations for the prevention and treatment of GIOP in adults, with the purpose of issuing clear recommendations available for use by all practitioners especially those who are not bone specialists. A comprehensive systematic review of the literature was carried out by 2 investigators to encompass all aspects of GIOP prevention and treatment in adults. The simplified GRADE method was used to indicate the strength of the recommendations and the quality of the supporting evidence. The following text presents 25 recommendations organized into 5 sections: who to assess (R1-2), how to assess (R3-6), who to treat (R7-12), how to treat (R13-18), and follow-up and monitoring (R19-25).

It is important to note that while some may differentiate between the prevention of GIOP and the treatment of confirmed GIOP, we will not make this distinction and will refer to both concepts interchangeably. We believe that this distinction is arbitrary and not clinically relevant.

Materials and methods

A systematic search of the literature on human studies published in English between 2000 and March 2023 was conducted to identify all different aspects of GIOP prevention and treatment in adults ≥ 18 years, in women and men, on GCs for common conditions.

The search terms are provided in Appendix S1.

The following inclusion criteria with reference to PICOS (population, intervention, comparator, outcome, and study type) were defined. Priority was given to fracture outcomes; however, in their absence, BMD and bone turnover markers (BTMs) were also included.

The initial search performed by 2 authors (M.P.Y. and A.M.N.) revealed almost 4000 articles (Figure 1). All relevant publications, including case series, observational studies,

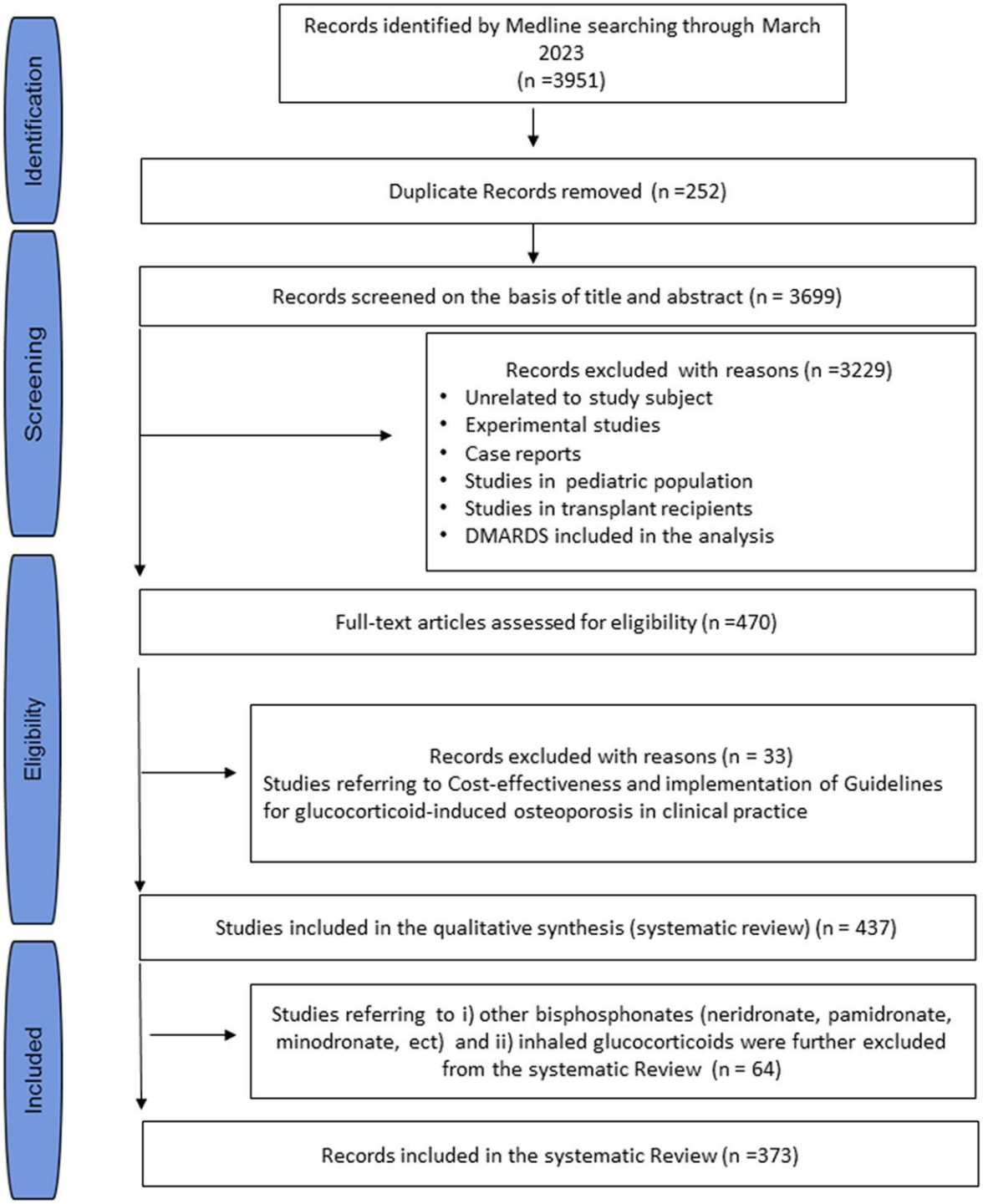

Figure 1. Flow chart.

randomized and nonrandomized trials, and existing systematic and narrative reviews, were included. Articles were excluded if they were: (1) case reports and conference proceedings, (2) on cost-effectiveness and implementation of GIOP guidelines in clinical practice, (3) focused on certain bisphosphonates seldom used and not registered for use in GIOP (ie, neridronate, pamidronate, and minodronate), (4) studies in children and/or adolescences, (5) meta-analyses focusing exclusively on specific populations, (6) restricted to local (eg, inhaled, topical, epidural, and intra-articular use)[23] or intravenous use of GCs, (7) addressed endogenous hypercortisolemia, (ie, Cushing syndrome), (8) confounded by concomitant use of GCs and disease-modifying antirheumatic drugs in RA, and (9) of GC use in patients with solid organ and bone marrow transplantation.

Of the 373 remaining abstracts, original articles of larger studies and systematic reviews with meta-analyses were prioritized for review.

Unless otherwise specified, oral GC doses used are prednisolone-equivalent. Deflazacort is an oxazoline derivative

Table 1. Simplified GRADE approach.

Strength of recommendation	
Strong recommendation	Wording: "we recommend" A strong recommendation implies that the benefits clearly outweigh the risks and burdens (or vice versa) and that virtually all informed patients would choose to follow this recommendation
Weak recommendation	Wording: "we suggest" or "consider" A weak recommendation implies that the benefits, risks, and burdens are closer together or uncertain and that patients are likely to make different informed choices based on their individual values and preferences
Quality of evidence	
High	• Clear evidence from a large meta-analysis or at least 1 large ($N \geq 1000$), methodologically sound randomized controlled trial • Very large ($N \geq 10\,000$) observational studies showing large and consistent effects
Moderate	• Meta-analysis yielding significant effects, but with few participants ($N < 1000$), some heterogeneity or limited generalizability • Randomized trial(s) with small sample size, moderate risk of bias, or limited generalizability • Large ($N \geq 1000$) observational studies showing consistent effects
Low	• Most non-randomized studies, poor-quality randomized trials, small observational studies, or expert opinion

of prednisolone that has shown less deleterious effects on bone, less growth retardation in children with juvenile chronic arthritis, and less induction of hyperglycemia and Cushing's syndrome. It is prescribed in Latin American and some European countries but not in the United States because it was not approved by Food and Drug Administration due to conflicts with its equipotency compared to prednisone. We have not included deflazacort in these recommendations.

We used the simplified GRADE method[24] to indicate the strength of the recommendations and the quality of the supporting evidence (Table 1).

All coauthors were asked to review and opine on recommendations, and all of them revised the different subtopics in consecutive revisions. Furthermore, all coauthors discussed and agreed upon the grading of the recommendations and assessment of the quality of the supporting evidence. The members of the working group then voted on each recommendation in the final version, using a scale ranging from 0 (totally disagree) to 10 (fully agree).

The authors were all members of the European Calcified Tissue Society (ECTS) Clinical Action Group, and 3 members were added, based on both their expertise (K.G.S., O.D.M., and M.C.) and because of their background from 3 different continents. The recommendations were initially discussed at an ECTS webinar on May, 7, and at the annual ECTS meeting on May, 25, 2024, in Marseille, both giving participants of the webinar and the annual meeting the opportunity to bring in their comments. Within the confines of the GRADE method, the authors modified the manuscript according to the comments, and the final set of ECTS recommendations was approved by the ECTS board. The content of these recommendations was validated by a patients' association AFLAR (*Association Française de Lutte Antirhumatismale*).

Results

Twenty-five recommendations were formulated, based on quality evidence. An overview is provided in Table 2 and Figure 2. The different subtopics of this review and their corresponding recommendations (with the strength of the recommendation and quality assessment of the underlying evidence) are summarized in Table 1 and discussed below in more detail.

- Who to assess? (recommendations 1 and 2)
- How to assess? (recommendations 3-6)
- Who to treat? (recommendations 7-12)
- How to treat? (recommendations 13-18)
- Follow-up and monitoring (recommendations 19-25)

We classify patients into 3 categories based on the risk of fractures and the most appropriate first line of treatment):

- Patients at *medium* risk of fractures, ie, adults without recent history of fracture (less than 2 years)
- Patients at *high* risk of fractures, ie, adults with recent history of fracture, and/or at least one vertebral fracture (grade ≥ 2 according to Genant classification)
- Patients at *very high* risk of fractures, ie, in the presence of recent hip fracture, pelvis fracture, and/or at least one vertebral fracture (grade ≥ 2 according to Genant classification) in adults aged $\geq$70 years

Who to assess (recommendations 1 and 2)

The assessment described in recommendations 1 and 2 should ideally be done before starting oral GCs for $\geq$3 months. In patients who have already started oral GCs, this assessment may be done as soon as possible during follow-up.

Recommendation 1: preliminary assessment for all patients on GCs for $\geq$3 months (strong recommendation, low-quality evidence)

The following steps are recommended for *all patients* with an indication for being prescribed GCs for $\geq$3 months or who have already started oral GCs, regardless of age, GC dosage, and underlying disease requiring GCs: (i) inform the patient about the risk of bone fragility with GCs; (2) measure patient's height and check, for height loss (compared to young adult height), acute back pain, and falls risk; (3) check for history of fragility fractures; (4) assess dietary calcium intake; and (5) measure serum calcium, albumin, phosphate, 25-hydroxyvitamin D 25(OH) vitamin D, and creatinine.

Recommendation 2: patients for whom assessment of fracture risk should be performed beyond preliminary assessment (strong recommendation, moderate-quality evidence)

An initial *assessment of fracture risk* is recommended in patients likely to receive oral GCs for $\geq$3 months (ideally before

Table 2. Summary of the ECTS recommendations for patients on oral glucocorticoids for ≥3 months.

Topic	Recommendations	Strength of the recommendation	Quality of evidence	Level of agreement
Who to assess?				
R1. Preliminary assessment for all patients on GCs for ≥3 months	(1) Inform the patient on the risk of GC-induced osteoporosis (GIOP); (2) check for height loss, back pain, and history of fragility fractures; (3) assess dietary calcium intake; (4) laboratory testing	Strong	Low	9.9 ± 0.3
R2. Patients for whom assessment of fracture risk should be performed beyond preliminary assessment	(1) Women and men ≥ 50 years and (2) patients at increased risk of fracture (history of fragility fracture and/or comorbidities/medications that are frequently associated with osteoporosis)	Strong	Moderate	9.8 ± 0.4
How to assess?				
R3. Assessment tools	(1) Clinical risk factors including history of fragility fracture, (2) systematic vertebral imaging, and (3) GC dose-adjusted FRAX	Strong	Moderate	9.8 ± 0.4
R4. Bone mineral density (BMD) measurement	Assessment of fracture risk should include measuring BMD at the lumbar spine and proximal femur using DXA	Strong	Moderate	9.8 ± 0.4
R5. Fall risk	Assessment of fracture risk should include assessment of the risk of falls	Strong	Low	9.5 ± 0.7
R6. Biochemical testing	The following bone health work-up is recommended: serum calcium, albumin, phosphate, 25(OH) vitamin D, and creatinine	Strong	Low	9.5 ± 0.7
Who to treat?				
R7. History of fragility fracture	In women and men ≥ 50 years, in the presence of a recent history of vertebral and/or non-vertebral fracture (less than 2 years), anti-osteoporosis treatment is recommended	Strong	Moderate	9.7 ± 0.5
R8. GC dosage	In women and men ≥ 50 years, if the GC dosage is ≥7.5 mg/day of prednisone or equivalent, anti-osteoporosis treatment is recommended	Strong	Moderate	9.1 ± 1.1
R9. Age	In adults aged ≥70 years, anti-osteoporosis treatment is recommended regardless of the T-score, GC dosage, prior fragility fracture, or the underlying disease requiring GCs	Strong	Moderate	9.0 ± 1.1
R10. BMD criteria	In women and men ≥ 50 years with a *T*-score ≤ −1.5, anti-osteoporosis treatment is recommended	Strong	Moderate	9.1 ± 1.0
R11. FRAX®	In women and men ≥ 50 years, anti-osteoporosis treatment is recommended in patients with a 10-year probability risk of major osteoporotic fracture or hip fracture above the country specific thresholds as per GC dose-adjusted FRAX®	Strong	Low	8.9 ± 1.4
R12. Premenopausal women and men < 50 years	In premenopausal women and men < 50 years with a *Z*-score ≤ −2 and/or a history of fragility fracture, it is recommended to refer the patient to a bone specialist	Weak	Low	9.0 ± 1.2
How to treat?				
R13. General measures	(1) Manage modifiable clinical risk factors, (2) use oral GCs at the lowest possible dosage and as short as possible, (3) ensure sufficient intake of calcium and protein, (4) attain a 25(OH) vitamin D concentration of 20-50 ng/mL (50-125 nmol/L), (5) prevent falls, and (6) introduce a program of physical activity	Strong	Moderate	9.5 ± 0.7
R14. Selection of anti-osteoporosis treatment	The selection of treatment should be tailored not only based on the risk of fractures but also considering contraindications, treatment efficacy, patient preference, national recommendations, cost, and the potential for better adherence	Strong	Low	9.8 ± 0.4
R15. First line of treatment according to the risk of fractures	(1) Alendronate or risedronate in patients at medium risk of fractures, (2) zoledronic acid or denosumab in patients at high risk of fractures, and (3) teriparatide in patients at very high risk of fractures	Strong	Low	8.7 ± 1.2
R16. Criteria to start immediately the first line of treatment	In women and men ≥ 50 years starting oral GCs ≥ 7.5 mg/day and without a recent history of fracture, we recommend to start immediately alendronate or risedronate as the first line of treatment without waiting for the DXA result	Strong	Low	8.5 ± 1.3

(*continued*)

Table 2. Continued

Topic	Recommendations	Strength of the recommendation	Quality of evidence	Level of agreement
R17. Premenopausal women and men < 50 years	In premenopausal women and men < 50 years, we recommend to start vitamin D and calcium. In addition, it is possible to refer patients with a *Z*-score ≤ −2 and/or a history of fragility fracture and/or at least 1 vertebral fracture (grade ≥ 2 according to Genant classification) to a bone specialist to determine whether anti-osteoporosis treatment is indicated	Weak	Low	8.8 ± 1.1
R18. Sequential therapy	It is imperative that sequential therapy be implemented in individuals receiving denosumab or teriparatide as their first-line treatment regimen	Strong	Moderate	9.3 ± 1.1
Follow-up and monitoring				
R19. Clinical and imaging follow-up	In GC-treated patients receiving anti-osteoporosis treatment, an annual clinical follow-up is recommended. Assessment of fracture risk should be based on the identification of new fractures (vertebral and/or non-vertebral) and the systematic use of vertebral imaging	Strong	Low	9.3 ± 1.1
R20. Biochemical follow-up	In GC-treated patients receiving anti-osteoporosis treatment, an annual biological work-up with measurement of serum calcium, phosphate, and 25(OH) vitamin D is recommended	Strong	Low	9.2 ± 0.9
R21. Bone mineral density follow-up	In GC-treated patients receiving anti-osteoporosis treatment, BMD measurement is recommended if anti-osteoporosis treatment is discontinued, or resumed with a new cycle, or if treatment is changed. Apart from these circumstances, we recommend BMD reassessment initially after 1-2 years and then every 2 years or more thereafter	Strong	Low	9.5 ± 0.7
R22. Fracture risk reassessment in patients who are not receiving anti-osteoporosis treatment	In patients continuing GCs ≥ 2.5 mg/day who are not receiving anti-osteoporosis treatment, a regular reassessment of fall risk and fracture risk, including a new DXA, is recommended during follow-up	Strong	Low	9.2 ± 0.8
R23. Anti-osteoporosis treatment failure	For adults continuing GCs who have had ≥2 new fragility fractures ≥12 months following initiation of anti-osteoporosis treatment or who have experienced a significant BMD loss after 1-2 years of anti-osteoporosis treatment, we recommend switching to another class of treatment or switching to another route of administration if taken orally	Strong	Low	9.5 ± 0.7
R24. Discontinuation of GCs	In patients receiving anti-osteoporosis treatment and discontinuing GCs, with no new fragility fracture, no new clinical risk factors, and a *T*-score ≥ −1.5, we recommended stopping anti-osteoporosis treatment and continuing non-pharmacological management	Strong	Low	9.0 ± 1.2
R25. Discontinuation of anti-osteoporosis treatment	In patients receiving anti-osteoporosis treatment for ≥3-5 years for GIOP and continuing GCs < 7.5 mg/day, with no evidence of a new fragility fracture including vertebral fracture, no new clinical risk factors, no significant BMD loss, and a current *T*-score ≥ −1.5, we recommend considering the need for ongoing anti-osteoporosis treatment	Strong	Low	8.8 ± 1.3

starting oral GCs given the rapid bone loss and increase in fracture risk):

- In women and men ≥ 50 years, regardless of GC dosage and underlying disease requiring GCs
- In patients at *increased risk of fracture**, regardless of age, GC dosage, and underlying disease requiring GCs

*Patients at *an increased risk of fracture* are those with the following:

- A *history of fragility fracture*** during the adulthood, *and/or*
- *Comorbidities* that are frequently associated with osteoporosis, ie, certain endocrinopathies (eg, hyperparathyroidism, hyperthyroidism, and diabetes mellitus), neurological disorders with neurosensory impairment, hepatic cirrhosis, COPD > stage 1, chronic inflammatory diseases, and chronic kidney disease mineral and bone disorder (CKD-MBD), *and/or*

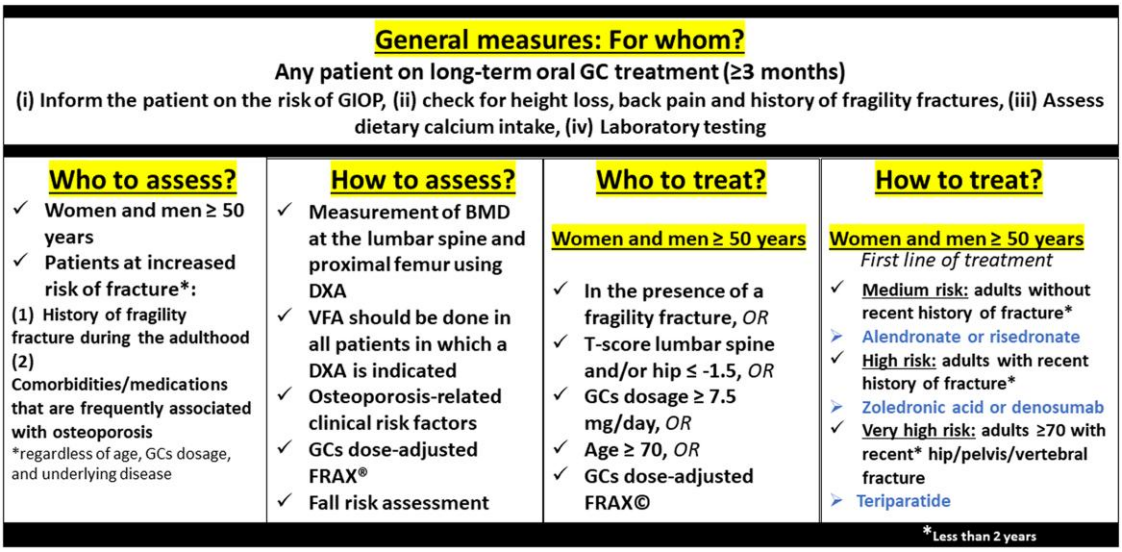

Figure 2. Assessment of fracture risk in patients with an indication for or who have already started glucocorticoids.

- *In addition to GCs are on medications* that are frequently associated with osteoporosis (eg, GnRH antagonists, antiretroviral drugs, and aromatase inhibitors)

**A *fragility fracture* is defined as a fracture occurring as a result of low-energy trauma, such as falling from a standing height.

Comment: The population affected by GIOP is heterogeneous. A large proportion of adults who are exposed to GC therapy are young. Fragility fracture rates in women receiving GCs are higher in postmenopausal (41.9%) than in premenopausal cohorts (5.4%).[25] However, premenopausal women also have an increased risk of vertebral fractures (up to 29%) with GC use.[26] The population at risk of fractures due to oral GCs may be larger than generally appreciated. Furthermore, in age-stratified exploratory analyses, fracture incidence in patients < 40 years was lower than that observed in patients < 50 years, although the small number of events precluded further analysis in this study.[27]

How to assess (recommendations 3-6)

The assessment tools described in recommendations 3-6 should ideally be used before starting oral GCs. In patients who have already started oral GCs, these tools may be used as soon as possible during follow-up.

Recommendation 3: assessment tools (strong recommendation, moderate-quality evidence)

Assessment of fracture risk and osteoporosis-related *clinical risk factors* should be based on the determination of the *history of fractures* (vertebral and/or non-vertebral) and the *systematic use of vertebral imaging* to ascertain the presence of fractures. Calculation of the *GC dose-adjusted FRAX®* should be applied in patients aged 40 years or older, weighing less than 125 kg and more than 25 kg.

Comment: FRAX® is an assessment tool for the prediction of fractures in men and women with use of clinical risk factors with or without femoral neck BMD. FRAX® calculates the 10-year probability of a major osteoporotic fracture (MOF) (in the proximal part of the humerus, the wrist, the hip, or a clinical vertebral fracture) and of a hip fracture.

Vertebral imaging is systematically recommended to ascertain the existence of a prevalent fracture when assessing fracture risk. Indeed, there is 2-4 times higher risk of morphometric vertebral fractures in patients with rheumatologic diseases treated with oral GCs.[28] The recommended first-line vertebral imaging modalities are vertebral fracture assessment (VFA). We recommend the systematic use of VFA when a dual-energy X-ray absorptiometry (DXA) is performed.[29] Standard frontal and lateral radiographs of the lumbar and thoracic spinal sections can also be used for morphological assessment of the spine. Systematic use of vertebral imaging in the context of GIOP would allow to detect more undiagnosed fractures and to identify, assess, and monitor more high-risk patients in need of treatment.

When examining standard radiographs, care should be taken in differentiating between spinal deformities (eg, Schmorl's nodes or Scheuermann disease) and vertebral fractures. Other imaging techniques, such as magnetic resonance imaging and/or computed tomography (CT) scan, can be indicated in special situations. Moreover, opportunistic use of previous vertebral images is possible (eg, a thoracic abdominopelvic plain radiograph or CT scan), provided they are less than 6 months old and depict the entire lumbar and *thoracic* spine.

Recommendation 4: BMD assessment (strong recommendation, moderate-quality evidence)

Assessment of fracture risk should include measuring *BMD* at the lumbar spine and proximal femur using DXA.

Comment: Mean BMD is normal or almost normal in pharmacological clinical trials. The DXA is the standard technique used to measure BMD of the lumbar spine and proximal femur. The DXA results are expressed in absolute values (areal density, g/cm²) as *T*-scores in men aged ≥50 years and menopausal women.

We do not recommend measuring the BMD at the forearm. We believe that no diagnostic threshold for osteoporosis (including GIOP) has been validated for this measurement site, but we

concede that in individual situations (eg, patient with 2 hip prosthesis and/or spinal deformities), it may have added value.

Trabecular bone score (TBS®) is a bone texture index derived from a DXA scan of the lumbar spine. It correlates with bone microarchitecture parameters and provides information that complements lumbar spine BMD measurements for fracture prediction.

While some authors argue that this method could be used as a complementary tool in the diagnosis of GIOP,[30-32] we do not recommend using the TBS® for fracture risk evaluation in GIOP management.

We also do not recommend using other BMD measurement techniques *in daily practice*, as some of these techniques—such as (1) quantitative computed tomography (QCT) or peripheral QCT (pQCT), (2) HR-pQCT, and (3) ultrasound techniques—are only used in clinical research. Measuring the Bone Material Strength Index (BMSi) by impact microindentation using an osteoprobe is also not recommended for routine use in GIOP management for the same reason.

Recommendation 5: assessment of the risk of falls (strong recommendation, low-quality evidence)

The assessment of fracture risk should include assessment of the risk of falls, using standardized assessment tools (eg, timed up and go test and fall risk assessment tool) or by obtaining a history of falls in the past 6-12 months.

Comment: Muscle weakness and wasting are well-recognized side effects of GCs, resulting in an increased risk of falls. Fall rates increase rapidly after the commencement of GCs (1.6 per 100 PY in the year before baseline and 2.8 in the first 3 months of treatment). The rates decrease to baseline values fairly rapidly after stopping GCs.[5]

The methodology to assess fall risk in patients with GIOP does not differ from the one applied for patients evaluated for osteoporosis (assess the number of falls in the past 6-12 months; perform a timed up and go test, etc.).

One way to rapidly determine risk is to simply ask the number of falls in the past 6-12 months. If the number of falls is ≥2 in the past 6-12 months in patients ≥ 70 years, then they should be referred to a physician with expertise in fall prevention.

Recommendation 6: biochemical assessment (strong recommendation, low-quality evidence)

The following bone health work-up is recommended *for all GC-treated patients*: serum calcium, albumin, phosphate, 25(OH) vitamin D, and creatinine.

Comment: This biological work-up, at a minimum, is essential in all GC-treated patients to rule out calcium and phosphorus metabolism disorders; to exclude other causes of bone diseases, such as osteomalacia, primary hyperparathyroidism, and CKD-MBD; and to rule out contraindications to certain anti-osteoporosis treatment options. It is important to screen for bone mineralization disorders due to severe vitamin D deficiency or malabsorption, because their treatment differs from that of osteoporosis. Glucocorticoids are a risk factor for vitamin D deficiency. The younger the subject, the more detailed the biological work-up should be to identify secondary contributors to osteoporosis if BMD is low. Urine tests, and particularly 24 h calcium excretion tests, are not recommended since they have not shown to provide added value.

Due to the lack of data specific to this population and the various factors that affect BTMs levels in individuals with GIOP, their use in predicting fracture risk is not recommended. However, administration of antiresorptive treatments for GIOP leads to predictable changes in BTMs.[9] Therefore, BTMs offer a convenient and economical option for therapeutic monitoring in patients with stable disease (see recommendation 17).

Who to treat (recommendations 7-12)

These recommendations (7-12) should be applied to *all patients with an indication for being started on oral GCs ≥ 3 months*. Ideally, they should be applied before starting oral GCs. Treatment can be implemented as soon as possible during follow-up in patients who have already started GCs. We would like to emphasize the *notable increase in fracture risk that occurs within the initial 3 months of GC treatment* as well as the persistence of a stable long-term risk while under treatment for extended periods of time. This warrants an exceptional vigilance. In the event of difficult management, it is advisable to refer patients to bone specialists.

Recommendation 7: history of fragility fracture (strong recommendation, moderate-quality evidence)

In GC-treated women and men ≥ 50 years, in the *presence of a recent history* of vertebral and/or non-vertebral *fracture (less than 2 years)*, anti-osteoporosis treatment is recommended, regardless of GC dosage, *T*-score, or the underlying disease requiring GCs.

Comment: This recommendation is warranted when the timing of the fragility fracture is 2 years before or less, given the imminent risk of a new fracture. Fracture recency is a major risk factor for the occurrence of new fractures in the short term.[33]

Recommendation 8: GC dosage (strong recommendation, moderate-quality evidence)

In women and men ≥ 50 years, if *the GC dosage is ≥7.5 mg/day of prednisone or equivalent*, anti-osteoporosis treatment is recommended, regardless of the *T*-score, prior fragility fracture, or the underlying disease requiring GCs.

Comment: The threshold dose of prednisolone at which adverse skeletal effects occur is debatable.[34] Evidence suggests that harmful effects may be observed at daily doses as low as 2.5 mg/day of prednisone. Ingestion of more than 2.5 mg of oral prednisone equivalents per day was associated with an increased fracture risk (any fracture, hip, spine, and forearm) in a case-control study. Moreover, there was a dose-dependent risk of fracture with the use of GC.[6] In a retrospective cohort study previously discussed, with a standardized daily dose of less than 2.5 mg prednisolone, hip fracture risk was 0.99 (0.82-1.20) relative to control, rising to 1.77 (1.55-2.02) at daily doses of 2.5-7.5 mg and 2.27 (1.94-2.66) at doses of 7.5 mg or greater.[5] The relative rates for vertebral fractures were 1.55 (1.20-2.01), 2.59 (2.16-3.10), and 5.18 (4.25-6.31), respectively.

Recommendation 9: age (strong recommendation, low-quality evidence)

In adults aged ≥70 years, anti-osteoporosis treatment is recommended, regardless of the *T*-score, GC dosage, prior fragility fracture, or the underlying disease requiring GCs.

Comment: This age threshold (≥70 years) is supported by the fact that the risk of fracture in a 70-year-old woman starting

GCs is equivalent to that of a 70-year-old woman who has already had a fragility fracture (according to the FRAX®).[35]

Recommendation 10: BMD (strong recommendation, low-quality evidence)

In women and men ≥ 50 years with a *T-score* ≤ *−1.5*, anti-osteoporosis treatment is recommended, regardless of GC dosage, prior fragility fracture, or the underlying disease requiring GCs.

Comment: This *T*-score threshold (≤−1.5), and more generally the use of an intervention threshold that is higher than that for the general population, is supported by the findings of several studies.[36]

Recommendation 11: FRAX® (strong recommendation, low-quality evidence)

In women and men ≥ 50 years, anti-osteoporosis treatment is recommended in patients with a *10-year probability risk of MOF or hip fracture above the country specific thresholds* as per GC dose-adjusted FRAX®, regardless of GC dosage, *T*-score, prior fragility fracture, or the underlying disease requiring GCs.

Comment: Alternative to country specific thresholds, we suggest considering an estimated 10-year fracture risk of 20% (MOF) and/or 3% (hip fracture) as an intervention threshold as proposed in several consensus recommendations.[19,20] Moreover, FRAX probabilities can be adjusted using FRAXplus® for exposure to higher-than-average doses of GCs (ie, 5 mg daily).

Recommendation 12: premenopausal women and men < 50 years (weak recommendation, low-quality evidence)

In premenopausal women and men < 50 years with a *Z*-score ≤ −2 and/or a history of fragility fracture, it is recommended to refer the patient to a bone specialist to individualize anti-osteoporosis treatment.

Comment: Evidence supporting the prevention and treatment of GIOP in younger adults is weak, and referral to a bone specialist may be appropriate.

How to treat (recommendations 13-18)

The purpose of treatment is to reduce fracture risk, ideally through primary prevention or through secondary prevention in patients who have already sustained a fracture. Treatment is both pharmacological and non-pharmacological and is based on a joint decision between the patient and the physician. The patient is informed of the nature of GCs and the risks inherent in fragility fractures, the various treatment options, the importance of adhering to treatments and follow-up, and the expected efficacy of the treatments and their possible side effects. The anti-fracture benefits of anti-osteoporosis drugs have been established in osteoporosis populations defined based on BMD criteria or the presence of a fracture. Pharmacological clinical trials including patients who have started or need to start oral GCs mainly focus on the impact of anti-osteoporosis treatment on BMD.

Recommendation 13: general measures (strong recommendation, moderate-quality evidence)

For all patients, the following are recommended (Box 1): manage modifiable fragility fracture clinical risk factors; use oral GCs at the lowest possible dosage and as short as possible; ensure sufficient intake of calcium (~1000 mg/day) and protein (at least 60 g/day, or 1.2 g/kg/day for a reference weight corresponding to a BMI of 25 kg/m²); attain a 25(OH) vitamin D concentration of 20-50 ng/mL (50-125 nmol/L); prevent falls; and introduce a program of weight-bearing physical activity (PA).

Comment: This recommendation applies to all patients to maintain good bone health and to prevent the risk of osteoporosis. The nutritional recommendations that generally apply in the context of osteoporosis should be followed.[37] Furthermore, this recommendation defines the global framework for managing osteoporosis patients using a combination of pharmacological (described below) and non-pharmacological measures. It is important to encourage patients to take a proactive approach to implementing these measures to achieve better adherence to all aspects of the management process.

Box 1. Non-pharmacological prevention and treatment of GIOP in all GC-treated patients: 10 rules to follow

- Use oral GC at the lowest possible dosage and as short as possible
- Lower dosage of oral GC with concomitant use of immunosuppressive drugs such as methotrexate, azathioprine, and/or eventually biologics
- Administering GCs locally (topical, inhaled, intra-articular) rather than systemically when this may be equally effective
- Optimal treatment of the underlying disease
- Adequate calcium intake
- Normalize the intake of protein (at least 60 g/day)
- Vitamin D ideally per day (400IU-800 IU) or per month (50,000-100,000 units) throughout the year [attain a 25(OH) vitamin D concentration of 20-50 ng/mL]
- Prevention of falls
- Promote weight-bearing physical activity and progressive resistance training program
- No smoking, limited alcohol intake

Reduce modifiable risk factors. As bone fragility in the context of GIOP is multifactorial, it is important to reduce as many risk factors as possible, including sedentary behavior, smoking, and alcohol consumption, and the prescribed dosage of GCs should be regularly reviewed and kept to a minimum. Evidence for the benefits of lifestyle interventions specifically in GIOP is limited. While robust evidence for smoking cessation, moderation of alcohol intake, and weight-bearing exercise is unavailable for GIOP, their benefits are well established in postmenopausal women and remain important for general health and well-being throughout adulthood. It might be possible to taper the dose of GCs by adding immunosuppressive drugs such as methotrexate depending of the underlying disease.

Vitamin D and calcium supplementation. Vitamin D deficiency may lead to mineralization disorders and excessive bone resorption induced by secondary hyperparathyroidism. Vitamin D supplementation is recommended to achieve a 25(OH) vitamin D concentration of at least 20 ng/mL (50 nmol/L) but no greater 50 ng/mL (125 nmol/L). In principle, vitamin D intake should be between 400 and 800 IU daily or between 50 000 and 100 000 units/month.[38] Caution is advised to avoid unnecessary supplementation or higher dosages which have been shown to be associated with increased fall and fracture risk and greater loss of BMD.[39]

The GCs induce secondary hyperparathyroidism by decreasing intestinal calcium absorption and renal tubular calcium reabsorption.[4] For all these reasons, calcium intake (dietary ± supplementation) should be at least 1000 mg/day. Dietary intake of calcium is preferred, that is, dairy products (low fat if needed) and calcium-rich mineral water (>250-300 mg calcium/L), but since this does not always meet the 1000 mg/day requirement, calcium supplements are often needed to attain these levels.

The efficacy of vitamin D and calcium supplementation alone as a means to prevent fragility fractures has not been demonstrated in the context of GIOP. On the other hand, vitamin D and calcium supplementation have always been used in randomized controlled trials evaluating the efficacy of anti-osteoporosis treatment in GIOP.

Protein intake. Dietary protein intake should be sufficient and regular. A minimum intake of 60 g/day is recommended. Protein supplementation (powdered protein) is sometimes necessary to meet protein requirements. Quality of protein intake (essential amino acids) is also important.[40-42]

Prevent falls and introduce a program of PA. Fall risk factors should be addressed in GC users particularly due to the risk of GC-induced myopathy. Impaired vision should be corrected, vitamin D deficiency treated, environmental fall risks in the home reduced, footwear adapted, and medications that could cause falls should be minimized and/or adjusted. Physical activity, including specific exercises to improve balance, is a key determinant in reducing fall risk, particularly in GC-treated patients, because of the potential risk of GC-induced myopathy and increased fall risk.

Recommendation 14: selection of anti-osteoporosis treatment (strong recommendation, low-quality evidence)

It is recommended that the selection of anti-osteoporosis treatment be tailored not only based on the risk of fractures but also considering contraindications, treatment efficacy, patient preference, national recommendations, cost, and the potential for better adherence.

Recommendation 15: first line of treatment according to the risk of fractures (strong recommendation, moderate-quality evidence)

In women and men ≥ 50 years starting or who have already started oral GCs, if anti-osteoporosis treatment is indicated, we recommend the following:

(A) The use of alendronate or risedronate as the first line of treatment in patients at medium risk of fractures, ie, adults without recent history of fracture (less than 2 years)

(B) The use of zoledronic acid or denosumab as the first line of treatment in patients at high risk of fractures, ie, adults with recent history of fracture, and/or at least one vertebral fracture (grade ≥ 2 according to Genant classification)

(C) The use of teriparatide as the first line of treatment in patients at very high risk of fractures, ie, in the presence of recent hip fracture, pelvis fracture, and/or at least one vertebral fracture (grade ≥ 2 according to Genant classification) in adults aged ≥70 years

Recommendation 16: criteria to start immediately the first line of treatment (strong recommendation, moderate-quality evidence)

In women and men ≥ 50 years starting oral GCs ≥ 7.5 mg/day and *without* a recent history of fracture, we recommend to *immediately start* alendronate or risedronate as the first line of treatment without waiting for the DXA result (DXA-VFA should be ordered as baseline value, to compare changes in BMD and to differentiate incident from prevalent vertebral fractures).

Comment: The reason for immediately starting GC is that the dosage of GC is initially highest, and the underlying disease is initially usually most severe. Moreover, we know that many patients with GC are not treated with anti-osteoporotic medications. Then, we try to reduce barriers such as waiting to start anti-osteoporosis treatment until DXA result is available.

Recommendation 17: premenopausal women and men < 50 years (weak recommendation, low-quality evidence)

In premenopausal women and men < 50 years starting or who have already started oral GCs, we strongly recommend to start vitamin D and calcium. In addition, it is possible to refer patients with a *T*- or *Z*-score ≤ −2 and/or a history of fragility fracture and/or at least one vertebral fracture (grade ≥ 2 according to Genant classification) to a bone specialist to determine whether anti-osteoporosis treatment is indicated and consider further risk fracture stratification.

Recommendation 18: sequential therapy (strong recommendation, moderate-quality evidence)

It is imperative that sequential therapy be implemented in individuals receiving denosumab or teriparatide as their first-line treatment regimen. What therapy to switch to after the completion of the first-line treatment should be decided upon the initiation of the first-line medication. We recommend that antiresorptive therapy be administered following the discontinuation of teriparatide. Bisphosphonates (orally or intravenously) should be administered following the discontinuation of denosumab.

Pharmacological management

Antiresorptive agents. It should be noted that head-to-head studies between antiresorptive agents have had only BMD and not fracture outcomes as a primary endpoint (Table 3).

Bisphosphonates. Data show beneficial effects of bisphosphonates on BMD in the spine and hip as well as on both vertebral and non-vertebral fractures, including hip fracture, in GC-treated individuals.[11,43-47]

Table 3. Summary of prospective head-to-head comparator studies in the prevention and treatment of glucocorticoid-induced osteoporosis.

Publication	Study design and duration	Population	Intervention	Control	Main outcome(s)		
					BMD (DXA)	BTM	Fractures
Saag et al., 2007[12]	Randomized, double-blind, double-dummy, active-comparator clinical trial 18 m	428 pts on ≥5 mg/d PSL or equivalent for ≥3 m • 80.6% female Mean age TPTD: 56.1 yrs ALN: 57.3 yrs	TPTD 20 µg/d + placebo (orally administered)	ALN 10 mg/d + placebo (sc administered)	LS[a], ↑ 7.2% with TPTD vs 3.4% with ALN ($P < .001$) TH, ↑ 3.8% with TPTD vs 2.4% with ALN ($P = .005$)	TPTD: P1NP and CTX ↑ ($P < .05$) at 1 m and peaked at 6m ALN: P1NP and CTX ↓ ($P < .05$) at 1 m and remained suppressed at 18 m	Incidence of new VF: TPTD vs ALN (0.6% vs 6.1%), $P = .004$ Incidence of NVF: TPTD vs ALN (5.6% vs 3.7%) $P = .3$
Saag et al., 2018[9]	Randomized double-blind, active-controlled, double-dummy, non-inferiority study 24 m	795 pts 505 continuing GCs (≥7.5 mg/d PSL or equivalent) (370 female) Mean age: DMAB: 61 ± 11 yrs RIS: 61 ± 11 yrs • 290 initiating GCs (186 female) Mean age: DMAB: 67.5 ± 10 yrs RIS: 64.4 ± 10 yrs Additional osteoporosis criterion • All patients < 50 years old had a history of osteoporotic Fx • Glucocorticoid-continuing patients ≥ 50 years old had *T*-scores of −2.0 or less (or −1.0 or less with Fx history)	DMAB sc (60 mg/6 m) + placebo (orally administered)	RIS 5 mg/d + placebo (sc administered/6 m)	GC continuing group DMAB: LS[a], ↑6.4%; FN, ↑ 2.2%; TH, ↑ 2.9%; R, ↑ 0.2% RIS: LS[a], ↑3.2%; FN, ↑0.4%; TH, ↑0.5%; 1/3R, ↓1.4% GC initiating group DMAB: LS[a], ↑6.2%; FN, ↑ 1.5%; TH, ↑ 3.1%; R, ↑ 0.7% RIS: LS[a], ↑ 1.78%; FN, ↓ 0.9%; TH, 0.0%; R, ↓0.8% DMAB was superior to RIS in increasing BMD at all sites	N/A	Osteoporosis-related FX DMAB: 8.8% vs RIS: 9.1% (ns) New and worsening VF DMAB: 4.4% vs RIS: 6.9% (ns) Low-trauma NVF DMAB: 5.3% vs RIS: 3.8% (ns) Fracture incidence at the 2nd year did not differ significantly between groups Fx were a safety endpoint
Reid et al., 2009[11]	Randomized double-blind, double-dummy, non-inferiority clinical trial 12 m	833 pts on ≥7.5 mg/d PSL Subgroups based on GC treatment duration Before randomization • Treatment subgroup ≥ 3 m ($n = 545$) • 67.5% female • Mean age: 53 ± 13 yrs • Prevention subgroup ≤ 3 m ($n = 288$) • 69% female • Mean age: 57 ± 15 yrs	ZOL 5 mg iv	RIS 5 mg/d	Treatment subgroup ZOL: LS, ↑ 4.06%; FN, ↑ 1.45%; Tr, ↑ 1.97%; TH, ↑1.65%; DR, ↑ 0.85% RIS: LS, ↑ 2.71%; FN, ↑ 0.39%; Tr, ↑ 0.63%; TH, ↑0.45%; DR, ↑ 0.09% Prevention subgroup ZOL: LS, ↑ 2.6%; FN, ↑ 1.30%; Tr, ↑ 2.75%; TH, ↑1.54%; DR, ↑ 0.06% RIS: LS, ↑ 0.64%; FN, ↓ 0.03%; Tr, ↑ 0.48%;	N/A	N/A

(*continued*)

Table 3. Continued

Publication	Study design and duration	Population	Intervention	Control	Main outcome(s)		
					BMD (DXA)	BTM	Fractures
					TH, ↑0.03%; DR, ↑ 0.47% ZOL increased significantly BMD more than RIS at all skeletal sites in both treatment groups, except for *R* in the prevention group		

[a]Primary outcome.
Abbreviations: ALN, alendronate; BMD, bone mineral density; BPs, bisphosphonates; CTX, C-terminal telopeptide of type 1 collagen; DMAB, denosumab; DXA, BTM, bone turnover markers; FN, femoral neck; Fx, fracture; LS, lumbar spine; m, months, w, weeks, yrs, years; NTx, N-terminal telopeptide; NVF, non-vertebral Fx; OC, osteocalcin; P1NP, amino-terminal propeptide of type 1 procollagen; PMO, postmenopausal osteoporosis; PMW, postmenopausal women; PreMW, premenopausal women; PSL, prednisolone; pts, patients; TH, total hip; TPTD, teriparatide; Tr, trochanter; TRACP-5b, tartrate-resistant acid phosphatase; VF, vertebral Fx.

In a phase 3 randomized double-blind, double-dummy, non-inferiority clinical trial of adults taking ≥7.5 mg/d prednisone, zoledronic acid (5 mg intravenously once a year) was superior to risedronate (5 mg orally per day) in increasing BMD at the lumbar spine, femoral neck, and total hip at 12 months in both treatment groups (treatment and prevention of GIOP subgroups)[11] (Table 3). This study was not powered to demonstrate differences in the incidence of fractures. Among subgroups of patients (eg, age, sex, menopausal status, dose, and duration of prednisone), lumbar spine BMD increased more in patients receiving zoledronic acid than in those receiving risedronate.[48]

In a retrospective cohort study of 3604 patients using medium or high doses of prednisolone, the treatment with alendronate was associated with a significantly lower risk of hip fracture over a median 1.32 years of follow-up (9.5 vs 27.2 fractures per 1000 person-years).[44] Evidence from extensions to the original clinical trials and UK Technology assessment report[43,49,50] and network meta-analyses[51,52] suggests that both alendronate and risedronate reduce the rate of vertebral fractures.

Denosumab. In a phase 3 randomized double-blind, active-controlled, double-dummy, non-inferiority study of adults taking ≥7.5 mg prednisone, denosumab (60 mg subcutaneously every 6 months) was superior to risedronate (5 mg orally per day) in increasing BMD at the lumbar spine, total hip, and femoral neck at 12 and 24 months[9,53] (Table 3). These results referred to patients initiating or continuing GC treatment, regardless of age, race, baseline BMD *T*-score, GC dose, or menopausal status. Fractures were a safety endpoint in this study, which was not powered to demonstrate differences in the fracture incidence.

A subset of 110 patients had HR-pQCT at the distal radius and tibia at baseline and after 12 and 24 months of treatment.[54] Cortical and trabecular microarchitectures were assessed using standard analyses, and failure load was assessed using micro-finite element analysis to evaluate bone strength. Denosumab was superior to risedronate in terms of preventing failure load at the distal radius and tibia in the GC-initiating group and in increasing failure load at the radius in the GC-continuing group, with significant differences in changes in the cortical and trabecular bone compartments noted between the denosumab and risedronate groups.

Two head-to-head open-label trials showed the superiority of denosumab over alendronate in increasing lumbar spine BMD and decreasing BTMs in long-term GC users.[55]

The effect of denosumab discontinuation on bone outcomes of patients with RA treated with GCs was evaluated in a phase 2 randomized, double-blind, placebo-controlled study.[56] In this analysis of patients with short-term denosumab use (12 months of treatment), discontinuation resulted in a gradual increase in BTMs after 12 months of follow-up, which was associated with a return to baseline of lumbar spine and total hip BMD. Thus, the rebound effect following denosumab discontinuation must also be a concern in GIOP.[57]

Bone anabolic drugs. Given the pathophysiology of this disease (pivotal role of reduced bone formation),[1] there is a strong rationale for the use of anabolic drugs in GIOP. Teriparatide has been mostly studied in this context, although abaloparatide and romosozumab could also represent potential treatment options.

Teriparatide. In a phase 3 randomized, double-blind, double-dummy, active-comparator clinical trial of adults (428 men and women) taking ≥5 mg/d of prednisone ≥ 3 months, teriparatide (20 µg/d subcutaneously) was superior to alendronate (10 mg/d orally) in increasing BMD at the lumbar spine and total hip at 18 months[12] (Table 3). Although fracture was not a primary endpoint of the study, significantly fewer new vertebral fractures occurred in patients treated with teriparatide than in those treated with alendronate (0.6% vs 6.1%, $P = .004$). In contrast, there was no difference in nonvertebral fractures (5.6% vs 3.7%; $P = .3$). After 24 months and 36 months of treatment, a continued increase in lumbar spine and total hip BMD in the teriparatide-treated group was reported, which was superior to that observed in the alendronate group.[55] In another study, among men and pre- and postmenopausal women with GIOP, lumbar spine BMD increased more in patients receiving teriparatide than in those receiving alendronate.[58]

Comparative efficacy of teriparatide vs risedronate was evaluated in men with GIOP in an 18-month randomized, open-label trial (EuroGIOPs trial).[59] At 18 months, trabecular lumbar spine vBMD measured by QCT significantly increased with both treatments, with greater increases in the teriparatide group (16.3% vs 3.8%; $P = .004$). High-resolution QCT trabecular and cortical variables at the 12th thoracic vertebra significantly increased with both treatments, with larger improvements for teriparatide in integral and trabecular vBMD. Vertebral strength increases at 18 months were significant in both groups (teriparatide: 26.0%-34.0%; risedronate:4.2%-6.7%), with higher increases in the teriparatide group.

Romosozumab. Published data on its effects in GIOP are sparse, but an observational retrospective study reported similar effects on BMD at the lumbar spine, femoral neck, and total hip in 36 patients with RA over 12 months compared to denosumab.[60]

We do not recommend romosozumab or abaloparatide as a treatment for GIOP due to current lack of evidence.

Follow-up and monitoring (recommendations 19-25)

The first part of these recommendations (R19-21) (clinical risk factors including history of fragility fracture, systematic vertebral imaging, fall risk, BMD measurement by DXA, and biochemical testing) should be applied in patients receiving anti-osteoporosis treatment. Furthermore, fracture risk reassessment in patients who are not receiving anti-osteoporosis treatment is described (R22).

The second part of these recommendations (R23-25) addresses more complex concepts including treatment failure (R23) and discontinuation of GCs (R24) in patients receiving anti-osteoporosis treatment and finally discontinuation of anti-osteoporosis treatment in patients continuing GC (R25).

Recommendation 19: clinical and imaging follow-up in patients receiving anti-osteoporosis treatment (strong recommendation, low-quality evidence)

In GC-treated patients receiving anti-osteoporosis treatment, an *annual clinical follow-up* is recommended. Assessment of fracture risk and osteoporosis-related CRFs should be based on the identification of new fractures (vertebral and/or nonvertebral) and the systematic use of vertebral imaging, preferably with DXA/VFA. Fall risk should also be reevaluated annually. Lowering the GC dosage should be evaluated, eventually with the use of other immunosuppressive drugs.

Recommendation 20: biochemical follow-up in patients receiving anti-osteoporosis treatment (strong recommendation, low-quality evidence)

In all GC-treated patients, *during the follow-up*, *a regular biological work-up* with measurement of serum calcium, phosphate, and 25(OH) vitamin D *is recommended*.

Recommendation 21: BMD follow-up in patients receiving anti-osteoporosis treatment (strong recommendation, low-quality evidence)

In GC-treated patients receiving anti-osteoporosis treatment, *BMD* measurement is recommended if anti-osteoporosis treatment is discontinued, or resumed with a new cycle, or if treatment is changed. Measuring BMD in patients receiving anti-osteoporosis treatment is also useful to document efficacy and improve adherence. Apart from the circumstances described above, we recommend BMD reassessment including VFA initially after 1-2 years and then every 2 years or more thereafter.

Recommendation 22: fracture risk reassessment in patients who are not receiving anti-osteoporosis treatment (strong recommendation, low-quality evidence)

In patients continuing GCs ≥ 2.5 mg/day who are not receiving anti-osteoporosis treatment, a regular reassessment of fall risk and fracture risk, including a *new DXA/VFA*, is recommended *during follow-up*. We recommend fracture risk reassessment every 1-2 years, depending on the initial level of risk and the presence of new clinical risk factors.

Recommendation 23: treatment failure in patients receiving anti-osteoporosis treatment (strong recommendation, low-quality evidence)

For adults continuing GCs who have had ≥2 new fragility fractures including vertebral fractures with grade ≥2 (according to Genant classification) ≥12 months following initiation of anti-osteoporosis treatment *or* who have experienced a significant BMD loss* after 1-2 years of anti-osteoporosis treatment, given that they are adherent to treatment, we recommend switching to another class of anti-osteoporosis treatment or, if the patient was on an oral agent, switching to another route of administration (subcutaneous or intravenous).

*Defined as greater than the least significant change (LSC) for the skeletal sites and DXA center. The LSC is defined as the least amount of change between 2 measurements over time that must be exceeded before a change can be considered true (with 95% confidence).

Recommendation 24: discontinuation of GCs in patients receiving anti-osteoporosis treatment (strong recommendation, low-quality evidence)

When GCs are discontinued, we recommend a reevaluation of fracture risk. In patients receiving anti-osteoporosis treatment and discontinuing GCs, with no new fragility fracture, no new clinical risk factors, and a current BMD T-score ≥ −1.5, we recommended stopping current anti-osteoporosis treatment

and continuing non-pharmacological management. It is recommended that antiresorptive therapy be administered following the discontinuation of teriparatide for at least 1 year. Bisphosphonates (orally or intravenously) should be administered following the discontinuation of denosumab for at least 1 year.

Comment: After termination of oral prednisolone/prednisone, fracture risk is reduced, although the period required for this to be observed varies among studies. For example, in one study, risk of all fractures declined toward baseline rapidly after cessation of GCs.[5] Other studies have demonstrated that most of the excess risk disappeared within 1 year of GC discontinuation or that it took more than 1 year for the fracture risk to return to the levels of the background population.[61] Several studies in patients with RA reported increases in BMD after cessation of GCs.[62,63]

Recommendation 25: discontinuation of anti-osteoporosis treatment in patients continuing GC (strong recommendation, low-quality evidence)

In patients receiving anti-osteoporosis treatment for ≥3-5 years for GIOP and continuing GCs < 7.5 mg/day, with no evidence of a new fragility fracture including vertebral fracture, no new clinical risk factors, no significant BMD loss, and a current BMD *T*-score ≥ −1.5, we recommend considering the need for ongoing anti-osteoporosis treatment.

In patients discontinuing anti-osteoporosis treatment, we recommend sequential therapy if needed (see recommendation 18) and fracture risk reassessment every 1-2 years (see recommendation 20).

Comment: Randomized controlled trials for GIOP prevention and treatment typically have a limited duration, making it impossible to determine the most appropriate treatment duration. Clinical data suggest that bisphosphonates for this condition are typically continued for a period of 2-3 years, after which time point the benefit-risk ratio should be reassessed on a case-by-case basis every 1-2 years. Ultimately, the benefit-risk ratio to discontinue bisphosphonates (drug holiday) in patients continuing GC is largely unknown.

Discussion

The ECTS guidance for GIOP outlined in this manuscript provides 25 clear recommendations for all practitioners, especially those who are not bone specialists who prescribe GC for their patients. Table 2 and Figure 2 summarize all of these recommendations. As we have noted earlier, GIOP is the most common cause of secondary osteoporosis[1] and remains underdiagnosed and undertreated. The treatment gap for GIOP remains substantial, as although many practitioners prescribe GCs, they frequently do not prioritize the prevention of this disease. Our recommendations should help them to identify those most at risk and manage them appropriately.

This manuscript provides up-to-date evidence-based expert guidance for the prevention and treatment of GIOP in adults. These 25 recommendations are pragmatically divided chronologically into 5 sections for clinical practice which address various aspects of care for adults at risk of GIOP.

Although the risk of fracture associated with GC use is well established, guidance for the management of GIOP continues to evolve as new evidence emerges and additional treatments become available. In developing these recommendations, we take this opportunity to introduce *new concepts of practice*. Firstly, vertebral imaging is systematically recommended when assessing fracture risk initially and during follow-up, and we recommend *the systematic use of VFA when a DXA is performed* to ascertain the existence of a prevalent fracture. Secondly, *treatment should not be delayed while waiting for a DXA scan in certain circumstances*, and we recommend alendronate or risedronate in postmenopausal women and men ≥ 50 years starting oral GCs ≥ 7.5 mg/day *and* without a recent history of fracture. Thirdly, we recommend the use of alendronate or risedronate as the first line of treatment for the prevention and treatment of GIOP in patients *at medium risk of fractures* allowing to prioritize teriparatide, zoledronic acid, or denosumab over oral bisphosphonates *in patients at (very) high risk of fracture*. Lastly, we have also produced a comprehensive set of recommendations on *follow-up and monitoring* in patients receiving or not receiving anti-osteoporosis treatment for GIOP.

We acknowledge that our recommendations have some limitations. The majority of these recommendations were supported by low- to moderate-quality evidence, underscoring the need for additional research into the clinical aspects of GIOP. Furthermore, we did not involve representatives from relevant national societies such as pneumologists, gastroenterologists, hematologists, or primary care physicians. However, because we intend to disseminate our recommendations widely, we expect and encourage the critical dialogue surrounding GIOP and its management to continue even post publication.

In summary, updated recommendations on the management of GIOP are necessary. We provide 25 practical considerations divided into a 5-step logical sequence. These are based on a critical review of current evidence and expert consensus and to be useful for all prescribers of GC in the management of their patients. We highlight areas where the evidence is clear and strong, as well as others where more research is needed to direct and support such recommendations.

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Supplementary material

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