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SPECIAL ARTICLE

2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

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Objective. **To develop recommendations for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP).**

Methods. **We conducted a systematic review to synthesize the evidence for the benefits and harms of GIOP prevention and treatment options. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of evidence. We used a group consensus process to determine the final recommendations and grade their strength. The guideline addresses initial assessment and reassessment in patients beginning or continuing long-term (≥3 months) glucocorticoid (GC) treatment, as well as the relative benefits and harms of lifestyle modification and of calcium, vitamin D, bisphosphonate, raloxifene, teriparatide, and denosumab treatment in the general adult population receiving long-term GC treatment, as well as in special populations of long-term GC users.**

Results. **Because of limited evidence regarding the benefits and harms of interventions in GC users, most recommendations in this guideline are conditional (uncertain balance between benefits and harms). Recommendations include treating only with calcium and vitamin D in adults at low fracture risk, treating with calcium and vitamin D plus an additional osteoporosis medication (oral bisphosphonate preferred) in adults at moderate-to-high fracture risk, continuing calcium plus vitamin D but switching from an oral bisphosphonate to another antifracture medication in adults in whom oral bisphosphonate treatment is not appropriate, and continuing oral bisphosphonate treatment or switching to another antifracture medication in adults who complete a planned oral bisphosphonate regimen but continue to receive GC treatment. Recommendations for special populations, including children, people with organ transplants, women of childbearing potential, and people receiving very high-dose GC treatment, are also made.**

Conclusion. **This guideline provides direction for clinicians and patients making treatment decisions. Clinicians and patients should use a shared decision-making process that accounts for patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.**

INTRODUCTION

Glucocorticoids (GCs) play an important role in the treatment of many inflammatory conditions. It is estimated that 1% of the US population is treated long-term with GCs (1). However, GC use causes significant toxicity, including bone loss and fractures (2,3). More than 10% of patients who receive long-term GC treatment are diagnosed with a fracture, and 30–40% have radiographic evidence of vertebral fractures (4,5). The highest rate of bone loss occurs within the first 3–6 months of GC treatment, and a slower decline continues with persistent use (6). Both high daily and high cumulative GC doses increase risk of fracture, particularly vertebral fracture, due to the greater effects of GCs on trabecular bone than on cortical bone. Risk factors for GC-induced fracture include low bone strength at the beginning of GC treatment and the rate of decline in bone mass during treatment, which is largely determined by the dose and duration of GC use. In children, GC treatment also affects bone strength, growth, and total adult skeletal mass, with a similar profile of risk factors (7–10).

However, GC treatment is a potentially reversible risk factor for glucocorticoid-induced osteoporosis (GIOP); if GC treatment is terminated, bone mineral density (BMD) increases and fracture risk declines (6,11,12). In addition, the absolute risk of future fracture in an individual is substantially influenced by demographic and other characteristics (age, race, sex, and concomitant OP risk factors). For these reasons, it is important to identify those patients taking GCs for whom the benefits of preventive therapy sufficiently outweigh potential harms.

Numerous risk calculators can be applied in clinical practice to provide estimates of risk of major OP fracture and hip fracture clinically diagnosed, with adjustment for GC dose in some but not all calculators (13–15). Most stratify GC use into 2 categories: low (prednisone ≤7.5 mg/day) or high (>7.5 mg/day), based on data from clinical trials and epidemiologic studies (15,16) demonstrating increasing fracture risk with higher daily doses. However, these calculators may underestimate the fracture risk in patients with prolonged treatment with very high doses of GCs for conditions such as giant cell arteritis, vasculitis, lupus, and dermatomyositis (16,17). Van Staa et al reported a marked increase in relative risk of vertebral and hip fractures in patients who had received treatment with prednisolone ≥30 mg/day with a cumulative dose of >5 gm (15).

There are insufficient data to develop individual prediction tools for children and for adults <40 years of age. Nevertheless, observational data indicate a substantial risk of clinically diagnosed vertebral fracture among premenopausal women ≥30 years of age receiving very high doses of GCs (10-year risk 5–20%) (18–25).

Despite increasing information about risk factors for fracture in GC users and the availability of effective therapies to prevent fracture, many long-term GC users never receive therapy to prevent bone loss or are treated

only after a fracture has occurred (26,27). The American College of Rheumatology (ACR) identified GIOP as an important public health issue and first published recommendations for its prevention and treatment in 1996 (28). The ACR updated these guidelines in 2001 and 2010, as new techniques for assessing fracture risk and new information about risk factors and therapies became available (28–30). The present ACR guideline outlines the treatment recommendations for GIOP. The guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (see below) and included therapies for the treatment of OP approved by the US Food and Drug Administration before 2015. No other therapies have been approved as of the time of publication of these guidelines.

METHODS

Methodology overview. We developed this guideline according to the ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes the GRADE methodology (www.gradeworkinggroup.org) (31–33). Conflicts of interest and disclosures were determined and managed according to ACR policy (https://www.rheumatology.org/Portals/0/Files/GIOP-Guidelines-Disclosure-Summary.pdf). The full methods are described in detail in Supplementary Appendix 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). This work involved 4 teams: 1) a Core Leadership Team (4 members), which supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, which completed the literature search and abstraction; 3) an Expert Panel, which developed the clinical questions (PICO [population/intervention/comparator/outcomes] questions) and the scope of the guideline project; and 4) a Voting Panel, which included adult and pediatric rheumatologists, internists, a nephrologist, a pulmonologist, a gastroenterologist, medical specialists with clinical expertise in treating GIOP, and a patient who provided input from the patient perspective and voted on the recommendations. Rosters of the team and panel members are shown in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract).

Framework for the GIOP guideline development. The Panel ranked fracture (hip, vertebral, nonvertebral) as the *critically important outcome measure* for treatment evaluation. *Important outcome measures* included adverse effects of treatments, in particular the incidence of serious and total adverse events (see Supplementary Appendix 3 [http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract] for a list of adverse events).

At the initial meeting, the Voting Panel and Expert Panel agreed that the scope of the project should be the assessment, prevention, and treatment of OP and fractures in children and adults taking glucocorticoids (prednisone at >2.5 mg/day for ≥3 months), including patients with organ transplants, women of childbearing potential, and people receiving very high-dose GCs. Treatment of people using inhaled GCs and those with a glomerular filtration rate of <30 ml/minute were not addressed in these guidelines.

Adult men and women were divided into 2 groups based on age (≥40 years or <40 years). After population risk groups were defined, interventions and comparators for each clinical scenario were specified using a PICO question (see list of PICO questions in Supplementary Appendix 3). PICO questions included assessment and reassessment of fracture risks, treatment comparisons, and questions about duration and reassessment of treatment. When it was necessary to use BMD to support a recommendation (which was the case in only 4 PICO questions, all addressing pediatric patients with GIOP), the Voting Panel downgraded the quality of evidence for indirectness, since BMD provides only indirect evidence of the impact on fracture.

Systematic synthesis of the literature. We performed systematic searches of the published English-language literature including OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through October 6, 2015 (Supplementary Appendix 4, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract), and update searches were conducted on April 23, 2016. We performed duplicate screening of literature search results using DistillerSR software (https://distillercer.com/products/distillersr-systematic-review-software/) (Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). Data were extracted into RevMan software (http://tech.cochrane.org/revman), and the quality of each study was evaluated using the Cochrane risk of bias tool (http://handbook.cochrane.org/). We exported RevMan files into GRADEpro software to formulate a GRADE summary of findings table (Supplementary Appendix 3) for each PICO question (34). The overall quality of evidence was evaluated using GRADE quality assessment criteria (31).

In clinical scenarios not addressed by data from randomized clinical trials, data from observational cohort studies were used to estimate relative effects. In situations in which the question had not been tested in a sample of patients taking GCs but had been tested in a non-GIOP population, we applied the relative risk values from that study, making the assumption that the effect was generalizable, but we downgraded the quality of evidence for indirectness.

We projected absolute risk reduction within each risk stratum according to hypothetical baseline fracture risk ranging from 1% to 20%. The following cut points were used to stratify levels of risk: <5% incidence of vertebral fractures over 5 years, between 5% and <10%, and ≥10%. The Voting Panel then made recommendations based on absolute fracture reduction with treatment in each of these strata. We focused on vertebral fracture rates because this outcome was more consistently reported in the literature and because of the greater effects of GCs on trabecular bone.

Moving from evidence to recommendations. GRADE methodology specifies that panels make recommendations based on the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences. Key to the recommendation is the

Table 1. Fracture risk categories in GC-treated patients

	Adults ≥40 years of age	Adults <40 years of age
High fracture risk	Prior osteoporotic fracture(s) Hip or spine bone mineral density T score ≤−2.5 in men age ≥50 years and postmenopausal women FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ ≥20% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture(s)
Moderate fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ 10–19% FRAX* (GC-adjusted†) 10-year risk of hip fracture >1% and <3%	Hip or spine bone mineral density Z score <−3 **or** rapid bone loss (≥10% at the hip or spine over 1 year) **and** Continuing GC treatment at ≥7.5 mg/day for ≥6 months
Low fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ <10% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≤1%	None of above risk factors other than GC treatment

* https//www.shef.ac.uk/FRAX/tool.jsp.
† Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is >7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%).
‡ Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus.

tradeoff between desirable and undesirable outcomes and cost; recommendations require estimating the relative value patients place on the outcomes. We are unaware of published literature exploring patient values and preferences regarding these issues. Our judgments were based on the experience of the Panel members (which included a patient) in shared decision-making with their patients. Below we outline the Voting Panel's assessment of these tradeoffs that informed the final recommendations.

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. An 80% level of agreement was used as the threshold for a recommendation; if 80% agreement was not achieved during an initial vote, the Panel members held additional discussions before re-voting. Consistent with GRADE guidance, in some instances the Voting Panel chose to provide a strong recommendation despite a low quality rating of evidence (33). In such cases, a written explanation is provided, describing the reasons for this decision.

Moving from recommendations to practice. When applying these risk-stratified recommendations in clinical settings, adults ≥40 years of age receiving long-term GCs should be designated as being at moderate-to-high risk or low risk of fracture (Table 1) based on BMD, history of fracture, and 10-year risk of major OP fracture and hip fracture calculated using a tool that combines risk factors with GC dose. Although many tools that incorporate GC use are available, the Voting Panel suggested using FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) for fracture risk assessment. When GC use is included as a risk factor in FRAX, the fracture risk generated is the risk associated with a prednisolone dose of 2.5–7.5 mg/day (prednisolone and prednisone doses are nearly equivalent). For people receiving doses of >7.5 mg/day, the fracture risk generated with FRAX should be increased by a relative 15% for major osteoporotic fracture and 20% for hip fracture risk (13). For example, if the 10-year hip fracture risk is 2.0% with GC use entered in FRAX, the risk estimate should be increased to 2.4% if the prednisone dose is >7.5 mg.

There are no tools available to estimate absolute fracture risk in children or in adults <40 years of age. These groups were considered to be at high fracture risk if they have previously sustained an OP fracture. The Voting Panel designated men and women <40 years of age to be at moderate risk if they were expected to continue GC treatment at >7.5 mg/day for 6 months and had either 1) a hip or spine BMD Z score of <−3 or 2) a rapid decline in hip or spine BMD (equivalent to ≥10% in 1 year) during GC treatment.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations

1. The Voting Panel's assessment was that patients would be willing to take calcium and vitamin D with only a very small absolute risk reduction, that all or virtually all would be willing to take bisphosphonates to achieve a 5-year absolute reduction in vertebral fracture risk of 5%, and that most would choose to take oral bisphosphonates if the fracture

reduction were ≥3% to <5% (leading to a conditional recommendation in favor). The 5-year time period was chosen because few clinical trials have data on fracture risk reduction past 3–5 years. Further, the Panel members thought that most patients would decline oral bisphosphonates with an absolute reduction in 5-year risk of vertebral fractures of 1.6–2.9% (leading to a conditional recommendation against), and all or virtually all would decline if the risk reduction were <1.5% (leading, in the presence of high- or moderate-quality evidence, to a strong recommendation against).

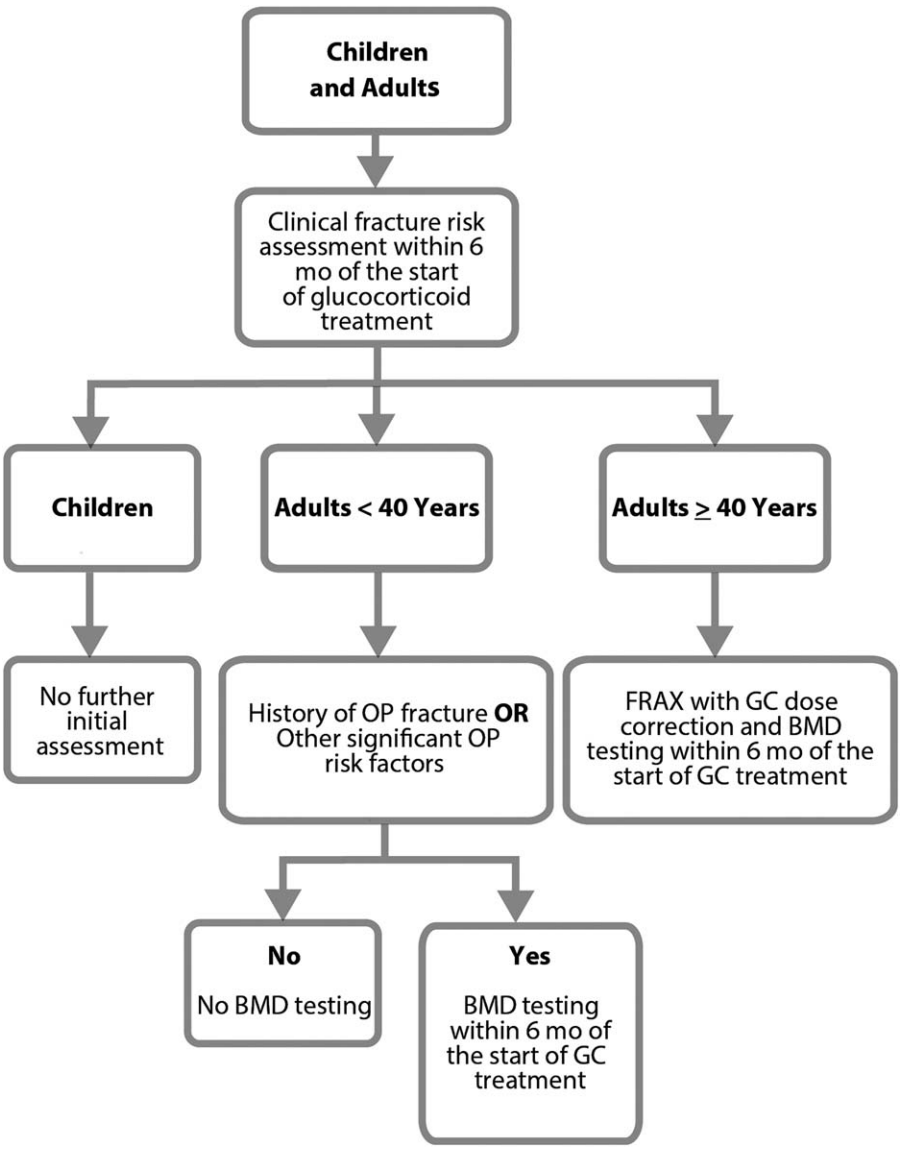

Figure 1. Initial fracture risk assessment. A clinical fracture risk assessment includes obtaining a history with the details of glucocorticoid (GC) use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis (OP) risk factors (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at ≥3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age. The risk of major osteoporotic fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is >7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available.

For intravenous (IV) bisphosphonates, denosumab, raloxifene, and teriparatide, which have greater harms or burden of treatment, the threshold was higher, although the Panel did not specify a threshold value. Because raloxifene may increase the risk of death due to stroke in postmenopausal women with documented coronary heart disease or at increased risk of major coronary events and/or may increase the risk of deep vein thrombosis and pulmonary embolism (35), and there is no evidence of its benefit in fracture reduction in GC-treated patients, the Voting Panel considered the drug as a treatment option only for postmenopausal women with contraindications to all other treatments. We are unaware of published literature exploring patient values and preferences regarding these issues. The judgments are based on the experience of the Panel members (which included a patient) in shared decision-making with their patients.

2a. A *strong recommendation* means that the Panel was *confident* that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation.

2b. A *conditional recommendation* means that the Panel believed the desirable effects of following the recommendation *probably* outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach.

2c. A *good practice recommendation* (36) means that although the Panel believed the benefits of proceeding according to the guidance far outweigh the harms, the supporting evidence is indirect, and the Panel did not formally assess the relevant evidence. The logic for the good practice statements is as follows: Appropriate management regarding bone health is based on an initial assessment and reassessment of fracture risk. However, there are inadequate data directly addressing outcomes in patients whose cases were managed with, versus those without, initial and follow-up fracture risk assessments. The chain of evidence—limited antifracture treatment with limited adverse effects in those at low risk; more aggressive antifracture treatment with resultant decrease in fractures in those at high risk—is nevertheless compelling, though without a structured review of the evidence for the benefits and harms, the statement in question does not warrant a formal GRADE recommendation.

3. For each recommendation, details regarding the PICO questions and the GRADE evidence tables are listed in Supplementary Appendices 1 and 3 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract).

4. Recommendations for BMD testing are based on the assumption that it is available in the region where the patient receives treatment and that there are no significant barriers, including the patient's functional status or financial barriers, that preclude testing, and that the results are likely to have an impact on clinical decision-making.

Recommendations for fracture risk assessment and reassessment

Initial fracture risk assessment. All of the fracture risk assessment and reassessment recommendations are made as good practice recommendations. In all adults and children, an *initial clinical fracture risk assessment should be performed as soon as possible, but at least within 6 months of the initiation of long-term GC treatment* (Figure 1). This assessment should include a history with the details of GC use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other risk factors for fracture (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at $\geq$3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age.

In addition, for adults $\geq$40 years of age, the initial absolute fracture risk should be estimated using FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) with the adjustment for GC dose and BMD testing (if available, or without BMD if it is not available) as soon as possible, but at least within 6 months of the initiation of GC treatment.

For adults $<$40 years of age, BMD testing should be done as soon as possible but at least within 6 months of the initiation of GC treatment if the patient is at high fracture risk because of a history of previous OP fracture(s) or if the patient has other significant OP risk factors (malnutrition, significant

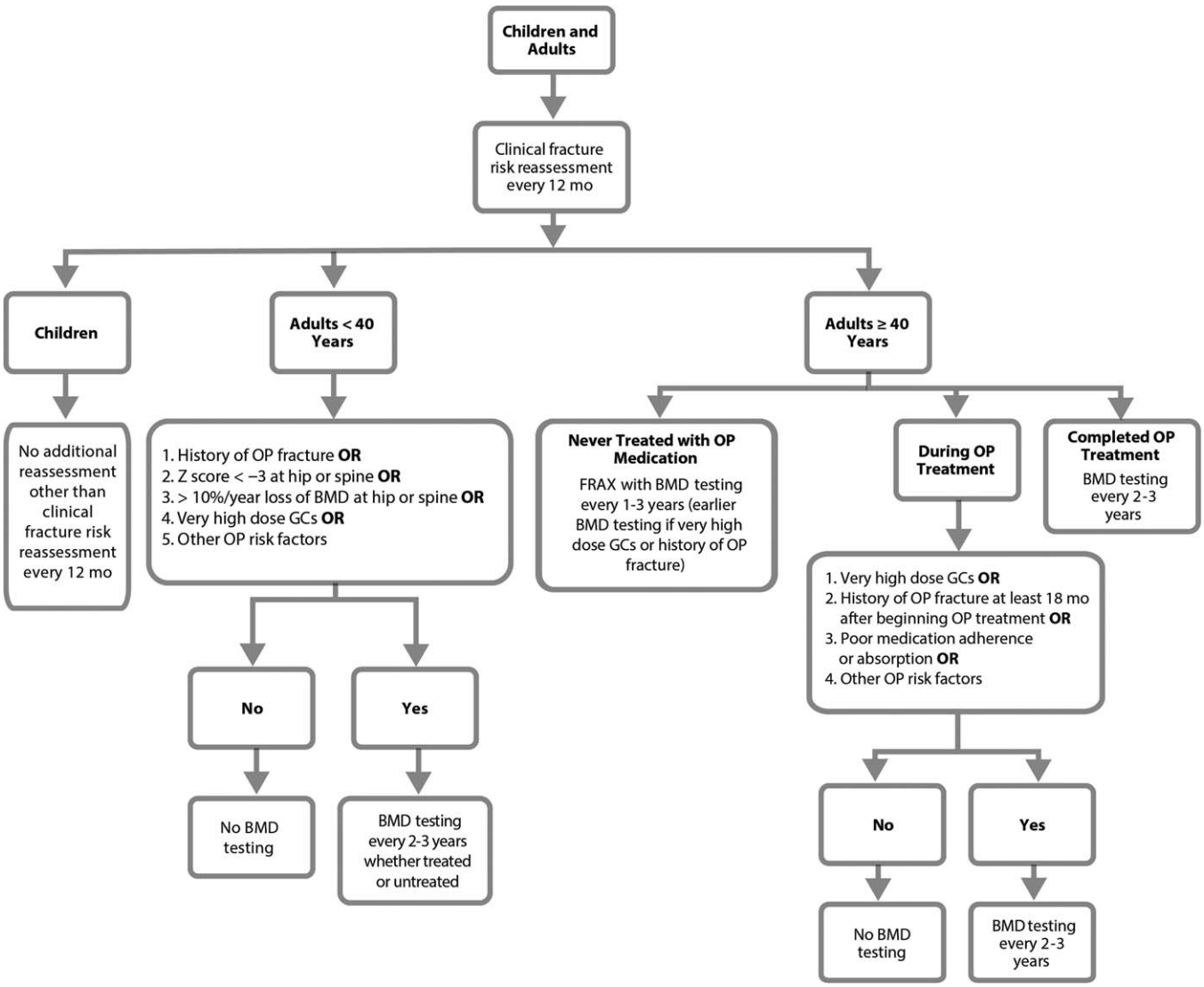

Figure 2. Reassessment of fracture risk. A clinical fracture risk reassessment includes obtaining a history with the details of glucocorticoid (GC) use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis (OP) risk factors (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at ≥3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age. Very high-dose GC treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. Reliability of FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) after OP treatment is debated, but FRAX calculation can be repeated in adults age ≥40 years who have not received treatment. It is recognized that in some cases, bone mineral density (BMD) testing may not be available.

weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, smoking, alcohol use at ≥3 units/day).

Reassessment of fracture risk. In all adults and children who continue GC treatment, a *clinical fracture risk reassessment should be performed every 12 months* (Figure 2).

Adults ≥40 years of age. For adults ≥40 years of age who continue GC treatment and are *not treated with an OP medication beyond calcium and vitamin D,* reassessment with FRAX, with BMD testing if available,

Table 2. Recommendations for initial treatment for prevention of GIOP in adults (women not of child-bearing potential and men) beginning long-term GC treatment*

All adults taking prednisone at a dose of ≥2.5 mg/day for ≥3 months

Optimize calcium intake (1,000–1,200 mg/day)* **and vitamin D intake** (600–800 IU/day) **and lifestyle modifications** (balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day) **over no treatment or over any of these treatments alone.**

Conditional recommendation because of indirect evidence on the impact of lifestyle modifications on fracture risk, low-quality evidence on the impact of calcium and vitamin D on fractures in GC users, and indirect evidence on the benefit of calcium and vitamin D on fracture risk in the general OP population

Adults age ≥40 years at low risk of fracture

Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, denosumab, or raloxifene.

Conditional recommendation for calcium and vitamin D over oral bisphosphonates, teriparatide, and denosumab because of low-quality evidence on additional antifracture benefit of the alternative treatments in this low-risk group, costs, and potential harms

Strong recommendation for calcium and vitamin D over IV bisphosphonates and raloxifene because of low-quality evidence on additional antifracture benefit in this low-risk group and their potential harms

Adults age ≥40 years at moderate risk of major fracture

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- IV bisphosphonates
  - Higher risk profile for IV infusion over oral bisphosphonate therapy
- Teriparatide
  - Cost and burden of therapy with daily injections
- Denosumab
  - Lack of safety data in people treated with immunosuppressive agents
- Raloxifene (for postmenopausal women in whom none of the medications listed above is appropriate)
  - Lack of adequate data on benefits (impact on risk of vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality)

Conditional recommendations because of indirect and low-quality evidence comparing benefits and harms of alternative treatments in people with moderate fracture risk

Adults age ≥40 years at high risk of fracture

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- IV bisphosphonates
  - Higher risk profile for IV infusion over oral bisphosphonate therapy
- Teriparatide
  - Cost and burden of therapy with daily injections
- Denosumab
  - Lack of safety data in people treated with immunosuppressive agents
- Raloxifene (for postmenopausal women in whom none of the medications listed above is appropriate)
  - Lack of adequate data on benefits (impact on risk of vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality)

Strong recommendation for oral bisphosphonates over calcium and vitamin D alone because of the strength of the indirect evidence of antifracture efficacy and low harms

All other recommendations **conditional** because of indirect and low-quality evidence comparing benefits and harms of alternative treatments in people with high fracture risk

Adults age <40 years at low risk of fracture

Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, or denosumab.

Conditional recommendation for calcium and vitamin D over oral bisphosphonates, teriparatide, and denosumab because of low-quality evidence on additional antifracture benefit of the alternative treatments, costs, and potential harms

Strong recommendation for calcium and vitamin D over IV bisphosphonates because of low-quality evidence for additional antifracture benefit in this low-risk group and potential harms

*Correction added after online publication 27 September 2017: the dosage for optimized calcium intake has been changed from 800–1,000 mg/day to 1,000–1,200 mg/day.

Table 2. *(Cont'd)*

Adults age <40 years at moderate-to-high risk of fracture
Treat with an oral bisphosphonate over calcium and vitamin D alone.
Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.
Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications. Other therapies if oral bisphosphonates are not appropriate, in order of preference: IV bisphosphonates Higher risk profile for IV infusion over oral bisphosphonate therapy Teriparatide Cost and burden of therapy with daily injections Denosumab Lack of safety data in people treated with immunosuppressive agents
Conditional recommendations because of low- to very low-quality evidence on absolute fracture risk and indirect and low-quality evidence comparing relative harms and benefits of alternative treatments in this age group

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

should be completed every 1–3 years. This reassessment should be performed earlier within this 1–3-year time range for adults age ≥40 years who are receiving very high doses of GCs (initial prednisone dose ≥30 mg/day, cumulative dose >5 gm in the previous year) or those with a history of OP fracture(s). Later or less frequent testing within this range can be done for adults age ≥40 years who are taking lower doses of GCs with no other OP risk factors.

For adults ≥40 years old who continue GC treatment and are *currently treated with an OP medication in addition to calcium and vitamin D*, BMD testing should be completed every 2–3 years during treatment in high-risk patients such as those receiving very high-dose GCs (initial prednisone dose ≥30 mg/day, cumulative dose >5 gm in the previous year), a history of OP fracture occurring after ≥18 months of treatment with antifracture medication (other than calcium and vitamin D), risks for poor medication adherence or absorption, or other significant OP risk factors.

For adults ≥40 years old who *received an OP treatment in the past but are no longer being treated with an OP medication other than calcium and vitamin D,* BMD testing should be done every 2–3 years. Within this range, reassessment should be conducted earlier in patients receiving higher doses of GCs and those with a history of fracture or low BMD, and later in those receiving lower doses of GCs, with higher BMD and no other OP risk factors.

Adults <40 years of age. For all adults <40 years of age who continue GC treatment and are *at moderate-to-high fracture risk* (history of previous fracture, BMD Z score <−3, received very high-dose prednisone [≥30 mg/day and cumulative dose >5 gm] in the previous year, risks for poor medication adherence or absorption, or multiple OP risk factors), BMD testing should be done every 2–3 years.

Recommendations for treatment

The Voting Panel's rationale and strength of recommendations for treatment are detailed in Table 2.

Calcium and vitamin D intake and lifestyle modifications. Optimizing calcium intake (1,000–1,200 mg/day) and vitamin D intake (600–800 IU/day; serum level ≥20 ng/ml) (37) as well as lifestyle modifications (a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day) are conditionally recommended for all patients receiving GC treatment.

Initial pharmacologic treatment. *Adults ≥40 years of age.* Women ≥40 years of age and not of childbearing potential and men ≥40 years of age (Figure 3) who are at moderate-to-high risk of fracture should be treated with an oral bisphosphonate (strong recommendation for those at high risk; conditional recommendation for those at moderate risk). For patients in whom oral bisphosphonates are not appropriate (for example, due to comorbidities, patient preference, or concerns about adherence with an oral medication regimen), IV bisphosphonates should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If bisphosphonate treatment is not appropriate, teriparatide should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If neither oral nor IV bisphosphonates nor teriparatide treatment is appropriate, denosumab should be used rather than the patient receiving no additional treatment beyond calcium and

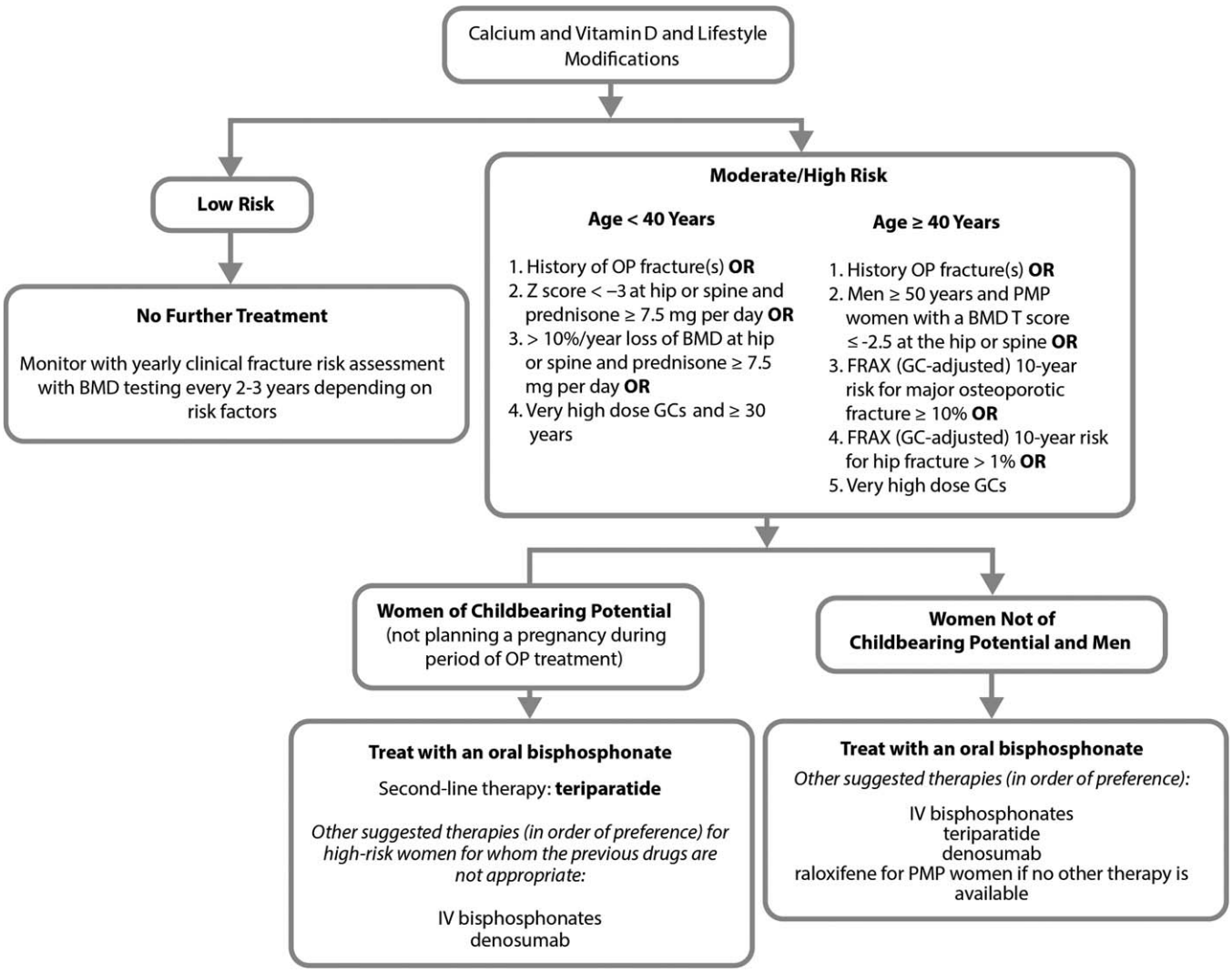

Figure 3. Initial pharmacologic treatment for adults. Recommended doses of calcium and vitamin D are 1,000–1,200 mg/day and 600–800 IU/day (serum level ≥20 ng/ml), respectively. Lifestyle modifications include a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing and resistance training exercise, and limiting alcohol intake to 1–2 alcoholic beverages/day. Very high-dose glucocorticoid (GC) treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. The risk of major osteoporotic (OP) fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is >7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available. PMP = postmenopausal; IV = intravenous.

vitamin D. For postmenopausal women in whom none of these medications is appropriate, raloxifene should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. The order of the preferred treatments was determined based on a comparison of efficacy (fracture reduction), toxicity, and cost. These are conditional recommendations.

Adults <40 years of age. For adults <40 years of age (women not of childbearing potential and men) (Figure 3) with a history of OP fracture, or those continuing GC treatment (≥6 months at a dose of ≥7.5 mg/day) who have either a hip or spine BMD Z score < -3 or bone loss of ≥10%/year at the hip or spine as assessed by dual x-ray absorptiometry (DXA), an oral bisphosphonate should

Table 3. Recommendations for initial treatment for prevention of GIOP in special populations of patients beginning long-term GC treatment*

Women of childbearing potential at moderate-to-high risk of fracture (Table 1) who do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active

Treat with an oral bisphosphonate over calcium and vitamin D alone, teriparatide, IV bisphosphonates, or denosumab.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- Teriparatide
  - Safety, cost, and burden of therapy with daily injections

Consider the following therapies only for **high-risk** patients because of lack of safety data on use of these agents during pregnancy:
- IV bisphosphonates
  - Potential fetal risks of IV infusion during pregnancy
- Denosumab
  - Potential fetal risks during pregnancy

Conditional recommendations because of indirect and very low-quality evidence on benefits and harms of these treatments to the fetus during pregnancy

Adults age ≥30 years receiving very high-dose GCs (initial dose of prednisone ≥30 mg/day and cumulative dose >5 gm in 1 year)

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of additional antifracture benefits from other OP medications.

If bisphosphonate treatment is not appropriate, alternative treatments are listed by age (≥40 years and <40 years) in Table 2.

Conditional recommendations because of low-quality evidence on absolute fracture risk and harms in this population

Adults with organ transplant, glomerular filtration rate ≥30 ml/minute, and no evidence of metabolic bone disease who continue treatment with GCs

Treat according to the age-related guidelines for adults without transplants (Table 2), with these additional recommendations:

An evaluation by an expert in metabolic bone disease is recommended for all patients with a renal transplant.

Recommendation against treatment with denosumab due to lack of adequate safety data on infections in adults treated with multiple immunosuppressive agents.

Conditional recommendations because of low-quality evidence on antifracture efficacy in transplant recipients and on relative benefits and harms of the alternative treatments in this population

Children ages 4–17 years treated with GCs for ≥3 months

Optimize calcium intake (1,000 mg/day) and vitamin D intake (600 IU/day) and lifestyle modifications over not optimizing calcium and vitamin D intake and lifestyle modifications.

Conditional recommendation because of lack of antifracture efficacy of calcium and vitamin D in children but limited harms

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

Treat with an oral bisphosphonate (IV bisphosphonate if oral treatment contraindicated) plus calcium and vitamin D over treatment with calcium and vitamin D alone.

Conditional recommendation because of very low-quality antifracture data in children but moderate-quality evidence of low harms of oral bisphosphonates in children and less potential harm of oral over IV bisphosphonates

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If treatment with an oral bisphosphonate is not appropriate, the same alternative medications listed for adults ≥40 years of age are recommended with the exception of raloxifene, which is not used in men and premenopausal women. These are conditional recommendations.

Special populations. For women who meet criteria for *moderate-to-high risk of fracture* (Table 1) and are of *childbearing potential* (Table 3 and Figure 3), *but do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active,* an oral bisphosphonate should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If oral bisphosphonate treatment is not appropriate, teriparatide should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. Because of the lack of safety data and the potential fetal harm associated with denosumab in animal studies and with high-dose IV bisphosphonates (38–53), these therapies should be used only in women who are at high risk of fracture in whom treatment with an oral bisphosphonate and teriparatide is not appropriate. Denosumab or IV bisphosphonate treatment should be initiated only after a discussion with the patient about the very low quality of evidence about fetal harms in the event of an unplanned pregnancy. These are conditional recommendations.

There is a lack of data on the safety of currently available OP treatments during pregnancy. Therefore, these guidelines do not include recommendations about OP prevention or treatment, other than calcium and vitamin D intake and lifestyle modification, in women who are pregnant.

For *adults ≥30 years of age who are receiving very high-dose GC treatment* (initial prednisone dose of ≥30 mg/day [or equivalent GC exposure] and a cumulative annual dose of >5 gm) (Table 3), oral bisphosphonate treatment should be initiated. If treatment with an oral bisphosphonate is not appropriate, the age-related recommendations for second-line therapy (Table 2) should be followed (with adjustments for women of childbearing potential as outlined in these guidelines). These are conditional recommendations.

For adults *who have received an organ transplant and who are continuing treatment with GCs* (Table 3),

Table 4. Recommendations for follow-up treatment for prevention of GIOP*

Adults age ≥40 years continuing GC treatment who have had a fracture that occurred after ≥18 months of treatment with an oral bisphosphonate or who have had a significant loss of bone mineral density (≥10%/year)

Treat with another class of OP medication (teriparatide or denosumab; or, consider IV bisphosphonate if treatment failure is judged to be due to poor absorption or poor medication adherence) with calcium and vitamin D over calcium and vitamin D alone or over calcium and vitamin D and continued oral bisphosphonate.

Conditional recommendation because of very low-quality evidence comparing benefits and harms of the compared treatment options in this clinical situation

Adults age ≥40 years who have completed 5 years of oral bisphosphonate treatment and who continue GC treatment and are assessed to be at moderate-to-high risk of fracture

Continue active treatment (with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate [if concern with regard to adherence or absorption] or switch to an OP treatment in another class) over calcium and vitamin D alone.

Conditional recommendation because of very low-quality data on benefits and harms in GC-treated patients, but moderate-quality data in the general OP literature on benefits and harms of continuing treatment with oral bisphosphonates past 5 years for people at high risk of fracture

Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at low risk of fracture

Discontinue the OP medication but continue calcium and vitamin D over continuing the OP medication.

Conditional recommendation made by expert consensus; evidence informing it too indirect for the population and very low-quality

Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at moderate-to-high risk of fracture

Complete the treatment with the OP medication over discontinuing the OP medication.

Strong recommendation for high-risk patients based on expert consensus that patients who are at high risk should continue an OP treatment in addition to calcium and vitamin D

Conditional recommendation for moderate-risk patients because of lower fracture risk compared to potential harms

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

the age-related treatment recommendations outlined in these guidelines for men and women who do not have transplants should be followed if the glomerular filtration rate is ≥30 ml/minute and there is no evidence of metabolic bone disease. An evaluation by an expert in metabolic bone disease is recommended before initiating pharmacologic treatment in adults with a renal transplant (54). The Panel made a recommendation against the use of denosumab because of lack of safety data in this population of patients who are treated with multiple immunosuppressive agents. These are conditional recommendations.

For *GC-treated children 4–17 years of age,* a calcium intake of 1,000 mg/day and vitamin D intake of 600 IU/day is recommended. For children who have had an OP fracture who continue GC treatment at a dose of ≥0.1 mg/kg/day for ≥3 months, treatment with an oral bisphosphonate (or an IV bisphosphonate if oral treatment is not appropriate) is recommended (Table 3). These are conditional recommendations.

Follow-up treatment recommendations. *Initial treatment failure.* For adults ≥40 years of age who are continuing GC treatment who have had a fracture that occurred ≥18 months after beginning treatment with an oral bisphosphonate or had a significant decline in BMD (≥10%/year) after 1 year of treatment (Table 4), treatment with another class of OP medication (teriparatide, denosumab) or an IV bisphosphonate (if treatment failure is judged to be due to poor absorption or poor medication adherence) is recommended rather than the patient receiving no additional treatment beyond calcium and vitamin D alone or continuing oral bisphosphonate treatment. These are conditional recommendations.

Treatment if moderate-to-high fracture risk persists after bisphosphonate therapy. For adults ≥40 years of age who have completed 5 years of oral bisphosphonate treatment (Table 4) who are continuing GC treatment and are assessed to be at moderate-to-high risk of fracture (Table 1), continuation of active OP treatment (in addition to calcium and vitamin D) is recommended rather than the patient receiving no additional treatment beyond calcium and vitamin D. Suggested treatment options include continuing the oral bisphosphonate for 7–10 years, switching to an IV bisphosphonate if absorption or adherence is a problem, or treatment with another class of OP medication (teriparatide or denosumab), depending on the response to the initial bisphosphonate treatment (change in BMD, new fractures) and with consideration of rare risks, including jaw necrosis and atypical femur fractures, which might increase with the duration of antiresorptive therapy. These are conditional recommendations.

Treatment if GCs are discontinued. For adults ≥40 years of age who are treated with OP medication in addition to calcium and vitamin D and are discontinuing GC treatment (Table 4), discontinuation of the OP medication is recommended if fracture risk at the time of GC discontinuation is assessed to be low. Otherwise, the OP treatment course should be completed or continued until the fracture risk is assessed to be low. Continuation of OP treatment in the setting of high risk is a strong recommendation. The others are conditional recommendations.

Application of these treatment recommendations. These recommendations are made for average or typical GC-treated patients. They may not be applicable to GC-treated patients with multiple risk factors or feasible for patients with financial or social barriers to testing and treatment.

DISCUSSION

This report presents the updated ACR recommendations for the prevention and treatment of osteoporosis and fractures in patients receiving glucocorticoid treatment. The goal is to optimize identification of patients at risk of GC-induced fractures so that they can be appropriately treated while limiting the risk and the burden of testing and treatment. The guiding principle for these guidelines was to use outcome measures that are clinically relevant to patients and providers, so in decision-making, data about absolute fracture risk reduction were given priority over BMD changes. The recommendations on the order of first-line treatments were based on the Voting Panel's assessment of antifracture efficacy, potential harms, and costs. Thus, oral bisphosphonates were recommended as the preferred first-line therapy in most clinical situations given their antifracture benefit, safety, and low cost, unless there are contraindications, intolerance, or concerns about patient adherence to treatment.

Robust methodology was used in the literature search. The Voting Panel had a broad representation of clinicians, both primary care providers and subspecialists, with experience in bone health and in prescribing GC medications. In addition, these guidelines include recommendations for the assessment and reassessment of fracture risk and antifracture therapy during GC treatment and for special populations, such as children, people with organ transplants, people receiving very high doses of GCs, and women of childbearing potential.

There are limitations to these recommendations. First, many important clinical situations could not be addressed given the limited scope of this guideline

project. Recommendations addressing initial assessment and reassessment of fracture risk were made as good practice recommendations (36) because, although the Panel believes that the benefits of proceeding according to the guidance far outweigh the undesirable consequences, the supporting evidence is indirect or not available, and the Panel did not formally gather, summarize, or assess the relevant evidence.

We adopted generally accepted thresholds to define high, medium, and low levels of absolute risk of incident fracture (i.e., <10%, 10–19%, and ≥20% 10-year risk of major osteoporotic fracture). These cut points were used to stratify PICO questions and weigh potential benefits versus harms in those different clinical situations. However, the application of these recommendations to a clinical setting requires that the physician assign the individual patient into a risk stratum. For adults age ≥40 years, this can be accomplished using fracture risk calculators that take the GC dose into account, such as the FRAX tool. However, FRAX has important limitations. First, the fracture risk generated when GC use is included as a risk factor estimates the risk that would be associated with moderate-dose prednisone (2.5–7.5 mg/day). To accurately estimate the risk associated with doses of >7.5 mg/day, the clinician must multiply the risk of major osteoporotic fracture and the risk of hip fracture generated with the FRAX by 1.15 and by 1.2, respectively. This adjustment may not adequately estimate the risk associated with very high-dose GC use. FRAX uses hip BMD to calculate fracture risk, but GC use has a greater impact on spine BMD. For GC-treated patients with discordant spine and hip BMD (with lower spine BMD), the Fracture Risk Calculator, which includes spine BMD in absolute fracture risk estimation, is available (https://riskcalculator.fore.org). Finally, there is debate about the validity of FRAX fracture risk estimates after pharmacologic treatment for OP, which should be considered in the reassessment of fracture risk in treated patients.

The available evidence about fracture risk and risk reduction was particularly limited with regard to treatment recommendations in adults <40 years of age and children, and there are no tools available to estimate absolute fracture risk in these age groups. Younger people are often treated with higher doses of GCs, but they have higher bone mass and greater potential for recovery of bone mass when the GC treatment is discontinued. To try to better categorize fracture risk in adults <40 years of age, the Panel considered several risk factors as indicators of moderate-to-high fracture risk—including history of previous fragility fracture, significant decrease in BMD, or low BMD Z score with continued use of prednisone (limiting the recovery of bone mass) at a dose of ≥7.5 mg/day for at least 6 months—in patients <40 years old, as well as in patients ≥30 years old treated with very high doses of GCs (initial prednisone dose ≥30 mg/day with a cumulative dose of >5 gm) (15,18,21–25). The lack of data on long-term outcomes with OP treatment in this age group may lead to under- or overtreatment, but the possible benefits to long-term bone health and the relatively low risks associated with the recommended OP treatments led to the recommendation of treatment with an oral bisphosphonate in addition to calcium and vitamin D. There is a need for more research about absolute risk of fracture in this age group during and after GC use and into later adult life.

Fracture data are very limited in GIOP-specific clinical trials and population studies. Lacking these data, the relative fracture reduction associated with OP medications was extrapolated from the risk reduction ascertained in clinical trials of many different treatments for OP in general. While this step introduced indirectness into the quality of evidence for many PICO questions, it is reassuring that where parallel data from GIOP and non-GIOP trials exist, the derived relative risks for treatment effects from the same intervention are often similar, indicating that the assumption of generalizability may be reasonable (Supplementary Appendix 3 [Summary of Findings Tables 1.4a/b/c, 1.9a/b/c], available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). Imprecision in the estimate of benefits of treatment is increased by these extrapolations. Future clinical trials in GC-treated patients should include fracture as a primary outcome measure.

The Panel faced low-quality evidence regarding the magnitude of benefit GC-treated patients would require as a tradeoff for assuming the burden and risks of treatment for lowering fracture risk, particularly given the uncertainties associated with estimates of benefit. Awareness of the need to attain "minimally disruptive medicine" (55) has increased in recent years, and many of the candidate patients already bear the burden of multiple medications. This burden may influence their willingness to tolerate yet additional treatment. The Panel's assessment was that patients would be willing to take calcium and vitamin D with only a very small absolute risk reduction, that all or virtually all would be willing to take bisphosphonates to achieve a 5-year absolute reduction in vertebral fracture risk of 5%, and that most would choose to take oral bisphosphonates if the fracture reduction were between ≥3% and <5%. Patients who value these small absolute reductions less

highly than the Panel estimated may decide against recommended treatment after discussion of risks and benefits with their providers.

There are concerns about the potential harms of calcium and vitamin D supplementation with regard to cardiovascular risks (56,57). Optimizing calcium intake, however, may be even more important in GC-treated patients because of the increase in urinary calcium excretion during GC use. For this reason, the guidelines suggest optimizing dietary intake of calcium. More research about the benefits and harms of supplemental calcium and vitamin D in GC-treated patients is needed.

Because of these limitations, most of the recommendations in this guideline are conditional or good clinical practice recommendations. Further studies are needed to examine differences in fracture risk in people with different OP risk factors (age, race, and sex), the role of spine imaging using vertebral fracture assessment with DXA or radiography in assessing fracture risk in GC users, the risk of OP medications to the fetus in women of childbearing potential, and the impact of OP treatment versus no treatment on adult bone health and fracture risk in GC-treated children.

GIOP is not a problem that is unique to rheumatology; GCs are widely prescribed by primary care providers and subspecialists. The Panel's judgments regarding patients' values and preferences were informed by input from the primary care physicians, non-rheumatology specialists, and the patient who served on the Panel. This patient highlighted the significant challenges that patients and clinicians confront when making decisions about optimizing bone health during GC treatment of chronic inflammatory conditions.

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

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REFERENCES

1. Fardet L, Petersen I, Nazareth I. Monitoring of patients on long-term glucocorticoid therapy: a population-based cohort study. Medicine (Baltimore) 2015;94:e647.
2. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994;96:115–23.
3. Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endocrinol Metab Clin North Am 1998;27:465–83.
4. Curtis J, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 2006;55:420–6.
5. Angeli A, Guglielmi G, Dovio A, Capelli G, de Feo D, Giannini S, et al. High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. Bone 2006;39:253–9.
6. Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis: a randomized, controlled study. Ann Intern Med 1993;119:963–8.
7. Hansen KE, Kleker B, Safdar N, Bartels CM. A systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children. Semin Arthritis Rheum 2014;44:47–54.
8. Van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. J Bone Miner Res 2003;18:913–8.
9. Rodd C, Lang B, Ramsay T, Alos N, Huber AM, Cabral DA, et al. Incident vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: a national observational study. Arthritis Care Res (Hoboken) 2012;64:122–31.
10. LeBlanc CM, Ma J, Taljaard M, Roth J, Scuccimarri R, Miettunen P, et al. Incident vertebral fractures and risk factors in the first three years following glucocorticoid initiation among pediatric patients with rheumatic disorders. J Bone Miner Res 2015;30:1667–75.
11. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993–1000.
12. Hall GM, Spector TD, Griffin AJ, Jawad AS, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum 1993;36:1510–6.
13. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 2011;22:809–16.

14. Ettinger B. A personal perspective on fracture risk assessment tools. Menopause 2008;15:1023–6.
15. Van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. QJM 2005;98: 191–8.
16. De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C, van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis Rheum 2007:56:208–14.
17. Bultink IE, Lems WF, Kostense PJ, Dijkmans BA, Voskuyl AE. Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. Arthritis Rheum 2005;52:2044–50.
18. Sugiyama T, Suzuki S, Yoshida T, Suyama K, Tanaka T, Sueishi M, et al. Incidence of symptomatic vertebral fractures in women of childbearing age newly treated with high-dose glucocorticoid. Gend Med 2010;7:218–29.
19. Almehed K, Hetenyi S, Ohlsson C, Carlsten H, Forsblad-d'Elia H. Prevalence and risk factors of vertebral compression fractures in female SLE patients. Arthritis Res Ther 2010;12:R153.
20. Li EK, Tam LS, Griffith JF, Zhu TY, Li TK, Li M, et al. High prevalence of asymptomatic vertebral fractures in Chinese women with systemic lupus erythematosus. J Rheumatol 2009; 36:1646–52.
21. Borba VZ, Matos PG, da Silva Viana PR, Fernandes A, Sato EI, Lazaretti-Castro M. High prevalence of vertebral deformity in premenopausal systemic lupus erythematosus patients. Lupus 2005;14:529–33.
22. Sugiyama T, Tatsuno I, Suzuki S, Yoshida T, Tanaka T, Sueishi M, et al. Incidence of symptomatic vertebral fracture with high-dose glucocorticoid treatment in the Chiba-Shimoshizu Rheumatic Cohort between 1986 and 2006. Endocr J 2009;56:591–9.
23. Tatsuno I, Sugiyama T, Suzuki S, Yoshida T, Tanaka T, Sueishi M, et al. Age dependence of early symptomatic vertebral fracture with high-dose glucocorticoid treatment for collagen vascular diseases. J Clin Endocrinol Metab 2009;94:1671–7.
24. Sugiyama T, Suzuki S, Yoshida T, Mayama T, Hashimoto N, Suyama K, et al. Age, initial dose and dose increase are independent risk factors for symptomatic vertebral fractures in glucocorticoid-treated male patients. Intern Med 2011;50: 817–24.
25. Kumagai S, Kawano S, Atsumi T, Inokuma S, Okada Y, Kanai Y, et al. Vertebral fracture and bone mineral density in women receiving high dose glucocorticoids for treatment of autoimmune diseases. J Rheumatol 2005;32:863–9.
26. Solomon DH, Katz JN, Jacobs JP, La Tourette AM, Coblyn J. Management of glucocorticoid-induced osteoporosis in patients with rheumatoid arthritis: rates and predictors of care in an academic rheumatology practice. Arthritis Rheum 2002;46:3136–42.
27. Feldstein AC, Elmer PJ, Nichols GA, Herson M. Practice patterns in patients at risk for glucocorticoid-induced osteoporosis. Osteoporos Int 2005;16:2168–74.
28. American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 1996; 39:1791–801.
29. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. Arthritis Rheum 2001;44:1496–503.
30. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 2010;62:1515–26.
31. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
32. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719–25.
33. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726–35.
34. GRADEpro web site. URL: https://gradepro.org/.
35. EVISTA (raloxifene hydrochloride) tablet for oral use initial US approval: 1997 prescribing information. Indianapolis (IN): Eli Lilly and Company; 2007. URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022042lbl.pdf.
36. Guyatt GH, Schünemann HJ, Djulbegovic B, Akl EA. Guideline panels should not GRADE good practice statements. J Clin Epidemiol 2015;68:597–600.
37. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53–8.
38. Bussiere JL, Pyrah I, Boyce R, Branstetter D, Loomis M, Andrews-Cleavenger D. Reproductive toxicity of denosumab in cynomolgus monkeys. Reprod Toxicol 2013;42:27–40.
39. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. Teratology 1999;60:68–73.
40. Ornoy A, Wajnberg R, Diav-Citrin O. The outcome of pregnancy following pre-pregnancy or early pregnancy alendronate treatment. Reprod Toxicol 2006;22:578–9.
41. Illidge TM, Hussey M, Godden CW. Malignant hypercalcaemia in pregnancy and antenatal administration of intravenous pamidronate. Clin Oncol (R Coll Radiol) 1996;8:257–8.
42. Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D, et al. Pregnancy outcome following in utero exposure to bisphosphonates. Bone 2009;44:428–30.
43. Green SB, Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. Am J Health Syst Pharm 2014; 71:2029–36.
44. Stathopoulos IP, Liakou CG, Katsalira A, Trovas G, Lyritis GG, Papaioannou NA, et al. The use of bisphosphonates in women prior to or during pregnancy and lactation. Hormones (Athens) 2011;10:280–91.
45. McNicholl DM, Heaney LG. The safety of bisphosphonate use in pre-menopausal women on corticosteroids. Curr Drug Saf 2010;5:182–7.
46. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.
47. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can 2008;30:1146–8.
48. Okazaki A, Matsuzawa T, Takeda M, York RG, Barrow PC, King VC, et al. Intravenous reproductive and developmental toxicity studies of cimadronate (YM175), a novel bisphosphonate, in rats and rabbits. J Toxicol Sci 1995;20 Suppl 1:1–13.
49. Graepel P, Bentley P, Fritz H, Miyamoto M, Slater SR. Reproduction toxicity studies with pamidronate. Arzneimittelforschung 1992;42:654–67.
50. Sakiyama Y, Tada I, Yamamoto H, Nakanishi T, Yasuda Y, Soeda Y, et al. The effect of ethane-1-hydroxy-1,1-diphosphonate (EHDP) on fetal mice during pregnancy: with emphasis on implantation and fetal weight. J Osaka Dent Univ 1986;19:87–90.
51. Ibrahim A, Scher N, Williams G, Sridhara R, Li N, Chen G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clin Cancer Res 2003;9:2394–9.
52. Boyce RW, Varela A, Chouinard L, Bussiere JL, Chellman GJ, Ominsky MS, et al. Infant cynomolgus monkeys exposed to denosumab in utero exhibit an osteoclast-poor osteopetrotic-like

skeletal phenotype at birth and in the early postnatal period. Bone 2014;64:314–25.
53. Minsker DH, Manson JM, Peter CP. Effects of the bisphosphonate, alendronate, on parturition in the rat. Toxicol Appl Pharmacol 1993;121:217–23.
54. Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney Int Suppl 2009;76 Suppl 113:S1–130.
55. May C, Montori VM, Mair FS. We need minimally disruptive medicine. BMJ 2009;11;339:b2803.
56. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
57. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:827–8.