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SPECIAL ARTICLE

American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

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These recommendations have been reviewed and endorsed by the American Society for Bone and Mineral Research.

INTRODUCTION

Although glucocorticoids may effectively be used in the management of many inflammatory conditions, their use is associated with significant morbidity and mortality. Osteoporosis, with resultant fractures, constitutes one of these morbid complications and is associated with significant pain and disability. A rapid decline in bone mineral density (BMD) begins within the first 3 months of glucocorticoid use and peaks at 6 months, followed by a slower,

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steady loss with continued use (1). An increased risk of both vertebral and nonvertebral fractures has been reported with dosages of prednisolone or equivalent as low as 2.5–7.5 mg daily, and this risk may relate more strongly to daily rather than to cumulative doses of glucocorticoids (2,3). However, there has been some controversy regarding the dose at which an increased risk of fracture occurs, as some smaller studies have found no appreciable decline in bone density with mean daily 8.0 mg dosages of prednisone (4), or prednisone <5 mg/day (5). In a large meta-analysis, prior and current use of oral glucocorticoids increased the risk of any type of fracture, with no significant difference in relative risk between men and women (6).

A number of treatment options for the prevention and management of glucocorticoid-induced osteoporosis (GIOP) are now available. Both alendronate and risedronate improve BMD and decrease the risk of vertebral fractures in patients treated with glucocorticoids (7–10). More recently, teriparatide and zoledronic acid have demonstrated efficacy in the management of GIOP with increases in BMD above that of the comparator arms, which employed alendronate and risedronate, respectively (11,12).

Despite the availability of therapies to reduce the risk of fractures, many patients receiving long-term glucocorticoid therapy do not receive any interventions to prevent or treat osteoporosis. In some populations, less than one-third received BMD testing or had documented use of calcium and vitamin D supplementation (13–15). Similarly, the use of bisphosphonate therapy is low, particularly among men and younger women (14–16).

In 2001, the American College of Rheumatology (ACR) published their Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (17). Since their development, additional therapies and new data on therapies included in the previous recommendations have become available. Updated approaches to identify patients at highest risk for fracture have also been developed. Bone density alone may not be the sole reliable diagnostic approach for some patients receiving glucocorticoids, since fracture in patients receiving glucocorticoids may occur independently of a decline in bone mass (6). In 2008, the National Osteoporosis Foundation incorporated the 10-year absolute probability of fracture calculated by the FRAX tool (18) into their guidelines for the treatment and prevention of osteoporosis and included glucocorticoid use as a clinical risk factor (19). Furthermore, the methodology for guideline development has evolved since 2001, when a more informal consensus approach was used (17). Collectively, these factors support the need for a reappraisal and update of the 2001 recommendations.

In order to revise these recommendations on behalf of the ACR, a primary Core Executive Panel utilized the Research and Development/University of California at Los Angeles (RAND/UCLA) method, the assistance of 2 expert panels (the Expert Advisory Panel to frame the development of the recommendations and the Task Force Panel to vote on the specific recommendations), and a systematic literature review (methodology described in detail below). The 2010 recommendations are reported below.

Since even rigorously developed guidelines have limitations in informing individual patient care, we selected the term "recommendations" to describe this work. These recommendations should not supplant clinical judgment, nor are they intended to serve as indicators of quality of care. Rather, they provide expert opinion and evidence-based guidance on the prevention and treatment of GIOP.

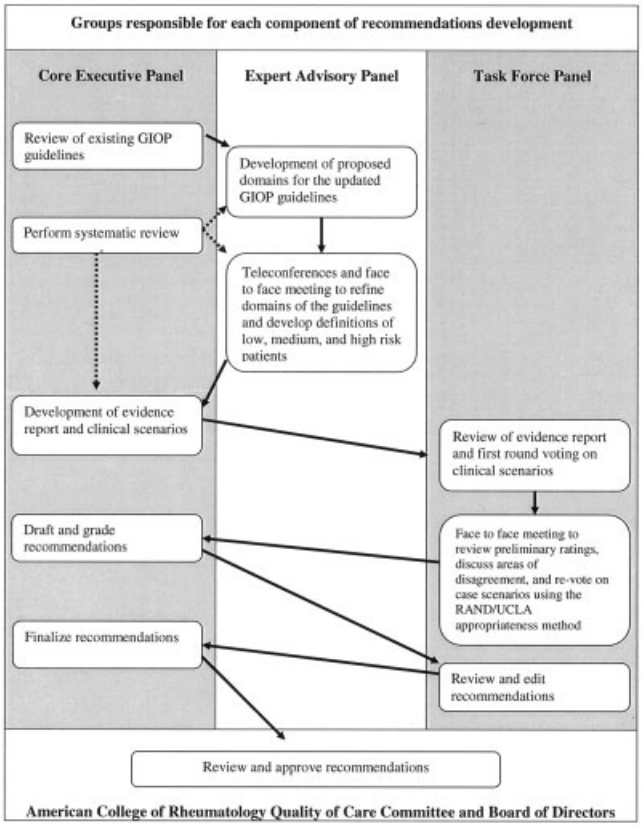

Figure 1. Groups responsible for each component of the glucocorticoid-induced osteoporosis (GIOP) recommendations development. RAND/UCLA = Research and Development/University of California at Los Angeles.

MATERIALS AND METHODS

The methods used to update the ACR GIOP recommendations followed the same general principles that were employed in developing the ACR recommendations for the use of biologic and nonbiologic disease-modifying antirheumatic drugs in rheumatoid arthritis (20). Figure 1 illustrates this process, which is described in more detail below.

Topic development. To update the recommendations, we incorporated the existing concepts from the 2001 guidelines and also refined the scope of the project. We convened an Expert Advisory Panel comprised of 6 rheumatologists with expertise in GIOP, including guideline development. To narrow the scope of the work and because of limited available data in certain areas, the Expert Advisory Panel set the following restrictions for our recommendations: first, the inclusion of medications approved for use in the treatment of osteoporosis in the US,

Canada, or the European Union; second, the exclusion of GIOP in the transplant populations; third, the exclusion of GIOP in the pediatric population; and fourth, the exclusion of inhaled glucocorticoids.

We next constructed the clinical scenarios that would be used by the Task Force Panel to develop the recommendations. An example of a clinical scenario was "In a high risk patient starting glucocorticoids with an anticipated duration of >3 months or on long-term therapy, which of the following medications would be appropriate to use based on a range of glucocorticoid doses?" followed by the list of all potential medications to treat or prevent GIOP. The complete set of scenarios is available in the Supplementary Appendix (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

In an effort to make the process of evaluating the clinical scenarios both feasible and clinically meaningful, we collapsed multiple risk factors for fractures into 3 fracture risk categories: high, medium, and low risk, guided in part by the FRAX risk assessment tool (21). The FRAX tool uses updated, evidence-based estimates of absolute fracture risk and was created for the purpose of quantitatively integrating numerous clinical factors into a clinically useful risk prediction model (22). To determine the cut points for each of the risk categories, the Expert Advisory Panel rated 48 patient examples that were derived by permuting each of the following 4 variables in all possible combinations: sex, age (55, 65, and 75 years of age), race/ethnicity (white and African American), femoral neck density T scores (0.0, −1.0, −1.5, −2.0, and −2.5), and obtaining the corresponding major osteoporotic and hip fracture FRAX scores. Glucocorticoid use was assumed to be present for all subjects. An average body mass index (BMI) of 25 kg/m^2 was also assumed. The remaining variables used in the calculation of the FRAX score (secondary osteoporosis, prior fracture, chronic alcohol use, current smoker, rheumatoid arthritis, and parental history of a hip fracture) were presumed absent. Because the FRAX scores for the race/ethnicity categories of Hispanic and Asian fell consistently between the scores for African American and white, the Hispanic and Asian categories were not used in the rating process, which included only the more extreme categories of African American and white. All of these modifications and compressions were done to reduce the number of scenarios to a total that was manageable by the Task Force Panel and were clinically meaningful as well.

The Expert Advisory Panel recommended the use of either the actual FRAX tool to define low-, medium-, and high-risk patients or the reliance by clinicians upon examples of patients that were typical of low-, medium-, and high-risk categories (as shown in Figure 2). Using the FRAX calculator, the Expert Advisory Panel defined a 10-year risk of a major osteoporotic fracture of 10% or less as low risk, 10–20% as medium risk, and greater than 20% or a T score of less than or equal to −2.5 or a history of a fragility fracture as high risk (which is the threshold for cost-effective treatment recommended by the National Osteoporosis Foundation) (22).

Because the FRAX equations are dynamic and will likely be refined over time (changes occurred in October 2008 [FRAX version 2.0] and September 2009 [FRAX version 3.0]) and because the equations have not been validated specifically for glucocorticoid-treated cohorts, the Expert Advisory Panel did not want to limit the GIOP recommendations by requiring the use of FRAX. Moreover, the same panel recognized that health care providers may confront logistical limitations in calculating a FRAX score within the clinic setting. Therefore, Figures 2A–D were constructed to provide clinicians with examples of typical patients to "match" their individual patient with the most closely fitting category. Determining risk category for other ethnic/racial groups using typical patient examples may be more complicated because of limited data. A study using Medicare claims data found that osteoporosis and fracture risk prevalence were 2-times higher for

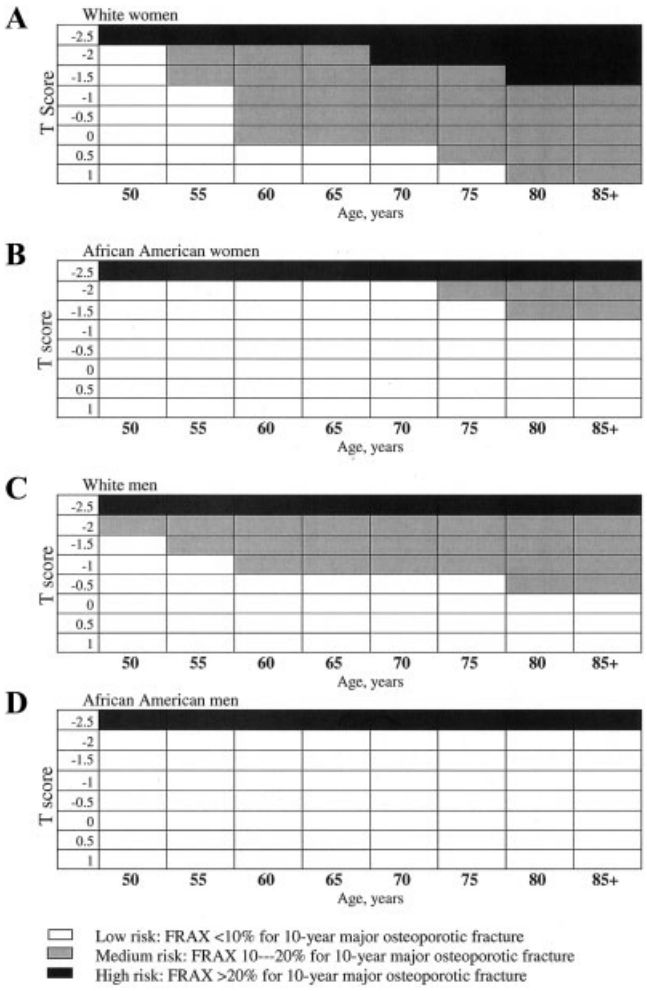

Figure 2. Typical examples of postmenopausal women and men age ≥50 years with a history of glucocorticoid use at high, medium, and low risk of fracture in the absence of other risk factors in **A**, white women, **B,** African American women, **C,** white men, and **D,** African American men. High-, medium-, and low-risk patient classification based on an approximation of FRAX 3.0 using age, sex, race, T score, and the presence of glucocorticoids for the calculation, with all other risk factors in the FRAX calculation absent. For example, a 65-year-old white man receiving glucocorticoids with a T score of −1.5 at the total hip would be considered a medium-risk patient if other risk factors listed in Table 1 were absent. Recommendations for this type of medium-risk patient are found in Tables 2, 3, and 4.

Table 1. Clinical factors that may shift an individual to a greater risk category for glucocortcoid-induced osteoporosis

Low body mass index
Parental history of hip fracture
Current smoking
≥3 alcoholic drinks per day
Higher daily glucocorticoid dose
Higher cumulative glucocorticoid dose
Intravenous pulse glucocorticoid usage
Declining central bone mineral density measurement that exceeds the least significant change

whites, Asian Americans, and Hispanic Americans than African Americans (23). In postmenopausal women in the US, African Americans have the highest BMD and lowest fracture risk, Hispanics and whites have a lower BMD and highest fracture risk, and Asians have the lowest BMD but a fracture risk that is similar to African Americans (24).

Fracture risk in the "typical patient" (Figures 2A—D) may be increased in patients who have additional risk factors that were presumed to be absent in our scenarios (such as low BMI, parental history of hip fracture, current smoking, and consuming three or more alcoholic drinks per day). Since FRAX uses an average glucocorticoid dose to calculate the 10-year probability of a major osteoporotic fracture, those receiving higher doses are likely to have a greater absolute fracture risk than estimated by the FRAX. Higher cumulative glucocorticoid dose (3) and intravenous pulse glucocorticoids may also increase the risk of fractures (25,26). A declining central BMD measurement that exceeds the least significant change may be another reason that clinicians would move a patient to a higher risk category. These factors (Table 1) need to be considered in the health care provider's assessment of the patient and may shift an individual into a greater risk category (low→medium, or medium→high).

Systematic literature review. We conducted a systematic review of the therapies currently approved for the treatment of postmenopausal osteoporosis or GIOP in the US, Canada, or the European Union as well as calcium, vitamin D, and testosterone. Articles were limited to randomized clinical trials (RCTs) or controlled clinical trials (CCTs) of human subjects reported in English with an available abstract. The study duration must have been ≥6 months and all subjects were required to have incident or prevalent glucocorticoid use. With the assistance of a professional research librarian, we replicated the search strategy employed in the Comparative Effectiveness of Treatments for Low Bone Density (including Osteoporosis) Report prepared for the Agency for Health Care Research and Quality for alendronate, risedronate, ibandronate, zoledronic acid, calcitonin, teriparatide, and strontium (27). We searched Medline (through PubMed) by applying MeSH headings and relevant keywords with references from January 1966 through August 28, 2008 using Cochrane's Highly Selective Search Strategy (28) to improve the specificity of the search. Searches for calcium, vitamin D, estrogen, and testosterone were performed in a similar manner, but limited to GIOP. Using the Cochrane Handbook's guidance, we also conducted similar searches of EMBase in CENTRAL (28). Details of the search strategy are listed in Supplementary Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Additionally, abstracts from the 2007–2008 ACR Annual Scientific Meeting, European League Against Rheumatism annual European Congress of Rheumatology, Annual Meeting of the American Society for Bone and Mineral Research, and European Calcific Tissue Society European Symposium on Calcified Tissues were manually searched for relevant RCTs. The Core Executive Panel and Expert Advisory Panel members contributed expert-identified studies to complete the search.

Three reviewers screened each title and abstract for relevance to the specific aims of the predefined inclusion criteria for the evidence report. This process resulted in a total of 53 articles (7–9,11,12,29–76) meeting inclusion criteria and these publications formed the basis of the evidence report. Accepted articles were then reviewed independently by 2 of the 7 reviewers (RG, MM, EV, NMP, LC, VKR, JMG), and the consensus on the relevant data was entered into a standardized data abstraction form. For each RCT and CCT, study characteristics, sample size, outcomes, and quality assessment (calculated using the 5-point Jadad score) (77) were reported in tabular form. Jadad scores are based on a 5-point scale, with higher scores suggesting higher-quality studies. The mean Jadad score for the 53 included articles was 2.44 (interquartile range 1–3). This score indicated that the articles as a whole were of only moderate quality. The principal investigator (JMG) adjudicated discrepant results. Relevant meta-analyses (78–84) were also described in the report.

The function of the evidence report was to provide the data for evaluation of clinical scenarios used to illustrate the key permutations of potential clinical interventions for the evaluation and management of GIOP. Some clinical scenarios, such as those involving repeat BMD testing, did not have RCT data as supportive evidence. In those situations, qualitative literature reviews and expert-identified articles were used to summarize existing evidence. This summarized data helped to guide the development of the clinical scenarios and formed the basis for the evidence report that was used in the next phase of the recommendations development.

RAND/UCLA Appropriateness Method used by the Task Force Panel. The RAND/UCLA Appropriateness Method (85–87), which incorporates elements of the nominal and Delphi method, was used to generate the recommendations presented in this report. The RAND/UCLA Appropriateness Method was developed to combine the best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of a treatment based on patient-specific symptoms, medical history, and test results. The method combines a systematic review of the scientific literature with expert opinion and yields specific criteria of appropriateness that can be used as the basis for review criteria, practice guidelines, or both. This technique has previously

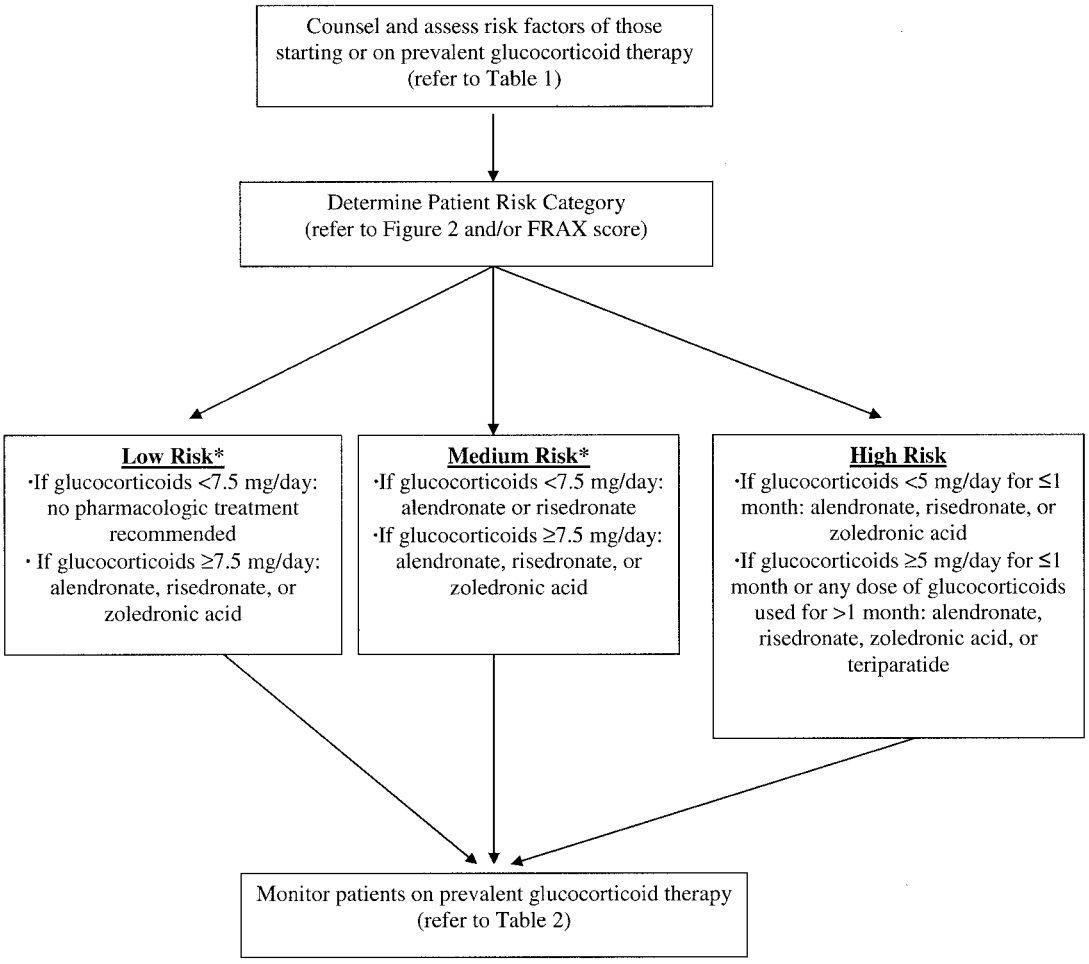

Figure 3. Approach to postmenopausal women and men age >50 years initiating or receiving glucocorticoid therapy. * = for low- and medium-risk patients, recommendations are for an anticipated or prevalent duration of ≥3 months of glucocorticoids.

been described as the best systematic method of combining expert opinion and evidence (88,89).

As the first step in this process, the Task Force Panel, which consisted of 10 individuals from the fields of rheumatology, endocrinology, and geriatrics, and a patient care advocate, received the evidence report and case scenarios. The Task Force Panel independently rated the appropriateness of the specific interventions within the context of the clinical scenarios with varying fracture risk, glucocorticoid dose, and duration. Instructions for grading scenarios and definitions of all variables were provided by e-mail and discussed during a conference call. The Task Force Panel was asked to use the evidence as summarized in the evidence report as well as their own clinical judgment to rate the appropriateness of employing a particular therapy in the context of each clinical scenarios using a 9-point Likert scale, where 1 = appropriate and 9 = not appropriate. Results from the first round of voting were tabulated and presented at a face-to-face panel meeting comprised of the Core Expert Panel and Task Force Panel. The summarized anonymous scores, including range and median as well as the panelist's own ranking, were provided to each voting member. Areas of discrepancy as well as areas of agreement were discussed and a second round of anonymous voting by the Task Force Panel alone occurred using the same scale. Vitamin D and calcium were evaluated as additive therapy and testosterone and estrogen as primary therapy in hypogonadal patients. The results of the second round of voting determined the updated recommendations. The clinical scenarios specifically did not attempt to prioritize the use of one drug over another when both were deemed appropriate in a particular circumstance.

At the face-to-face meeting, additional questions related to risk factors for premenopausal patients arose that were not adequately addressed by the systematic review. Therefore, voting for premenopausal women and for men age <50 years without prior fragility fracture was deferred until an additional literature search to identify non-RCT/CCT studies had been performed and disseminated to panel members and discussed in a subsequent conference call.

Statistical analysis. Recommendations applying to individual scenarios were endorsed when the median score from the panelist voting fell in the 1 to 3 range and there was no disagreement. Disagreement was defined as 3 or more of the 10 voting panelists rating the scenario in the

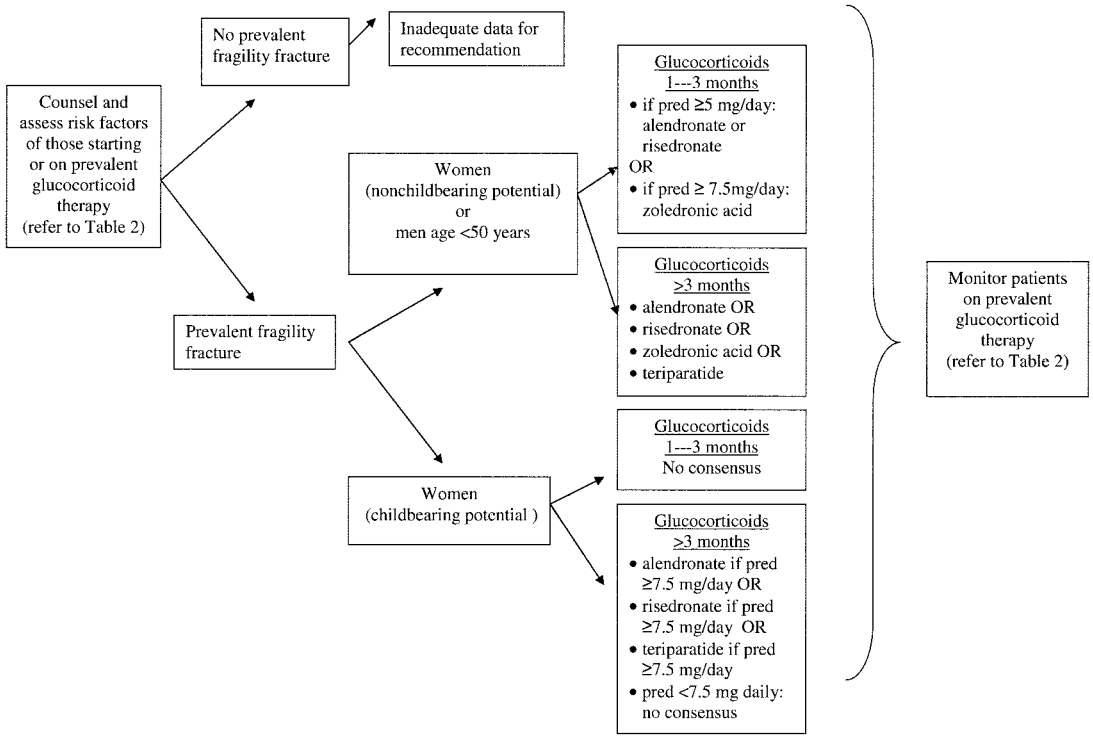

Figure 4. Approach to premenopausal women and men age <50 years initiating or receiving glucocorticoid therapy. pred = prednisone.

middle or highest tertiles (i.e., 4 to 9). Only positive statements were included in the recommendations. Absence of any recommendation should not be construed to suggest that a treatment was inappropriate in particular settings; the absence of a recommendation generally implied only inadequate or conflicting evidence.

We used the AGREE instrument to help assure that the updated recommendations covered all the important domains and attributes (90). The AGREE instrument grades elements of validity and includes 6 sections: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence.

Rating the strength of evidence. The strength of evidence was graded using the methods reported by the American College of Cardiology (91) as follows: 1) for level of evidence A, data were derived from multiple RCTs or a meta-analysis, 2) for level B evidence, data were derived from a single RCT or nonrandomized study, and 3) for level C evidence, data were derived from consensus, expert opinion, or case series. Although few RCTs were performed exclusively in premenopausal patients, many studies did include premenopausal women as part of the overall cohort. These studies were therefore included when determining the evidence grade for recommendations for premenopausal women and men younger than age 50 years.

ACR review of recommendations. In addition to traditional manuscript review, a draft of the evidence report was submitted to the ACR Guidelines Subcommittee, ACR Quality of Care Committee, and ACR Board of Directors for comments and recommendations, which were incorporated into the final recommendations.

RESULTS

The results of the modified RAND/UCLA method produced the recommendations shown below. Figures 3 and 4 represent proposed approaches to the management of GIOP. A synopsis of the recommendations are shown in the Supplementary Appendix entitled Clinician's Guide (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Recommendations for assessment, counseling for lifestyle modifications, and followup of all patients receiving glucocorticoid therapy. The 17 recommendations concerning counseling for lifestyle modifications and followup of patients receiving glucocorticoids are shown in Tables 2 and 3. In addition to the recommendations listed, using the smallest dose of glucocorticoid for the shortest duration possible was recommended as an important strategy to minimize osteoporosis risk. Since there may be no dose of glucocorticoids that does not accelerate bone loss or increase fracture risk (3), recommendations for counseling and assessment are extended to all doses of glucocorticoids used or expected to be used for at least 3 months.

The panel recommended that an assessment of fall risk could include asking patients about previous falls and observing their gait. A variety of other approaches to fall risk evaluation are also available (92,93). The panel rec-

Table 2. Recommendations on counseling for lifestyle modification and assessment of patients starting glucocorticoids at any dose with an anticipated duration ≥3 months

Recommendation	Level of evidence
Weight-bearing activities	C
Smoking cessation	C
Avoidance of excessive alcohol intake (>2 drinks per day)	C
Nutritional counseling on calcium and vitamin D intake	C
Fall risk assessment	C
Baseline dual x-ray absorptiometry	C
Serum 25-hydroxyvitamin D level	C
Baseline height	C
Assessment of prevalent fragility fractures	C
Consider radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone ≥5 mg/day or its equivalent	C
Calcium intake (supplement plus oral intake) 1,200–1,500 mg/day*	A
Vitamin D supplementation*	A

* Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids, rather than a duration of >3 months.

ommended that clinicians consider vertebral fracture assessment (VFA), especially in the setting of significant height loss or a history of back pain consistent with a fracture, or conventional spine imaging because vertebral fractures are often asymptomatic, and might change treatment recommendations for patients receiving steroids who would otherwise be considered a low or medium risk (94,95). While grade 2 and 3 vertebral fractures classified according to the Genant semiquantitative method (96) have been shown to have high specificity for vertebral fracture, the panel noted that more research is needed to improve the specificity of grade 1 fractures noted on vertebral fracture assessment.

Calcium and vitamin D supplementation counseling was recommended for all patients beginning glucocorticoid therapy. Vitamin D supplementation to achieve "therapeutic" levels of 25-hydroxyvitamin D, or dosages of 800–1,000 IU/day are 2 target dosing regimens; however, glucocorticoids can interfere with vitamin D absorption and may necessitate a higher supplementation dose to achieve therapeutic levels (97). Although serial bone density testing was recommended, the interval of such testing remains controversial (98,99). Factors that will influence the frequency of testing include the presence of additional risk factors for fracture, whether or not osteoporosis therapy has already been initiated, the results of the previous BMD, the dose of steroids, and the rate of change of the BMD.

Table 3. Recommended monitoring for patients receiving prevalent glucocorticoid therapy for a duration of ≥3 months

Recommendation	Level of evidence
Consider serial bone mineral density testing	C
Consider annual serum 25-hydroxyvitamin D measurement	C
Annual height measurement	C
Assessment of incident fragility fracture	C
Assessment of osteoporosis medication compliance	C

Table 4. Pharmacologic recommendations for postmenopausal women and men age ≥50 years starting glucocorticoid therapy with an anticipated duration of ≥3 months, or prevalent glucocorticoid therapy of a duration of at least 3 months (unless otherwise noted)

Recommendations	Level of evidence
Low-risk patient	
Alendronate for ≥7.5 mg/day prednisone	A
OR	
Risedronate for ≥7.5 mg/day prednisone	A
OR	
Zoledronic acid for ≥7.5 mg/day prednisone*	B
Medium-risk patient	
Alendronate for any dose of glucocorticoids	A
OR	
Risedronate for any dose of glucocorticoids	A
OR	
Zoledronic acid for ≥7.5 mg/day prednisone*	B
High-risk patient†	
Alendronate	A
OR	
Risedronate	A
OR	
Zoledronic acid*	B
OR	
Teriparatide‡	B

* Head-to-head comparison data available in the Discussion section.
† Any anticipated dose or duration of glucocorticoids justifies initiating prescription therapy for high-risk patients.
‡ For ≥5 mg/day prednisone with a duration ≤1 month and for any dose of glucocorticoids with a duration >1 month. Head-to-head comparison data available in the Discussion section.

Recommendations for low- and medium-risk postmenopausal glucocorticoid-treated women and glucocorticoid-treated men age ≥50 years. The recommendations for low- and medium-risk patients, as shown in Table 4, were to start prescription osteoporosis therapy for patients with an anticipated glucocorticoid usage duration of ≥3 months or those on prevalent glucocorticoid therapy for at least 3 months. The glucocorticoid dose warranting therapeutic intervention represents the practitioner's intended average daily dose and varies according to the specific medication being considered.

Recommendations for high-risk postmenopausal glucocorticoid-treated women and glucocorticoid-treated men age ≥50 years. Consistent with the National Osteoporosis Foundation Guidelines (19) that suggest treatment

when the 10-year risk of major osteoporotic fractures is ≥20% (our high-risk group), the Task Force Panel recommended that these patients receive prescription osteoporosis therapy even in the absence of glucocorticoid use, hence the recommendations for a duration of glucocorticoids of <1 month (Table 4).

Recommendations for premenopausal women and men age <50 years. Men younger than age 50 years were considered together with the premenopausal women. These 2 populations were thought to represent a similar patient group, insofar as there is limited evidence for the treatment of GIOP in both these populations. Furthermore, the risk factors that influence fracture propensity in these populations have not been well defined. The FRAX tool is currently not applicable to premenopausal women or men younger than age 40 years. Additionally, the long-term safety of medications used to treat GIOP in this population, and the risk of these medications to a fetus, either from current or previous exposure, is not well defined. For these reasons, the panel concluded that they could make recommendations only for those with a prevalent fragility fracture who were clearly at higher risk for additional fracture. For women of childbearing potential, drugs with shorter half-lives were recommended (as shown in Table 5). For those of nonchildbearing potential, the recommendations were similar to those for postmenopausal women and for men except that the anticipated duration of glucocorticoids required to trigger therapy was 3 months. The panel suggested this area warranted further research.

Table 5. Recommendations for premenopausal women and men under age 50 years with a history of fragility fracture

	Grade of recommendation
1–3 MONTHS OF GLUCOCORTICOIDS	
Nonchildbearing potential	
Alendronate if receiving prednisone ≥5 mg/day	A
OR	
Risedronate if receiving prednisone ≥5 mg/day	A
OR	
Zoledronic acid if receiving prednisone ≥7.5 mg/day*	B
Childbearing potential—Inadequate data for recommendation	
≥3 MONTHS OF GLUCOCORTICOIDS	
Nonchildbearing potential	
Alendronate for any dose	A
OR	
Risedronate for any dose	A
OR	
Zoledronic acid for any dose*	B
OR	
Teriparatide for any dose*	B
Childbearing potential	
Alendronate if prednisone ≥7.5 mg/day	A
OR	
Risedronate if prednisone ≥7.5 mg/day	C
OR	
Teriparatide if prednisone ≥7.5 mg/day*	C

* Head-to-head comparison data available in the Discussion section.

DISCUSSION

Developed using state-of-the-art validated methodology for guideline development, this report provides the updated ACR recommendations for adult patients receiving oral glucocorticoid therapy. The 2001 recommendations included counseling those patients receiving glucocorticoid therapy on smoking cessation or avoidance, limiting excessive alcohol intake, weight-bearing activities, calcium and vitamin D intake and supplementation, and obtaining baseline and followup BMD measurement. Recommendations for counseling and monitoring are now expanded to include fall risk assessment, height and 25-hydroxyvitamin D measurement, evaluation for prevalent and incident fragility fractures, and consideration for vertebral fracture assessment or radiographic imaging of the spine and calcium and vitamin D supplementation for any duration of glucocorticoid use. Updated pharmacologic recommendations are delineated for postmenopausal women and men over age 50 years, premenopausal women not of childbearing potential and men under the age of 50 years with a history of a fragility fracture, and premenopausal women of childbearing potential with a history of a fragility fracture. The newer therapies zoledronic acid and teriparatide are now recommended along with alendronate and risedronate for the treatment of GIOP, while the previously included therapies estrogen replacement and testosterone are no longer endorsed. Since BMD may not be as consistent a risk factor for fracture in GIOP when compared with other forms of osteoporosis (6), these recommendations are guided in part by the FRAX score or patients' overall clinical risk profiles. This represents an advance over previous recommendations, which relied on T scores.

While these recommendations improve upon previous statements, they are not without their limitations. The categorization of high, medium, and low risk for fracture assessment of patients is based largely on the FRAX tool (21), and there are limitations to FRAX that are important to consider. Several of the clinical risk factors contributing to FRAX do not take into account dose response but use "average" dose or exposure. However, there is good evidence that the risk associated with alcohol consumption and glucocorticoid use is dose related. Also, the computer modeling underlying FRAX uses only the bone density value for the hip, and this may be an issue in GIOP, since patients receiving glucocorticoids frequently lose bone mass in the spine before the hip, leading to a possible underestimation of fracture risk. Thus, FRAX alone cannot replace clinical judgment in risk stratification. Furthermore, based on the iterative formal group process, these

updated recommendations have added a greater number of thresholds around glucocorticoid dosing, reflecting the populations studied in clinical trials and the differing risk–benefit values of the agents. While the recommendations support the use of a variety of therapies, all medications have their own risk profiles (reviewed in the evidence report available in the Supplementary Appendix, which is available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) that need to be considered when evaluating individuals. Furthermore, every set of recommendations is limited by the quality of the available evidence, and in many situations additional clinical judgment will influence the application of these proposed recommendations.

The Task Force Panel discussed the incremental impact of various rheumatic diseases such as rheumatoid arthritis on GIOP risk and concluded that there was insufficient evidence to make disease-specific recommendations. Furthermore, this panel discussed the use of osteoporosis therapies for patients with chronic renal insufficiency and a creatinine clearance level <30 mg/minute. The panel did not reach a consensus in this population due to limited evidence, but concluded that there were certain circumstances in which therapeutic intervention should be considered for these patients, noting that these decisions should be individualized (100). Guidelines exist for the management of calcium, vitamin D, and phosphorus in patients with chronic renal insufficiency (101), and these areas were not specifically considered by the panels. Additionally, very little literature exists regarding the risk of and treatment for patients who receive intermittent pulse or intramuscular glucocorticoids without daily oral doses, and this population was not addressed in these recommendations.

The recommendations for premenopausal women and younger men are constrained by the paucity of evidence for fracture risk and the treatment of GIOP in this population. Low bone density in premenopausal patients has been associated with a lower fracture risk when compared with the same BMD in postmenopausal patients (102). However, some data also suggest that premenopausal patients receiving high-dose glucocorticoids may experience fracture at higher BMD than postmenopausal patients (103). Additionally, the majority of RCTs (with the exception of 4 that were limited to premenopausal patients) (30,33,42,44) include small proportions of premenopausal women (7–22% of the total population), thereby restricting the conclusions that can be drawn (7–9,11,12). The absence of specific recommendations should not be construed as counseling against treatment for premenopausal women and young male patients, but as an indication of the need for further research.

Despite the fact that some limited data address their efficacy in GIOP (31,50,73,83,84), the amount and quality of the data were considered insufficient for the panel to recommend the use of the following agents: ibandronate, etidronate, calcitonin, estrogen, testosterone, and raloxifene. Additionally, while these recommendations do not rate one drug as preferential over others, there are 2 recent active comparator studies of GIOP therapies. In an 18-month study with additional 36-month data, teriparatide (20 μg/day) was more effective than alendronate (10 mg/day) at improving spine and hip BMD and reducing the risk of new vertebral fractures (11,104). In a 1-year trial, intravenous zoledronic acid (once yearly) was compared with risedronate (5 mg/day) (12). At 12 months, both treatment arms showed improvement in BMD; however, the BMD in the patients receiving zoledronic acid rose significantly more than in the patients receiving risedronate at both the lumbar spine and femoral neck. The vertebral fracture rates were low and did not differ between the 2 arms.

Glucocorticoid-induced osteoporosis is an undertreated condition. With more than an estimated 1 million patients in the US receiving a prescription for glucocorticoids yearly (16), GIOP has wide-reaching consequences. The goal of these recommendations is to improve awareness and increase the rate of counseling and treatment of GIOP. Despite significant advances in the understanding of the epidemiology of GIOP and despite an increased number of higher-quality clinical trials in recent years, gaps in knowledge still exist. It is anticipated that GIOP recommendations will undergo future revisions as new evidence is developed, which will further the aim of improving care for patients treated with glucocorticoids.

Addendum. Therapies that were approved after the original literature review are not included in these recommendations.

AUTHOR CONTRIBUTIONS

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 submitted for publication. Dr. Grossman 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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