Postmenopausal Osteoporosis

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Our ultimate goal is to make donor-candidate education and acceptance more empiric and defensible. Our study provides a framework for donor evaluation that is centered on the simultaneous consideration of many clinical factors relevant to the risk of end-stage renal disease, but its application requires insight and sensitivity to nuance on the part of the clinician. Suggested framing is described in detail in the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for clinical practice.⁵ We see our work as a starting point and advocate strongly for continued efforts to improve the precision and generalizability of estimates of risk before and after donation.

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Since publication of their article, the authors report no further potential conflict of interest.

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Postmenopausal Osteoporosis

TO THE EDITOR: According to the results of two trials presented in Table 3 of the article by Black and Rosen (Jan. 21 issue),¹ the first 3 years of bisphosphonate use are beneficial for the prevention of fracture. However, the data presented in the table are misleading. The steep increase in the incidence of atypical fracture with prolonged bisphosphonate use is concomitant with little or no added efficacy in the prevention of fracture. On the basis of population-based data,² rather than theoretical calculations,¹ the risk of atypical femoral fractures for patients who receive 4 years of treatment is 126 times as high as the risk for those who did not receive treatment, which corresponds to a number needed to harm of 909 per year (odds ratio for the fifth year, 116).² When all available data on the efficacy of treatment for the prevention of hip fracture are considered — not just two out of all randomized, controlled trials — the number needed to treat (NNT) is 501 per year for the initial 3 years of use.³ Because the extension of treatment beyond 5 years does not appear to prevent nonvertebral or hip fractures,⁴ the NNT for a sixth year would be high — close to infinity. For the fourth and fifth years, the NNT would lie somewhere between 501 and infinity. It is uncertain whether there is a positive benefit:risk ratio when the duration of treatment is longer than 3 to 4 years. Recently suggested widening of the treatment indications⁵ will in-

crease the NNT. A consequence may be that the risks will outweigh the benefits even after treatment of shorter duration.

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Dr. Aspenberg reports receiving consulting fees from Eli Lilly and Amgen and grant support to his institution, Linköping University, from Eli Lilly and Amgen; holding stock in AddBio, a company trying to commercialize a method for applying a bisphosphonate coating to implants to be inserted in bone; and holding a patent for this method. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Black and Rosen suggest that the discontinuation of bisphosphonates after 5 years

of treatment should be considered for patients with a low risk of fracture. Although the data provide strong evidence that these drugs reduce the risk of fracture during the first years of use, the evidence that they do so after 5 years is weak and points toward discontinuation regardless of the risk of fracture. In an analysis of pooled data from the Food and Drug Administration, the fracture rate for patients who received continuous bisphosphonate treatment for 6 to 9 years was 10.6% and the rate for those receiving treatment for more than 9 years was 9.3%; in those switched to placebo after 3 to 4 years the fracture rate at 6 to 9 years was 8.9% and the rate at more than 9 years was 8.0%.¹ Furthermore, in the Fracture Intervention Trial Long-Term Extension (FLEX) of alendronate, participants with mineral density T scores lower than -2.5 in the hip bone had similar fracture rates regardless of whether or not they were receiving alendronate or placebo after 5 years. The authors of a recent abstract observed 28,620 patients who were receiving bisphosphonates. Patients who discontinued bisphosphonates after more than 3 years had an adjusted hazard ratio for fracture of 0.90 as compared with those who continued use.² In dogs, a longer duration of alendronate use increases brittleness.³ To date there is no evidence that longer-term use reduces the overall risk of ordinary osteoporotic fractures, whereas the risk of atypical fractures increases with time.⁴

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Dr. Ott reports receiving travel fees from Amgen. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We wish to clarify the 2010 Osteoporosis Canada guidelines¹ for the case presented

by Black and Rosen: a white woman with severe osteoporosis (T score, -2.5 or less, and a prior wrist fracture). Our guidelines recommend daily administration of 800 to 2000 IU of vitamin D for women older than 50 years of age with osteoporosis; the dose of 400 to 1000 IU, as specified in Table 1 of the article, is our recommendation for healthy adults with a low risk of fracture.

In Canada, the United States, and the United Kingdom, the 10-year risk of a major osteoporotic fracture for the case presented is more than 20% (considered high risk), and there is consensus regarding drug therapy. Canadian guidelines specifically do not recommend treatment on the basis of a T score of less than -2.5 alone (as indicated in Table 1); instead, the recommendation is based on the absolute risk of fracture over the next 10 years. For persons with a moderate risk of fracture over 10 years (10 to 20%), there are differences in the recommendations from the three countries. Canadian guidelines recommend the consideration of screening for vertebral fractures and of treatment for patients with vertebral fractures and the consideration of drug therapy for those with risk factors, whereas U.S. guidelines recommend drug therapy on the basis of T score and recommendations from the United Kingdom are age-dependent.

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THE AUTHORS REPLY: The letters from Michaëlsson and Aspenberg and from Ott question the benefits versus the risk of long-term treatment for

osteoporosis, and Michaëlsson and Aspenberg also question the short-term benefits as presented in our analysis. With regard to short-term benefits, Michaëlsson and Aspenberg state that the NNT to prevent one hip fracture is 501 (per year of treatment), whereas we estimate an NNT of 90 (per 3 years of treatment) to prevent one hip fracture. Part of the discrepancy is explained by the difference in treatment duration, but our NNT is still substantially lower. Our estimated NNT is based on two of the largest randomized, controlled trials (RCTs) involving patients treated with bisphosphonates, including the Fracture Intervention Trial, which is the pivotal study of alendronate, the drug representing the vast majority of bisphosphonate use. These two large trials included a high proportion of the women with osteoporosis who were studied in all other known large, randomized trials. The NNTs for hip fracture from these other large trials involving osteoporosis are consistent with our estimate of 90.¹ Furthermore, when all fracture types are considered, benefits are larger (and the overall NNTs smaller), since the consideration of hip fractures alone ignores about 90% of the numerical treatment benefit: our analysis shows that among 100 fractures prevented, only 11 were hip fractures.

We agree that the determination of the longer-term balance between benefit and risk is more challenging. Whereas the two small RCTs of the long-term continuation of treatment did not show a benefit with regard to nonvertebral or hip fractures, the large confidence intervals indicate that the possibility of some benefit cannot be excluded. In the FLEX study, long-term continuation of alendronate significantly reduced clinical vertebral fractures by approximately 50% and also reduced bone loss.² On the basis of these results, we recommend the use of the risk of vertebral fracture as the criterion for continuation and believe that those at the highest risk for vertebral fracture will benefit most from continuing treatment.³ With regard to the risk of atypical femoral fracture that is associated with long-term treatment for osteoporosis, there are substantial

inconsistencies in the data, as indicated by the wide range of relative risks reported in a meta-analysis.⁴ The high relative risk of atypical femoral fractures (126 for >4 years of bisphosphonate use) reported in the study by Schilcher et al. that is cited in the letter from Michaëlsson and Aspenberg is an extreme outlier when compared with all the results reported in the meta-analysis by Gedmintas et al. (relative risk, 1.70; 95% confidence interval, 1.22 to 2.37). This meta-analysis included two randomized trials of bisphosphonates with nonsignificant relative risks for atypical femur fracture. We note that the values reported in Table 3 of our article are not “theoretical” but are based on the most inclusive set of population-based studies.⁴ The inconsistencies in the data point to the urgent need for more information on both the risks and the benefits of long-term bisphosphonate treatment. We are concerned that clinicians and patients facing the uncertainties associated with long-term treatment may forgo such treatment despite its proven benefits for appropriate patients.

We thank Cheung et al. for clarifying our interpretation of the Canadian treatment guidelines.

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Since publication of their article, the authors report no further potential conflict of interest.

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Physicians and Youth Tackle Football

TO THE EDITOR: Contrary to the argument presented by Bachynski in her Perspective article (Feb. 4 issue),¹ the American Academy of Pediatrics state-

ment arguing for the continued play of youth contact sports is reasonable and evidence-based. Tackle football, with 10 deaths per million participants,