The Cost-effectiveness of Therapy With Teriparatide and Alendronate in Women With Severe Osteoporosis

Hau Liu, MD, MBA, MPH; Kaleb Michaud, MS; Smita Nayak, MD; David B. Karpf, MD; Douglas K. Owens, MS, MD; Alan M. Garber, MD, PhD

Background: Teriparatide is a promising new agent for the treatment of osteoporosis.

Methods: The objective of this study was to evaluate the cost-effectiveness of teriparatide-based strategies compared with alendronate sodium for the first-line treatment of high-risk osteoporotic women. We developed a microsimulation with a societal perspective. Key data sources include the Study of Osteoporotic Fractures, the Fracture Intervention Trial, and the Fracture Prevention Trial. We evaluated postmenopausal white women with low bone density and prevalent vertebral fracture. The interventions were usual care (UC) (calcium or vitamin D supplementation) compared with 3 strategies: 5 years of alendronate therapy, 2 years of teriparatide therapy, and 2 years of teriparatide therapy followed by 5 years of alendronate therapy (sequential teriparatide/alendronate). The main outcome measure was cost per quality-adjusted life-year (QALY).

Results: For the base-case analysis, the cost of alendronate treatment was $11,600 per QALY compared with UC. The cost of sequential teriparatide/alendronate therapy was $156,500 per QALY compared with alendronate. Teriparatide treatment alone was more expensive and produced a smaller increase in QALYs than alendronate. For sensitivity analysis, teriparatide alone was less cost-effective than alendronate even if its efficacy lasted 15 years after treatment cessation. Sequential teriparatide/alendronate therapy was less cost-effective than alendronate even if fractures were eliminated during the alendronate phase, although its cost-effectiveness was less than $50,000 per QALY if the price of teriparatide decreased 60%, if used in elderly women with T scores of −4.0 or less, or if 6 months of teriparatide therapy had comparable efficacy to 2 years of treatment.

Conclusions: Alendronate compares favorably to interventions accepted as cost-effective. Therapy with teriparatide alone is more expensive and produces a smaller increase in QALYs than therapy with alendronate. Sequential teriparatide/alendronate therapy appears expensive but could become more cost-effective with reductions in teriparatide price, with restriction to use in exceptionally high-risk women, or if short courses of treatment have comparable efficacy to that observed in clinical trials.

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While the cost-effectiveness of alendronate and other osteoporotic agents has been assessed, to our knowledge, the cost-effectiveness of teriparatide-based strategies in the United States has not been evaluated.

We evaluated the cost-effectiveness of 3 promising first-line treatment strategies in women with severe osteoporosis: alendronate therapy alone, teriparatide therapy alone, and teriparatide therapy followed by alendronate therapy. Given incomplete clinical data, we performed extensive sensitivity analyses to evaluate the effects of key variables on the cost-effectiveness of these strategies.

METHODS

We constructed a cost-effectiveness model incorporating morphometric (ie, radiologic) vertebral and clinical vertebral, hip, and wrist fractures to compare usual care (UC) (calcium or vitamin D only) with UC plus 3 treatment strategies: 3 years of alendronate therapy (alendronate alone), 2 years of teriparatide therapy (teriparatide alone), and 2 years of teriparatide therapy followed by 5 years of alendronate therapy (sequential teriparatide/alendronate). The model produced a set of incremental cost-effectiveness ratios for the treatment strategies in units of cost per quality-adjusted life-year (QALY) gained. We designed the model to be consistent with published guidelines on osteoporosis modeling. A technical appendix, which provides additional detail regarding our model, can be found online.

OSTEOPOROSIS MODEL

As recommended by Vanness et al and Kanis et al, we developed a microsimulation using computer software (TreeAge Pro 2004; TreeAge Software, Williamstown, Mass). Our model consists of 6 key elements: treatment strategy chosen, fracture state, survival during cycle, entrance to nursing home, new fracture occurrence, and adverse events from medication (data available in the previously described technical appendix). Each microsimulation consisted of 200,000 trials. We used a lifetime horizon, societal perspective, and a 3-month cycle. We discounted costs and health utilities by 3%.

PATIENT POPULATION

The target population for our analysis was postmenopausal white women with severe osteoporosis, defined by low bone mass (base case, femoral neck bone mineral density [BMD] T score of −2.5) and preexisting vertebral fracture. We chose this population because the Food and Drug Administration recommends that teriparatide be used in “postmenopausal women who are at high risk for fracture.” We chose a 70-year-old woman as our base case to mirror the age of participants of the clinical trials used in our analysis.

TREATMENT STRATEGIES

Our model consisted of UC (calcium or vitamin D supplementation) and 3 active treatment arms (alendronate alone, teriparatide alone, and sequential teriparatide/alendronate, all incremental to UC). We assumed 100% compliance in our base case. The effectiveness of a strategy consisting solely of calcium or vitamin D supplementation is uncertain, particularly in the community-dwelling ambulatory population. Consequently, we assumed in the base case that there was no additional fracture reduction benefit with calcium or vitamin D supplementation (relative risk, 1) and varied this in sensitivity analyses.

The alendronate-alone strategy consisted of alendronate sodium, 10 mg/d, with a 5-year treatment period. For teriparatide alone, we assumed that teriparatide was used at 20 µg/d subcutaneously for 2 years. For sequential teriparatide/alendronate, we assumed treatment with teriparatide for 2 years at 20 µg/d followed by alendronate therapy for 5 years at 10 mg/d.

MORBIDITY AND MORTALITY

We based fracture rates for women receiving UC on the Study of Osteoporotic Fractures, a large observational study of elderly US women. We developed logistic regressions to predict future fracture probabilities based on age, femoral neck BMD, and the presence of prior vertebral fracture (data available in the previously described technical appendix). In our base case, we assumed that clinical vertebral fractures accounted for 35% of morphometric vertebral fractures.

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COSTS

We based prescription drug prices on average wholesale prices listed in the Drug Topics Red Book and calculated costs for medical services and fractures from Medicare diagnosis related group and Current Procedural Terminology reimbursement rates or other published cost reviews (data available in the previously described technical appendix).

UTILITIES AND NURSING HOME VARIABLES

We obtained health state utilities from studies that applied time trade-off or standard gamble methods, where available; otherwise, we used values obtained from expert opinion or surrogate values (data available in the previously described technical appendix). For the base case, we assumed the same disutility for clinical and morphometric vertebral fractures within the first year after fracture (0.82), although we assumed a greater disutility during the first year of clinical vertebral fracture (0.62) in sensitivity analysis.

We used data from multiple sources to determine rates of nursing home admission, length of stay, discharge rates, and mortality rates for patients with a hip fracture (data available in the previously described technical appendix).

ADVERSE EVENTS

The model incorporates mild hypercalcemia and osteosarcoma (teriparatide) and esophagitis and esophageal ulceration (alendronate) as possible adverse events from active therapy (data available in the previously described technical appendix). We assumed that patients who experienced osteosarcoma or esophageal ulceration discontinued therapy, while patients who experienced gastrointestinal discomfort or hypercalcemia received treatment for these conditions and continued therapy. We obtained adverse event rates from pub-

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lished trials.\textsuperscript{1,11} We assumed that no cases of osteosarcoma occurred in the base case.

**FRACTURE RISK REDUCTION: BASE CASE**

We reviewed studies\textsuperscript{1,10,11,17,62-65} reporting fracture rates in osteoporotic women with prevalent fractures taking alendronate or teriparatide. We calculated relative risks for each treatment strategy, and multiplied these risks by UC fracture rates to determine treatment fracture rates (data available in the previously described technical appendix). We assumed that the reduction in the relative risk of fractures reached published rates on initiation of therapy.\textsuperscript{17,38}

For the alendronate-alone strategy, we assumed a relative risk of 0.53/0.49/0.52 for vertebral/hip/wrist fractures while receiving therapy (Table 1).\textsuperscript{1} We assumed that fracture risk returned to UC rates in a linear fashion over 5 years after cessation of alendronate therapy.\textsuperscript{26}

For the teriparatide-alone strategy, we assumed a relative risk of 0.35/0.47/0.47 for vertebral/hip/wrist fractures during therapy (Table 1).\textsuperscript{11} We applied the overall nonvertebral fracture relative risk from the teriparatide Fracture Prevention Trial (FPT)\textsuperscript{11} to determine hip and wrist fracture rates. We assumed that the fracture relative risks from the FPT (18 months of treatment) remained constant during the 2 years of teriparatide treatment. On cessation of teriparatide treatment, we assumed fracture risk returned to UC rates in a linear fashion over 5 years.

We assumed that before initiating alendronate therapy, fracture relative risk in the sequential teriparatide/alendronate strategy was the same as that of teriparatide alone. When alendronate treatment was started, we assumed that fracture risk decreased in the same proportion as it would in a treatment-naive patient. For example, we assumed a relative risk of vertebral fracture of 0.53 for alendronate\textsuperscript{4} and of 0.35 for teriparatide compared with UC.\textsuperscript{11} We assumed that subsequent alendronate therapy would, therefore, result in a relative risk of vertebral fracture of 0.19 (ie, 0.53 × 0.35) (Table 1). We assumed that fracture risk returned to UC rates in a linear fashion over 5 years after cessation of alendronate therapy.\textsuperscript{26}

**SENSITIVITY ANALYSIS**

We performed sensitivity analyses to evaluate the effects of key variables on cost-effectiveness. We varied the duration of effectiveness.

### Table 1. Key Model Variables

<table>
<thead>
<tr>
<th>Domain</th>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost, $\textsuperscript{*}</strong></td>
<td>Alendronate sodium, annual cost</td>
<td>894\textsuperscript{44}</td>
</tr>
<tr>
<td></td>
<td>Teriparatide, annual cost</td>
<td>6720\textsuperscript{44}</td>
</tr>
<tr>
<td></td>
<td>Hip fracture, direct medical costs</td>
<td>17 353\textsuperscript{44}</td>
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<tr>
<td></td>
<td>Clinical vertebral fracture, direct medical costs</td>
<td>7097\textsuperscript{44}</td>
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<tr>
<td></td>
<td>Wrist fracture, direct medical costs</td>
<td>3853\textsuperscript{44}</td>
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<tr>
<td></td>
<td>Nursing home, annual cost</td>
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<td><strong>Health state utility</strong></td>
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<td></td>
<td>Aged 60-64 y</td>
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<td>Aged 65-69 y</td>
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<td>Aged 70-74 y</td>
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<td>Aged 75-79 y</td>
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<td>Aged 80-84 y</td>
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<td>Aged ≥85 y</td>
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<td>Hip fracture, first year/subsequent year (multiplier)</td>
<td>0.797/0.90\textsuperscript{55}</td>
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<td>Vertebral fracture, first year/subsequent year (multiplier)</td>
<td>0.82 (0.62)\textsuperscript{17}/0.93\textsuperscript{17}</td>
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<td>Wrist fracture, first year/subsequent year (multiplier)</td>
<td>0.981\textsuperscript{55}/1.055</td>
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<td><strong>Relative risk of fracture, base case (while taking drug)</strong></td>
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<td>Wrist fracture</td>
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<td>Teriparatide-alone strategy</td>
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<td>Wrist fracture</td>
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</tr>
<tr>
<td></td>
<td>QALYs</td>
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</tbody>
</table>

Abbreviation: QALYs, quality-adjusted life-years.

\textsuperscript{*}Given in 2003 US dollars.

\textsuperscript{†}Used in sensitivity analysis. Further detail is given in the “Utilities and Nursing Home Variables” subsection of the “Methods” section and in the “Health State Utilities” section in the technical appendix.

\textsuperscript{‡}In our base case for sequential teriparatide/alendronate strategy, we assumed that alendronate would decrease fracture risk in the same proportion as it would in a treatment-naive patient. Further detail is given in the “Fracture Risk Reduction: Base Case” subsection of the “Methods” section.
costs $156,500 per QALY relative to alendronate alone compared with UC, and sequential teriparatide/alendronate treatment with alendronate alone costs $11,600 per QALY compared with usual care. Teriparatide alone is not a rational choice because it is more expensive and produces a smaller increase in QALYs than alendronate alone. However, in those for whom alendronate use is not feasible, teriparatide alone costs $172,300 per QALY compared with usual care.

**SENSITIVITY ANALYSIS**

**Fracture Efficacy of Alendronate**

Even if teriparatide could exert an antifracture effect for 15 years after treatment cessation, teriparatide alone remains less cost-effective than alendronate alone ($3,464,900/QALY compared with alendronate alone). Sequential teriparatide/alendronate therapy, the BMD, age, teriparatide treatment length, compliance, and other variables to evaluate their effect on cost-effectiveness.

**RESULTS**

**BASE CASE**

Treatment with alendronate alone costs $11,600 per QALY compared with UC, and sequential teriparatide/alendronate costs $156,500 per QALY relative to alendronate alone (Figure 1). Teriparatide alone is not a rational choice, because it is more expensive and produces a smaller increase in QALYs compared with alendronate alone; however, in those in whom alendronate use is not feasible, teriparatide alone costs $172,300 per QALY relative to UC.

**Teriparatide Efficacy After Treatment Cessation**

Even if teriparatide could exert an antifracture effect for 15 years after treatment cessation, teriparatide alone remains less cost-effective than alendronate alone ($3,464,900/QALY compared with alendronate alone).

**Fracture Efficacy of Alendronate Following Teriparatide**

Sequential teriparatide/alendronate remains less cost-effective than alendronate alone even if fractures are eliminated during the alendronate treatment phase of sequential teriparatide/alendronate therapy ($91,400/QALY compared with alendronate alone). If alendronate therapy could only maintain the fracture benefits gained while receiving teriparatide treatment, the cost of sequential teriparatide/alendronate would be $3,892,000 per QALY compared with alendronate alone.

**Teriparatide and Alendronate Cost**

At 40% ($2,688/y) of the base cost of teriparatide therapy, sequential teriparatide/alendronate costs $40,200 per QALY compared with alendronate alone (Figure 2A). At 25% ($1,680/y) of the base cost of teriparatide therapy, the cost of sequential teriparatide/alendronate ($11,400/QALY) would be better than that of alendronate alone.
Alendronate alone is cost saving at half its base-case price ($447/y) (data not shown).

**Teriparatide Treatment Length**

Assuming 6 months of teriparatide therapy could attain the fracture relative risks reported in the FPT, sequential teriparatide/alendronate costs $41 600 per QALY compared with alendronate alone (Figure 2B).

**BMD and Age**

The cost-effectiveness of alendronate alone and sequential teriparatide/alendronate generally improves with increasing age and decreasing femoral neck BMD (Figure 3A and B, respectively), except when sequential teriparatide/alendronate is used in very elderly women. The cost-effectiveness of sequential teriparatide/alendronate worsened from the age of 70 to 80 years (Figure 3B), likely because of the high cost of teriparatide and the limited residual lifespan in which to obtain benefit.

**Additional Sensitivity Analyses**

The relationship between the cost-effectiveness of treatment strategies does not change appreciably with modification in the discount rate, adverse event rates, costs, health state utility values, baseline fracture rates, compliance rates, or other key variables (Table 2).

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**COMMENT**

Although teriparatide is a promising new agent for the treatment of osteoporosis, we find that teriparatide-based strategies are consistently less cost-effective than alendronate, primarily because of the high cost of teriparatide. Specifically, using teriparatide alone is not a cost-effective first-line strategy in women with severe osteoporosis; it is more expensive and produces a smaller increase in QALYs than alendronate alone. While the cost-effectiveness ratio of sequential teriparatide/alendronate is consistently higher than that of alendronate alone, the ratio would decrease to less than $50 000 per QALY if the price of teriparatide was reduced 60%, if used in women with an exceptionally low BMD (femoral neck T score, ≤−4.0), or if shorter courses of teriparatide (6 months) could provide the same fracture reduction efficacy as those reported in longer clinical trials.

Two studies on the cost-effectiveness of teriparatide as a single agent compared with no active treatment reported conflicting results. Stevenson et al performed an economic evaluation of osteoporosis medications for the United Kingdom’s National Health Service. By using cost and fracture data from the British health care system, they found teriparatide alone costs £134 700 per QALY ($24 000–$77 000/QALY) compared with usual care, and the incremental cost-effectiveness ratio of sequential teriparatide/alendronate was compared with alendronate alone. Teriparatide alone is not shown because it is more expensive and produces fewer quality-adjusted life-years (QALYs) than alendronate alone in all scenarios. (The figures have different scales.) In A, at a femoral neck (FN) T-score of −3.5 or −4.0, alendronate alone is cost saving at the ages of 60, 70, and 80 years. At a femoral neck T score of −3.0, alendronate alone is cost saving at the ages of 70 and 80 years. In B, the cost-effectiveness of sequential teriparatide/alendronate worsens from the age of 70 to the age of 80 years, likely owing to the high cost of teriparatide and the limited residual lifespan in which to obtain benefit from therapy.

T score of −3.0 to range from €20 000 to €64 000 per QALY ($24 000–$77 000/QALY) compared with calcium and vitamin D supplementation alone. However, their analysis hinges on Swedish epidemiologic data for fracture and mortality risk in the years immediately following fracture, findings that remain to be validated in other populations. More important, Lundkvist et al. evaluate only teriparatide treatment vs no active treatment, and they do not compare the cost-effectiveness of teriparatide against other viable osteoporosis treatments (such as bisphosphonates), thus improving the apparent cost-effectiveness of teriparatide. Selection of appropriate comparison interventions is critical in cost-effectiveness analysis, particularly if the evaluated intervention is more costly and intensive than existing therapies. We believe our results, which compare teriparatide with the most commonly prescribed osteoporosis agent in the US market and UC, to be more relevant to clinical practice.

The effect of teriparatide on fracture risk following cessation of therapy is unclear. In the follow-up observational study of the FPT, participants treated with teriparatide who did not take subsequent osteoporosis medication
lost one third of their vertebral BMD gains within 18 months. Although teriparatide therapy’s fracture effect after its cessation is unknown, it has minimal effect on the cost-effectiveness of the teriparatide-alone strategy. Even if we assumed that the effect of teriparatide lasted 15 years after cessation of therapy with it, teriparatide alone is dominated by the other treatment strategies.

Recent studies suggest that antiresorptive therapy following cessation of teriparatide therapy increases BMD and possibly reduces fractures. Rittmaster et al.69 showed that vertebral BMD gains nearly doubled in osteoporotic women after 1 year of alendronate therapy following 12-month treatment with recombinant human parathyroid hormone (1-84). Similar increases in vertebral BMD after bisphosphonate use following the use of teriparatide or other forms of parathyroid hormone have been found in other populations.68,70,71 These studies suggest that a potent antiresorptive agent following teriparatide treatment withdrawal will likely maintain or increase BMD gains and may result in fewer fractures. While the precise fracture reduction relative risk for teriparatide therapy followed by alendronate is unknown, our results suggest that sequential teriparatide/aldronate would not be more cost-effective than alendronate even if it could eliminate hip, wrist, and vertebral fractures during the alendronate phase of therapy.

Our results are sensitive to the costs of alendronate and teriparatide therapy. A 50% reduction in the price of alendronate would make it cost saving, a price decrease that might occur after alendronate’s scheduled loss of patent protection in 2008.72 At 25% of the base price of teriparatide, the cost-effectiveness of sequential teripa-
and undertreated, we believe our results are relevant to patients receiving treatment for osteoporosis. How-

treatment of high-risk osteoporotic women compares favorably to patients receiving treatment for osteoporosis. How-

The cost-effectiveness of sequential teriparatide/alendronate may improve substantially if shorter courses of teriparatide reduce fracture at the same rate as observed in the FPT. A recent study demonstrated that cyclic teriparatide therapy in patients taking alendronate, resulting in a 50% reduction in teriparatide dose over 2 years, may be as effective as continuous teriparatide therapy in these patients. Given the potential clinical and economic benefits of such strategies, determining the optimal therapy length and dose for teriparatide and other anabolic agents remains an important area for future research.

The cost-effectiveness of alendronate alone is consistently less than $30 000 per QALY and is cost saving under certain conditions. These findings are consistent with those of prior published cost-effectiveness evaluations of alendronate. Our analysis differs from prior models in that others have used shorter time horizons and primarily non-US data sources and have developed cohort-based Markov models. The consistency of our results with prior work strengthens our conclusion that the cost-effectiveness of alendronate for treatment of high-risk osteoporotic women compares favorably with other interventions accepted as cost-effective.

Our model has several limitations. First, the results are specific to treatment-naïve women and may not be applicable to patients receiving treatment for osteoporosis. However, given that osteoporosis is significantly underdiagnosed and undertreated, we believe our results are relevant to many patients. Second, we assumed that teriparatide decreased hip and wrist fractures, although the FPT showed teriparatide to only decrease nonvertebral fractures collectively. Teriparatide-based therapies would be less cost-effective if teriparatide does not decrease hip or fracture rates individually. Third, while weekly alendronate dosing is commonly used, our model relies on fracture efficacy data from the Fracture Intervention Trial, which used daily dosing. Given that recent studies have suggested that the 2 dosing schemes are equal in efficacy, we believe our results are also applicable to weekly alendronate dosing. Fourth, our model did not evaluate raloxifene hydrochloride, because it seems to be less effective than alendronate in reducing fractures. Given that risedronate sodium and alendronate seem to have comparable antifracture effect and cost, our findings are also likely broadly applicable to risedronate.

Fifth, we did not include a quality-of-life decrement for daily subcutaneous injection of teriparatide, although including such a decrement would only strengthen our conclusions. Finally, the results of our model are specific to our model inputs. The Study of Osteoporotic Fractures, the Fracture Intervention Trial, and the FPT enrolled elderly volunteers, who may be different from elderly women in the general population, although the Study of Osteoporotic Fractures and the Fracture Intervention Trial used a population-based recruitment strategy.

The cost-effectiveness of alendronate alone for the treatment of high-risk osteoporotic women compares favorably with other interventions accepted as cost-effective. The use of teriparatide alone is more expensive and produces a smaller increase in QALYs than alendronate. Sequential therapy with teriparatide followed by alendronate is expensive; this strategy could become more cost-effective with significant reductions in the price of teriparatide, with restriction to use in exceptionally high-risk women, or if short courses of treatment have comparable efficacy to that observed in clinical trials.

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Author Contributions: Dr Liu and Mr Michaud had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

Error in Byline. In the Original Investigation by Marcus et al titled “Relationship Between Accurate Auscultation of a Clinically Useful Third Heart Sound and Level of Experience,” published in the March 27 issue of the Archives (2006;166:617-622), an error occurred in the byline. The lead author’s name should have appeared as follows: Gregory M. Marcus, MD.