

Bisphosphonates for the Prevention and Treatment of Postmenopausal Osteoporosis

by Janet Espirito, Pharm.D.

Currently in the United States, 10 million individuals have osteoporosis and 18 million more have low bone mass, placing them at risk for the disorder¹ (see Table I and Table II). Osteoporosis is a significant risk factor for fractures, which can cause chronic disabling pain and reduced quality of life (see Table III). Osteoporotic fractures account for more than 300,000 hospital admissions each year.³ Direct costs for treating osteoporotic fractures are estimated at \$10–15 billion annually.¹

Bisphosphonates are used clinically for a number of bone-related disorders, and are one of the pharmacologic options available for treating osteoporosis. As a class, they have been shown to decrease bone resorption, increase bone mineral density (BMD), and reduce the risk of fractures.⁴ For postmenopausal osteoporosis, the oral bisphosphonates can be administered at either daily, weekly, or cyclical intervals. Intravenous alternatives to oral therapy are also being studied. The intent of this article is to: (1) review the pharmacology of the bisphosphonates; (2) summarize the evidence for their use in the prevention and treatment of postmenopausal osteoporosis; and (3) discuss recent research on extended dosing intervals.

Mechanism of Action:

The pharmacologic properties of the various bisphosphonates are similar. Proposed effects on bone include: (1) direct inhibition of osteoclast function; (2) physical incorporation into the skeletal matrix thus inhibiting the process of bone resorption; and/or (3) direct inhibition of osteoblast-mediated cytokine production.⁵ Other proposed mechanisms include: inhibiting the recruitment, activation, and differentiation of osteoclast precursors, interfering with chemotaxis and attachment of osteoclasts to bone, and promoting osteoclast apoptosis.⁴ While the exact mechanism of action is unclear, the net result is decreased bone resorption and increased bone density.

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Table I: Diagnostic Criteria for Osteoporosis^{1,2}

The World Health Organization (WHO) recommends using bone mineral density (BMD) measurements to diagnose osteoporosis and predict fracture risk. T-score assignments are based on BMD as measured by dual-energy x-ray absorptiometry (DEXA).

- The T-score is defined as the number of standard deviations above or below the average BMD value for young, healthy white women.
- Osteoporosis is present when the T-score is below -2.5. It is not clear how this criteria applies to men, children, and other ethnic groups.
- The National Osteoporosis Foundation recommends pharmacologic treatment of all postmenopausal women with T-scores below -2.0, and those with T-scores below -1.5 with risk factors for osteoporosis.

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UWMC cost for a DEXA scan, including physician interpretation, is \$258.

**Table II:
Risk Factors for
Osteoporosis¹**

- Female gender
- Advanced age
- Estrogen deficiency
- White race
- Low body weight
- Low body mass index (BMI)
- Family history of osteoporosis
- Smoking
- History of prior fracture
- Use of alcohol and caffeine-containing beverages
- Diminished physical activity
- Lifestyle devoid of weight bearing exercise

**Table III:
Risk Factors for
Bone Fractures¹**

- Low bone mineral density
- History of falls
- Low physical function (slow gait, decreased quadriceps strength)
- Impaired cognition
- Impaired vision
- Environmental hazards (e.g. throw rugs)

**Table IV:
Contraindications
for Oral
Bisphosphonates⁶⁻⁸**

- Allergy to bisphosphonates
- Hypocalcemia
- Esophageal abnormalities
- Inability to remain upright for 30 minutes post-dose
- Renal insufficiency:
 - Alendronate: CrCl < 35mL/min
 - Etidronate: Scr > 5mg/dL
 - Risedronate: CrCl < 30mL/min

Pharmacokinetics:

Bisphosphonates are poorly absorbed from the gastrointestinal (GI) tract.⁵ Ingestion with food, calcium supplements, antacids, or anything other than water almost completely inhibits absorption. Therefore, patients are advised to take bisphosphonates in the morning, on an empty stomach, with a full glass of water only.⁶⁻⁸ Following oral ingestion, patients must remain upright, and not take anything else by mouth for at least 30 minutes.⁶⁻⁸ Once absorbed, bisphosphonates are retained in bone and slowly released, with a half-life of several years.⁹ An estimated 20–50% of the dose is sequestered in bone, with the rest excreted unchanged in the urine.⁵ Because elimination is primarily renal, bisphosphonates should be given with caution, or not at all, to patients with renal insufficiency⁴ (see Table IV).

Side Effects:

The main side effects of oral administration of bisphosphonates are nausea, diarrhea, and dyspepsia.⁶⁻⁸ Although rare, esophageal erosions, ulceration, or bleeding have been reported. Esophageal adverse effects may be minimized by following the labeled administration guidelines.⁵ In large randomized controlled clinical trials, GI side effects were similar to those observed with placebo. However, GI complaints may be relatively more common in clinical practice due to the elderly target population, the use of concomitant medications (e.g. NSAIDs, aspirin), and because patients with pre-existing GI disorders were often excluded from the clinical trials.¹⁰ In addition to having GI side effects, bisphosphonates can cause a reduction in serum levels of calcium and phosphorus. Patients on bisphosphonates should also receive adequate calcium and vitamin D supplementation. Calcium supplementation was a routine aspect of the bisphosphonate efficacy trials, but this convention is often overlooked in clinical practice.⁹

Prevention and Treatment of Postmenopausal Osteoporosis:

In evaluating the effectiveness of bisphosphonates for osteoporosis, the endpoints studied included evaluation of vertebral and nonvertebral fracture risk, biochemical markers of bone resorption or bone formation, and BMD. Although BMD is a good predictor of fracture risk, it is only a surrogate for the gold standard measure of efficacy, reduction in the rate of fractures.¹¹ Compared to other pharmacologic therapies for osteoporosis, the bisphosphonates have been associated with the greatest reduction in fracture rates.¹² However, this association is difficult to interpret as very few published clinical trials have compared bisphosphonates to their pharmacologic alternatives head-to-head. Selected prospective, randomized, controlled clinical trials of oral bisphosphonates for osteoporosis prevention and treatment are summarized in Table V (see page 28-29). Significant increases in BMD at several skeletal sites and/or reduced risk of fractures have been shown with etidronate, alendronate, and risedronate in early postmenopausal women with normal BMD and in postmenopausal women with established osteoporosis and a history of fractures.¹³⁻²⁶

Etidronate was the first bisphosphonate studied for use in postmenopausal osteoporosis. Despite a long history of use in other countries, etidronate is not FDA-approved in the U.S. for osteoporosis, most likely due to its paradoxical potential to inhibit mineralization of newly formed bone causing osteomalacia, bone pain, and an increased risk of fractures when given continuously at therapeutic doses.⁵ The *intermittent cyclic dosage regimen* of etidronate, however, has proven to avoid this problem, and data on the safety of treating osteoporosis with cyclic etidronate for up to seven years have been published.^{9,13-15} In these trials, etidronate demonstrated sustained clinical benefit beginning two years after initiation of treatment. Although all bisphosphonates share the potential to adversely inhibit bone mineralization if given at higher than

BMD has been demonstrated to be a good predictor of fracture risk in clinical trials; however, fracture reduction is considered the gold standard for measuring the efficacy of agents used for osteoporosis.

**UWMC/HMC
Formulary
Bisphosphonates**

Oral agents:
alendronate (Fosamax^R)
etidronate (Didronel^R)
risedronate (Actonel^R)

Intravenous agents:
pamidronate (Aredia^R)
zoledronate (Zometa^R)

Once weekly dosing appears to be a therapeutically equivalent alternative to daily doses of alendronate. Future studies are needed to prove whether there is a difference between daily and weekly dosing regimens on long-term adherence to therapy.

Two dosage strengths of alendronate are FDA-approved for once weekly dosing: a 70mg tablet for treatment, and a 35mg tablet for prevention.

recommended doses, it should be noted that the newer agents, alendronate and risedronate, can be administered *continuously* at the recommended doses, without evidence of this adverse effect.⁹ Dosage schedules and costs are shown in Table VI.

Alendronate was FDA-approved for osteoporosis in 1995. Its effectiveness for postmenopausal osteoporosis has been evaluated in several large trials, including the Fracture Intervention Trial (FIT) and the Fosamax International Trial (FOSIT), both of which showed reductions in the risk of fracture by up to 40–50%.¹⁷⁻¹⁹ In the portion of the FIT trial reported by Cummings et al., the risk of vertebral fractures was significantly reduced compared to placebo; however, the rate of clinical fractures of the spine, hip, and wrist were not significantly different from placebo.¹⁸ The latter only reached statistical significance in the subgroup of patients with T-scores ≤ -2.5.

Risedronate is the most recent oral bisphosphonate FDA-approved for osteoporosis. Of note, the risedronate trials shown in Table V *did not* exclude patients with pre-existing GI disorders or patients using concomitant NSAIDs, aspirin, H2-blockers, proton-pump inhibitors, or antacids.²¹⁻²⁴ In these trials, adverse events and discontinuation rates were similar to placebo.²¹⁻²⁴ Similar to trends in the alendronate trials, the Vertebral Efficacy with Risedronate Therapy (VERT) trial showed that risedronate reduced the risk of new vertebral fractures by up to 40–50%.^{23,24}

Table VI: Oral Dosing Recommendations for Postmenopausal Osteoporosis

Drug	Osteoporosis		HMC/UWMC Cost to patient for 3-month supply
	Treatment	Prevention	
Alendronate	10mg q day or 70mg q week	5mg q day or 35mg q week	5mg tablet (qty #90) = \$204.70 10mg tablet (qty #90) = \$198.95 35mg tablet (qty #12) = \$209.40 70mg tablet (qty #12) = \$209.50
Risedronate	5mg q day	5mg q day	5mg tablet (qty #90) = \$192.20
Etidronate (90-day administraion cycle)	400mg q day x 14 days followed by 500mg elemental calcium q day x 76 days (not FDA approved)	not FDA approved	200mg tablet (qty #28) = \$43.75

Extended Dosing Intervals:

Patients taking oral bisphosphonates must be capable of following restrictive administration precautions that may negatively affect long-term compliance. The inconvenience associated with daily administration, coupled with the long duration of effect on bone tissue, have prompted investigators to examine extending the recommended dosing intervals for bisphosphonates. The use of cyclic etidronate (daily for the first two weeks of every 90-day administration cycle) has already been mentioned as safe and effective in maintaining and increasing BMD.¹³⁻¹⁵ Two other studies have examined the safety and efficacy of once weekly alendronate for the prevention and treatment of osteoporosis.^{27,28} In a year long, double-blind, randomized, controlled trial of 1258 postmenopausal women with osteoporosis, Schnitzer et al., compared alendronate doses of 70mg once weekly, 35mg twice weekly, or 10mg daily.²⁷ Women with pre-existing GI disease or concomitant aspirin or NSAID use *were not excluded*. All three regimens produced similar increases in BMD in the lumbar spine, hip, femoral neck, trochanter, and total body. There were no significant differences in adverse effects between the three dosage regimens. The authors concluded that once weekly dosing of

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Table V: Selected Trials of Bisphosphonates for Prevention and Treatment of Postmenopausal Osteoporosis

Author	Study Subjects	Treatment	Duration	Endpoints	BMD Results	Fracture Results	
Etidronate							
Watts et al. ¹³ (n = 429)	Postmenopausal women < 75 years old with established osteoporosis, at least 1 vertebral fracture	Cyclic etidronate (400mg qd x 14 days + calcium carbonate 500mg qd x 76 days) vs. placebo x 14 days + calcium carbonate 500mg qd x 76 days	2 years	Change in BMD of spine; Rate of vertebral fractures	Significant ↑ from baseline (from 4.2% to 5.2%) in mean spinal BMD (p < 0.017) with etidronate vs. no significant change from baseline with placebo	Significant ↓ in rate of new vertebral fractures with etidronate vs. placebo (29.5 vs. 62.9 fractures/1000 patient years, p = 0.043)	
Harris et al. ¹⁴ (n = 357 after 3 years, n = 277 after 4 years)		Continuation of same trial above x 1 year, followed by open label treatment x 1 additional year	4 years		Significant ↑ from baseline in mean spinal BMD maintained after 3 years with etidronate vs. placebo (5.1%, p < 0.01); Similar effects maintained after 4 years	Non-significant ↓ in rate of new vertebral fractures with etidronate vs. placebo after 3 years (86 vs. 117 fractures/1000 patient years, p = NS); Vertebral fracture rates were lower in all groups during 4th year of study	
Miller et al. ¹⁵ (n = 193 after 7 years)	Same as above	Continuation of same trial above with 1-year open label treatment followed by 2-year double-blind re-randomization with cyclical etidronate or placebo	7 years	Same as above	Significant ↑ from baseline (from 1.8% to 2.2%) in mean spinal BMD in patients who continued therapy with etidronate vs. placebo (p < 0.05); Significant ↑ in spinal BMD from baseline (p < 0.05): 7yrs of treatment = ↑ 7.6% 5yrs of treatment = ↑ 8.6% 4yrs of treatment = ↑ 8.1% 2yrs of treatment = ↑ 3.9%	Trend toward lower vertebral fracture rates in patients with longer treatment years with etidronate than with placebo (per 1000 patient years): 7yrs = 12 5yrs = 52 4yrs = 95 2yrs = 238	
Alendronate							
Lieberman et al. ¹⁶ (n = 994)	Postmenopausal women aged 45-80 years with established osteoporosis, with or without fractures (T-score ≤ -2.5)	Alendronate 5mg qd x 3 years vs. 10mg qd x 3 years vs. 20mg qd x 2 years followed by 5mg qd x 1 year vs. placebo.	3 years	Change in BMD; Incidence of new vertebral fractures	Significant ↑ in mean BMD with all alendronate groups vs. significant ↓ in BMD with placebo; Alendronate 10mg qd (most effective dose) ↑ BMD of lumbar spine (8.8%), femoral neck (5.9%), trochanter (7.8%), and total body (2.5%) (p < 0.001 for all sites)	Significant ↓ in new vertebral fractures (6.2% of placebo patients had fractures vs. 3.2% of combined alendronate patients, 48% ↓ relative risk, p = 0.03); Trend toward reduced number of non-vertebral fractures in the alendronate group (21% ↓ relative risk, p = NS)	
Fracture Intervention Trial (FIT)	Black et al. - Vertebral Fracture Arm ¹⁷ (n = 2027)	Postmenopausal women aged 55-81 years with low bone density, at least 1 vertebral fracture (T-score ≤ -2.1)	Alendronate 5mg qd x 2 years followed by 10mg qd x 1 year vs. placebo	3 years	New vertebral fractures; Clinical fractures; Change in BMD	Significant ↑ in mean BMD of lumbar spine (6.2%), femoral neck (4.1%), trochanter (6.1%), total hip (4.7%), whole body (1.8%), and forearm (1.6%) with alendronate vs. placebo (p < 0.001 for all sites)	Significant ↓ in new vertebral fractures (15% of placebo group had fractures vs. 8% of alendronate patients, 47% ↓ relative risk, p < 0.001); Cumulative proportion of women with any clinical fracture (including vertebral, hip, and wrist) significantly lower in the alendronate group (p = 0.004)
	Cummings, et al. - Clinical Fracture Arm ¹⁸ (n = 4432)	Postmenopausal women aged 54-81 years with low bone density, no vertebral fractures (T-score ≤ -2)	Alendronate 5mg qd x 2 years followed by 10mg qd x 2 years vs. placebo	4 years	New clinical and vertebral fractures; Change in BMD	Significant ↑ in BMD at all sites including femoral neck (4.6%), total hip (5.0%), and lumbar spine (6.8%) with alendronate vs. placebo (p < 0.001 for all sites)	Non-significant ↓ in clinical fractures (14.1% of placebo group had fractures vs. 12.3% of alendronate patients, 14% ↓ relative risk, p = NS); Significant ↓ in the subgroup of patients with T-scores ≤ -2.5; Significant ↓ in new vertebral fractures (3.8% of placebo patients had fractures vs. 2.1% of alendronate patients, 44% ↓ relative risk, p = 0.001)
Fosamax Intervention Trial (FOSFIT)	Pols et al. ¹⁹ (n = 1908)	Postmenopausal women < 85 years old with low bone density (T-score ≤ -2)	Alendronate 10mg qd vs. placebo	1 year	Change in BMD	Significant ↑ in mean BMD beginning after 3 months; After 1 year, BMD ↑ at the lumbar spine (4.9%), femoral neck (2.4%), trochanter (3.6%), and total hip (3.0%) with alendronate vs. placebo (p ≤ 0.001 for all sites)	Significant ↓ in risk of clinical non-vertebral fractures (3.9% of placebo patients had fractures vs. 2% of alendronate patients, 47% ↓ relative risk, p = 0.021); Vertebral fractures were not assessed
Hoskings et al. ²⁰ (n = 1609)	Postmenopausal women < 60 years old with normal BMD	Alendronate 2.5mg qd x 2 years vs. 5mg qd x 2 years vs. placebo vs. open-label estrogen-progestin	2 years	Change in BMD	Significant ↑ from baseline in mean BMD at the lumbar spine (3.5%), hip (1.9%), and total body (0.7%) with alendronate 5mg qd vs. ↓ BMD from baseline with placebo (p < 0.001 for all sites); Response to estrogen-progestin was 1-2% greater than alendronate 5mg dose	Not assessed	
Risedronate							
Mortensen et al. ²¹ (n = 111)	Early postmenopausal women aged 40-61 years with normal BMD (T-score ± 2)	Daily risedronate (5mg qd x 2 years) vs. cyclic risedronate (5mg qd x 2 weeks followed by placebo for remainder of month x 2 years) vs. placebo	2 years + 1-year treatment free follow-up	Change in BMD	Significant ↑ from baseline in mean BMD at the lumbar spine (1.4%), prevention of bone loss occurred at the femoral neck, and trochanter with risedronate 5mg qd vs. significant ↓ from baseline in BMD with placebo (p < 0.05 for all sites); Spinal BMD ↓ to below baseline value following treatment free follow-up.	Not assessed	
Fogelman et al. ²² (n = 543)	Postmenopausal women < 80 years old with low bone mass (T-score ≤ -2)	Risedronate 5mg qd vs. placebo	2 years	Change in BMD	Significant ↑ from baseline in mean BMD at the lumbar spine (4.1%), femoral neck (1.3%), and femoral trochanter (2.7%) with risedronate 5mg qd vs. slight ↓ in BMD with placebo (p < 0.05 for all sites)	Not assessed	

Table V: Selected Trials of Bisphosphonates for Prevention and Treatment of Postmenopausal Osteoporosis (continued)

Author	Study Subjects	Treatment	Duration	Endpoints	BMD Results	Fracture Results	
Risedronate (cont.)							
Vertebral Efficacy with Risedronate Therapy [VERT]	Harris et al. - North American Study Group ²³ (n = 2458)	Postmenopausal women < 85 years old with established osteoporosis and at least 1 vertebral fracture (T-score ≤ -2)	Risedronate 5mg qd vs. placebo	3 years	Incidence of new vertebral fractures; Incidence of non-vertebral fractures; Change in BMD	Significant ↑ from baseline in mean BMD of the lumbar spine (5.4%), femoral neck (1.6%), and femoral trochanter (3.3%) with risedronate vs. placebo (p < 0.05 for all sites)	Significant ↓ in cumulative incidence of new vertebral fractures by 41% (16.3% with placebo vs. 11.3% with risedronate, p = 0.003); Significant ↓ in cumulative incidence of non-vertebral fractures by 39% (8.4% with placebo vs. 5.2% with risedronate, p = 0.02)
	Reginster et al. - Multi-National Study Group ²⁴ (n = 1226)	Postmenopausal women < 85 years old with established osteoporosis and 2 or more vertebral fractures	Risedronate 5mg qd vs. placebo	3 years	Incidence of vertebral/non-vertebral fractures; Change in BMD	Significant ↑ in mean BMD of the lumbar spine (5.9%), femoral trochanter (6.4%), and femoral neck (3.1%) with risedronate vs. placebo (p < 0.001 for all sites)	Significant ↓ in risk of new vertebral fractures by 49% (29% incidence of fracture with placebo vs. 18.1% with risedronate, p < 0.001); Non-significant ↓ in risk of non-vertebral fractures by 33% (16% with placebo vs. 10.9% with risedronate, p = NS)

Patients on bisphosphonates should also receive adequate calcium and vitamin D supplementation. This convention is often overlooked in clinical practice.⁹

Ingestion with food, calcium supplements, antacids, or anything other than water almost completely inhibits absorption. Therefore, patients are advised to take bisphosphonates in the morning, on an empty stomach, with a full glass of water only. Following oral ingestion, patients must remain upright, and not take anything else by mouth for at least 30 minutes.⁶⁻⁸

Because elimination is primarily renal, bisphosphonates should be given with caution, or not at all, to patients with renal insufficiency.⁴

alendronate provided a more convenient, yet therapeutically equivalent, alternative to daily dosing. Further studies are needed to determine if there is a difference between daily and weekly dosing regimens on long-term adherence to therapy. The safety and tolerability of alendronate 70mg once weekly were confirmed in a double-blind, placebo-controlled endoscopy study by Lanza et al.²⁸ Mean gastric erosion scores and incidences of upper GI symptoms were similar between alendronate and placebo. Thus, the once weekly regimen appears to be a safe and effective alternative to the daily dosing regimen. The favorable findings of these trials led to FDA-approval of two new alendronate dosage strengths labeled for once weekly dosing: a 70mg tablet for treatment, and a 35mg tablet for prevention.

Although not FDA approved for osteoporosis, the use of intermittent intravenous (IV) therapy with bisphosphonates is also being evaluated. Limited data suggests that IV pamidronate given every 3 months may have favorable effects on BMD in women with postmenopausal osteoporosis.²⁹ Recently, Reid et al., evaluated the use of IV zoledronate, in a one-year, randomized, double-blind, placebo-controlled trial of 351 postmenopausal women with low BMD.³⁰ This trial compared five different dosing regimens, all given as a 5-minute infusion: 0.25mg, 0.5mg, or 1mg every 3 months; 2mg every 6 months; or 4mg once yearly. All women received 1gm of supplemental calcium per day. The primary endpoint was lumbar-spine BMD. There were similar increases in BMD in all groups, ranging from 4.3–5.1% higher than placebo at 12 months (p < 0.001), with no significant difference among the treatment groups. The study was not powered to detect differences in fracture rates. Adverse events were significantly greater in the treatment group (45–67%) than in the placebo group (27%), though they did not differ significantly within the active treatment groups. Musculoskeletal pain, nausea, or fever, generally rated as mild, were the most common side effects. No adverse renal effects were reported. Treatment with zoledronate resulted in spinal BMD increases (5%) comparable to that of historic controls with daily oral alendronate 10mg/day (5%) and oral risedronate 5mg/day (3%). Markers of bone turnover remained suppressed at 12 months, prompting the authors to speculate that intervals longer than 1 year might also be effective. While larger studies are needed, this data suggesting that a once yearly IV administration of zoledronate is effective for postmenopausal osteoporosis is encouraging.

Conclusion:

Osteoporosis is preventable. Yet, obstacles to optimal treatment remain. Maintaining daily and long-term adherence to therapy for an asymptomatic disease can be challenging due to the inconvenience and side effects associated with the available

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Bisphosphonates for Postmenopausal Osteoporosis (cont.)

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medications. Bisphosphonates have been shown to be effective for osteoporosis. Based on their retention in bone, less frequent dosing is possible and may help improve compliance. Alternatives to daily oral regimens have been studied. In the future, annual or less frequent IV administration may be an option, especially for high-risk, non-compliant patients. Before use of IV bisphosphonate therapy can be recommended, however, more studies are needed to determine the optimal dose and dosing interval, the relative long-term safety, whether risk of fractures is reduced, and whether compliance is improved. Patient preference for oral versus IV therapy should be considered, as should the comparable economics of oral versus IV administration.

References available on request.

New 800 Poison Emergency Number Announced

During the recent National Poison Prevention Week, consumers were encouraged to post a new national "in case of poisoning" number next to telephones. The Consumer Product Safety Commission (CPSC), the American Association of Poison Control Centers, and the Poison Prevention Week Council recently launched the new poison emergency line (800-222-1222) that connects all callers in the United States, 24 hours a day, seven days a week, to their regional poison control center. In its first month of operation, the new toll-free number received 44,000 calls about potential poisonings.

Errata:

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Heparin-Induced Thrombocytopenia Type II: Criteria for Diagnosis and Options for Treatment: Page 11, Paragraph 4, last sentence, should read: Despite the discontinuation of heparin following the development of HIT Type II, 38% of patients will still develop thromboembolic complications, making obvious the paradoxical need for anticoagulation in these thrombocytopenic patients.⁶

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