

# Osteoporosis in postmenopausal women

## Therapy options across a wide range of risk for fracture

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Osteoporosis is a highly prevalent skeletal disorder characterized by compromised bone strength predisposing individuals to an increased risk of fractures. Fractures related to osteoporosis are frequently associated with chronic pain and decreased quality of life, as well as significant morbidity and mortality. Postmenopausal women are at higher risk for developing osteoporosis and osteoporosis-related fractures. Osteoporotic fractures are commonly asymptomatic, necessitating a need for proactive screening, diagnostic testing, and more importantly, therapeutic intervention that will rapidly reduce the risk of fractures in at-risk patients. Current pharmacologic prevention and treatment options for osteoporosis include antiresorptive therapies (alendronate, risedronate, ibandronate, raloxifene, hormone therapy, and calcitonin) and the anabolic agent teriparatide.

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**Drugs discussed:** alendronate/Fosamax • calcitonin/Miacalcin • ibandronate/Boniva • raloxifene/Evista • risedronate/Actonel • teriparatide/Forsteo

**O**steoporosis is a highly prevalent skeletal disorder characterized by compromised bone strength predisposing individuals to an increased risk of fractures.<sup>1</sup> Approximately 8 million women in the United States have osteoporosis and 22 million have low bone mineral density (BMD) of the hip.<sup>1</sup> Twenty percent of non-Hispanic white and Asian women age 50 and older are

estimated to have osteoporosis and 52% are estimated to have low bone mass. The corresponding figures for non-Hispanic black women are 5% and 35% (for osteoporosis and low bone mass, respectively); these figures are slightly higher in Hispanic women (10% and 49%). One out of every 2 white women will experience an osteoporosis-related fracture (ie, a fracture in which the associated

trauma would not have resulted in a fracture of normal bone; also called a fragility fracture). Moreover, after sustaining a vertebral fracture, risk of subsequent fracture increases 5-fold within just 1 year.<sup>2</sup> Osteoporotic fractures are painful and can be associated with decreased quality of life, as well as significant morbidity and mortality. Those who experience fractures often have some degree of permanent disability, and in the United States, up to 25% of patients who experience a hip fracture may be transferred to a nursing home.<sup>3</sup>

This review examines how women at high risk for osteoporotic fracture can benefit from an osteoporosis therapy with a rapid onset of antifracture efficacy.

### Risk factors/need for protection

Postmenopausal women are at risk for developing osteoporosis and related fractures. Risk factors for osteoporotic fractures include low BMD, prevalent fracture, increasing age, low body weight, height loss, certain medical disorders (eg, inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism, celiac disease), and history of fracture in a first-degree relative (see Table 1).<sup>3</sup> In addition to menopause, conditions or procedures associated with accelerated bone loss include use of some medications (eg, glucocorticoids, anticonvulsants such as phenytoin and phenobarbital, and cytotoxic drugs), transplantation, and immo-

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bilization (due to disease or trauma).<sup>3</sup>

Fragility fractures most commonly occur in the vertebrae (spine), proximal femur (hip), and distal forearm (wrist). A fracture at any of these sites increases the risk of future fractures.<sup>2,3</sup> Women with prevalent or pre-existing vertebral fractures have a substantial increased risk for refracturing within 1 year.<sup>2</sup> One analysis looked at data from 4 large 3-year studies of 2725 postmenopausal women with 1 or more vertebral fractures at baseline. The women were receiving only calcium (1000 mg/d) and vitamin D (up to 500 IU/d in patients with low 25-hydroxyvitamin D levels) supplementation. The analysis found a 5-fold increased risk of sustaining another vertebral fracture within the first year of the study compared with those women without prevalent vertebral fractures at baseline; fracture risk increased with increasing number of baseline fractures (see figure 1A).<sup>2</sup> In addition, those who sustained a vertebral fracture during the study had a 20% chance of sustaining another vertebral fracture within the year (see figure 1B). In another analysis of 3-year studies, 1 in 13 women with osteoporosis and no baseline vertebral fractures experienced a vertebral fracture within 1 year.<sup>4</sup>

The World Health Organization defines osteoporosis as a BMD T-score of  $\leq -2.5$ . Many patients with T-scores  $> -2.5$ , however, experienced fragility fractures in the Study of Osteoporotic Fractures (SOF), the Rotterdam Study, and the National Osteoporosis Risk Assessment (NORA) study. Results from the SOF showed that 32% of patients with hip fracture and 54% of patients with any nonvertebral fracture had a baseline BMD T-score  $> -2.0$  as measured by central (hip or spine) dual-energy x-ray absorptiometry (DXA).<sup>5</sup> Nonvertebral fractures typically include those of the clavicle, humerus, wrist, pelvis, hip, and leg. These findings were further substantiated in the Rotterdam Study, in which 56% of women with central DXA T-scores above  $-2.5$  had nonvertebral fractures during the 6.8-year follow-up.<sup>6</sup> An equal num-



Osteoporosis is a highly prevalent skeletal disorder characterized by compromised bone strength predisposing individuals to an increased risk of fractures. Nearly 30 million women in the United States have osteoporosis or low bone mineral density.

Illustration for Geriatrics by Alexandra Baker

ber of fractures occurred in both osteopenic and osteoporotic populations. Using peripheral BMD (obtained at the finger, heel, or forearm), the NORA study showed that postmenopausal women with a T-score

$\leq -1.8$  had an approximate 2-fold increased risk of fracture within the 1-year follow-up, even if they were relatively young (age 50-59).<sup>7</sup> These data show that even women with non-osteoporotic BMD experience

# Fracture risk reduction

**Table 1 Osteoporosis and fragility fracture risk factors in postmenopausal women\***

**Major risk factors**

- Current smoker
- History of fracture as an adult
- History of fragility fracture in a first-degree relative
- Low body weight (<127 lb)
- Oral glucocorticoids use >3 mo

**Additional risk factors**

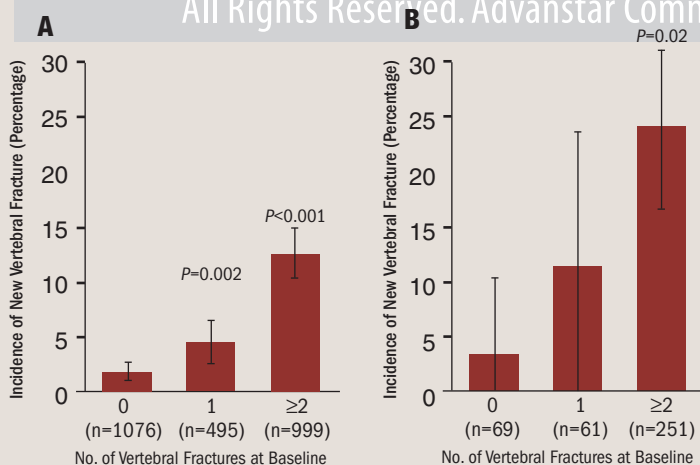
- Alcohol intake (>2 drinks/d)
- Dementia
- Estrogen deficiency at an early age (age <45)
- Impaired vision
- Low calcium intake (lifelong)
- Low physical activity
- Subjective "poor" health/fragility
- Recent falls

\*The National Osteoporosis Foundation recommends BMD testing in all women age > 65, in younger postmenopausal women with 1 or more of the above risk factors, and in postmenopausal women with a fragility fracture to confirm diagnosis and assess disease severity. Treatment is recommended in patients with no risk factors and a central DXA T-score below -2.0, with 1 or more risk factors and a central DXA T-score below -1.5, and in those with a prior vertebral or hip fracture.

DXA: dual-energy x-ray absorptiometry.

Source: Adapted with permission from the National Osteoporosis Foundation. Physician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2003.

**Figure 1 Incidence of vertebral fracture by number of baseline vertebral fractures**



A. First year of study. B. First year after vertebral fracture during study.

Source: Reprinted with permission from Lindsay R et al. Risk of new vertebral fracture in the year following a fracture. JAMA 2001;285(3):320-3

fragility fractures, emphasizing the importance of assessing risk factors beyond BMD to identify women at risk for fracture. Accordingly, the National Osteoporosis Foundation (NOF) recommends that any postmenopausal woman with a hip or vertebral fracture should be considered a candidate for osteoporosis therapy.<sup>3</sup>

Although osteoporosis is treatable, less than 1 in 4 patients with any fragility fracture are referred for further evaluation.<sup>8</sup> This finding signifies the need for more aggressive diagnostic, and, more importantly, therapeutic intervention to rapidly reduce the risk of the first fracture or subsequent fractures in at-risk patients. Primary care physicians are in a unique position to play this role. Current pharmacologic prevention and treatment options approved for osteoporosis by the U.S. Food and Drug Administration (FDA) are the antiresorptive therapies, including the bisphosphonates (alendronate, risedronate, and ibandronate), raloxifene, hormone therapy (HT), salmon calcitonin, and the anabolic agent teriparatide.

**Types of osteoporotic fractures**

When evaluating osteoporosis therapies, fracture reduction is the most important outcome in clinical trials. Morphometric (radiologically defined) vertebral fractures are diagnosed on the basis of reduced vertebral body height on radiographs (vertebral fracture typically defined as a loss of 15% to 20% or > 4 mm of vertebral height). Clinical vertebral fractures are those that cause pain and prompt patients to see their physicians. Whereas approximately 75% of vertebral fractures are asymptomatic, morphometric vertebral fracture measurement provides a more rigorous and comprehensive end point in clinical trials than clinical vertebral fracture.<sup>2</sup> As noted previously, nonvertebral fractures are often measured as a composite end point of multiple sites, such as the clavicle, humerus, wrist, pelvis, hip, and leg.

**Antifracture efficacy**

Women who are at risk for osteoporotic

**Table 2** Prospective fracture risk reduction data for osteoporosis therapeutic agents

Vertebral fractures				All nonvertebral fractures		
Agent	Fracture type	Earliest prospective end point*	Relative risk reduction (%)	Agent	Earliest prospective end point*	Relative risk reduction (%)
<b>Alendronate</b>				<b>Alendronate</b>		
FIT 1 <sup>9</sup> (5-10 mg/d)	Morphometric	3 y	47	FIT 1 <sup>9</sup> (5-10 mg/d)	3 y	NS
	Clinical	3 y	45	FIT 2 <sup>10</sup> (5-10 mg/d)	4 y	NS
FIT 2 <sup>10</sup> (5-10 mg/d)	Morphometric	4 y	44			
<b>Risedronate</b>				<b>Risedronate</b>		
VERT-NA <sup>13</sup> (5 mg/d)	Morphometric	1 y	65	HIP <sup>17</sup> (2.5-5 mg/d)	3 y	20
VERT-MN <sup>14</sup> (5 mg/d)	Morphometric	1 y	61	VERT-NA <sup>13</sup> (5 mg/d)	3 y	39
				VERT-MN <sup>14</sup> (5 mg/d)	3 y	NS
<b>Ibandronate</b>				<b>Ibandronate</b>		
BONE <sup>19</sup> (2.5 mg/d)	Morphometric	3y	62	BONE <sup>19</sup> (2.5 mg/d)	3 y	NS
<b>Raloxifene</b>				<b>Raloxifene</b>		
MORE <sup>20</sup> (60 mg/d)	Morphometric	3 y	30	MORE <sup>20</sup> (60 mg/d)	3 y	NS
	Clinical	3 y	49			
<b>Hormone therapy</b>				<b>Hormone therapy</b>		
WHI <sup>23</sup> (0.625 mg/d CEE plus progestin)	Clinical	5.6 y	35	WHI <sup>23</sup> (0.625 mg/d CEE plus progestin)	5.6 y	25
	Clinical	6.8 y	38			
<b>Calcitonin</b>				<b>Calcitonin</b>		
PROOF <sup>26</sup> (200 IU/d)	Morphometric	5 y	33	PROOF <sup>26</sup> (200 IU/d)	5 y	NS
<b>Teriparatide</b>				<b>Teriparatide</b>		
Neer et al <sup>27</sup> (20 µg/d)	Morphometric	21 m	65	Neer et al <sup>27</sup> (20 µg/d)	21 m	35

BONE=Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe; CEE=conjugated equine estrogen; FIT=Fracture Intervention Trial; MORE=Multiple Outcomes of Raloxifene Evaluation; NS=not significant; PROOF=Prevent Recurrence of Osteoporotic Fractures; VERT-MN and VERT-NA=Vertebral Efficacy With Risedronate Therapy-Multinational and -North American trials, respectively; WHI=Women's Health Initiative.

\*Only prospective end points from clinical trials are summarized. Results from retrospective analyses are not included.

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fractures should be counseled on ways to reduce their risk factors, including adequate dietary intake of calcium and vitamin D, exercise, fall prevention measures, and pharmacotherapy. The NOF recommends all patients consume at least 1200 mg/d of calcium, including supplements if necessary, and 400 to 800 IU/d of vitamin D for patients at risk for defi-

ciency.<sup>3</sup> Fall prevention measures, including modification of medications, vision/hearing examination, neurologic assessment, balance training, and environmental modification (eg, removing loose throw rugs), may be considered in individual patients, as well as hip protectors to reduce the impact of a fall should one occur.<sup>3</sup> A number of pharmacologic

agents have been evaluated in terms of antifracture efficacy. Although many studies have focused on vertebral fractures, it is important also to consider the risk of nonvertebral fractures. Table 2 provides detailed information on studies specifically designed to evaluate fracture incidence prospectively, indicating the earliest time point that risk reduction was sig-

# Fracture risk reduction

nificant in the planned analyses. An overall summary of fracture efficacy over time from both prospective and retrospective analyses is provided in Table 3. As these tables indicate, physicians have several treatment options to offer accelerated protection against osteoporotic fractures.

**Bisphosphonates:** The strongest data for rapid fracture risk reduction are seen with the bisphosphonates. Three bisphosphonates are currently approved by the FDA for the prevention and treatment of postmenopausal osteoporosis: alendronate, risedronate, and ibandronate.

Alendronate has shown efficacy in reducing the risk of vertebral and nonvertebral fractures. In the Fracture Intervention Trial, a significant reduction in the risk of new vertebral fractures, but not all nonvertebral fractures, was observed 3 and 4 years following initiation of treatment in postmenopausal women with and without baseline vertebral fractures, respectively.<sup>9,10</sup> Subsequent evaluation of women with confirmed osteoporosis showed that

the earliest time point at which a difference in clinical vertebral fracture rate was observed between treatment and placebo was 1 year.<sup>11</sup> In the same osteoporotic group, a significant reduction in nonvertebral fracture risk occurred after 2 years. The Fosamax International Trial reported nonvertebral fractures as adverse events and found that alendronate reduced this risk after 1 year of treatment.<sup>12</sup>

Risedronate has demonstrated fracture efficacy within 1 year. In the Vertebral Efficacy With Risedronate Therapy (VERT) studies, vertebral fracture risk was significantly reduced after 1 year of treatment.<sup>13,14</sup> Fracture risk reduction was shown to be sustained for up to 7 years.<sup>15</sup> When data from the VERT studies were further evaluated, the occurrence of new clinical vertebral fractures was significantly reduced after 6 months of treatment.<sup>16</sup> Risedronate has also shown reductions in nonvertebral fracture risk, with 2 studies demonstrating efficacy after 3 years.<sup>13,17</sup> In addition, a subsequent analy-

sis of large pivotal trials indicated that after only 6 months, treatment with risedronate significantly reduced the risk of nonvertebral fractures.<sup>18</sup>

Daily (2.5 mg) and intermittent (20 mg every 3 mo for 12 doses) ibandronate doses were effective in reducing the risk of both morphometric and clinical vertebral fractures over 3 years.<sup>19</sup> The incidence of nonvertebral fractures was similar in the ibandronate and placebo groups.

**Other osteoporosis therapies:** Raloxifene is a selective estrogen receptor modulator that has been shown to reduce vertebral fracture risk. Patients treated with raloxifene (60 mg/d) in the Multiple Outcomes of Raloxifene Evaluation study had a significant reduction in the risk of morphometric vertebral fractures after 3 years of treatment that continued through year 4.<sup>20,21</sup> An analysis of new clinical vertebral fractures found a risk reduction after the first year.<sup>22</sup> Treatment with raloxifene did not significantly reduce the occurrence of nonvertebral fractures.<sup>20</sup>

**Table 3 Significant fracture risk reductions\* for osteoporotic therapies over time**

	6 Month	1 Year	2 Years	3 Years	4 Years	5 Years	6-7 Years
Alendronate <sup>†9-12</sup>		□ ●	□ ●	■ □ ●	■		
Risedronate <sup>‡13-18,28</sup>	□ ●	■ □ ●	■ ●	■ ●		■ ●	■
Ibandronate <sup>19</sup>			■	■ □			
Raloxifene <sup>20-22</sup>		□	□	■ □	■		
Hormone therapy <sup>§23,24</sup>							□ ●
Calcitonin (200 IU/d) <sup>26</sup>				■		■	
Teriparatide <sup>¶27</sup>			■ ●				

■=morphometric vertebral fractures; □=clinical vertebral fractures; ●=nonvertebral fractures

FIT=Fracture Intervention Trial; FOSIT=Fosamax International Trial.

\*Clinical comparisons performed between patients receiving therapeutic agent vs placebo at each specified time point. Both prospective and retrospective analyses from clinical studies are included.

†In the 1-year FOSIT study, nonvertebral fractures were captured through adverse event reporting. For the 2- and 3-y results from the FIT study, nonvertebral fractures were confirmed by radiologic procedure and defined as all nonvertebral fractures with the exception of those of the skull or face. Also excluded were pathologic fractures and those due to trauma that would fracture a bone in a young adult.

‡Nonvertebral fractures were confirmed radiographically and defined as fractures of the clavicle, humerus, wrist, pelvis, hip, or leg, regardless of trauma.

§Nonvertebral fractures were reported in a semiannual questionnaire and confirmed radiographically. Reports of nonvertebral fractures excluded those of the skull, face, ribs, chest/sternum, cervical vertebrae, toes, and fingers.

¶Nonvertebral fractures were confirmed radiographically and included all nonspine fractures.


Source: Created for Geriatrics by RG Miller, MD, MBA

Other agents that have been investigated include HT, calcitonin, and teriparatide; however, short-term (1 year) efficacy data are not available for these agents. The Women's Health Initiative study demonstrated that long-term treatment with estrogen alone or in combination with progestin resulted in a reduction in clinical vertebral fractures, although the benefits of HT may not outweigh the risks.<sup>23,24</sup> In addition, when data from other HT studies were evaluated, the risk of nonvertebral fractures was significantly reduced; however, this benefit was diminished if women started therapy after the age of 60 years.<sup>25</sup> Intranasal salmon calcitonin, 200 IU/d, reduced vertebral fracture risk after 3 and 5 years of treatment.<sup>26</sup> There are no published data showing non-vertebral fracture reduction with the approved dosage of salmon calcitonin. Finally, teriparatide, a recombinant parathyroid hormone administered subcutaneously, is the only anabolic agent currently available in the United States. In the only pivotal fracture trial reporting to date, treatment with teriparatide 20 µg/d was shown to significantly reduce the risk of both vertebral and nonvertebral fractures after 21 months.<sup>27</sup>

## Summary

Osteoporotic fractures can result in significant morbidity that may affect an individual's quality of life and increase the risk of mortality. Postmenopausal women are at high risk of experiencing fractures even before BMD has declined to the diagnostic threshold of osteoporosis. Once a fracture occurs, there is an increased risk of subsequent fracture within the year. Indeed, 20% of patients experience another vertebral fracture within 1 year of sustaining a vertebral fracture.

Physicians have a number of therapeutic options that not only quickly reduce the risk of fracture but also consistently provide protection over many years. Risedronate has demonstrated a reduction in the risk of clinical vertebral and nonvertebral fractures as early as 6 months. Available data for alendronate

and raloxifene demonstrate a reduction in clinical vertebral fracture risk within 1 year. Therefore, given the high risk of recurrent fracture and the availability of therapies with a fast onset of action, efforts to provide rapid protection against osteoporotic fractures are warranted in at-risk patients. 

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### Additional Resources

**NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA.* 2001;285:785-795.**

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