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THE HIP TRIAL

Risedronate prevents hip fractures, but who should get therapy?

ABSTRACT

The Hip Intervention Program (HIP) trial establishes that risedronate (Actonel) prevents hip fracture in elderly women with osteoporosis. However, the drug had no statistically significant effect on hip fracture risk in elderly women in whom bone density status was not known. Patients should be selected for bisphosphonate therapy on the basis of low bone density. A history of vertebral fractures increases the risk for hip fractures.

KEY POINTS

In women age 70 to 79 with low bone density, risedronate had a statistically significant effect in reducing hip fractures. Patients with a history of vertebral fractures are a subset most likely to benefit.

Although women age 80 and older who did not necessarily have low bone density saw no effect of risedronate, it is possible that a properly selected subgroup of older patients with multiple risk factors may benefit from bisphosphonate therapy.

The HIP study did not rigorously evaluate or systematically record risk factors other than bone density. Thus the effect of these factors, singly or in combination, cannot be analyzed.

The contribution of low bone mass to hip fracture risk may actually decline with age as other skeletal and nonskeletal factors, such as the increased risk of falls, become more important.

BISPHOSPHONATES increase bone density and reduce vertebral and nonvertebral fractures, but, until recently, no randomized controlled trial of bisphosphonates has had hip fracture as the primary outcome measured. The Hip Intervention Program (HIP) is the first randomized controlled trial of a bisphosphonate with hip fracture incidence as the primary outcome.

The HIP trial results[1] show that the bisphosphonate risedronate (Actonel) reduced the risk of hip fracture in women age 70 to 79 with osteoporosis; the effect appeared most significant in those women who had a history of vertebral fractures.

Although no effect was found in older women in whom bone density was not measured, the HIP study did not evaluate or record risk factors for hip fractures in a systematic manner.

At the end of this article, I discuss my recommendations for treatment strategies for different patients.

HIP FRACTURE AS A PUBLIC HEALTH ISSUE

Preventing hip fracture is an important public health issue as the American population ages. In 1991, there were 300,000 hip fractures in the United States, a number expected to double by the year 2025.[2]

Aging has a marked effect on risk of falls; yearly risk increases from 1 in 5 in the 60-to-64 age bracket to 1 in 3 in the 80-to-84 bracket.[3] At age 50, a white woman has a 17% lifetime risk of hip fracture.[4]

Up to 50% of hip fracture patients will have permanent functional disability, and hip

TABLE 1

Clinical risk factors for hip fractures in the HIP trial

Difficulty standing from a seated position
Poor tandem gait
Fall-related injury in the previous year
Psychomotor score ≤ 5 on the Clifton modified spiral maze test
Smoking within the past 5 years
Maternal history of hip fracture
Previous hip fracture
Hip axis length ≥ 11.1 cm

fracture raises the risk of death by 12% to 20%.[5,6] In addition, the costs of hip fractures account for approximately 55% of the $17 billion per year spent on osteoporosis.

THE HIP STUDY DESIGN

Hip fracture increases the risk of death by up to 20%

The HIP study was a randomized controlled trial comparing risedronate with placebo in 9,331 elderly women at high risk of hip fracture.

Inclusion criteria

The researchers chose two groups of women at high risk of hip fracture: a relatively younger group and an older group.

The younger group (age 70–79; n = 5,445) was chosen on the basis of confirmed osteoporosis. They had either extremely low bone density (a T score < –4.0), or low bone density (a T score < –3.0) plus at least one additional clinical risk factor for hip fracture (TABLE 1).

The bone density T scores were later recalculated in light of a discrepancy between the densitometer's reference database and the data from the Third National Health Assessment and Nutrition Examination Survey (NHANES III). After recalculation, the T scores in the younger group were between –2.7 and –2.9.

The older group (age 80 and older; n = 3,886) was chosen primarily on the basis of clinical risk factors. These women had to have at least one clinical risk factor (TABLE 1). If no risk factors were present the patient could be enrolled if bone densitometry revealed a T score lower than –4.0, or a T score lower than –3.0 with a hip axis length of 11.1 cm or more (this represented 16% of the 3,886 women).

Treatment

All women took calcium 1,000 mg daily. Vitamin D (up to 500 IU daily) was prescribed if the serum 25-hydroxyvitamin D level at baseline was less than 16 ng/mL.

The trial was designed to have three treatment groups, with patients randomly assigned to receive placebo, risedronate 2.5 mg/day, or risedronate 5.0 mg/day. However, data from the two risedronate groups were pooled in the primary analysis. Previous risedronate trials[7,8] had shown that the 2.5-mg and 5.0-mg doses were equally effective in reducing the frequency of vertebral compression fractures. In addition, pooling increased the study's power because there were relatively few hip fractures in the cohort.

The mean duration of therapy was 2.0 years, and the mean follow-up was 2.3 years. Complete follow-up data were available on only 64% of the patients. Only about half of the women took the study medication for the entire prespecified 3-year study period.

The *New England Journal of Medicine* reviewers requested that the study be analyzed as an intent-to-treat trial, meaning that data from patients who took *any* risedronate or placebo were analyzed as if they had taken the entire course of medication. To comply with the request, the investigators obtained data from about half of the patients who had dropped out or discontinued therapy.

The value of intent-to-treat analysis

Intent-to-treat analysis helps reduce any bias that would occur if the proportion of dropouts was not the same in both treatment groups (for example, if side effects made patients taking the active drug more likely to drop out than patients taking placebo).

Intent-to-treat analysis is also a statistically conservative strategy. Patients who dropped out of the risedronate group were analyzed as

TABLE 2

The HIP study: Risedronate reduces hip fractures...

	% WITH HIP FRACTURES*		RELATIVE RISK	*P* VALUE
	PLACEBO	RISEDRONATE		
Overall group	3.9	2.8	0.7	.02
Younger group†	3.2	1.9	0.6	.009
With vertebral fractures	5.7	2.3	0.4	.003
Without vertebral fractures	1.6	1.0	0.6	.14
Older group‡	5.1	4.2	0.8	.35

...and all nonvertebral fractures

	% WITH NONVERTEBRAL FRACTURES*		RELATIVE RISK	*P* VALUE
	PLACEBO	RISEDRONATE		
Overall group	11.2	9.4	0.8	.03
T score < –2.5	10.7	8.4	0.8	.03
Younger group† with vertebral fractures	16.1	10.3	0.7	.01

*Mean 2.0 years of therapy; risedronate 2.5 mg or 5.0 mg
†Women 70 to 79 years old at baseline with a T score lower than –4.0 or a T score lower than –3.0 with at least one clinical risk factor (TABLE 1)
‡Women 80 years and older at baseline with at least one clinical risk factor (TABLE 1), or a T score lower than –4.0, or a T score lower than –3.0 with a hip axis length ≥ 11.1 cm

ADAPTED FROM MCCLUNG MR, GEUSENS P, MILLER PD, ET AL. EFFECT OF RISEDRONATE ON THE RISK OF HIP FRACTURE IN ELDERLY WOMEN. THE HIP INTERVENTION PROGRAM STUDY GROUP. N ENGL J MED 2001; 344:333–340.

< 1/2 of 80-to-84-year-old women have osteoporosis (hip T score < –2.5)

part of the treatment group even if they didn't take the drug long enough to produce any effect. This strategy makes the average effect in the treatment group smaller than it would be if everybody in the treatment group had taken the full course of the drug. If this attenuated effect size is statistically significant, the researchers can be confident that the true effect size is also significant.

RESULTS OF THE HIP STUDY

Effect on hip fractures significant, but history of vertebral fractures important

Hip fractures occurred in 232 of the 9,311 women who received at least one dose of study medication: 3.9% of those taking placebo vs 2.8% of those taking risedronate (TABLE 2). There was a statistically significant reduction in the younger patients with osteoporosis, but not in the older, at-risk group.

A post hoc analysis was done in the younger age cohort, based on presence or absence of vertebral fractures. The relative risk of hip fracture in risedronate-treated women with vertebral fractures was 0.4 (P = .003), while in those without vertebral fractures the relative risk was 0.6 (P = .14).

The 2.5-mg and 5-mg treatment groups were pooled because of the lower-than-expected number of hip fractures. A post hoc analysis revealed a relative risk for hip fracture of 0.5 (95% confidence interval 0.3–0.9) for the 2.5-mg dose and 0.7 (0.3–1.1) for the 5-mg dose. Since these confidence intervals overlap there is no statistically significant difference between the two groups.

Effect on all nonvertebral fractures

The primary end point was hip fractures alone, but a secondary analysis of all nonvertebral fractures grouped together showed that

TABLE 3

Comparing the FIT and HIP trials

	FIT*	HIP (YOUNGER GROUP WITH VERTEBRAL FRACTURES)†
Number of patients	2,027	1,703
Mean age	71 years	74 years
Mean hip T score	–2.1	–2.7 to –2.9
Patients who completed the study	94%	69%
No. of hip fractures	33	47
Hip fractures in the placebo group	2.2%	5.7%
Reduction in hip fractures with therapy	50%	60%
Reduction in nonvertebral fractures	19%	36%‡

*FIT = Fracture Intervention Trials[10]
†HIP = Hip Intervention Program[1]; group with vertebral fractures determined in post hoc analysis
‡16% in the entire cohort (younger and older groups combined)

risedronate protected against this end point as well (TABLE 2).

CONCLUSIONS FROM HIP: DO NOT TREAT BY AGE ALONE

Combinations of clinical risk factors and low bone density may elevate fracture risk

On the basis of the HIP study, we can conclude that risedronate reduces the frequency of hip fracture in elderly women with confirmed osteoporosis, but not in women over age 80 in whom bone density was not measured.

This study suggests that treating women on the basis of their age alone is not an effective therapeutic strategy. It is more effective to target therapy to older women with low bone density.

Comparing HIP's conclusions with other trials

The conclusions from HIP are compatible with those from many of the other trials of interventions for osteoporosis. Nevertheless, direct comparisons should be made cautiously, because the trials differed in design and in study populations.

The Fracture Intervention Trials evaluated the effect of alendronate (Fosamax) in postmenopausal women with low bone mass, with vertebral fractures (FIT 1) or without vertebral fractures (FIT 2).[9,10] Alendronate was associated with a 50% reduction in risk for hip fractures among women with vertebral fracture (mean hip T score of –2.1) and a smaller (19%–27%) reduction in all nonvertebral fractures. FIT 2 did not show a reduction in hip fracture; however, a post hoc analysis of women with T scores lower than –2.5 did show a reduction in hip fractures, and alendronate reduced hip fractures in women with T scores higher than –2.5 who had vertebral fractures.

Although the FIT and HIP trials will inevitably be compared (TABLE 3), any apparent differences or similarities must be viewed with caution because of important differences in the study samples. Nevertheless, both studies suggest a significant reduction in hip fracture risk with bisphosphonates in women with low bone mass and vertebral fractures.

Unfortunately, the HIP study did not rigorously evaluate or systematically record risk factors other than bone density. Thus the effect of single or multiple risk factors on fracture risk and bisphosphonate efficacy cannot be analyzed.

In the **Study of Osteoporotic Fractures** (SOF),[11] risk factors such as family history of osteoporosis, low body weight, current smoking, previous fracture, and increased risk of falling contributed to the risk of fracture inde-

pendently of bone density and in an additive fashion. In the SOF cohort, patients in the lowest tertile for bone density with 0, 1, or 2 additional risk factors had a risk of hip fracture of 0.26% per year. However, subjects in the lowest tertile for bone density with 5 or more risk factors had a hip fracture rate of 2.7% per year, a rate of fracture 10 times greater despite similar bone density.

The importance of bone density

Bisphosphonates require low bone mass to exert their antifracture effect. If an increase in fracture risk is caused by increased tendency to fall rather than by decreased bone mass,[12] bisphosphonates are not likely to be effective.

The commonly held notion that all women over the age of 80 are osteoporotic is not true. The Third National Health Assessment and Nutrition Examination Survey (NHANES III) found that only 42% of women age 80 to 84 have a T score lower than –2.5 in the femoral neck (**TABLE 4**).[13]

Although age is a significant risk factor for fractures, since many patients over age 80 do not have osteoporosis, measurement of bone density is necessary to choose subjects who will benefit from bisphosphonate treatment.

Falls increase in importance in older patients

The contribution of low bone mass to hip fracture risk may actually decline with age as other skeletal and nonskeletal factors become more important. This can be inferred from analysis of the Rotterdam study,[14] which followed a large European cohort for hip fracture and risk factors for fracture. A 58-year-old patient with a femoral neck bone density of 0.5 g/cm^2 has a 1-year risk for hip fracture of 0.5%, but a similar patient at age 90 with the same bone density has a 5% 1-year risk for hip fracture. This 10-fold increase is caused by factors related to aging and not by a decline in bone density.

In a study that demonstrated the declining importance of bone density in older patients, Cooper et al[15] examined Singh lines, which are radiologically evaluated stress lines in the upper femur that are surrogates for bone density. In patients younger than 65 years, the risk of hip fracture in the most osteoporotic subjects (those in the lowest quartile of Singh grade) was 33 times the risk in the least osteoporotic subjects. However, in the over-85 age group, the risk of fracture in the most osteoporotic patients was only five times the risk in the least osteoporotic ones. Thus, in elderly patients, osteoporosis is a relatively less important risk factor for fracture.

TABLE 4

Prevalence of osteoporosis in women: Two studies

AGE, YEARS	PERCENT WITH HIP T SCORE ≤ –2.5	
	NHANES III*	EPIDOS*
80–84	42%	46%
85–89	51%	56%
≥ 90	57%	60%

*NHANES = National Health and Nutrition Examination Survey; EPIDOS = *Epidémiologie de l'ostéoporose* (Epidemiology of Osteoporosis)

DATA FROM LOOKER AC, JOHNSTON CC JR, WAHNER HW, ET AL. PREVALENCE OF LOW FEMORAL BONE DENSITY IN OLDER U.S. WOMEN FROM NHANES III. J BONE MINER RES 1995; 10:796–802; AND SCHOTT AM, CORMIER C, HANS D, ET AL. HOW HIP AND WHOLE-BODY BONE MINERAL DENSITY PREDICT HIP FRACTURE IN ELDERLY WOMEN: THE EPIDOS PROSPECTIVE STUDY. OSTEOPOROS INT 1998; 8: 247–254.

Further evidence that skeletal factors are not the sole risk factors comes from a study by Beck et al,[16] which showed that the elastic modulus, a measure of the bending and torsional strength of the femoral neck, does not decline after age 50 in men. Even though bone density decreases, the decrease is mechanically offset by expansion of a bone's subperiosteal diameter.

An increased tendency to fall, and to experience more damaging falls, is a significant cause of the increase in fracture risk. Laboratory tests show that falls can generate a force 10 times that needed to fracture a femur.[17] An 80-year-old is more likely to fall to the side on the greater trochanter and transmit all the force to the hip, and is less likely to cushion the fall with his or her arm.

The implication is that bisphosphonates can reduce the risk for fracture when the primary reason for fracture is low bone mass, but not when the reason is falling per se.

Increased hip fracture risk with age may be due to more falls, as well as lower bone density

TABLE 5

Number needed to treat (NNT) and cost to prevent one hip fracture

INTERVENTION	GROUP	NNT*	COST
Risedronate	HIP study (entire cohort)[1]	91	$229,000
	HIP study (younger group)	77	$194,000
	HIP study (younger group with vertebral fracture)	29.4	$74,000
Alendronate	FIT 1[10]	91	$229,000
	FIT 2 (T score ≤ –2.5)[9]	81	$204,000
Hip protectors	Kannus et al[21]	13.6	$3,672
Fall prevention	Tinetti et al[19,20]	NA	$194,700†

*NNT = number needed to treat for 3 years to prevent one hip fracture, NA = not applicable
†Assuming 1% of all falls result in hip fracture; if 2% of falls result in hip fracture, the cost would be $97,350

WHEN ARE BISPHOSPHONATES COST-EFFECTIVE?

Determining the cost-effectiveness of bisphosphonate therapy requires a complex calculation.

Hip protectors are cheap and effective but patients don't like them

The number needed to treat

If the absolute reduction in risk is divided into 1, the result is the *number needed to treat* (NNT), the number of patients that need to be treated with a drug to prevent an event. For example, if the absolute risk reduction is 5% or 0.05, the NNT is 20. The total cost to prevent an event is the NNT times the cost of the drug.

The NNT depends on the baseline rate of events. Consider a study subgroup in which 10% of the patients receiving placebo had a fracture, vs 5% of the treated patients. In this case, the relative risk reduction is 50%, the absolute risk reduction is 5 percentage points, and the NNT is 1 / 0.05 = 20.

In contrast, consider a second subgroup in which the risk of fracture in the placebo recipients was 5%, and the risk in the treated patients fell to 2.5%. The relative risk is still halved, but the absolute risk reduction is only 2.5 percentage points, so the NNT would be 1 / 0.025 = 40. Twice as many patients would have to be treated to prevent a single event—at twice the cost.

Thus, a cost-effective strategy requires selecting patients at high risk for fracture. The HIP trial found that the osteoporotic patients ages 70 to 79 without vertebral fractures had hip fractures too rarely for risedronate to show a statistically significant effect. Similarly, patients in the placebo group in the MORE (Multiple Outcomes of Raloxifene Evaluation) trial had a low rate of hip fracture. The frequency was only 0.7% over 3 years, even though they had a mean hip T score of –2.6.[18]

Bisphosphonate therapy

Preventing hip fractures with medication is costly because these medications cost about $70 per month, or $840 per year. The NNT for the HIP patients ages 70 to 79 who had vertebral fractures was 29.4; the 3-year cost to prevent a hip fracture would be 29.4 × $840 × 3 = $74,088. However, the NNT for similar patients without vertebral fracture was 77; the 3-year cost would thus be $194,040 (TABLE 5).

Fall prevention programs

Fall prevention programs are also costly, and the 3-year cost to prevent one fracture has been estimated at $194,700.[19,20]

Hip protectors

Hip protectors are much less expensive, but are unlikely to be used by ambulatory patients

who do not live in a nursing home. Kannus et al[21] estimated that the NNT to prevent a hip fracture using the hip protector was 13.6. The cost of the device is $90. If the hip protector is replaced yearly, the cost spent over 3 years to prevent one fracture is thus 13.6 × $270 = $3,672.

Calcium and vitamin D

All patients should receive calcium and vitamin D, which have been shown to reduce nonvertebral fracture risk in randomized controlled trials.[22,23]

Fall protection in patients at high risk of falling

In patients at high risk for falls, fall prevention using physical therapy, balance programs, or tai chi can reduce the fall risk. Those who fall frequently should consider a hip protector.

Therapy in women with a history of vertebral fractures

In addition to calcium and vitamin D, bisphosphonates are indicated in patients with low bone mass and are especially effective in patients with vertebral fractures. In the FIT 1 study, a bisphosphonate reduced the risk of hip fracture for patients with a mean T score of –2.1 and a vertebral fracture. In addition, it is possible that patients with T scores between –1.5 and –2.1 with vertebral fracture and other risk factors would benefit from treatment.

Therapy in women without vertebral fractures

For patients without vertebral fractures, a lower bone density is needed to result in effective hip fracture reduction, as demonstrated in the FIT 2 and HIP studies.

Women with other risk factors

The presence of other risk factors (TABLE 1), especially multiple risk factors, should probably lower the effective threshold for treatment, but important questions remain about how these risk factors interact with bone density and affect treatment efficacy.

Recent studies show that only about half of all hip fractures occur in patients with T scores lower than –2.5. Using SOF data, Wainwright et al[24] estimated that 54% of all hip and spine fractures occur in patients with a T score lower than –2.5. An analysis of data from the Rotterdam study estimated that only 22% of nonvertebral fractures would be targeted using a T score cut point of –2.5.[25]

Thus, to make a large reduction in the number of hip fractures, patients with so-called osteopenic T scores (scores between –1.0 and –2.5) would have to be treated. However, using bone density as the sole criterion would select a large number of low-risk women and thus would be expensive. Bone density, age, and other clinical risk factors should all be considered in developing cost-effective strategies for hip fracture prevention.

PREVENTING HIP FRACTURES: MY RECOMMENDATIONS

What can we conclude from the HIP study and prior studies?

- We now have two bisphosphonates demonstrated in randomized controlled trials to reduce the risk of hip fracture: alendronate and risedronate.
- The most significant reduction in hip fracture with risedronate treatment occurred in patients with low bone mass and vertebral fracture.
- Treatment of women based on older age without measurement of bone density is not an effective strategy to reduce hip fractures, since fewer than 50% of women 80 to 84 years old have a hip T score lower than –2.5.

Prescribe calcium and vitamin D for all patients at risk of hip fracture

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