In three consecutive years 462 patients over the age of 60 years presented at Waikato Hospital, Hamilton, New Zealand, with a fracture of the proximal femur. Within two years, 11 (2.4%) returned with a fracture of the contralateral femur. If the effectiveness of any form of treatment aiming at reducing the incidence of contralateral fracture were subjected to a trial, a sample size of 5000, randomly distributed equally between treatment and placebo groups, would be needed for the trial to have a power of 80% to detect a reduction.

Received 23 March 1998; Accepted after revision 24 August 1998

One aspect of the treatment of serious morbid conditions such as myocardial infarctions or strokes is to attempt to prevent their recurrence. This principle applies to fractures associated with bone fragility. Since operative fixation is the preferred treatment for most fractures of the proximal femur, institutions with acute orthopaedic services are well placed to provide treatment aimed at reducing the risk of contralateral fractures. To date, no randomised controlled trial has been done to determine whether any form of treatment would effectively reduce the risk of a second fracture. This paper discusses the size of the sample which would be required in such a trial.

Patients and Methods

Waikato Hospital in Hamilton, New Zealand, serves a population of 250 000, 13% of which are over the age of 60 years. Since 1991, all patients over 60 years of age admitted with a proximal femoral fracture have been placed on a computerised register and reviewed by either a consultant geriatrician or a senior geriatric registrar. Ward rounds three times a week have provided close and regular contact between the geriatric liaison and the acute orthopaedic services.

When patients with a fracture of the proximal femur were admitted in the years 1992, 1993 and 1994, the orthopaedic records were checked to see whether they had previously been admitted with a similar contralateral injury. Fractures resulting from metastases, those with substantial subtrochanteric extension, and those around or adjacent to previous arthroplasty or internal fixation were excluded.

The calculation of the incidence of contralateral fracture uses as a denominator all patients who appeared in the orthopaedic records in the first year of interest for the particular cohort. The number of participants needed for a trial to be effective is based on the normal approximation to the binomial distribution.

Results

Table I gives the number of patients with fracture of the proximal femur and the number of those who had a second fracture within two years. Overall, the incidence of contralateral fracture at two years was 2.38%. The 95% confidence interval, based on the 462 patients listed, was 2.37% to 2.39%. The mean time to the second fracture was 372 days (SD 172, median 368, range 67 to 651).

The low incidence of contralateral fracture means that a large number of patients would have to participate in a trial before a difference became detectable. For example, in a trial involving 2500 subjects in a placebo group and 2500 in a treatment group, 60 contralateral fractures could be expected to occur in the placebo group within two years. To refute the null hypothesis that the incidence of contralateral fracture was the same in both groups, the number of contralateral fractures in the placebo group would have to be smaller than a critical number. Using the normal approx-

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients with initial fracture</th>
<th>Patients with second fracture within 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>168</td>
<td>4</td>
</tr>
<tr>
<td>1993</td>
<td>144</td>
<td>2</td>
</tr>
<tr>
<td>1994</td>
<td>150</td>
<td>5</td>
</tr>
</tbody>
</table>

Table I. Incidence of contralateral fracture of the proximal femur
Table II. Sizes required for a trial to have a power of 80% to detect a reduction in the incidence of contralateral fracture from 2.4% in two years

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Alpha 0.05</th>
<th>Percentage reduction in fracture rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>3000</td>
<td>50</td>
</tr>
<tr>
<td>4000</td>
<td>5600</td>
<td>40</td>
</tr>
<tr>
<td>6000</td>
<td>7400</td>
<td>35</td>
</tr>
<tr>
<td>7400</td>
<td>10400</td>
<td>30</td>
</tr>
<tr>
<td>15000</td>
<td>21000</td>
<td>20</td>
</tr>
</tbody>
</table>

The first step in calculating the power of this hypothetical study is to nominate a hypothetical incidence of contralateral fracture at two years. If a treatment were to reduce the incidence of contralateral fracture by 38% (from 2.4% to 1.5%), then the normal approximation to the binomial distribution would give a calculated type-2 error rate of 20%. In other words, there is a 20% chance that the incidence in the treatment group may be greater than 1.7% if the ‘true’ incidence is 1.5%. This in turn means that there is a 20% chance of accepting a false null hypothesis. The complement of the type-2 error rate, in this example 80%, measures the power of the trial. Thus this trial, with a sample size of 5000 divided equally between treatment and placebo groups, would have a power of 80% to detect a reduction of 38% (from 2.4% to 1.5%) in the incidence of contralateral fracture. Table II shows the number of participants necessary to give a trial a power of 80% to detect, from a placebo rate of 2.4%, the reduction in the incidence of contralateral fracture. Alpha is given at two levels, 0.05 and 0.025, to correspond to one- and two-sided tests of significance, respectively.

**Discussion**

Because of the regular routine contact between the acute orthopaedic and the geriatric liaison services, it is probable that details of all the patients admitted with a proximal femoral fracture were complete. The follow-up data may be less comprehensive. Each year about 5% of the patients came from outside the hospital’s usual catchment area. It is also possible that some people normally resident in this area had a contralateral fracture that was treated elsewhere. The overall influence of these two factors on the incidence of contralateral fracture, however, is likely to be quite small. A follow-up study of patients with a fracture of the proximal femur carried out at the hospital in 1991 indicated that no surviving patients had moved from the catchment area. It seems likely therefore that nearly all those who sustained a second fracture were readmitted and registered.

In 1991-1992, 27% of patients treated for a fracture of the proximal femur at Waikato Hospital died within the following year. A lower mortality rate, by increasing the potential number of second fractures, would lead to an apparently higher incidence. Variations in the death rate thus affect the calculation of the required sample size.

Data from the study undertaken in 1991-1992 showed that 13% of patients presenting with a fracture of the proximal femur had sustained this type of fracture before. A similar figure, 10.6%, was reported in another study. If these rates were used to plan the numbers needed for a prospective trial, underestimation would occur principally because the apparent increase in the incidence of contralateral fractures results from ‘the survivor effect’.

A further consideration is that the practicalities of planning a large trial suggest that the period of follow-up should be relatively limited, such as the two-year period used in this study.

In this example, a 35% reduction in the incidence of contralateral fractures at follow-up was selected. This corresponds to the reduction in adverse outcomes reported in two large trials dealing with treatment of fractures of the proximal femur. In a study of 301 people aged over 70 years, a multifactorial intervention to reduce the risk of falls decreased the incidence from 47% in the control group to 35% in the intervention group. The follow-up period for this trial was one year. After adjustment, this represented a 31% reduction in the risk of falling. In a randomised study of 2027 women with vertebral fractures, the use of alendronate reduced the risk of any clinical fracture in three years from 18.2% in the placebo group to 13.6% in the treatment group, with a relative hazard of 0.72. Based on the cited figures, the crude reduction of risk is 25%. Thus it seems reasonable to expect a treatment that either improves bone stock or reduces the risk of falls to decrease the incidence of contralateral fracture by 35%. When the incidence of adverse outcomes is higher, the number of participants in a trial could be reduced without diminishing the power of the trial. Examples that could be subjected to trial include fall rates after fracture of the femoral neck, rates of institutionalisation and death rate.

Studies of the effects of bone-strengthening agents present difficulties since the primary objective would be to decrease the incidence of fracture rather than improve bone density. To date, there have been no controlled trials on the use of drugs to reduce risks of subsequent fracture in patients with a fracture of the proximal femur. It is difficult to extrapolate, from the results of treatment of osteoporosis in young people or people who have not previously sustained a fracture of the femoral neck, the effectiveness of bone-strengthening agents. Patients with a fractured neck of femur are typically older and more frail than those recruited for drug trials. In New Zealand, for example, the average age of patients with a fractured proximal femur is 81 years, and 45% are resident in long-term care facilities at the time of occurrence of their fracture. In this vulnerable group...
the potentially high rate of adverse reactions to drugs may reduce the effectiveness of treatment. Further, because of low base-line bone density and age-related changes to bone biology, drug treatment may simply be less effective in these patients. Conversely, it may be considered more effective if even a small increase in bone density reduces the risk of fracture.\(^7\)

This paper raises some of the difficulties which may occur in designing a study of the effectiveness of treatment in reducing the incidence of contralateral fracture of the proximal femur. The estimated number of participants required for such a trial suggests that it would be difficult to conduct.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**References**