Risk of Hip/Femur Fracture After Stroke
A Population-Based Case-Control Study

Sander Pouwels, PharmD; Arief Lalmohamed, BSc; Bert Leufkens, PhD; Anthonius de Boer, MD, PhD; Cyrus Cooper, MD, FMedSci; Tjeerd van Staa, MD, PhD; Frank de Vries, PhD

Background and Purpose—Stroke increases the risk of hip/femur fracture, as seen in several studies, although the time course of this increased risk remains unclear. Therefore, our purpose is to evaluate this risk and investigate the time course of any elevated risk.

Methods—We conducted a case-control study using the Dutch PHARMO Record Linkage System database. Cases (n=6763) were patients with a first hip/femur fracture; controls were matched by age, sex, and region. Odds ratio (OR) for the risk of hip/femur fracture was derived using conditional logistic regression analysis, adjusted for disease and drug history.

Results—An increased risk of hip/femur fracture was observed in patients who experienced a stroke at any time before the index date (adjusted OR, 1.96; 95% CI, 1.65–2.33). The fracture risk was highest among patients who sustained a stroke within 3 months before the index date (adjusted OR, 3.35; 95% CI, 1.87–5.97) and among female patients (adjusted OR, 2.12; 95% CI, 1.73–2.59). The risk further increased among patients younger than 71 years (adjusted OR, 5.12; 95% CI, 3.00–8.75). Patients who had experienced a hemorrhagic stroke tended to be at a higher hip/femur fracture risk compared with those who had experienced an ischemic stroke.

Conclusions—Stroke is associated with a 2.0-fold increase in the risk of hip/femur fracture. The risk was highest among patients younger than 71 years, females, and those whose stroke was more recent. Fall prevention programs, bone mineral density measurements, and use of bisphosphonates may be necessary to reduce the occurrence of hip/femur fractures during and after stroke rehabilitation. (Stroke. 2009;40:00-00.)

Key Words: bone density ■ fracture ■ risk factors ■ stroke

Stroke is a major cause of death and long-term disability in most industrialized populations. More than half of all strokes occur in people older than 75 years of age, and there is a trend toward increasing stroke incidence, especially in the elderly population, because the population is living longer.

Osteoporosis has been recognized as a serious complication after stroke. Stroke has been associated with a 1.5- to 4-times higher risk of hip fractures, and there is an increasing prevalence of hip/femur fractures among stroke survivors. Several long-term, prospective studies investigated bone mineral density (BMD) after stroke. Those studies reported nonuniform patterns of changes in BMD with significant bone loss on the paretic side, with a rapid onset after stroke, especially in patients with the most severe functional deficits.

Information about the time course of increased risk of hip/femur fracture during the first year after stroke is scarce. Most studies, but not all, that investigated fracture risk in relation to time after stroke adjusted for a limited number of confounders (age and sex) and did not distinguish between hemorrhagic and ischemic stroke. The objective of this study, therefore, was to evaluate the association between stroke and the risk of hip/femur fracture, and to identify any impact of stroke type and recency of stroke on that risk.

Materials and Methods

Study Design
A case-control study was conducted using the PHARMO Record Linkage System database (www.pharmo.nl). PHARMO Record Linkage System is a database that contains the pharmacy dispensing data of 1 million community-dwelling Dutch residents. These data are linked to a nationwide hospital discharge register. In the Netherlands, pharmacies maintain a virtually complete register of dispensed medications that have been prescribed by specialists and general practitioners. Patients are included irrespective of health insurance or socioeconomic status and represent 7% of the general population. Several independent validation studies have shown that the PHARMO Record Linkage System database has a high level of completeness and validity.

Received April 2, 2009; final revision received June 6, 2009; accepted June 23, 2009.


Correspondence to Frank de Vries, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, P.O. Box 80082, 3508 TB Utrecht, The Netherlands. E-mail f.devries@uu.nl

© 2009 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.109.554055
Cases and Control Subjects
Cases were patients aged 18 years or older who had sustained a hip/femur fracture during the study period (January 1, 1991 to December 31, 2002). Each case was matched with up to 4 control patients by year of birth, sex, and region of residence. Control patients were those registered on the database without evidence of having sustained any type of fracture at any time during enrollment. Among cases, the date of hospital admission for first hip/femur fracture was defined as the index date. Each control was assigned the index date of the matched case.

Stroke Definition
For each patient, the history of stroke before the index date was determined. Stroke was defined according to the ICD codes 430 to 436, excluding 435. Types of stroke included: hemorrhagic (ICD-9: 430, 431, and 432), ischemic (ICD-9: 433 and 434), and unspecified (ICD-9: 436). The recency of stroke was determined by calculating the time between the index date and the most recent hospital admission for stroke before the index date.

Statistical Analysis
Conditional logistic regression was used to estimate odds ratio (OR) for fracture risk (SAS version 9.1.3; PHREG procedure). Using backward elimination, adjustments were made for the following potential risk factors that have been associated with an increase or decrease in fracture risk: use of benzodiazepines in the 3 months before the index date; use of bronchodilators, inhaled corticosteroids, oral corticosteroids, antipsychotics, lithium, antidepressants, β-blockers, opioids, antiepileptics, thiazide diuretics, renin-angiotensin-sin-aldosterone system inhibitors, thyroid hormones, ≥2 dispensing occurrences of a nonsteroidal antiinflammatory drug, disease-modifying antirheumatic drugs, nitrates, diuretics, calcium channel blockers, bisphosphonates, hormone replacement therapy, digoxin, and other antithrombinics within the 6 months before the index date. In addition, a hospital diagnosis of anemia, mental disorder, impaired renal function, skin, or subcutaneous disease, any serious injury within the year before the index date, or a diagnosis of malignant neoplasm, endocrine disorder, cardiovascular disease, obstructive airways disease, inflammatory bowel disease, musculoskeletal and connective tissue diseases, or rheumatoid arthritis at any time before the index date were considered as potential confounding factors.

Results
Baseline characteristics of the study subjects are shown in Table 1. We identified 6763 patients who sustained a hip/femur fracture and matched these cases with 26,341 controls. The mean age of cases and controls was 75 years and the majority (73%) was female. Among cases, 225 (3.3%) had a history of stroke, compared with 407 (1.5%) control patients. Table 1 shows that patients with hemorrhagic stroke tended to be at highest risk of hip/femur fracture (adjusted OR, 1.94; 95% CI, 1.65–2.33). After adjustment the OR was decreased by 12%, yielding an adjusted OR of 1.96 (95% CI, 1.65–2.33).

The hip/femur fracture risk was highest soon after the stroke occurred (<3 months before the index), yielding an adjusted OR of 3.35 (95% CI, 1.85–5.97). This risk was attenuated with a longer time since stroke exposure: stroke occurrence between 3 and 12 months before the index resulted in an adjusted OR of 1.98 (95% CI, 1.33–2.94). Figure 1 shows that hip/femur fracture risk remained largely steady when the time since most recent stroke exceeded 1 year, except for the time point after 4 years. However, strokes occurring between 1 and 3 years before the index did not result in a higher fracture risk (adjusted OR, 1.73; 95% CI, 1.28–2.33) when compared with a longer time since stroke (adjusted OR, 1.94; 95% CI, 1.49–2.53).

Table 2 shows that patients with hemorrhagic stroke tended to be at higher risk of hip/femur fracture (adjusted OR, 1.94; 95% CI, 1.27–2.96) compared with patients who had an ischemic stroke (adjusted OR, 1.85; 95% CI, 1.42–2.39). However, the difference did not reach statistical significance.

Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (%) (n=6763)</th>
<th>Controls (%) (n=26341)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>75.7</td>
<td>75.3</td>
</tr>
<tr>
<td>N females, %</td>
<td>4929 (72.9)</td>
<td>19138 (72.7)</td>
</tr>
<tr>
<td>Disease history (ever)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>359 (5.3)</td>
<td>1289 (4.9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>296 (4.4)</td>
<td>565 (2.1)</td>
</tr>
<tr>
<td>Medication use within the 6 months before the index date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>816 (12.1)</td>
<td>2970 (11.3)</td>
</tr>
<tr>
<td>Renin-angiotensin-aldosterone system inhibitors</td>
<td>963 (14.2)</td>
<td>3280 (12.5)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>914 (13.5)</td>
<td>3850 (14.6)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>718 (10.6)</td>
<td>2560 (9.7)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>639 (9.4)</td>
<td>2405 (9.1)</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>748 (11.1)</td>
<td>2207 (8.4)</td>
</tr>
<tr>
<td>Antiarrhythmics and digoxin</td>
<td>526 (7.8)</td>
<td>1793 (6.8)</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>216 (3.2)</td>
<td>532 (2.0)</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>77 (1.1)</td>
<td>347 (1.3)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>366 (5.4)</td>
<td>918 (3.5)</td>
</tr>
</tbody>
</table>

Table 2. Baseline Characteristics
The oldest patients (older than 80 years) showed the smallest excess risk (adjusted OR, 1.51; 95% CI, 1.18–1.94) after stroke. We observed a similar trend among patients who had a hospital diagnosis or a dispensing within the 3 months before the index date. The results show an adjusted OR of 5.90 (95% CI, 2.42–14.38) for the youngest stroke survivors (70 years or younger), adjusted OR of 2.13 (95% CI, 1.45–3.10) for subjects aged between 71 and 80 years and an adjusted OR of 1.73 (95% CI, 1.23–2.45) for the oldest patients (older than 80 years). When we stratified patients younger than 71 years by recency of stroke, the risk of hip/femur fracture appeared to be increased 23-fold within the year after a stroke (adjusted OR, 23.17; 95% CI, 4.93–108.79; 12 cases and 2 controls; data not shown). Female survivors of stroke had a higher risk of hip/femur fracture (adjusted OR, 2.12; 95% CI, 1.73–2.59) compared with males (adjusted OR, 1.63; 95% CI, 1.17–2.28).

**Discussion**

In this study, we found that stroke was associated with a 2.0-fold increased risk of hip/femur fracture. A shorter time period between stroke and index date, younger age, and being female further increased the risk of hip/femur fracture. Our findings of an increased risk of hip/femur fracture soon after stroke, which attenuated when the stroke had occurred 3 to 12 months previously, extend results from other epidemiological studies. A retrospective study among 273,288 Swedish stroke patients reported a rapid decrease in fracture risk within the first year after stroke. After the first year, the risk remained slightly elevated, which is similar to our findings. The same study reported that women aged 50 to 54 years at the time of stroke had a 12-fold risk of hip fracture in the first year after stroke. This could contribute to our finding of a 23-fold increased risk for stroke patients younger than 71 years. Patients aged older than 70 are more likely to have other risk factors for hip fracture, and it is likely that the relative contribution of stroke to the overall risk of hip fracture decreases with age. A study by Ramnemark et al reported that stroke patients had an incidence of hip fracture that was 2–4 times higher than the reference population. Subsequently, they found that the incidence of hip fracture increased with age, whereas the prevalence of previous strokes among patients with fracture increased significantly.
over time. A nationwide Danish case-control study reported a 1.8-fold increased risk of hip fracture within the 3 years after a stroke. In line with our results, they found that this risk was attenuated as the time since stroke increased. Therefore, the 4-fold increased risk of hip fracture, 4.5 years after stroke in Figure 1, is probably an outlier of the trend, as described by the smoothing spline method.

An increased risk of falling and a decreased femoral BMD in the year after a stroke have been reported. Falls in elderly people are common; 28% to 35% of people aged 65 years and older fall at least once during a 1-year time period. It has been estimated that 1% of these falls result in a hip fracture. In a follow-up study among 1139 Swedish patients admitted for acute stroke, Ramnemark et al reported that 84% of all fractures after stroke were caused by falls and that hip fracture was the most frequent fracture. Additionally, in a survey in the United Kingdom that included 108 stroke patients, Forster and Young found that 46% fell at least once while in hospital and 73% fell within the 6 months after hospital discharge. They reported a total of 270 falls after hospital discharge, of which 145 (54%) were reported in the first 8 weeks after hospital discharge, whereas 125 (46%) were reported in the 8-week to 6-month period. In an observational study by Mackintosh, 92% of the subjects who had recurrent falls within 6 months after discharge from stroke rehabilitation had fallen at least once while being in the hospital or during stroke rehabilitation. The increased risk of falling soon after stroke supports our findings of highest risk of fracture in the first 3 months after stroke.

Our finding of a rapid increase in hip/femur fracture risk is in line with data from longitudinal studies, which report substantially higher rates of BMD loss within the first 6 months after stroke (4% to 10% BMD loss of the femoral region); this attenuated to 1% to 3% for the second half of the year. Loss of BMD was most obvious in paralyzed extremities, such as the femoral neck and the proximal humerus, as a result of decreased mobility. Jørgensen et al also found that less disabled patients, with functional ambulation category scores of 2 to 6, had only a 3% decrease in BMD at the femoral neck. Conversely, in healthy elderly patients, annual rates of loss of total BMD have been estimated at 0.5% to 1.0%. Femoral neck BMD loss in osteoporotic patients has been reported to be \( \approx 0.4\% \) per year and to increase significantly with age.

The strengths of our study include its reasonable sample size, the duration of follow-up available to study the associations between stroke and risk of hip/femur fracture, and its external validity (ie, PHARMO is representative for the total Dutch population). Linkage with the Dutch National Hospitalization Registry assured routine collection of hospitalizations for stroke. Moreover, we were able to distinguish between fracture risk among patients with ischemic and hemorrhagic stroke types.

Our study had some limitations. First, patients were included irrespective of whether the stroke was associated with hemiplegia. Kanis et al found a significant increase in relative risk of 2.42 in hemiplegic stroke patients, whereas stroke without hemiplegia was associated with a much lower (insignificant) increase in risk (RR, 1.51). In the PHARMO database, the types of stroke diagnosis (ischemic, hemorrhagic, or unspecified) have not been internally validated. However, a similar distribution of stroke diagnoses was reported in a clinical study performed by Potter et al in the United Kingdom. They included patients obtained from 5 hospitals in England who were admitted with a clinical diagnosis of suspected stroke in the years 2004 to 2008. The proportions of hemorrhagic, ischemic, and unspecified stroke were 15%, 56%, and 27%, respectively, compared to 16%, 45%, and 39% for the control patients in our study. We have not been able to assess whether risk of mortality after hip fracture was different between patients with and without stroke. Finally, we were not able to adjust for confounders such as body mass index and smoking.

In conclusion, after adjustment for general risk factors of fracture risk, patients with stroke had a 2.0-fold increased risk of hip/femur fracture. The risk was greatest in those who were younger than 71 years, female, and who had recently sustained a stroke. Our findings imply that it is important to conduct fracture risk assessment immediately after a patient is hospitalized for stroke. Severity of stroke (ie, the degree of paresis or immobility), being female, and age of 70 years or younger are important risk factors to take into account. Fall prevention programs, BMD measurements, and use of bisphosphonates may be necessary to minimize hip fractures in the elderly during and after stroke rehabilitation.

Acknowledgments

The authors thank Dr Helen Seaman for her assistance in the preparation of this manuscript for publication.
Sources of Funding
The Department of Pharmacoepidemiology and Pharmacotherapy, employing authors Sander Pouwels, Arief Lalmohamed, Bert Leufkens, Anthonius de Boer, Tjeerd van Staa, and Frank de Vries, have received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private–public-funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health.

Disclosure
Tjeerd van Staa and Frank de Vries also work for the General Practice Research Database (GPRD), UK. GPRD is owned by the UK Department of Health and operates within the Medicines and Healthcare products Regulatory Agency (MHRA). GPRD is funded by the MHRA, Medical Research Council, various universities, contract research organizations, and pharmaceutical companies.

References
Risk of Hip/Femur Fracture After Stroke. A Population-Based Case-Control Study
Sander Pouwels, Arief Lalmohamed, Bert Leufkens, Anthonius de Boer, Cyrus Cooper, Tjeerd
van Staa and Frank de Vries

Stroke. published online August 6, 2009;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/early/2009/08/06/STROKEAHA.109.554055.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/