Timing of Stroke in Patients Undergoing Total Hip Replacement and Matched Controls
A Nationwide Cohort Study

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Background and Purpose—Stroke is a potentially fatal complication of total hip replacements (THR). However, timing of stroke in THR patients compared with matched controls and influence of drug use remain unknown. The objective of this study was to determine timing of stroke in patients with THR compared with matched control subjects.

Methods—A nationwide cohort study was conducted within the Danish registers (1998–2007). Included patients were those with a primary THR in the study period (n=66 583) and were matched by age, sex, and region to three referent subjects without THR or total knee replacements. Time-dependent Cox models were used to derive hazard ratios and were adjusted for disease history and drug use.

Results—A 4.7-fold increased risk of ischemic stroke (adjusted hazard ratio, 4.69; 95% CI, 3.12–7.06), and a 4.4-fold increased risk of hemorrhagic stroke (adjusted hazard ratio, 4.40; 95% CI, 2.01–9.62) were found within 2 weeks following THR, compared with matched controls. The risk remained elevated during the first 6 postoperative weeks for ischemic stroke, and the first 12 weeks for hemorrhagic stroke. Outpatient antiplatelet drug use lowered the 6-week hazard ratios for ischemic stroke by 70%, although not affecting risk of hemorrhagic stroke.

Conclusions—This study shows that THR patients have a 4.7-fold increased risk of ischemic stroke, and a 4.4-fold increased risk of hemorrhagic stroke during the first 2 weeks postsurgery. Risk assessment of stroke in individual patients undergoing THR (ie, evaluate other risk factors for stroke) should be considered during the first 6 to 12 weeks. (Stroke. 2012;43:3225-3229.)

Key Words: arthroplasty ■ intracranial hemorrhages ■ osteoarthritis ■ pharmacoepidemiology ■ hip replacement ■ stroke

Stroke is a major cause of death and long-term disability in most industrialized populations.1 The majority of these events occur among patients aged >75 years, and incidence rates of stroke are increasing given the aging of the population.1,2 Stroke has been recognized as a serious perioperative complication after total hip replacements (THR).3 These orthopedic procedures effectively reduce pain and increase quality of life in patients with moderate-to-severe osteoarthritis.4 Epidemiological studies demonstrated perioperative stroke incidence rates as high as 0.6%.3,5,6 This complication has become of particular interest, given the fact that THRs are performed in large numbers (>1 million annually worldwide) and the surgery is offered to older patients more often.9,10 Although incidence rates of perioperative stroke following THR have been described reasonably well, the rates have not been compared with control subjects who did not have surgery. Furthermore, the timing of these events has not been thoroughly evaluated, in particular the period after THR discharge. None of the previous studies were able to evaluate effect modification by comorbidities and drug use. This is of particular interest, as THR patients widely use pain relievers, which have been associated with both an increased and decreased risk of stroke.11-13 Other drugs that may be associated with a decreased or increased risk of stroke include antiplatelet drugs, anticoagulants, statins, thiazide diuretics, estrogen-containing drugs, selective serotonin reuptake inhibitors, and antipsychotics.1,4,14-16 Its use in THR patients in relation with perioperative stroke, however, remains unknown.

The objectives of this study were to evaluate timing of stroke after THR compared with matched control subjects...
who did not have surgery and to assess effect modification by comorbidities and drug use.

Methods

Data Sources
We carried out a nationwide retrospective cohort study using Danish national registries. These registries include all 5.5 million Danish residents and contain detailed information on hospitalizations (including emergency room visits), outpatient clinic visits, drugs sold at retail pharmacies, vital status, date and cause of death (underlying cause, and up to three additional immediate causes), geographical residence, migration status, and socioeconomic status. The Danish national registries have been the source of numerous recent epidemiological studies, and previous studies have reported high completeness and validity. Positive predictive values of 81% to 86% have been demonstrated for stroke in the Danish national registries.

Study Population
All patients aged ≥18 years, who had undergone a primary THR (International Classification of Diseases [ICD], 10th revision: ICD10 procedure codes NFB) between January 1, 1998, and December 31, 2007, were included in the study cohort. Patients with primary or secondary total knee replacement (TKR) during the study period were excluded. The date of hospital admission for the primary THR was defined as the index date. Each THR patient was matched to three control subjects by year of birth, sex, and geographical location, and had not undergone a primary or secondary THR or TKR at any time during the study period. Control subjects were assigned the same index date as their matched THR patient. Patients with a record for stroke within 6 weeks before the index date were excluded.

Outcome Assessment
All patients were followed up from the index date until death, migration (and in many cases a magnetic resonance imaging) within 24 hours (due to national requirements). For deceased individuals, the diagnosis will be made postmortem using imaging techniques. To assess the potential for diagnosis-recording bias (ie, a higher recording rate shortly after THR), we additionally followed all patients for cancer (which should yield a hazard ratio [HR] close to 1; ICD10 codes C).

Potential Risk Factors
Total follow-up time was divided into 6-week periods, and for the first 6 weeks into 1-week periods. Risk factors considered at baseline (ie, before surgery) in this study included sex, socioeconomic status, indication for surgery, and a history of cerebrovascular disease (ICD10-codes I60-I69, including carotid stenosis and occlusion), heart failure, atrial fibrillation, malignancies, and falls ever before. Age and current drug use was assessed in a time-dependent manner (before and during follow-up), that is, age was calculated at the start of each 6-week interval, and drug prescribing was evaluated in the 6 months before the start of each 6-week interval. We chose an exposure window of 6 months, because this is likely to reflect current use (in Denmark, drugs are generally prescribed for 3 months, and most of these drugs are used on a chronic basis). Drugs that were assessed using this time-dependent approach included: pain relievers (stratified by drug type: paracetamol, nonsteroidal anti-inflammatory drugs, and opioids [tramadol or stronger]), estrogen-containing drugs, antithrombotic agents (stratified by type: vitamin K antagonists [eg, warfarin], antiplatelet drugs [eg, low-dose aspirin], and others [eg, enoxaparin]), systemic corticosteroids, antipsychotics, selective serotonin reuptake inhibitors, tricyclic antidepressants, statins, thiazide diuretics, organic nitrates, β-blockers, renin–angiotensin–aldosterone system inhibitors, loop diuretics, calcium channel blockers, and oral antidiabetics or insulin.

Statistical Analysis
Disease and drug use adjusted (adj.) HRs for stroke were derived among THR patients versus age- and sex-matched control subjects (SAS 9.2). Potential confounders were included in the final model, if they independently changed the β-coefficient for THR or TKR by at least 5% (ie, change-in-estimate method using univariate analyses). Timing patterns were evaluated using time-interaction terms (time period × surgery) into the Cox model. HRs were estimated for the following time periods: <2 weeks, 2 to 6 weeks, 6 to 12 weeks, 3 to 6 months, 6 to 12 months, and ≥1 year after surgery. Smoothing spline regression was used to visualize the time trend of stroke following THR in the first postoperative year. The 6-week relative risk was stratified by the presence of risk factors to determine effect modification. This study was approved by the National Board of Health and the Danish Data Protection Agency.

Results
Baseline characteristics of THR patients (n=66 583), and age- and sex-matched control subjects (n=199 995) are shown in Table 1 (after exclusion of 102 patients with a stroke event in the 6 weeks before or on the index date, or without at least 1 day of follow-up). For both patients and controls, the mean age was 71.9 years, and 36.9% of the study population was male. Within each matched set, THR patients and matched controls were of same sex, exact same age, and originated from the same geographical region. In general, THR patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THR Patients n=66 583</th>
<th>Controls n=199 995</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up time (years, SD)</td>
<td>3.9 (2.8)</td>
<td>4.1 (2.7)</td>
</tr>
<tr>
<td>Males</td>
<td>36.9%</td>
<td>36.9%</td>
</tr>
<tr>
<td>Mean age (years, SD)</td>
<td>71.9 (12.5)</td>
<td>71.9 (12.5)</td>
</tr>
<tr>
<td>Mean THR hospital stay (days, SD)</td>
<td>10.8 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Disease history (ever before, unless specified otherwise)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>7.7%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Carotid stenosis or occlusion</td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Drug use (within 6 mo before)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>50.7%</td>
<td>16.4%</td>
</tr>
<tr>
<td>SSRIs</td>
<td>11.0%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>5.6%</td>
<td>5.5%</td>
</tr>
<tr>
<td>β-blockers</td>
<td>13.3%</td>
<td>12.1%</td>
</tr>
<tr>
<td>RAAS inhibitors</td>
<td>19.1%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>17.9%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Statins</td>
<td>8.7%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>3.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Antiplatlet drugs</td>
<td>22.4%</td>
<td>20.9%</td>
</tr>
</tbody>
</table>

Values are means or percentages (among THR patients or controls), unless stated otherwise. NSAIDs indicates nonsteroidal anti-inflammatory drugs; RAAS, renin–angiotensin–aldosterone system; SSRIs, selective serotonin reuptake inhibitors; THR, total hip replacement.
and controls were comparable in terms of socioeconomic status and comorbidities, although THR patients were slightly more likely to have used cardiovascular drugs, and had a modestly higher prevalence of prior cerebrovascular disease. Pain reliever use was substantially more frequent among THR patients as compared with matched controls.

Table 2 and Figure 1 demonstrate a substantially increased risk of ischemic stroke (adj. HR, 4.69; 95% CI, 3.12–7.06), and hemorrhagic stroke (adj. HR, 4.40; 95% CI, 2.01–9.62) during the first 2 weeks after THR. This is probably not the result of higher diagnosis-recording rates shortly after THR: for cancer, the HR during the first 2 weeks was 0.90 (95% CI=0.64–1.27). For both types of stroke, the risk dropped steadily afterward, but remained significantly elevated during at least the first 6 postoperative weeks for ischemic stroke, and the first 12 weeks for hemorrhagic stroke. The association tended to be stronger for fatal events, although this difference did not reach statistical significance (Table 3).

Table 4 shows that current outpatient antiplatelet drug use substantially lowered the 6-week HR for ischemic stroke (70% decrease, calculated as a synergy index, ie, 1-RR1 divided by 1-RR2). These results did not change when we used an exposure time window of 2 weeks (adj. HR, 2.08; 95% CI, 0.95–5.06) instead of the original 6 months (adj. HR, 1.81; 95% CI, 1.24–2.66). Among THR patients using aspirin, 15.7% were concomitantly using ibuprofen (adj. HR, 2.37; 95% CI, 0.22–26.2) and 29.9% were on any other nonsteroidal anti-inflammatory drugs (adj. HR, 1.46; 95% CI, 0.56–3.79), but the association was not stronger as compared with aspirin users, who did not concomitantly use nonsteroidal anti-inflammatory drugs (adj. HR, 2.46; 95% CI, 1.55–3.91). In general, antiplatelet users were less healthy than nonusers, and this could therefore not explain the seemingly protective effect (Supplemental Appendix Table 1). No other effect modification was observed for any of the other investigated covariates (including pain relievers, statins, thiazide diuretics, antidepressants, and selective serotonin reuptake inhibitors). For hemorrhagic stroke, statistical power was too low to detect significant effect modification.

**Discussion**

This nationwide study demonstrated a substantially increased risk of ischemic (4.7-fold) and hemorrhagic stroke (4.4-fold) during the first 2 weeks after THR. The risk remained significantly elevated for at least the first 6 postoperative weeks.
This study shows a potential beneficial effect of antiplatelet drugs on ischemic stroke occurrence in patients undergoing THR. Patients who had currently used antiplatelet drugs experienced a 70% reduction in HR of ischemic stroke during the first 6 weeks after THR, compared with subjects who had not been dispensed any antithrombotic agent. Antiplatelet drugs, such as low-dose aspirin, are widely used for secondary prevention of ischemic stroke, and its benefits have been demonstrated in several randomized controlled clinical trials. A meta-analysis revealed a 15% risk reduction of any secondary stroke event with aspirin, and the magnitude of benefit was consistent among doses between 50 and 1500 mg/day. Randomized clinical trials should further investigate our finding of a potential beneficial effect in patients who require THR surgery.

Strengths and Limitations of the Study
The nationwide population-based design, large sample size, detailed information on matched controls, and completeness of follow-up are the major strengths of this study. We had access to outpatient prescription data, which is particularly important given the relationship of the widely used nonsteroidal anti-inflammatory drugs (the majority of our THR patients) and stroke. Furthermore, we had the ability to differentiate between hemorrhagic and ischemic stroke. An important limitation is the lack of information on body mass index, since a higher body mass index is associated with an increased risk of stroke and osteoarthritis—the main indication for THR. However, the relationship between body mass index and osteoarthritis seems to be stronger for knee osteoarthritis, and a large cohort study could not demonstrate a relationship with hip osteoarthritis. Furthermore, we could not assess in-hospital use of antithrombotic agents. Previous Danish data have shown that up to 99.1% of those undergoing THR or TKR received medical thromboprophylaxis (primarily subcutaneous low-molecular-weight heparins). Several authors proposed that low-molecular-weight heparins may lower risk of stroke, although a meta-analysis could not confirm this beneficial effect. We cannot exclude the possibility of ascertainment or recording bias toward the diagnosis of stroke soon after THR. However, we could not find an increased risk of cancer during the first 2 weeks, which implies that the presence of this Berkson-type bias is unlikely. Unfortunately, we were not able to differentiate between lacunar and territorial infarctions, which may have different rates following THR. Controls were not chosen from hospitalization or other surgery. The increased risk of stroke may therefore not be exclusive for THR only, but may apply to other surgeries or hospitalizations as well.

Conclusions and Implications
This study showed an increased risk of ischemic (4.7-fold) and hemorrhagic stroke (4.4-fold) during the first 2 weeks after THR surgery. The risk remained significantly elevated for at least 6 weeks for ischemic stroke and 12 weeks for hemorrhagic stroke. Current use of antiplatelet drugs lowered the increased risk of ischemic stroke by 70% during the first 6 weeks. This seemingly protective effect should be interpreted with caution, given the observational design and the lack of information on inpatient antithrombotic use. Risk assessment of stroke in individual patients undergoing THR (ie, evaluate other risk factors for stroke) should be considered during the first 6 to 12 weeks.
Sources of Funding
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Disclosures
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References
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### Online Appendix Table 1. Baseline characteristics of THR patients and matched controls, stratified by antiplatelet drug use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THR patients, n = 66,583</th>
<th>Controls, n = 199,995</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiplatelets n = 14,889</td>
<td>No antiplatelets n = 51,694</td>
</tr>
<tr>
<td>Mean follow-up time (years, SD)</td>
<td>3.8 (2.8)</td>
<td>3.9 (2.8)</td>
</tr>
<tr>
<td>Males</td>
<td>35.9%</td>
<td>37.2%</td>
</tr>
<tr>
<td>Mean age (years, SD)</td>
<td>77.7 (9.4)</td>
<td>70.3 (12.8)</td>
</tr>
<tr>
<td>Mean THR hospital stay (days, SD)</td>
<td>11.5 (10.4)</td>
<td>10.7 (9.2)</td>
</tr>
<tr>
<td>Disease history (ever before, unless specified otherwise)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>21.9%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Drug use (within six months before)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>45.5%</td>
<td>52.2%</td>
</tr>
<tr>
<td>SSRIs</td>
<td>17.7%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>10.6%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>26.7%</td>
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</tr>
<tr>
<td>RAAS inhibitors</td>
<td>32.7%</td>
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<td>Vitamin K antagonists</td>
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</table>

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