Sex Differences and Similarities in the Management and Outcome of Stroke Patients

Jayna M. Holroyd-Leduc, MD, BSc; Moira K. Kapral, MD, MSc, FRCPC; Peter C. Austin, PhD; Jack V. Tu, MD, PhD, FRCPC

Background and Purpose—Previous studies have documented sex differences in the management and outcome of patients with cardiovascular disease. However, little data exist on whether similar sex differences exist in stroke patients. We conducted a study to determine whether sex differences exist in patients with acute stroke admitted to Ontario hospitals.

Methods—Using linked administrative databases, we performed a population-based cohort study. The databases contained information on all 44,832 patients discharged from acute-care hospitals in Ontario between April 1993 and March 1996 with a most responsible diagnosis of acute stroke. The main outcomes measured consisted of sex differences in comorbidities, the use of rehabilitative services, the use of antiplatelet therapy and anticoagulants (in elderly stroke survivors aged ≥65 years only), discharge destination, and mortality.

Results—Male stroke patients were more likely than female stroke patients to have a history of ischemic heart disease (18.1% versus 15.3%, respectively; P<0.001) and diabetes mellitus (20.1% versus 18.7%, respectively; P<0.001), whereas female patients were more likely than male patients to have hypertension (33.8% versus 30.0%, respectively; P<0.001) and atrial fibrillation (12.9% versus 10.2%, respectively; P<0.001). There were no sex differences in the usage of in-hospital rehabilitative services. The overall 90-day postdischarge use of aspirin and ticlopidine was similar in stroke survivors aged 65 to 84 years. However, among stroke survivors aged ≥85 years, men were more likely than women to receive aspirin (36.0% versus 30.7%, respectively; P<0.001) and ticlopidine (9.2% versus 6.8%, respectively; P=0.007). Use of warfarin was similar for the two sexes. Men were more likely than women to be discharged home (50.6% versus 40.9%, respectively; P<0.001) and less likely to be discharged to chronic care facilities (16.8% versus 25.2%, respectively; P<0.001). The risk of death 1 year after stroke was somewhat lower in women than men (adjusted odds ratio 0.939, 95% CI 0.899 to 0.980; P=0.004). The mortality differences were greatest among elderly stroke patients.

Conclusions—Elderly men are more likely than elderly women to receive aspirin and ticlopidine and equally likely to receive warfarin after a stroke. Despite these differences, elderly women have a better 1-year survival after a stroke. (Stroke. 2000;31:1833-1837.)

Key Words: anticoagulants — antiplatelet therapy — gender — stroke, acute

The potential for sex bias in the provision of necessary medical services is an issue of increasing concern. Several studies have reported sex differences in the management of patients with cardiovascular disease. Women have been shown to be less likely than men to receive major cardiovascular diagnostic and therapeutic procedures. In one study, the adjusted odds ratio for invasive coronary procedures in men compared with women was 1.3 for angioplasty and 1.6 for coronary artery bypass surgery. These differences exist even after accounting for sex differences in the average age of clinical presentation and other possible confounding factors.

In contrast, the literature on stroke and sex differences is not as comprehensive. In particular, there are limited data on sex differences in the medical and surgical management of stroke patients. Previous population-based studies have shown that men appear to be at a higher risk of stroke. However, women, on average, live longer than men, and stroke rates increase with advancing age, so that in persons aged ≥85 years, women have a higher incidence of stroke.
There do not appear to be any sex differences in stroke severity.\textsuperscript{12,13} Stroke mortality rates vary between studies, but after adjusting for age, men appear to have a higher mortality rate.\textsuperscript{5,14}

Previous clinical trials have also examined sex differences in the effectiveness of various medical therapies for stroke prophylaxis. Subgroup analyses of some trials of aspirin have failed to show a benefit in women.\textsuperscript{15–17} However, all these studies contained small numbers of women and, therefore, lacked the power to detect a benefit in women. Other studies have found aspirin to be effective in stroke prophylaxis for both sexes.\textsuperscript{18–21}

Ticlopidine has also been found to be effective in both men and women.\textsuperscript{22,23} The Ticlopidine Aspirin Stroke Study Group demonstrated a trend toward greater response to ticlopidine in women.\textsuperscript{23} Warfarin is recommended for stroke prevention in patients with nonvalvular atrial fibrillation and specific stroke risk factors.\textsuperscript{24} Among those patients with coronary artery disease and atrial fibrillation, women have been found to have a higher incidence of stroke.\textsuperscript{25} This would suggest that women with nonvalvular atrial fibrillation might obtain more benefit from warfarin use than men.

Sex differences in the therapeutic management of stroke patients have not been previously investigated. The purpose of the present study was to conduct a population-based

### Analysis of Sex Differences in the Medical Management and Outcome of Stroke Patients

### Subjects and Methods

#### Inclusion Criteria

Data on all patients discharged from acute-care Ontario hospitals for the fiscal years 1993 to 1995 (inclusive) with a most responsible diagnosis (the diagnosis that accounts for most of a hospital stay) of an acute stroke (International Classification of Diseases, 9th Revision [ICD-9] code 431, intracerebral hemorrhage; 434, occlusion of cerebral arteries; or 436, acute but ill-defined cerebrovascular disease) were obtained from the Canadian Institute for Health Information (CIHI) database. A fiscal year was defined as April 1 of that calendar year to March 31 of the subsequent year.

The CIHI database contains demographic, length of stay (LOS), comorbidity, in-hospital mortality, and discharge destination information on all patients admitted to Ontario hospitals. The most responsible and up to 15 secondary diagnoses are coded in the CIHI database according to the ICD-9 coding system.\textsuperscript{26} The CIHI database also codes as many as 10 procedures according to the Canadian Classification of Procedures\textsuperscript{27} and documents each patient’s receipt of rehabilitation services, such as occupational therapy, physiotherapy, and speech/language pathology.

Prescriptions filled for aspirin, ticlopidine, and warfarin in stroke survivors aged $\geq 65$ years were obtained from the Ontario Drug Benefit (ODB) database from April 1, 1993, to June 30, 1996. The ODB database contains all prescriptions filled in Ontario by persons aged $\geq 65$ years for prescription medications from a minimally restrictive formulary. This database was linked to the CIHI database by use of anonymous patient identifiers and observed for 90 days after discharge. The 30-day and 1-year mortality status of patients were obtained from provincial vital statistics.

#### Stroke Risk Factors and Comorbidities

The frequency of patients with various stroke risk factors and other comorbid diseases was determined with use of the appropriate ICD-9 codes in the 15 secondary diagnosis fields of the CIHI database. The stroke risk factors and comorbidities included ischemic heart disease, congestive heart failure, atrial fibrillation, peripheral vascular disease, chronic pulmonary disease, peptic ulcer disease, liver disease, malignancy, renal disease, hypertensive disease, and diabetes mellitus. The adaptation by Deyo et al\textsuperscript{28} of the Charlson index score was also used to quantify overall comorbid disease status.

#### Exclusion Criteria

We excluded from the present study patients who were aged <20 or $\geq 105$ years, persons with a total LOS of $\geq 365$ days, and strokes occurring as an in-hospital procedural complication.

#### Outcome Measures

The outcome measures assessed included rehabilitative services, prescription use of aspirin, ticlopidine, and warfarin within 90 days of discharge, median LOS after stroke, destination at discharge, and unadjusted and adjusted 30-day and 1-year mortality.

#### Statistical Analysis

Two-way contingency tables were used to test for associations between sex and each variable, stratified by age. $x^2$ tests were used to test for statistically significant differences between the sexes. Median 2-sample tests were used to test the equalities of LOS between the sexes within each age range. Logistic regression was used to determine the adjusted odds ratio of mortality at 30 days and at 1 year. Age, age$^2$, age$^3$, sex, risk factors, and comorbid conditions were used as regressors. All statistical analyses were conducted by use of the statistical program SAS Release 6.11 (SAS Institute, Inc).\textsuperscript{29}
Results

Patient Demographics and Comorbid Disease

Overall, 44,832 patients were admitted to an Ontario hospital with an acute stroke during the fiscal years 1993 to 1995. The distribution by sex was approximately equal, with 49.7% men and 50.3% women. However, the male patients tended to be younger than the female patients (mean age 71.3 versus 75.5 years, respectively; P<0.001).

The most common comorbid conditions were ischemic heart disease, diabetes mellitus, hypertension, and atrial fibrillation (Table 1). Men were more likely than women to have a history of ischemic heart disease and diabetes mellitus, whereas women had a higher prevalence of atrial fibrillation and hypertension. The Deyo-Charlson index scores indicated that men had a higher overall frequency of comorbid diseases at the time of presentation.

Use of Rehabilitative Services and Secondary Stroke Prevention Medications

The in-hospital utilization of rehabilitation services was similar in men and women (Table 2). Among patients aged <85 years, use of aspirin and ticlopidine was similar in men and women (Table 3). However, among patients aged ≥85 years, men were more likely than women to receive aspirin (36.0% versus 30.7%, respectively; P<0.001) and ticlopidine (9.2% versus 6.8%, respectively; P=0.007). There was no sex difference in the use of warfarin within any age group.

Outcome Measures

Although in the younger age group, there was no sex difference in short-term and long-term mortality rates, older men had higher mortality rates than did older women (Table 4). The adjusted odds ratio for 30-day mortality in females compared with males was 0.956 (95% CI 0.910 to 1.005, P=0.004). The adjusted odds ratio for 1-year mortality in females compared with males was 0.980 (95% CI 0.910 to 1.005, P=0.079). The sex difference in the use of warfarin within any age group.

Men had a shorter median LOS than did women (9 days versus 11 days, respectively; P<0.001). Men were more likely than women to be discharged home (50.6% versus 40.9%, respectively; P<0.001) and less likely than women to be discharged to chronic care facilities (16.8% versus 25.2%, respectively; P<0.001) (Table 5). Men and women were equally likely to be discharged to rehabilitation facilities.

Discussion

The present study is one of the first population-based studies to examine sex differences in the management and outcome of stroke patients. We found no significant differences in the outcome of younger men and women with stroke. Among older patients, however, men were more likely than women to receive secondary preventative therapy with aspirin and ticlopidine. This sex difference in prescribing is not supported by current evidence and recommendations for the use of aspirin and ticlopidine for secondary stroke prevention in men and women.

The sex difference in the use of antiplatelet therapy cannot be accounted for by the use of warfarin. In fact, although women had a higher rate of atrial fibrillation, there was no sex difference in the use of warfarin.

One explanation for the lower use of antiplatelet therapy in older women might be the presence of comorbid conditions or contraindications. However, we found that older women in fact appeared to have less comorbidity at the time of stroke and were more likely to survive the event. Men may have been more likely to be on aspirin because of their higher rate of ischemic heart disease; however, this is unlikely to be the full explanation, given the similar prevalence of ischemic heart disease in men and women aged ≥85 years.

Another possible contributing factor to the sex differences in antiplatelet therapy may be that among older stroke survivors, women were more likely to be institutionalized and possibly to have more disability. Physicians may be more aware of the benefits of stroke prevention when the individual is living in the community with only minimal disability.

TABLE 3. Percentage of Elderly Stroke Survivors on Aspirin, Ticlopidine, and Warfarin Within 90 Days of Hospital Discharge, Based on Sex and Stratified by Age, in Ontario, Canada, 1993–1995

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Aspirin</th>
<th>Ticlopidine</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>P</td>
</tr>
<tr>
<td>65–74</td>
<td>40.3</td>
<td>39.8</td>
<td>0.621</td>
</tr>
<tr>
<td>75–84</td>
<td>38.1</td>
<td>36.4</td>
<td>0.069</td>
</tr>
<tr>
<td>≥85</td>
<td>36.0</td>
<td>30.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Age, y</th>
<th>30-Day Mortality, %</th>
<th>1-Year Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10.8</td>
<td>16.3</td>
</tr>
<tr>
<td>Women</td>
<td>10.9</td>
<td>16.9</td>
</tr>
<tr>
<td>P</td>
<td>0.837</td>
<td>0.422</td>
</tr>
<tr>
<td>65–74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>15.4</td>
<td>27.8</td>
</tr>
<tr>
<td>Women</td>
<td>14.9</td>
<td>26.0</td>
</tr>
<tr>
<td>P</td>
<td>0.428</td>
<td>0.019</td>
</tr>
<tr>
<td>75–84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>22.4</td>
<td>39.9</td>
</tr>
<tr>
<td>Women</td>
<td>20.4</td>
<td>36.8</td>
</tr>
<tr>
<td>P</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>33.0</td>
<td>57.0</td>
</tr>
<tr>
<td>Women</td>
<td>31.3</td>
<td>54.0</td>
</tr>
<tr>
<td>P</td>
<td>0.147</td>
<td>0.018</td>
</tr>
</tbody>
</table>
The present study has a number of limitations. First, comorbid diseases may be undercoded in the CIHI database. However, we would not expect to see sex differences in data coding, making the impact of undercoding less important to the overall conclusions of the present study. Also, the accuracy of ICD-9 coding of stroke, patient demographics, and discharge disposition in the CIHI database has been validated in other studies. Second, the ODB database does not contain drug data on patients aged <65 years. Therefore, our conclusions regarding prescribing patterns are limited to individuals aged ≥65 years. Although aspirin can be purchased by the patient without a prescription, the Ontario government assumes the complete cost if aspirin is prescribed by a physician. Therefore, a few stroke patients on aspirin may be missing from the ODB database, but this is probably a minor contribution.

In conclusion, we found there were no differences in the outcome of stroke for younger men and women. Among older patients, in contrast, men were more likely than women to be prescribed aspirin and ticlopidine, both of which have been shown to be effective in secondary stroke prevention. We also found that despite the higher rate of atrial fibrillation among women, there was no sex difference in the use of warfarin. Overall, elderly women had better short-term and long-term survival rates than did elderly men. Further research is needed to determine the reasons for these differences in stroke management and outcome.

Acknowledgments
This study was supported by the Institute for Clinical Evaluative Sciences in Ontario. Dr Tu is supported in part by a Medical Research Council of Canada Scholar Career Award.

References


Sex Differences and Similarities in the Management and Outcome of Stroke Patients
Jayna M. Holroyd-Leduc, Moira K. Kapral, Peter C. Austin and Jack V. Tu

Stroke. 2000;31:1833-1837
doi: 10.1161/01.STR.31.8.1833

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 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/31/8/1833

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/