Persistent Use of Secondary Preventive Drugs Declines Rapidly During the First 2 Years After Stroke

Eva-Lotta Glader, MD, PhD; Maria Sjölander, MPH; Marie Eriksson, PhD; Michael Lundberg, MPH

Background and Purpose—To prevent new cardiovascular events after stroke, prescribed preventive drugs should be used continuously. This study measures persistent use of preventive drugs after stroke and identifies factors associated with persistence.

Methods—A 1-year cohort (21 077 survivors) from Riks-Stroke, the Swedish Stroke Register, was linked to the Swedish Prescribed Drug Register.

Results—The proportion of patients who were persistent users of drugs prescribed at discharge from hospital declined progressively over the first 2 years to reach 74.2% for antihypertensive drugs, 56.1% for statins, 63.7% for antiplatelet drugs, and 45.0% for warfarin. For most drugs, advanced age, comorbidity, good self-perceived health, absence of low mood, acute treatment in a stroke unit, and institutional living at follow-up were independently associated with persistent medication use.

Conclusion—Persistent secondary prevention treatment declines rapidly during the first 2 years after stroke, particularly for statins and warfarin. Effective interventions to improve persistent secondary prevention after stroke need to be developed. (Stroke. 2010;41:397-401.)

Key Words: medication persistence ■ secondary prevention ■ stroke

The available evidence suggests that nonadherence to secondary prevention medication prescribed after stroke is a major clinical problem.1–6 Improved medication persistence would be a key target in secondary prevention strategies. In the present study, long-term medication persistence has been followed by linking Riks-Stroke, the Swedish Stroke Register, with the Swedish Prescribed Drug Register that covers all prescribed drugs dispensed at Swedish pharmacies. This circumvents the problem of incorrect self-reporting of medication. The objective of the study was to measure persistent medication during the first 2 years after stroke and to identify patient characteristics and factors related to stroke services that may affect persistence.

Subjects and Methods

This prospective observational study was based on a 1-year cohort (September 1, 2005–August 31, 2006) from Riks-Stroke, the Swedish Stroke Register. The register includes all hospitals admitting patients with acute stroke in Sweden, and validation studies have shown that the register covers 80% to 90% of all acute stroke events (detailed information on Riks-Stroke is available at http://www.riks-stroke.org).

We used Riks-Stroke data on antihypertensive drugs, statins, antiplatelet agents, and warfarin at discharge from hospital and information from a 3-month questionnaire follow-up (response rate, 87.6%) on patient-reported processes and outcomes. The use of antihypertensive drugs was followed-up in all stroke patients, whereas persistence in using statins and antiplatelet agents was analyzed in patients with ischemic stroke only. The use of warfarin was studied in ischemic stroke patients with atrial fibrillation.

Using individual social security numbers, Riks-Stroke data were linked with the Prescribed Drug Register at the National Board of Health and Welfare. The register includes all prescriptions dispensed in Swedish pharmacies. To cover a 24-month follow-up of all patients, filled prescriptions between July 1, 2005 and October 31, 2008 were included in the study.

A persistent medication user was defined as a patient who had purchased the drug at a pharmacy at least once during each 4-month interval after hospital discharge. The 4-month delineation is based on the fact that in Sweden, for a drug to be subsidized by the state, each filling cannot exceed what is estimated to be used during a maximum of 3 months; in this study, we allowed for an additional 1-month interval between dispensations of the drug.

Multiple logistic regression with stepwise backward variable removal (P > 0.10 as removal criterion) was performed with the SPSS software (version 16.0.2) to test for association between persistence at 24 months after stroke, and factors are shown in Table 2. Explanatory variables were included as categorical variables, with missing values used as an independent category (data not reported).

All analyses were performed in agreement with privacy legislation in Sweden. The project was approved by the Ethics committee at Umeå University.
Between September 1, 2005 and August 30, 2006, 24,024 stroke patients were included in Riks-Stroke, of whom 21,077 were discharged alive. The mean age was 75.2 years (SD, 11.7). There were more men than women (51.5% vs 48.5%), and 23.6% of the patients had a previous stroke. Cerebral hemorrhage contributed to 9.5% of the stroke events; 86.5% were ischemic strokes and 4.0% were undefined strokes.

Table 1. Proportion of Persistent Users Among Patients Discharged With Respective Drugs From Hospital

<table>
<thead>
<tr>
<th>At Discharge*†</th>
<th>1–4 Mo‡</th>
<th>1–8 Mo‡</th>
<th>1–12 Mo‡</th>
<th>1–16 Mo‡</th>
<th>1–20 Mo‡</th>
<th>1–24 Mo‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>All patients</td>
<td>15,809</td>
<td>13,806/14,457 (95.5)</td>
<td>12,517/13,849 (90.4)</td>
<td>11,511/13,344 (86.3)</td>
<td>10,376/12,817 (81.0)</td>
<td>9,542/12,351 (77.3)</td>
</tr>
<tr>
<td>Any antihypertensive drug</td>
<td>7,829</td>
<td>6,209/6,938 (89.5)</td>
<td>5,226/5,657 (97.9)</td>
<td>4,604/5,243 (73.7)</td>
<td>3,968/5,022 (67.0)</td>
<td>3,534/5,065 (62.5)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7,843</td>
<td>6,730/7,358 (81.5)</td>
<td>5,782/7,112 (81.3)</td>
<td>5,084/6,902 (73.7)</td>
<td>4,378/6,574 (66.6)</td>
<td>3,902/6,455 (60.4)</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>9,025</td>
<td>7,460/8,218 (80.8)</td>
<td>6,416/7,857 (81.7)</td>
<td>5,703/7,571 (75.3)</td>
<td>5,049/7,269 (69.5)</td>
<td>4,566/6,975 (65.5)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>4,459</td>
<td>3,716/4,151 (89.5)</td>
<td>3,151/4,008 (78.6)</td>
<td>2,791/3,880 (71.9)</td>
<td>2,415/3,753 (64.3)</td>
<td>2,175/3,634 (59.9)</td>
</tr>
<tr>
<td>Calcium inhibitors</td>
<td>7,275</td>
<td>6,444/7,027 (91.7)</td>
<td>5,509/6,886 (80.2)</td>
<td>4,960/6,741 (73.6)</td>
<td>4,306/6,585 (65.4)</td>
<td>3,881/6,445 (60.2)</td>
</tr>
<tr>
<td>Patients with ischemic stroke</td>
<td>14,904</td>
<td>13,226/13,720 (96.4)</td>
<td>11,263/13,157 (85.6)</td>
<td>10,057/12,688 (79.3)</td>
<td>8,761/11,230 (71.6)</td>
<td>7,947/11,798 (67.4)</td>
</tr>
<tr>
<td>Any antithrombotic drug</td>
<td>24,21</td>
<td>20,242/23,199 (87.3)</td>
<td>15,588/22,332 (69.8)</td>
<td>13,577/21,842 (62.1)</td>
<td>11,682/21,277 (54.9)</td>
<td>10,300/20,577 (50.1)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>11,130</td>
<td>9,666/10,571 (81.9)</td>
<td>6,171/6,105 (60.2)</td>
<td>5,269/6,991 (53.1)</td>
<td>4,363/9,599 (45.5)</td>
<td>3,919/9,243 (42.3)</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>12,016</td>
<td>10,022/11,387 (86.4)</td>
<td>8,911/10,105 (80.6)</td>
<td>7,767/9,322 (82.2)</td>
<td>6,619/9,103 (72.6)</td>
<td>5,689/8,175 (65.1)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>11,305</td>
<td>9,109/10,571 (85.9)</td>
<td>6,510/7,679 (85.5)</td>
<td>5,117/6,492 (79.3)</td>
<td>4,115/7,271 (64.4)</td>
<td>3,549/6,944 (59.9)</td>
</tr>
</tbody>
</table>

Data are shown for surviving stroke patients at the end of each time interval. *Discharged with respective drug according to Riks-Stroke. †Internal missing value 0.7%–1.1%. ‡Drug dispensed at pharmacy.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

Results

Between September 1, 2005 and August 30, 2006, 24,024 stroke patients were included in Riks-Stroke, of whom 21,077 were discharged alive. The mean age was 75.2 years (SD, 11.7). There were more men than women (51.5% vs 48.5%), and 23.6% of the patients had a previous stroke. Cerebral hemorrhage contributed to 9.5% of the stroke events; 86.5% were ischemic strokes and 4.0% were undefined strokes.

Among patients in whom treatment with secondary preventive drugs was prescribed at discharge, the propor-
Table 2. Association Between Background Factors and Medication Persistence During First 2 Years After Stroke Using Backward Selection Logistic Regression

<table>
<thead>
<tr>
<th></th>
<th>Anthihypertensive Drugs, N=12 152</th>
<th>Statins, N=6233</th>
<th>Antiplatelet Drugs, N=11 589</th>
<th>Warfarin, N=1250</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P OR (95% CI)</td>
<td>P OR (95% CI)</td>
<td>P OR (95% CI)</td>
<td>P OR (95% CI)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.07</td>
<td>0.04</td>
<td>Ref</td>
<td>NS</td>
</tr>
<tr>
<td>Men</td>
<td>0.81 (0.75–0.89)</td>
<td>0.91 (0.82–1.01)</td>
<td>0.92 (0.85–0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>1.08 (0.97–1.21)</td>
<td>0.69 (0.47–1.01)</td>
<td>0.58 (0.40–0.83)</td>
<td></td>
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<tr>
<td>75–84</td>
<td>1.18 (1.06–1.31)</td>
<td>0.58 (0.40–0.83)</td>
<td>0.57 (0.34–0.94)</td>
<td></td>
</tr>
<tr>
<td>&gt;85</td>
<td>1.37 (1.20–1.57)</td>
<td>0.57 (0.34–0.94)</td>
<td>0.57 (0.34–0.94)</td>
<td></td>
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<tr>
<td><strong>Type of stroke</strong></td>
<td>0.004</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Ischemic stroke</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.24 (1.07–1.43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>1.25 (0.99–1.57)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Recurrent stroke</strong></td>
<td></td>
<td>&lt;0.001</td>
<td>NS</td>
<td>0.04</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.77 (0.68–0.88)</td>
<td>0.70 (0.53–0.93)</td>
<td>0.70 (0.53–0.93)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0.62 (0.33–1.18)</td>
<td>1.46 (0.32–6.65)</td>
<td>1.46 (0.32–6.65)</td>
<td></td>
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<tr>
<td><strong>Diabetes</strong></td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.17 (1.06–1.30)</td>
<td>0.78 (0.70–0.87)</td>
<td>0.78 (0.70–0.87)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0.96 (0.50–1.92)</td>
<td>1.34 (0.82–2.16)</td>
<td>1.34 (0.82–2.16)</td>
<td></td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.24 (1.12–1.38)</td>
<td>0.78 (0.70–0.87)</td>
<td>0.78 (0.70–0.87)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0.65 (0.41–1.03)</td>
<td>1.34 (0.82–2.16)</td>
<td>1.34 (0.82–2.16)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke unit care</strong></td>
<td>NS</td>
<td>0.007</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.25 (1.06–1.46)</td>
<td>1.25 (1.06–1.46)</td>
<td>1.25 (1.06–1.46)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment before stroke onset</strong></td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.07 (1.89–2.27)</td>
<td>1.28 (1.15–1.42)</td>
<td>1.28 (1.15–1.42)</td>
<td></td>
</tr>
<tr>
<td><strong>At 3 months’ follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living situation</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Living at home</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Institutional living</td>
<td>1.47 (1.27–1.70)</td>
<td>1.64 (1.32–2.04)</td>
<td>1.78 (1.55–2.05)</td>
<td>0.45 (0.27–0.76)</td>
</tr>
<tr>
<td>Missing</td>
<td>0.94 (0.73–1.19)</td>
<td>0.96 (0.69–1.32)</td>
<td>0.81 (0.67–0.99)</td>
<td>1.46 (0.75–2.83)</td>
</tr>
<tr>
<td><strong>Low mood</strong></td>
<td>0.001</td>
<td>0.09</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.88 (0.79–0.98)</td>
<td>1.12 (0.98–1.28)</td>
<td>0.92 (0.83–1.02)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1.28 (1.05–1.56)</td>
<td>1.37 (1.07–1.74)</td>
<td>1.16 (0.98–1.39)</td>
<td></td>
</tr>
<tr>
<td><strong>Self-perceived general health</strong></td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Good</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>0.86 (0.76–0.98)</td>
<td>0.69 (0.59–0.80)</td>
<td>0.79 (0.70–0.89)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0.83 (0.67–1.01)</td>
<td>0.70 (0.55–0.90)</td>
<td>0.77 (0.64–0.91)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
tion on persistent medication during the first 4 months after discharge varied from 95.5% for antihypertensive drugs to 89.1% for warfarin (Table 1 and Figure). At 2 years, the rates had decreased to 74.2% for antihypertensives and 45.0% for warfarin, with intermediate proportions for statins and antiplatelet drugs. The persistence rates were very similar for different types of antihypertensive drugs (Figure B). Patients prescribed aspirin were still using treatment 2 years after stroke more often than patients prescribed other antiplatelet drugs (Figure C).

In the multiple logistic regression model, institutional living was the variable most strongly correlated with persistent drug use (Table 2); it was associated with an increased odds of persistent use of antihypertensives and 45.0% for warfarin, with intermediate proportions for statins and antiplatelet drugs. The persistence rates were very similar for different types of antihypertensive drugs (Figure B). Patients prescribed aspirin were still using treatment 2 years after stroke more often than patients prescribed other antiplatelet drugs (Figure C).

In the multiple logistic regression model, institutional living was the variable most strongly correlated with persistent drug use (Table 2); it was associated with an increased odds of persistent use of antihypertensives (P<0.001), antiplatelet agents, and statins (P<0.001), but it was associated with an reduced odds of persistent warfarin use (P=0.004). Other factors that were independently associated with high persistence of one or several of the secondary prevention drugs included female gender, a history of previous stroke, comorbidity (diabetes, atrial fibrillation), stroke unit care, and support by next-of-kin. Advanced age was associated with high persistence of antiplatelet drugs but low persistence of warfarin (Table 2). Poor self-perceived general health and low mood tended to reduce the chance of being a persistent medication user.

### Discussion

In this nationwide follow-up study, only between 74% and 45% of the patients discharged with a specific preventive drug were still regularly using the drug 2 years after stroke. Not only patient characteristics but also aspects of stroke services were associated with persistence rates; this included stroke unit care, institutional living at follow-up, and support by next-of-kin.

Previous studies of patients remaining on long-term secondary drug treatment after stroke have shown highly varying results. Different definitions of persistence and different follow-up times contribute to the variations. Studies of self-reported drug use1,2,5,7 are associated with a risk of overestimation of persistence. Cross-sectional studies, such as the recently published study based on the Swedish Prescribed Drug Register,6 do not take into account whether medication is continuous and thus give higher estimates than studies of continuous/persistent drug use. Several studies are based on data from clinical trials, which probably yield higher rates of continuation of treatment than data from clinical practice.3,4 The strengths of our study are that it is nationwide, based on objective measures, and reflects drug treatment in clinical practice. However, the method we used to measure drug persistence (prescription refills within fixed time periods) probably underestimates the proportion of patients who continue treatment during the follow-up period, because some patients may have accumulated pills and then not refilled the prescription within the next 4-month period.

### Conclusions

Although not confirmed by well-controlled trials, it seems that well-structured secondary prevention programs may improve persistence. If such a program has been implemented, then persistence rates >90% at 12 months have been reported.7 Our observations that more persistent medication use was seen in patients who had comorbidity (with presumed more intense medical follow-up), who had been treated in a stroke unit, who were cared for in an institution, and who had help by next-of-kin support the contention that structural interventions may promote persistent use of secondary prevention drugs.

### Acknowledgments

The authors thank all persons working with Riks-Stroke, the Swedish Stroke Register. The authors also thank Professor Kjell Asplund for valuable guidance and comments on the manuscript.
Sources of Funding
The authors received grant support from Apoteket AB, Swedish Heart and Lung Foundation, and Västerbotten County Council to perform this study.

Disclosures
None.

References
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Stroke. 2010;41:397-401; originally published online January 14, 2010;
doi: 10.1161/STROKEAHA.109.566950

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/41/2/397