Ischemic Stroke and Secondary Prevention in Clinical Practice
A Cohort Study of 14,529 Patients in the Swedish Stroke Register

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Background and Purpose—Secondary prevention is recommended after stroke, but adherence to guidelines is unknown. We studied the prescription of antiplatelet drugs, angiotensin-converting enzyme inhibitors, statins, and anticoagulant drugs and their relation to risk of death.

Methods—Patients with first-ever ischemic stroke in 2005 were registered in the Swedish Stroke Register. Odds ratios, hazard ratios, and 95% CIs were calculated using logistic and Cox proportional hazard regression models. Adjustments were performed for age, sex, cardiovascular risk factors, other drug therapies, and activities of daily living function.

Results—In total, 14,529 patients with a mean age of 75.0 (±11.6) years were included. They were followed for 1.4 (±0.5) years: 52% had hypertension, 26% atrial fibrillation, 19% diabetes, and 15% were smokers. The odds ratio for prescription of antiplatelet was 2.20 (95% CI, 1.86 to 2.60) among the oldest patients (≥85 years of age) compared with the youngest (18 to 64 years of age). The corresponding odds ratio was 0.38 (0.32 to 0.45) for prescriptions of angiotensin-converting enzyme inhibitors, 0.09 (0.08 to 0.11) for statins, and 0.07 (0.05 to 0.09) for anticoagulant therapy. Prescription of statin and anticoagulant therapy was associated with reduced risk of death (hazard ratio, 0.78 [0.65 to 0.91] and hazard ratio, 0.58 [0.44 to 0.76], respectively) but not the prescription of antiplatelet drugs or angiotensin-converting enzyme inhibitors.

Conclusions—The prescription of antiplatelet, angiotensin-converting enzyme inhibitors, statins, and anticoagulant therapy was strongly age related. Statin and anticoagulant therapy was associated with reduced risk of death and seemed to be underused among elderly patients. These findings should encourage physicians to follow today’s guidelines for stroke care. (Stroke. 2010;41:1338-1342.)

Key Words: cerebral infarction • risk factors • secondary prevention • age groups

Hypertension, diabetes, atrial fibrillation, and smoking are, together with hypercholesterolemia, classical risk factors for ischemic stroke,¹⁻³ and cardiovascular disease is the most common cause of death after an event of stroke. Therefore, effective secondary preventive therapy is warranted.⁴⁻⁷ Evidence-based therapy after ischemic stroke, as recommended by guidelines,⁸⁻⁹ includes the use of antiplatelet drugs,¹⁰ angiotensin-converting enzyme (ACE) inhibitors,¹¹⁻¹⁴ and statins¹⁵⁻¹⁶ for a wide spectrum of stroke patients and anticoagulant therapy¹⁷⁻¹⁹ for patients with atrial fibrillation. Today, disparities in the use of secondary preventive drug therapy in clinical practice are not thoroughly studied.²⁰ However, in addition to secondary prevention and cardiovascular risk factors, death after stroke is also affected by high age and stroke severity.²¹,²² The aim of this study, performed in a representative cohort of hospitalized ischemic stroke patients, was to investigate the prescription of antiplatelet, ACE inhibitor, statin, and anticoagulant therapy at discharge from hospital, by age categories, and the associations between the prescription of these drugs and mortality rates.

Methods
This study was based on cases registered in the Swedish Stroke Register (Riks-Stroke) during the period of January 1 through December 31, 2005. Riks-Stroke includes information on stroke admissions in Sweden, and coverage is estimated at 82%. A detailed case-by-case validation of Riks-Stroke indicates that patients who died early, were not treated at a stroke unit, or were cared for in a nursing home were less likely to be included in the register.²³

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Participants
In the Swedish population of 9 million inhabitants, 21,765 stroke patients were admitted to hospital and registered in Riks-Stroke during the study period. Information on any previous stroke, defined as a previous episode of hospital care for International Classification of Diseases, 10th revision (ICD-10), codes I61, I63, and I64, from January 1, 1987, until 7 days before index stroke, was obtained from the Swedish Hospital Discharge Register. After exclusion of non-ischemic, recurrent, or acute fatal stroke, 14,529 patients, discharged (and hence classified as nonfatal events) with first-ever ischemic stroke (I63; ICD-10), were included in the study. Death dates were retrieved from the Swedish Cause of Death Register. The patients were followed from time of stroke until death or end of follow-up (February 9, 2007). No patients were lost to follow-up with respect to death date. In subanalyses, 10,788 patients, with complete data on activities of daily living function 3 months after stroke, were included. This subgroup had a similar cardiovascular risk profile but was modestly younger (by 0.8 years) and had a slightly longer period of follow-up (43 days) compared with the original cohort.

Variables in Riks-Stroke
Riks-Stroke contained data on age, sex, cardiovascular risk factors, drug therapies, and activities of daily living 3 months after stroke. Cardiovascular risk factors comprised diabetes, atrial fibrillation, hypertension, and smoking history. Diabetes (E10-E14, ICD-10, including type 1 and type 2) and atrial fibrillation (I48, ICD-10, including atrial flutter or chronic or intermittent atrial fibrillation) were registered if previously known (in the case history) or diagnosed during hospital stay. Hypertension (I10-I15, ICD-10) was scored as present if the patient used antihypertensive drug therapy on hospital admission. Smoking was reported if a patient smoked tobacco on a daily basis or had stopped smoking within the last 3 months before hospital admission. All cardiovascular risk factors were coded as yes, no, or unknown. The prescription of antplatelet drugs at discharge was dominated by aspirin (90%), followed by clopidogrel (5%) and dipyridamole (5%). Anticoagulant therapy was synonymous to warfarin because no other oral anticoagulants were available in Sweden. Three months after stroke, patients were contacted and asked to answer a questionnaire by either telephone or mail. The patients’ living arrangement, activities of daily living, and need for support were recorded and transformed into an estimated grade on modified Rankin Scale (mRS). The mRS, graded from 0 to 5, is a frequently used tool to evaluate recovery and activities of daily living function after stroke. A higher grade indicates a more severe stroke.

Missing Data
All 14,529 patients had information on age, gender, and all-cause mortality. Fewer than 1% of the patients had missing data on atrial fibrillation, diabetes, or hypertension. However, smoking habits were unknown in 10.3% of all patients, and the uncertainty was more pronounced in the 2 age categories ≥75 years (10.6% and 13.7%). To address any bias of missing data, regression analyses were conducted twice: first with missing data excluded, and second with missing data included as one category. These analyses did not differ radically, and missing data were, henceforth, included in models that contained risk factors as covariates. Data on therapy, on admission and at discharge, were unknown in 0.6% to 1.1% of all patients, and because these missing data were few and did not affect the result, they were not included in the study. At the 3-month follow-up, 1669 patients were lost, giving a follow-up frequency of 88%. Further, 1062 patients did not answer all questions regarding living conditions, need of support, and activities of daily living function, all of which were essential to estimate an mRS grade. These patients were not included in the Cox proportional hazard models, giving a total follow-up frequency of 80% concerning functional impairment.

Statistical Analyses
Odds ratios and 95% CIs for prescription of secondary preventive drug therapy at discharge (antiplatelet drugs, ACE inhibitors, statins, and anticoagulants, yes versus no, as dependent variables), were calculated using separate multiple logistic regression models. All estimates were adjusted for age (4 categories: 18 to 64, 65 to 74, 75 to 84, and ≥85 years), sex (male or female), and available cardiovascular risk factors, including diabetes, hypertension, atrial fibrillation, and smoking (yes, no, or unknown), all as categorical variables. In addition, all odds ratios of secondary therapy were adjusted for its matching therapy on admission (antiplatelet drugs, ACE inhibitors, statins, or anticoagulants; yes or no) as binary variable. Cox proportional hazard regression models were used to estimate hazard ratios of death, 95% CIs, and plots of survival function (supplemental Figure I, available online at http://stroke.ahajournals.org) in relation to therapy at discharge. The models included age as continuous variable and study therapy, sex, cardiovascular risk factor, and activities of daily living function (mRS grades 0 to 2, 3, 4, or 5) as categorical variables. The covariates were included because they are considered to influence mortality and were used simultaneously to achieve adjustments for each other. We assessed interaction between age and functional status as dichotomous variables (<75 years of age versus ≥75 years of age and functional status; mRS grade 0 to 3 versus 4 to 5). This analysis revealed no interaction between age and functional status (P=0.24) on observed survival. Further, the stratum-specific hazard ratio estimates of death by age and functional status were approximately the same as in the original analyzes. SPSS version 15.01.1 was used for all analyses.

Ethics
This study was approved by the ethical committee of Umeå University Hospital, May 5, 2006 (reg. No. 69106).

Results
Presence of Risk Factors
Overall, 14,529 patients with a first-ever, nonfatal ischemic stroke were included in the present study (Table 1). In this cohort, 73.9% of the patients had ≥1 of the study risk factors (Table 2). When the 4 age categories were compared (Figure 1), the frequency of diabetes did not differ noticeably (19.8%, 21.9%, 18.5%, and 15.0%, respectively). The frequency of hypertension increased between the first 2 age categories but not among the 3 oldest age categories (39.3%, 52.7%, 56.6%, and 53.1%). Atrial fibrillation increased considerably by each age category (9.4%, 20.1%, 28.9%, and 41.3%), whereas the

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**Table 1. Characteristics of Study Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Patients</td>
<td>7290</td>
<td>50.2</td>
<td>7239</td>
</tr>
<tr>
<td>Mean age (y, SD)</td>
<td>72.7</td>
<td>(11.5)</td>
<td>77.3</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–64 y</td>
<td>1767</td>
<td>24.2</td>
<td>937</td>
</tr>
<tr>
<td>65–74 y</td>
<td>1941</td>
<td>26.6</td>
<td>1387</td>
</tr>
<tr>
<td>75–84 y</td>
<td>2532</td>
<td>34.7</td>
<td>2938</td>
</tr>
<tr>
<td>≥85 y</td>
<td>1050</td>
<td>14.4</td>
<td>1977</td>
</tr>
<tr>
<td>Mean follow-up time (days, SD)</td>
<td>522</td>
<td>(184)</td>
<td>505</td>
</tr>
</tbody>
</table>

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opposite was found for smoking (35.9%, 18.3%, 8.7%, and 2.8%).

Secondary Preventive Therapy
The prescription of secondary preventive drugs at discharge differed by age category and type of drug (Figure 2). Irrespective of age, antiplatelet drugs were prescribed to >80% of all patients and to >87% of patients without atrial fibrillation. The prescription rate of ACE inhibitors was even among patients <85 years of age (varying from 34.0% to 38.9%) but was lower in patients >85 years of age (22.7%). The prescription of statins decreased from 54.1% among patients <75 years of age to 10.0% in patients ≥85 years of age. Among patients with atrial fibrillation, anticoagulant drugs were prescribed to 63% of the patients in the youngest age category (18 to 64 years of age) but only to 9.1% in the oldest age category (≥85 years of age). In addition to the frequency, we examined the odds of being prescribed specific secondary preventive drug therapy (Table 3). The adjusted odds ratio for antiplatelet prescription increased by age, whereas the corresponding odds ratio for ACE inhibitor, statin, and anticoagulant therapy decreased by age.

Survival Estimates
Hazard ratios of death, crude and adjusted, were estimated in relation to the prescription of secondary preventive drugs (Table 4). After adjustment, the hazard ratio was lower (21.9% and 42.3%, respectively) among patients prescribed statin or anticoagulant therapy (survival plots in supplemental Figure II, available online at http://stroke.ahajournals.org). Among patients prescribed antiplatelet therapy, there was a trend toward a lower mortality (hazard ratio, 0.83; 0.68 to 1.01), but among patients prescribed ACE inhibitors, there was no association with mortality (1.00; 0.87 to 1.14).

Discussion
In this representative cohort of hospitalized patients with first-ever, nonfatal ischemic stroke, nearly 3 of 4 patients had ≥1 of the cardiovascular risk factors, diabetes, hypertension, atrial fibrillation, and smoking. In the majority of patients (ie, those ≥75 years of age), the prescription rate of secondary preventive drug therapy was low, with exception for anti-
platelets, and the question may be raised whether secondary prevention was underprescribed to older patients. In the subgroup of patients surviving for ≥90 days, prescription of statins and anticoagulants was associated with decreased mortality. This indicates that statin and anticoagulant therapies were underused among elderly patients in clinical practice.

Some limitations deserve comment. We had no information on initiation and duration of drug therapy after hospital discharge or serum concentrations of blood lipids. Hypertension was, according to the Riks-Stroke protocol, defined by treatment for the disease and not by digital values of blood pressure. Twenty percent of the participants were lost at 3-month follow-up or had incomplete information (regarding functional impairment) on data that were essential for the estimation of mRS grades.24 Despite these limitations, our study contributes an understanding of clinical practice reflected in a database with good national coverage.

This study, based on data from a whole country with a publicly financed health care system, indicates a conservative attitude toward the initiation of secondary preventive therapy among stroke patients in general, and among older stroke patients in particular.

In contrast to recent recommendations,9 the guidelines that were current at the study period8 neither promoted ACE inhibitors in favor of other blood pressure lowering agents nor emphasized statin therapy to the stroke population. However, aspirin was recommended to patients with nonembolic ischemic stroke and anticoagulation to patients with atrial fibrillation, without specific guidance for elderly and frail patients. In our study, two thirds of patients with atrial fibrillation did not receive anticoagulation, and this proportion is replicated in other Scandinavian register studies.26,27 In addition, our observations confirm the results of the 2004 National Stroke Audit in England, Wales, and Northern Ireland, where patients ≥85 years of age are less likely to receive secondary prevention.28 There are at least two possible explanations for the conservative attitude toward treatment of elderly patients. The first considers the frequency of comorbid diseases, which is higher among older patients, and the impact of comorbid diseases on lifespan and complication rates. Little is known about this topic in broad patient categories. The second possible explanation is lack of evidence from randomized clinical trials, and hence clear guidelines, with respect to old age. In stroke trials, concerning secondary prevention with ACE inhibitors and statins, the mean age is <65 years,11,15 and in trials with anticoagulation, it is <73 years.17 However, in recent years, clinical trials and subgroup analyses report similar results in younger as well as in older patients.29–31 In our observational study, in contrast to randomized clinical trials, statin therapy had an association with reduced all-cause mortality.15,16 Anticoagulant therapy was correlated positively to survival, which is in line with a Danish observational study27 including older patients, and with a meta-analysis17 of trials with younger patients.

In summary, although cardiovascular risk factors were prevalent, many patients at risk did not receive the secondary drug therapy recommended in current guidelines. Age was an important negative predictor for prescription of ACE inhibitor, statin, and anticoagulant therapy. Moreover, treatment with anticoagulants and statins was associated with reduced risk of death. These findings should encourage physicians to follow today’s guidelines for stroke care, but randomized clinical trials alone can provide evidence for positive prevention effects in broad patient categories.

Table 3. Adjusted Odds Ratios With 95% CIs for Prescription of Secondary Preventive Drug Therapy Among 14 529 Patients With First-Ever, Nonfatal Ischemic Stroke

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Antiplatelets</th>
<th>ACE Inhibitors</th>
<th>Statins</th>
<th>Anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR* 95% CI</td>
<td>OR* 95% CI</td>
<td>OR* 95% CI</td>
<td>OR* 95% CI</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td>1.09</td>
<td>0.93–1.27</td>
<td>0.83</td>
<td>0.68–1.01</td>
</tr>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td>0.83</td>
<td>0.74–0.95</td>
<td>1.00</td>
<td>0.87–1.14</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td>0.40</td>
<td>0.35–0.46</td>
<td>0.78</td>
<td>0.67–0.91</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td>0.28†</td>
<td>0.22–0.36</td>
<td>0.58</td>
<td>0.44–0.76</td>
</tr>
</tbody>
</table>

*Adjusted for study therapy at discharge (antiplatelet, ACE inhibitor, statin, anticoagulant; no/yes), sex (male/female), available cardiovascular risk factor (diabetes, hypertension, atrial fibrillation, smoking; no/yes/unknown), and activities of daily living function (mRS grade; 0 to 2/3/4/5), all as categorical variables, and age as continuous variable; †among 2607 patients with atrial fibrillation.
Acknowledgments

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Disclosures

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References

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