Compliance With Secondary Prevention of Ischemic Stroke
A Prospective Evaluation

Tanja Sappok, MD; Andreas Faulstich; Erika Stuckert; Holger Kruck; Peter Marx, MD; Hans-Christian Koennecke, MD

Background and Purpose—Compliance with pharmacological therapy is essential for the efficiency of secondary prevention of ischemic stroke. Few data exist regarding patient compliance with antithrombotic and risk factor treatment outside of controlled clinical trials. The aim of the present study was to assess the rate of and predictors for compliance with secondary stroke prevention 1 year after cerebral ischemia and to identify reasons for noncompliance.

Methods—Patients with a diagnosis of ischemic stroke or TIA and antithrombotic discharge medication were prospectively recruited. At 1 year, the proportion of patients compliant with antithrombotic treatment and with medication for risk factors (eg, hypertension, diabetes, hyperlipidemia) was evaluated through structured telephone interviews. In addition, the reasons for nontreatment with antithrombotic and risk factor medication were determined. Independent predictors for compliance were analyzed by logistic regression analyses.

Results—Of 588 consecutive patients admitted to our stroke unit, 470 had a discharge diagnosis of cerebral ischemia (TIA 26.2%, cerebral infarct 73.8%) and recommendations for antithrombotic therapy. At 1 year, 63 patients (13.4%) had died and 21 (4.5%) were lost to follow-up, thus, 386 could finally be evaluated. Of the patients, 87.6% were still on antithrombotic medication, and 70.2% were treated with the same agent prescribed on discharge. Of the patients with hypertension, diabetes, and hyperlipidemia, 90.8%, 84.9%, and 70.2% were still treated for their respective risk factors. Logistic regression analyses revealed age (OR 1.03, 95% CI 1.00 to 1.06), stroke severity on admission (OR 1.09, 95% CI 1.00 to 1.20), and cardioembolic cause (OR 4.13, 95% CI 1.23 to 13.83) as independent predictors of compliance.

Conclusions—Compliance with secondary prevention in patients with ischemic stroke is rather good in the setting of our study. Higher age, a more severe neurological deficit on admission, and cardioembolic stroke cause are associated with better long-term compliance. Knowledge of these determinants may help to further improve the quality of stroke prevention. (Stroke. 2001;32:1884-1889.)

Key Words: antithrombotic therapy ■ medical management ■ prevention ■ stroke, ischemic

Stroke is a leading cause of death and disability in industrialized countries. The efficacy of antithrombotic medication to prevent recurrence of stroke and death has been proven in several trials. Furthermore, little doubt exists regarding the efficiency of secondary stroke prevention through the treatment of major stroke risk factors. However, in particular, the stroke-preventive effect of antiplatelet treatment is only moderate and is further reduced, if not abolished, by poor compliance.

Patient compliance may be different under the monitoring conditions of controlled trials compared with daily life conditions. Information regarding compliance with antithrombotic medication and with therapy of stroke risk factors in routine general practice is scarce. In the present study, we therefore sought to (1) determine the prevalence of compliance with antithrombotic medication and pharmacological therapy of stroke risk factors (hypertension, diabetes, and hyperlipidemia) 1 year after an ischemic stroke or a TIA and to (2) identify the predictors for compliance and reasons for discontinuation or changes of a specific medication.

Subjects and Methods
The study was conducted at an academic medical center in the south of Berlin, Germany, serving a population of ~500 000. Every year, ~400 patients with acute stroke are admitted to our stroke unit. Consecutive patients with a confirmed diagnosis of TIA or nonfatal ischemic stroke treated with an antithrombotic agent (eg, aspirin, ticlopidine/clopidogrel, phenprocoumon) at discharge were prospectively enrolled. Patients with a diagnosis of cerebral hemorrhage, migrainous aura, seizure, or any other nonischemic pathology were excluded. Patients were considered to have had an ischemic stroke or a TIA if there was a focal neurological deficit of sudden onset with no known alternative to an ischemic vascular cause. All patients included in this study underwent CT or MRI. Deficits that lasted >24 hours were diagnosed as infarctions, and those with a duration of <24 hours and a negative brain scan were diagnosed as TIAs.

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From the Department of Neurology, Stroke Unit, Universitätssklinikum Benjamin Franklin, Freie Universität Berlin, Germany.
Correspondence to Hans-Christian Koennecke, MD, Department of Neurology, Ev Krankenhaus Königin Elisabeth Herzberge, Herzbergerstr 79, 10362 Berlin, Germany. E-mail h.koennecke@keh-berlin.de
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Informed consent was obtained from all patients or their next of kin. The study was approved by the ethics committee of our hospital. In addition to the respective discharge medication, different sociodemographic and medical variables were recorded, including age, sex, care situation, occupation, major stroke risk factors, stroke severity (as measured by the National Institutes of Health Stroke Scale [NIHSS] on admission and the Barthel Index and Rankin Scale at discharge), and subtype of cerebral ischemia (according to the TOAST criteria).

Compliance with discharge medication, smoking habits, and complications were evaluated at 1 year after admission. Follow-up information was obtained through a structured telephone interview with the patient. If the patient could not be contacted, information was obtained from relatives, caregivers, or the patient’s general practitioner. The interview consisted of questions regarding complications (death, recurrent cerebral ischemia or hemorrhage, myocardial infarction) and the patient’s current medication. If the medication differed from the recommendations at discharge, the questionnaire was extended to reveal (1) the person who initiated the discontinuation or change (general practitioner, physician at rehabilitation facility, patient, unknown) and (2) the reasons for the change or discontinuation (side effects, contraindication, inefficacy, other [eg, costs, drug interaction], unknown). For antithrombotic therapy, inefficacy was assumed in patients with recurrent cerebrovascular ischemic events, whereas insufficient control of the respective risk factor was the criterion for inefficacy of risk factor medication. The primary analyses were focused on the proportion of patients treated with any antithrombotic agent or stroke risk factor medication at 1 year and predictors for compliance with antithrombotic treatment. A secondary analysis assessed changes among different subgroups of antithrombotic agents during follow-up.

Data were recorded in a personal computer using a special mask for data entry. In a first step, univariate analyses (χ² test for categorical factors, Mann-Whitney U test for ordinal factors) were conducted to reveal associations of different variables with compliance with antithrombotic treatment. In a second step, the independent effects of the variables with P<0.1 in the univariate analyses were assessed by stepwise backward logistic regression analyses. For each association of interest, an adjusted OR and the 95% CI were calculated. OR, 95% CI, and P value were determined just before elimination. A difference was regarded as statistically significant at P<0.05. Data were analyzed with SPSS (release 9.0.1) statistical software.

Results

Between March 1998 and June 1999, a total of 588 consecutive patients were admitted to our stroke unit. One hundred eight patients were excluded from the study due to intracranial hemorrhage or other discharge diagnoses (eg, migrainous aura, seizures), and 10 were excluded due to fatal ischemic stroke. Of the remaining 470 patients with cerebral ischemia (for baseline characteristics, see Table 1), 63 (13.4%) died during the year after the event and an additional 21 (4.5%) were lost to follow-up. Thus, 386 patients were finally evaluated at 1 year (Figure 1). The distributions of stroke severity on admission and at discharge for patients with cerebral infarction are given in Figure 2. During the

![Figure 1. Compliance with antithrombotic therapy as recommended on discharge. Numbers in bold and percentages refer to the 470 patients who were initially enrolled. Numbers in parentheses indicate percentages of the 386 patients who were finally evaluated at 1 year.](http://stroke.ahajournals.org/)

![Figure 2. Frequency distribution of stroke severity on admission and at discharge of patients with confirmed cerebral infarction (n=347).](http://stroke.ahajournals.org/)
follow-up period, 25 (6.5%) patients had a recurrent cerebral ischemia, 1 patient had a cerebral hemorrhage, and 3 patients had a myocardial infarction. Treatment rates at 1 year are given in Table 2. Of 386 patients, 87.6% were still on antithrombotic treatment, and 70.2% received the same anti-thrombotic agent as prescribed on discharge.

Table 3 demonstrates the different compliance rates according to subclasses of antithrombotic medication. In particular, poor compliance (<60%) was determined in patients discharged on thienopyridines (ticlopidine n=35, compliance 40%; clopidogrel n=55, compliance 54.5%), whereas >75% of the patients discharged on aspirin or phenprocoumon were on the identical medication at follow-up. Only 4.5% of the patients with a recommendation for anticoagulation were without any antithrombotic medication at 1 year, whereas 14% of the patients discharged on aspirin or thienopyridines at discharge received no antithrombotic agent at follow-up. Changes in therapy among the different antithrombotic agents during the first year after cerebral ischemia are depicted in Figure 3. About one third of patients discharged on thienopyridines had been switched to aspirin at 1 year.

Compliance rates for risk factor treatment were highest in patients with hypertension and lowest in patients with hyperlipidemia (Table 2). At 1 year, 47 (35.9%) of 131 smokers had quit smoking. In the majority of patients, changes in the antithrombotic and risk factor medication were initiated by the general practitioner (Table 2). Among the reported reasons for discontinuation or changes of antithrombotic therapy, side effects (47.5%) and inefficacy (23.7%) were most common, whereas contraindications (13.6%) and other reasons (15.2%) accounted for the remainder. For risk factor medication, inefficacy (40.7%) was stated most frequently, followed by other reasons (33.9%), side effects (20.3%), and contraindications (5.1%). However, due to the large proportion of unknown reasons in either group (48.7% and 62.4% for antithrombotic and risk factor medication, respectively), these numbers have to be regarded with caution.

Univariate analyses revealed no association of compliance with the patient’s care situation or occupation, whereas higher age, nonsmoking status, more severe clinical deficit (NIHSS on admission and Rankin Scale at discharge), cardioembolic cause, and anticoagulation at discharge were associated with better compliance ($P<0.1$) (Tables 4 and 5). In logistic regression analyses, higher age, stroke severity, and cardioembolic cause were independently associated with better compliance, but only higher age and cardioembolic cause remained as significantly associated predictors (Table 6).

**Discussion**

Detailed knowledge about long-term compliance with secondary stroke prevention is necessary to focus future strategies for improvement in stroke prevention. No long-term in-depth analyses exist regarding the use of antithrombotic agents after hospital discharge. The observed compliance...
with antithrombotic treatment in the present study is higher than that in 2 recent studies, which reported rates of 64% and 76%, respectively.14,15 However, 1 study was focused on young adults (age 15 to 44 years) only,14 and the duration of the follow-up period was either markedly shorter (3 months)15 or significantly longer (mean 8 years)14 in these studies than in the present study. The present surprisingly high rate of adherence to therapy might further be due to the specific setting of our study, because all our patients were recruited from a stroke unit. In other studies, recruitment of patients relied on a population-based register15 or multiple centers of a study group.14 Stroke unit staff might be more committed to provide detailed explanations about the disease and the necessity of long-term treatment to the patients and their relatives. Moreover, compliance rates may be lower with extended follow-up periods. Finally, different treatment guidelines used in various countries could account for the different results.16 In 2 other studies that reported lower treatment rates, either compliance was evaluated retrospectively17 or compliance was defined as the hospital physician’s adherence to published guidelines for treatment.18 Consequently, these results are hardly comparable to our study. Even worse treatment rates, ranging from 39% to 62%, have been reported for primary stroke prevention in patients with atrial fibrillation.19–21 On the other hand, compliance with antithrombotic medication for secondary prevention of myocardial infarction is much higher and similar to our results (92%).22

To the best of our knowledge, the present study is the first to compare compliance with different antithrombotic agents. Overall, changes to a different antithrombotic medication occurred in only 17% of the patients. However, in consideration of the subclasses in detail, only one third of patients discharged on thienopyridines were on this medication at 1 year. Aspirin replaced ticlopidine/clopidogrel in the majority of changes (88%), although the discharge recommendations for thienopyridines were either aspirin failure (ie, pretreatment with aspirin) or contraindications for aspirin. Drug prescriptions for outpatients with nonprivate health insurance are limited by a yearly budget in our country. Thus, the much higher costs for thienopyridines may account for some changes in treatment. However, because the cost factor was not a specific part of our questionnaire and because the

### Table 4. Association of Patient Characteristics and Compliance With Antithrombotic Therapy in 386 Patients Evaluated at 1 Year

<table>
<thead>
<tr>
<th>Categorical Factor</th>
<th>Frequency of Nontreatment</th>
<th>( \chi^2 ) Test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>221</td>
<td>23</td>
<td>10.4</td>
</tr>
<tr>
<td>Women</td>
<td>165</td>
<td>25</td>
<td>15.2</td>
</tr>
<tr>
<td>History of cigarette smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>131</td>
<td>22</td>
<td>16.8</td>
</tr>
<tr>
<td>No</td>
<td>255</td>
<td>26</td>
<td>10.2</td>
</tr>
<tr>
<td>Cigarette smoking at follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>85</td>
<td>16</td>
<td>18.8</td>
</tr>
<tr>
<td>No</td>
<td>301</td>
<td>32</td>
<td>10.6</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>50</td>
<td>7</td>
<td>14.0</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>88</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Lacunar</td>
<td>81</td>
<td>14</td>
<td>17.3</td>
</tr>
<tr>
<td>Unknown/other</td>
<td>167</td>
<td>24</td>
<td>14.4</td>
</tr>
<tr>
<td>Syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>112</td>
<td>16</td>
<td>14.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>274</td>
<td>32</td>
<td>11.7</td>
</tr>
<tr>
<td>Discharge medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>229</td>
<td>32</td>
<td>14.0</td>
</tr>
<tr>
<td>Ticlopidine/clopidogrel</td>
<td>90</td>
<td>13</td>
<td>14.4</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>67</td>
<td>3</td>
<td>4.5</td>
</tr>
</tbody>
</table>

#### Figure 3. Changes among subgroups of antithrombotic agents compared with discharge treatment (386 patients).

### Table 5. Association of Patient Characteristics and Compliance With Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Ordinal Factor</th>
<th>Compliant</th>
<th>Noncompliant</th>
<th>Mann-Whitney Test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.7 ± 12</td>
<td>62.2 ± 14.8</td>
<td>0.062</td>
<td></td>
</tr>
<tr>
<td>Barthel Index at discharge</td>
<td>88.0 ± 24.2</td>
<td>90.8 ± 24.8</td>
<td>0.265</td>
<td></td>
</tr>
<tr>
<td>Rankin Scale score at discharge</td>
<td>1.5 ± 1.4</td>
<td>1.1 ± 1.4</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>4.4 ± 4.9</td>
<td>2.6 ± 4.12</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD. n = 386.

### Table 6. Predictors for Compliance With Antithrombotic Agents

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Rank*</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rankin Scale score at discharge</td>
<td>1</td>
<td>0.88 (0.62–1.24)</td>
<td>0.458</td>
</tr>
<tr>
<td>Anticoagulant at discharge</td>
<td>2</td>
<td>1.91 (0.50–7.26)</td>
<td>0.344</td>
</tr>
<tr>
<td>History of cigarette smoking</td>
<td>3</td>
<td>0.64 (0.33–1.25)</td>
<td>0.193</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td></td>
<td>1.09 (1.00–1.20)</td>
<td>0.058</td>
</tr>
<tr>
<td>Cardioembolic cause</td>
<td></td>
<td>4.13 (1.23–13.83)</td>
<td>0.022</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>1.03 (1.00–1.06)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

*Rank of elimination in stepwise backward logistic regression.

# ORs were derived from a backward logistic regression model. An OR <1 indicated a lower likelihood of being on treatment for those with the indicated characteristic compared with those without the characteristic.

n = 386.
reasons for treatment changes remained unknown in >60% of patients receiving thienopyridines, this assumption remains speculative.

Another noteworthy result is the low nontreatment rate in the anticoagulant subgroup (4.5% versus 14% in the antiplatelet group). A higher awareness of risk for stroke recurrence by these patients and their general practitioners may account for this result. Moreover, in contrast to treatment with antiplatelet agents, anticoagulant therapy requires regular physician-patient contact. Compliance with antihypertensive treatment was excellent in the present study, which concurs with the results of other studies.23,24 Again, the possibility of directly assessing treatment effects (ie, measuring blood pressure) might account for patient adherence to the recommended medication. In contrast, the high costs for statins and the remaining uncertainty regarding their efficiency in stroke prevention may have contributed to the relatively low compliance rate (70%) in this subgroup.

In the present study, patients of older age, those with a more severe neurological deficit, and a cardioembolic stroke cause were more likely to adhere to the recommended medication, whereas another study from Great Britain reported that patients with severe strokes were less compliant at 3 months after stroke.15 This phenomenon was explained by “possible difficulties experienced in attending hospital outpatient clinics and general practitioner surgeries for monitoring of the anticoagulation status or blood pressure.”15 In our country, patient access to general practitioners and other medical institutions for outpatients may be easier and thus facilitate poststroke medical care. Hence, differences in medical health care systems among countries may account for the diversity of these results. Moreover, patient-physician contact may be closer in sicker patients, and patients with more severe or cardioembolic strokes are more likely to have a recurrence of stroke than are those with, for example, lacunes.14,25,26 A British survey demonstrated that primary care is mainly focused on the management of patients at high absolute risk of stroke recurrence.25 As a result, monitoring conditions in patients with higher treatment benefits may account for better compliance rates.

To date, reasons for changes in discharge medication have merely been reported for primary stroke prevention in patients with atrial fibrillation.26,27 These were similar to our findings for secondary prevention that changes were based on the general practitioner’s decision in most instances. Remarkably, in the present study, 12.2% of changes in antithrombotic therapy but only 2.5% of changes in stroke risk factor therapy were initiated by the patient. This might be due to side effects; the lack of biochemical antiaggregation control, resulting in fewer physician contacts; and a lack of motivation to continue medication in patients with minor or no disabilities.30 Thus, our results stress the importance of providing detailed and repeated information about the cause and prognosis of stroke and the possibilities of reducing the risk of recurrence to increase long-term patient compliance.

The present study has potential limitations. Patients who were lost to follow-up or died were not evaluated for compliance, which may have led to an overestimation of compliance, because no follow-up data on the actual treatment in these subgroups were available. Moreover, because we gained information mainly from the patients via telephone interviews, the results of the study are limited by the credibility of patients. However, the statements about cessation of smoking are within the range reported from the literature, suggesting that the information obtained was quite reliable.14,23,24 Due to the study design, patients who were treated insufficiently with regard to anticoagulation were not identified. Because insufficiency of treatment is a common phenomenon in clinical practice,21,23 our study does not allow statements to be made on the quality of secondary stroke prevention in general.

In conclusion, long-term compliance with preventive stroke therapy is surprisingly good in the setting of the present study. Higher age, a more severe neurological deficit, and cardioembolic stroke cause predict higher compliance rates, whereas treatment with thienopyridines decreases the adherence to treatment recommendations. Consequently, special attention should be paid to younger patients with less severe deficits to improve their long-term compliance with secondary stroke prevention.

References


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