Antithrombotic and Antihypertensive Management 3 Months After Ischemic Stroke
A Prospective Study in an Inner City Population

Thomas Hillen, MD; Ruth Dundas, MSc; Enas Lawrence, MRCP; Judith A. Stewart, MRCP; Anthony G. Rudd, FRCP; Charles D.A. Wolfe, FFPHM

Background and Purpose—We sought to examine the frequency, predictors, and effects of nontreatment with antithrombotic and antihypertensive therapies 3 months after ischemic stroke.

Methods—The population-based South London Community Stroke Register prospectively collected data on first-in-a-lifetime strokes between 1995 and 1997. Among patients registered with ischemic stroke, treatment status with antithrombotic and antihypertensive therapies was examined 3 months after the event.

Results—In a cohort of 457 patients with ischemic stroke, 393 (86.0%) were considered appropriate for antiplatelet medication, 32 (7.0%) for anticoagulant medication, and 254 (55.9%) for antihypertensive medication. The rates of nontreatment observed 3 months after the event were 24.4% for antiplatelet, 59.4% for anticoagulant, and 29.5% for antihypertensive medication. Independent risk factors for nontreatment with antithrombotic therapies (antiplatelets and anticoagulants) were the subtype of stroke (nonlacunar infarct: OR \(1.60, 95\%\ CI 1.07 \text{ to } 2.54\)), stroke severity measured by the Glasgow Coma Scale (GCS) score (GCS \(\leq 13\): OR 2.08, 95% CI 1.18 to 3.66) and the Barthel Index (BI) score 5 days after the event (BI \(\leq 10\): OR 1.85, 95% CI 1.17 to 2.93). For antihypertensive therapies the stroke subtype (OR 2.46, 95% CI 1.33 to 4.54), GCS score (OR 2.97, 95% CI 1.35 to 6.53), BI score (OR 2.33, 95% CI 1.27 to 4.29), and ethnicity (Caucasian: OR 2.43, 95% CI 1.15 to 5.14) were independently associated with nontreatment. Cox regression modeling showed no significant association between the treatment status and recurrence-free 3-year survival rates after controlling for severity and subtype of stroke.

Conclusions—Secondary prevention for a common disease such as stroke appears to be inadequate in the study area. Healthcare professionals need to consider antithrombotic and antihypertensive therapies for all stroke patients. (Stroke. 2000;31:469-475.)

Key Words: antithrombotic therapy ■ epidemiology ■ hypertension ■ prevention ■ stroke management

Randomized controlled trials have clearly shown the beneficial effects of secondary prevention with antithrombotic and antihypertensive therapies in patients with ischemic stroke.\(^1\)\(^,\)\(^2\) The meta-analysis of the Antiplatelet Trialists’ Collaboration demonstrated a 23% risk reduction in important vascular events through the use of prophylactic antiplatelet agents among patients who have had a previous stroke.\(^3\) An even higher risk reduction (>50%) can be achieved in stroke patients with nonhemorhtic atrial fibrillation through the use of anticoagulants, which are superior to antiplatelet agents in this group.\(^4\) Although fewer studies have examined the effectiveness of antihypertensive therapies in hypertensive patients after stroke, there is good evidence of their efficacy in general.\(^5\)\(^,\)\(^6\)

The use of research evidence for clinical guidelines does not necessarily result in a change in clinical practice.\(^7\)\(^,\)\(^8\) Many patients who could benefit from antiplatelet,\(^9\) anticoagulant,\(^10\) or antihypertensive\(^11\)\(^,\)\(^12\) medication do not receive it. Although stroke patients are at a high risk of further vascular events\(^13\) and may benefit from secondary prevention, population-based data on their vascular risk management is limited, and most of the available studies comprise hospital-based cohorts.\(^14\)\(^,\)\(^16\)

In England and Wales the prevention of vascular disease has been identified as a priority.\(^17\) With the aim of maximizing the efficacy of such a program, the present study has the following objectives: (1) to quantify the underutilization of antithrombotic and antihypertensive therapies among newly diagnosed patients with a first-in-a-lifetime ischemic stroke; (2) to identify patient groups at risk of not being on preventive treatment; and (3) to examine the effect of non-treatment on the recurrence-free survival in these stroke patients.

Subjects and Methods

Case Ascertainment
The South London Community Stroke Register was established in 1995 to study the incidence, management, and outcome of stroke in a multiethnic population. This population-based register prospec-
Table 1. Baseline Characteristics of Patients Registered Between 1995 and 1997 With Ischemic Stroke, Primary Intracerebral Hemorrhage, Subarachnoid Hemorrhage, and Unclassified Stroke

<table>
<thead>
<tr>
<th></th>
<th>Ischemic Stroke</th>
<th>Primary Intracerebral Hemorrhage</th>
<th>Subarachnoid Hemorrhage</th>
<th>Unclassified Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects registered, n</td>
<td>638</td>
<td>111</td>
<td>55</td>
<td>95</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>72.7 (12.4)</td>
<td>69.5 (13.5)</td>
<td>55.0 (20.6)</td>
<td>79.4 (10.0)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>320 (50.2)</td>
<td>56 (50.5)</td>
<td>24 (43.6)</td>
<td>38 (40.4)</td>
</tr>
<tr>
<td>GCS score 0–13, n (%)</td>
<td>183 (28.9)</td>
<td>61 (55.5)</td>
<td>35 (63.6)</td>
<td>48 (53.3)</td>
</tr>
<tr>
<td>Death within 3 mo, n (%)</td>
<td>159 (24.9)</td>
<td>44 (39.6)</td>
<td>29 (52.7)</td>
<td>65 (68.4)</td>
</tr>
<tr>
<td>Recurrence within 3 mo, n (%)</td>
<td>17 (2.7)</td>
<td>5 (11.4)</td>
<td>1 (1.8)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Lost to 3-mo follow-up, n (%)</td>
<td>22 (3.4)</td>
<td>3 (2.7)</td>
<td>3 (5.5)</td>
<td>5 (5.3)</td>
</tr>
</tbody>
</table>

*There is overlapping group membership between deaths and recurrences.

Information on the secondary preventive antithrombotic and antihypertensive management was obtained at a 3-month follow-up assessment with the patient and by communicating with the GP. The number of GP visits (domiciliary and practice) and hospital outpatient sessions with specialists since registration was ascertained.

Recurrence-Free Survival
The register was notified of death by the Office for National Statistics (ONS). The definition of recurrent stroke was the same as for first stroke, with additional criteria: there had to be either a new neurological deficit or a deterioration of the previous deficit not considered to be caused by edema, hemorrhagic transformation, or intercurrent illness. Only recurrences 21 days after the index stroke, or if earlier, clearly in another part of the brain, were included. Registration of stroke recurrence was performed in the same way as for the index stroke. Recurrence-free survival rates were compared between patients appropriate for preventative therapies who were found and those who were not found on treatment at 3-month follow-up. However, it is acknowledged that this is an imperfect way to assess the effectiveness of preventative therapies, because important confounding factors might not have been controlled for.

Statistics
The association between patient characteristics and the treatment status was analyzed by the χ² test. Backward logistic regression was used to estimate the ORs for individual risk factors for non-treatment controlling for other risk factors. Recurrence-free survival in the treatment and nontreatment groups was examined by Kaplan-Meier analysis. The multivariate analysis of the relationship between risk factors and recurrence-free survival was done by backward Cox regression analysis. For both backward logistic and Cox regression analysis, the likelihood ratio statistic was used for the removal of variables (P=0.05, P=0.10).

Table 2. Frequency of Nontreatment With Antithrombotic and Antihypertensive Therapies 3 Months After Ischemic Stroke

<table>
<thead>
<tr>
<th></th>
<th>Frequency of Nontreatment, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Appropriate for Antithrombotic Therapies (n=245)</td>
<td>Patients Appropriate for Antihypertensive Therapies (n=254)</td>
</tr>
<tr>
<td>Total</td>
<td>27.1 (22.9–31.3)</td>
</tr>
<tr>
<td>1995</td>
<td>27.8 (20.2–35.4)</td>
</tr>
<tr>
<td>1996</td>
<td>30.4 (23.2–37.6)</td>
</tr>
<tr>
<td>1997</td>
<td>22.4 (15.3–29.5)</td>
</tr>
</tbody>
</table>

χ² = 2.403, P = 0.30
χ² = 4.300, P = 0.12

Documentary of Secondary Prevention
To monitor the secondary preventive management after stroke, the following data were collected. The diagnosis of hypertension was made when a patient’s general practitioner (GP) and hospital records indicated that a patient was hypertensive (160/95 mm Hg were found in the patient’s general practitioner (GP) and hospital records). The presence of contraindications to antithrombotic therapies (peptic ulcer disease, cancer, recent operation [1 month], bleeding disorder, and alcohol intake > 75 g/d) was also ascertained by reviewing GP and hospital records. The diagnosis of atrial fibrillation (AF) was made by the study doctor on the basis of the ECG performed after the stroke. When no ECG was available and there was no record in the GP notes (n = 77), the patient was assumed not to have AF. This meant that conservative estimates of the prevalence of non-treatment would be derived. All patients with AF who had no contraindications to anticoagulants were considered appropriate for anticoagulant medication. Patients without AF and those with AF and coexisting contraindications to anticoagulants were considered appropriate for antiplatelet therapies unless they had peptic ulcer disease.

To monitor the secondary preventive management after stroke, the methodology has been described in detail elsewhere and is summarized here.

Stroke was defined according to the WHO criteria. The diagnosis of stroke and the initial assessment was made by one of the study doctors within the first week after the event when possible. The classification of the subtype of stroke was based on clinical and radiological (CT or MRI scan) findings within the first 30 days after stroke. Only patients with cerebral infarction diagnosed by CT or MRI were included in this study. The distinction between lacunar and nonlacunar infarcts was made on the basis of the Bamford Classification. The severity of stroke was documented by the Glasgow Coma Scale (GCS) score until the first week and by the Barthel Index (BI) score ascertained 5 days after the stroke.

Sociodemographic data collected included social class, place of residence before the stroke, and ethnic group. Social class was coded according to the last occupation, or according to the last occupation of the spouse if the patient was a housewife. Social class categories were stratified into nonmanual (I, II and nm-III) and manual (m-III, IV, V) and unclassified/inactive (student, never employed, unable to work because disability, being a carer, and no information on last occupation available). Place of residence was categorized into “private household alone” and “other” and ethnicity into “Caucasian origin” and “African-Caribbean, African, and other origin.” Drug compliance was classified according to patient self-reporting as “regular” and “irregular.”

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The frequency of atrial fibrillation (AF) was 68 (14.9%). Among the patients with AF, 36 had at least 1 contraindication to anticoagulants: peptic ulcer disease (n=6), cancer (n=7), recent surgery (n=3), alcohol intake >75g/d (n=6), and age ≥85 years (n=19). A minimum of 32 (47.1%) of the patients with AF were therefore appropriate for anticoagulation, of whom 19 (59.4%) were not on treatment. Of the 389 patients without AF, 26 (6.7%) had a history of peptic ulcer disease. Thus, 393 patients (363 without AF and 30 with AF) were appropriate for antiplatelet medication, of whom 96 (24.4%) were not on treatment 3 months after the stroke.
Altogether, 425 (93.0%) patients were considered appropriate for antithrombotic (either anticoagulant or antiplatelet) medication, of whom 115 (27.1%) were not on treatment.

Hypertension was diagnosed in 254 (55.9%) of the stroke patients, of whom 75 (29.5%) were not on treatment. There was no evidence of change over the 3 years in the frequency of antithrombotic and antihypertensive treatment (Table 2).

Bivariate associations between patient characteristics and treatment status are given in Table 3. Backward logistic regression showed that the GCS score, BI score, and subtype of stroke were independently associated with nontreatment (Table 4). A second backward logistic regression model was fitted for nontreatment with antihypertensive medication among the 254 hypertensive patients. Therefore, indicators of severity of stroke (GCS and BI) and subtype of stroke were independently related to nontreatment (Table 3). Differences between the 2 models occurred regarding ethnic group, which was significant only in the second model, where subjects of Caucasian origin appeared to be less likely to receive antihypertensive medication.

Kaplan-Meier curves showed that patients who received antithrombotic or antihypertensive treatment had slightly higher recurrence-free survival rates compared with patients without treatment; however, these differences did not reach statistical significance (Figure 1). Backward Cox regression analysis on the 425 patients appropriate for antithrombotic therapies showed age and stroke severity (GCS and BI 5 days after stroke) significantly associated with recurrence-free survival, for the treatment status results did not reach significance (Table 5). The second Cox regression model, which included the 254 hypertensive stroke patients, showed similar results.

### Discussion

The aim of this study was to provide population-based information on the secondary preventive management of stroke patients. Cardiovascular and stroke risk factor management has been prioritized in national and international strategies for health care. Previously, research has revealed potential for further improvements in the primary prevention of stroke in Britain. Information on the state of secondary prevention of stroke is limited. The present study found considerable high rates of nontreatment among patients with ischemic stroke 3 months after the event. Of the patients considered appropriate for antiplatelet medication, 24.4% did not receive it; results for anticoagulant medication were 59.4% and for antihypertensive medication 29.5%. This suggests that secondary prevention in the study area needs improving.

The present study used data of a population-based stroke register, which was designed to look at the relationship between the process of care and outcome. However, the register was not specifically designed to assess the preventive management of the patients. The classification of the patients’ appropriateness for preventive therapies was based on available data and did not meet all the criteria applied in large, randomized controlled trials. Hence, the nontreatment rates found in the present study could have been biased by the misclassification of the patients’ appropriateness for preventive therapies, and the results had to be interpreted carefully.

Data from the initial assessment were used to ascertain contraindications against antithrombotic therapies. Patients who were started on antithrombotic medication that was later discontinued because of complications were not identified. Patients who had ischemic strokes with secondary hemorrhagic complications were not eliminated from the study. Nevertheless, the proportion of patients classified appropriate

### Table 4. Backward Logistic Regression Models to Predict Nontreatment With Antithrombotic or Antihypertensive Therapies 3 Month After Ischemic Stroke

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients Appropriate for Antithrombotic Therapies (n=425)</th>
<th>Patients Appropriate for Antihypertensive Therapies (n=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Rank* OR 95% CI P</td>
<td>Rank* OR 95% CI P</td>
</tr>
<tr>
<td>&lt;60</td>
<td>2 1 0.64</td>
<td>1 1 0.73</td>
</tr>
<tr>
<td>61–80</td>
<td>0.80 (0.44–1.45) 0.46</td>
<td>0.79 (0.34–1.86) 0.60</td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.99 (0.49–2.00) 0.97</td>
<td>1.03 (0.38–2.78) 0.94</td>
</tr>
<tr>
<td>Male sex</td>
<td>1 0.89 (0.56–1.42) 0.64</td>
<td>2 1.14 (0.63–2.08) 0.67</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3 1.20 (0.70–2.07) 0.50</td>
<td>... 2.43 (1.15–5.14) 0.02</td>
</tr>
<tr>
<td>Irregular use of medication</td>
<td>5 1.26 (0.76–2.10) 0.37</td>
<td>4 1.63 (0.81–3.31) 0.17</td>
</tr>
<tr>
<td>GCS ≤13</td>
<td>... 2.08 (1.18–3.66) 0.01</td>
<td>... 2.97 (1.35–6.53) &lt;0.01</td>
</tr>
<tr>
<td>BI ≤10 5 d after stroke</td>
<td>1.85 (1.17–2.93) &lt;0.01</td>
<td>... 2.33 (1.27–4.29) &lt;0.01</td>
</tr>
<tr>
<td>Nonlacunar infarct</td>
<td>... 1.60 (1.07–2.54) 0.05</td>
<td>... 2.46 (1.33–4.54) &lt;0.01</td>
</tr>
<tr>
<td>No physician contact after discharge</td>
<td>4 1.28 (0.74–2.19) 0.38</td>
<td>3 1.62 (0.81–3.24) 0.18</td>
</tr>
</tbody>
</table>

*Indicates the rank of elimination in stepwise backward logistic regression. OR, 95% CI, and P were determined just before elimination.
stroke were carried out in the late 1980s and early 1990s. Therefore the time lag may have been insufficient to see these results adopted into routine clinical practice by 1995. Nevertheless we observed no significant improvements in the secondary preventive management between 1995 and 1997.

Previous studies have reported that the secondary preventive vascular risk management is haphazard after patient discharge from the hospital. The present study, however, identified patient characteristics predictive of nontreatment with antithrombotic and antihypertensive therapies after stroke. This is useful for the implementation of targeted interventions in preventive management. It is noteworthy that indicators of severity of stroke and subtype of stroke were found to be associated with nontreatment with both antithrombotic and antihypertensive therapies. Similar results have been obtained previously for myocardial infarction, in which patients with a poorer overall health status were found less frequently on antiplatelet medication after discharge from hospital.

Patients with severe strokes and with nonlacunar strokes are more likely to have a recurrence of stroke, which is why effective preventive management is required in this group. At the same time, these patients are more likely to be frail individuals, to have significant comorbidities, and to have a higher risk of falls. Yet, most major trials have excluded patients with severe strokes, and few studies examined the efficacy of antithrombotic therapies in patients with severe stroke. The latter studies, however, were able to show that patients with severe strokes would benefit most from antithrombotic therapies.

Another possible rationale behind nontreatment of patients with severe or nonlacunar strokes is the difficulty experienced in attending hospital outpatient clinics and GP surgeries for monitoring of the anticoagulation status or blood pressure. Almost 25% of the stroke patients had not seen their GP or a specialist after discharge, and nontreatment with preventive therapies was higher in this patient group. Correspondingly, research on avoidable factors in deaths from stroke and hypertension found failures in follow-up to be one of the most important problems.

Ethnic-related differences occurred in the treatment rates for antihypertensive but not for antithrombotic therapies. The explanation may be that GPs are more aware of blood pressure problems in their patients of non-Caucasian origin. Correspondingly higher detection rates were found in hypertensive non-Caucasian subjects than in hypertensive Caucasian subjects.

The Kaplan-Meier and Cox regression analyses failed to show significant differences in the recurrence-free survival rates between stroke patients who received antithrombotic or antihypertensive therapies and those who did not. It needs to be acknowledged that the present observational study cannot replace large, randomized controlled trials. Although secondary prevention with antiplatelets should be administered immediately after stroke, the present study did not provide data on when treatment was started, and only the treatment status at 3 months’ time was reported. Hence, some of the 159 deaths observed before the 3-month follow-up might have been related to nontreatment. Despite the fact that the Cox
regression models controlled for a number of confounding variables, there might have been other confounding variables not accounted for which could have biased the results. The sample size of the present observational study was low compared with the large, randomized controlled trials, which have demonstrated the beneficial effects of secondary preventive therapies in stroke patients. Also no attempt was made to assess whether recipients of anticoagulant and antihypertensive therapies were effectively treated, although there is evidence suggesting that a high proportion of patients are in fact undertreated.10,36

From the present study, we are unable to determine whether the observed low rates of treatment are a result of the hospitals’ failure to communicate the need of preventive therapies, patients’ problems with attendance to consultations in GP surgeries and hospital outpatient clinics, or the discontinuation of the treatment by the GP or the patient.

Altogether, this population-based study showed a high rate of nontreatment with known effective secondary preventive therapies in stroke patients, especially among patients at high risk for recurrence of stroke. Clinical guidelines may address some of these issues, and new strategies developed to improve clinical practice, such as the implementation of routine follow-ups after stroke, academic detailing, and multifaceted educational strategies, should be implemented.37–39

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**References**

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