Current Strategies of Secondary Prevention After a Cerebrovascular Event

The Vienna Stroke Registry

Wolfgang Lalouschek, MD; Wilfried Lang, MD; Markus Müllner, MD; on behalf of the Vienna Stroke Study Group

Background and Purpose—Oral anticoagulation (OAC) and antiplatelet drugs are effective in the secondary prevention of ischemic cerebrovascular events. Only few data exist about the factors influencing the choice of a specific therapy for secondary prevention in patients with a recent stroke or transient ischemic attack (TIA).

Methods—Within a cross-sectional study, nested in a cohort we identified 931 patients with a recent ischemic stroke or TIA who were discharged with OAC or with one of the antiplatelet medications aspirin, clopidogrel, or the combination of aspirin and extended-release dipyridamole. By means of multivariate logistic regression analysis, we determined the influence of several clinical variables on the decision between OAC and overall antiplatelet therapy as well as on the decision between different antiplatelet therapies.

Results—A cardioembolic etiology of the index event and atrial fibrillation were independently associated with the use of OAC. Age was inversely associated with the use of OAC. Different estimations of contraindications to OAC were the main reason for the considerable variability among the participating centers. The most important factor promoting the use of clopidogrel was therapy with aspirin before the index event. Patients with large- or small-vessel disease received clopidogrel more often than those with an event of undetermined etiology. We found an extremely high interhospital variability for the use of the combination of aspirin with extended-release dipyridamole.

Conclusions—Current recommendations are applied in clinical practice, but great variability between different centers remains. More clearly defined guidelines for indications for, as well as contraindications against, a specific therapy are necessary. (Stroke. 2001;32:2860-2866.)

Key Words: anticoagulants | antiplatelet agents | prevention, secondary | stroke

Patients with a recent ischemic stroke or transient ischemic attack (TIA) are at high risk for further cerebrovascular or other vascular events and vascular death.1–3 Oral anticoagulation (OAC) was of significant benefit over placebo and aspirin in the secondary prevention of stroke in patients with atrial fibrillation (AF) in the European Atrial Fibrillation Trial (EAFT).4 OAC is also used in other indications without evidence of randomized controlled trials (eg, aortic arch atheroma, high-grade stenoses of intracranial vessels).5–9 Previous studies investigated the use or underuse of OAC in primary prevention in patients with AF.10–12 The factors determining the prescription of OAC in secondary prevention in patients with ischemic stroke or TIA have not been investigated thus far.

Several platelet inhibitors (aspirin, clopidogrel, and the combination of aspirin with extended-release dipyridamole) have proven effective in patients with various causes of TIA/ischemic stroke.13–15 Several recommendations about the choice of antiplatelet drugs in patients with TIA/stroke have been published.16–20 However, there are no data available regarding how these recommendations translate into clinical practice and which factors affect the choice of antiplatelet drugs in patients with a recent ischemic cerebrovascular event. We sought (1) to determine how current recommendations concerning OAC and antiplatelet agents are applied in clinical practice in patients with a recent ischemic stroke or TIA and (2) to investigate clinical decision making in situations without clear evidence in favor of a specific therapy.

Subjects and Methods
The study was performed within a prospective stroke registry on 9 neurological departments in Vienna (Vienna Stroke Registry [VSR]).

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A complete list of members of the Vienna Stroke Study Group appears in the Appendix.

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TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Medication at discharge</th>
<th>Department 1 (n=48)</th>
<th>Department 2 (n=180)</th>
<th>Department 3 (n=47)</th>
<th>Department 4 (n=89)</th>
<th>Department 5 (n=89)</th>
<th>Department 6 (n=85)</th>
<th>Department 7 (n=209)</th>
<th>Department 8 (n=184)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>45.8</td>
<td>58.9</td>
<td>74.5</td>
<td>38.2</td>
<td>55.1</td>
<td>47.1</td>
<td>24.9</td>
<td>62.5</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>8.3</td>
<td>20.0</td>
<td>14.9</td>
<td>34.8</td>
<td>24.7</td>
<td>31.8</td>
<td>9.1</td>
<td>25.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin/dipyridamole</td>
<td>27.1</td>
<td>5.6</td>
<td>0</td>
<td>21.3</td>
<td>13.5</td>
<td>16.5</td>
<td>43.1</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>OAC</td>
<td>18.8</td>
<td>15.6</td>
<td>10.6</td>
<td>5.6</td>
<td>6.7</td>
<td>4.7</td>
<td>23.0</td>
<td>9.2</td>
<td></td>
</tr>
</tbody>
</table>

Values are percentages.

*χ² test.

Details of the VSR have been published elsewhere. In short, all patients with TIA/stroke who are admitted to 1 of the participating centers within 72 hours of symptom onset are prospectively documented, on the basis of informed consent, with respect to clinical and neurological parameters (National Institutes of Health Stroke Scale, Scandinavian Stroke Scale, modified Rankin Scale, Barthel Index), medical history, results of technical and laboratory investigations, presumptive etiology, and follow-up investigations at 3, 12, and 24 months. The study has been approved by the local ethics committees. The VSR started in October 1998. For the present cross-sectional study, the data of the first 1440 patients were analyzed. Patients were included in the analysis if (1) they had suffered an acute ischemic cerebrovascular event (TIA or stroke), (2) they were either without prior antiplatelet or anticoagulant treatment or under therapy with aspirin, and (3) they were discharged or transferred from the neurological department with any antiplatelet or oral anticoagulant medication. Patients with hemorrhagic stroke and patients who received only heparin at discharge (or transfusion) were not included in the analysis. On the basis of these criteria, 931 patients were included in the analysis.

Statistical Methods

Continuous data are given as mean or median, as appropriate. Categorical data are given as counts and percentages.

The univariate comparison of continuous variables was performed with the t test or the Mann-Whitney U test, as appropriate. Binary and categorical data were analyzed with contingency tables and a χ² statistic.

To assess the influence of various clinical factors simultaneously on the choice of a specific therapy, we applied multivariate logistic regression. We used a stepwise procedure to retain only variables that significantly contributed to the model. The Nagelkerke pseudo R² was used to assess the variability explained by each model. The Hosmer-Lemeshow χ² test was used to assess the model fit; probability value >0.1 indicates an agreeable model fit. We were interested in assessing the effect of clinical factors in clinically relevant situations comparing the following treatment options: (1) antiplatelet versus anticoagulant treatment; (2) aspirin versus clopidogrel; (3) aspirin versus aspirin/dipyridamole; or (4) clopidogrel versus aspirin/dipyridamole.

The following parameters were included in the multivariate analysis as independent variables: age (<40, 40 to 49, 50 to 59, 60 to 69, 70 to 79, ≥80 years); sex; stroke severity (TIA [clinical symptoms resolving within 24 hours]/minor stroke [symptoms lasting >24 hours and no or only slight disability at discharge]/major stroke [all other patients]); etiology (large-vessel disease [ipsilateral carotid stenosis ≥70%], presumable local thrombosis of a large intracranial vessel, arterio-arterial embolism from aortic plaques/thrombi); small-vessel disease [clinical lacunar syndrome and no lesion or subcortical lesion <1.5 cm on CT or MRI]/cardioembolic [high-risk source of cardiac embolism ≥1%/no determined etiology; hypertension defined as blood pressure >130/80 mm Hg and/or antihypertensive treatment at discharge); diabetes; current cigarette smoking; previous ischemic cerebrovascular disease (CVD); clinically manifest coronary artery disease (CAD); clinically manifest peripheral artery disease (PAD); chronic or paroxysmal AF; index event under aspirin therapy; nitroglycerine therapy; and total cholesterol level (<5.2/5.2 to 6.18/≥6.21 mmol/L [<200/200 to 239/≥240 mg/100 mL]).

Results

Medication at discharge at the participating departments is shown in Table 1. General characteristics of the patients in the 4 medication subgroups are shown in Table 2.

Antiplatelet Treatment Versus Anticoagulation

We found that 63% of the patients in the OAC group had AF compared with 6% to 12% in the anticoagulated groups (P<0.001). Additionally, 50.3% of patients with AF were on OAC at the time of hospital discharge or transfer. This proportion was almost identical in patients with chronic AF (50.5%) and with paroxysmal AF (50%). The rate of OAC in patients with AF differed significantly between the departments (P<0.001). Seventy-six patients with AF were discharged with antiplatelet mediation instead of OAC. In 19 (25%) of these patients, no explicit reasons for non-anticoagulation at discharge were given. The following medical reasons were given in the other patients: history of gastrointestinal bleeding or ulcers (n=10), risk of falls (n=16), and multimorbidity (n=14). Advanced age (n=8) and questionable compliance (n=14) were other arguments for nonuse of OAC. Six patients with paroxysmal AF who had no AF at discharge under antiarrhythmic therapy were not anticoagulated.

Seventy-nine percent of the anticoagulated patients had a cerebrovascular event of presumable cardioembolic origin compared with 7% to 15% in the antiplatelet groups (P<0.001). Reasons for OAC in patients with a cause of stroke other than cardioembolism were as follows: stenoses of intracranial arteries (vertebral artery, basilar artery, middle cerebral artery stem), complex plaques in the ascending part of the thoracic aorta, recurrent events under antiplatelet medication, or additional pulmonary embolism and thrombophilia and/or antiphospholipid antibody syndrome.

In the multivariate analysis (Table 3), the following factors were associated with the prescription of OAC: cardioembolism, AF, large-vessel disease (compared with
patients with a cerebrovascular event of undetermined etiology), and therapy with aspirin before the index event. The risk of OAC decreased with each decade by a factor of 5.9; \( t \) test for independent samples; total cholesterol, Mann-Whitney \( U \) test; all other variables, \( x^2 \) test.

\[ P < 0.05; \] \( P < 0.01; \] \( P < 0.001. \]

\( \dag \)Antiplatelet vs OAC; \( \dag \)Aspirin vs clopidogrel; \( \dag \)Aspirin vs aspirin/dipyridamole; \( \dag \)Clopidogrel vs aspirin/dipyridamole.

| TABLE 2. Patient Characteristics According to Medication Subgroup |
|---------------------|---------------------|---------------------|---------------------|
|                    | OAC (n=122)         | Aspirin (n=453)     | Clopidogrel (n=193) |
| Female, %          | 56.6\( ^\dag \)    | 48.3                | 42.5                |
| Age, mean±SD, y    | 66.2±14.5           | 66.8±14.2           | 68.8±12.4           |
| Hypertension, %    | 77.0                | 70.6                | 76.7                |
| Diabetes, %        | 23.0                | 22.3                | 29.5\( ^\# \)     |
| Current cigarette smoking, % | 23.8                | 26.0                | 26.4                |
| Previous cerebrovascular event, % | 23.8                | 26.9\( ^\dag \)   | 34.7\( ^\dag \)   |
| CAD, %             | 24.6                | 16.8\( ^\| \)    | 32.2\( ^\| \) $\dag$ |
| PAD, %             | 9.0                 | 8.6\( ^\| \)      | 16.6\( ^\| \) $\dag$ |
| Total cholesterol, mmol/L (median/25th/75th percentile) | 5.64 (4.73/6.41) | 5.79 (5.07/6.57) | 5.59 (4.76/6.52) |
| AF, %              | 63.1\( ^\dag \) $\dag$ | 9.7                | 11.9\( ^\# \)     |
| Index event under aspirin, % | 37.7\( ^\dag \) $\dag$ | 19.4\( ^\dag \) $\dag$ | 52.3\( ^\dag \) $\dag$ |
| Stroke severity, %  | 14.8                | 25.2                | 19.7                |
| TIA                | 34.4                | 32.2                | 30.6                |
| Minor stroke       | 50.8                | 43.6                | 49.7                |
| Major stroke       | \( ^\dag \) \( ^\dag \) \( ^\dag \) \| \| \| $\dag$ |
| Etiology, %        | \| \| \| $\dag$ |
| Large artery       | 13.1                | 12.8                | 17.6                |
| Cardioembolism     | 78.7                | 14.3                | 15.0                |
| Small artery       | 2.5                 | 25.6                | 35.8                |
| No determined etiology | 5.7                 | 47.2                | 31.6                |

Aspirin Versus Clopidogrel

The factors significantly associated with the use of clopidogrel compared with aspirin in univariate analysis are shown in Table 2. Clopidogrel was almost as frequently used in patients with TIA (17.9%) as in patients with ischemic stroke (minor stroke, 20.2%; major stroke, 22.5%). Multivariate analysis (Table 3) revealed pretreatment with aspirin as the most important factor in favor of clopidogrel. This association was found in all etiologic subgroups. The relation between aspirin and clopidogrel also varied significantly between the departments. The model explained 22% of the observed variance with a good model fit (Hosmer-Lemeshow \( x^2 = 4.6; df = 8; P = 0.800 \)).

Exclusion of department as a factor from the analysis did not substantially change the results. In those patients who suffered the index event under aspirin, a history of CAD was significantly associated with the use of clopidogrel (\( P = 0.047 \); odds ratio = 1.9; 95% CI, 1.0 to 3.7).

Aspirin Versus Aspirin/Dipyridamole

Univariate and multivariate analyses showed relatively few differences between patients who received aspirin or aspirin/dipyridamole at discharge. Patients in the aspirin/dipyridamole group more often had a history of a cerebrovascular event (\( P = 0.026 \)) or had suffered the index event under aspirin therapy (\( P = 0.029 \)) (Table 2). The department was by far the most prominent factor affecting the decision between aspirin and aspirin/dipyridamole (compare Table 1). Multivariate analysis confirmed that the department was the main factor affecting the choice between aspirin and aspirin/dipyridamole (department 3 had to be excluded from this analysis because aspirin/dipyridamole was never prescribed there) (Table 3). Whereas 35% of the observed variance could be explained by the model, 34% were explained only by department as a factor (Hosmer-Lemeshow \( x^2 = 4.6; df = 8; P = 0.800 \)).

Clopidogrel Versus Aspirin/Dipyridamole

The differences between patients receiving clopidogrel or aspirin/dipyridamole were similar to those between patients receiving clopidogrel or aspirin (Table 2). In the logistic regression analysis the following factors were associated with the use of clopidogrel: PAD, large-vessel disease, cardioembolism, and an index event under aspirin therapy. The most important determinant of the choice between clopidogrel and
aspirin/dipyridamole was the department (Table 3). The variables in this model accounted for 46% of the observed variance (Hosmer-Lemeshow $\chi^2=6.1; df=8; P=0.637$).

**Discussion**

This is the first time that a study has investigated factors influencing therapeutic decisions between OAC and antiplatelet drugs in a large cohort of patients who suffered an acute cerebrovascular event.

**OAC Versus Antiplatelet Drugs**

The benefit of OAC for prevention of recurrent stroke in patients with TIA or ischemic stroke and nonvalvular AF has been demonstrated in the EAFT. Many patients (388/1007) were found to be ineligible for OAC in EAFT, mainly because of advanced age. Whether these results can be generalized to an expectedly older and sicker population is controversial. Other studies on OAC in AF (eg, the Stroke Prevention in Atrial Fibrillation Trial) used different exclu-
vascular event under therapy with aspirin therapy. Although it is a drug of second choice once a patient has suffered a cerebrovascular event, aspirin and clopidogrel was the use of aspirin before the index event. This indicates that clopidogrel is commonly used as a first-line therapy in the secondary prevention of stroke.

**Antiplatelet Agents**
Several recommendations and guidelines concerning the use of antiplatelet agents in the secondary prevention of stroke have been published. Recommendations for clopidogrel are usually restricted to patients who are intolerant of aspirin or who have had a recurrent ischemic event while on aspirin. Clopidogrel is also sometimes recommended in patients with additional vascular disease (CAD, PAD). Aspirin/dipyridamole, on the other hand, is usually classified as a potential first-line therapy in the secondary prevention of stroke without further specifying whether it should be preferred over aspirin or whether it should be restricted to specific situations. Thus far the strategies of the use of these 3 antiplatelet agents in clinical practice have not been studied in patients with ischemic cerebrovascular events.

**Aspirin Versus Clopidogrel**
The most important determinant for the choice between aspirin and clopidogrel was the use of aspirin before the index event. This indicates that clopidogrel is commonly used as a drug of second choice once a patient has suffered a cerebrovascular event under therapy with aspirin therapy. Although it may seem plausible to switch to an alternative drug once a patient has suffered a cerebrovascular event under aspirin therapy, this strategy is not based on existing evidence because this question was not addressed in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. Clopidogrel was also preferably used in patients with a known cause of the event (large- or small-artery disease compared with events of undetermined origin). In those patients who suffered the index event under therapy with aspirin, a history of CAD was also associated with the use of clopidogrel. Again, this finding is not directly supported by the results of the CAPRIE trial, in which no significant benefit of clopidogrel in patients with CAD was found. Interestingly, clopidogrel was almost as frequently prescribed in patients who suffered a TIA, although clopidogrel has not been formally tested in this group of patients and is currently not registered in Austria for patients with TIA.

**Aspirin Versus Aspirin/Dipyridamole**
Multivariate analysis revealed that the choice between aspirin and aspirin/dipyridamole was almost exclusively dependent on department as a factor, whereas other variables were only of minor or no importance. This finding obviously reflects the current situation in which there are no clear guidelines for the use of aspirin/dipyridamole, and the therapeutic decision remains largely based on individual preferences. If the benefit of aspirin/dipyridamole over aspirin is really as high as it was in the second European Stroke Prevention Study (ESPS-2), then the majority of our patients are left with a suboptimal treatment, namely aspirin alone. If, however, the benefit of aspirin/dipyridamole is actually lower compared with higher doses of aspirin (eg, 100 mg/d), the relation between benefit and possible disadvantages might even be reversed. An ongoing large, multicenter, randomized trial comparing the efficacy of OAC, aspirin plus dipyridamole, or aspirin alone in patients with cerebral ischemia of arterial origin may reduce uncertainty and variability of current treatment decisions.

**Clopidogrel Versus Aspirin/Dipyridamole**
The comparison between clopidogrel and aspirin/dipyridamole revealed that, again, the most important determinant of the therapeutic decision was the department. However, our results also reflect the preference to prescribe clopidogrel in situations with a known cause of the event (large-vessel disease or a cardioembolic event, if not anticoagulated) and to favor aspirin/dipyridamole, which is much less expensive, in patients with an unknown cause, although there is no evidence to support this behavior.

**Variability Between Hospitals**
In a post hoc attempt to explore the reasons for the large differences between the departments, we performed a survey by means of a structured questionnaire and interviews with representatives of the participating departments. If a department differed in univariate or multivariate analysis with a P<0.1 from the others, we asked for probable reasons (level of evidence/individual good or bad experience with the drug/costs of the drug/differences in patient characteristics/
other reasons) why OAC or a specific antiplatelet drug was given more or less frequently in this department. For OAC, individual experiences (bleeding complications) and differences in patient characteristics were judged most important. For clopidogrel and aspirin/dipyridamole, the most prominent factor influencing their use or nonuse was divergent interpretations of the existing evidence. Other main factors were the higher costs (clopidogrel) or individual experiences and side effects (aspirin/dipyridamole). However, a more detailed approach to explore possible reasons would require a qualitative approach.27 As a consequence of our results, we are now attempting to establish common recommendations and will continuously monitor and analyze treatment behavior.

In summary, our results demonstrate that current recommendations find their way into clinical practice, but to a limited extent. There remains a large variability between different departments, even in situations in which clear recommendations exist; this variability is even larger when this is not the case. More clearly defined guidelines as well as further studies on the efficacy of different antiplatelet agents with respect to specific patient groups are urgently needed.

Appendix

The Vienna Stroke Study Group

Participating Neurological Departments

(1) Department of Neurology, Krankenanstalt Rudolfstiftung; (2) Clinical Department of Clinical Neurology, University Clinic of Neurology, University of Vienna; (3) Department of Neurology, Kaiser-Franz-Josef-Spital; (4) Department of Neurology, Krankenhaus Lainz; (5) Neurological Hospital Rosenhigl, Department A; (6) Neurological Hospital Rosenhigl Department B; (7) Department of Neurology, Wilhelminenspital; (8) Neurological Hospital Maria-Theresien Schlössel; (9) Department of Neurology, Donauspital; in cooperation with the following centers: (10) University Clinic of Emergency Medicine, University of Vienna; (11) Department of Neuroradiology/University Clinic of Radiology, University of Vienna; (12) Vienna Emergency Services.

Local Investigators (in Alphabetical Order With Department Number)

C. Alf (5); C. Bancher (4); O. Berger (3); H. Binder (8); T. Brücke (7); L. Deecke (2); H. Domanovits (10); J. Donis (7); E. Gatterbauer (8); B. Glawar (6); W. Grisold (3); K. Heinberger (11); M. Hirschl (10); M. Hoberstoffer (4); A. Kaff (12); W. Kristoferitsch (9); A. Laggner (10); W. Lalouschek (2); W. Lang (2); J. Lassmann (9); B. Mamoli (6); W. Pankl (9); S. Parigger (7); I. Podreka (1); C. Prainer (1); W. Santha (7); T. Schlager (1); M. Schlederer (9); M. Schmidbauer (4); G. Schnabbert (5); B. Segall (12).

Follow-Up Examinations and Data Documentation


Biostatistics and Epidemiology

M. Müllner, University Clinic of Emergency Medicine, University of Vienna.

Cooperating Centers

Departments of Radiology of the following hospitals: Krankenanstalt Rudolfstiftung, Kaiser-Franz-Josef-Spital, Krankenhaus Lainz, Neurological Hospital Rosenhigl, Wilhelminenspital, Donauspital.

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