Determination of Lipid Profiles and Use of Statins in Patients With Ischemic Stroke or Transient Ischemic Attack

Wolfgang Lalouschek, MD; Wilfried Lang, MD; Stefan Greisenegger, MD; Marcus Müllner, MD; for the Vienna Stroke Study Group

**Background and Purpose**—Statins reduce the risk of myocardial infarction and stroke in patients with vascular disease. Inappropriate serum lipid determination and underuse of statins have been documented in patients with coronary artery disease. Evaluation of hyperlipidemia and treatment with statins in patients with recent ischemic cerebrovascular events have not yet been investigated.

**Methods**—We determined the frequency of total cholesterol (TC) and low-density lipoprotein cholesterol measurements and the use of statins in a multicenter prospective cohort study of 1743 patients with acute ischemic stroke or transient ischemic attack (TIA). Using multivariate logistic regression analysis, we determined the influence of several clinical variables on lipid measurements and the prescription of statins at hospital discharge.

**Results**—TC was measured in 90% and low-density lipoprotein cholesterol was measured in 48% of the patients. Differences between the centers accounted for most of the observed variability in a multivariate model. Statin prescription also varied widely between the centers. The prescription of a statin at discharge was most strongly associated with statin intake before the event and with increasing TC levels; elderly patients received statins less often. Coronary artery disease, peripheral artery disease, and other manifestations of atherosclerosis were not independently associated with the use of statins; 68% of the patients with manifest atherosclerosis and TC levels >200 mg/dL were discharged without a statin.

**Conclusions**—The determination of serum lipid profiles varies widely between different centers. Statins are highly underused in patients with recent ischemic stroke or TIA, particularly in those in whom statins are indicated according to existing recommendations (eg, patients with additional coronary artery disease and hypercholesterolemia). Currently, international guidelines concerning the use of statins are not adequately implemented in clinical practice in patients with stroke or TIA. *(Stroke. 2003;34:105-110.)*

**Key Words:** lipids ■ prevention ■ statins ■ stroke

Treatment with HMG-COα reductase inhibitors (statins) reduces the risk of myocardial infarction, stroke, and vascular death in patients with coronary artery disease (CAD).1–6 Treatment with statins should be initiated in all patients with an ischemic stroke or transient ischemic attack (TIA) who have evidence of or high risk for developing CAD over the next years if their cholesterol concentration is >5.0 mmol/L or low-density lipoprotein cholesterol (LDL-C) exceeds 3.0 mmol/L.7–13

In patients with CAD, the rate of lipid evaluation is low, and statins are underused.14–20 There is no comparable information for patients with recent ischemic stroke or TIA, even though myocardial infarction is the main cause of death in survivors of ischemic stroke and in patients who suffered a TIA.21–23

The aim of this cohort study was to assess (1) the proportion of patients in whom lipid profiles were determined during hospitalization after an acute ischemic stroke or TIA and (2) the use of statins.

**Patients and Methods**

This study is nested in a prospective population-based stroke registry of patients admitted to 8 neurological departments in Vienna, Austria (Vienna Stroke Registry [VSR]), serving a community of 1.9 million people.24,25 All patients with TIA or ischemic stroke who are admitted to a participating center within 72 hours of symptom onset are prospectively documented, with 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, presumed stroke origin, and follow-up investigations at 3, 12, and 24 months. The study was approved by the local ethics committees and was started in October 1998.
Table 1. Baseline Characteristics of the Participating Departments

<table>
<thead>
<tr>
<th>Department</th>
<th>Total</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1743</td>
<td>323</td>
<td>122</td>
<td>80</td>
<td>161</td>
<td>189</td>
<td>150</td>
<td>348</td>
<td>370</td>
<td></td>
</tr>
<tr>
<td>TC measurement, %</td>
<td>90</td>
<td>97</td>
<td>96</td>
<td>38</td>
<td>95</td>
<td>98</td>
<td>93</td>
<td>90</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C measurement, %</td>
<td>48</td>
<td>76</td>
<td>39</td>
<td>21</td>
<td>6</td>
<td>7</td>
<td>9</td>
<td>58</td>
<td>82</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Statin at discharge, %

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=1743) (fibrates in parentheses)</th>
<th>Patients with CAD and TC&gt;200 mg/dL (5.17 mmol/l) (n=195)</th>
<th>Patients with other forms of atherosclerosis* and TC&gt;200 mg/dL (5.17 mmol/l) (n=339)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23 (2)</td>
<td>32 (25 (2) 32 (7) 8 (0) 11 (1) 23 (3) 19 (3) 25 (2) 25 (1)</td>
<td>32 (38 53 40 14 30 17 31 38 0.027</td>
</tr>
</tbody>
</table>

TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; CAD, coronary artery disease; PAD, peripheral artery disease.

*Symptomatic carotid stenosis, PAD, plaques of the aortic arch of more than 4-mm thickness.

†χ² Test.

For the present cohort study, data from 1743 patients with acute ischemic stroke or TIA for whom clinical data were available at the time of analysis and who were admitted between October 1998 and June 2001 were analyzed. Patients with hemorrhagic stroke and patients who died before discharge were excluded. Recruitment of patients to the registry is an ongoing process, and we arbitrarily closed the database for this study on June 2001. At that time, 3069 patients were admitted because of suspected ischemic or hemorrhagic stroke, and complete data for 2171 patients were entered into the database. Patients for whom detailed clinical information was still missing (n=898) were excluded from the analysis. These excluded patients were comparable in terms of age (67.4 ± 15.6 and 66.2 ± 18.5 years [mean ± SD], P=0.5) and sex (47% and 45% female, P=0.4). We estimate that ~15% of these would not meet our inclusion criteria because of a nonischemic cerebrovascular event (intracerebral hemorrhage, subarachnoid hemorrhage, sinus vein thrombosis) or posthoc verification of a noncerebrovascular diagnosis (epileptic seizure, hypertensive crisis, etc). Data are entered into the database in batches, and we are not aware of a selection mechanism other than order of admission.

Statistical Analysis

Univariate comparison of continuous variables was performed with the unpaired t test or Mann-Whitney U test as appropriate. Binary and categorical data were analyzed with χ² statistics.

To determine the influence of clinical variables simultaneously on the prescription of statins (yes versus no), we applied multivariate logistic regression. We included all variables that were at least weakly associated with the use of statins (P<0.2 in univariate analyses). 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. We assumed that treatment strategies may be determined partly by “local culture.” Therefore, we also investigated the potential impact of a cluster effect with regard to hospital (center) on determinants for the prescription of statins. We used a random-effects logit model.26

The following variables were treated as dependent variables: (1) determination of total cholesterol (TC) levels (yes versus no), (2) determination of LDL-C levels (yes versus no), and (3) prescription of a statin at hospital discharge or transfer (yes versus no). The few patients (2%) treated with fibrates were classified as not receiving statins.

The following parameters were included in the analyses as independent variables: age (<55, 55 to 64, 65 to 74, 75 to 84, ≥85 years); sex; stroke severity at 1 week according to the Rankin Scale (0 to 1, 2 to 3, 4 to 5); cause (large-vessel disease [ipsilateral carotid stenosis ≥70%], presumable local thrombosis of a large intracranial vessel, arterioarterial 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 embolism27), or no determined etiology); history of hypertension as reported by patient or relative or documented in previous medical records (yes versus no); history of diabetes as reported by patient or relative (yes versus no); current cigarette smoking (yes versus no); previous stroke (yes versus no); clinically manifest CAD (yes versus no); clinically manifest peripheral artery disease (PAD); chronic or paroxysmal atrial fibrillation (yes versus no); index event under lipid-lowering drug therapy; index event under antplatelet drug (yes versus no); index event under oral anticoagulation; and TC level (≥200, 201 to 220, 221 to 240, 241 to 260, 261 to 280, 281 to 300, >300 mg/100 mL [≥5.17, 5.19 to 5.69, 5.71 to 6.21, 6.23 to 6.72, 6.75 to 7.24, 7.27 to 7.76, >7.76 mmol/L]). Any question answered with “unknown” was classified as “no.”

Results

Determination of Lipid Profiles During Hospitalization

TC determination varied between departments from 38% to 98% of patients (P<0.001; Table 1). Overall, TC levels were determined in 1562 (90%) of the patients. Multiple regression analysis revealed that department was the only factor significantly determining the performance of TC measurements. We also found a trend for a negative association between TC determination and male sex (odds ratio [OR], 0.7; 95% CI, 0.5 to 1.0; P=0.072). The model explained 23% of the observed variability; 22% of the variability was explained by department alone. The model had an acceptable fit (Hosmer-Lemeshow χ²=4.33; df=8; P=0.825).

LDL-C levels were measured in 835 (48%) of the patients. Again, department was the only factor significantly associated with LDL-C determination.

Statin Treatment at Hospital Discharge

Most patients (68%) with clinically relevant atherosclerosis (CAD, PAD, symptomatic carotid stenosis, plaques of the aortic arch >4 mm) and TC levels >200 mg/dL (>5.17 mmol/L) were not treated with a statin (Table 2). Almost 40% of the patients with manifest atherosclerosis and TC levels >300 mg/dL (7.76 mmol/L) were discharged without a statin.

Overall, 1342 patients (77%) received antiplatelet agents and another 505 patients (29%) received oral anticoagulants or heparin at discharge. We found that 1081 of all 1743 patients (62%) and 909 of those 1109 patients with known
hypertension (82%) were treated with antihypertensive agents at discharge.

Determinants of Statin Treatment at Hospital Discharge
Statin prescription varied widely between departments for both the total study population and patients with manifest atherosclerosis and TC levels >200 mg/dL ($P<0.001$ and $P=0.027$, respectively; Table 1). Not surprisingly, statin treatment was used less often when TC and LDL-C levels were not measured (OR, 0.4; 95% CI, 0.2 to 0.7; $P=0.001$ adjusted for history of hypertension, history of diabetes, cigarette smoking, CAD, PAD, previous intake of a lipid-lowering drug, previous intake of antiaggregants, atrial fibrillation, stroke cause, Rankin Scale at 1 week, and department).

Other clinical factors associated with statin treatment at discharge are shown in Table 3. The factor most strongly associated with the prescription of statins, as expected, was the intake of a lipid-lowering medication before the index event (Table 4). TC levels were strongly and almost linearly associated with the use of statins. Elderly patients were less

<table>
<thead>
<tr>
<th>TABLE 2. Use of Statins in Patients with Clinically Significant Atherosclerosis (n=622)</th>
</tr>
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<tbody>
<tr>
<td>Total Cholesterol (mg/dL)*</td>
</tr>
<tr>
<td>(n)</td>
</tr>
<tr>
<td>(n)</td>
</tr>
<tr>
<td>No statin, %</td>
</tr>
<tr>
<td>Statin, %</td>
</tr>
</tbody>
</table>

*To convert to SI units multiply by 0.02586.

<table>
<thead>
<tr>
<th>TABLE 3. Patient's Characteristics According to Statin Prescription at Discharge (Only Patients with Determined TC Level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1562</td>
</tr>
<tr>
<td>Female, %</td>
</tr>
<tr>
<td>Age mean±SD</td>
</tr>
<tr>
<td>Hypertension, %</td>
</tr>
<tr>
<td>Diabetes, %</td>
</tr>
<tr>
<td>Current cigarette smoking, %</td>
</tr>
<tr>
<td>Previous stroke, %</td>
</tr>
<tr>
<td>CAD (angina or MI), %</td>
</tr>
<tr>
<td>PAD, %</td>
</tr>
<tr>
<td>Lipid lowering drug before admission, %</td>
</tr>
<tr>
<td>TC mg/dL (mean±SD)*</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
</tr>
<tr>
<td>Index event under antiplatelet medication, %</td>
</tr>
<tr>
<td>Stroke severity, %</td>
</tr>
<tr>
<td>TIA</td>
</tr>
<tr>
<td>Minor stroke</td>
</tr>
<tr>
<td>Major stroke</td>
</tr>
<tr>
<td>Etiology, %</td>
</tr>
<tr>
<td>Large artery</td>
</tr>
<tr>
<td>Cardiomebolic</td>
</tr>
<tr>
<td>Small artery</td>
</tr>
<tr>
<td>No determined etiology</td>
</tr>
<tr>
<td>RS at 1 wk</td>
</tr>
<tr>
<td>0–1</td>
</tr>
<tr>
<td>2–3</td>
</tr>
<tr>
<td>4–5</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease; TC, total cholesterol; age, TC: Mann-Whitney $U$ test; all other variables: $\chi^2$ Test; RS, stroke severity.

*To convert to SI units multiply by 0.02586.
TABLE 4. Factors Influencing Prescription of Statins at Hospital Discharge in Patients with Ischemic Stroke/TIA (n=1562)

<table>
<thead>
<tr>
<th>OR (95 CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>1.0</td>
</tr>
<tr>
<td>55–64</td>
<td>1.2 (0.8–1.9)</td>
</tr>
<tr>
<td>65–74</td>
<td>1.0 (0.6–1.5)</td>
</tr>
<tr>
<td>75–84</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td>85+</td>
<td>0.2 (0.1–0.3)</td>
</tr>
<tr>
<td>Prior lipid-lowering drug</td>
<td>16.5 (10.7–25.4)</td>
</tr>
<tr>
<td>Total cholesterol (TC)</td>
<td></td>
</tr>
<tr>
<td>&lt;200 mg/dL*†</td>
<td>1.0</td>
</tr>
<tr>
<td>201–220 mg/dL</td>
<td>1.2 (0.7–1.9)</td>
</tr>
<tr>
<td>221–240 mg/dL</td>
<td>2.5 (1.6–3.9)</td>
</tr>
<tr>
<td>241–260 mg/dL</td>
<td>3.3 (2.0–5.3)</td>
</tr>
<tr>
<td>261–280 mg/dL</td>
<td>8.3 (4.9–13.9)</td>
</tr>
<tr>
<td>281–300 mg/dL</td>
<td>9.8 (5.5–17.7)</td>
</tr>
<tr>
<td>&gt;300 mg/dL</td>
<td>11.4 (6.4–20.1)</td>
</tr>
<tr>
<td>Department</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.5 (0.3–0.7)</td>
</tr>
<tr>
<td>2</td>
<td>1.0 (0.6–1.7)</td>
</tr>
<tr>
<td>3</td>
<td>0.4 (0.1–1.2)</td>
</tr>
<tr>
<td>4</td>
<td>0.1 (0.1–0.3)</td>
</tr>
<tr>
<td>5</td>
<td>0.6 (0.3–0.9)</td>
</tr>
<tr>
<td>6</td>
<td>0.5 (0.2–0.8)</td>
</tr>
<tr>
<td>7</td>
<td>0.6 (0.4–0.9)</td>
</tr>
<tr>
<td>8*</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Only those variables that were significant in the final models are shown; the following variables were included in the model: age, gender, history of hypertension, history of diabetes, current cigarette smoking, total cholesterol level (TC), CAD, PAD, atrial fibrillation, etiology, stroke severity at 1 week (Rankin Scale), prior lipid-lowering drug, prior antiaggregant drug, department.

*Reference category.
†To convert to SI units multiply by 0.02586.

Discussion

Secondary preventive measures such as measuring serum cholesterol levels and treatment with statins are underused in patients with acute stroke or TIA. Whether a patient is treated with statins depends mainly on where he or she is treated, not on clinical reasons or published guidelines.

To the best of our knowledge, this is the first study to investigate factors influencing the evaluation and management of lipid disorders in a large cohort of patients with acute stroke or TIA. Previous studies have reported low rates of lipid screening in patients with acute myocardial infarction.15,28

The value of educational programs in hospitals for the improvement of lipid evaluations could be demonstrated,28 and we are trying to establish common guidelines for lipid evaluation as a consequence of our results.

Overall, 23% of our patients and 32% of those with clinically relevant atherosclerosis and cholesterol levels >200 mg/dL received a statin at discharge. This rate is comparable to those reported in a meta-analysis of patients with hyperlipidemia and CAD, which found that only 37% of 622 patients with CAD and hyperlipidemia were treated with statins.17 A very recent investigation of a large national sample of patients with acute myocardial infarction found an overall frequency of the use of statins of 32%.29 Another investigation found an overall rate of statin use of 30% at discharge in 17 732 German patients with acute myocardial infarction.30 In patients with PAD, a recent study described that 35% of all patients (and only 30% of those with lower-extremity disease) were on a lipid-lowering agent,31 whereas yet another investigation found that only 5% of their patients with critical lower-extremity vascular disease received lipid-lowering treatment.32 There is also evidence that patients with PAD receive lipid-lowering treatment less often than patients with CAD.33

We found a very high variability for the use of statins between the participating departments. Furthermore, there was a highly significant association between lipid evaluation and statin treatment. Small area variation for the use of lipid-lowering drugs has been described previously.13,15 That 35% of all patients (and only 30% of those with lower-extremity disease) were on a lipid-lowering agent,31 whereas yet another investigation found that only 5% of their patients with critical lower-extremity vascular disease received lipid-lowering treatment.32 There is also evidence that patients with PAD receive lipid-lowering treatment less often than patients with CAD.33

The recently published British Heart Protection Study found a strong reduction in vascular events with simvastatin compared with placebo in a mixed population of vascular patients, including patients after cerebrovascular events.6 The risk reduction was significant not only in patients with hypercholesterolemia but also in patients with normal or low-normal cholesterol levels. Patients with previous cerebrovascular disease had a risk reduction with statins similar to that of the other patient groups in this study. Considering the high annual risk of myocardial infarction, stroke, or vascular death in patients with a recent ischemic stroke or TIA, it might therefore be reasonable to advocate the use of statins in most patients with stroke or TIA. However, until now, no guidelines or recommendations have existed for the general use of statins in patients with ischemic stroke or TIA. At first glance, this might explain the low overall frequency of statin use and the large variability between different centers. But even in patients with a given indication for statin use according to international guidelines, almost two thirds are left untreated, and a large variability remains between different centers according to our data. Assigning a 5-year risk of
a major vascular event or vascular death of 30% to these high-risk patients, which is a conservative estimate, and assuming that treatment with statins would reduce this risk by 20% means that 40 serious vascular events and deaths per 1000 patients would not be prevented in the current clinical setting.

Study Limitations
We collected data on the determination of lipid levels and initiation of statin therapy during hospitalization, but we did not determine the frequency of lipid evaluation and therapy after discharge. Failure to implement screening and treatment in the outpatient setting, however, has been documented, and it has been suggested that these measures be implemented during the predischarge phase of hospitalization.

Our investigation was limited to patients treated in neurological departments. Patients with stroke admitted to general medical departments may receive a more appropriate lipid-lowering treatment. This is not very likely because the data from patients with myocardial infarction were collected in medical departments. The frequency of lipid evaluation and the use of statins in our study compare favorably.

Finally, 29% of our sample were not analyzed because of logistical reasons caused by the ongoing nature of the registry: of these subjects, ~15% would not meet the inclusion criteria. Those not included were comparable in terms of age and sex distribution to those included, and we are not aware of any selection mechanism other than order of admission and batch size. Thus, we believe that selection bias is not a problem in our study.

Study Strengths
Randomized, controlled trials are necessary to establish the effectiveness of healthcare interventions. Large-scale observational studies such as our stroke registry are the next necessary step in evaluating healthcare interventions in real-life settings. The multicenter approach incorporates clinical practices of primary, secondary, and tertiary care hospitals serving a large urban population. Although geographic variation is to be expected, we believe that our results are generalizable to a Western medical setting.

Conclusions
There is an urgent need to optimize lipid evaluation and treatment with statins in patients with stroke or TIA, particularly in high-risk patients for whom guidelines already exist but are not adequately followed.

Appendix

The Vienna Stroke Study Group

Participating Neurological Departments and Local Investigators
Department of Neurology, Krankenanstalt Rudolfstiftung (I. Podreka; C. Prainer, T. Schlager); Clinical Department of Clinical Neurology, University Clinic of Neurology, University of Vienna (L. Deecke, W. Lalouschek; W. Lang); Department of Neurology, Kaiser-Franz-Josef-Spital (O. Berger, W. Grisold); Department of Neurology, Krankenhaus Lainz (C. Bancher, M. Hoberstorfer, M. Schmidbauer); Neurological Hospital Rosenhügel, Department A (C. Alf, G. Schnaberth); Neurological Hospital Rosenhügel, Department B (B. Glawar, B. Mamoli); Department of Neurology, Wilhelminenspital (T. Brücke, J. Donis, S. Parigger, W. Santha); Neurological Hospital Maria-Theresien Schlössel (H. Binder, E. Gatterbauer); Department of Neurology, Donaupass (W. Kristofersich, J. Lassmann, W. Pankl, M. Schlederer), in cooperation with the following centers: University Clinic of Emergency Medicine, University of Vienna (H. Domanovits, M. Hirschl, A. Laggner); Department of Neuroradiology/University Clinic of Radiology, University of Vienna (K. Heimberger); and Vienna Emergency Services (A. Kaff, B. Segall).

Follow-Up Examinations and Data Documentation

Biostatistics and Epidemiology
M. Müller, 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 Rosenhügel, Wilhelminenspital, and Donaupass.

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References
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