Risk Profile of Symptomatic Lacunar Stroke Versus Nonlobar Intracerebral Hemorrhage

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Background and Purpose—Although lacunar stroke (LS) and deep intracerebral hemorrhage (dICH) represent acute manifestations of the same pathological process involving cerebral small vessels (small vessel disease), it remains unclear what factors predispose to one phenotype rather than the other at individual level.

Methods—Consecutive patients with either acute symptomatic LS or dICH were prospectively enrolled as part of a multicenter Italian study. We compared the risk factor profile of the 2 subgroups using multivariable logistic regression.

Results—During a time course of 9.5 years, 1931 subjects (1434 LS and 497 dICH; mean age, 71.3±13.3 years; males, 55.5%) qualified for the analysis. Current smoking was associated with LS (odds ratio [OR], 2.17; *P*=0.001). Conversely, dICH cases were more likely to be hypertensive (OR, 1.87; *P*<0.001), excessive alcohol consumers (OR, 1.70; *P*=0.001), and more frequently under treatment with warfarin (OR, 2.05; *P*=0.010) and statins (OR, 3.10; *P*<0.001). Hypercholesterolemia, diabetes mellitus, and antiplatelet treatment were not associated with a specific small vessel disease manifestation.

Conclusions—The risk factor profile of dICH differs from that associated with LS. This might be used for disease risk stratification at individual level. (Stroke. 2016;47:2141-2143. DOI: 10.1161/STROKEAHA.116.013722.)

Key Words: cerebrovascular disorders ■ intracerebral hemorrhage ■ lacunar stroke ■ risk factors

The term cerebral small vessel disease (SVD) encompasses a wide spectrum of pathological processes affecting the small vessels of the brain, among which, arteriolosclerosis, also known as hypertensive microangiopathy, is the most common. Lacunar strokes (LS) and hemorrhages located in the deep brain regions (nonlobar or deep intracerebral hemorrhage [dICH]) represent the acute symptomatic consequences of this progressive microangiopathy. Because these two phenotypes share the same pathological substrate, it is still matter of debate why some individuals are more prone to develop acute small vessel occlusion, whereas others are more susceptible to vascular rupture. To date, few studies have attempted to address this issue, with conflicting results. Most of the inconsistency arise from methodological drawbacks of the study designs, including the relatively small number of subjects in some analyses, the exclusion of subjects without hypertension in others, as well as the lack of a clear distinction between ischemic stroke subtypes and between lobar and dICH. Therefore, in this study we aimed at investigating whether differences in individual risk factor profile underlie the propensity for developing dICH, rather than LS.
For the purpose of the present analysis, we reviewed data from the prospectively collected registries of 4 Italian neurological centers. Consecutive patients who were admitted between January 2002 and July 2011 were considered if their presenting symptoms were consistent with a first-ever acute cerebrovascular event. Eligibility for study participation required neuroimaging (computed tomography or magnetic resonance imaging) confirmation of LS or dICH. Patients’ selection criteria and risk factors definition are provided in the online-only Data Supplement.

### Methods

Categorical variables are reported as proportion and continuous variables as mean (SD). Descriptive differences between groups were examined with the χ² test and 1-way ANOVA F test, when appropriate. Multivariable logistic regression was performed including demographics (age and sex), as well as hypertension, diabetes mellitus, hypercholesterolemia, current smoking, antiplatelet therapy, use of oral anticoagulants, statin treatment, and alcohol consumption as covariates. P<0.05 on 2-sided test was considered significant. Data were analyzed using SPSS v.16 (http://www.spss.com).

### Results

A total of 1931 patients fulfilled the inclusion criteria (mean age, 71.3±13.3 years; males, 55.5%). Of these, 1434 (74.2%) had LS and 497 (25.8%) had dICH. The characteristics of the whole study group are summarized in Table 1.

Patients presenting with dICH were more likely to be hypertensive, to have a history of ischemic heart disease, excessive alcohol consumption, as well as statin and oral anticoagulant treatment compared with LS subjects. However, current smoking and hypercholesterolemia were significantly more frequent in the group of patients with LS.

Hypertension, excessive alcohol use, anticoagulant, and statin therapy were associated with dICH in the multivariable logistic regression model, whereas current smoking was associated with LS (Table 2).

### Discussion

The main finding of this study is that dICH and LS exhibit distinct risk factor profiles.

First, our study corroborates previous findings indicating hypertension as major risk factor for dICH.2,6 Our results are indirectly supported by previous reports suggesting that

### Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LS (n=1434)</th>
<th>dICH (n=497)</th>
<th>P Values</th>
<th>OR (95% CI)*</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>71.3 (13.3)</td>
<td>71.7 (13.2)</td>
<td>0.809</td>
<td>1.00 (0.99–1.01)</td>
<td>0.521</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>1071 (55.5)</td>
<td>1071 (55.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of coronary artery disease, n (%)</td>
<td>1412 (73.1)</td>
<td>1412 (73.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>1412 (73.1)</td>
<td>1412 (73.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission systolic blood pressure, mean (SD), mm Hg</td>
<td>154.5 (26.6)</td>
<td>154.5 (26.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission diastolic blood pressure, mean (SD), mm Hg</td>
<td>83.9 (13.7)</td>
<td>83.9 (13.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>420 (21.8)</td>
<td>420 (21.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission serum glucose, mean (SD), mg/dL</td>
<td>119.3 (47.4)</td>
<td>119.3 (47.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hypercholesterolemia, n (%)</td>
<td>467 (24.2)</td>
<td>467 (24.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission serum total cholesterol, mean (SD), mg/dL</td>
<td>182.2 (38.9)</td>
<td>182.2 (38.9)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Current smoking, n (%)</td>
<td>312 (16.2)</td>
<td>312 (16.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of excessive alcohol consumption, n (%)</td>
<td>252 (12.9)</td>
<td>252 (12.9)</td>
<td></td>
<td></td>
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<tr>
<td>Statin treatment, n (%)</td>
<td>167 (8.6)</td>
<td>167 (8.6)</td>
<td></td>
<td></td>
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<tr>
<td>Antiplatelet treatment, n (%)</td>
<td>413 (21.4)</td>
<td>413 (21.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulant treatment, n (%)</td>
<td>56 (2.9)</td>
<td>56 (2.9)</td>
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</tr>
</tbody>
</table>

CI indicates confidence interval; dICH, deep intracerebral hemorrhage; LS, lacunar stroke; and OR, odds ratio.

*Reference, LS.
the benefit of long-term antihypertensive therapy might be greater for the prevention of hemorrhagic stroke than of brain ischemia.\textsuperscript{7} Second, as opposed to hypertension, diabetes mellitus was not associated with a specific clinical manifestation of SVD in our study. This is in an apparent disagreement with previous reports.\textsuperscript{8} Such discrepancy might be explained by the lack of a precise identification of ischemic stroke subtypes and of pathogenic subgroups of cerebral bleeding based on hemorrhage location (deep versus lobar). Third, consistently with previous evidence that excessive alcohol intake is an important susceptibility factor for cerebral bleeding,\textsuperscript{8} excessive alcohol consumption turned out to be related to dICH in our analysis. Conversely, in line with previous findings from Kaplan et al,\textsuperscript{9} current smoking was associated with the occurrence of LS. Fourth, as expected, we observed a strong relationship between oral anticoagulant therapy and dICH,\textsuperscript{6} as opposed to a neutral effect of antiplatelet medications. Finally, statin use seems related to the hemorrhagic manifestation of SVD. Although the benefits of statin treatment in primary and secondary prevention of ischemic stroke are widely recognized, the association between these molecules and the risk of cerebral bleeding is still controversial.\textsuperscript{10} Although this study was not specifically designed to investigate this hypothesis, our results are in agreement with previous reports suggesting a possible relationship between statin therapy and increased risk of ICH.\textsuperscript{10} Statins pleiotropic effects, including reduction of platelet aggregation and inhibition of the coagulation cascade,\textsuperscript{11} make the relation between statins and cerebral bleeding in subjects with underlying SVD biologically plausible.

The major strengths of our study are the large number of participants, the homogeneous demographic characteristics of the cohort along with the standardized diagnostic workup and evaluation of risk factors. Some limits should also be acknowledged. The lack of a systematic magnetic resonance imaging screening prevented us from investigating the potential role of imaging markers, such as white matter lesions and cerebral microbleeds. Hospital referral selection bias and the long inclusion period may also have affected our analysis. Finally, because of the lack of a stroke-free control group, we cannot but speculate that the observed associations might represent causality.

Conclusions
Symptomatic clinical manifestations of cerebral SVD may depend on distinct risk factor profiles predisposing to bleeding and thrombosis, respectively.

Disclosures
Dr Zini received speaker fees from Boehringer-Ingelheim, Medtronic-Covidien and consulting fees from Nestec, Medronic-Covidien.

References
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SUPPLEMENTAL MATERIAL

Supplemental Methods

Participants

The study was approved by relevant local authorities at each study site. Written informed consent was obtained from all patients (or next of kin). The LS subgroup was composed of patients with a clinical subcortical lacunar stroke syndrome (1) who did not have surgically amenable ipsilateral carotid artery disease or major risk factors for cardioembolic sources of stroke (2). The dICH subgroup was composed of patients with deep (non-lobar) hematomas. ICH location was assigned based on admission CT scan by stroke neurologists at each participating center. Deep hemorrhages were those selectively involving the thalamus, basal ganglia, or brainstem. Multiple concurrent bleeds involving deep and lobar territories were defined as mixed ICH and represented an exclusion criterion. Additional exclusion criteria for ICH included the presence of trauma, brain tumor, hemorrhagic transformation of a cerebral infarction, vascular malformation, or any other perceived cause of secondary bleeding. Demographic and clinical information, as well as neuroimaging data were ascertained by neurologists in each Center.

Risk factor definition

Subjects were classified as current smokers if they were currently smoking one or more cigarettes per day on a regular basis. Hypertension was defined as systolic blood pressure (SBP) >140 mm Hg and/or diastolic (DBP) >90 mm Hg out of the acute phase, or using pharmacological treatment for hypertension. Hypercholesterolemia was considered as cholesterol >240 mg/dL (6.18 mmol/L) out of the acute phase or using pharmacological treatment to lower blood lipids. Diabetes mellitus was defined as fasting glucose levels >125 mg/dl (6.94 mmol/L) out of the acute phase or current treatment with anti-diabetic drugs. Based on daily alcohol consumption subjects were dichotomized into excessive drinkers (>45 g of alcohol) and light-moderate drinkers or non-drinkers. We also collected information on coronary artery disease (medical history of angina, myocardial infarction, coronary artery bypass graft, or percutaneous trans-luminal coronary angioplasty, and pre-stroke medications (in particular, warfarin, aspirin or other antiplatelet agents). Data were obtained from interviews with patients, next of kin and/or attending physicians or general practitioners. Fasting lipids and glucose measurements were carried out on venous blood samples obtained within 24 hours of stroke occurrence in each participating center, using comparable procedures.

Supplemental References
