Differing Risk Factor Profiles of Ischemic Stroke Subtypes
Evidence for a Distinct Lacunar Arteriopathy?

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Background and Purpose—Differences in risk factor profiles between lacunar and other ischemic stroke subtypes may provide evidence for a distinct lacunar arteriopathy, but existing studies have limitations. We overcame these by pooling individual data on 2875 patients with first-ever ischemic stroke from 5 collaborating prospective stroke registers that used similar, unbiased methods to define risk factors and classify stroke subtypes.

Methods—We compared risk factors between lacunar and nonlacunar ischemic strokes, altering the comparison groups in sensitivity analyses, and incorporated these data into a meta-analysis of published studies.

Results—Unadjusted and adjusted analyses gave similar results. We found a lower prevalence of cardioembolic source (adjusted odds ratio, 0.33; 95% CI, 0.24 to 0.46), ipsilateral carotid stenosis (odds ratio, 0.21; 95% CI, 0.14 to 0.30), and ischemic heart disease (odds ratio, 0.75; 95% CI, 0.58 to 0.97) in lacunar compared with nonlacunar patients but no difference for hypertension, diabetes, or any other risk factor studied. Results were robust to sensitivity analyses and largely confirmed in our meta-analysis.

Conclusions—Hypertension and diabetes appear equally common in lacunar and nonlacunar ischemic stroke, but lacunar stroke is less likely to be caused by embolism from the heart or proximal arteries, and the lower prevalence of ischemic heart disease in lacunar stroke provides additional support for a nonatherosclerotic arteriopathy causing many lacunar ischemic strokes. Our findings have implications for how clinicians classify ischemic stroke subtypes and highlight the need for additional research into the specific causes of and treatments for lacunar stroke.

Key Words: stroke ■ lacunar ■ risk factors ■ stroke subtypes

About one quarter of ischemic strokes are caused by lacunar infarcts1 resulting from the occlusion or, perhaps, leakiness2 of one of the small perforating arteries supplying the deep subcortical areas of the brain. The arterial pathology remains poorly understood, with proposed mechanisms including lipohyalinosis, arteriosclerosis, poor cerebral blood flow, vasospasm, or abnormal endothelial function.3 Much of our current understanding is based on the clinicopathological studies of Miller Fisher et al in the 1960s and 1970s. Progress since then has been limited, but there is growing evidence to suggest that the lacunar arteriopathy may differ from the atheroscleromboembolic processes that lead to occlusion of large intracranial and extracranial arteries, causing most other ischemic strokes.2-4

One indirect approach to better understanding the arterial pathology of lacunar ischemic stroke is to look for differences in the vascular risk factor profiles of lacunar versus nonlacunar ischemic stroke, which may reflect distinct underlying pathologies and causes. In a previous meta-analysis of published studies that used an unbiased method (independent of vascular risk factors) to classify ischemic stroke subtypes, we found no difference in the prevalence of most risk factors.5 In particular, contrary to the widespread view that hypertension and diabetes are more common in lacunar ischemic stroke,6 we found no excess of diabetes and only a slight excess of hypertension, but we did find a lower prevalence of atrial fibrillation and carotid stenosis in patients with lacunar ischemic stroke. However, we could not adjust for the potential confounding effects of age, sex and other vascular risk factors, the definitions of risk factors and the nonlacunar comparison group varied between studies, and data on several risk factors of potential interest were sparse.
We overcame these shortcomings in the present study by pooling individual patient data from 5 prospective stroke registers that used identical, unbiased methods of classifying ischemic stroke subtypes and consistent risk factor definitions. We compared risk factors for lacunar versus nonlacunar ischemic stroke, assessing the effects of adjusting for potential confounders and varying the comparison groups in predefined sensitivity analyses. We also updated our previous meta-analyses, incorporating data from our stroke register pooling project.

Methods
We obtained data from stroke registers that had not necessarily (indeed, most had not) already published on risk factor–ischemic stroke subtype associations but were able to provide data for inclusion in pooled individual patient data analyses. There were 2 phases of our hospital-based stroke register in Edinburgh7,8 and 3 community-based stroke registers in Perth, Australia, and in Lund and Orebro, Sweden, all of which recruited from predominantly white populations.9–11 Each register had the required ethical approvals. In each, a stroke physician had assessed patients as soon as possible after the stroke, prospectively recording demographic and clinical details, including vascular risk factors and results of brain imaging and other investigations. Definitions of risk factors are given in the footnotes to supplemental Table I (available online at http://stroke.ahajournals.org).

We included all patients with a clinically evident stroke, demonstrated to be ischemic by the absence of recent intracerebral hemorrhage on appropriately timed CT or MRI, or at autopsy. We assigned ischemic stroke subtypes according to the presumed site and size of the causative infarct (anterior circulation lacunar or cortical [including striatocapsular] infarction, or posterior circulation infarction) using the clinical features of the stroke (Oxfordshire Community Stroke Project syndromes),12 modified if necessary by the findings on brain imaging (or at autopsy) if an infarct considered relevant to the presenting stroke was present. We excluded patients whose subtype was either undetermined or known to be attributable to a specific unusual cause such as arterial dissection.

Statistical Analyses
We analyzed data with STATA version 8. In the primary analysis, we included all patients with a first-ever-in-a-lifetime anterior circulation ischemic stroke, excluding cases of posterior circulation stroke, among which lacunar and nonlacunar ischemic strokes are often difficult to distinguish reliably. We determined the crude association between each risk factor and ischemic stroke subtype by calculating register-specific and Mantel–Haenszel fixed-effect pooled odds ratios (ORs), using I² to assess heterogeneity between registers.13 We used Student t test to compare mean ages.

We used logistic regression to obtain ORs adjusted for age, sex, and register and, in a second model, also adjusted for hypertension, diabetes, and any other risk factors that differed significantly between lacunar and nonlacunar groups in unadjusted analyses. We estimated extent of misclassification of ischemic stroke subtypes by calculating the proportion of patients with a visible relevant infarct on their brain scan whose final classification placed them in a different comparison group from that based on the clinical syndrome alone. We applied this proportion to the patients with no visible relevant infarct to estimate the extent of residual misclassification.

We also calculated ORs as described above in 5 predefined sensitivity analyses: (1) including patients with recurrent as well as first-ever events; (2) excluding those with a potential cardioembolic source; (3) including posterior circulation ischemic strokes in the nonlacunar comparison group; (4) comparing small versus large vessel disease ischemic strokes, using a modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification14 (supplemental Figure I, available online at http://stroke.ahajournals.org); and (5) among patients with a visible relevant infarct only, to assess the effects of excluding all potentially misclassified patients.

Updated Meta-Analysis
We updated our previous meta-analysis of published studies comparing risk factors in lacunar versus nonlacunar ischemic strokes, following the same rigorous methods (details published previously13). We pooled unadjusted data from the primary analysis of our collaborative stroke register project with data extracted from all other studies published by June 2008 that had used a similar method for classifying ischemic stroke subtypes. We used Cochrane Review Manager13 to determine study-specific and Mantel–Haenszel fixed-effect pooled ORs, assessing heterogeneity between studies using I².13

Results
The 5 registers contributed data on a total of 5101 patients with stroke, of whom 2875 had a first-ever-in-a-lifetime anterior circulation ischemic stroke (1062 lacunar and 1813 nonlacunar).

Mean age ranged from 67 to 76 years. Patients in the hospital-based registers were younger than in the community-based ones, and lacunar cases were younger than nonlacunar (mean 68 versus 71 years of age; P<0.001). There were approximately equal numbers of men and women in the nonlacunar group but slightly more men (58%) in the lacunar group (P<0.001). The proportion of lacunar cases (32% to 42% of first-ever anterior circulation ischemic strokes) was similar in the different registers. All registers provided data on hypertension, diabetes, ischemic heart disease, and smoking. Data were not available from all registers for the remaining risk factors (supplemental Table I).

For each risk factor, unadjusted ORs were generally very similar across all registers, with no significant between-register heterogeneity. Unadjusted and adjusted analyses generally yielded very similar results (Figure 1). Cardioembolic source and carotid stenosis were much less common in lacunar than in nonlacunar ischemic stroke, whereas hypertension and diabetes did not differ between subtypes. A history of ischemic heart disease was less common in lacunar ischemic stroke and remained so in the fully adjusted analyses (lacunar versus nonlacunar OR, 0.75; 95% CI, 0.58 to 0.97). Although both smoking and excess alcohol consumption appeared more common in lacunar versus nonlacunar ischemic stroke, these associations did not persist after multivariable adjustment.

A total of 343 of 1806 patients in the primary analysis with a visible relevant infarct on their brain scan were allocated to a different comparison group (and so correctly reclassified) than would have been the case based on their clinical syndrome alone. Applying this proportion to the 1069 patients with no visible relevant infarct gave an estimated 203 patients residually misclassified of 2875 in the primary analysis population (7%), with similar proportions misclassified in each comparison group.

For each of the 5 planned sensitivity analyses, results were generally very similar to those from the primary analyses (supplemental Table II, available online at http://stroke.ahajournals.org).
Previously, we identified 10 published studies that had used a risk factor–independent clinical syndrome and imaging-based method of classifying ischemic stroke subtypes. One overlapped with the Lund register in our pooled stroke register analysis and was therefore excluded from our updated meta-analysis. We found 3 additional relevant studies, one of which superseded a previous study. Figure 2 shows ORs for lacunar versus nonlacunar ischemic stroke from our previous meta-analysis, from the unadjusted primary analyses of our collaborative stroke register project, and from our updated meta-analysis, including our collaborative data and newly identified published data. These 3 estimates were generally very similar for all risk factors. The most consistent findings were a lower frequency among patients with lacunar ischemic stroke of ischemic heart disease (updated meta-analysis OR, 0.76; 95% CI, 0.68 to 0.85), cardioembolic source (OR, 0.40; 95% CI, 0.35 to 0.46); and carotid stenosis (OR for ipsilateral stenosis, 0.23; 95% CI, 0.19 to 0.29; for contralateral stenosis, 0.29; 95% CI, 0.21 to 0.41); and no difference between subtypes for diabetes or previous transient ischemic attack. The updated meta-analysis showed a slight excess of hypertension among patients with lacunar ischemic stroke (OR, 1.12, 95% CI, 1.02 to 1.24). It also suggested that smoking and excess alcohol consumption were more common in lacunar ischemic stroke, but these results may be subject to residual confounding because these associations disappeared in our fully adjusted individual patient data analyses. There was moderate heterogeneity between studies in our updated meta-analysis for ischemic heart disease, cardioembolic source, ipsilateral stenosis, previous transient ischemic attack, and smoking.

**Discussion**

Analyses of our large collaborative stroke register data set revealed important differences in the risk factor profiles among patients with lacunar compared with nonlacunar ischemic stroke. There was a striking similarity between unadjusted and adjusted results and robustness to a series of sensitivity analyses for most risk factors, justifying our updated meta-analysis of unadjusted results from published studies. The individual patient data results were largely confirmed by the updated meta-analysis and suggest that many fewer lacunar than nonlacunar ischemic strokes are...
caused by emboli from the heart or proximal arteries. Further, the lower prevalence of atherosclerosis in not only carotid but also coronary arteries among lacunar cases shows that these patients are less likely to have atherosclerosis in other vascular territories. Thus, a distinct nonatherosclerotic arteriopathy may cause many lacunar ischemic strokes.

There are several strengths to our study. First, our pooled analyses benefited from methodological similarities between the included registers, large numbers of patients, and adjustment for potential confounding factors. Second, the inclusion of our individual patient data in the updated meta-analyses almost doubles the existing published data on hypertension and diabetes from studies using risk factor–independent methods of classifying ischemic stroke subtypes and more than doubles the existing data for many other risk factors. Third, a series of sensitivity analyses in which we varied the comparison groups did not materially alter the results.

Our study has some potential weaknesses. First, the distribution of ischemic stroke subtypes and risk factors may differ between hospitalized and nonhospitalized patients. However, hospital-based register patients were recruited from both hospital admissions and outpatient clinics, making them more representative. Further, classification of pathological types and subtypes of stroke requires early specialist clinical assessment, appropriately timed brain imaging, and other investigations, essentially confining analyses from community-based stroke registers to those patients having hospital-based assessment. Second, although a clinical syndrome and brain imaging–based method of classification is probably the least biased method to use when investigating risk factor–stroke subtype associations, there will still be some misclassification of stroke subtypes. Because the estimated proportion of misclassified patients (7%) in the 2 compared groups of patients was similar, misclassification may have diluted any true risk factor–ischemic subtype associations. However, it is reassuring that our analyses confined to patients with a visible relevant infarct on brain imaging produced similar results to the primary analysis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Lacunar</th>
<th>Nonlacunar</th>
<th>OR (95% CI)</th>
<th>Heterogeneity (I²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>0.62 (0.51 to 0.74)</td>
<td>0.76 (0.68 to 0.85)</td>
<td>0%</td>
<td>66%</td>
</tr>
<tr>
<td>Cardioembolic source</td>
<td>0.44 (0.35 to 0.56)</td>
<td>0.33 (0.26 to 0.41)</td>
<td>65%</td>
<td>66%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.24 (1.08 to 1.43)</td>
<td>0.94 (0.80 to 1.10)</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.94 (0.78 to 1.12)</td>
<td>1.07 (0.85 to 1.35)</td>
<td>0%</td>
<td>23%</td>
</tr>
<tr>
<td>Ipsilateral stenosis</td>
<td>0.26 (0.19 to 0.34)</td>
<td>0.24 (0.17 to 0.34)</td>
<td>67%</td>
<td>0%</td>
</tr>
<tr>
<td>Contralateral stenosis</td>
<td>0.23 (0.10 to 0.29)</td>
<td>0.23 (0.10 to 0.29)</td>
<td>48%</td>
<td>0%</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>0.18 (0.09 to 0.37)</td>
<td>0.51 (0.34 to 0.77)</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.33 (0.89 to 1.85)</td>
<td>0.84 (0.67 to 1.04)</td>
<td>62%</td>
<td>0%</td>
</tr>
<tr>
<td>Alcohol excess</td>
<td>0.91 (0.76 to 1.08)</td>
<td>0.91 (0.76 to 1.08)</td>
<td>58%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Figure 2. Unadjusted ORs for each risk factor (lacunar vs nonlacunar ischemic stroke) in the previous and updated meta-analysis. Open diamonds indicate ORs obtained in previous meta-analysis; gray diamonds, ORs obtained in unadjusted individual patient data analysis; black diamonds, ORs obtained in updated meta-analysis (including the individual patient data).
Third, there may have been some misclassification of risk factors because in our stroke registers, we ascertained exposure to risk factors retrospectively. Misclassification of risk factor status is likely to have occurred to a similar extent in both comparison groups and so may have diluted estimates of association. Thus, we may have failed to detect some risk factor–subtype associations, but there are no robust prospective data to check this. The level of detail required for adequate distinction between ischemic stroke subtypes has rarely been available in prospective studies with detailed assessment of risk factors at baseline, and the limited amount of subtype information available is based on potentially biased risk factor–dependent or purely imaging-based classification methods. Finally, we were unable to assess the relationship between raised cholesterol and ischemic stroke subtypes because data on prestroke cholesterol levels were not available. Current evidence suggests no definite association between cholesterol level and ischemic stroke subtypes.

A previous meta-analysis of 4 population-based studies found risk factor–stroke subtype associations broadly similar to our own but did not assess ischemic heart disease. Hypertension was more frequent in lacunar compared with nonlacunar ischemic stroke, but this result could be attributed to a single large study that used strict application of the TOAST criteria with their reliance on risk factors (including hypertension) to define subtypes.

In a recently published study that compared risk factors in patients with presumed small versus large vessel disease (using a modified TOAST classification similar to ours, excluding hypertension and diabetes from the risk factor definitions), hypertension appeared much more common in patients with small vessel disease. However, the comparison groups were not recruited consecutively or contemporaneously, and the definition of hypertension included raised blood pressure after stroke. Our study found no excess of hypertension in patients with small versus large vessel disease.

Our findings have important implications for both clinicians and researchers. We consistently found no evidence for the still widely held belief that hypertension and diabetes are more prevalent in lacunar than nonlacunar ischemic stroke. Thus, clinicians should not be guided by the presence or absence of these risk factors when assigning an etiologic stroke subtype. Our data suggest that few lacunar ischemic strokes are caused by emboli from the heart or proximal arteries, and our newly established finding of a lower prevalence of previous ischemic heart disease in lacunar versus nonlacunar cases suggests that the former are less prone to atherosclerosis in other vascular territories, providing additional indirect evidence for a distinct nonatherosclerotic arteriopathy underlying many lacunar strokes. However, because patients with lacunar stroke can have any of the aforementioned risk factors, they should still be investigated for all of these.

Additional clinical, pathological, and imaging-based studies are needed to unravel the nature of the vascular pathology underlying lacunar ischemic stroke to enable the development of specific approaches to the acute treatment and prevention of this common stroke subtype. However, this study adds to an increasing body of evidence for a distinct arteriopathy of lacunar stroke, including differences in the retinal microvasculature and in the leakiness of the blood–brain barrier.

In addition, because the most appropriate therapeutic interventions for different ischemic subtypes may differ, future trials of treatments for acute stroke and long-term secondary prevention after stroke (eg, trials of thrombolytic and antithrombotic drugs) should accurately distinguish ischemic stroke subtypes and ideally have sufficient statistical power to detect differences between subtypes in the effects of the treatments being assessed.

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Disclosures

None.

References

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