Counting cavitating lacunes underestimates the burden of lacunar infarction

Citation for published version:

Digital Object Identifier (DOI):
10.1161/STROKEAHA.109.566307

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Early version, also known as pre-print

Published In:
International Journal of Stroke

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Counting Cavitating Lacunes Underestimates the Burden of Lacunar Infarction
Gillian M. Potter, Fergus N. Doubal, Caroline A. Jackson, Francesca M. Chappell, Cathie L. Sudlow, Martin S. Dennis and Joanna M. Wardlaw

Stroke. 2010;41:267-272; originally published online December 31, 2009;
doi: 10.1161/STROKEAHA.109.566307
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/2/267

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
Counting Cavitating Lacunes Underestimates the Burden of Lacunar Infarction

Gillian M. Potter, MBChB, BSc (Hons), MRCP, FRCR; Fergus N. Doubal, MBChB, MRCP; Caroline A. Jackson, MSc, PhD; Francesca M. Chappell, MSc; Cathie L. Sudlow, DPhil, FRCP; Martin S. Dennis, MD, FRCP(E); Joanna M. Wardlaw, MD, FRCR, FRCP, FMedSci

Background and Purpose—On brain imaging, lacunes, or cerebrospinal fluid–containing cavities, are common and are often counted in epidemiological studies as old lacunar infarcts. The proportion of symptomatic lacunar infarcts that progress to lacunes is unknown. Noncavitating lacunar infarcts may continue to resemble white matter lesions.

Methods—We identified patients with acute lacunar stroke, with or without an acute lacunar infarct on computed tomography or MRI, who had follow-up imaging. A neuroradiologist classified lacunar infarcts progressing to definite or possible cavities on follow-up imaging. We tested associations between cavitation and patient-related, stroke-related, and imaging-related features, including other features of small vessel disease.

Results—Among 90 patients (mean age 67 years), any cavitation was present on follow-up imaging in 25 (28%), and definite cavitation in 18 (20%). Definite cavitation was associated with increasing time to follow-up imaging (median 228 days, range 54 to 1722, versus no cavitation 72 days, range 6 to 1440; \( P = 0.0003 \)) and deep cerebral atrophy (\( P = 0.03 \)) but not with age, stroke severity, larger initial infarct size, or other features of small vessel disease. Hypertension and diabetes were negatively associated with cavitation (\( P = 0.01 \) and 0.02, respectively).

Conclusions—Definite cavitation occurs in one fifth of symptomatic lacunar ischemic strokes, implying that most continue to resemble white matter lesions. Epidemiology and pathophysiology studies of lacunar stroke, which have only counted lacunes as lacunar infarcts, may have substantially underestimated by as much as 5 times the true burden of lacunar stroke disease. (Stroke. 2010;41:267-272.)

Key Words: brain imaging ■ lacunar infarction ■ lacunes ■ epidemiology

A lacune is commonly defined as a small, deep, 3- to 20-mm (or in some cases, 3- to 15-mm) cerebrospinal fluid (CSF)–containing cavity. The term lacune was first used by Dechambre in 1838\(^1\) and later in 1901 by Marie,\(^2\) who suggested these could be attributable to infarcts. Sixty years later, Fisher defined lacunes pathologically as infarcts, either clinically silent or symptomatic, resulting from occlusion of a penetrating branch of a cerebral artery.\(^3\)–\(^5\) The term lacune is often used interchangeably with the terms lacunar infarct and lacunar stroke. Tissue loss replaced by CSF (or near-CSF) is also known radiologically as cerebromalacea and can affect gray or white matter, but this term is usually applied to cortical infarcts.

Silent lacunes (on imaging or histopathology, without clear evidence of relevant stroke symptoms) are often termed silent lacunar infarcts or silent brain infarcts. Silent lacunes are frequently seen in healthy older people, occur in 8% to 28% of the general population, are associated with increasing age, hypertension, and subtle deficits in physical and cognitive function, and more than double the risk of stroke and dementia.\(^6\) In most studies of silent brain infarcts, there is no definitive pathological evidence that the lesion was attributable to infarction.

The association between clinically evident lacunar ischemic stroke and silent lacunes is unclear because the proportions in whom the symptomatic lacunar infarct progresses to a cavity and in whom the lesion continues to resemble a white matter lesion are unknown. This has significant implications for epidemiology (including risk factor) and pathogenesis studies of lacunar infarction and cerebral small vessel disease, in which it is common practice to count lacunes and only consider these as silent lacunar infarcts, omitting to correlate these with symptoms.

We investigated the proportion of symptomatic lacunar strokes progressing to lacunes and assessed patient-related, stroke-related, and imaging-related associations of cavitation.

Subjects and Methods

We identified patients with acute lacunar ischemic stroke, diagnosed after clinical and radiological evaluation, with baseline and follow-up MRI or computed tomography (CT) brain imaging, from 2 studies: a

Received August 22, 2009; final revision received September 8, 2009; accepted September 11, 2009.

From the Division of Clinical Neurosciences and SINAPSE Collaboration, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, United Kingdom.

Correspondence to Professor J.M. Wardlaw, SFC Brain Imaging Research Centre, Division of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, United Kingdom. E-mail Joanna.Wardlaw@ed.ac.uk

© 2010 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.109.566307

Downloaded from http://stroke.ahajournals.org on June 8, 2013
prospective register of consecutive stroke patients presenting to an academic teaching hospital, and a prospective study of acute lacunar stroke. A stroke physician assigned a classification using the Oxfordshire Community Stroke Project Classification, measured the National Institutes of Health Stroke Scale score (NIHSS), and assessed vascular risk factors. Written consent was obtained from all patients. Both studies were approved by the local research ethics committee.

We included patients with baseline imaging with either MRI (diffusion-weighted imaging [DWI], T2-weighted imaging, and fluid-attenuated inversion recovery [FLAIR]) or CT brain imaging. We included patients with or without an acute lacunar infarct on MRI (because the high sensitivity of magnetic resonance enabled us to exclude as fully as possible patients with cortical infarction), but on CT, we only included patients with a visible recent lacunar infarct in the appropriate area for symptoms (because the low sensitivity of a negative CT would not allow us to exclude cortical stroke, which may give rise to lacunar-type symptoms). Baseline and follow-up imaging was performed unblinded to clinical symptoms (to be certain of correct identification of the index lesion) but blind to all other clinical data.

At follow-up, a “definite” cavity was defined as a lesion of CSF, or near-CSF, attenuation on CT, or of CSF signal on T2-weighted imaging or FLAIR MRI, at the site of the index infarct (Figure 1). A “possible” cavity was defined on FLAIR as a lesion of spongiform appearance with areas of marked hypointensity showing early confluence at the site of the index infarct. “Definite” (CT and MRI) and “possible” cavitation (FLAIR only) were considered together as “any evidence of cavitation.” In cases of uncertainty, images were reviewed by a second experienced neuroradiologist (J.M.W.). Lacunes developing elsewhere in the brain between baseline and follow-up imaging were also recorded; correlation with appropriate symptoms was not sought for these lesions.

Statistical Analysis
We calculated proportions with any evidence of, and definite, cavitation (with 95% CIs) in the whole group, the “pure” subgroup and the subgroup with an index infarct. We assessed statistical significance of differences in baseline characteristics and imaging features in patients with “definite” and any (“definite” plus “possible”) cavitation of the index lacunar infarct in the whole group and “pure” subgroup. We used the Student t test for continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and the χ² test for dichotomous variables. We performed multivariate analysis using logistic regression to determine independent predictors of cavitation, allowing one variable per 5 outcome events. We obtained adjusted odds ratios (ORs) and 95% CIs, comparing patients with “any” and “definite” cavitation versus those without. For “any” cavitation, we used significant variables from univariate analysis (hypertension, diabetes, time to follow-up), and concomitant lacunes at baseline and deep atrophy, considered more likely than other features to be associated with cavitation; for “definite” cavitation, we included time to follow-up (significant on univariate analysis), hypertension (significant in univariate analysis for “any” cavitation), and deep atrophy. We dichotomized scores for WMLs (Fazekas 0 to 1 versus 2 to 3; van Swieten 0 versus 1 to 2), brain tissue loss, and enlarged perivascular spaces (0 to 2 versus 3 to 4) attributable to low frequencies. We also examined the proportion with any progression of cavitation of existing “spongiform” nonindex lesions. All statistical analyses were performed using Minitab (Version 15; Minitab Inc).

Results
Ninety patients met our inclusion criteria. Mean age was 67±12 years, 48 (53%) had a history of hypertension, 18 (20%) diabetes, and 12 (13%) a history of previous stroke. A “pure” subgroup of 47 of 90 (52%) patients had a DWI-positive acute lacunar infarct and follow-up MRI (Table 1); 6 had baseline MRI and follow-up CT; and 21 had baseline CT with either CT or MRI follow-up.

Of the 74 of 90 (82%) patients with an acute index lacunar infarct, 45 (60%) were in the centrum semiovale, 18 (24%) in the brain stem; correlation with appropriate symptoms was not sought. Cavity was performed unblinded to clinical symptoms (to be certain of correct identification of the index lesion) but blind to all other clinical data.

At follow-up, a “definite” cavity was defined as a lesion of CSF, or near-CSF, attenuation on CT, or of CSF signal on T2-weighted imaging or FLAIR MRI, at the site of the index infarct (Figure 1). A “possible” cavity was defined on FLAIR as a lesion of spongiform appearance with areas of marked hypointensity showing early confluence at the site of the index infarct. “Definite” (CT and MRI) and “possible” cavitation (FLAIR only) were considered together as “any evidence of cavitation.” In cases of uncertainty, images were...
group, 7 of 47 (18%) had definite cavitation, and an additional 7 showed possible cavitation, making a total of 14 of 47 with any evidence of cavitation (30%; 95% CI, 17% to 43%).

In sensitivity analyses to exclude patients without a DWI-positive lesion at baseline (ie, 74 patients with visible lacunar infarction), definite cavitation was visible in 18 (24%; 95% CI, 15% to 34%), and possible cavitation in an additional 7. Therefore, 25 of 74 (34%; 95% CI, 23% to 45%) showed any evidence of cavitation. In one case, an acute lacunar infarct on baseline CT was not visible on follow-up MRI.

In the entire group of 90 patients, cavitation was associated with increasing time to follow-up imaging in those with both definite and any evidence of cavitation on univariate analysis ($P=0.0003$ and $P=0.03$, respectively; Tables 2 and 3) and with deep atrophy in patients with definite cavitation ($P=0.03$). Figure 2 shows the time from stroke onset to follow-up imaging in patients with any evidence of, and definite, cavitation. In patients with any evidence of cavitation, hypertension and diabetes were negatively associated with cavitation ($P=0.01$ and 0.02, respectively). In multivariate analysis, increasing time to follow-up and deep atrophy remained significant for patients with definite cavitation (OR, 1.81; 95% CI, 1.12% to 2.92% and OR, 3.24; 95% CI, 1.02% to 10.27%). No other patient-related, stroke-related, or imaging-related variables (age, NIHSS, and all

Table 1. Type of Brain Imaging, Including Follow-Up Appearance of Symptomatic Lacunar Infarct (n=90)

<table>
<thead>
<tr>
<th>Type of Imaging</th>
<th>Baseline Imaging</th>
<th>Follow-Up Imaging</th>
<th>Infarct Visible at Follow-Up</th>
<th>Cavitation of Infarct at Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline DWI</td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MRI</td>
<td>Yes</td>
<td>Yes</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>MRI</td>
<td>Yes</td>
<td>No</td>
<td>4</td>
<td>n/a</td>
</tr>
<tr>
<td>MRI</td>
<td>No</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CT</td>
<td>MRI</td>
<td>n/a</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>CT</td>
<td>CT</td>
<td>n/a</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

**Pure subgroup.

definite and any evidence of cavitation on univariate analysis ($P=0.0003$ and $P=0.03$, respectively; Tables 2 and 3) and with deep atrophy in patients with definite cavitation ($P=0.03$). Figure 2 shows the time from stroke onset to follow-up imaging in patients with any evidence of, and definite, cavitation. In patients with any evidence of cavitation, hypertension and diabetes were negatively associated with cavitation ($P=0.01$ and 0.02, respectively). In multivariate analysis, increasing time to follow-up and deep atrophy remained significant for patients with definite cavitation (OR, 1.81; 95% CI, 1.12% to 2.92% and OR, 3.24; 95% CI, 1.02% to 10.27%). No other patient-related, stroke-related, or imaging-related variables (age, NIHSS, and all

Table 2. Clinical and Imaging Associations of Cavitation in Patients With Any Evidence of Cavitation (n=90)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Any Evidence of Cavitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Where Not 90</td>
</tr>
<tr>
<td>Age in years (mean±SD)</td>
<td>68.3±12.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>NIHSS median score (range)</td>
<td>86</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Imaging parameters</td>
<td></td>
</tr>
<tr>
<td>Onset to assessment, median days (range)</td>
<td>16 (0–43)</td>
</tr>
<tr>
<td>Onset to baseline imaging, median days (range)</td>
<td>17 (0–43)</td>
</tr>
<tr>
<td>Onset to follow-up imaging, median days (range)</td>
<td>102 (39–1722)</td>
</tr>
<tr>
<td>Lacunar size mm (mean±SD)</td>
<td>74</td>
</tr>
<tr>
<td>Other lacunes baseline</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Deep* WML dichotomized 0:1 vs 2:3</td>
<td>80</td>
</tr>
<tr>
<td>Periventricular* WML dichotomized 0:1 vs 2:3</td>
<td>80</td>
</tr>
<tr>
<td>Anterior† WML dichotomized 0 vs 1:2</td>
<td>10</td>
</tr>
<tr>
<td>Posterior† WML dichotomized 0 vs 1:2</td>
<td>10</td>
</tr>
<tr>
<td>Deep atrophy dichotomized 0:1 vs 2:3</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Superficial atrophy dichotomized 0:1 vs 2:3</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Basal ganglia EPVS dichotomized 0:2 vs 3:4</td>
<td>80</td>
</tr>
<tr>
<td>Centrum semiovale EPVS dichotomized 0:2 vs 3:4</td>
<td>80</td>
</tr>
</tbody>
</table>

*Fazekas scale; †van Swieten scale.
EPVS indicates enlarged perivascular spaces.
other features of small vessel disease) were associated with any evidence of, or definite, cavitation.

In the subgroup of 47 patients with a positive baseline diffusion scan and follow-up MRI, definite cavitation was associated on univariate analysis with increasing time to follow-up ($P=0.009$) and superficial atrophy ($P=0.03$). In those with any evidence of cavitation, hypertension was negatively associated with cavitation ($P=0.009$). No other clinical or imaging features were associated with cavitation in either the whole group or “pure” subgroup.

At baseline, 13 of 90 patients (14%) had subcortical spongiform lesions separate from the index acute lacunar infarct (single lesion in 10; 2 lesions in 3). Progression to a definite cavity on follow-up occurred in 2 of these patients, but in neither patient did the index lesion show any evidence of cavitation. From the 11 spongiform lesions that did not progress to a definite cavity, the index lacunar infarct showed progression to a definite cavity in 2 patients.

At baseline, 31 of 90 (34%) patients had concomitant lacunes. Of these 31, 18 (58%) had higher WML scores than the 17 of 59 (29%) without concomitant lacunes at baseline ($P=0.007$); 4 of 31 (4%) patients developed new lacunes between baseline and follow-up imaging (unrelated to the index lesion) over an interval ranging from 76 to 185 days.

**Discussion**

The proportion of symptomatic lacunar infarcts that undergo cavitation to lacunes is unknown. In this study, one fifth of patients with acute lacunar ischemic stroke showed definite cavitation on follow-up imaging at a median of 227 days (range 54 to 1722) after stroke onset. In a “pure” subgroup (DWI-positive infarct with follow-up MRI), 15% of patients showed definite cavitation. Definite cavitation was associated with increasing time to follow-up in univariate and multivariate analysis, but not with age, NIHSS, lesion size or location, or other features of cerebral small vessel disease, including other lacunes.
The association with increasing time to follow-up remained significant in the “pure” subgroup. If these proportions are similar in other populations, up to four fifths of symptomatic lacunar infarcts may resemble, and be misidentified as, WML at any time up to \( \approx 5 \) years after stroke, possibly longer.

Definite cavitation was associated with deep atrophy in univariate and multivariate analysis and with superficial atrophy in the “pure” subgroup. Our data indicate that age, stroke severity, and other features of small vessel disease (WML, concomitant lacunes, and enlarged perivascular spaces) were not linked to cavitation. On the other hand, hypertension was negatively associated with cavitation in patients with any evidence of cavitation (in both the whole group and “pure” subgroup) and diabetes in the whole group.

The main strengths of our study are that patients were carefully characterized clinically to be certain of the clinical diagnosis of lacunar stroke, all data were collected according to prespecified criteria, and most patients had baseline MRI, including diffusion. Thus, we can pinpoint precisely when the index lesion started and follow its evolution with precision. The 2 studies from which these data are derived were performed prospectively in the same hospital, using the same data collection, case ascertainment, diagnostic methods, physicians, radiologists, and imaging equipment. We tested associations in the whole, as well as “pure” subgroup and found that they were similar.

Potential limitations were inclusion of a small proportion of patients without a lesion on MRI at baseline; some patients with nonlacunar stroke may have been inadvertently included, despite careful clinical characterization. This may have meant we underestimated the proportion of patients with cavitation. However, after excluding MRI-negative patients, proportions with any evidence of and definite cavitation were similar to the whole group, and to the “pure” subgroup, with overall point estimates \( \approx 15\% \) to \( 33\% \).

Minimum time to follow-up imaging was relatively short, but several patients without definite cavitation had follow-up imaging at \( \approx 4 \) years, and we identified patients with definite cavitation at 54 days. Sample size was relatively small and precluded more complex analyses, so we cannot exclude weak associations between cavitation and imaging-, stroke-, or patient-related features. We were unable to investigate the influence of some factors (eg, duration of symptoms or contrast enhancement) because this information was not collected. Follow-up timing was not fixed, with variable times to follow-up; in the study of lacunar stroke, follow-up was at between one and 3 months, and all patients were recalled for imaging (although not all attended), whereas in the stroke registry, follow-up mostly occurred if the patient developed new symptoms. These selection criteria in the original studies may have influenced cavitation detection rates. Larger studies with fixed follow-up time points are required to obtain more precise data on cavitation.

No previous studies have examined cavitation rates in symptomatic lacunar ischemic stroke, so there is little information with which to draw comparisons. Longitudinal studies show that WML and lacunes increase in number over time, with hypertension (among others) being a risk factor for new lacunes, and diabetes and hypertension being risk factors (among others) for WML progression. We found that increased WML severity was associated with concomitant lacunes on baseline imaging, in agreement with previous studies. Gouw found that WML progression was modestly correlated with number of new lacunes at follow-up; we were unable to investigate for such a correlation. The apparent coassociation of lacunes and WML suggests that lacunes may represent the extreme end of a spectrum of small vessel changes.

Factors associated with cavitation have been investigated in multiple sclerosis; in longitudinal studies, a ring-enhancing lesion pattern is associated with cavity development, but predictive power is limited because of variability in cavity development, with some evidence that cavitation is patient-specific. Differences in multiple sclerosis lesion evolution in the same patient have also been demonstrated, suggesting local inflammatory reaction or location may be more relevant than individual susceptibility in leading to permanent axonal loss. Duration of symptoms may influence whether cavitation occurs (we did not record this), although we found no association with NIHSS, another marker of stroke severity. In animals, duration of middle cerebral artery occlusion has been shown to influence infarct cavitation.

The molecular processes underlying cerebral tissue damage and repair, through the stages of tissue infarction and “rarefaction,” leading to gliosis and cavitation, are complex, and as yet incompletely identified. Histologically, a phase of chronic inflammation, including cavitation, was identified from 10 days to 53 years in patients with cortical and lacunar infarction. In our study, the earliest time at which a lesion demonstrated any evidence of cavitation was 39 days, and 54 days for definite cavitation. Matrix metalloproteinases are important factors for tissue remodeling implicated in all main cerebrovascular diseases including ischemia and WML in vascular dementia. Higher levels of matrix metalloproteinase-9 may be related to neurological deterioration in the first 7 days after acute lacunar infarction, but there is no information on whether high matrix metalloproteinase levels are associated with cavitation.

Thirteen patients in our study had spongiform lesions (possible cavities) separate from the index lesion at baseline; in 2 patients, these progressed to definite cavities, but the index lesion showed no cavitation. Similarly, 2 patients with definite cavitation of the index lesion showed no progression to cavitation in nonindex spongiform lesions. Cavitation may therefore occur on a “per lesion” rather than “per patient” basis.

What are the implications if only one of 5 acute symptomatic lacunar infarcts becomes a cavity and the other 4 continue to resemble WML? In epidemiology (including risk factor) and pathophysiology studies of lacunar infarction, which only count lacunes as old lacunar infarcts, the true burden of lacunar disease may be underestimated by as much as 5 times. With the difficulties in distinguishing between WML and noncavitated lacunar infarction, consideration should be given to abandoning the term WML in favor of a term such as small vessel changes, correlating acute lacunar infarcts, WML, and lacunes with symptoms wherever possible. Our findings should be confirmed in larger prospective studies of acute lacunar stroke, with follow-up at prespecified time intervals.
Summary
Lacunes are often counted in epidemiological studies as old lacunar infarcts, but we found definite cavitation of symptomatic lacunar infarcts occurring in only one fifth of patients; most lacunar infarcts may continue to resemble WML. The true burden of lacunar stroke disease on imaging may thus be substantially underestimated in studies that only count lacunes. We found that cavitation was associated with increasing time to follow-up imaging and deep cerebral atrophy. Larger prospective studies, with prespecified follow-up intervals, are required.

Acknowledgments
We thank the patients and caregivers and the doctors, administrators, radiographers, stroke clinical audit, and programming staff who contributed to the collection of data. We are especially grateful for clinical input from Professors Charles Warlow and Peter Sandercoc, neuroradiological input from Dr Andrew Farrall, programming assistance from Aidan Hutchison and Mike McDowall, and administrative support from Isabel Jennings.

Sources of Funding
The stroke research register, C.L.S., and C.A.J. were funded by the Wellcome Trust (grant number 063668; Clinician Scientist Award to C.L.S.) and the Binks Trust. The Lacunar Stroke Study was funded by the Chief Scientist Office of the Scottish Executive (grant number 217 NTU R43933) and the Wellcome Trust (grant number 075611). J.M.W. was funded by the Scottish Funding Council SINAPSE Initiative (Scottish Imaging Network, A Platform for Scientific Excellence). G.M.P. was funded by NHS Lothian R&D and the Initiative (Scottish Imaging Network, A Platform for Scientific Excellence). J.M.W. was funded by the Scottish Funding Council SINAPSE Initiative (Scottish Imaging Network, A Platform for Scientific Excellence).

Disclosures
None.

References