Large Subcortical Infarcts

Clinical Features, Risk Factors, and Long-Term Prognosis Compared With Cortical and Small Deep Infarcts

Patricia H.A. Halkes, MD; L. Jaap Kappelle, MD; Jan van Gijn, MD, FRCP, FRCPE; Iris van Wijk, MD; Peter J. Koudstaal, MD; Ale Algra, MD

Background and Purpose—In this study we compared risk factors, clinical features, and stroke recurrence in a large series of patients with large subcortical, cortical, or small deep infarcts.

Methods—Patients with a transient or minor ischemic attack (modified Rankin Scale grade of $\leq 3$) who had a single relevant supratentorial infarct of presumed noncardioembolic origin on CT were classified as suffering from a large subcortical (n = 120), small deep (n = 324), or cortical (n = 211) infarct. Mean follow-up was 8 years. Rates of recurrent stroke were compared with Cox regression.

Results—The clinical deficits caused by large subcortical infarcts resembled either those of a cortical or those of a small deep infarct. Risk factor profiles were similar in the 3 groups. The rate of recurrent stroke in patients with a large subcortical infarct (25/120; 21%) did not differ from that of patients with a cortical infarct (46/211; 22%) or with a small deep infarct (60/324; 19%). After adjustment for age, sex, and vascular risk factors, hazard ratios for recurrent stroke of large subcortical and cortical infarcts were 1.05 (95% CI, 0.65 to 1.70) and 1.17 (95% CI, 0.79 to 1.73), respectively, compared with small deep infarcts.

Conclusions—Clinical features, risk factor profiles, and stroke recurrence rate in patients with a large subcortical infarct only differ slightly from those in patients with small deep or cortical infarcts. (Stroke. 2006;37:1828-1832.)

Key Words: classification ■ epidemiology ■ stroke, ischemic

Ischemic strokes are often categorized into small-vessel lesions and large-vessel lesions. This distinction can usually be made by means of the clinical features and more reliably by CT or MRI scanning. A third type of infarction is the large subcortical infarct, also termed giant lacune. They are located in the carotid territory, like most symptomatic small deep infarcts, but are larger and supposedly not caused by small-vessel disease.

Clinical features, risk factors, and long-term outcome of these infarcts have been studied in small series, but without comparison with other types of infarction. In the present study we evaluated clinical features, risk factors, overall outcome, and type of recurrent infarction in a large series of patients with recent cerebral ischemia of presumed arterial origin who participated in a large clinical trial. We compared these characteristics with those of patients with a small deep infarct or with a cortical infarct.

Subjects and Methods

Patients participated in the Dutch TIA Trial, a multicenter trial performed in the Netherlands from 1986 to 1990. In this randomized, double-blind, controlled trial, the preventive effects of 30 and 283 mg acetylsalicylic acid per day were compared in patients with a transient ischemic attack (TIA) or minor stroke (modified Rankin Scale score of $\leq 3$). In addition, in eligible patients the effects of 50 mg of atenolol versus placebo were tested. A total of 3150 patients from 63 different hospitals were enrolled. Exclusion criteria were a possible cardioembolic source and clotting disorders. The mean follow-up was 2.6 years. Risk factors such as hypertension or hyperlipidemia were considered present if the patient had a history of this disorder or received treatment. A CT scan of the brain was mandatory for each patient, except for those with transient monocular blindness.

Additional follow-up data were obtained from the Life Long After Cerebral ischemia (LiLAC) study, in which the follow-up of 2447 of 3150 Dutch TIA Trial participants was extended to a mean period of 10 years after inclusion in the Dutch TIA Trial.

During the study period, all patients received aspirin in a dose of 38 or 283 mg per day. The Dutch TIA Trial showed that both doses were equally effective in the prevention of vascular events. After the trial, all patients were treated by their neurologist according to current international guidelines.

Stroke at Baseline

For the purpose of the present study, all baseline CT scans were reviewed by a neurologist and a neurologist in training to select
patients with a single “relevant” supratentorial infarct on the CT scan, ie, the location of the infarct matched the clinical features. These infarcts were classified as large subcortical, small deep, or cortical. Large subcortical infarcts were diagnosed if they were located in the basal ganglia, internal capsule, or corona radiata, with a diameter between 15 and 40 mm. Small deep infarcts were defined according to the same locations but with a diameter of <15 mm. Cortical infarcts were defined as wedge-shaped, superficial ischemic lesions in the territory of one of the large major cerebral arteries or lesions in a border zone; the underlying white matter might be involved as well.

**Stroke During Follow-Up**

All patients in the Dutch TIA Trial visited their neurologist or general practitioner every 4 months. A stroke during follow-up was considered “definite” if relevant clinical features were accompanied by a fresh infarct or hemorrhage on a repeat CT scan and “probable” if clinical deficits without CT changes caused an increase in handicap of at least 2 grades on the modified Rankin Scale.13,14,16 For the present study, clinical reports and CT scans of all strokes during the follow-up of the Dutch TIA Trial and LiLAC were reviewed again. Two investigators independently reviewed these and adjudicated, without any information on the baseline strokes, whether the infarcts on follow-up were caused by small- or large-vessel disease. If findings on the scan were not conclusive, they relied on clinical deficits. If the investigators did not agree, a third opinion of a neurologist was requested. Clinical features suggesting small-vessel disease were pure motor stroke, pure sensory stroke, sensorimotor stroke, or ataxic hemiparesis.4 Large-vessel disease was assumed when cortical functions were involved, ie, dysphasia, visuospatial disorder, or hemianopia, with or without motor or sensory deficits. Ischemia in the posterior fossa was diagnosed with at least 2 of following symptoms: vertigo, dysarthria, dysphagia, diplopia, and ataxia. If CT or MRI scans were not available, the scan report of the attending neurologist was used. If no detailed information on the recurrent event was available but stroke had been diagnosed by a physician in a nursing home, it was classified as “stroke with undetermined clinical syndrome.” If no physician had confirmed a stroke reported to us, it was considered “possible stroke” and excluded in our analysis.

### TABLE 1. Baseline Characteristics and Vascular Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Cortical (n=211)</th>
<th>Large Subcortical (n=120)</th>
<th>Small Deep (n=324)</th>
<th>Total (n=655)</th>
<th>( \chi^2 ) Large Subcortical vs Cortical; ( P )</th>
<th>( \chi^2 ) Large Subcortical vs Small Deep; ( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>144 (68)</td>
<td>79 (66)</td>
<td>221 (68)</td>
<td>444 (68)</td>
<td>0.20; 0.65</td>
<td>0.23; 0.64</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>63 (10.3)</td>
<td>66 (9.4)</td>
<td>65 (9.7)</td>
<td>65 (9.9)</td>
<td>0.05†</td>
<td>0.99†</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>88 (42)</td>
<td>58 (48)</td>
<td>146 (45)</td>
<td>292 (45)</td>
<td>1.36; 0.24</td>
<td>0.37; 0.54</td>
</tr>
<tr>
<td>Untreated (% of positive history)</td>
<td>22 (25)</td>
<td>21 (37)</td>
<td>39 (27)</td>
<td>82 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current SBP ≥160 mm Hg (%)</td>
<td>90 (43)</td>
<td>64 (53)</td>
<td>182 (56)</td>
<td>336 (51)</td>
<td>3.51; 0.06</td>
<td>0.29; 0.59</td>
</tr>
<tr>
<td>Current DBP ≥90 mm Hg (%)</td>
<td>139 (66)</td>
<td>77 (64)</td>
<td>221 (68)</td>
<td>437 (67)</td>
<td>0.10; 0.75</td>
<td>0.65; 0.42</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>96 (46)</td>
<td>61 (51)</td>
<td>149 (46)</td>
<td>306 (47)</td>
<td>0.87; 0.35</td>
<td>0.83; 0.36</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>18 (9)</td>
<td>14 (12)</td>
<td>35 (11)</td>
<td>67 (10)</td>
<td>0.86; 0.35</td>
<td>0.67; 0.80</td>
</tr>
<tr>
<td>History of hyperlipidemia (%)</td>
<td>5 (2)</td>
<td>3 (3)</td>
<td>10 (3)</td>
<td>18 (3)</td>
<td>0.01; 0.94</td>
<td>0.11; 0.75</td>
</tr>
<tr>
<td>History of myocardial infarction (%)</td>
<td>24 (11)</td>
<td>11 (9)</td>
<td>24 (7)</td>
<td>59 (9)</td>
<td>0.39; 0.53</td>
<td>0.37; 0.54</td>
</tr>
<tr>
<td>History of claudication (%)</td>
<td>11 (5)</td>
<td>4 (3)</td>
<td>13 (4)</td>
<td>28 (4)</td>
<td>0.63; 0.43</td>
<td>0.11; 0.74</td>
</tr>
<tr>
<td>History of vascular surgery (%)</td>
<td>8 (4)</td>
<td>1 (1)</td>
<td>15 (5)</td>
<td>24 (4)</td>
<td>2.53; 0.11</td>
<td>3.63; 0.06</td>
</tr>
<tr>
<td>Heart rate ≥70 bpm (%)</td>
<td>125 (59)</td>
<td>77 (64)</td>
<td>191 (59)</td>
<td>393 (60)</td>
<td>0.78; 0.38</td>
<td>1.00; 0.32</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (%)*</td>
<td>5 (2)</td>
<td>5 (4)</td>
<td>15 (5)</td>
<td>25 (4)</td>
<td>0.89; 0.35</td>
<td>0.06; 0.82</td>
</tr>
<tr>
<td>White matter lesion on brain CT (%)</td>
<td>12 (6)</td>
<td>10 (8)</td>
<td>47 (15)</td>
<td>69 (11)</td>
<td>0.86; 0.35</td>
<td>0.98; 0.08</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

*Known for 638 patients.

†P, independent samples \( t \) test.

### Statistical Analysis

Baseline characteristics, vascular risk factors, clinical features at baseline, and clinical syndromes associated with subsequent strokes were compared between the 3 types of infarct with \( \chi^2 \) values, \( t \) tests, and Mann–Whitney \( U \) tests. The frequency of recurrent stroke in the 3 groups was compared with Cox proportional hazards analysis and reported with hazard ratios and corresponding 95% CIs. In multivariate analysis, hazard ratios were adjusted for known risk factors of vascular disease.

### Results

Of the 2899 patients with a transient or nondisabling ischemic attack who underwent CT scanning, 732 patients (25%) had a single relevant ischemic lesion at baseline. These were classified as large subcortical in 120 patients (16%), as small deep in 324 patients (44%), and as cortical in 211 patients (29%). In 77 patients (11%), the symptomatic infarct on the CT scan could not be assigned to any of these categories (ie, combination of cortical and subcortical infarct or infarct in posterior fossa); these were excluded from the present study.

### Baseline

Baseline characteristics and vascular risk factors of the 655 patients are summarized in Table 1. Patients with a large subcortical infarct only differed slightly with respect to the vascular risk factor profile from patients with a small deep infarct or a cortical infarct.

The clinical features of the stroke at baseline of patients with a large subcortical infarct were different in distribution from those of patients with a cortical or small deep infarct (Table 2). In this group, 63% presented with a lacunar syndrome versus 35% of patients with a cortical infarct and 78% of those with a small deep infarct (\( P<0.05 \)). Patients with a cortical infarct more often showed features of cortical dysfunction than patients with a large subcortical infarct and patients with a small deep infarct (62% versus 32% versus...
and more often had a complete or partial hemianopia (29% versus 6% versus 2%; \(P<0.05\)).

**Follow-Up**

In the Dutch TIA Trial, no patients were lost to follow-up. For the patients selected for LiLAC, follow-up was nearly complete: 99%. Of the 655 patients, 503 (77%) also participated in LiLAC. For these patients, a mean follow-up of 9.2 years was available versus 2.8 years for the remaining 152 patients. A total of 131 patients suffered a recurrent stroke (Table 3).

Of patients with a cortical infarct at baseline, 46 (22%) had a recurrent stroke; of those with a large subcortical infarct at baseline, 25 (21%) had a recurrent stroke; and of those with a small deep infarct at baseline, 60 (19%), had a recurrent stroke.

The adjusted hazard ratio for recurrent stroke was 1.05 (95% CI, 0.65 to 1.70) for patients with a large subcortical infarct at baseline and 1.17 (95% CI, 0.79 to 1.73) for patients with a cortical infarct at baseline compared with patients with a small deep infarct at baseline.

The 2 investigators who adjudicated the stroke findings on follow-up agreed on classification in all but 2 cases. In 46% of patients with recurrent stroke, after a subcortical infarct at baseline the new clinical syndrome was cortical. This was the case for 67% of patients with a cortical infarct at baseline and for 37% of patients with a small deep infarct at baseline (\(P<0.05\)). Of the patients with recurrent stroke and a large subcortical infarct at baseline, a lacunar syndrome was found in 42% versus 14% of patients with a cortical infarct at baseline and 41% of patients with a small deep infarct at baseline (\(P<0.05\)).

The patients with a large subcortical infarct at baseline had their recurrent stroke after a median interval of 2.4 years after the index event. New small deep infarcts occurred after a longer interval (median = 5.1 years) than recurrent cortical strokes (median = 1.7 years). For patients with a small deep infarct at baseline, the recurrent stroke occurred after a median of 4.3 years (4.7 years for small deep strokes and 2.8 years for cortical strokes), and for patients with a cortical infarct at baseline, the stroke occurred after a median interval of 2.8 years (4.6 years for small deep strokes and 2.1 years for cortical strokes).

**Discussion**

We found no significant differences in vascular risk profile, clinical features, and the rate of recurrent stroke between patients with a large subcortical infarct and those with a cortical or small deep infarct.

The generalizability of our study results may be limited by the selection processes of the study population. All patients were referred to a neurologist and consented to participate in a clinical trial. Patients, however, originated from 50 centers in the Netherlands, both university medical centers (5) and general hospitals (45). The generalizability is also somewhat limited by the fact that only patients with a relevant ischemic lesion that was visible on a CT scan were included in our study, but this was the only way that large subcortical infarcts could be identified.
Part of our data were also used in a previous study, in which the clinical course in patients with an infarct caused by small-vessel disease was compared with that in patients with an infarct caused by large-vessel disease.17 In that study, patients with a large subcortical infarct were included among those with large-vessel disease. The number of patients in the present study was much smaller because the inclusion criteria were more strict than those in the previous study. This was because in the present study only patients with a single symptomatic infarct at baseline scan were included, whereas the distinction between small- and large-vessel disease in the previous study was based on clinical features if the CT scan was not conclusive. The number of events, however, was much larger in the present study because of the extended follow-up.15 Although the relatively small number of patients in this study might limit the conclusions, our study cohort represents the largest series of patients with a large subcortical infarct.

Four methodological issues merit consideration. First, the definition of large subcortical infarcts differs between studies. We defined all infarcts in the subcortical region with a diameter between 15 and 40 mm as large subcortical,5,6,10,18 whereas others used a diameter of 20 mm as the lower limit.8,9,11,12

Second, in previous studies by others, approximately half of the patients with a large subcortical infarct had a potential cardioembolic source. Because these patients were excluded from the Dutch TIA Trial, our analyses of the risk factor profile apply only to patients with cerebral ischemia of noncardioembolic origin. Whereas in our study the vascular risk profile of patients with a large subcortical infarct did not differ from that of patients with a small deep infarct or with a cortical infarct, in patients with subcortical infarcts of both noncardioembolic and cardiac origin the risk profile may more closely resemble that of a cortical infarct because of the greater proportion of cardioembolic sources in these types of infarcts.6,8–10,12 Moreover, in a recent large systematic review, atrial fibrillation and carotid stenosis were the only 2 risk factors shown to differ between patients with lacunar and nonlacunar infarcts.19 Unfortunately, in the Dutch TIA Trial we did not collect information about the presence of a carotid stenosis. Consequently, we unfortunately could not determine whether such a difference also exists in our cohort, which would have been interesting because it would have provided a clue about the most likely pathogenesis of the large subcortical infarcts.

Third, in previous studies a higher stroke recurrence rate was found in patients with large-vessel disease than in patients with small-vessel disease, whereas in our study there is no difference in recurrence rate between the 3 groups. This is probably the result of our inclusion criteria. On the one

### TABLE 3. Stroke and Death During Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Cortical (n=211)</th>
<th>Large Subcortical (n=120)</th>
<th>Small Deep (n=324)</th>
<th>Total (n=655)</th>
<th>$\chi^2$ Large Subcortical vs Cortical; $P$</th>
<th>$\chi^2$ Large Subcortical vs Small Deep; $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stroke (%)</td>
<td>46 (22)</td>
<td>25 (21)</td>
<td>60 (19)</td>
<td>131 (20)</td>
<td>0.04; 0.84</td>
<td>0.30; 0.58</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>1.03 (0.70–1.52)</td>
<td>1.08 (0.68–1.72)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted* hazard ratio (95% CI)</td>
<td>1.14 (0.77–1.68)</td>
<td>1.06 (0.66–1.70)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted† hazard ratio (95% CI)</td>
<td>1.17 (0.79–1.73)</td>
<td>1.05 (0.65–1.70)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Assessment of stroke (n, %‡)

<table>
<thead>
<tr>
<th></th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
<th>Stroke, unknown cause</th>
<th>Fatal ischemic stroke</th>
<th>Fatal hemorrhagic stroke</th>
<th>Fatal stroke, unknown cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia</td>
<td>25 (54)</td>
<td>9 (36)</td>
<td>26 (43)</td>
<td>9 (15)</td>
<td>14 (22)</td>
<td>19 (30)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4 (9)</td>
<td>1 (4)</td>
<td>5 (8)</td>
<td>1 (2)</td>
<td>3 (2)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>No ischemia/hemorrhage</td>
<td>12 (26)</td>
<td>11 (44)</td>
<td>15 (25)</td>
<td>38 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No scan made</td>
<td>5 (11)</td>
<td>4 (16)</td>
<td>10 (17)</td>
<td>19 (15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical syndrome (n, %§)

<table>
<thead>
<tr>
<th></th>
<th>Cortical</th>
<th>Lacunar</th>
<th>Vertebrobasilar</th>
<th>Undeterminable</th>
<th>Median interval baseline follow-up stroke, y</th>
<th>Death from all causes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia</td>
<td>28 (67)</td>
<td>6 (14)</td>
<td>3 (7)</td>
<td>5 (12)</td>
<td>2.8</td>
<td>110 (52)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4 (9)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>2.4</td>
<td>62 (52)</td>
</tr>
<tr>
<td>No ischemia/hemorrhage</td>
<td>12 (26)</td>
<td>10 (42)</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>4.3</td>
<td>162 (50)</td>
</tr>
<tr>
<td>No scan made</td>
<td>5 (11)</td>
<td>10 (42)</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>4.3</td>
<td>334 (51)</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex; †adjusted for age, sex, history of hypertension, white matter lesions on CT or MRI scan, and left ventricular hypertrophy; ‡percentage of all strokes during follow-up; §percentage of nonhemorrhagic strokes during follow-up; \( \chi^2 \); Mann–Whitney U test.
hand, we only included patients with a relevant ischemic lesion on CT scan, which probably resulted in relatively few patients with small, lacunar TIA, who are probably less likely to experience a recurrent stroke. On the other hand, in the Dutch TIA Trial all patients with a modified Rankin Scale score $\geq 3$ were excluded, i.e., patients who were severely disabled as result of the stroke. That group includes many patients with large cortical infarcts and a high risk of recurrence. Exclusion of the extremes of the stroke severity spectrum probably resulted in a more or less similar prognosis for the patients with large- and small-vessel disease in the present study. Another explanation for the lower than expected recurrence rate is the definition of recurrent stroke in this study. We used the definition that was adopted in the Dutch TIA Trial, when patients had to have a (temporary) change in Rankin Scale score of $\geq 2$ points when there was no detectable lesion on CT scan. This may have led to an understimation of recurrent strokes that caused minor symptoms, which are often associated with small, lacunar strokes. A final possible explanation for the similar recurrence rate is that recent evidence suggests that there might be no difference in recurrence rates between lacunar and nonlacunar infarction in the long term.

Fourth, ideally, stroke classification in epidemiological studies is based on MRI. Because of the time period of this study, no MRI was performed. Moreover, not all patients with a recurrent stroke had a CT at the time of the recurrent stroke. This might have influenced the classification of recurrent stroke because $\approx 10\%$ to $20\%$ of strokes that are lacunar clinically are actually due to cortical infarct and vice versa. Future studies in this field should preferably use MRI for the classification of both index and recurrent stroke.

Our study supports the notion that a distinction between large subcortical and other infarcts is difficult to make on clinical grounds alone. Patients with a large subcortical infarct can have signs of cortical involvement, such as aphasia or hemineglect, but also signs of a small deep infarct, for example, a pure motor stroke. The vascular risk factors of patients with large subcortical infarcts fail to show a distinctive profile. Our study shows that recurrence rates and clinical syndromes of recurrent strokes also show overlap with those of either small deep infarcts or cortical infarcts. We conclude from the data in this study that the clinical distinction between large subcortical infarcts and other infarcts in the acute stage seems to be unreliable and does not appear to have clear practical implications.

**References**


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