Recurrent stroke after transient ischaemic attack or minor ischaemic stroke: does the distinction between small and large vessel disease remain true to type?

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Abstract

The incidence and vascular type of recurrent ischaemic stroke was studied in patients with supratentorial transient ischaemic attacks or non-disabling ischaemic strokes, who were treated with aspirin (30 or 283 mg). Patients were divided into groups with small vessel disease (SVD) (n = 1216) or large vessel disease (LVD) (n = 1221) on the grounds of their clinical features and CT at baseline. Patients with evidence of both SVD and LVD (n = 180) were excluded from further analyses. During follow up (mean 2·6 years) annual stroke rate was 3·6% in both groups. Of the 107 patients with SVD at baseline who had recurrent strokes, 83 proved to have an identifiable infarct: 30 (28%) again had a small vessel infarct, 39 (36%) had a large vessel ischaemic stroke and in 14 (13%) the recurrent ischaemic stroke was in the posterior fossa. Of the 110 patients with LVD at baseline and recurrent stroke, 91 had an identifiable infarct: 67 (61%) again had a large vessel ischaemic stroke, 16 (15%) had a small vessel ischaemic stroke, and eight (7%) had the recurrent ischaemic stroke in the posterior fossa. Thus patients with a transient ischaemic attack or non-disabling ischaemic stroke caused by LVD were more likely to have an ischaemic stroke of the same vessel type during follow up than patients with SVD (relative risk 2·2; 95% confidence interval 1·5–3·4). Possible explanations for this difference are: (1) patients with a small vessel ischaemic stroke at baseline had both SVD and LVD or were misdiagnosed; (2) recurrent small vessel ischaemic strokes may have occurred more often than reported, because they were silent or only minimally disabling; (3) recurrent large vessel ischaemic strokes occurring in patients initially diagnosed as having SVD might have been related to potential cardiac sources of emboli that had not been previously recognised; (4) the antiplatelet drug aspirin (30 or 283 mg) prescribed in this patient group may have prevented thrombosis in small vessels better than in large vessels.

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Cerebral ischaemia can be classified according to underlying pathogenesis, duration of the neurological deficit, affected region of the brain, or the type of vessel involved. For the last classification a useful distinction is that between small vessel and large vessel involvement. In the case of large vessel disease (LVD) artery to artery embolism, or, in a minority, local obstructive thrombosis has caused occlusion of one of the large cerebral arteries or their main branches.[1] By contrast, small deep (lacunar) infarcts are usually caused by occlusion of a small perforating artery at the base of the brain (small vessel disease (SVD)).[2] In this case the underlying arterial lesion usually involves the perforating artery itself,[3] but can also involve the parent artery from which it originates.[4] The clinical features of lacunar infarction are very specific; only 6% of patients with lacunar syndromes have lesions other than lacunar infarcts on CT.[5,6] Even if the deficits are transient, most patients with SVD can be reliably distinguished on the basis of the history alone.[7]

Differentiation between SVD and LVD is important not only for a better understanding of the pathophysiology, but also for practical reasons. Patients with SVD have a lower mortality and better chances of recovery than patients with LVD.[8,9] It is unknown whether antiplatelet drugs that reduce the overall risk of ischaemic stroke by almost 25% are equally effective in patients with SVD or LVD, because this issue was not considered in placebo controlled stroke prevention trials. It is also uncertain if carotid endarterectomy should be performed in cases of ischaemic small vessel stroke. Until now, it has been unclear even whether vessels involved in recurrent ischaemic stroke are of the same type (small or large) as the initial transient ischaemic attack or non-disabling ischaemic stroke. We have considered this issue in the present study using a patient cohort from the Dutch TIA trial.

Patients and methods

The Dutch TIA trial was a double blind, randomised study in which 3150 patients from 63 Dutch neurological centres were enrolled.[10,11] The study aimed to compare the

effectiveness of two doses of aspirin (30 mg and 283 mg/day) in preventing important vascular events in patients who had had a transient ischaemic attack or non-disabling ischaemic stroke (Rankin grade $\leqslant 3$)[12] within the past three months. At the same time, the treatment effect of atenolol (50 mg) was compared with that of placebo by means of a two by two factorial design. Not included were patients with potential sources of embolism in the heart or conditions other than atherosclerosis that might have caused the cerebral ischaemia.

In the Dutch TIA trial details of the history and the presence of vascular risk factors of each patient were recorded at baseline on a standard checklist.[13] Brain CT was mandatory except in cases of transient monocular blindness. The scans were re-reviewed specifically for this study by two independent neurologists or a neurologist and a neuroradiologist. In cases of disagreement another neurologist arbitrated. Cerebral infarcts were classified as having been caused by SVD (small deep infarcts with an axial diameter < 15 mm) or by LVD (subcortical infarcts with an axial diameter $\geqslant$ 15 mm, border zone infarcts, or superficial infarcts). After classification the observers were given access to the clinical details to assess the clinical relevance of the infarcts. An infarct was judged to be asymptomatic if the presenting clinical features were not likely to have been caused by the lesion that was visible on CT.

For the present study, the following exclusion criteria were applied: non-ischaemic cause for the neurological deficit, no CT available, transient monocular blindness, or clinical findings suggesting ischaemia in the posterior fossa. This last group of patients was excluded because we thought that it was impossible to classify them confidently as having either SVD or LVD. Cortical syndromes were diagnosed if the clinical features included language disorder, hemianopsia, apraxia, or neglect. Lacunar syndromes were defined as unilateral motor or sensory deficit without evidence of cortical findings. On the basis of the clinical features and CT findings patients were divided into three groups: (*a*) SVD (symptomatic lacunar infarct(s) on CT, or clinical features typical of a lacunar syndrome with normal CT, or only asymptomatic lacunar infarcts), (*b*) LVD (symptomatic cortical infarct(s) on CT, or clinical features typical of a cortical syndrome with normal CT, or only asymptomatic cortical infarcts on CT), and (*c*) patients in whom the clinical features together with the CT findings, or the CT findings alone, showed evidence of both SVD and LVD. This last group was excluded from further analysis.

Recurrent stroke during follow up (mean 2·6 years), was defined as the occurrence of new neurological deficits, with sudden onset, resulting in deterioration of the Rankin score of at least 1 grade and lasting longer than one day. If at all possible these new strokes had to be confirmed by CT. If CT could not be performed the recurrent stroke was classified as unspecified. All recurrent strokes were independently assessed by three neurologists and, in the case of an ischaemic or unspecified stroke, classified as SVD or LVD by means of the same criteria as for the entry events.

Vascular risk factors in patients with SVD and with LVD were correlated with the type of stroke recurrence.

Results

Of the initial patient cohort of 3150 patients, 533 patients were excluded for one of the following reasons: patients inappropriately randomised (n = 23), qualifying event consisting of monocular blindness (n = 182) or of clinical findings originating from the posterior fossa (n = 280), or no baseline CT available (n = 48). The SVD group consisted of 1216 patients (729 with a normal CT), and the LVD group of 1221 patients (753 patients with a normal CT); 180 patients who had evidence of both LVD and SVD were subsequently excluded.

During follow up 107 of the 1216 patients with SVD had a recurrent cerebral event (8·8%, 3·6% per year); 51 of them had normal CT at randomisation with a lacunar syndrome diagnosed from history or the neurological examination, and the other 56 patients had a lacunar infarct on their baseline CT. In the LVD group 110 of the 1221 patients had a recurrent cerebral event during follow up (9·0%, 3·6% per year); 51 of them had normal CT at baseline and the other 59 patients had a cortical infarct on their baseline CT. In both groups a recurrent stroke was more likely if an infarct had been detected on baseline CT (relative risk (RR) 1·8; 95% confidence interval (95% CI) 1·4–2·3). In earlier

Table 1 Type of stoke on follow up in patients with small or large vessel disease at baseline, with or without confirmatory infarct on CT

	Baseline			
Follow up	*Small vessel disease all (n (%))*	*Large vessel disease all (n (%))*	*Lacunar infarct at baseline CT (n (%))*	*Cortical infarct at baseline CT (n (%))*
Symptomatic stroke during follow up	107 (100)	110 (100)	56 (100)	59 (100)
Small vessel ischaemic stroke	30 (28)	16 (15)	15 (27)	9 (15)
Large vessel ischaemic stroke	39 (36)	67 (61)	19 (34)	34 (58)
Posterior fossa ischaemic stroke	14 (13)	8 (7)	8 (14)	5 (8)
Ischaemic stroke of uncertain localisation	1 (1)	1 (1)	1 (1)	1 (1)
Haemorrhage	12 (11)	9 (8)	7 (13)	5 (8)
Unspecified stroke	11 (11)	9 (8)	6 (11)	5 (8)

Table 2 Incidence and type of intracerebral haemorrhage at follow up (mean 2·6 years) in patients with small or large vessel transient ischaemic attacks or non-disabling ischaemic strokes at baseline

Follow up (type of haemorrhage)	Baseline: Small vessel disease (n = 1216)	Baseline: Large vessel disease (n = 1221)
Basal ganglia	9	3
Lobar	1	2
Posterior fossa	1	4
Subarachnoid haemorrhage	1	0

studies of the total patient cohort, this factor was found to be largely independent in multivariate analysis.[14]

Table 1 summarises the different types of stroke that occurred during follow up. In 11 patients with SVD and in nine patients with LVD the distinction between recurrent ischaemia or intracranial haemorrhage could not be made as new CT was not available. In these 11 patients with SVD at baseline the clinical features of the recurrent stroke were compatible with a small vessel stroke in two patients, with a large vessel stroke in six patients, and with a stroke in the posterior fossa in one patient; in two patients the clinical features were unknown. In the nine patients with LVD at baseline and unspecified stroke the clinical features were compatible with a large vessel stroke in three patients, with a small vessel stroke in four patients, and with a stroke in the posterior fossa in one patient; in one patient the clinical features were unknown. Patients with SVD at baseline did not have intracranial haemorrhage more often than patients with LVD at baseline (RR 1·3; 95% CI 0·6–3·2). Table 2 specifies the type of haemorrhage.

Of the 84 patients with SVD at baseline who had a recurrent ischaemic stroke during follow up, 30 (28% of the total series of 107) again had a small vessel ischaemic stroke whereas in 39 (36%) patients the new neurological deficit was caused by LVD and 14 (13%) patients had an infarct in the posterior fossa (table 1). In one patient no further classification could be made due to lack of clinical information. Of the 92 patients with LVD at baseline and an ischaemic stroke on follow up 67 (61% of the entire group of 110) patients again had evidence of LVD, 16 (15%) had a small vessel infarct, and eight (7%) had clinical or radiological features of an ischaemic stroke in the posterior fossa (table 1). Again for one patient with LVD at baseline it was not possible to further classify the ischaemic stroke owing to lack of clinical information. For both the SVD and the LVD group these results were similar if the analysis was restricted to patients with a visible infarct on baseline CT (table 1).

Asymptomatic infarcts, in addition to a new symptomatic infarct, were detected in 14 patients with SVD at baseline and a recurrent ischaemic stroke. In nine of these 14 patients the asymptomatic infarcts were of the small vessel type. Nine patients with LVD at baseline had new asymptomatic infarcts on their outcome event scans; in six patients these asymptomatic infarcts were of the small vessel type.

It is of course highly relevant how often new hemispheric infarcts occur on the same side. In patients with initial SVD, the recurrent ischaemic stroke was in the same hemisphere as at baseline in 16 of 30 patients with recurrent small vessel stroke and in 25 of 39 patients with a recurrent large vessel stroke. In patients with initial LVD, the recurrent ischaemic stroke was in the same hemisphere as at baseline in 35 of 67 patients who had remained "true to type" and in 10 of 16 patients who had developed new small vessel disease.

Because the clinical distinction between SVD and LVD can be more difficult for events involving the right hemisphere, we performed an additional analysis with only patients with left hemispheric events at baseline. This restricted analysis resulted in similar

Table 3 Distribution of baseline characteristics of patients with small or large vessel TIAs or non-disabling ischaemic strokes who had a recurrent stroke during follow up (mean 2·6 years)

Type of baseline event	Small vessel disease (n = 1216)			Large vessel disease (n = 1221)		
		Ischaemia			Ischaemia	
Type of recurrent stroke	All (n = 107)	SVD (n = 30)	LVD (n = 39)	All (n = 110)	LVD (n = 67)	SVD (n = 16)
Interval (mean days (SD))	472 (346)	386 (309)	494 (395)	407 (332)	391 (324)	465 (399)
Risk factors at baseline:						
Age (SD)	69 (8)	70 (8)	67 (8)	69 (9)	68 (10)	68 (9)
Male	82 (77)	20 (67)	29 (74)	73 (66)	46 (69)	11 (69)
Transient ischaemic attack	24 (22)	6 (10)	9 (23)	22 (20)	12 (18)	4 (25)
RIND	19 (18)	10 (33)	3 (8)	16 (15)	11 (16)	2 (13)
Non-disabling stroke	64 (60)	14 (47)	27 (69)	72 (66)	44 (66)	10 (63)
Hypertension	54 (50)	16 (53)	18 (46)	45 (41)	24 (36)	7 (44)
Smoking	47 (44)	12 (40)	20 (51)	52 (47)	32 (48)	11 (69)
Diabetes	17 (16)	6 (20)	8 (21)	19 (17)	13 (19)	2 (13)
Myocardial infarction	11 (10)	3 (10)	4 (10)	14 (13)	10 (15)	1 (6)
White matter lesions on CT	23 (21)	7 (23)	7 (18)	20 (18)	13 (19)	2 (13)
Infarction on CT	56 (52)	15 (50)	19 (49)	59 (54)	34 (51)	9 (56)

Unless otherwise stated values in parenthes are %. RIND = reversible ischaemic neurological deficit.

proportions as the full analysis. Thirty five of the 566 (6%) patients with left hemispheric SVD at baseline had a recurrent ischaemic stroke; 14 of them (40%) had a small vessel ischaemic stroke, 15 (43%) had a large vessel ischaemic stroke, five (14%) had an ischaemic stroke involving the posterior fossa, and in one patient further classification was not possible. Fifty one patients of the 595 (9%) with LVD of the left hemisphere at baseline had a recurrent ischaemic stroke; 37 (73%) of them remained true to type, eight (16%) had a small vessel stroke, five (10%) had an ischaemic stroke in the posterior fossa, and in one patient further classification was not possible. If the analysis was further restricted to patients with a symptomatic left sided infarct on CT at baseline the proportions again remained the same.

Table 3 gives the distribution of vascular risk factors for patients with LVD or SVD at baseline. Patients with SVD at baseline who had a recurrent cerebral event were more often men and hypertensive than patients with LVD who had a recurrent cerebral event, but none of these differences reached significance. There were no risk factors associated with an increased likelihood of developing new SVD rather than LVD or vice versa, although there was some indication that patients with SVD and a permanent neurological deficit at baseline were more likely to develop LVD in the future. The mean interval between baseline event and recurrent cerebral event was not different for patients with SVD or LVD at baseline ($P = 0{\cdot}57$). Neither was there a difference in time lag between the cross overs and the patients who remained true to type.

Discussion

In patients with transient ischaemic attacks or non-disabling ischaemic stroke, the overall rate of subsequent stroke during treatment with aspirin was similar in patients with SVD or with LVD (3·6% per year). An important difference was that almost two thirds of the patients with LVD who had a recurrent cerebral event had a large vessel ischaemic stroke whereas in patients with SVD recurrent small and large vessel ischaemic strokes occurred in more or less equal numbers. This significant difference could not be explained by a classification bias caused by laterality of the clinical features or by the fact that only infarcts of a certain size can be visualised by CT, or by differences in vascular risk factors at baseline. Recurrent ischaemic strokes did not occur significantly more often in the same hemisphere that was affected at baseline.

Previously we showed that 64% of patients with transient ischaemic attacks who participated in the Dutch TIA trial had a history suggestive of SVD.[7] In the present study we also included patients with deficits lasting longer than one day, or permanent deficits, provided that they were independent in their daily activities; altogether about half of the patients had evidence of SVD at randomisation. This proportion is much higher than in hospital based series of acute stroke in general, in which SVD constituted about 25% of all ischaemic strokes.[15,16] This difference must be attributed to the selection criteria that were employed in this secondary prevention trial in which patients were excluded from participation if they were dependent on others (Rankin grade 4 or 5) as were patients with potential sources of emboli from the heart, which are thought to cause mainly large vessel infarcts.[17] On the other hand, patients with SVD may be underrepresented in hospital series because they often have only mild signs and symptoms, leading to less frequent referral.[5] Patients who had an ischaemic stroke in the posterior fossa at baseline were excluded, and in cases of a recurrent ischaemic stroke in the posterior fossa the stroke type was not included in the analysis. Both small vessel and large vessel strokes occur in the posterior fossa and it is improbable that this selection method substantially influenced the main results.

In two previous studies patients with large vessel atherosclerotic infarcts had a higher recurrence rate of stroke than patients with lacunar infarcts.[8,18] Our results agree more with a third study which showed that the risk of recurrent infarction does not differ between patients with SVD or LVD.[9] In the Oxfordshire community stroke project recurrent strokes tended to occur at a steady rate only in patients with SVD, whereas in patients with LVD most recurrent strokes were clustered in the first three months.[8] By contrast, we found the mean interval between the initial event and the recurrent stroke to be somewhat shorter in patients with LVD than in patients with SVD, but this difference was not significant.

Probably the most intriguing finding of this study is the fact that new infarcts in patients who entered the study with SVD were not usually of the same type, but in half of the patients consisted of cortical, large artery infarcts. A similar but even more striking difference emerged in the population based study in Rochester; only 17% of the recurrent infarcts that occurred in the patients with lacunar infarcts at onset were again of the lacunar type.[9] In other smaller follow up studies small vessel infarcts were followed by both large and small vessel infarcts.[19,20] In the North American stroke data bank most recurrent strokes were of the same subtype as the initial stroke, but details were not given.[18]

Several explanations are possible for our results. The first is that patients with SVD often have atherosclerosis in large as well as in small vessels, and that it is merely a matter of chance in which of the two vessel types the disease manifests itself. The finding that recurrent strokes occur in both hemispheres in more or less equal numbers supports this explanation. In that case, however, it is difficult to understand why narrowing of the carotid artery is found in only a minority of patients with SVD.[21,22] In our multicentre study non-invasive investigations of the carotid artery were not systematically performed. A

second explanation is that we may have misclassified the type of vessel involved. Because the positive predictive value of a lacunar history has been estimated as between 0·6 and 0·9[7] this might certainly have been the case in patients with a normal baseline CT. Analyses restricted to patients with appropriate infarcts on their CT, however, showed the same distribution of infarct types on follow up as for all patients (table 1). Nor did the results differ when analysis was restricted to patients with initial events in the left hemisphere, for whom the diagnosis of SVD on the basis of symptoms only is more reliable.[7 23] A third possibility is that the patients with SVD at baseline who had a large vessel ischaemic stroke on follow up may in fact have had LVD from the outset, but in the form of an atherosclerotic plaque in the main trunk of the middle cerebral artery that blocked the origin of one or more small perforating arteries.[4] Fourthly, small vessel ischaemic strokes on follow up could have been more common than large vessel ischaemic strokes, but most of these were not reported by the patient because they were clinically silent or only minimally disabling. The few silent lacunar infarcts found in patients who developed a symptomatic infarct on follow up and in whom a second CT was available (23/176), argues against this possibility. Fifthly, large vessel ischaemic strokes that occurred in patients with SVD may have been caused by emboli from the heart. Patients with potential sources of emboli from the heart were excluded from the Dutch TIA trial, however, implying that, if this suggestion is true, these sources of cardiac emboli should have developed soon after randomisation. If they existed beforehand but were not detected it is improbable that the small vessel ischaemic strokes at baseline were caused by an embolus from the heart.[17] Lastly, in patients taking aspirin a recurrent ischaemic stroke is more often caused by LVD than by SVD.[24] Therefore aspirin may prevent thrombosis in small vessels better than in large vessels. We cannot pursue this explanation in our study, because all patients were treated with aspirin (either 30 or 283 mg), whereas placebo controlled trials have not distinguished between SVD and LVD.

Which of these explanations is the most probable remains unclear; the previous existence of LVD in the patients with SVD at baseline is probably the most plausible, although differing responses to aspirin in patients with SVD or LVD cannot be excluded. For a definitive answer we need large follow up studies in which not only different subtypes of ischaemic strokes are distinguished from the onset, but ancillary investigations are also systematically employed to unravel the dynamic features of recurrent stroke. In the meantime we recommend investigation for treatable sources of embolism in patients with clinical features of SVD.

1 Fieschi C, Argentino C, Lenzi GL, Sacchetti ML, Toni D, Bozzao L. Clinical and instrumental evaluation of patients with ischemic stroke in the first six hours. *J Neurol Sci* 1989;**91**:311–22.
2 Bamford JM, Warlow CP. Evaluation and testing of the lacunar hypothesis. *Stroke* 1988;**19**:1074–82.
3 Fisher CM. Capsular infarcts. The underlying vascular lesions. *Arch Neurol* 1979;**36**:65–73.
4 Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied and underused concept. *Neurology* 1989;**39**:1246–50.
5 Bamford J, Sandercock P, Jones L, Warlow C. The natural history of lacunar infarction: the Oxfordshire community stroke project. *Stroke* 1987;**18**:545–51.
6 Kappelle LJ, Ramos LMP, van Gijn J. The role of computed tomography in patients with lacunar stroke in the carotid territory. *Neuroradiology* 1989;**31**:316–9.
7 Kappelle LJ, van Latum JC, Koudstaal PJ, van Gijn J. Transient ischaemic attacks and small vessel disease. *Lancet* 1991;**337**:339–41.
8 Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;**337**:1521–6.
9 Sacco SE, Whisnant JP, Broderick JP, Philips SJ, O'Fallon MO. Epidemiological characteristics of lacunar infarcts in a population. *Stroke* 1991;**22**:1236–41.
10 The Dutch TIA Study Group. The Dutch TIA trial: protective effects of low dose aspirin and atenolol in patients with transient ischaemic attacks or nondisabling stroke. *Stroke* 1988;**19**:512–7.
11 The Dutch TIA trial study group. A comparison of two doses of aspirin (30 mg v 283 mg) in patients after a transient ischaemic attack or minor ischaemic stroke. *N Engl J Med* 1991;**325**:1261–6.
12 Bamford JM, Sandercock P, Warlow C, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989;**20**:828.
13 Koudstaal PJ, van Gijn J, Staal A, Duivenvoorden HJ, Gerritsma JGM, Kraayeveld CL. Diagnosis of transient ischaemic attack: improvement of interobserver agreement by a checklist in ordinary language. *Stroke* 1986; **17**:723–8.
14 The Dutch TIA Study Group. Predictors of major vascular events in patients with a transient ischaemic attack or nondisabling stroke. *Stroke* 1992;**24**:527–31.
15 Chamorro A, Sacco RL, Mohr JP, Foulkes MA, Kase CS, Tatemichi TK, *et al*. Clinical computed tomographic correlations of lacunar infarction in the stroke data bank. *Stroke* 1991;**22**:175–81.
16 Bogousslavsky J, van Melle G, Regli F. The Lausanne stroke registry: analysis of 1000 consecutive patients with first stroke. *Stroke* 1988;**19**:1083–92.
17 Lodder J, Bamford JM, Sandercock PAG, Jones LN, Warlow CP. Are hypertension or cardiac embolism likely causes of lacunar infarction? *Stroke* 1990;**21**:375–81.
18 Hier DB, Foulkes MA, Swiotoniowski M, Saco RL, Gorelick PB, Mohr JP, Price TR, Wolf PA. Stroke recurrence within 2 years after ischaemic infarction. *Stroke* 1991;**22**:155–61.
19 Nadeau SE, Jordan JE, Mishra SK, Haerer AF. Stroke rate in patients with lacunar and large vessel cerebral infarctions. *J Neurol Sci* 1993;**114**:128–37.
20 Clavier I, Hommel M, Besson G, Noëlle B, Ferjus Perres JE. Long-term prognosis of symptomatic lacunar infarcts: a hospital-based study. *Stroke* 1994;**25**:2005–9.
21 Kappelle LJ, Koudstaal PJ, van Gijn J, Ramos LMP, Keunen JEE. Carotid angiography in patients with lacunar infarction—a prospective study. *Stroke* 1988;**19**: 1093–6.
22 Norrving B, Cronqvist S. Clinical and radiological features of lacunar versus nonlacunar minor stroke. *Stroke* 1989; **20**:59–64.
23 Hankey GJ, Warlow CP. Lacunar transient ischaemic attacks: a clinically useful concept? *Lancet* 1991;**337**: 335–8.
24 Chimowitz MI, Furlan A, Nayak S, Sila CA. Mechanism of stroke in patients taking aspirin. *Neurology* 1990; **40**:1682–5.