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Risk factors and outcome of patients with symptomatic intracranial stenosis presenting with lacunar stroke

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Abstract

Background and Purpose—We hypothesized that patients with intracranial stenosis with lacunar stroke presentations would face lower risks of recurrent stroke than those with index non-lacunar strokes, and that their recurrent strokes would predominantly be lacunar.

Methods—We analyzed subjects enrolled with an index stroke into the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial. The index stroke was classified as lacunar or non-lacunar. The primary endpoint was recurrent ischemic stroke. Cox proportional hazard models were generated with stratification for severity of stenosis.

Results—347 subjects were enrolled after an index stroke, 38 were lacunar and 309 were non-lacunar. Over a mean follow-up of 1.8 years there was no significant difference in stroke recurrence between patients whose index stroke was lacunar (7/38; 18%) vs. non-lacunar (69/309; 22%) (HR 0.79, 95%CI:0.36–1.71). Further, no significant differences were found when groups were stratified by 50–69% stenosis (HR 0.50, 95%CI:0.12–2.1) and ≥70% stenosis (HR 0.87, 95%CI:0.34–2.2). Of the 7 recurrent strokes in patients whose index stroke was lacunar, all 7 were non-lacunar and 3 were in the territory of the stenotic artery.

Conclusions—In patients with symptomatic intracranial stenosis, the risk of recurrent stroke was similar in patients who presented with lacunar and non-lacunar strokes, and recurrent strokes in patients presenting with lacunar stroke were typically non-lacunar. These findings suggest that the pathophysiology of these strokes is related to the stenosis rather than small vessel disease. Patients presenting with lacunar strokes should be included in trials investigating secondary prevention for symptomatic intracranial stenosis.

Lacunar strokes account for approximately one-quarter of all ischemic strokes,[1] and are typically attributed to distinctive microvascular pathology. Typically, lacunar strokes confer a lower risk of subsequent stroke than non-lacunar strokes, with about half of those recurrent strokes being lacunes as well. [2,3]

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Lacunar strokes are attributed to disease of penetrating branches of large cerebral arteries.[4] Occlusion of these penetrating arteries may occur in the absence of any disease of the parent artery, and therefore truly represent small vessel disease. However, the so-called "lacunar hypothesis" has been challenged since some apparent lacunes are identified in patients with cardiac sources of embolism and large artery atherosclerosis.[5] In particular, atheromatous disease of the parent artery has been observed to involve the origin of the penetrating branches and result in lacunar infarction.[4,6] Some patients with intracranial arterial stenosis present with a lacunar type infarction in close proximity to the intracranial arterial stenosis, which poses the question whether the infarction is caused by the stenosis or is a result of coesixtent penetrating small vessel disease with the intracranial stenosis being asymptomatic. In the latter case, one might expect a low risk of recurrent stroke in the territory of the stenotic artery, whereas in the former one might expect a higher risk of recurrent stroke. The distinction between these two scenarios may be relevant for characterizing the pathophysiology and more importantly, determining prognosis and treatment.

We hypothesized that patients with intracranial stenosis who presented with typical lacunar clinical syndromes and small deep (subcortical or brainstem) infarctions would face lower risks of recurrent stroke than those with an index non-lacunar stroke, and that their recurrent strokes would predominantly also be lacunar. We tested these hypotheses in the cohort evaluated in the Warfarin vs Aspirin for Intracranial Disease (WASID) trial.

Methods

Study Population and Design

The WASID study cohort consisted of 569 patients enrolled between February 1999 and July 2003 from 59 sites in the U.S. and Canada[7]. The major eligibility criteria were transient ischemic attack (TIA) or nondisablingstroke that occurred within 90 days before randomization andthat was attributable to angiographically verified 50 to 99percent stenosis of a major intracranial artery (carotid, middlecerebral, vertebral, or basilar), a modified Rankin score of3 or less, and age ≥40 years, without an alternative cause for stroke. A small deep infarction in the territory of the stenotic intracranial artery was deemed eligible for the study.

For this post hoc analysis, subjects with a qualifying event of TIA were excluded, leaving 347 subjects with a qualifying stroke for analysis. Patients were followed for a mean of 1.8 years. Lacunar stroke was defined specifically in WASID as presenting clinically with one of 6 typical lacunar syndromes (pure motor hemiparesis, pure sensory stroke, clumsy-hand dysarthria, ataxic hemiparesis, hemiballismus, or sensory-motor stroke with involvement of at least two of three of the following areas: face, arm, or leg)[4] lasting ≥24 hours and occurring in association with either a clinically appropriate subcortical infarct ≤1.5 cm in diameter or absence of evidence of an infarct (presumed too small to visualize) on MRI or CT. All strokes were reviewed by a central rater (MIC) to ensure they met the WASID definition of lacunar stroke. Notably, this definition differs from that of the lacunar stroke subtype in the TOAST classification system[8] which requires exclusion of all other etiologies, since all patients in the WASID cohort had intracranial artery stenosis.

Statistical Analysis

The primary endpoint for this analysis was recurrent ischemic stroke. Secondary endpoints included recurrent lacunar stroke and non-lacunar stroke (according to the WASID definition), and any stroke in the territory of intracranial stenosis. These analyses were further stratified by severity of stenosis (50–69% versus >70%). Baseline risk factors were

compared between the two groups, using t-tests, chi-squared tests, and/or Fisher's exact tests as appropriate. A Cox proportional hazards model was generated to compare the incidence of recurrent stroke (all ischemic stroke, stroke in the territory, lacunar stroke, non-lacunar stroke) between those presenting with lacunar vs. non-lacunar stroke according to the WASID definition. Analyses were stratified by severity of stenosis (50–69% vs. 70–99%) but further multivariable analysis was not performed due to the sample size.

Results

Of the 347 patients who presented with an index stroke, 38 were lacunar and 309 were non-lacunar according to the central adjudicators. Baseline characteristics and risk factors of subjects according to initial stroke subtype are shown in Table 1. Prior ischemic stroke and pre-existing coronary artery disease were more common in subjects with an index lacunar presentation. Central reviews of imaging studies were available for 37 of the 38 lacunar index strokes (31 MRI, 6 CT). Lacunar-appearing infarctions were most commonly found in the pons (15), corona radiata or centrum semiovale (6), thalamus (4), caudate or putamen (3), and internal capsule (2), with the remainder (6) in various subcortical regions. One subject had no abnormality detected on their scan.

During a mean follow-up period of 1.8 years, 76 ischemic strokes occurred (Table 2). Of the 38 patients with an index lacunar presentation, 7 recurrent ischemic strokes occurred (18%): all (100%) were classified nonlacunar, and 3 (43%) were in the territory of the symptomatic artery. Of the 309 patients with an initial nonlacunar stroke, 69 ischemic strokes occurred (22%): the vast majority (90%) were nonlacunar and 50 (73%) were in the territory of the symptomatic artery. There were no significant differences in stroke recurrence risk between the lacunar and non-lacunar groups overall (HR 0.80, 95% CI 0.37–1.73; p=0.56). There was no significant difference in the risk of recurrent stroke specifically in the territory of the symptomatic artery (HR 0.48, 95% CI 0.15 – 1.55; p=0.21), though confidence intervals were wide. Table 3 shows the proportion and rate of recurrent strokes stratified by severity of stenosis. Lacunar presentation had no significant bearing on the risk of stroke recurrence in either stratum, though power was limited to detect differences in these subgroups.

Discussion

In this prospective cohort of stroke patients with symptomatic intracranial arterial stenosis, those with lacunar and non-lacunar presentations had similar risks of recurrent stroke, and the vast majority of recurrent strokes in both groups were non-lacunar. In the absence of intracranial disease, multiple previous studies demonstrated a lower risk of recurrent stroke following an index lacunar subtype, particularly early in the post-stroke period.[1,2,9,10] In contrast, the recurrence rate after stroke of large-vessel origin is relatively higher, particularly in the short-term, and increases with greater degrees of stenosis.[1,2,10,11]

Several potential parallels can be drawn to stroke presentation in patients with symptomatic carotid artery stenosis. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the three-year stroke recurrence risk was similar between patients with lacunar and nonlacunar stroke presentations when treated with medical management alone (25.5% and 24.9%, respectively). [12]

Further, among patients enrolled with a lacunar presentation, carotid endarterectomy was associated with a similar magnitude of reduction of recurrent stroke as with non-lacunar stroke presentations, though that subgroup did not achieve statistical significance.[12] These findings, like ours, suggest that in the setting of large artery disease, lacunar vs. nonlacunar presentations have little bearing on prognosis or treatment decisions. Together, these results suggest that the clinicoradiographic picture of a small subcortical infarction associated with

a large artery stenosis may have a distinct pathophysiology compared to the conventional lacunar stroke subtype due to small artery occlusive disease.[13]

We found that among the patients whose initial stroke appeared lacunar, none of the recurrent strokes were lacunar. This contrasts with findings from lacunar stroke in the setting of carotid artery stenosis: an analysis of NASCET found a three-fold higher risk of lacunar stroke in patients whose index stroke was lacunar. [12] Further, a meta-analysis of 19 pooled studies found a two-fold higher such risk, [13] although this analysis was limited by significant heterogeneity among studies.

The recurrent stroke risk in patients presenting with lacunar stroke in WASID was 18%, which is greater than would be expected if the intracranial stenosis were an unrelated asymptomatic bystander, as a separate WASID cohort study found a very low risk of stroke in patients with an asymptomatic intracranial stenosis during the same follow-up period.[14] Further, the annualized recurrence rate after a lacunar stroke in one population-based study was 2–3%.[1] Additionally there was a proportional increase in recurrent stroke risk relative to increasing degrees of intracranial artery stenosis in both the lacunar and nonlacunar groups.

There are several notable limitations to this study. The number of recurrent events was relatively low, so the ability to detect smaller differences between groups was attenuated. The high recurrence rate in the lacunar group could have been confounded by other factors, including the higher proportion of prior coronary and cerebrovascular disease or other unmeasured factors. Further, the clinical descriptions of each stroke were limited to information collected on study case report forms, and it is possible that some unavailable clinical details could have been useful for further refining this analysis.

Overall our findings support the idea that the lacunar-appearing strokes in the territory of an intracranial arterial stenosis are attributable to that stenosis rather than a separate coexistent pathophysiologic process (e.g., lipohyalinosis) in an adjacent penetrating artery. The involvement of the penetrating artery is likely due to stenosis or occlusion of its ostium by atheroma in the parent artery[4,6], or less likely due to artery-to-artery embolism from the parent to the pentrating artery. Consequently, patients with lacunar strokes should be evaluated for large artery disease and potentially other causes before ascribing them to isolated small penetrating artery disease. Further, our findings suggest that the pathophysiology and risk of recurrent stroke in the subset of patients with lacunar presentations in the territory of a severe intracranial artery stenosis differ from lacunar strokes as a whole. As such, future trials investigating the potential benefit of interventions for intracranial arterial stenosis should include patients with lacunar stroke presentations.

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Table 1

Baseline characteristics and clinical presentation of qualifying stroke

	Non-lacunar presentation (n=309)	Lacunar presentation (n=38)	p value
<70% intracranial stenosis	193 (63%)	22 (58%)	0.53
≥70% intracranial stenosis	113 (37%)	16 (42%)	
MCA stenosis	117 (39%)	9 (24%)	0.44
Intracranial ICA stenosis	66 (22%)	9 (24%)	
VA stenosis	52 (17%)	8 (22%)	
BA stenosis	51 (17%)	9 (24%)	
Combination	17 (6%)	2 (5%)	
Subsequent warfarin	165 (53%)	18 (47%)	0.48
Subsequent aspirin	144 (47%)	20 (53%)	
Age<64	166 (54%)	16 (42%)	0.18
Age ≥64	143 (46%)	22 (58%)	
Men	175 (57%)	27 (71%)	0.09
Women	134 (43%)	11 (29%)	
White	153 (50%)	14 (37%)	0.34
Black	118 (38%)	18 (47%)	
Other race	38 (12%)	6 (16%)	
Smoking	66 (21%)	6 (16%)	0.53
Previous smoking hx	135 (44%)	15 (40%)	0.46
Drinks alcohol	117 (38%)	12 (32%)	0.45
Prior myocardial infarction	40 (13%)	8 (22%)	0.20
Prior coronary angioplasty	20 (7%)	3 (8%)	0.72
Prior CABG	24 (8%)	5 (13%)	0.35
Congestive heart failure	16 (5%)	1 (3%)	1.00
Peripheral arterial disease	17 (6%)	2 (5%)	1.00
Bioprosthetic heart valve	2 (1%)	0 (0%)	1.00
Prior ischemic stroke	65 (22%)	15 (40%)	0.02
Prior TIA	51 (17%)	4 (11%)	0.48
Hypertension	260 (85%)	34 (90%)	0.63
Diabetes	130 (42%)	20 (53%)	0.22
Lipid disorder	200 (67%)	28 (78%)	0.26
Coronary artery disease	69 (23%)	14 (38%)	0.07
Prior CEA	8 (3%)	0 (0%)	0.61
On antihypertensive agent	238 (77%)	28 (74%)	0.65
On ACEI	142 (46%)	14 (37%)	0.29
On statin	185 (60%)	22 (58%)	0.82

The severity and location of the arteries listed in this table specifically refer to the symptomatic stenotic artery related to the initial qualifying stroke.

Table 2

Type of recurrent stroke according to lacunar vs. non-lacunar index stroke

Qualifying Stroke	Endpoint Stroke	Endpoint Stroke In Territory	n
Lacunar (n=38)	No Stroke	--	31
	Lacunar	No	0
		Yes	0
	Non-Lacunar	No	4
		Yes	3
Non-Lacunar (n=309)	No Stroke	--	240
	Lacunar	No	2
		Yes	4
	Non-Lacunar	No	17
		Yes	45
	Unknown Type	No	1
Total			347

Table 3

Risk of recurrent stroke in relation to percent stenosis and lacunar vs. non-lacunar index stroke

	Recurrent stroke (95%CI)	HR (95%CI)*	p value
<70% stenosis			
Lacunar presentation	9% (1–29%)	0.50 (0.12–0.2.1)	0.34
Non-lacunar presentation	18% (13–24%)		
≥70% stenosis			
Lacunar presentation	31% (11–59%)	0.87 (0.34–2.2)	0.78
Non-lacunar presentation	31% (23–40%)		

* Hazard ratio, HR, compares lacunar to non-lacunar index strokes