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Severe stenosis of the internal carotid artery is not associated with borderzone infarcts in patients randomised in the European Carotid Surgery Trial

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Abstract Borderzone infarcts are usually regarded as being caused by low cerebral blood flow distal to a severely stenosed or occluded artery, particularly the internal carotid artery. To explore this hypothesis we have related borderzone infarction, defined by CT both in the classical way and by taking into account the variable extent of the territory of the blood supply of the cerebral arteries, to the severity of any disease of the symptomatic artery in 384 patients in the European Carotid Surgery Trial in whom a scan showing infarction was available. Although there was a tendency for borderzone infarction to occur more often distal to severe carotid disease, this was not significant, and many cases of borderzone infarcts occurred in patients with mild or moderate carotid disease. Therefore, the topography of infarction on CT cannot be used to imply a particular pathophysiology based on the severity of disease of the artery supplying that area of the brain. Severe carotid stenosis is neither sufficient nor necessary to produce borderzone infarction. However, it has to be emphasized that patients with carotid occlusion are not included in this study.

Key words Borderzone infarct · Watershed infarct · Carotid artery · Carotid stenosis · Carotid endarterectomy

Introduction

Different brain infarct types have been distinguished by means of CT: those involving the cortex, lacunar infarcts, striatocapsular infarcts, and borderzone infarcts [7–10, 13, 23, 29]. Aetiologically, borderzone infarcts have often been associated with haemodynamic factors, mostly sustained periods of hypotension and/or high-grade internal carotid artery stenosis or occlusion [1, 4, 5, 8, 17, 24–26, 28, 30, 31]. However, some authors have questioned the validity of considering borderzone infarcts as a separate pathophysiological entity [18, 19] when defined either according to the most currently used computed tomography (CT) topographical brain scan atlases [11, 15], or taking into account the considerable variability in the territories of vascular supply of the major cerebral arteries, as recently described by van der Zwan [32]. Analysis of the clinical characteristics of borderzone infarcts (superficially or deeply located) compared with non-borderzone (i.e. territorial) infarcts, defined in either way, did not reveal any significant association with high-grade carotid stenosis, nor were there any other associations with haemodynamic factors currently regarded as being associated with borderzone infarcts [19]. However, carotid stenosis was diagnosed non-invasively, and approximately 25% of the patients did not have a carotid artery study, whereas only stenosis > 50% was considered "significant". To investigate further the borderzone infarct concept we analysed most patients in the European Carotid Surgery Trial (ECST) who had an infarct shown by CT, all of whom had an angiogram. We were, therefore, able to study the angiographically graded carotid stenosis and other baseline characteristics in borderzone and non-borderzone infarct patients.

Patients and methods

The methods of the ECST have been described previously [14, 27]. In brief, the ECST is an international multicentre randomised trial of carotid endarterectomy in patients with a recent transient ischaemic attack, retinal infarct or minor ischaemic stroke in the carotid territory, who have some degree of stenosis of the symptomatic carotid artery. Patients were randomised to either carotid endarterectomy and medical treatment (60%) or to medical treatment alone (40%). Eligibility of patients was based on the "uncertainty principle", which means that only when the referring neurologist and vascular surgeon were substantially uncertain as to whether carotid surgery was indicated could the patient be randomised. In all patients certain baseline characteristics were recorded (Table 1).

CT of the brain was strongly recommended unless the patients had only retinal ischaemia. Carotid angiography was required for all patients before randomisation. Copies of the angiograms were sent to the trial office where the degree of stenosis, expressed as the maximum percentage reduction in diameter at the site of the symptomatic lesion [27], was measured. Subsequently, patients were classified as having mild (under 30%), moderate (30–69%), or severe (70–99%) stenosis of the symptomatic carotid artery. In all, 3026 patients had been randomised when recruitment ended on 31 March 1994. The interim results showed that carotid endarterectomy was beneficial in patients with severe carotid stenosis, but of no value in patients with mild carotid stenosis [14]. For patients with moderate carotid stenosis the balance of surgical risk and eventual benefit remains uncertain. Follow-up continues for all patients.

Copies of most randomisation CT brain scans that showed evidence of infarction were sent to the Trial Office until January 1992. A total of 626 CT scans were initially classified as having an infarct on the symptomatic side. Of these, 393 were still available for re-evaluation (the remaining CT scans were not sent by the collaborators or could not be found). We distinguished superficial territorial infarcts, small deep territorial infarcts, superficial borderzone infarcts, and small deep borderzone infarcts. A superficial territorial infarct was defined as a hypodense lesion compatible with ischaemia in a territory supplied by the main stem, the cortical or medullary branches of one of the three large cerebral arteries. A small deep territorial infarct was defined as a sharply delineated hypodense lesion with a diameter of less than 20 mm on CT, likely to be caused by occlusion of a small perforating artery at the base of the brain. Striatocapsular infarcts were included in the superficial infarct group, because of their similar pathogenesis [7, 29]. We defined borderzone infarcts in two different ways, as described elsewhere [19]. First, we used a "classic" definition derived from currently used CT scan templates [11, 15] indicating superficial borderzone areas between the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and posterior cerebral artery (PCA), and a deep borderzone area between the deep penetrating arteries and the medullary branches of the major cerebral arteries. Any infarct situated across these demarcation lines was called a borderzone infarct (superficial or small deep) regardless of its size, shape or extension. Secondly, we defined borderzone infarcts taking into account the individual variability of the territory of the vascular supply of the major cerebral arteries, as described by van der Zwan et al. [32]. In this way the superficial supply areas of the ACA, MCA and PCA could be divided into areas always supplied by one of these three arteries and into areas sometimes supplied by the ACA, or the MCA, or the PCA, or combinations of these arteries, so-called areas of variable vascular supply. According to this classification, infarcts located mainly in an area of variable vascular supply were considered as variability borderzone infarcts; the remaining superficial infarcts were called non-variability zone (territorial) infarcts. Van der Zwan did not describe the demarcation between the deep and superficial MCA systems, and therefore small deep infarcts were excluded. CT scans were evaluated by RH blind to the clinical details, results of angiography and

Table 1 Baseline characteristics for superficial, small deep and variability zone borderzone and non-borderzone (territorial) infarcts. Percentages are in parentheses and standard deviation in brackets (*BDZ* borderzone, *OR* odds ratios, *CI* confidence intervals)

	Superficial infarcts (classical CT definition)				Small deep infarcts (classical CT definition)				Superficial infarcts (variability blood supply definition)			
	BDZ $n = 25$	Non-BDZ $n = 209$	OR	95% CI	BDZ $n = 40$	Non-BDZ $n = 110$	OR	95% CI	BDZ $n = 41$	Non-BDZ $n = 179$	OR	95% CI
Mean age	65 [6.3]	62 [9.0]			61 (8.7)	61 (7.5)			63 (8.0)	62 (8.9)		
Male	16 (64)	144 (69)	0.80	0.31– 2.18	30 (75)	78 (71)	1.23	0.51– 3.16	29 (71)	120 (67)	1.19	0.54–2.75
Previous: amaurosis fugax or retinal infarction	1 (4)	6 (3)	1.41	0.03–12.39	2 (5)	3 (3)	1.88	0.15–16.97	1 (2)	6 (3)	0.72	0.02–6.21
TIA	6 (24)	26 (12)	2.22	0.66– 6.47	10 (25)	22 (20)	1.33	0.50– 3.34	8 (20)	23 (13)	1.64	0.58–4.23
Major stroke	10 (40)	131 (63)	0.40	0.15– 1.00	18 (45)	56 (51)	0.79	0.36– 1.74	20 (51)	111 (62)	0.58	0.28–1.23
Myocardial infarction and/or angina	5 (20)	50 (24)	0.80	0.22– 2.34	5 (13)	15 (14)	0.90	0.24– 2.88	6 (15)	48 (27)	0.47	0.15–1.23
Peripheral vascular disease	2 (8)	28 (13)	0.56	0.06– 2.50	5 (13)	10 (9)	1.43	0.36– 4.97	6 (15)	24 (13)	1.11	0.34–3.06
Diabetes mellitus	4 (16)	28 (13)	1.23	0.29– 4.04	5 (13)	18 (16)	0.73	0.20– 2.25	5 (12)	25 (14)	0.86	0.24–2.49
Smoking	15 (60)	109 (52)	1.38	0.55– 3.59	20 (50)	58 (53)	0.90	0.41– 1.97	26 (63)	91 (51)	1.68	0.79–3.64
Mean systolic blood pressure (mmHg)	149 [18.9]	151 [21.6]			154 [17.0]	151 [20.4]			149 (12.4)	151 (22.2)		
Mean diastolic blood pressure (mmHg)	84 [11.5]	86 [10.2]			88 [9.5]	87 [11.2]			85 (10.6)	86 (10.5)		

Table 2 Frequency of mild (0–29%), moderate (30–69%) and severe (70–99%) stenosis of the symptomatic carotid artery in various categories of infarcts. Percentages are in brackets (*BDZ* borderzone, *OR* odds ratios, *CI* confidence intervals)

Degree of symptomatic stenosis	Superficial infarcts (classical CT definition)				Small deep infarcts (classical CT definition)				Superficial infarcts (variability definition)			
	BDZ $n = 25$	Non-BDZ $n = 209$	OR	95% CI	BDZ $n = 40$	Non-BDZ $n = 110$	OR	95% CI	BDZ $n = 41$	Non-BDZ $n = 179$	OR	95% CI
Mild	4 (16)	25 (12)	1.40	0.32–4.65	6 (15)	34 (31)	0.39	0.12–1.08	6 (15)	19 (11)	1.44	0.44–4.11
Moderate	9 (36)	100 (47)	0.61	0.23–1.56	24 (60)	58 (53)	1.34	0.61–3.02	15 (37)	89 (50)	0.58	0.27–1.23
Severe	12 (48)	84 (40)	1.37	0.54–3.44	10 (25)	18 (16)	1.70	0.63–4.40[a]	20 (49)	71 (40)	1.45	0.69–3.03

[a] Although χ^2 for trend is just statistically significant ($P < 0.05$), a more appropriate Mann-Whitney test for differences in stenosis between borderzone and non-borderzone infarcts is not

treatment allocation. A CT lesion was considered "symptomatic" if located in the hemisphere from where the signs and symptoms originated; in the surgical cases this side usually corresponded with the side of operation. In cases of multiple infarcts, or where there was insufficient clinical information, the infarct with a radiologically estimated age most consistent with the time of the estimated stroke was considered as the symptomatic one (old lesions being more hypodense, more sharply delineated or showing signs of retraction of brain structures towards the lesion site).

Borderzone infarct patients were compared with non-borderzone (territorial) infarct patients with respect to the degree of symptomatic carotid stenosis and various vascular risk factors. Infarct groups were studied with respect to both borderzone infarct definitions. The association between categorical variables and infarct type was assessed using either a chi square test with Yates' correction or crude odds ratios with 95% confidence intervals.

Results

A total of 393 CT brain scans were re-evaluated. On 7 of these no infarct was seen; in one patient the radiologically estimated symptomatic infarct was not consistent with the site of the clinical symptoms; and in one patient the quality of the CT scan was too poor, leaving 384 CT scans for analysis. According to the classical borderzone infarct definition, there were 234 superficial infarcts of which 25 were borderzone and 209 non-borderzone (territorial) infarcts. There were 150 small deep infarcts of which 40 were borderzone and 110 non-borderzone (territorial) infarcts. When defining borderzone infarcts as infarcts in an area of variable arterial vascular supply of the major cerebral arteries, the large deep infarcts ($n = 9$) were excluded from the initial 234 superficial infarcts. On 5 CTs the infarct could not be allocated to either the variability borderzone or non-borderzone (territorial) group, leaving 220 superficial infarcts for analysis. Of these, 41 were classified as variability borderzone and 179 as variability non-borderzone (territorial) infarcts. The intraobserver variability was studied by way of re-evaluating the initial 50 CT scans 2 weeks after the first evaluation. According to the classical definition, 9 infarcts were classified as borderzone infarcts both times, 39 as non-borderzone both times and 2 infarcts were classified differently.

In Table 1 the baseline data of the different borderzone and non-borderzone (territorial) groups are shown. There were no statistically significant differences. The frequency of mild, moderate and severe symptomatic carotid stenosis in the different infarct subgroups is shown in Table 2. Comparison between the borderzone and non-borderzone (territorial) groups with respect to the degree of symptomatic stenosis revealed no statistically significant differences. Graphical reproduction of the degree of symptomatic stenosis from 1 to 100% (Fig. 1A–C) shows that there was a tendency to higher stenosis in the borderzone group than in the non-borderzone (territorial) group, but this was not statistically significant. Moreover, it was clear that many borderzone infarcts (defined in either way) were not associated with high levels of stenosis.

Discussion

The term "borderzone" originally referred to defined anatomical areas of brain in pathological studies [3, 20, 25, 31]. More recently, haemodynamic mechanisms, mostly sustained periods of hypotension and/or high-grade carotid stenosis/occlusion, have often been regarded as the cause of infarcts in these borderzone areas [1, 8, 17, 21, 22, 25, 26, 28, 31].

Wodarz [30] described 55 patients with an angiographically estimated carotid artery stenosis or occlusion and found CT topographically "watershed processes" in 40%. No further clinical details on the patients were given. Bogousslavsky [6, 7] studied 154 patients with either transient ischaemic attacks (TIA) or infarcts and an occlusion of the internal carotid artery and found in 5% watershed infarcts. After a follow-up of 48 months, 30 patients had a recurrent infarct, 18 of which were watershed infarcts. Symptoms of heart disease, periods of hypotension and syncope were more frequent in the watershed infarct group, which, according to the authors, pointed at a haemodynamic cause of stroke. Mounier-Véhier [22] described 26 territorial watershed infarcts in 493 consecutive patients with TIA or stroke and found that a carotid stenosis of more than 50% was associated with watershed infarcts.

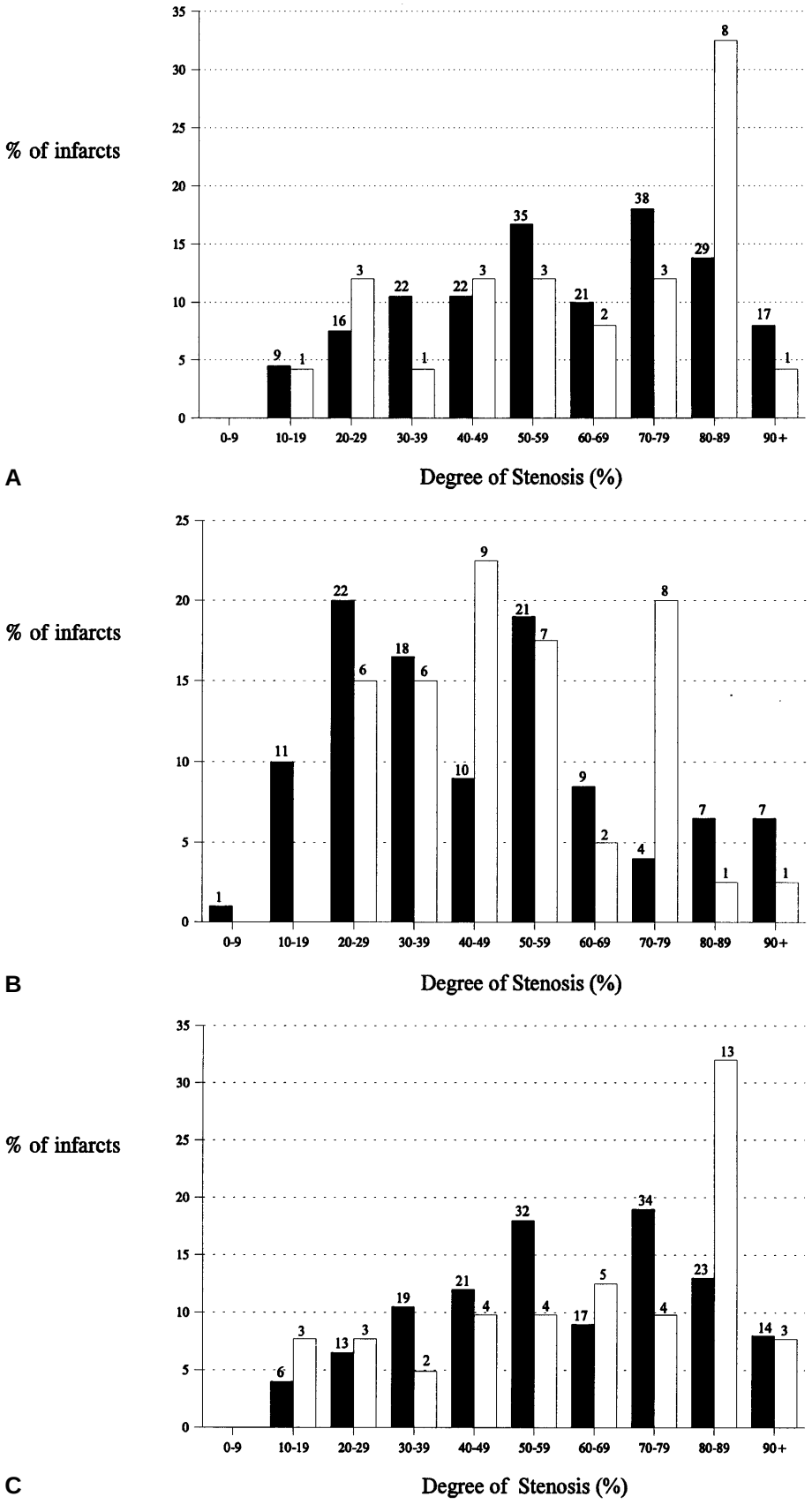

Fig. 1A–C Degree of stenosis, indicated in percentages, in borderzone versus non-borderzone (territorital) infarcts: **A** superficial infarcts; **B** small-deep infarcts; **C** variability zone superficial infarcts. The *numbers above the bars* refer to the number of infarct patients in each stenosis group. **A** Comparison of degree of symptomatic carotid stenosis between superficial borderzone infarcts (□) and superficial non-borderzone (territorial) infarcts (■) using the classical definitions. **B** Comparison of degree of symptomatic carotid stenosis between small deep borderzone infarcts (□) and small deep non-borderzone (territorial) infarcts (■) using the classical definitions. **C** Comparison of degree of symptomatic carotid stenosis between superficial borderzone infarcts (□) and superficial non-borderzone (territorial) infarcts (■) using the variability blood supply definition

With respect to CT topography, Ringelstein [24] supposed there to be a haemodynamic stroke cause in 8 superficial and in 36 "terminal supply" (subcortical) "watershed" infarcts in 107 patients with a carotid artery occlusion. In an autopsy study of 320 patients with ischaemic cerebrovascular disease, 37 "watershed" infarcts were found [20]. In eight (22%) of these carotid occlusions were found. In 5 patients who sustained a period of hypotension prior to the stroke, only one had a watershed infarct. In another autopsy study, multiple causes of watershed infarcts were suggested: haemodynamic (hypotension), showers of microemboli or thromboemboli [28]. Several other authors have suggested in classical (CT/angiography) studies thromboembolism in watershed infarcts [2, 16]. Howard and Ross Russell [17, 26] described, in patients without carotid artery stenosis, superficial watershed infarcts after cardiovascular surgery and supposed that these infarcts were caused by haemodynamic insufficiency. Several authors have described pathophysiological aspects of (small) deep watershed infarcts. Using SPECT, Weiller et al. reported 17 patients with subcortical watershed infarcts or "low-flow infarcts" who had an ICA occlusion and a severely decreased cerebral perfusion reserve (SPECT) in comparison with (territorial) infarcts [29]. According to these authors, the decreased cerebral perfusion reserve was due to "distant haemodynamic effects of extracranial occlusive disease". In a series of 300 stroke patients, 6 patients with "confluent internal watershed infarction" (CIWI) and 12 patients with "partial internal watershed infarction" (PIWI) were described [4]. Six of the CIWI and 9 of the PIWI patients showed "factors capable of producing haemodynamic compromise". "Heart disease" and "carotid disease" was significantly more frequent in the watershed groups than in the remaining infarcts.

Although the findings in these studies suffered from methodological flaws, most authors associated superficially and/or deeply located "watershed" infarcts with haemodynamic mechanisms, especially when a significant carotid stenosis or occlusion was present. However, the a priori inclusion of such mechanisms in the *definition* of borderzone infarcts should be avoided, particularly as there is seldom any direct evidence for such mechanisms in most patients with infarction in so-called borderzone areas of the brain. Therefore, it would seem most appropriate to define borderzone infarcts exclusively on topographical grounds, which nowadays is facilitated by the advent of CT and MRI. However, in an individual patient one can never be sure that an infarct with certain topographical characteristics is indeed located in adjacent end zones of two separate arteries, instead of being located in the end zone of just one of them, and indeed not all infarcts will show an abnormality on CT in the acute phase. Moreover, the large inter-individual and side-to-side variability in the brain areas supplied by the different cerebral arteries makes a uniform topographical definition almost impossible.

A recent study on consecutive ischaemic strokes, taking into account these difficulties in defining borderzone infarcts, revealed no statistically significant differences in clinical characteristics between the borderzone infarcts and the remaining (territorial) infarcts [18, 19]. A striking finding was the absence of the expected association of a high-grade carotid stenosis with borderzone infarcts. However, when borderzone infarcts were defined in a "classic way" (superficially located, slit-like or right-angled and extending over two or more CT slices) five infarcts in a consecutive series of 813 patients were borderzone; four of these had ipsilateral carotid occlusion, which was significantly more frequent than in the remaining infarct group.

To address further this issue of the relationship between infarct topography, severity of the disease of the symptomatic carotid artery and vascular risk factors, we have had the opportunity to study patients from the ECST, all of whom had a carotid angiogram. Major disabling strokes were excluded from randomisation in the ECST, but this should not have biased our results because such strokes are not, as far as we know, more or less likely to be associated with borderzone rather than non-borderzone territorial ischaemia [20]. Also, the relative proportion of infarct types in this study was very similar to a previous study of much less selected stroke patients [19]. However, the results of our study are based on a relatively small population of the patients included in the ECST, although selection bias is unlikely. In essence we found that borderzone infarcts, whether defined on the basis of classical CT templates or by taking into account the variability of the area of brain supplied by particular cerebral arteries, were not definitely related to the severity of symptomatic carotid stenosis or to any particular vascular risk factor. Although there was a tendency for borderzone infarcts to be associated with more severe carotid disease, many such infarcts occurred distal to quite mild carotid stenosis. These findings compare with those of Del Sette et al. [12] who described a possible association of small deep borderzone infarcts with carotid stenosis in 108 small deep borderzone infarcts out of 413 patients with an ischaemic lesion and ipsilateral carotid stenosis. Unfortunately, they did not describe the frequency of borderzone infarcts in patients who did not have a carotid stenosis. We cannot comment on the relationship between borderzone infarction and internal carotid artery occlusion because such patients were not randomised in the ECST; this is unfortunate because several authors point to an association of carotid artery occlusions – particularly superficially located – with borderzone infarcts [4–6, 19, 21, 24, 27, 30]. "Classic" borderzone infarcts (superficially located , extending over two or more CT slices and slitlike or right-angled) may especially be associated with carotid occlusions; however, we found only one such infarct, moreover not associated with a significant carotid stenosis.

In conclusion, it seems that if an infarct on CT is classified as being in a borderzone (however borderzone is

defined), this cannot in itself imply a particular infarct cause, at least not with respect to the presence of any particular degree of stenosis of the appropriate internal carotid artery. It is necessary, therefore, to have other means of deciding whether an infarct distal to carotid stenosis is due to ischaemia within the territory of supply of a cerebral artery or within a borderzone area of supply between two or more cerebral arteries.

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