Branch Atheromatous Disease: A Clinically Meaningful, Yet Unproven Concept

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Key Words

Acute ischemic stroke · Advanced MRI · Intracranial atherosclerotic diseases · Vascular risk factors · Small vessel disease

Abstract

Background: In 1989, Louis Caplan first used the term branch atheromatous disease (BAD) to describe an occlusion or stenosis at the origin of a deep penetrating artery of the brain, associated with a microatheroma or a junctional plaque, and leading to an internal capsule or pontine small infarct. BAD remained an understudied concept for decades. In recent years, the increasing diffusion of high-resolution magnetic resonance imaging (HRMRI) techniques brought new attention to the BAD debate. We have reviewed clinical studies dealing with BAD-related stroke checking whether a univocal definition of BAD existed, as well as to what extent were consistently associated clinical and imaging features reported. **Summary:** We conducted a search of the available literature published up to October 20, 2015 via PubMed using the following search terms: 'branch atheromatous disease,' 'intracranial branch atheromatous disease,' 'cerebral branch atheromatous disease,' combined with 'stroke.' Forty-six ar-

ticles were included. We found discrepant definitions and a large variation among clinical features reported in BAD-related stroke patients: among others, a consistent association between BAD and any specific vascular risk factor profile was not detected. Despite this, early neurological deterioration (END) was consistently reported to occur frequently in such patients, although no clear-cut rate range or specific predictor or mechanism of progression was established. In a majority of the studies reporting imaging data, BAD diagnosis was not based on the selective site or type of arterial walls changes, but was inferred based on the vascular territory, size and/or shape of the ischemic lesion. Following the concept that these changes are seated proximally along the perforator artery, differently from to lipohyalinosis changes located distally, the consequent ischemic lesion was hypothesized to be larger in BAD than in lacunar infarcts. However, across reviewed studies, there was little consistency on the dimensional cutoff used to define BAD-related infarcts. In the last few years, a still limited number of studies using HRMRI techniques is providing preliminary proofs that atheromatous changes causing selective remodeling in the parent vessel and extending through the proximal segment of perforating vessel may subtend BAD. **Key Messages:** Our literature search showed the lack of a clear-cut definition of BAD, al-

though BAD-related strokes were consistently considered a high risk of END. The use of high-resolution imaging techniques in the assessment of small subcortical strokes may represent the cornerstone in the perspective to better delimiting the boundaries of BAD as a nosological entity.

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Introduction

Intracranial branch atheromatous disease (BAD) was first described in 1989 [1] as a mechanism alternative to lipohyalinosis, considered the arteriopathy selectively linked with lacunar infarction pathogenesis. In its initial meaning, the term BAD had been applied to the pathological finding of an occlusion or stenosis at the origin of a deep penetrating artery, due to the presence of a microatheroma or a junctional plaque [2]. Since the first reports by Fisher and Caplan in the 1970s, there has been a distinct lack of further pathological studies on the subject. Thus, BAD remained a neglected concept for decades. The wider diffusion of MRI techniques brought new attention to the BAD debate. The term BAD is being used again to label imaging features supposedly associated with the proximal occlusion of a penetrating artery due to microatheroma or to large parent artery plaque. Routine imaging techniques are unable to depict small vessel changes; thus, features used to define BAD results to be mostly indirect, consisting of selective morphological characteristics of the ischemic lesion presumed to be produced by it. These characteristics are thought to separate BAD lesions from those related to lipohyalinotic degeneration (true lacunar infarcts). Despite the increasing number of neuroimaging studies, there is still lack of consistency both in the terminology used to describe the aforementioned atheromatous lesions and in the subsequent ischemic infarctions. Very recently, high-resolution (HR) and high-field MRI proved capable of revealing and describing in much more detail intracranial vessels wall changes, including plaques involving perforators' parent arteries [3].

We review and discuss here the definition of BAD, as well as the associated clinical and imaging features.

Materials and Methods

We conducted a search of the available literature published up to October 20, 2015 via PubMed. We used the following search terms: 'branch atheromatous disease,' 'intracranial branch atheromatous disease,' 'cerebral branch atheromatous disease,' com-

bined with 'stroke.' The PubMed search yielded 58 results. We excluded studies according to the following criteria: (1) articles for which an English full translation was not available ($n = 14$); (2) studies with no relevance to the review subject, as was evident examining titles and abstracts ($n = 8$). Thus, we identified 36 eligible articles; thorough reading of these articles led to the exclusion of one additional item that did not focus on the topic. Furthermore, 11 articles that were listed in bibliographies of selected works were included because they appeared relevant to the subject (fig. 1).

Clinical Features

The BAD risk factor profile encompasses common vascular risk factors, such as high blood pressure (HBP), diabetes mellitus (DM), dyslipidemia and tobacco dependence. Among the examined studies, prevalence of HBP ranged from 50 to 92% in groups of stroke patients whose etiology could be attributed to BAD [4, 5]. In the same groups, prevalence of DM varied from 23 to 63% [6, 7]; smoking habit and dyslipidemia prevalence also varied greatly, ranging from 0 to 50% and from 17 to 86% respectively [8, 9]. Diabetes or an Asian/African ancestry was identified as selectively associated with BAD since its first description [1, 10]. More recently, however, a number of studies have reported risk factors similar to those commonly found in both large artery atherosclerosis [5, 11] or to lacunar infarctions [12, 13]. The mean age of onset ranged from 54 to 75 [6, 13]; male gender was overall more prevalent. Table 1 summarizes the clinical correlates of BAD, as reported in the examined studies. It is worth noting that all but one of the original studies [9] whose data are shown in table 1 included only patients from Korean, Japanese or Chinese populations.

Early neurological deterioration (END) was reported to occur frequently in BAD-related strokes: the examined studies show an incidence ranging from about 17 to 75% [9, 14]. Although mechanisms underlying progression are not completely understood, numerous hypotheses have been formulated, including local thrombosis, local blood-brain barrier disruption, edema, inflammation and excitotoxicity [15]. It has to be noted, however, that the definition of END lacks consistency among different studies: while most of the studies based the definition on a clinical worsening, as measured by the National Institute of Health Stroke scale (NIHSS), there is no consensus on the NIHSS cut-off needed to define END in a homogeneous fashion across studies (current definitions range from an increase of at least 1 point in NIHSS motor items to at least 4 points in overall NIHSS score). There is no agreement on the time elapsed from the times of symp-

Fig. 1. Summary of the literature search.

toms onset in relation to which the worsening can be defined ‘early’ (ranging from an hour to 14 days) [9, 16]. Thus, comparing studies is difficult and sometimes not viable. From studies that focused on both stroke types, END was definitely more frequent in BAD-related stroke than in true lacunar stroke [12, 13, 17, 18]. Yamamoto et al. [19] studied a cohort of 218 patients with what they called large lacunar infarction, identifiable as related to BAD, in order to compare the effect of a combined treatment regimen with cilostazol and edaravone to that of a regimen including either argatroban or ozagrel sodium with regards to the reduction of END. While neither treatment showed a superior effect, in this study, the absence of END was related to a better short-term outcome. Only 2 studies specifically addressed factors potentially involved in END. In a recent study of acute BAD patients [7], an association was reported with an elevated blood homocysteine and a high C-reactive protein level. Nakase et al. [13] studied END in 99 patients with small vessel

disease. In the BAD subgroup, mean admission NIHSS score was significantly higher and serum LDL >140 mg/dL on admission were significantly more prevalent in patients with END compared with non-deteriorating patients.

Functional prognosis in BAD stroke could be described as halfway between large artery disease-related stroke and lacunar infarctions. Suto et al. [11] conducted a follow-up study of 1,310 stroke patients assessed in the acute phase and followed-up for a mean time of 751 days. Larger subcortical infarction patients (whose etiology can be attributed to BAD) had a short-term prognosis (measured by mRS at discharge) that was similar to that found in atherothrombotic stroke patients, while it was significantly worse than that observed in lacunar infarction patients. On the other hand, in-hospital mortality was similar when compared to large subcortical with lacunar infarctions (0.8 vs. 0%). Conversely, long-term outcome was reported to be similar to lacunar infarctions (mortal-

Table 1. Demographic and clinical correlates of BAD

First author, year	Total numerosity	BAD number	Males, %	Age, years, mean	HBP, %	DM, %	Smoke, %	Dyslipidemia, %	Progression, %	OTP
Kim et al. [6], 1995	37	13	61.5	53.9	61.5	23.1	30.8	n.a.	n.a.	n.a.
Kumral et al. [9], 2002	11	8	83.3	57	83.3	33.3	50.0	16.7	18.2	>1 h
Nakase et al. [4], 2008	105	9	44.4	71	50	50	37.5	50.0	n.a.	n.a.
Lee et al. [40], 2009	205	22	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Suto et al. [11], 2009	1,460	138	47.8	71.0	73.9	29.7	20.2	43.8	55.4	Undefined
Kim et al. [39], 2009	86	50	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Aoki et al. [48], 2010	51	28	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	46.4	7 days
Kwan et al. [5], 2011	372	147	65.0	69	92.0	36.0	43.0	67.0	n.a.	n.a.
Yamamoto et al. [49], 2011	218	218	58.2	69.2	81.5	35.7	31	52.3	47.6	5 days
Yamamoto et al. [12], 2011	394	173	56.6	71.1	81.5	40.9	41.6	42.1	40.5	5 days
Chung et al. [8], 2012	15	9	44.4	70.2	77.8	44.4	0.0	33.3	n.a.	n.a.
Oyama et al. [33], 2013	21	8	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Men et al. [7], 2013	308	179	68.0	63	87.2	43.0	31.0	86.0	41.0	5 days
Deguchi et al. [14], 2013	8	8	63.00	70	38.0	25	25	50.0	75.0	7 days
Nakase et al. [13], 2013	99	42	59.5	73.9	76.2	42.8	45.3	42.9	38.0	48 h
Tanaka et al. [16], 2013	242	21	n.a.	n.a.	n.a.	40.0	n.a.	n.a.	n.a.	14 days
Miyamoto et al. [45], 2013	576	32	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	40.6	7 days
Yoon et al. [50], 2013	202	28	50.5	61.7	69.2	36.3	23.1	17.6	n.a.	n.a.
Nakase et al. [51], 2014	453	203	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	67.5	48 h
Kim et al. [52], 2013	248	124	46.8	65.6	60.5	23.4	25.8	39.5	16.9	5 days
Jeong et al. [18], 2015	587	220	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	21.4	n.a.
Nakase et al. [44], 2015	166	101	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	45.5	7 days
Ryoo et al. [42], 2015	80	36	55.6	67.6	63.9	44.4	22.2	47.2	n.a.	n.a.
Chung et al. [41], 2015	286	80	67.5	73.3	78.8	52.5	13.8	30	n.a.	n.a.

OTP = Onset to progression; n.a. = non-applicable.

ity 8.4 vs. 8.2%; recurrence rate 9.3 vs. 14.1%), with significantly lower mortality rate and recurrence rate compared with cardioembolic (41.1 and 23.8% respectively) or atherothrombotic stroke (22.3 and 16.6% respectively). Likewise, Kwan et al. [5] found that while the length of hospitalization and level of residual disability after rehabilitation were significantly greater in BAD patients than lacunar infarction patients, mortality proved similar between the 2 groups, and lower than mortality observed in large artery stroke patients.

Neuroimaging Features

Although the term BAD was originally created based on pathological findings, pathological studies have been very few so far. Indeed, our search identified only one such record published in recent years [20]. In contrast,

studies based on neuroimaging have been definitely more numerous. In a majority of them, BAD-related infarctions were broadly identified as those occurring in the subcortical regions whose blood perfusion depends on deep small penetrating vessels [5, 21]. In the anterior circulation, these pertain to lenticulostriate artery terminations stemming from the middle cerebral artery (MCA) and Heubner's artery originating from the anterior cerebral artery [22]. They supply basal ganglia and the internal capsule. In the posterior circulation, thalamoperforating branches, originating from the posterior cerebral artery (thalamic-subthalamic artery), and the posterior communicating artery (tuberothalamic artery) supply the thalamus, while paramedian and short circumferential branches from the basilar artery (BA) supply the pons [23, 24]. These branches are small enough that an atheromatous lesion of the parent artery involving a branching point can cause ischemia in the whole territory perfused

Fig. 2. Example of BAD-related infarction.

by one or few adjacent vessels. Subcortical infarcts can also be caused by occlusion of the anterior choroidal artery (AChA), a larger caliber vessel arising directly from the internal carotid. Specifically, this vessel supplies the posterior part of the corona radiata and of the internal capsule, the tail of the caudate nucleus and the medial part of the globus pallidus, as well as some cortical regions in the temporal cortex [25]. There is no definitive evidence, however, as to what would be the etiology of ischemic events regarding this vessel. In fact, some authors reported that the risk profile and clinical presentation of AChA infarcts are similar to lacunar infarctions [25], while others [26] reported that larger (>20 mm) AChA lesions may be etiologically linked to large artery embolism or cardioembolism.

BAD vascular lesions are located proximally along the perforator artery in comparison to lipohyalinosis. Thus, the ensuing ischemic lesion may be expected to be larger in BAD-related infarcts than in lacunar infarcts [27].

There is little consistency on the dimensional cutoff accepted to define BAD-related infarcts. In a majority of the examined works, these lesions were considered identifiable by a diameter ≥ 15 mm and by the appearance of a lesion in ≥ 3 consecutive slices on a transversal plane (fig. 2) [28]. It is noteworthy that the thickness of the considered slice is different across the included studies (online suppl. Appendix, see www.karger.com/doi/10.1159/000442577). Posterior circulation lesions were usually considered to involve unilaterally the pons and to extend to the ventral pontine surface [12, 13, 29]. Table 2 summarizes these data.

Wardlaw et al. [30] recently published the STAndards for ReportIng Vascular changes on nEuroimaging (STRIVE) recommendations, in which they proposed an

internationally standardized nomenclature for small vessel disease neuroimaging features. Specifically, the term ‘small subcortical infarct’ is to define small (<20 mm transversal diameter) lesions in the territory of a penetrating arteriole. The authors explicitly stated that the proposed definition aims not to imply any specific etio-pathogenesis; they also stated that lesions exceeding the 20 mm limit are to be labeled either striatocapsular infarcts or ACh infarcts according to the appropriate vascular territory. The authors did not suggest a criterion to be applied selectively to BAD-related infarcts.

In fact, currently there is no consensus as to whether BAD should be included either among small vessel or among large vessel intracranial disease [11, 17, 31–34]. Some studies reported BAD as one of the stroke mechanisms linked with intracranial atherosclerotic disease, and characterized by a milder degree of stenosis and comma-shaped infarcts extending to the basal surface of the parent artery [34, 35]. Considering common imaging markers of small vessel disease, Nah et al. [27] retrospectively reviewed data from 805 small subcortical stroke patients, 114 of whom were attributed to BAD. Small vessel disease features such as leukoaraiosis and microbleeds were significantly less prevalent among BAD patients, while these patients showed a significantly larger atherosclerotic burden, that is a higher prevalence of asymptomatic intracranial atherosclerosis or coronary artery disease. In contrast, Men et al. [29] observed an unusually high prevalence of leukoaraiosis (86.4%) in a retrospectively analyzed series of 220 BAD Chinese patients. These striking discrepancies likely reflect different inclusion criteria: in fact, some of the studies we examined excluded the diagnosis of BAD on the basis of laboratory data suggestive for widespread large artery disease (table 2).

Table 2. Neuroimaging features used to define BAD-related infarctions across studies

First author, year	Lesion location and size					Large vessel disease excluded	HR MRI
	anterior circulation			posterior circulation			
	vascular territory	transversal diameter, mm	longitudinal diameter	vascular territory	extension to ventral surface		
Kim et al. [6], 1995	–	–	–	VB perforators	Yes	NS	No
Kumral et al. [9], 2002	–	–	–	VB perforators	NS	No	No
Kim et al. [39], 2009	–	–	–	VB perforators	NS	No	Yes
Lee et al. [40], 2009	–	–	–	PCA perforators	NS	No	Yes
Suto et al. [11], 2009	MCA perforators	≥15	NS	VB perforators	NS	Yes	No
Aoki et al. [48], 2010	–	–	–	VB perforators	Yes	No	No
Kwan et al. [5], 2011	MCA perforators, HA and AchA	≥15	NS	VB and PCA perforators	NS	Yes	No
Yamamoto et al. [49], 2011	MCA perforators and AchA	>10 and ≤20	≥3 slices	VB perforators	Yes	Yes	No
Yamamoto et al. [12], 2011	MCA perforators	> 10 and ≤20	≥3 slices	VB perforators	Yes	Yes	No
Chung et al. [8], 2012	MCA perforators	≤20	NS	VB perforators	Yes	Yes	Yes
Oyama et al. [33], 2013	MCA perforators	NS	>20 mm	–	–	No	No
Deguchi et al. [14], 2013	MCA perforators	NS	≥3 slices	VB perforators	Yes	Yes	No
Men et al. [29], 2013	MCA perforators	≥15	≥3 slices	VB perforators	Yes	Yes	No
Nakase et al. [13], 2013	MCA perforators	≥15	>3 slices	VB perforators	Yes	Yes	No
Tanaka et al. [16], 2013	MCA perforators	>10	≥3 slices	VB perforators	Yes	Yes	No
Yoon et al. [50], 2013	MCA perforators	NS	≥4 slices	VB perforators	Yes	Yes	No
Nakase et al. [51], 2014	MCA perforators	≥15	>3 slices	VB perforators	Yes	Yes	No
Kato et al. [47], 2015	–	–	–	VB perforators	Yes	Yes	No
Jeong et al. [18], 2015	MCA perforators	≤20	4 slices	VB perforators	Yes	Yes	Yes
Nakase et al. [44], 2015	MCA perforators	≥15	>3 slices	VB perforators	Yes	Yes	No
Ryoo et al. [42], 2015	MCA perforators	n.a.	n.a.	VB perforators	n.a.	No	Yes
Chung et al. [41], 2015	–	–	–	VB perforators	Yes	Yes	Yes

HA = Heubner's artery; VB = vertebro-basilar; PCA = posterior cerebral artery; NS = non-specified; n.a. = non-applicable.

Current imaging techniques such as CT angiography, digital subtraction angiography and magnetic resonance angiography (MRA) are of limited utility in the diagnosis of the arteriopathy supposed to subside BAD, because they depict just the external morphology of arteries, and are unable to show inner vessel wall changes. Recently, 3-tesla HR MRI has been used for the visualization of inner MCA and BA plaques in vivo. Klein et al. [3] were able to image MCA atheromatous plaques using HR MRI in 6 patients with MCA stenosis documented by MRA and

transcranial doppler. Klein et al. [36] were also able to visualize inner atherosclerotic lesions in the basilar arteries of patients with paramedian pontine infarctions whose MRA had showed normal vessel's profile. They found that either a BA plaque or a wall contrast enhancement was visible on 13 such patients out of a sample of 17. More recently, Chung et al. [8] performed 3 Tesla HR MRI scans on 15 patients with acute small subcortical infarctions and no relevant vessel disease on MRA (MCA or BA). They identified a relevant branch atheromatous

Fig. 3. HR MRI findings of BAD-related infarct and branch atheromatous plaque in the middle cerebral artery (a) and in the basilar artery (b).

plaque in 9 subjects (fig. 3). Niizuma et al. [37] obtained similar results from a small case series: the use of 3 Tesla HR MRI was able to detect MCA plaques in 2 of 3 patients with acute MCA perforator territory infarcts; in one of them, no significant stenosis of the intracranial arteries was apparent on MRA. Similarly, Miyaji et al. [38] reported a patient with acute paramedian pontine infarction in whom HR MRI revealed the presence of BA plaque spreading to the origin of a paramedian pontine artery. We found 3 articles examining clinical and neuroimaging features of different types of vertebro-basilar strokes. In the studies by Kim et al. [39] and by Lee et al. [40], the diagnosis of BAD was assumed in the presence of an infarction in the territory of one or a few perforating branches arising from a stenosed (of any degree) major vessel (vertebral, basilar or posterior cerebral artery). Chung et al. [41] included patients with posterior circulation stroke and identified BAD by the presence of wall thickening of the BA at the level of the infarct. All these studies used both 1.5 and 3 Tesla MRI although the number of patients studied using HR MRI was not specified. A recent study using HR imaging in 36 patients with deep infarctions within the striatocapsular territory has reported about the presence of the negative type of arterial remodeling (i.e. just limited to the inner arterial wall, and not producing modification of the external vessel profile) in the parent artery [42]. This could be the selective change involved in BAD, and may explain why the vessel caliber may appear normal using current MRA techniques.

As far as END is concerned, we found almost no or very little evidence regarding morphological imaging fea-

tures predicting END in BAD-related infarcts. An acute increase in lesion size has been reported as the morphologic hallmark of END in ischemic stroke [43, 44]; Yamamoto et al. [12] observed an association between END and radiologically defined BAD. In a series of 587 with small subcortical infarction, Jeong et al. [18] identified the presence of BAD or relevant artery stenosis as predictor of END. Miyamoto et al. [45] studied 536 stroke patients looking for clinical and radiological predictors. They also observed a significantly higher prevalence of BAD among patients whose condition deteriorated. They found a significant association between neurological deterioration and a lesion diameter between 15 and 30 mm. Recently, Feng et al. [46] identified leukoaraiosis severity as a predictor of neurological deterioration in small (<15 mm) subcortical infarctions. To the best of our knowledge, no study has hitherto specifically investigated early clinical or imaging predictors of END in BAD patients.

Discussion and Conclusions

Based on our literature search, we observed a large variability of the clinical features in patients where strokes were attributed to BAD. In particular, we were unable to identify a consistent association between BAD and any specific vascular risk factor profile. It is therefore difficult to discuss BAD epidemiology and related clinical correlates.

Although no specific predictor or mechanism of progression has been identified, we can conclude that END

is importantly frequent in BAD-related strokes. This seemed the most consistent data emerging from our review, definition discrepancies notwithstanding.

Among heterogeneities that emerge from our review, we have to point out that an agreement does not exist either as to whether BAD is an aspect of large or small vessels disease.

While BAD radiological diagnosis was based until now on vascular territory, dimensions and/or shape of the acute ischemic lesion, since conventional imaging techniques can only show indirect evidence of parent artery disease [12, 31, 47], there is increasing evidence that high field and HR MRI techniques may allow direct exploration of at least the atheromatous changes inner to parent vessel that are supposed to subtend BAD [34, 38]. Finally, although most authors identify dimensional limits to describe BAD-related lesions, there is no consensus on the exact values of such limits.

It is not possible to perform a comparison between studies where BAD is confirmed by arteries' inner wall imaging with those where BAD was only suspected based on the features of the subcortical infarction due to the large inhomogeneity of collected data, as shown in tables 1 and 2. Out of 6 articles using HR MRI to study BAD, only 3 reported clinical features [8, 41, 42]. In the small series studied by Chung et al. [8], where 2 groups of patients with and without HR MRI proved BAD were compared, no patient had potential sources of heart embolism, while other major risk factors such as hypertension and diabetes were equally distributed. Similarly, Ryoo et al. [42] found no significant differences about

vascular risk factors distribution between 36 patients with confirmed BAD and 44 patients with non-BAD intracranial atherosclerotic disease. Chung et al. [41] studied 286 patients with posterior circulation stroke of whom 80 with BA atheromatous branch occlusive disease. The comparison of clinical characteristics showed no difference in the distribution of vascular risk factors and stroke severity among the different etiology groups examined.

Despite the almost general assumption that END is particularly frequent in BAD-related stroke, no firm data are available from reviewed studies about its rate range.

Considering the whole material examined in our review, we are confident that HR MRI may represent the switchover leading eventually to a clear and reproducible definition of BAD that might match the original description done in pathology studies. This will hopefully help in conclusively identifying BAD-related strokes, discriminating it reliably from lacunar infarctions due to lipohyalinosis, or from other types of subcortical strokes.

As a translational further objective emerging from our review, we can suggest an ad hoc prospective study enrolling an adequately large sample of patients presenting with small subcortical infarct studied, and using HR MRI combined with clinical data collection. This study should describe carefully the clinical features, risk factors and stroke mechanisms associated with it, and follow up patients for an appropriately long duration to estimate the selective outcomes.

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