Study Protocol

Efficacy and Safety of Intravenous Thrombolysis in Branch Atheromatous Disease

International multicenter observational study

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List of abbreviations

BAD	branch atheromatous disease
LSA	lenticulostriate artery
PPA	paramedian pontine artery
ACHA	anterior choroidal artery
μm	micrometer
END	early neurological deterioration
SAPT	single antiplatelet therapy
DAPT	dual antiplatelet therapy
DWI	diffusion-weighted
MRI	magnetic resonance imaging
RSSI	recent small subcortical infarction
BA	basilar artery
MCA	middle cerebral artery
ICA	internal carotid artery
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
IVT	intravenous thrombolysis
LMWH	low-molecular-weight heparin
mmHg	millimeter of mercury
INR	international normalised ratio

Background

Intracranial branch atheromatous disease (BAD) describes an occlusion of deep penetrating intracranial arteries, leading to subcortical infarction (1). Perforating arteries include the lenticulostriate artery (LSA), paramedian pontine artery (PPA), anterior choroidal artery (ACHA), thalamoperforating artery, and Heubner's artery (1-3). This study focuses on BAD affecting the ACHA, LSA, and PPA.

In contrast to lacunar ischemia, which is caused by hypertensive lipohyalinotic degeneration of the distal segment of a perforating artery with a diameter ≤200 μm, BAD involves larger vessels (700-800 μm) affected by atherosclerosis of the parent artery (4). BAD has not been classified as a major cause of cerebral infarction by the National Institute of Neurological Disorders and Stroke (NINDS) or the Trial of Org 10172 in Acute Stroke Treatment (TOAST), which has contributed to a rather scarce data regarding clinical trajectories of this particular stroke etiology (5, 6). According to TOAST criteria, BAD-related strokes are often categorized under small vessel occlusion or classified as an undetermined cause (4, 6, 7). Due to their vessel size, high pressure and flow, these arteries are more susceptible to endothelial damage and atherosclerosis, leading to fluctuating symptoms (8, 9). At admission, BAD often presents similarly to lacunar ischemia (8). But in comparison, a main clinical characteristic of BAD is the frequent occurrence of early neurological deterioration (END), often manifesting as progressive motor deficits, which contribute to poorer outcomes and increased disability (2, 10, 11). Consequently, BAD has been recognized as a major vascular mechanism of progressive motor deficits in penetrating artery infarcts (11). Because of its unique pathophysiology and clinical progression, finding effective treatment strategies remains difficult. Intravenous thrombolysis (IVT) appears to be less effective for BAD compared to other etiologies of acute ischemic stroke (12). Previous studies have explored various treatment strategies, including dual antiplatelet therapy, tirofiban, and anticoagulation therapy, but results have been inconsistent (9, 13-15). This study will assess the efficacy and safety of IVT versus antiplatelet therapy in BAD-related stroke. Furthermore, we will examine the impact of blood pressure on END and functional outcomes.

Aims

The primary aim of this study is to assess the efficacy and safety of IVT compared to single (SAPT) or dual antiplatelet therapy (DAPT) in patients with BAD-related stroke. Secondary aim is to explore the impact of blood pressure fluctuations on END and functional outcomes and its potential interactions with acute therapies.

Methods

This study is an international multicenter observational study recruiting patients with BAD-related stroke in the acute phase on the stroke unit up to 24 hours before admission. As of March 15, 2025, this study has invited and confirmed 5 collaborating institutions, led by Department of Neurology, St. John's

Hospital and SFU Med Vienna, Austria

Study Population

All patients with a BAD-related stroke, aged over 18 years, with symptom onset no more than 24 hours before admission, who were treated in one of the stroke units of the participating institutions between 2010 and 2025, will be included based on the following inclusion criteria. All enrolled patients must have undergone a cerebral MRI for inclusion.

Inclusion criteria

1. DWI lesion: single isolated deep subcortical stroke **AND**
2. The affected vessel involves the LSA, PPA, or ACHA, and the infarct lesion on DWI conforms to one of the following characteristics (A, B, **OR** C):

A. LSA: "Comma-like" infarct lesions with "fan-shaped" extension from bottom to top in the coronary position **OR** ≥ 3 layers (layer thickness 5 mm) on axial DWI.
B. PPA: Infarct lesion extending from the deep pons to the ventral pons on axial DWI.
C. ACHA: Infarct within the anterior choroidal artery territory.

Exclusion criteria

1. Typical recent small subcortical infarction (RSSI) (oval, <20mm in all axes).
2. ≥ 50% stenosis on the parent artery (i.e., BA, MCA, or ICA)
3. Stroke due to other clearly identified causes or possible cardioembolic etiology.

Endpoints

The primary endpoints of this study include:

1. Modified Rankin Scale (mRS) score at three months, with a favorable outcome defined as mRS 0-1 at three months.
2. Early neurological deterioration (END), defined as a worsening of the NIHSS score by ≥4 points within 24-48 hours after symptom onset.
3. Occurrence of symptomatic intracerebral hemorrhage.

Interventions

Intravenous thrombolysis (IVT), single antiplatelet therapy (SAPT), dual antiplatelet therapy (DAPT), blood pressure treatment. All intervention s are indicated clinically based on local protocols and international guidelines and their indication is not related to this study

Hypothesis

H1. Patients with BAD related stroke treated using IVT will achieve better functional outcome as compared to those treated with SAPT.

H2. Patients with BAD related stroke treated using IVT will not achieve better functional outcome as compared to those treated with DAPT.

H3. Patients with BAD-related stroke experiencing blood pressure drop >=30 mmHg in the first 24 hours after admission will experience worse functional outcome as compared to those without blood pressure drop. Interaction with IVT will be significant.

Informed consent

Due to the retrospective nature of the study and the use of anonymized data, obtaining patient informed consent is not necessary.

Study sites

Institutions participating in this study, with a full list of institutions provided under collaborating institutions. The leading institution is the Department of Neurology, St. John's Hospital, Vienna, Austria

Study design

The study will be conducted as an international multicenter retrospective observational study according to the STROBE guideline (16).

Sample size

The estimated sample size is approximately 200-400 patients. As additional institutions are expected to join the study, the total sample size may further increase.

Collected Data

The collected data are listed in

Table 1.

Table 1: collected data

Category		Variables
Baseline characteristics		Age, Gender
Medical history		Arterial hypertension (yes/no), Diabetes mellitus (yes/no), Atrial fibrillation (yes/no), Myocardial infarction (yes/no), Hypercholesterolemia (yes/no), Peripheral artery disease (yes/no), Smoking (yes/no), Renal insufficiency (yes/no)
Pre-Stroke Condition		mRS before stroke
Current Stroke		
	Time information	Year of stroke, Onset-to-Door Time (min), Door-to-Needle Time (min)
	Clinical Information	NIHSS on admission, Onset type (known, wake-up, unknown), NIHSS after 24 to 48h and/or NIHSS at stroke unit discharge, mRS at stroke unit discharge, mRS after 3 months, END (yes/no)
	Localization	Radiological classification into LSA, PPA, or ACHA based on inclusion criteria, Localization (supratentorial - right/left/bilateral; brainstem; other), Internal capsule involvement (yes/no)
	Medication before Stroke	Antiplatelet therapy (none, mono, dual), Vitamin K antagonist (yes/no), INR at admission, Apixaban

		(yes/no), Dabigatran (yes/no), Edoxaban (yes/no), Rivaroxaban (yes/no)
	Therapy after admission	IVT (yes/no), Alteplase (yes/no), Tenecteplase (yes/no), Antiplatelet therapy (none, mono, dual), Vitamin K antagonist (yes/no), Apixaban (yes/no), Dabigatran (yes/no), Edoxaban (yes/no), Rivaroxaban (yes/no), Full-dose LMWH anticoagulation (yes/no)
	Blood Pressure after admission	Systolic blood pressure at admission (mmHg), Diastolic blood pressure at admission (mmHg), Need for antihypertensive therapy before IVT or DAPT (yes/no), Minimum systolic blood pressure within the first 24h on the stroke unit (mmHg), Minimum diastolic blood pressure within the first 24h on the stroke unit (mmHg), Blood pressure decrease ≥30 mmHg within 24h (yes/no)

Data management

Collected data will be entered into an electronic database at the primary study site. All data will be fully anonymized and only shared in this form with researchers. Therefore, a data monitoring committee will not be required. All datasets will be exclusively used for this study, and no third party will be granted access at any time.

Statistics

The statistical analysis will be conducted using SPSS version 29.0.1.0 (IBM Corp., Armonk, NY, USA) and R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables will be presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on their distribution. Categorical variables will be expressed as frequencies (n) and percentages (%). This includes variables such as baseline characteristics, medical history, and treatment modalities. For the analysis of statistical significance in outcome measures, Pearson's χ^2 test or Fisher's exact test will be applied for categorical data, while Wilcoxon rank-sum tests or t-tests will be used for continuous variables, as appropriate. Statistical uncertainty will be reported using 95% confidence intervals (CI). To evaluate the association between three-month mRS and clinical or therapeutic predictors, IPTW and Poisson regression models will be utilized (17). The results of the Poisson regression analysis will be reported as adjusted relative risks (RR) with corresponding 95% CI. A favorable functional outcome is

defined as mRS ≤1 at three months post-stroke. Statistical significance will be set at $p<0.05$.

Ethical considerations

This study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines throughout the whole research process. Approval from the ethics committee will be obtained prior to data collection. As this is a retrospective, non-interventional study, there is no additional physical risk for patients. Data collection is exclusively based on previously recorded medical records. The primary ethical concern in this study relates to data transfer between institutions. To minimize this risk, only fully anonymized data will be shared with researchers. All collected data will be used solely for scientific research purposes, and no personal information will be disclosed or made accessible to third parties.

Time frame

The study is projected to start after approval is granted by the ethics committee of SFU Med (submitted).

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