Study Protocol

Stroke incidence and cognitive outcomes of intracranial atherosclerotic stenosis: study protocol for a multicenter, prospective, observational cohort study

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Background: Intracranial atherosclerotic stenosis (ICAS) is one of the leading causes of stroke worldwide. Current diagnostic evaluations and treatments remain insufficient to assess the vulnerability of intracranial plaques and reduce the recurrence of stroke in symptomatic ICAS. On the other hand, asymptomatic ICAS is associated with an increased risk of cognitive impairment. The pathogenesis of ICAS related cognitive decline is largely unknown. The aim of SICO-ICAS study (stroke incidence and cognitive outcomes of ICAS) is to elucidate the pathophysiology of stroke and cognitive impairment in ICAS population, comprehensively evaluating the complex interactions among life-course exposure, genomic variation, vascular risk factors, cerebrovascular burden and coexisting neurodegeneration.

Methods: SICO-ICAS is a multicenter, prospective, observational cohort study. We aim to recruit 3,000 patients with symptomatic or asymptomatic ICAS (>50% or occlusion) who will be followed up for ≥12 months. All participants will undergo pre-designed magnetic resonance imaging packages, blood biomarkers testing, as well as detailed cognitive domains assessment. All participants will undergo clinical visits every 6 months and telephone interviews every 3 months. The primary outcome measurement is ischemic stroke or cognitive impairment within 12 months after enrollment.

Discussion: This study will establish a large prospective ICAS cohort, hopefully discover new biomarkers associated with vulnerable intracranial plaques, identify subjects at high risk for incident ischemic stroke or cognitive impairment, and eventually propose a precise diagnostic and treatment strategy for ICAS population.

Trial Registration: Chinese Clinical Trials Register ChiCTR2200061938.

Keywords: Intracranial atherosclerosis stenosis (ICAS); stroke; cognitive impairment

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Introduction

Intracranial atherosclerotic stenosis (ICAS) is a major cause of stroke and associated with substantial morbidity and mortality (1,2). Currently, the rate of recurrent stroke is high in symptomatic ICAS and few biomarkers have been found to identify the vulnerable plaques (3). On the other hand, asymptomatic ICAS accounts for 7% in Chinese patients aged ≥40 years (4) and is related to an increased risk of cognitive impairment (5,6). Early recognition of cognitive impairment in ICAS patients has raised concerns, as these individuals may greatly benefit from early intervention of vascular risk factors. However, the pathogenesis of ICAS related cognitive decline is largely unknown.

Beyond the degree of luminal stenosis, intraplaque hemorrhage and positive artery remodeling have been found valuable for identifying vulnerable plaques by high-resolution intracranial vessel wall imaging (IVWI) (7-11). However, relying solely on the information from IVWI to predict future stroke is far from sufficient. Multimodal magnetic resonance imaging (MRI) examinations should be performed to quantitatively evaluate the effects of ICAS on cerebral blood flow (CBF), brain structure and function. In addition to blood lipid and glucose, attention should be paid to blood pressure variability, a potential indicator associated with stroke occurrence (12). The impact of the environment on ICAS should not be ignored. Epidemiological studies have shown that ischemic stroke is closely related to air pollution (13).

According to the Atherosclerosis Risk in Communities (ARIC) study, the overall prevalence of cognitive impairment is 39.3% in the elderly and 47.1% in patients with ICAS (14). Clinical studies have observed that cognitive decline in patients with ICAS occurs several years before a stroke event (15,16). It is uncertain which intracranial artery stenosis results in a higher risk of cognitive impairment (14,17,18). The interactions among ICAS, small vessel disease (SVD) and Alzheimer's disease (AD) pathology need to be clarified. It is expected to build a comprehensive research framework to disclose the impact of ICAS on brain damage and cognition *in vivo*, and establish a score system for predicting cognitive impairment in ICAS population.

For the treatment of high-risk symptomatic ICAS patients, several studies have shown that the intensive medical treatment is superior to intravascular therapy (19,20). Recently, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, which are novel lipid-lowering medications, have attracted increasing attention. In patients with coronary atherosclerosis, PCSK9 inhibitors significantly reduced the risk of combined cardiovascular events by 20% (21), and effectively induced plaque regression (22). There has been no evidence regarding their effectiveness on intracranial plaque reversal.

To address all above challenges, we launch a large prospective ICAS cohort study. Multimodal MRI examinations, blood sample testing, and longitudinal neuropsychological assessment will be performed, with an emphasis on systematically investigating the influence of ICAS on stroke occurrence and cognitive impairment.

Methods

Design

This is a multicenter, prospective, observational cohort study, which plans to recruit ICAS patients who will be followed up for a minimum of 1 year. Patients will be divided into symptomatic and asymptomatic ICAS based on whether they had previously suffered an ischemic stroke or transient ischemic attack (TIA) in the territory of ICAS. The disease effects of ICAS will be assessed comprehensively through multimodal MRI examinations, neuropsychological assessment battery, blood sample testing, and routine examinations for vascular-related risk factors. Patients will undergo longitudinal cognitive and functional assessments during clinical visits every 6 months and telephone interviews every 3 months. An overview and schedule of assessments of this study is displayed in *Figure 1* and *Table 1*. This study has obtained approval from the institutional review board at Peking Union Medical College Hospital (PUMCH), the Chinese Academy of Medical Sciences (JS-3479D, April 14, 2022), and the ethics boards of local participating centers. All participants will be required to provide written informed consent and the study will be performed according to the Declaration of Helsinki (as revised in 2013).

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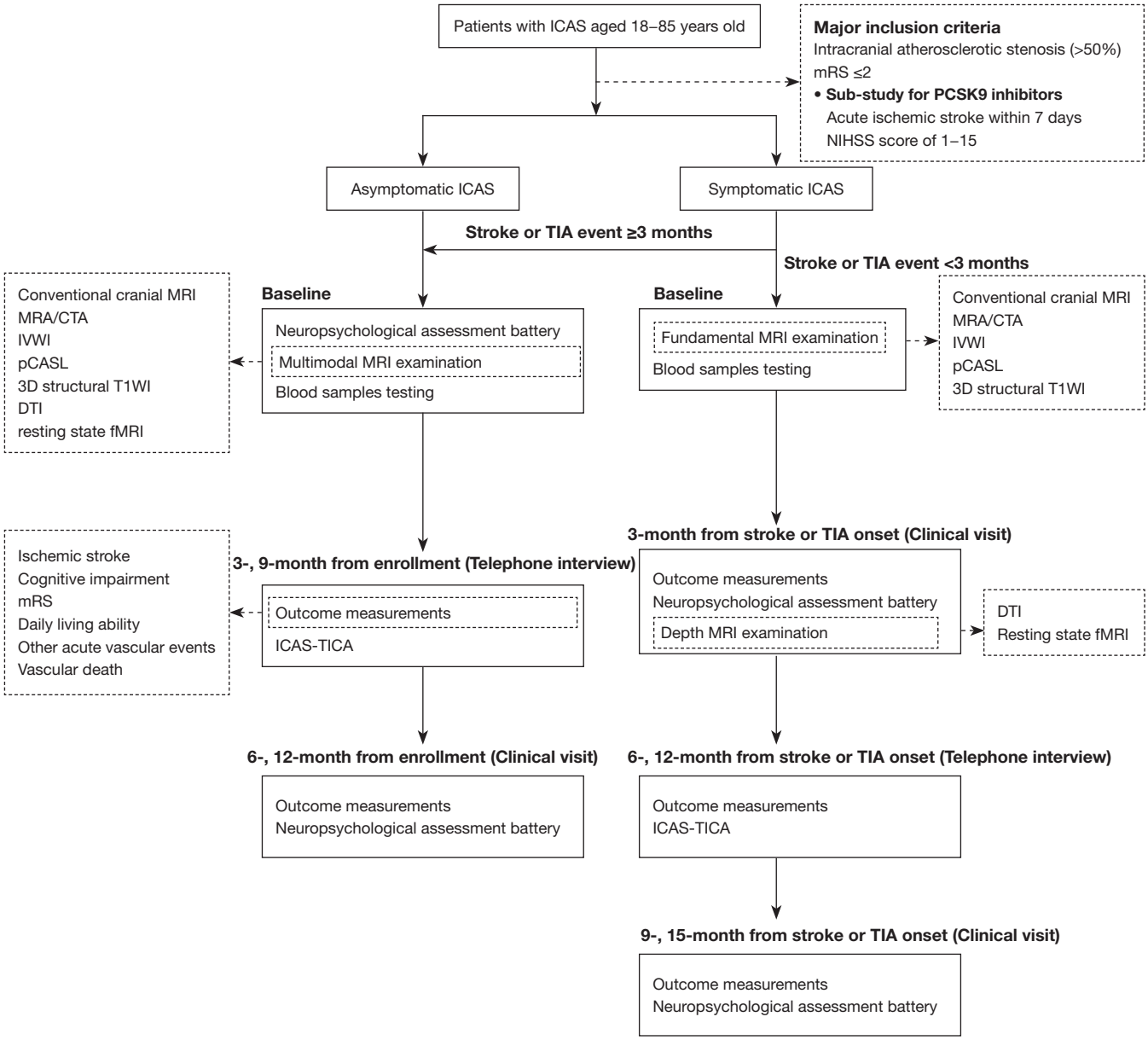

Figure 1 Flow chart of the SICO-ICAS study. SICO-ICAS, stroke incidence and cognitive outcomes of intracranial atherosclerotic stenosis; mRS, modified Rankin score; PCSK9, proprotein convertase subtilisin-kexin type 9; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; MRA, magnetic resonance angiography; CTA, computed tomography angiography; IVWI, intracranial vessel wall imaging; 3D-pCASL, three-dimensional pseudo-continuous arterial spin labeling; DTI, diffusion tensor imaging; fMRI, resting state functional MRI; MRI, magnetic resonance imaging; ICAS-TICA, ICAS version of telephone interview for cognition assessment.

Number of centers

The study is being conducted from August 2022 to August 2024. Approximately 100 tertiary centers in China will participate in this study. So far, more than 60 centers have participated in the first batch. Sites that do not recruit subjects within 3 months since site initiation may be closed.

Participants

The inclusion criteria are as follows: (I) patients aged

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Table 1 Schedule of assessments of the SICO-ICAS study

General procedures	Study day/timepoint					
	Screening	Baseline	Month 3*	Month 6*	Month 9*	Month 12*
Informed consent	×					
Demographic characteristics		×				
Medical and family history		×				
Medications		×				
mRS score[a]	×	×	×	×	×	×
NIHSS score[b]	×	×				
Routine laboratory tests (blood sample)[c]		×		×		×
Testing for exposome (blood sample)		×				
Conventional cranial MRI[d]	×	×				
3D time-of-flight MRA or CTA[e]	×	×				
IVWI[f]		×		×		
pCASL		×				
3D structural T1WI		×				
DTI[g]		×				
Resting state fMRI[h]		×				
Carotid artery ultrasound or other choice[i]	×	×				
24 h ambulatory blood pressure		×				
12 lead EEG		×				
Neuropsychological assessment battery[j]		×		×		×
ICAS-TICA[k]			×		×	
Concomitant therapy			×	×	×	×
Adverse events			×	×	×	×

[a], this score will be collected in symptomatic subjects with stroke history; [b], this score will be collected in symptomatic subjects with acute stroke event; [c], the complete blood count, hepatic and renal function, blood lipids [not limited to total cholesterol, triglyceride, LDL-C, HDL-C, lipoprotein(a)], HbA1c, HCY and CRP are necessary; [d,e,i], if images from local hospitals are used in screening, the examinations should be retaken in centers at baseline; [f], patients included in the sub-study should retake this imaging after 6 months of therapy; [g,h,j], symptomatic patients with a history of stroke or TIA <3 months will undergo these assessments at 3 months from the onset of stroke or TIA; [k], if the score is below to 32 and the patient judged to be cognitively normal at the last visit, this patient will be considered at high risk of developing cognitive impairment, and the subsequent clinical evaluation is suggested; *, the time-points of follow-up will keep up with the time of initial neuropsychological assessment battery, i.e., asymptomatic ICAS and symptomatic ICAS patients (with a history of stroke or TIA ≥3 months) will undergo telephone interviews at 3 and 9 months and clinical visits at 6 and 12 months after enrollment, while symptomatic ICAS patients with a history of stroke or TIA <3 months will undergo telephone interviews at 6 and 12 months and clinical visits at 9 and 15 months from the onset of stroke or TIA. SICO-ICAS, stroke incidence and cognitive outcomes of intracranial atherosclerotic stenosis; mRS, modified Rankin score; NIHSS, National Institutes of Health Stroke Scale; MRA, magnetic resonance angiography; CTA, computed tomography angiography; IVWI, intracranial vessel wall imaging; pCASL, pseudo-continuous arterial spin labeling; DTI, diffusion tensor imaging; fMRI, resting state functional MRI; MRI, magnetic resonance imaging; EEG, electrocardiogram; ICAS-TICA, ICAS version of telephone interview for cognition assessment; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; HCY, homocysteine; CRP, C-reactive protein; TIA, transient ischemic attack.

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between 18 and 85 years; (II) patients with ICAS {defined as intracranial artery stenosis (>50% or occlusion) at Willis circle branch [intracranial internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), basilar artery (BA) or intracranial segment of the vertebral artery (VA)]} confirmed by magnetic resonance angiography (MRA) or computed tomography angiography (CTA); (III) patients with a modified Rankin score (mRS) ≤2, which indicates no extra help is needed for daily life (note: a score of 0 represents no symptoms, while a score of 6 signifies death); and (IV) patients included in the sub-study about PCSK9 inhibitors requiring an acute ischemic stroke within 7 days of symptom onset and in the same territory of the symptomatic ICAS [a total National Institutes of Health Stroke Scale (NIHSS) score of 1–15].

The exclusion criteria are as follows: (I) patients with >50% extracranial artery stenosis; (II) patients with relative or absolute contraindications to MRI (e.g., metals in the body, claustrophobia, etc.); (III) those with intracranial stenosis due to non-atherosclerotic etiologies, such as vasculitis, dissection, moyamoya disease, embolus, immune system diseases, or other causes; (IV) patients with other known etiological types of stroke, such as cerebral hemorrhage or subarachnoid hemorrhage, and cardiac cerebral embolism; (V) patients diagnosed with neurodegenerative diseases such as AD, Lewy body dementia, frontotemporal dementia or Parkinson's disease; (VI) patients with a history of traumatic brain injury, multiple sclerosis, encephalitis, tumors, poisoning, syphilis, and serious heart, lung, liver, kidney, or endocrine system diseases; and (VII) patients who refuse to sign the informed consent.

We also will enroll healthy controls who have no stenoses of intracranial or extracranial vessels, and no history of stroke or TIA, cognitive impairment, traumatic brain injury, brain tumors, etc. The recruitment of these individuals will primarily come from communities and health examinations.

Clinical data collection

(I) Demographic characteristics: age, sex, education years, occupation, marital status, residence status, height, weight, waist circumference, physical activity, sleep duration and questionnaire about exposome; (II) previous medical history: stroke or TIA, hypertension, diabetes, hyperlipidemia, atrial fibrillation, myocardial infarction, heart failure, smoking, alcohol consumption, vitamin B12 deficiency, hyperthyroidism or hypothyroidism, immune system diseases, tumors, sleep disorders, anxiety and depression, brain trauma, poisoning, substance abuse, and other diagnosed neurological and psychiatric disorders; (III) family history: cardiovascular and cerebrovascular diseases, dementia, etc.; (IV) medications: stroke prevention drugs and concomitant medications; (V) routine laboratory tests [complete blood count, hepatic and renal function, blood lipids, glycated hemoglobin (HbA1c), homocysteine, C-reactive protein (CRP), other indicators related to vascular or cognitive impairment, and apolipoprotein E (APOE) genotyping (when available)]; and (VI) general examinations [carotid artery ultrasound, 12 lead electrocardiogram, Holter electrocardiogram, echocardiography, and 24 h ambulatory blood pressure (if available)].

Blood sample biomarkers testing

To test for additional biomarkers, a 12-mL venous blood sample will be collected and centrifuged at 2,000 rpm for 10 minutes at room temperature, after which blood cells, plasma, or serum will be separated as appropriate and stored at –80 ℃ for further study. Specifically, we will test biomarkers for exposomes such as heavy metals exposure. Furthermore, neurodegenerative biomarkers (amyloid-β, P-Tau, etc.), axon injury biomarkers (nerve filament light chain protein, etc.), and other multi-omics analyses (proteomics, transcriptomics, metabolomics, and genomics) will be performed as an optional choice.

Neuropsychological assessment battery

(I) Overall cognition: mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA); (II) daily living ability: activities of daily living scale (ADL), consisting of 14 items (23); (III) mental behavior: Hamilton anxiety and depression scale (24); (IV) a neuropsychological battery: (i) memory: auditory verbal learning test (AVLT, Chinese version), paired associate word learning, Rey complex figure recall test, episodic memory, working memory; (ii) visual-spatial function: Rey complex figure copy test, copy cube; (iii) attention: trail making test A (TMT-A), digit span backward and forward; (iv) executive function: TMT-A and TMT-B, digit symbol substitution, clock drawing test; (v) language: Boston naming test, word fluency, picture talk; and (V) evaluation of clinical dementia: using the clinical dementia rating (CDR) scale (25); a score of 0 signifies no dementia and a score of 3 denotes severe dementia. The

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overall assessment will take about 60 to 90 minutes.

We will first construct a Z-score for each test using the means and standard deviations from the Chinese norm. If more than half of the tests within the same cognitive domain are less than –1.5 Z, the cognitive domain will be considered impaired. If a patient has at least one impaired domain, their daily life ability and CDR should be evaluated by a neurologist who is specialized in cognitive decline. Patients whose daily life ability is relatively preserved (ADL ≤16 points) and CDR scale is 0.5 will be classified into the mild cognitive impairment group. Meanwhile, patients whose daily life ability is impaired (ADL >16 points) and CDR scale is ≥1 will be classified into the dementia group. Finally, the etiological classification for cognitive impairment can be acquired, and Hachinski Ischemic Scale (HIS) (26) will be used to facilitate the differentia diagnosis of vascular dementia and AD (27-29) (see below for the follow-up process).

Multimodal MRI examinations

Every participant will undergo pre-designed imaging packages, containing conventional cranial MRI [T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), T2-weighted fluid attenuation inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and T2*-WI or susceptibility-weighted imaging (SWI)], three-dimensional time-of-flight MRA, IVWI, three-dimensional pseudo-continuous arterial spin labeling (3D-pCASL), and 3D structural T1WI. Diffusion tensor imaging (DTI) and resting-state functional MRI (fMRI) are possible alternatives (if available). The above multimodal MRI examinations evaluate several aspects of ICAS, including the degree of stenosis, plaques information, CBF, brain structure, brain function, and SVD markers. The overall examination will take about 40 to 60 minutes.

During the MRI scanning, all participants will be asked to close their eyes, keep their heads still, and avoid sleep or cognitive activity. For the scanning process and parameters requirements refer to our previous study (30) and the expert consensus of the Chinese Brain Imaging Alliance on standardized acquisition and analysis of AD brain MRI.

Follow-up

Generally, all patients will be followed up for at least 1 year and will retake the neuropsychological assessment battery every 6 months during clinical visits and undergo a simple cognitive assessment every 3 months by telephone interview. The specific follow-up process of patients with symptomatic and asymptomatic ICAS is shown below.

Patients with asymptomatic ICAS will be followed up by telephone interviews at 3 and 9 months after enrollment, including end-point events assessment (see below), mRS score, daily living ability, control of vascular risk factors, medications status, as well as conducting a simple cognitive test by ICAS version of telephone interview for cognition assessment (ICAS-TICA). At 6 and 12 months after enrollment, the patients will be followed up face-to-face and will retake the neuropsychological assessment battery, along with repeated measurement of routine laboratory tests.

Symptomatic ICAS patients with a history of stroke or TIA ≥3 months will undergo the same follow-up process as those with asymptomatic ICAS. However, symptomatic ICAS patients with a history of stroke or TIA <3 months will undergo the initial neuropsychological assessment battery at 3 months from the onset of stroke or TIA. Based on the patients' cooperation, the optional advanced MRI examinations (DTI, resting-state fMRI) will also be performed 3 months from the onset of ischemic cerebrovascular event. The patients will subsequently be followed up by telephone interviews at 6 and 12 months and then face-to-face follow-up at 9 and 15 months from the event onset. The contents of the follow-up with symptomatic ICAS will be consistent with asymptomatic ICAS.

Outcome

The primary outcome measurement of this study is ischemic stroke or cognitive impairment within 12 months after enrollment. Ischemic stroke recurrence is defined by a focal neurological defect (confirmed by new ischemic lesions on DWI) and the diagnosis of cognitive impairment is described above. The secondary outcome measurements are the mRS score, daily living ability, other acute vascular events (new cerebral hemorrhage/subarachnoid hemorrhage, myocardial infarction, visceral hemorrhage, heart failure, pulmonary embolism, arrhythmia, etc.), and vascular death events (death from ischemic/hemorrhagic stroke, myocardial infarction, visceral hemorrhage, heart failure, pulmonary embolism, sudden death, arrhythmia, etc.).

Treatments

We will select 20 centers to join in the sub-study to observe the real-world effectiveness of PCSK9 inhibitors

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(evolocumab, subcutaneously at a dose of 140 mg every 2 weeks) in patients with symptomatic ICAS who had suffered an ischemic stroke within 7 days. Baseline and repeated IVWI examinations after 6 months of therapy will be performed to compare intracranial plaque burden changes between patients receiving PCSK9 inhibitors plus high-intensity statins and those receiving high-intensity statins alone. The primary efficacy endpoint is the nominal change in percent atheroma volume (PAV) of the lesion side from baseline to 6 months. The PAV will be calculated in line with a previous study (22). Exploratory endpoints include the changes in lipid parameters and CRP level, the percentage of patients with PAV regression, imaging changes of other plaque features (stenosis degree, plaque length, maximum thickness, etc.), ischemic stroke recurrence, cognitive impairment, other acute vascular events, and vascular death events. Individual treatments applied in the remaining centers will comply with the clinical guidelines (31).

Adverse events

All exploratory clinical events and laboratory adverse events that occur during the study will be reported and recorded.

Data management and interpretation

All participating centers will collect clinical data and complete the pre-designed electronic case report form (eCRF) on a commercial Internet database (brainscience.cc).

All blood samples will be delivered to and stored in the core labs (PUMCH) for unified management and analysis. The images will be interpreted independently by a radiologist and a neurologist who do not know the patients' clinical information. The diagnosis of mild cognitive impairment and dementia, and the etiological classification will be independently interpreted by two neurologists who are specialized in cognitive disorders, and differences between the two observers will be resolved by a third expert to reach a consensus.

Sample size and statistical analysis

The ARIC study (14) showed that the prevalence rates of cognitive impairment with ICA, MCA, ACA, BA, VA, and PCA plaques are 38.7%, 40.4%, 53.6%, 44.3%, 44.9%, and 49.0%, respectively. Meanwhile, based on the preliminary results of our unpublished data, the prevalence of cognitive impairment in the ICA, MCA, ACA, BA, VA, and PCA stenosis groups were 50.0%, 32.7%, 33.3%, 37.5%, 53.3%, and 58.3%, separately. Considering an attrition rate of 15%, the 95% confidence interval of the estimated total sample size is 2,527–2,699. Therefore, we plan to enroll approximately 3,000 cases. Regarding the sub-study for the evaluation of comparative effectiveness of statins with and without PCSK9 inhibitors, 220 patients in each treatment arm will be needed to achieve a 90% power at a 2-sided significance level of 0.05 to detect a nominal treatment difference of 0.9% (22), assuming a 2.9% standard deviation. Considering the potential attrition rate of 20%, 275 patients in each arm will be recruited. Further, we also plan to enroll about 2,000 healthy controls on the basis of feasibility.

Descriptive statistical analysis will be used to present the demographic and participant characteristics. Continuous data will be described by the mean (standard deviation) or median (inter-quartile range), and categorical data will be compared using the percentile. Continuous variables conforming to normal distribution will be compared using the two-sample *t*-test or one-way analysis of variance (ANOVA). Meanwhile, continuous variables that do not conform to a normal distribution will be compared using the Mann-Whitney U test or Kruskal-Wallis test. The Chi-square test or Fisher's exact test will be used for categorical variables. The relationships between baseline features and specific risk factors and prognostic events will be analyzed by multivariable logistic regression or Cox proportional hazards regression models, as appropriate. Propensity score matching method will be used in the comparative effectiveness study to generate a 1:1 matched cohort for patients treated with statins plus PCSK9 inhibitors versus solely statins. Cross-sectional analyses will also be conducted to explore the risk factors distinguishing symptomatic and asymptomatic ICAS.

Discussion

There is growing concern about the link among ICAS, stroke, and dementia (5,32). It is pressingly needed to establish a large prospective ICAS cohort to comprehensively assess the vulnerability of intracranial plaques, reveal the underlying mechanisms of ICAS related cognitive decline, and ultimately improve current prevention and intervention strategies for ICAS population.

The main objectives of the SICO-ICAS study are as follows. Firstly, this study will provide a panoramic assessment of the vulnerability of intracranial plaques

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by comparing the differences in multimodal imaging biomarkers between patients with symptomatic and asymptomatic ICAS, including IVWI (morphology of vessel wall, intracranial plaques features, neovascularization), pCASL (CBF), 3D structural T1WI (grey matter structure), DTI (white matter tracts), and resting-state fMRI (functional connectivity, brain network). Blood samples contain clues that allow us to match biological changes back to life-course exposure (33). Traditional risk factors like low-density lipoprotein cholesterol (LDL-C), HbA1c, and blood pressure variability will also be analyzed. Secondly, this study will calculate the prevalence of mild cognitive impairment and dementia in ICAS patients and analyze the relevant risk factors. The complete biological research framework examined by multimodal imaging biomarkers including brain vessels, network, and reserve will be integrated to comprehensively investigate the pathologies of ICAS on brain damage and cognition. The testing of blood biomarkers for neurodegeneration and axon injury-related factors and the APOE ε4 allele will be acquired if needed. The mechanisms that link ICAS with SVD and AD pathology in the development of dementia will be explored. Thirdly, the disease effects of ICAS will be further clarified by comparing ICAS patients to healthy controls. Fourthly, this study will assess the real-world effectiveness of PCSK9 inhibitors in symptomatic patients with acute ischemic stroke.

There are several limitations in this study. Firstly, this is an observational cohort study, so there may be some residual confounding bias even after multivariable adjustment. Secondly, participants in this study will be followed up for at least 1 year; however, the incidence of stroke with asymptomatic ICAS patients and the incidence of cognitive impairment may be relatively low at the 1-year stage. Lastly, the histological evidence to validate the imaging results, such as the plaque components, is lacking; although IVWI findings have been confirmed by postmortem pathological results (34-36).

In conclusion, this study has been designed to provide in-depth insights into the pathophysiology of ICAS and its disease effects on stroke and cognitive impairment. It is anticipated to eventually establish a precise diagnostic and treatment strategy for ICAS population.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3570/coif). WX serves as an unpaid editorial board member of *Annals of Translational Medicine* from Jun 2019 to May 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study has obtained approval from the institutional review board at Peking Union Medical College Hospital (PUMCH), the Chinese Academy of Medical Sciences (JS-3479D, April 14, 2022), and the ethics boards of local participating centers. All participants will be required to provide written informed consent and the study will be performed according to the Declaration of Helsinki (as revised in 2013).

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