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THE ROLE OF ATHEROCALCYNOSIS IN THE DEVELOPMENT OF THROMBOTIC SUBTYPE OF ISCHEMIC STROKE AS A CAUSE OF POSTSTROKE COGNITIVE DISORDERS AND DEMENTIA.

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Abstract:

Large artery atherosclerosis (LAA) stands out as a prevalent subtype within the spectrum of ischemic stroke, emerging as a primary contributor to cerebrovascular diseases. The etiology and risk factors associated with LAA stroke reveal a noteworthy association with cerebral small vessel disease (SVD). Clinical investigations have consistently indicated a positive correlation between LAA stroke and various magnetic resonance imaging (MRI) characteristics indicative of cerebral SVD in individuals experiencing ischemic strokes. Recognizing the intertwined nature of these conditions is crucial, given that the therapeutic approaches employed for LAA stroke necessitate concurrent consideration for patients grappling with cerebral SVD.

Keywords: ischemic stroke, cerebral small vessel disease, large artery atherosclerosis, cognitive dysfunction, dementia

INTRODUCTION: The World Health Organization has delineated "stroke" as the abrupt onset of clinical manifestations involving focal (or global) disturbances in cerebral function, enduring beyond 24 hours or resulting in fatality, without an evident cause other than of vascular origin [1]. Ischemic stroke (IS) predominates among stroke occurrences, encompassing cryptogenic, lacunar, and thromboembolic subtypes, typically arising from the interruption of blood supply to a specific brain region [2.3]. Recent research sources cite the Atherosclerosis Risk in Communities (ARIC) study, an ongoing investigation delved into the associations between dementia and dynamic ischemic stroke incidence, frequency, and severity, spanning an average of 4.4 assessments over a median follow-up duration of 25.5 years. Cox proportional hazards models were employed, adjusting for sociodemographic characteristics, apolipoprotein E, and vascular risk factors. [5]

The risk post-stroke risk of dementia escalates, particularly in cases of larger and more severe strokes. There is a pressing need for precise estimations regarding the likelihood of dementia following a stroke, with a specific emphasis on ischemic stroke (IS), given its predominant occurrence. Such estimations are imperative for guiding clinical practices, facilitating research initiatives, and informing policymaking. [6]

Evaluating cognitive function in individuals who have experienced a stroke presents numerous challenges. The timing of dementia onset becomes a critical factor, given that early cognitive alterations post-stroke may exhibit a transient nature, and attrition rates are notable in post-stroke follow-up. Additionally, challenges such as aphasia and neglect, frequently observed after a stroke, can introduce complexities in cognitive assessments. Consequently, it is advisable to undertake a comprehensive cognitive evaluation. Given that risk factors for stroke coincide with those for dementia, careful discrimination is essential to differentiate pre-existing cognitive dysfunction or dementia (present in 10% of hospitalized stroke patients) from newly emerging post-stroke impairments [7.8.9].

The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) integrates longitudinal data

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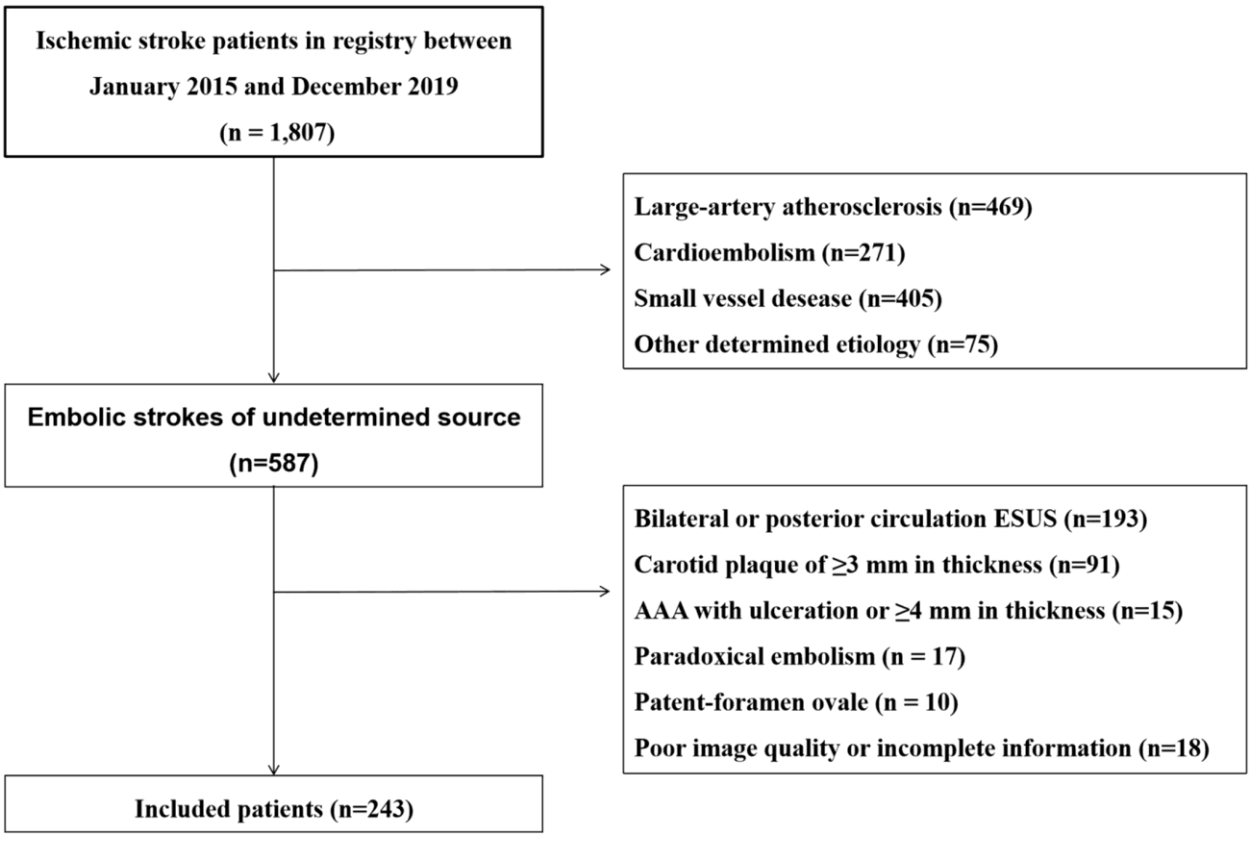
encompassing vascular risk factors, cognitive performance, adjudicated stroke incidents, and stroke severity, complemented by an extensive dementia surveillance protocol. With the evaluation of cognitive status and vascular risk undertaken at various intervals, this study enables an examination of the influence of stroke on dementia. The design of the study incorporates the consideration of shared risk factors, providing a comprehensive framework for understanding the interplay between stroke, cognitive decline, and other contributing elements. Researchers posit a hypothesis suggesting that, in comparison to individuals devoid of stroke and irrespective of vascular risk factors, the likelihood of poststroke dementia is elevated in patients experiencing ischemic stroke (IS), those with more severe strokes, and those encountering multiple recurrent strokes [10].

PURPOSE OF THE STUDY: The investigations aim to explore the components comprising overall fat quality and various types of lipid spectrum (LS) concerning the risk of atherothrombotic ischemic stroke. According to the World Health Organization, LS plays a pivotal role in the etiology of several diseases and is crucial for overall health [11A previous investigation has highlighted a negative correlation between lipid spectrum (LS) and the risk of ischemic stroke (IS). However, the precise influence of various LS patterns and the optimal quantity of LS necessary for maximal risk mitigation remain incompletely understood. Further elucidation of these aspects is warranted to better comprehend the nuanced relationship between LS and IS risk reduction. Additionally, distinct types of LS have exhibited varying effects on IS risk, with higher levels of occupational LS being correlated with an increased risk of stroke [13].

Utilizing high-resolution magnetic resonance imaging (HR-MRI), our recent investigation has substantiated that high-risk non-stenotic intracranial plaque serves as a plausible etiology for embolic stroke of undetermined source (ESUS). Nevertheless, the mechanisms associated with intracranial atherosclerosis contributing to embolic stroke of undetermined source (ESUS) are presumed to be multifactorial and are likely to exhibit variations contingent upon the distinctive characteristics of the involved plaques [14]. Another study, focusing on patients with recent strokes within the middle cerebral artery territory (>50% stenosis), posited that cortical/subcortical infarcts (artery-to-artery embolic infarcts) exhibit distinct vulnerable plaque features (see Figure 1) in contrast to deep infarctions (non-embolic infarcts) [15].



Flow diagram of the study.

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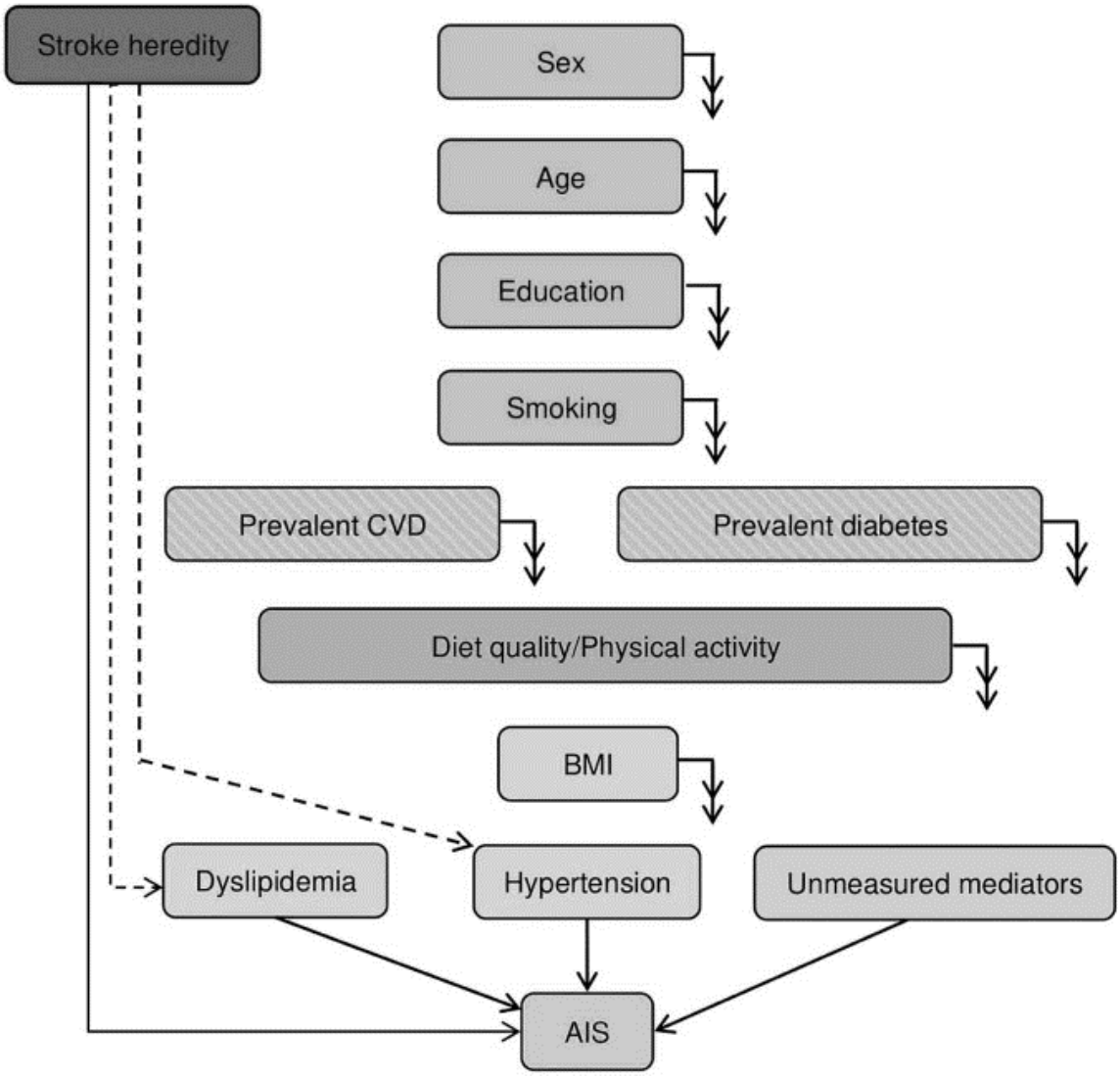
Indicates aortic arch atherosclerosis; and ESUS, embolic stroke of undetermined source. 27 Oct 2022 Journal of the American Heart Association. 2022;11:e026737

Baseline characteristics were gathered from the hospital information system, encompassing demographics, medical history, cerebrovascular disease risk factors, initial National Institutes of Health Stroke Scale (NIHSS) score, and findings from blood investigations.



Atherothrombotic stroke pathogenesis pathway. *Int. J. Mol. Sci.* 2021, *22*(16), 9032;

RESULTS AND DISCUSSION: In recent years, research sources indicate the recruitment of a total of patients diagnosed with embolic stroke of undetermined source (ESUS) in the initial cohort. Subsequent exclusions were applied to individuals with bilateral or posterior circulation ESUS, carotid plaque of ≥3 mm in thickness, aortic arch atherosclerosis exhibiting ulceration or ≥4 mm in thickness, cases involving paradoxical embolism, patent foramen ovale, and instances with poor image quality or incomplete information. Patients should be categorized into two groups, namely, an ischemic cerebral small vessel disease (SVD) group and a large artery atherosclerosis (LAA) group, based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Additionally, participants should have diverse clinical conditions such as sick headache, hypokalemic periodic paralysis, idiopathic facial paralysis, hypertension, or trigeminal

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neuralgia. Control individuals should not exhibit bleeding tendencies, cerebral aneurysms, arteriovenous malformations, mental illness, severe liver, kidney, heart, or lung diseases, autoimmune diseases, or cerebral SVD. Importantly, there were no significant differences in general information between the two groups [15].

The majority of studies conducted on patients treated at a tertiary hospital focused on analyzing risk factors and distinctions between ischemic cerebral small vessel disease (SVD) and large artery atherosclerosis (LAA) stroke utilizing the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. The findings revealed distinct associations with risk factors for each subtype. Hypertension, diabetes mellitus, high total cholesterol (TC), hypertriglyceridemia, and smoking were strongly correlated with ischemic cerebral SVD. In contrast, hypertension, diabetes mellitus, high low-density lipoprotein (LDL), hypertriglyceridemia, and smoking were associated with LAA. Furthermore, multivariate logistic regression analysis highlighted that, when comparing risk factors for ischemic cerebral SVD with those of LAA, elevated total cholesterol (TC) emerged as a prominent risk factor specifically for ischemic cerebral SVD[16-17].

Atherosclerosis represents a lifelong progressive condition, yet its precise etiology and risk factors remain incompletely understood. Large artery atherosclerosis (LAA), constituting approximately 30% of ischemic strokes, termed LAA type stroke, stands as a significant contributor to disability and mortality rates in China [18]. However, specific physiological abnormalities, traits, or habits may predispose individuals to atherosclerosis development. Commonly recognized risk factors encompass elevated cholesterol and low-density lipoprotein (LDL) levels, diminished high-density lipoprotein (HDL) levels, hypertension, tobacco smoking, diabetes mellitus, obesity, sedentary lifestyle, and advancing age. Hypertension and diabetes emerge as major risk factors identified in LAA. During the initial stages, oxidative stress impairs the biological activity of nitric oxide produced by vascular endothelial cells, resulting in endothelial cell damage and diminished vascular compliance, indicative of vascular functional alterations. Failure to timely detect such vascular functional changes and implement necessary interventions leads to inevitable structural alterations as the disease progresses. Once structural changes manifest, arterial elasticity alterations become irreversible [19].

Smoking stands out as of atherosclerotic stenosis. Smoking may exert its detrimental impact on stroke risk through multiple avenues. In the short term, smoking is believed to enhance thrombus formation within atherosclerotic arteries, thereby contributing to acute ischemic events. Over the long term, the chronic exposure to tobacco smoke is associated with the development and progression of atherosclerotic stenosis, further compromising vascular health. Moreover, smoking is implicated in reversible factors such as heightened platelet aggregation and arterial vasoconstriction. The augmentation of sympathetic activity induced by smoking may lead to increased platelet reactivity, fostering a pro-thrombotic state. Additionally, arterial vasoconstriction, driven by smoking-induced sympathetic activation, can contribute to reduced blood flow and potentially exacerbate the risk of ischemic events. These multifaceted effects underscore the complex interplay between smoking and the pathophysiology of ischemic stroke. The comprehensive understanding of these mechanisms is imperative for the development of targeted interventions aimed at reducing the impact of smoking on stroke risk. of atherosclerotic stenosis. Smoking's potential role in increasing stroke risk extends to reversible factors such as heightened platelet aggregation and arterial vasoconstriction, attributed to an augmentation of sympathetic activity. These factors collectively contribute to the overall stroke risk. A 10-year prospective cohort study conducted in China revealed that smoking could elevate the risk of ischemic stroke among individuals with hypertension. Furthermore, a significant interaction was identified between smoking and hypertension, amplifying the risk of ischemic stroke [20].

In recent years, numerous epidemiological studies have demonstrated a close association between dyslipidemia and the onset of ischemic stroke. Lipid metabolism appears to play a role not only in large vessel atherosclerosis but also in the occlusive pathology of small intra-cerebral arteries. Dyslipidemia emerges as a potential causal and modifiable risk factor for ischemic stroke. Despite this, a limited number of studies in the literature have explored the correlation between stroke subtypes and lipid profiles. Our investigation delved into the distinct associations between two crucial subtypes of ischemic stroke and lipid profiles.

Our findings revealed a significant association between hypertriglyceridemia and ischemic cerebrovascular disease, particularly atherosclerotic cerebral infarction. Elevated low-density lipoprotein (LDL) levels were closely linked to large artery atherosclerosis (LAA), while hypercholesterolemia exhibited a stronger association with ischemic cerebral small vessel disease (SVD).

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CONCLUSIONS. Ischemic cerebral small vessel disease (SVD) and large artery atherosclerosis (LAA) share certain risk factors, but also exhibit distinct ones. Consequently, strategies for mitigating the risk factors for ischemic cerebral SVD may necessitate different approaches compared to those for addressing the risk factors for LAA. Further exploration is warranted to delve into the pathogenesis, classification, and targeted therapeutic interventions specific to ischemic cerebral SVD and LAA. Enhanced understanding of these aspects is crucial for the development of more effective and tailored preventive measures and treatment strategies for each subtype of ischemic stroke.

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