ONLINE JOURNAL OF BIOLOGICAL SCIENCES

LITERATURE REVIEW

Intracranial Atherosclerotic Disease: Treatment Potential and Diagnostic Opportunities

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Abstract: Atherosclerosis, characterized by the accumulation of atherosclerotic plaques within large arteries, substantially increases the risk of cardiovascular events, including ischemic stroke. Intracranial atherosclerotic disease (ICAD) represents a particularly significant clinical threat given its strong association with ischemic stroke across multiple intracranial arterial territories. This review provides a comprehensive analysis of the pathogenesis, diagnosis, and management of intracranial atherosclerosis. Special attention is given to the interplay of lipid metabolism disorders, chronic inflammation, immune responses, and genetic factors in disease progression. The review further highlights the diagnostic value of non-invasive imaging modalities, including Transcranial Doppler ultrasound (TCD), CT Angiography (CTA), Magnetic Resonance Angiography (MRA), and Digital Subtraction Angiography (DSA). Beyond established treatments such as antithrombotic therapy and lipid-lowering interventions, emerging therapeutic approaches, including ischemic conditioning and novel anti-inflammatory agents, are examined. The role of risk factor modification and surgical options such as stenting and endarterectomy are also discussed. By synthesizing current evidence and highlighting evolving strategies, this review aims to serve as a practical resource for clinicians involved in the diagnosis and treatment of ICAD, with the ultimate goal of improving patient outcomes and reducing stroke-related morbidity and mortality.

Keywords: Intracranial atherosclerosis, Intracranial atherosclerotic disease, ICAD, Ischemic stroke, Atherosclerotic plaque, Lipid metabolism, LDL, Inflammation, Immune response, Genetic risk factors, Transcranial Doppler, TCD, CT Angiography, CTA, Magnetic Resonance Angiography, MRA, Digital Subtraction Angiography, DSA, Antithrombotic therapy, Lipid-lowering therapy, Stenting, Endarterectomy, Ischemic conditioning, Anti-inflammatory therapy, Risk factor modification, Cerebrovascular disease, Stroke prevention

Received: 09-01-2025 | **Revised:** 25-03-2025 | **Accepted:** 02-04-2025 | **DOI:** 10.3844/ojbsci.2026.26.01.002

Introduction

This review article aims to provide an overview of Intracranial Atherosclerosis (ICAS) or Intracranial Atherosclerotic Disease (ICAD), including its pathogenesis, diagnosis, medical treatments, non-pharmacological approaches and surgical options. It also discusses the association of genetic factors, risk factors and imaging techniques with ICAS. Additionally, the review explores the effectiveness of various treatment strategies, including antithrombotic therapy, lipid-lowering treatments and targeting the inflammatory cascade, in managing ICAS.

Intracranial Atherosclerosis (ICAS or ICAD) poses a significant health concern due to its association with ischemic stroke, leading to morbidity and mortality. The complex interplay of factors such as lipid metabolism disorders, inflammation, immune response and traditional cardiovascular risk factors contributes to the development and progression of ICAS. Diagnosis of ICAS can be challenging due to its asymptomatic nature, lack of specific imaging signs and the presence of comorbidities that complicate the diagnostic process. While various treatment options exist, including antithrombotic therapy, risk factor modification, lipid-lowering treatments and non-pharmacological and surgical interventions, optimal management strategies for ICAS remain a topic of ongoing research and debate. The review aims to consolidate current knowledge on ICAS to guide clinicians in the diagnosis and treatment of this prevalent and potentially life-threatening condition.

Intracranial Atherosclerosis (ICAS or Intracranial Atherosclerotic Disease, ICAD) is a disease characterized by the formation of fatty deposits (atherosclerotic plaques) on the walls of the vessels that feed the brain. We have schematically depicted the development of intracranial atherosclerosis in Fig. 1. This process can occur in various locations of the intracranial arteries, including the internal carotid arteries, the anterior and posterior cerebral arteries and the upper and lower cerebral artery basins [1]. The localization of intracranial atherosclerosis can vary depending on the individual patient and risk factors. It leads to a decrease in the lumen of the vessels and impaired blood supply to the brain. With the development of the disease and the long-term process of formation and further destruction of atherosclerotic plaques, there is a risk of thrombosis, thrombus breakage and strokes. In addition, the whole process of the disease is accompanied by inflammation caused by the immune response. It also negatively affects the nearby brain tissue and arterial walls [2].

Statistics on the incidence of intracranial atherosclerosis vary by country and region. In general, however, the disease is quite common and can occur in people of different ages and genders. There is evidence that men suffer from intracranial atherosclerosis more often than women. It has also been found that older people and some ethnicities (e.g., African Americans) have a higher risk of developing the disease [3]. In addition, there are correlations between intracranial atherosclerosis and other risk factors such as smoking, high blood cholesterol, diabetes, hypertension and obesity. Therefore, to prevent this disease, it is recommended to lead a healthy lifestyle, control cholesterol and blood pressure levels and have regular medical checkups [4].

Genetic variants play a significant role in influencing the development and progression of Intracranial Atherosclerosis (ICAS) and other cardiovascular diseases. Here are some key genetic factors associated with ICAS.

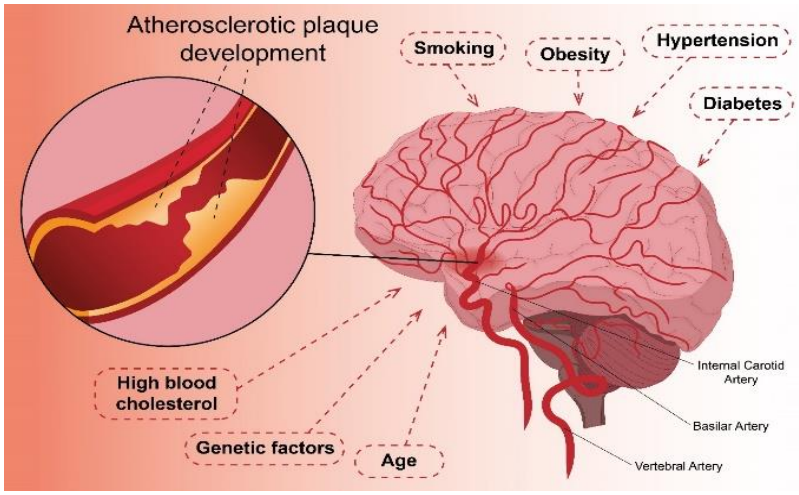

Fig. 1: Intracranial atherosclerosis development

Genetic Variants Influencing Blood Cholesterol Levels

Apolipoprotein B (APOB): Variants in the APOB gene have been linked to increased levels of Low-Density Lipoprotein (LDL) cholesterol, a major risk factor for atherosclerosis.

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9): PCSK9 gene variations can affect LDL receptor function, impacting cholesterol metabolism and predisposing individuals to atherosclerosis.

Low-Density Lipoprotein Receptor (LDLR): Mutations in LDLR can lead to impaired clearance of LDL cholesterol, contributing to atherosclerotic plaque formation.

Genes Involved in Lipid Metabolism

Hepatic Lipase (LIPC): Genetic variations in LIPC may influence High-Density Lipoprotein (HDL) cholesterol levels, impacting the balance of cholesterol in the body.

Lipoprotein Lipase (LPL): Variants in the LPL gene can affect triglyceride metabolism and play a role in atherosclerosis development.

Cholesteryl Ester Transfer Protein (CETP): Genetic variations in CETP have been associated with changes in HDL and LDL cholesterol levels, influencing atherosclerosis risk.

Genes Related to Inflammation and Immune Response

Interleukin-6 (IL6): Variants in the IL6 gene have been linked to inflammation and endothelial dysfunction, which are key processes in atherosclerosis.

Tumor Necrosis Factor Alpha (TNF-α): Genetic variants impacting TNF-α levels can modulate the inflammatory response, potentially affecting atherosclerosis development.

C-Reactive Protein (CRP): Variations in the CRP gene can influence levels of this marker of inflammation, which has been associated with cardiovascular risk.

Understanding how these genetic variants interact with environmental factors and lifestyle choices can provide valuable insights into individual susceptibility to ICAS. Further research into the genetic basis of ICAS may pave the way for personalized approaches to risk assessment, prevention and treatment strategies.

However, it should be noted that heredity and genetic predisposition are not the only cause of cardiovascular diseases (and intracranial atherosclerosis in particular) and many other factors such as lifestyle, environment, etc., may also play an important role in their occurrence [5].

Literature Search Methods

For this review entitled "Intracranial Atherosclerotic Disease: Treatment Potential and Diagnostics Opportunities," a comprehensive literature search was conducted to gather relevant studies and articles focusing on Intracranial Atherosclerosis (ICAS) or Intracranial Atherosclerotic Disease (ICAD) encompassing its pathogenesis, diagnosis, medical treatments, non-pharmacological approaches and surgical options. The search strategy aimed to consolidate current knowledge on ICAS to guide clinicians in the diagnosis and treatment of this prevalent and potentially life-threatening condition.

Search Sources

Databases: PubMed, Scopus, web of science. keywords: Search terms included "Intracranial Atherosclerosis," "Intracranial Atherosclerotic Disease," "ICAS," "ICAD," "pathogenesis," "diagnosis," "medical treatments," "non-pharmacological approaches," "surgical options," "genetic factors," "risk factors," "imaging techniques," "antithrombotic therapy," "lipid-lowering treatments," "inflammatory cascade," "endothelial dysfunction," "endothelial damage," "atherosclerotic plaques."

Inclusion criteria: Studies focusing on ICAS pathogenesis, diagnosis, treatments and surgical interventions. Articles published in English-language peer-reviewed journals.

Publication date: No specific date range constraints applied.

Exclusion criteria: Studies unrelated to ICAS, animal studies, non-peer-reviewed articles and non-English language publications.

Data collection and selection:

Screening: Titles and abstracts were screened to identify potentially relevant studies

Relevance: Full-text articles of potentially relevant studies were thoroughly assessed for inclusion

Data extraction: Data pertaining to pathogenesis, diagnosis, treatment strategies and surgical options for ICAS were extracted from selected studies

Synthesis: Information from selected studies was synthesized into a coherent narrative addressing the objectives of the review article

The search strategy employed was designed to ensure a comprehensive overview of the current landscape of ICAS research, encompassing diverse aspects ranging from molecular mechanisms to clinical interventions. The insights garnered from the selected literature aim to provide a nuanced understanding of ICAS for clinicians and researchers in the field.

Diagnosis

Imaging techniques such as CT Angiography (CTA) and Magnetic Resonance Angiography (MRA) are most commonly used to diagnose ICAD. These techniques allow imaging of cerebral arteries and the detection of the presence of plaques [6].

In addition to CTA and MPA, other imaging techniques such as Transcranial Doppler ultrasound (TCD) and Digital Subtractive Angiography (DSA) can also be used to diagnose ICAD. TCD measures the rate of blood flow in the arteries of the brain, while DSA is an invasive procedure that involves injecting contrast dye into the arteries to visualize blood flow [7]. Blood tests are also used to diagnose ICAD. These tests can detect the presence of specific biomarkers that are associated with the development of atherosclerosis. For example, high levels of Low-Density Lipoprotein cholesterol (LDL), C-Reactive Protein (CRP) and homocysteine are associated with an increased risk of developing atherosclerosis [8].

The Warfarin-Aspirin in Asymptomatic Intracranial Disease (WASID) trial was a large-scale, randomized clinical trial designed to determine the optimal treatment for patients with symptomatic intracranial stenosis, a condition in which arteries in the brain are narrowed or blocked by plaque accumulation. The study was conducted from 1998-2003 and included 569 patients from 59 centers in the United States and Canada [9].

The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study was a significant clinical trial that compared the effectiveness of two treatment strategies for symptomatic intracranial stenosis: Warfarin and aspirin. Warfarin is an anticoagulant that thins the blood to prevent clot formation, while aspirin is an antiplatelet drug that inhibits platelet aggregation, reducing the risk of blood clotting [10].

In the study, researchers aimed to determine which treatment approach - aspirin aspirin - was more effective at preventing recurrent strokes in patients with symptomatic intracranial stenosis. The study involved 569 participants and used the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method to measure the percent stenosis in intracranial arteries accurately.

The results of the WASID trial revealed that there was no significant difference in the risk of recurrent stroke between the warfarin and aspirin groups. Both medications were found to be similarly effective in preventing recurrent ischemic events in patients with symptomatic intracranial stenosis. This highlighted the importance of individualizing treatment approaches based on the specific characteristics and risk factors of each patient.

Overall, the WASID study provided valuable insights into the management of symptomatic intracranial stenosis and helped shape treatment decisions for healthcare providers caring for patients with this condition. The findings from the trial contributed to the evidence-based selection of antithrombotic therapy for individuals with intracranial artery stenosis [11].

Percent stenosis was determined by measuring the diameter of the normal (or distal) arterial segment and the narrowest (or stenotic) arterial segment on angiograms. Percent stenosis was calculated using the following formula: Percent stenosis = (1-narrowest diameter/normal diameter) ×100 [12].

The WASID study used a measure of percent stenosis to determine the severity of intracranial stenosis and to make treatment decisions. Patients with severe stenosis (70-99%) were considered to be at higher risk of stroke and were therefore more likely to be assigned to warfarin treatment, whereas patients with moderate stenosis (50-69%) were more likely to be assigned to aspirin treatment [13].

Intracranial atherosclerosis can be difficult to diagnose due to a number of factors, including its asymptomatic nature, lack of specific imaging signs and presence of other comorbidities that may confound the diagnosis. ICAD is often asymptomatic, especially in its early stages. According to several studies, up to 50% of people with ICAD are asymptomatic. This means that many people with ICAD may not seek medical attention until the disease has progressed and caused significant damage. In addition, many symptoms may coincide with residual symptoms of recent illnesses (e.g., during the post-stroke period) [14].

Also, patients with ICAD often have other, not only recent, but chronic comorbidities, such as hypertension, diabetes, or hyperlipidemia, which can confuse the diagnosis. For example, in a study published in the Journal of Stroke and Cerebrovascular Diseases, 43% of patients with ICAD had hypertension, 38% had hyperlipidemia and 34% had diabetes [15].

Diagnosing intracranial atherosclerosis poses several challenges due to its unique characteristics and the complexity of identifying it accurately. One primary challenge lies in the nature of ICAD itself, as it can often be asymptomatic, especially in its initial stages. This asymptomatic nature can delay diagnosis and intervention until the disease has progressed significantly, leading to potential complications.

Another hurdle in diagnosis arises from the lack of specific and distinctive imaging signs for ICAD. While imaging techniques like CT angiography, magnetic resonance angiography, transcranial Doppler ultrasound and digital subtractive angiography are commonly used for diagnosis, interpreting the results and distinguishing ICAD from other conditions can be challenging without clear indicators specific to ICAD.

Furthermore, the presence of comorbidities in individuals with ICAD, such as hypertension, diabetes and hyperlipidemia, can complicate the diagnostic process. These comorbidities may present overlapping symptoms or contribute to the progression of atherosclerosis, making it harder to isolate and attribute symptoms solely to ICAD.

Addressing these challenges requires a comprehensive approach that involves a high degree of clinical suspicion, combined with thorough evaluation using multiple diagnostic tools and consideration of the patient's overall health status. Continued research and advancements in diagnostic methodologies are crucial to refine the detection and characterization of intracranial atherosclerosis, ultimately improving patient outcomes and guiding appropriate treatment strategies.

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial was a landmark clinical trial that aimed to evaluate the effectiveness of aggressive medical management compared to Percutaneous Transluminal Angioplasty and Stenting (PTAS) in preventing recurrent stroke in patients with symptomatic intracranial arterial stenosis [16].

The study included 451 participants with recent Transient Ischemic Attack (TIA) or stroke attributed to 70-99% stenosis of a major intracranial artery. The participants were randomized to receive either aggressive medical management alone or aggressive medical management combined with PTAS. Aggressive medical management in this context typically included antiplatelet therapy, statin therapy and blood pressure control.

The primary endpoint of the SAMMPRIS trial was the occurrence of any stroke or death within 30 days after enrollment or stroke in the territory of the symptomatic artery beyond 30 days. The results of the trial showed that patients who received aggressive medical management alone had a significantly lower rate of stroke or death compared to those who underwent PTAS in addition to medical management.

These findings emphasized the importance of intensive medical treatment, including lifestyle modifications and optimal pharmacological management, in reducing the risk of recurrent stroke in patients with symptomatic intracranial arterial stenosis. The SAMMPRIS trial contributed to a shift in the treatment paradigm for intracranial arterial stenosis towards conservative management strategies that prioritize medical therapy over invasive interventions.

Additionally, a subgroup analysis of the SAMMPRIS trial suggested that dual antiplatelet therapy with aspirin and clopidogrel may be more effective than aspirin alone in reducing the risk of recurrent stroke in some patients with intracranial

arterial stenosis. This finding highlighted the potential benefits of personalized treatment approaches tailored to individual patient characteristics and risk factors to optimize outcomes in stroke prevention.

Medical Treatments

In Figure 2, we have summarized the most strategies of medical targeting intracranial atherosclerosis. Below, we are discussing them in detail.

Antithrombotic Therapy

Antithrombotic therapy is an important treatment for patients with ICAD.

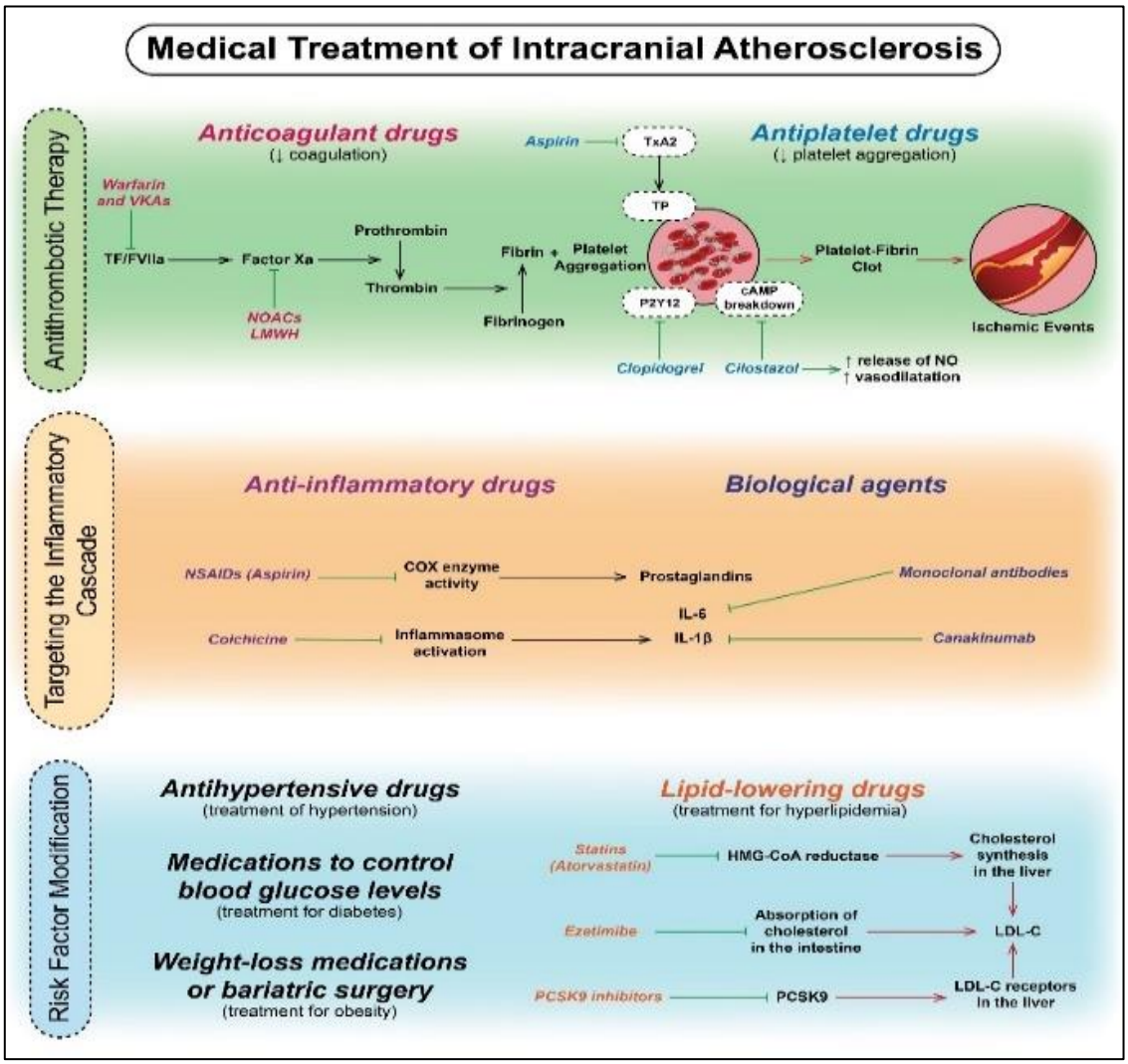

Fig. 2: Medical treatment of intracranial atherosclerosis. Abbreviations: cAMP-cyclic adenosine monophosphate; COX-Cyclooxygenase; FVIIa-Factor VIIa; HMG-CoA-3-hydroxy-3-methylglutaryl coenzyme A; IL-1β-Interleukin-1β; IL-6-Interleukin-6; LDL-C-Low-Density Lipoprotein Cholesterol; NO-nitric oxide; NOACs-Non-vitamin K antagonist oral anticoagulants; NSAIDs-Non-steroidal anti-inflammatory drugs; PCSK9-Proprotein convertase subtilisin/kexin type 9; TF-Tissue factor; TP-thromboxane receptor (thromboxane prostanoid); P2Y12-platelet purinoceptor; TxA2-Thromboxane A2; VKAs-Vitamin K antagonists

Warfarin works by competitively inhibiting the Vitamin K epoxide Reductase Complex 1 (VKORC1), which is a crucial enzyme responsible for activating the vitamin K present in the body. By doing so, warfarin can decrease the functional reserves of vitamin K, leading to a reduction in the production of active clotting factors. The liver relies on vitamin K for

synthesizing coagulation factors II, VII, IX and X, along with regulatory factors like protein C and protein S. Vitamin K plays a critical role as a cofactor in the synthesis of these vitamin K-dependent clotting proteins.

Aspirin irreversibly modifies Cyclooxygenase (COX) through acetylation, disrupting the metabolism of prostaglandins and the synthesis of thromboxane A2 (TXA2). This interference leads to a decrease in platelet aggregation triggered by collagen, Adenosine Diphosphate (ADP) and low concentrations of thrombin. Aspirin exhibits a more selective inhibition of COX-1 activity (predominantly found in platelets) than COX-2 activity (commonly expressed in tissues during inflammation). Consequently, lower doses of aspirin are sufficient to inhibit platelet aggregation, while higher doses are required to achieve its potential anti-inflammatory effects. Additionally, aspirin's inhibition of platelet activation by neutrophils and its promotion of enhanced nitric oxide production are among the proposed alternative mechanisms for its platelet-inhibiting effects.

The non-vitamin K Antagonist oral anticoagulants (NOACs) act as inhibitors of coagulation factors rather than as inactivators. The main physiological regulators of factors IXa, Xa and thrombin are the plasma Serine Protease Inhibitors (SERPINs) antithrombin and alpha-1-proteinase inhibitor, with some assistance from the non-SERPIN inhibitor alpha-2-macroglobulin. Similar to the NOACs, SERPINS and alpha-2-macroglobulin only interact with coagulation factors after they have been activated into functional proteases. However, SERPINS and alpha-2-macroglobulin deactivate their target proteases by forming complexes that are mostly irreversible. On the other hand, the NOACs create reversible complexes with the active site of their target proteases.

The anticoagulant and antithrombotic mechanisms of heparin have been extensively documented. A specific high-affinity pentasaccharide sequence present in heparin binds and activates antithrombin III (AT-III) by triggering a structural change in the AT-III protein, resulting in the rapid inhibition of thrombin (FIIa) and factor Xa, which underpins heparin's anticoagulant effect. Due to the diverse composition of the heparin molecule, this distinct pentasaccharide sequence is only present in approximately one-third of heparin chains. Inhibiting thrombin necessitates the simultaneous attachment of both AT-III and thrombin to the heparin molecule, a process reliant on the polysaccharide chain length of heparin, which must consist of a minimum of 18 saccharide units. In contrast, inhibiting factor Xa requires only the attachment of the pentasaccharide to AT-III without the need for factor Xa to bind to heparin. As a result, Low Molecular Weight (LMW) heparins exhibit stronger anti-Xa activity than anti-IIa activity.

The inhibitory action of clopidogrel on ADP receptors is subject to considerable variability among individuals. It takes a minimum of five days for a maintenance dose of 75 mg to achieve approximately 50% steady-state inhibition of ADP-induced platelet aggregation. Despite clopidogrel having a half-life of 4 h, its irreversible impact on platelet function means that normal platelet function is fully restored only after a 7–10-day interval required for platelet regeneration post-treatment cessation. Nevertheless, a notable decrease in clopidogrel's platelet inhibitory effects can be observed as early as 3-5 days following treatment discontinuation. Clinical research indicates that individuals with heightened platelet aggregation profiles often exhibit a greater proportion of immature platelets. These immature reticulated platelets possess an elevated thrombotic potential, potentially contributing to the occurrence of prothrombotic events shortly after clopidogrel therapy discontinuation.

Cilostazol, along with some of its breakdown products, acts as an inhibitor of cyclic AMP (cAMP) Phosphodiesterase III (PDE III), which hinders the activity of phosphodiesterase and reduces the breakdown of cAMP. This leads to elevated cAMP levels in platelets and blood vessels, resulting in the suppression of platelet aggregation and the promotion of vasodilation.

Aspirin is the most widely used antiplatelet drug, but aspirin monotherapy has been associated with a relatively high rate of recurrent stroke in patients with symptomatic ICAD. The primary goal of the WASID study (discussed in the previous section) was to compare the efficacy of two treatment strategies for symptomatic intracranial stenosis: Warfarin and aspirin. Warfarin is an anticoagulant that thins the blood and prevents blood clots and aspirin is an antiplatelet drug that prevents platelet aggregation, which is necessary for blood clotting [17].

In the study, patients were randomly assigned to receive either warfarin (target International Normalized Ratio (INR) of 2.0-3.0) or aspirin (1,300 mg daily) and were followed for approximately two years. The study showed that there was no significant difference in the rate of stroke between the groups taking warfarin and aspirin. The stroke rate was 22.1% in the warfarin group and 21.8% in the aspirin group. However, the study showed that the risk of stroke at the stenotic artery site was lower in the warfarin group (9.8 versus 18.9%) and the risk of major bleeding was higher in the warfarin group (7.9 versus 3.8%) [18].

In recent years, the effectiveness of antithrombotic therapy in the treatment of ICAD has been actively studied. Antiplatelet therapy with aspirin is the standard first-line treatment for ICAD. Several large randomized clinical trials have shown that aspirin reduces the risk of recurrent stroke in patients with ICAD [19].

However, the benefits of dual antiplatelet therapy must be weighed against the increased risk of bleeding. The role of anticoagulant therapy with warfarin or New Oral Anticoagulants (NOACs) in the treatment of ICAD is less clear. Some studies have shown that anticoagulation may be more effective than antiplatelet therapy in preventing recurrent stroke in patients with ICAD who have certain high-risk features, such as a history of cardioembolic stroke or atrial fibrillation. However, the risk of bleeding with anticoagulation should also be considered. Other antithrombotic agents, such as cilostazol and dipyridamole, have been studied in the treatment of ICAD. However, the evidence for their efficacy is limited and they are not currently recommended as first-line therapy [20].

Low Molecular Weight Heparin (LMWH) is a new type of anticoagulant that works by inhibiting the activity of blood clotting factors. LMWH binds to antithrombin III, a natural inhibitor of clotting factors and enhances its activity, resulting in decreased clot formation. LMWH has a lower molecular weight than unfractionated heparin, allowing more predictable dosing and reducing the risk of bleeding-related complications [21].

The therapeutic mechanism of clopidogrel involves the inhibition of platelet aggregation. Clopidogrel is a thienopyridine derivative that is metabolized in the liver to an active metabolite. This metabolite binds irreversibly to the P2Y12 receptor on the surface of platelets, inhibiting their ability to aggregate and form clots. Clopidogrel is commonly used in combination with aspirin to prevent recurrent stroke and other thrombotic events [22] and is a phosphodiesterase III inhibitor with both antiplatelet and vasodilatory effects. Cilostazol inhibits the breakdown of cyclic AMP in platelets, which leads to decreased platelet aggregation. In addition, cilostazol increases the release of nitric oxide, a potent vasodilator, which leads to increased blood flow and decreased vascular resistance. These effects combine to improve blood flow and reduce the risk of thrombotic events [23].

In terms of biochemical mechanisms, LMWHs primarily target the coagulation cascade, in particular by inhibiting thrombin and factor Xa, which are key participants in thrombus formation. Clopidogrel, on the other hand, suppresses platelet activation and aggregation by blocking the P2Y12 receptor on platelets, which is essential for platelet activation and aggregation. Finally, cilostazol acts by increasing cyclic AMP levels in platelets, which reduces their ability to aggregate and form clots and by stimulating the release of nitric oxide, which increases vasodilation and improves blood flow [24].

Risk Factor Modification

Risk factor modification is an important component of the treatment of intracranial atherosclerotic disease. The goal of risk factor modification is to reduce the risk of recurrent stroke and other cardiovascular events by eliminating the major risk factors that contribute to the development and progression of atherosclerosis [25]. High-risk factors are primarily diabetes, smoking, elevated cholesterol and obesity. High blood pressure is a major risk factor for ICAD and may accelerate the progression of atherosclerosis. Treatment of hypertension usually includes lifestyle changes, such as weight loss and increased physical activity, as well as the use of antihypertensive medications. Diabetes is associated with an increased risk of ICAD and other cardiovascular events. Treatment for diabetes usually includes lifestyle changes, such as dietary changes and increased physical activity, as well as the use of medications to control blood glucose levels [4]. Elevated levels of cholesterol and other lipids in the blood can contribute to the development of atherosclerosis. Treatment for hyperlipidemia usually includes lifestyle changes, such as dietary changes and increased physical activity, as well as the use of lipid-lowering drugs, such as statins. Cigarette smoking is a major risk factor for ICAD and other cardiovascular events. Treatment usually includes smoking cessation programs, which may include medications to help with nicotine withdrawal. Obesity is also associated with an increased risk of ICAD and other cardiovascular events [26]. Treatment usually includes lifestyle modifications, such as dietary changes and increased physical activity, as well as the potential use of weight-loss medications or bariatric surgery. Promoting a healthy lifestyle helps significantly reduce the likelihood of one or more of these factors and the development of atherosclerosis [27].

Lipid-Lowering Treatments

Elevated levels of cholesterol and other lipids in the blood can contribute to the development and progression of atherosclerosis and reducing these levels can help slow the progression of the disease and reduce the risk of recurrent stroke

and other cardiovascular events. The lipid-lowering drugs most commonly used to treat ICAD are statins [28]. Statins work by inhibiting the HMG-CoA reductase enzyme, which is involved in cholesterol synthesis in the liver. By reducing cholesterol synthesis, statins can lower LDL cholesterol ("bad" cholesterol) levels in the blood and reduce the risk of cardiovascular events [29].

Several large clinical trials have demonstrated the effectiveness of statins in reducing the risk of recurrent stroke and other cardiovascular events in patients with ICAD. For example, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed that atorvastatin treatment reduced the risk of recurrent stroke by 16% in patients with a recent stroke or Transient Ischemic Attack (TIA) and signs of intracranial atherosclerosis [30]. In addition to statins, other lipid-lowering drugs may be used in the treatment of ICAD depending on the individual risk profile and lipid levels of the patient. For example, ezetimibe, a drug that blocks the absorption of cholesterol in the intestine, can be used in combination with statins to further reduce cholesterol levels [31].

In some cases, more aggressive lipid-lowering therapy may be needed, such as the use of subtilisin/peroxin type 9 (PCSK9) proprotein convertase inhibitors. PCSK9 inhibitors block the PCSK9 protein, which plays a role in the cleavage of LDL cholesterol receptors in the liver. By blocking PCSK9, these drugs can increase the number of LDL cholesterol receptors in the liver, resulting in more efficient elimination of LDL cholesterol from the blood [32].

Targeting the Inflammatory Cascade

Atherosclerosis is thought to begin in response to endothelial damage, which causes an inflammatory response in the arterial wall. This response involves the activation of immune cells, such as monocytes and T cells and the release of proinflammatory cytokines and chemokines, such as IL-1, IL-6 and Tumor Necrosis Factor-alpha (TNF-α) [33]. One approach to controlling inflammation in ICAD is the use of anti-inflammatory drugs. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), such as aspirin, can reduce inflammation by inhibiting the activity of Cyclooxygenase (COX) enzymes, which play a role in the synthesis of proinflammatory molecules called prostaglandins. Aspirin is commonly used in the treatment of ICAD to reduce the risk of recurrent stroke and other cardiovascular events [34].

Another class of drugs that can affect inflammation in ICAD are biological agents such as monoclonal antibodies that target specific proinflammatory cytokines such as Interleukin-1 (IL-1) and Interleukin-6 (IL-6). These cytokines contribute to the recruitment and activation of additional immune cells, leading to the formation of atherosclerotic plaques [35]. The plaques contain many immune cells, including macrophages and foam cells, which are rich in proinflammatory molecules such as Reactive Oxygen Species (ROS), Matrix Metalloproteinases (MMPs) and proinflammatory cytokines [36].

Canakinumab and colchicine are two additional drugs that have been investigated for their potential role in influencing the inflammatory cascade in ICAD. Canakinumab is a monoclonal antibody directed against IL-1β, a proinflammatory cytokine that is involved in the development and progression of atherosclerosis. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) examined the use of canakinumab in patients with a history of myocardial infarction and elevated levels of high-sensitivity C-Reactive Protein (hs-CRP), a marker of systemic inflammation [37]. The study showed that canakinumab reduced the risk of recurrent cardiovascular events, including stroke, compared with placebo. It should be noted, however, that the CANTOS study did not include patients with ICAD.

Colchicine is an anti-inflammatory drug that has been used for decades to treat gout and other inflammatory diseases. More recently, it has been investigated for its potential use in the treatment of cardiovascular disease, including ICAD. Colchicine works by inhibiting the activation of inflammasomes, which are protein complexes that play a role in the production of pro-inflammatory cytokines such as IL-1β. The Low-Dose Colchicine for secondary prevention of cardiovascular disease (LoDoCo2) study examined the use of low-dose colchicine in patients with recent myocardial infarction and found a significant reduction in the risk of cardiovascular events, including stroke, compared with placebo [38].

Non-Pharmacological Approaches

Non-pharmacological options are summarized in Fig. 3.

Ischemic Conditioning

Ischemic conditioning is a therapeutic approach that involves inducing brief periods of ischemia (lack of blood flow) and reperfusion (restoration of blood flow) to protect tissues from subsequent ischemic injury. This approach has been investigated for its potential use in the treatment of various conditions, including ischemic heart disease and stroke, as well as ICAD [39].

Recent research has focused on investigating the optimal timing and duration of ischemic conditioning to maximize its therapeutic effects in ischemic heart disease, stroke and ICAD. Emerging studies are exploring the potential combination of ischemic conditioning with other non-pharmacological interventions, such as exercise training and dietary modifications, to enhance the protective effects against ischemic injuries. Ongoing research efforts are aimed at unraveling the underlying mechanisms of ischemic conditioning at the molecular level to develop novel therapeutic strategies for ischemic diseases.

There are several types of ischemic conditioning, including Remote Ischemic Conditioning (RIC), which involves inducing ischemia in a remote part of the body and preconditioning, which involves inducing brief periods of ischemia in the target tissue prior to an ischemic event. The exact mechanism by which ischemic conditioning works is not fully understood, but it is thought to involve the activation of a variety of cellular and molecular pathways that promote cell survival and reduce inflammation and oxidative stress [40].

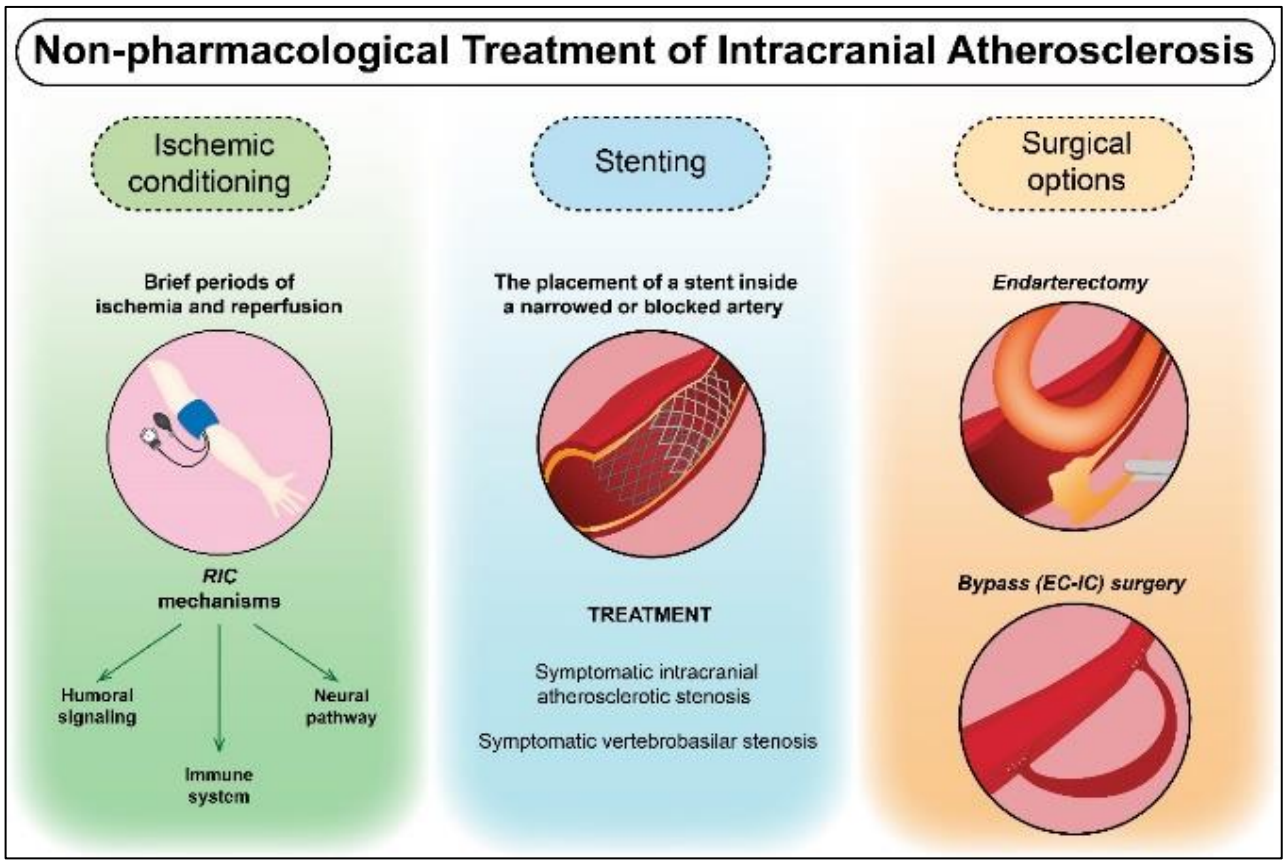

Fig. 3: Non-pharmacological treatment of intracranial atherosclerosis. Abbreviations: EC-IC extracranial-intracranial; RIC-remote ischemic conditioning

Ischemic conditioning has been investigated as a potential adjunct to traditional medical therapies, such as antiplatelet and antithrombotic medications. The rationale for this approach is that ICAD patients are at increased risk for recurrent stroke due to the presence of atherosclerotic plaque in the intracranial arteries and ischemic conditioning may help to protect the brain from subsequent ischemic injury [41].

Several clinical trials have investigated the use of RIC in patients with ICAD. The Remote Ischemic Conditioning in Intracranial Artery Stenosis (RICA-IS) trial investigated the use of RIC in combination with medical therapy in patients with symptomatic ICAD and found a significant reduction in the risk of recurrent stroke compared to medical therapy alone. However, a subsequent larger trial, the effect of remote ischemic conditioning on brain infarction and cognitive function in patients with symptomatic intracranial artery stenosis (RICA) trial, did not show a significant reduction in the risk of stroke or improvement in cognitive function with RIC [42].

Stenting

Stenting is a minimally invasive surgical procedure that involves the placement of a small, wire-mesh tube called a stent inside a narrowed or blocked artery. The stent helps to keep the artery open and improves blood flow to the affected area. Stenting is used to treat severe stenosis (narrowing) of the intracranial arteries that causes symptoms such as Transient Ischemic Attack (TIA) or stroke. Stenting is usually considered when medical therapy alone has failed to improve symptoms or when the risk of stroke is considered high despite medical therapy [43].

The efficacy of stenting for the treatment of ICAD has been studied in several clinical trials, but the results have been mixed. Some studies have shown that stenting can improve blood flow and reduce the risk of stroke in patients with ICAD, while others have not shown a significant benefit compared to medical therapy alone [41]. Current research is investigating advanced imaging techniques, such as intravascular ultrasound and optical coherence tomography, to optimize stent placement and assess the outcomes of stenting in ICAD. Novel stent designs, including drug-eluting stents and biodegradable stents, are being studied to improve the long-term safety and efficacy of stenting in intracranial atherosclerotic stenosis. The role of personalized medicine in guiding stent selection and antiplatelet therapy management for patients with ICAD is a growing area of interest within the research community to improve treatment outcomes and reduce complications.

For example, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial was a large, randomized, controlled trial that compared stenting plus medical therapy to medical therapy alone in patients with symptomatic ICAD. The study found that patients who received stenting had a higher risk of stroke or death within 30 days of the procedure compared to those who received medical therapy alone. As a result, the trial was stopped early and stenting is not routinely recommended for the treatment of ICAD [44].

The Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial was a significant clinical study that aimed to assess the safety and effectiveness of the Vitesse intracranial stent system in treating symptomatic intracranial atherosclerotic stenosis [45]. Involving 159 participants, the trial aimed to reduce major adverse events and enhance patient outcomes.

The trial's primary objective was to evaluate a composite of major adverse events at the 30-day mark, including stroke, death and target vessel revascularization. The findings showed a 14.4% rate for the composite endpoint, lower than the expected 18.9%. However, the 8.2% rate of stroke or death within 30 days was slightly higher than the target of 5.5%. This discrepancy raised concerns about the overall safety of the stent system.

While the results indicated promise in achieving the primary composite endpoint, further investigations and long-term follow-up studies are crucial to fully understand the safety and efficacy profile of the Vitesse intracranial stent system. More research is essential to evaluate its effectiveness in improving patient outcomes and minimizing risks associated with symptomatic intracranial atherosclerotic stenosis.

In conclusion, the VISSIT trial shed light on the potential benefits of intracranial stenting for ischemic stroke therapy, underlining the need for additional research to confirm its efficacy and safety in the long term.

The Vertebrobasilar flow Evaluation and Risk of Transient ischaemic Attack and Stroke (VERiTAS) study was a prospective observational study designed to evaluate the risk factors for recurrent stroke and TIA in patients with symptomatic vertebrobasilar stenosis [46]. The study found that intracranial atherosclerotic disease was a significant risk factor for recurrent stroke and TIA in patients with symptomatic vertebrobasilar stenosis. The 2-year risk of recurrent stroke or TIA in patients with intracranial atherosclerotic disease was 26.4%, compared to 7.4% in patients without intracranial disease. The study also found that aggressive medical management, including antiplatelet therapy, statins and blood pressure control, was an effective strategy for reducing the risk of recurrent events [47].

The Wingspan Stent System Post Market Surveillance (WEAVE) study was a prospective, multicenter, observational study designed to evaluate the safety and efficacy of the Wingspan stent system for the treatment of intracranial atherosclerotic disease in a real-world setting [48]. The study enrolled 152 patients and found that the stent system was associated with a low rate of major adverse events, but that further study was needed to determine its long-term safety and efficacy. The study found that the rate of major adverse events at 30 days was 10.5%, which was lower than the pre-specified performance goal of 14.6%. The study also found that the rate of stroke or death within 30 days was 6.6%, which was lower than the pre-specified performance goal of 10.0%. However, the study did not evaluate long-term outcomes beyond 30 days.

Surgical Options

Surgical options for the treatment of Intracranial Atherosclerotic Disease (ICAD) include endarterectomy, bypass surgery and Extracranial-Intracranial (EC-IC) bypass surgery [49].

Endarterectomy involves removing the plaque and the inner lining of the affected artery. This can help to improve blood flow to the brain and reduce the risk of stroke. However, this procedure can be technically challenging and carries a risk of complications such as bleeding, infection and stroke. Bypass surgery involves creating a new route for blood to flow around the blocked or narrowed artery [50]. This is typically done by taking a blood vessel from another part of the body and using it to bypass the affected area. This can help to improve blood flow to the brain and reduce the risk of stroke. However, this procedure can be technically challenging and carries a risk of complications such as bleeding, infection and stroke. EC-IC This involves creating a new route for blood to flow from the extracranial arteries to the intracranial arteries. This can help to improve blood flow to the brain and reduce the risk of stroke. However, this procedure is not commonly performed and has been associated with a high rate of complications [51].

Advancements in surgical techniques, such as minimally invasive endovascular procedures and robotic-assisted vascular surgery, are being explored to enhance the safety and efficacy of endarterectomy and bypass surgeries for ICAD. Multicenter collaborative studies are underway to establish standardized protocols and guidelines for selecting appropriate candidates for surgical interventions in ICAD based on individual risk profiles and disease characteristics. The integration of neuroimaging modalities, such as Magnetic Resonance Imaging (MRI) and Computed Tomography Angiography (CTA), into preoperative planning for surgical interventions is showing promise in improving patient selection and postoperative outcomes in ICAD treatment.

The international cooperative study of Extracranial/Intracranial arterial anastomosis (EC/IC Bypass Study) was a randomized clinical trial conducted in the 1980s to investigate the efficacy of the EC/IC bypass surgery for patients with severe atherosclerotic intracranial stenosis [52]. The study included 1,583 patients with either a recent ischemic stroke or Transient Ischemic Attack (TIA) due to severe stenosis or occlusion of the internal carotid artery or middle cerebral artery. Patients were randomly assigned to either an EC/IC bypass surgery group or a medical therapy group. The primary endpoint was a composite of fatal or nonfatal stroke and the secondary endpoint was death from any cause. The results of the study showed that there was no significant difference between the two groups in the primary endpoint, with 16.3% of the surgical group and 16.9% of the medical therapy group experiencing a stroke or death within two years. However, there was a statistically significant reduction in the risk of ipsilateral stroke in the surgical group (9.9%) compared to the medical therapy group (16.1%).

A study published in the Journal of Neurosurgery in 2016 evaluated the long-term outcomes of endarterectomy in Moyamoya disease patients. The study included 75 patients who underwent endarterectomy between 1992 and 2013. The researchers found that endarterectomy was effective in preventing stroke and improving neurological function in moyamoya patients, with a 10-year stroke-free survival rate of 94% [53].

Conclusion

Intracranial atherosclerosis stands as a primary culprit behind ischemic stroke, characterized by a multifaceted pathogenesis intertwining lipid metabolism disturbance, inflammatory cascades, immune responses, mitochondrial perturbations and a myriad of other intricate processes. The etiology of intracranial atherosclerosis is further compounded by factors such as unhealthy lifestyles, metabolic irregularities and conventional cardiovascular risk elements, emphasizing the need for a holistic approach to its management.

Non-invasive screening imaging modalities play a pivotal role in the timely detection and characterization of intracranial atherosclerotic lesions. Techniques like Transcranial Doppler ultrasound (TCD), Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) and Vessel Wall Magnetic Resonance Imaging (VW-MRI) offer valuable insights into the extent and severity of intracranial artery involvement, enabling clinicians to tailor treatment strategies effectively.

For patients diagnosed with intracranial atherosclerosis, aggressive management of risk factors and the implementation of short-term dual antiplatelet therapy followed by aspirin monotherapy are recommended to mitigate the risk of recurrent stroke events. Additionally, the utilization of tissue Plasminogen Activator (tPA) and endovascular interventions in select cases demonstrate efficacy in the acute treatment of stroke secondary to intracranial atherosclerosis.

Furthermore, the integration of non-pharmacological therapies like lifestyle modifications, diet optimization, physical activity promotion and cognitive interventions may offer synergistic benefits in conjunction with pharmacological and interventional treatments. However, the efficacy of these non-pharmacological approaches warrants validation through large-scale clinical trials to establish their role in enhancing outcomes for patients with intracranial atherosclerosis-induced ischemic stroke. Embracing a comprehensive and personalized care paradigm that leverages the synergy between traditional and innovative treatment modalities is imperative in addressing the complexity of intracranial atherosclerosis and improving the prognosis of affected individuals.

Acknowledgment

Thank you to the publisher for their support in the publication of this research article. We are grateful for the resources and platform provided by the publisher, which have enabled us to share our findings with a wider audience. We appreciate the efforts of the editorial team in reviewing and editing our work and we are thankful for the opportunity to contribute to the field of research through this publication.

Funding Information

This research was funded by the Russian Science Foundation, grant number 22-15-00064-П

Author Contributions

Anastasia V. Poznyak: Drafted Written.

Victoria A. Khotina, Anton Y Postnov Vasily N. Sukhorukov, Arthur A. Lee, Alexander L. Golovyuk and Alexander N. Orekhov: Drafted reviewed and edited.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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