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REVIEW ARTICLE

Treatment of Symptomatic Intracranial Atherosclerotic Stenosis: A Review

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Intracranial atherosclerotic stenosis (ICAS) is an important cause of ischemic stroke worldwide, accounting for 8-10% of strokes in North America and Europe and up to 50% in some Asian populations. Patients with symptomatic ICAS are at high risk of recurrent stroke, with rates up to 18% at 1 year despite medical therapy. This review discusses current evidence on prognosis, risk factors, and optimal medical and endovascular treatment for symptomatic ICAS. All patients should receive intensive medical therapy focused on antiplatelet agents, blood pressure control, cholesterol management, and lifestyle changes. Short-term dual antiplatelet therapy provides additional benefit for some patients. Endovascular stenting has not shown benefit over medical therapy in clinical trials and is not routinely recommended. However, selected patients who fail medical management may be considered for stenting or alternate endovascular approaches on an individual basis. Further research is critically needed to identify patients at highest risk of recurrence and evaluate novel therapies to improve outcomes. This review provides a framework for prognosis and management of symptomatic ICAS based on current evidence.

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ICAS is defined as atherosclerotic narrowing of major intracranial arteries and is an important cause of ischemic stroke worldwide. Symptomatic ICAS refers to ICAS that has resulted in a transient ischemic attack (TIA) or ischemic stroke attributable to the stenotic artery. Compared to extracranial atherosclerosis of the carotid or vertebral arteries, relatively less is known about the optimal management of intracranial atherosclerotic disease. However, research interest in ICAS has grown over the past two decades given its strong association with recurrent stroke risk.

This review aims to summarize current evidence on the following key aspects of symptomatic ICAS:

- Epidemiology and risk factors for recurrence
- Medical therapies to reduce recurrent stroke risk
- Imaging modalities
- Endovascular treatment approaches
- Identification of patients at high risk of recurrence
- Future directions for research

Understanding prognosis and evidence-based treatment strategies is imperative to improve outcomes in this high-risk population. This review provides a framework for clinicians managing patients with symptomatic ICAS in daily practice.

EPIDEMIOLOGY AND RISK FACTORS

The global prevalence of ICAS varies widely based on geographic region, age, and comorbidities. In the United States, ICAS accounts for approximately 8-10% of ischemic strokes.[1,2]However, in Asian countries, ICAS may cause up to 30-50% of strokes.[3–5] The REasons for Geographic and Racial Differences in Stroke (REGARDS) study found that black race/ethnicity, living in the Southeastern stroke belt region of the United States, and older age were all associated with increased prevalence of ICAS.[6]

Several modifiable vascular risk factors have consistently been linked with ICAS. These include hypertension, diabetes mellitus, cigarette smoking, and dyslipidaemia.[7–9] The severity of luminal stenosis is one of the strongest predictors of recurrent stroke risk. Multiple studies have shown that patients with severe stenosis ≥70% are at 2-3 times higher risk compared to those with moderate stenosis <70%.[4,10,11]

In addition to traditional risk factors and stenosis severity, certain clinical and imaging characteristics can help further stratify stroke risk in patients with symptomatic ICAS. These include:

- Recent TIA or ischemic stroke within 3 months[4]
- Presence of borderzone or watershed pattern infarcts[12]
- Impaired collateral flow noted on angiographic imaging[12]
- Posterior circulation location[13]
- Clinical features suggesting hemodynamic compromise such as symptoms related to positional change or blood pressure fluctuation[14]
- Female sex[1]

However, our ability to accurately predict individual risk remains limited. Ongoing studies are investigating novel imaging techniques and biomarkers to better guide prognosis in ICAS.

MEDICAL TREATMENT

All patients with symptomatic ICAS should receive intensive medical therapy focused on secondary stroke prevention. The key components include antiplatelet agents, blood pressure control, lipid management, and lifestyle modifications.

Antiplatelet Therapy

Antiplatelet agents reduce the risk of recurrent ischemic events in patients with non-cardioembolic stroke, including strokes attributed to ICAS. The optimal antiplatelet regimen for symptomatic ICAS has been evaluated in several trials and observational studies.

For patients with a recent TIA or ischemic stroke due to severe (70-99%) ICAS, short-term treatment with dual antiplatelet therapy (DAPT) generally refers to a duration of up to 3 months, as studied in the SAMMPRIS trial.[15] This is not yet an established standard but is commonly referenced in current practice. The recommended doses for long-term prevention are 75-100 mg daily for aspirin and 75 mg daily for clopidogrel. The most studied regimen is combination aspirin plus clopidogrel. The Clopidogrel

plus Aspirin for Infarction Reduction in Acute Ischemic Stroke Study (CLAIR) enrolled patients with TIA or minor stroke due to symptomatic intracranial stenosis.[16]Patients treated with DAPT had significantly fewer microembolic signals detected compared to aspirin alone, suggesting greater platelet inhibition.

Post-hoc analysis of the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial showed that patients with criteria similar to those enrolled in the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial (severe stenosis treated with DAPT for 3 months) had substantially lower rates of the primary endpoint compared to WASID patients treated with aspirin alone (12.2% versus 23%).[4,16]Although limited by between-study comparisons, these findings further support the benefit of short-term DAPT in patients with severe, symptomatic ICAS.

For long-term prevention, we generally recommend monotherapy with either aspirin or clopidogrel based on evidence from large, randomized trials showing efficacy of these agents for secondary stroke prevention.[15]The combination drug aspirin-dipyridamole and cilostazol are potential alternatives specifically studied in Asian populations with ICAS.[17,18]

Ongoing trials are investigating the optimal duration of DAPT in symptomatic ICAS. Prolonged DAPT up to 1 year may provide additional benefit but must be balanced with increased bleeding risk. The Combination of Ticagrelor Plus Aspirin for Prevention of Stroke in Intracranial Atherosclerosis (CAPTIVA) trial will compare 1 year of aspirin plus clopidogrel, aspirin plus ticagrelor, or aspirin plus low-dose rivaroxaban for stroke prevention in patients with severe ICAS (NCT05047172).

Blood Pressure Control

Hypertension is highly prevalent among patients with ICAS, and observational data has consistently shown an association between poor blood pressure control and increased risk of recurrent stroke.[7,19,20]The American Heart Association/ American Stroke Association guidelines recommend a target blood pressure <140/90 mmHg for all patients with ICAS.[17,21,22]

However, recent evidence indicates that over-aggressive lowering may be harmful in certain hemodynamically unstable subsets. The VERiTAS study used quantitative magnetic resonance angiography (QMRA) to identify patients with low flow distal to vertebrobasilar stenosis.[23] While QMRA can provide important insights into collateral flow status, it is not yet a standard tool for all TIAs and CVEs due to limited availability and the need for further validation. Among these patients, SBP <140 mmHg was associated with paradoxically higher stroke risk compared to SBP 140-150 mmHg. The mechanism is hypothesized to be further reduction in distal perfusion pressure in the setting of exhausted cerebrovascular reserve. Conversely, studies of patients with carotid occlusion did not show increased risk with lower blood pressure targets.[14,23]

These data illustrate that blood pressure targets in ICAS should be individualized based on collateral flow status and the anterior versus posterior circulation. More research is needed to clarify the optimal range and identify hemodynamic biomarkers to guide treatment.

Lipid Management

Statins substantially reduce the risk of recurrent cardiovascular events in patients with atherosclerotic disease by decreasing LDL cholesterol. High intensity statin therapy, defined as atorvastatin 40-80 mg or rosuvastatin 20-40 mg, lowers LDL by ≥50%.[24]

Among patients with ICAS, intensive statin treatment has been associated with improved outcomes and plaque stabilization in several studies.[21,24–26] The Treat Stroke to Target (TST) trial enrolled patients with a recent ischemic stroke or TIA and ipsilateral large artery atherosclerosis, either extracranial or intracranial.[24] Patients randomized to an LDL target <70 mg/dL versus a target of 90-110 mg/dL had significantly lower rates of cerebrovascular events. Based on available evidence, the American Heart Association (AHA) advises treating individuals with ischemic stroke by aiming for a low-density lipoprotein (LDL) cholesterol level below 70 mg/dL using high-intensity statin therapy.[22] Similarly, the joint guidelines from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) advocate for lower LDL cholesterol targets compared to prior recommendations. For

very-high-risk patients undergoing secondary prevention, the ESC/EAS guidelines propose reducing LDL cholesterol by 50% from baseline with a target level below 55 mg/dL (1.4 mmol/L). High-risk individuals are advised a similar reduction from baseline with a target below 70 mg/dL (1.8 mmol/L), while those at moderate risk are suggested to aim for LDL cholesterol levels below 100 mg/dL (2.6 mmol/L).[27]

Lifestyle Modification

Secondary stroke prevention guidelines emphasize lifestyle changes that may reduce vascular risk, including tobacco cessation, weight management, physical activity, and a Mediterranean style diet.[20,22] In the SAMMPRIS trial, patients who exercised were significantly less likely to have recurrent vascular events, including stroke, myocardial infarction, and vascular death.[2] The mechanisms are likely multifactorial, mediated through direct effects on endothelial function, inflammation, diabetes control, obesity, and blood pressure.[17,21] Patients with ICAS should be strongly counselled on the importance of a healthy lifestyle in combination with medications.

IMAGING MODALITIES

To diagnose ICAS, various techniques are used, including conventional cerebral angiography, magnetic resonance angiography (MRA), either computed tomography angiography (CTA), transcranial Doppler ultrasound (TCD), and high-resolution MRI, with non-invasive methods preferred for their lower risk and cost.[28] TCD and time-of-flight MRA are effective in ruling out 50-99% stenosis, but CTA, with higher sensitivity and specificity, is favoured in the USA.[29,30] MRI-based high-resolution imaging provides detailed visualization of the arterial wall, aiding in the identification of atherosclerosis indicators like an eccentric wall and lipid-rich necrotic core.[31,32] For acute ischemic stroke or TIA, brain and neurovascular imaging using CT or MRI, and large vessel imaging via CTA or MRA, are essential, supplemented by duplex ultrasound (DUS) and TCD. Non-invasive methods are generally preferred, reserving catheter angiography for inconclusive cases due to its associated stroke risk. Despite their limitations in accuracy and sensitivity, non-invasive imaging methods are crucial for excluding moderate to severe stenosis and guiding initial intensive medical therapy, with catheter angiography providing additional detailed assessment when necessary.

Differences Between Intracranial and Extracranial Carotid Artery Stenosis

Intracranial and extracranial carotid artery stenosis differ significantly in their pathophysiology, clinical presentation, and management. Intracranial stenosis occurs within the arteries inside the skull, such as the middle cerebral artery, while extracranial stenosis involves the carotid arteries in the neck. The smaller vessel diameters and more complex arterial branching of intracranial vessels contribute to a higher risk of ischemic events and present unique therapeutic challenges. Consequently, intracranial stenosis often requires more aggressive medical management, including strict control of risk factors and dual antiplatelet therapy.[28] In contrast, extracranial carotid artery stenosis is more frequently managed with surgical interventions, such as carotid endarterectomy or stenting, due to the accessibility and larger size of the affected vessels.[33] Clinically, patients with intracranial stenosis are at a higher risk for recurrent strokes, particularly in the presence of poor collateral circulation, whereas those with extracranial stenosis may present with transient ischemic attacks or strokes primarily due to embolic phenomena.[28] These differences necessitate tailored approaches to diagnosis, monitoring, and treatment to optimize outcomes for patients with carotid artery disease.

ENDOVASCULAR TREATMENT

Endovascular treatment for symptomatic ICAS aims to improve cerebral perfusion and reduce stroke recurrence through techniques such as percutaneous transluminal angioplasty with or without stenting (PTAS). However, several randomized controlled trials have failed to show benefit of endovascular treatment over medical therapy alone for initial management.

The SAMMPRIS trial, which enrolled patients with TIA or stroke within 30 days attributed to 70-99% intracranial stenosis, was halted early due to the significantly higher rate of stroke and death at 30 days in the PTAS arm versus the medical arm (14.7%

vs 5.8%, P=0.002).[34]This difference was driven largely by the periprocedural complications. At the end of follow-up (median 32 months), rates of the primary endpoint (stroke or death within 30 days or ipsilateral stroke thereafter) remained higher in the PTAS arm compared to medical therapy (23.9% vs 14.9%).

Similarly, the Vitesse Stent Ischemic Therapy Study (VISSIT) trial randomized 112 patients to PTAS or medical therapy and was stopped early after an interim analysis showed higher event rates at 30 days with stenting.[35]The primary endpoint (composite of any stroke, death, or intracranial haemorrhage within 30 days or ipsilateral stroke between 31 days and 1 year) occurred in 20.0% of the PTAS group versus 6.8% of the medical group.

A trial conducted in China randomized patients with symptomatic middle cerebral artery or basilar artery stenosis to stenting with the Wingspan system versus medical therapy.[36]This study enrolled patients at lower risk of complications by excluding those with perforator stroke as the qualifying event. Nonetheless, stenting remained non-superior to medical therapy alone.

Collectively, these data indicate that intracranial stenting provides no benefit over medical therapy as initial treatment for symptomatic ICAS and is associated with increased periprocedural risk. Endovascular stenting may be considered for carefully selected patients who experience recurrent TIAs or strokes despite adherence to optimal medical therapy. These patients should be evaluated on a case-by-case basis, considering factors such as lesion location, patient comorbidities, and potential benefits versus risks. Consequently, major society guidelines currently recommend against stenting for first-line treatment.[22,37]However, some patients may develop recurrent TIAs or strokes despite adherence to optimal medical therapy. Small case series indicate that for carefully selected individuals who fail medical management, stenting may be performed with lower complication rates approaching those seen with extracranial carotid stenting.[36] But controlled data for this subset are lacking.

Ongoing trials are investigating the use of intracranial stenting for secondary prevention after failure of medical therapy. The Chinese Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) study aims to enrol 380 patients with symptomatic severe ICAS who experience recurrence on medical therapy to compare Wingspan stenting versus continued medical treatment.[38] Future studies should focus on identifying patients at highest risk for recurrence who may derive the greatest benefit from endovascular intervention.

Alternate endovascular techniques that may carry lower procedural risk, such as angioplasty alone or submaximal angioplasty, have also been proposed as rescue options but require more data before routine implementation.[38–40]Indirect extracranial-intracranial bypass has similarly not shown definitive benefit over medical therapy but continues to be investigated in carefully selected patients.[41,42]

HIGH RISK GROUPS

High-risk patients typically include those with recent TIA or ischemic stroke within 3 months, severe stenosis (≥70%), borderzone or watershed infarcts, impaired collateral flow, posterior circulation involvement, and clinical features suggesting hemodynamic compromise. These patients may benefit from more aggressive treatment and closer monitoring. Given the generally unfavourable risk-benefit profile, endovascular treatment should be reserved for severely symptomatic patients with recurrent events despite optimized medical treatment. However, our methods for identifying the highest risk subset remain imperfect.

Several ongoing studies are using advanced neuroimaging techniques to evaluate novel markers that may better predict individual risk in ICAS. High-resolution MRI can identify characteristics of plaque vulnerability that could increase stroke risk independently of the degree of stenosis.[30] Studies using computational fluid dynamics have found that the hemodynamic significance of a stenosis depends on multiple factors including the length, morphology, and downstream vasculature.[31]

Alternate modalities such as measurement of microembolic signals on transcranial doppler may also predict increased risk.[43] If validated as an independent prognostic marker, detection of microemboli could help select patients for more aggressive medical therapy or endovascular intervention.

FUTURE DIRECTIONS

While our knowledge surrounding symptomatic ICAS has expanded greatly over the past decade, critical unanswered questions remain:

- What is the optimal blood pressure parameter and target in patients with impaired collateral flow?
- Should management differ for anterior versus posterior circulation ICAS?
- Does intensive medical therapy, including statins and newer antiplatelets, reduce progression of intracranial atherosclerosis and lower dementia risk?
- Can advanced neuroimaging identify plaque features or hemodynamic factors that improve prognostication?
- What subsets of patients with recurrent events despite medical therapy are most likely to benefit from endovascular therapy?
- Would early identification of ICAS and initiation of medical treatment in asymptomatic patients improve outcomes?

Promising areas of research include advanced neuroimaging techniques to better predict stroke risk, studies on novel antiplatelet and lipid-lowering therapies, and trials investigating optimal blood pressure targets based on individual hemodynamic profiles. Additionally, research on early identification and treatment of asymptomatic ICAS to prevent progression and stroke is crucial.

Further research on risk stratification and novel therapies is also greatly needed to address these issues and thereby reduce the burden of stroke and dementia attributed to intracranial atherosclerosis. Both optimized medical treatment and endovascular advances may contribute to improved outcomes in the future.

CONCLUSIONS

In summary, symptomatic ICAS is an important cause of ischemic stroke associated with high rates of recurrence despite standard medical therapy. All patients with symptomatic ICAS should receive intensive control of vascular risk factors, antiplatelet therapy, and lifestyle modification. Dual antiplatelet therapy provides additional benefit for reducing stroke risk in the short-term following ischemic events. Endovascular stenting has not demonstrated benefit over medical therapy alone in clinical trials and is not recommended as first-line treatment. However, carefully selected patients who experience recurrent events despite optimal medical management may be considered for stenting or alternate endovascular techniques on a case-by-case basis. Further research focused on risk stratification and novel therapies is critically needed to improve the historically poor prognosis associated with this disease.

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