Intracranial Atherosclerotic Disease

Neurologists need to be vigilant for this common cause of ischemic stroke, associated with the highest rates of recurrent stroke.

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Intracranial atherosclerotic disease (ICAD) can affect cerebral arteries distal to the internal carotid arteries (ICAs) after they enter the petrosal bone (C2 segment) and the vertebral arteries after they enter the foramen magnum and pierce the dura mater (V4 segment).¹ As such, ICAD is not amenable to surgical revascularization, making it a very different and independently important disease entity from extracranial carotid disease. In autopsy studies, ICAD accounted for 10% of strokes,² and in a pooled analysis of 2,593 patients, it was at least somewhat present in 3.5% to 13% of the population, varying with age and ethnicity.³ For the practicing neurologist, diagnosing and treating ICAD can be challenging because it can masquerade as and be confused with other conditions and because ICAD is associated with high rates of recurrent stroke. Here, we briefly discuss the epidemiology and pathophysiology of ICAD and strategies for acute and long-term management.

Epidemiology

Risk factors for ICAD fall into modifiable and nonmodifiable categories. Hypertension, diabetes mellitus, hyperlipidemia, and smoking are the most typical modifiable risk factors. Age, race, and sex are the most typical of the nonmodifiable risk factors. Although early-onset disease is well-described in certain populations, clinically meaningful atherosclerotic plaque does not typically appear until the fourth decade of life, and the highest rate of development of significant ICAD is between the sixth and seventh decades.⁴ Men have a higher rate of development of ICAD during their fourth and fifth decades, while women generally only begin developing plaque in their sixth decade. Asian, black, and Hispanic populations are more affected than the white population, although the prevalence in this latter group is higher than once commonly thought.⁵,⁶ Asians in particular have a higher burden of ICAD, with one study suggesting it accounts for 33% to 37% of ischemic stroke etiologies in China.⁷ At least part of this ethnic difference is thought to come from the higher rate of uncontrolled hypertension, diabetes, and hyperlipidemia in the Asian, Hispanic, and black populations, although genetic predispositions may also exist.⁷

Mechanism of Stroke in ICAD

ICAD may cause stroke via several different mechanisms, which may be inferred by the pattern of infarct on MRI. Artery-to-artery embolism from a ruptured plaque and thrombo-occlusion of the diseased artery are typically associated with a territorial pattern of infarct via occlusion of the stenotic artery or its more distal branches, which produces infarcts that are typically larger than 1.5 cm.⁸ Another mechanism, hypoperfusion distal to the stenotic artery, causes border zone infarcts either in the internal border zone comprising the corona radiata and centrum semiovale or in the cortical border zones between the anterior cerebral artery (ACA), middle cerebral artery (MCA), or MCA-posterior cerebral artery (PCA) vascular territories. Atheromatous encroachment on the opening or ostia of small perforators causing occlusion results in a subcortical perforating pattern of infarct (branch atheromatous disease), with infarcts usually less than 1.5 cm.⁸,⁹ Mixed patterns are common (eg, high-grade stenosis causing border zone and embolic patterns) and may be caused by endothelial abnormalities from ICAD inducing clot formation and distal embolization, compounded by hypoperfusion preventing appropriate washout of emboli in the border zones.¹⁰

Natural History

The natural history of patients with ICAD comprises 3 predominant courses that may coexist: transient ischemic attack (TIA), recurrent ischemic stroke, and chronic hypoperfusion that can cause cumulative white matter damage and gradual cognitive worsening.⁷ Among TIA presentations, limb-shaking
TIAs are peculiar transient symptoms frequently associated with high-grade stenosis, often in the ICA. They typically present as repetitive short duration paresis and “shaking,” sometimes triggered by exertion, caused by altered cerebrovascular hemodynamics. Recurrent ischemic stroke ipsilateral to a stenotic artery has been shown to range from 3.1% to 8.1% per year with annual mortality ranging from 7.8% to 17.2%. Generally, the highest risk of recurrent stroke is in the first 2 years, regardless of location of ICAD, and half of that risk is within the first month of the index stroke or TIA. There is less study of progressive cognitive consequences of ICAD. However, a prior study noted that 34% of subjects had dementia attributed primarily to ICAD.

**Evaluation and Diagnosis**

**Imaging Evaluation**

Although catheter angiography is considered the gold standard diagnostic study for ICAD, its invasiveness along with improvements in CT and magnetic resonance angiography (MRA) have shifted practice to utilizing these latter modalities as the primary initial screening tool. Transcranial Doppler (TCD) ultrasound can also offer additional information with regards to plaque stability via microemboli detection, vasomotor reactivity in response to a carbon dioxide challenge, and luminal narrowing based on elevated mean blood flow velocity. MR vessel-wall imaging has been used recently to better characterize plaque morphology. In practice, CT angiography is often particularly helpful to identify areas of calcific atherosclerotic disease, and can achieve spatial resolution to grade degree of stenosis accurately compared to catheter angiography. The severity of narrowing can be graded as normal (0%-9%), mild (10%-29%), moderate (30%-69%), severe (70%-99%), or completely occluded. Although the degree of stenosis is often used in stroke risk stratification, other features such as antegrade flow, plaque stability, and presence of collaterals likely influence stroke risk.

**Differential Diagnosis**

Because ICAD is a disease of the arterial wall that secondarily affects the lumen and blood flow, other disease processes may be mistaken for ICAD (Table). For example, nonocclusive or partially recanalized emboli within cerebral arteries may be mistaken for ICAD. Some characteristics that may assist with differentiating these is the presence of calcific atherosclerosis in cerebrovascular structures remote from the stenosis, which would favor ICAD, as opposed to an embolus, which more commonly is only seen within the affected artery. Arterial dissection, although rare intracranially, is also included in the differential, especially in milder forms that cause lumen irregularity as opposed to frank dissection flaps. High-resolution MRI

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**TABLE. COMPARISON OF IMAGING FEATURES OF INTRACRANIAL ARTERIOPATHIES**

<table>
<thead>
<tr>
<th>Appearance on Vessel Imaging</th>
<th>Stenosis Shape</th>
<th>Vessel Distribution</th>
<th>Wall Enhancement</th>
<th>Signal Intensity</th>
<th>Other Characteristic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAD</td>
<td>Calcific or lipid-laden stenosis</td>
<td>Eccentric</td>
<td>Any artery (typically bifurcations)</td>
<td>Depends on stage (+++ ⇒ +)</td>
<td>Lipid: T1 isointense T2 iso/hypointense Calcification: T1/T2 hypointense</td>
</tr>
<tr>
<td>Intraluminal thrombus</td>
<td>Vessel occlusion/stenosis</td>
<td>–</td>
<td>Usually single artery</td>
<td>Thrombus enhances (++)</td>
<td>T1 hyperintense T2 GRE hypointense</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>Lumen irregularity or intimal flap</td>
<td>Eccentric</td>
<td>Any artery (typically vertebral)</td>
<td>+/−</td>
<td>T1 hyperintense in intramural hematoma Intramural hematoma False lumen Pseudoaneurysm</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Alternating narrowing and dilatation (string of beads)</td>
<td>Concentric (occasionally eccentric)</td>
<td>Small-medium size arteries</td>
<td>Depends on stage (+++ ⇒ −)</td>
<td>T2 isointense</td>
</tr>
<tr>
<td>RCVS</td>
<td>Multifocal stenosis</td>
<td>Concentric</td>
<td>Small-medium size arteries</td>
<td>+ ⇒ −</td>
<td>T2 isointense</td>
</tr>
<tr>
<td>Moyamoya disease</td>
<td>Network of small vessels (puff of smoke)</td>
<td>Concentric</td>
<td>Terminal ICA Proximal MCA ACA</td>
<td>++/+</td>
<td>T1 and T2 isointense</td>
</tr>
</tbody>
</table>

Abbreviations: ACA, anterior carotid artery; ICA, internal carotid artery; GRE, gradient echo; ICAD, intracranial atherosclerotic disease; MCA, middle cerebral artery; RCVS, reversible cerebral vasospastic syndrome.
Multifocal narrowing of intracranial vessels is also characteristic of vasculitic processes, although importantly here, the resulting strokes are more frequently punctate and multifocal rather than affecting a single arterial distribution. Vessel imaging in vasculitis may have the classic string-of-beads appearance, although this does not definitively exclude ICAD, because extensive atherosclerosis may cause this appearance. Reversible cerebral vasoconstriction syndrome (RCVS) may similarly appear as multifocal artery narrowing. In vasculitis, contrast MRI and MRA may show brain and concentric artery wall enhancement, with spinal fluid analysis and sometimes tissue biopsy being additionally necessary for the diagnosis. Primary Moyamoya disease typically causes distal ICA and proximal MCA occlusion but can be difficult to differentiate from advanced ICAD due to slowly progressive stenosis/occlusion that permits proximal and distal collateral development.

**Management**

**Acute Care**

All patients with ischemic stroke presenting within the windows for thrombolysis or endovascular therapy should be evaluated and managed according to the current guideline, whether they are eventually found to have ICAD or not (Figure). Although stent retrievers are safe and highly effective for acute thrombectomy, it is not known whether adjunctive angioplasty or nonretrievable stenting is safe and effective in patients with underlying ICAD at the site of large artery occlusion. After these acute intervention decisions are made, if intracranial stenosis is found, the next most important consideration is blood pressure (BP) management. An analysis of patients enrolled in the SAMMPRIS trial suggested safety of early BP lowering with target systolic BP < 140 mm Hg. Although the earlier WASID trial did not aggressively lower BP after enrollment, patients in both WASID and SAMMPRIS with good BP control at outpatient follow-up had fewer recurrent vascular events. It is reasonable to maintain permissive hypertension (up to 220/120 mm Hg in nonreperfused patients and < 180/100 mm Hg in reperfused patients with high-grade stenosis from ICAD) for the first 24 hours while maintaining bed rest with subsequent slow liberalization of activity. If neurologic examination findings remain stable as activity is liberalized, we gradually (eg, by 10%) start the lowering of BP between 24 and 48 hours and titrate to normotension over the next 1 to 2 weeks. This process is typically started on an inpatient service but completed on an outpatient basis. If patients fail activity liberalization or BP lowering (eg, fluctuations that are flow or pressure dependent), we may consider further delaying activity and BP lowering. In rare cases, it may be necessary to consider submaximal angioplasty of the stenotic artery to improve flow and prevent fluctuations and recurrent stroke. All patients with nonhemorrhagic infarcts, and after 24 hours in those who receive thrombolysis, are treated with aspirin and clopidogrel.

**Secondary Prevention**

For the subacute and chronic management of ICAD, the WASID trial provided the first large randomized controlled trial data comparing medical management options. It compared aspirin 1,300 mg daily to warfarin with international normalized ratio goal 2 to 3 and observed lower all-cause death (4.3% vs 9.7%), major hemorrhage rates (3.2% vs 8.3%), and myocardial infarction or sudden death (2.9% vs 7.3%) in patients treated with aspirin compared with patients treated with warfarin. Lower rates of recurrent stroke were not statistically different between the 2 arms. This has since been extrapolated to indicate that an antiplatelet regimen is categorically safer and preferable to anticoagulants, although not necessarily superior for recurrent stroke prevention.

After WASID, the focus of optimal management shifted to whether endovascular therapy improved outcomes in patients with ICAD, particularly exploring angioplasty with stenting.
In 2005, the US Food and Drug Administration (FDA) approved the self-expanding Wingspan stent (Stryker Neurovascular) for symptomatic ICAD with 50% to 99% narrowing. The SAMMPRIS trial was conducted to determine whether maximal medical therapy with percutaneous transluminal angioplasty and stenting (PTAS) was superior to maximal medical therapy alone for patients with 70% to 99% symptomatic ICAD. Maximal medical therapy consisted of aspirin 325 mg with clopidogrel 75 mg for 90 days, antihypertensive therapy, statin therapy as needed to achieve low-density lipoprotein <70, and a lifestyle modification program including a coach to increase adherence to smoking cessation, weight loss, and physical activity. At 30 days, the rate of stroke or death in patients in the PTAS group was 14.7% compared with 5.8% in those who had medical therapy, predominantly due to immediate postprocedural complications that led to early stoppage of the trial. At the end of the eventual 32-month follow-up, stroke and death differences persisted (23% in patients treated with PTAS compared with 15% in those given medical therapy). Notably, patients in the medical arm of SAMMPRIS had less stroke and death at 30 days and 1 year than patients in WASID, primarily thought to be from dual antiplatelet therapy, increased statin use, more consistent antihypertensive medication use, and stringent lifestyle modification.

In subgroup analysis of SAMMPRIS, no cohort had greater benefit from PTAS with medical therapy compared to medical therapy alone. Owing to these results, the FDA revised their approval for the Wingspan stent to include only nondisabled patients who have 2 or more strokes with stenosis of 70% to 99%, were stable for at least 7 days, and were refractory to aggressive medical management. Another trial, VISSIT, evaluated a balloon-expandable stent vs medical therapy; it also stopped early due to an increase in complications and patient harm in the stenting group. Since SAMMPRIS and VISSIT, some have argued that submaximal angioplasty alone may have less periprocedural stroke risk and therefore may be safer than stenting. Additionally, there have been newer stents brought to the market since the Wingspan that are believed to be safer. Thus, further investigation of these approaches may be warranted.

It is reasonable to consider endovascular therapy with submaximal angioplasty or the Wingspan stent in patients with recurrent strokes despite maximal medical therapy or in whom hemodynamic symptoms do not permit BP lowering. Very rarely, extracranial-intracranial bypass may be offered in patients with advanced ICAD in whom a secondary Moyamoya syndrome exists and a distal (minimally diseased) recipient artery is present.

**Summary**

In summary, if ICAD resulting in 70% to 99% stenosis is the mechanism of ischemic stroke or TIA, the patient is placed on aspirin 325 mg and clopidogrel 75 mg for 3 months, after which single antiplatelet therapy is used with continued aggressive antihypertensive, lipid-lowering, and lifestyle modification. Target low-density lipoprotein, as outlined by the SPARCL trial, is < 70 mg/dL, as done in SAMMPRIS. Although SPARCL used atorvastatin 80 mg in their treatment arm, rosuvastatin 40 mg is also a reasonable alternative because it has similar high-intensity lipid-lowering effects. Endovascular or surgical therapy is reserved for patients who failed this maximal medical approach with evidence of well-controlled risk factors.

**Future Directions**

Current research in ICAD is evaluating various imaging and laboratory-based biomarkers to assist with stratifying patients with higher recurrent stroke risk and to select for targeted medical or endovascular treatments. The recently published VERITAS study used quantitative MRA to determine the extent of flow distal to a symptomatic vertebrobasilar stenosis, finding that lower flow is associated with higher risk of subsequent stroke. The biomarkers of ischemic outcomes in intracranial stenosis (BIOSIS) study found that plasminogen activator inhibitor-1 (PAI-1), high-sensitivity C-reactive protein (hsCRP), and low circulating progenitor cells are promising biomarkers of recurrent stroke distal to a stenotic artery. The MyRIAD study is also currently underway and looks at 3 mechanisms of recurrent stroke in patients with symptomatic ICAD:

1. antegrade flow compromise in the stenotic artery using quantitative MRA;
2. distal flow compromise using TCD with vasomotor reactivity and perfusion-weighted MRI; and
3. artery-artery embolism using TCD with emboli detection.

A nuanced and targeted approach to the management of ICAD may evolve that leverages these biomarkers to personalize treatment options that reduce risk of recurrent stroke. For example, patients with flow compromise may be selected in future trials of revascularization with submaximal angioplasty or newer-generation stents, and those with plaque instability and embolization may be suitable for enhanced medical treatments such as novel lipid-lowering drugs and antithrombotic therapy that stabilize the plaque and reduce embolic potential.

**Conclusions**

Intracranial atherosclerotic disease is a common cause of ischemic stroke, particularly among minorities. Although treatment tailored for this disease involves aggressive risk factor management coupled with short-term dual antiplatelet therapy, ICAD is still associated with the highest rates of recurrent stroke of any stroke subtype. It is imperative that treating neurologists stay vigilant of this stroke mechanism and the nuances of its evaluation and management.


