Symptomatic Intracranial Atherosclerotic Disease

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ABSTRACT

• **Objective:** To provide an overview of the diagnosis, clinical presentation, and management of symptomatic intracranial atherosclerotic disease (ICAD).
• **Methods:** Review of the current literature in the context of a clinical case.
• **Results:** ICAD is a common cause of ischemic strokes or transient ischemic attacks (TIAs), especially among Asian, black, and Hispanic patients. ICAD can be identified with noninvasive arterial imaging such as CT angiography, MR angiography, or transcranial Doppler ultrasound of the head when evaluating for the cause of an ischemic stroke or TIA. Aggressive medical management with dual antiplatelet therapy and lifestyle and risk factor modification has emerged as effective first-line therapy. In patients who have recurrent ischemic symptoms while on aggressive medical management, endovascular treatment can be considered.
• **Conclusion:** When symptomatic ICAD is identified early, aggressive medical management is effective in reducing the risk of recurrent ischemic events in this patient population.

Symptomatic intracranial atherosclerotic disease (ICAD) may represent the most common cause of ischemic stroke worldwide and the cause of approximately 8% to 10% of ischemic strokes in the United States [1–7]. It is a particularly important clinical entity due to the high recurrence rate of ischemic events in this population. The estimated recurrent stroke risk from symptomatic ICAD has been reported to be as high as 14.9% in the first year after an initial ischemic event [1]. There are multiple risk factors for ICAD. Non-modifiable risk factors include race (particularly Asian, black, or Hispanic race), age, and family history of coronary artery disease or stroke; modifiable risk factors include diabetes, hypertension, and hyperlipidemia [2].

CASE STUDY

Initial Presentation

A 78-year-old right-handed man presents to the outpatient clinic for follow-up evaluation after inpatient admission for acute ischemic stroke. The patient has an established medical history of hypertension, diabetes mellitus (diagnosed 10 years ago), dyslipidemia, and a 50 pack-year history of tobacco use.

Two weeks prior to the clinic visit, the patient presented to the emergency department (ED) via emergency medical services with right face and arm weakness and numbness and the inability to speak that had been ongoing for approximately 1 hour. The patient’s wife reported to ED providers that the patient had a similar episode 1 month prior that resolved completely in 30 to 45 minutes (and for which the patient never sought medical attention). Home medications at the time of admission included aspirin 81 mg and pravastatin 20 mg daily, both of which he takes intermittently.

The initial blood pressure was 185/76 mm Hg and blood glucose was 225 mg/dL. Initial exam was remarkable for the inability to answer orientation questions (but able to follow simple commands), forced gaze deviation to the left, right lower facial weakness, weakness in the right arm with no antigravity movement, moderately decreased sensation of the right face and arm, severe expressive aphasia, and severe dysarthria. A CT of the head without contrast showed no evidence of hemorrhage. Patient was suspected of having an acute ischemic stroke and was given intravenous tPA.

• What are the possible mechanisms for this patient’s presentation with ischemic stroke?

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This patient is presenting with right face and arm weakness with sensory loss, gaze deviation to the left, and expressive aphasia. Abnormalities of speech and gaze paresis that localize to the left frontal lobe with cortical involvement make a subcortical or brainstem lacunar ischemic event less likely. The syndrome is suggestive of a large artery occlusion of the left middle cerebral artery. This type of large artery occlusive disease in the anterior circulation is most often due to an embolus (artery-to-artery or cardiac origin) event and requires arterial imaging of the head and neck acutely as endovascular thrombectomy has been associated with reduced disability compared to intravenous tPA alone.

**Further Evaluation**

Due to the acute presentation, CT angiography of the head and neck was ordered to assess for a large vessel occlusion. Imaging demonstrated occlusion of a small branch (M3) of the left middle cerebral artery, which was not amenable to endovascular treatment. Additionally, the patient was noted to have severe stenosis of the left supraclinoid (intracranial) internal carotid artery (ICA) with minimal calcified atherosclerotic plaque in the left cervical ICA at the origin without hemodynamically significant stenosis ([Figure 1](#) and [Figure 2](#)).

**What imaging is recommended to identify patients with ICAD?**

Several options exist to identify ICAD including transcranial Doppler (TCD) ultrasound, MR angiography (MRA) of the head without contrast (time of flight), MRA with contrast, CT angiography (CTA), and cerebral angiography.

The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial sought to evaluate the reliability of noninvasive imaging modalities to identify a 50%–99% stenosis of large proximal cerebral arteries as compared with the gold standard of conventional angiography [3]. Qualifying vessels included the M1 segment of the middle cerebral artery, the carotid siphon, and intracranial vertebral and basilar arteries. Imaging techniques included MRA head without contrast (time of flight) and TCD ultrasound. Both of these imaging modalities demonstrated a high negative predictive value (NPV) for the presence of a 50%–99% intracranial stenosis; however, the positive predictive value (PPV) for TCD and MRA was only 55% and 66%, respectively. Subsequent studies of contrast-enhanced MRA and CTA of the head have shown high PPV (78%–94%) and NPV (95%–100%) when compared with cerebral angiography for the detection of 70%–99% ICAD [4,5]. Together these data suggest that TCD and MRA of the head without contrast can be used as screening tools to rule out ICAD when normal; however, subsequent contrast-enhanced MRA or CTA is required when abnormalities are identified.

When choosing the best noninvasive imaging modality for any given patient, concomitant medical issues including renal disease, age, presence of a pacemaker, implantable cardiac defibrillator or other metal, and claustrophobia are factors to consider.

**What are the potential mechanisms of ischemic stroke in patients with symptomatic ICAD?**

Stroke in the symptomatic ICAD group occurs as a result of either (1) thrombus formation at the site of a high-grade stenosis due to an unstable atherosclerotic plaque, (2) low flow through a narrow, stenotic artery (hypoperfusion) or (3) a combination of atheroembolism and...
hypoperfusion [6]. While a thrombus can occlude the parent vessel at the site of stenosis, more commonly the thrombus migrates distally as an artery-artery embolism to a smaller caliber artery.

What medical regimen is recommended for this patient with symptomatic ICAD?

Our understanding of what constitutes best medical therapy is based on protocols developed for patients in the Stenting versus Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial (Table) [7]. In the study, patients with recent (< 30 days) symptoms of ischemic stroke or TIA secondary to a high-grade (70%-99%) stenosis of a major intracranial artery were randomized to aggressive medical management alone vs. aggressive medical management plus percutaneous transluminal angioplasty and stenting (PTAS). Medical management consisted of dual antiplatelet therapy (DAT) with aspirin 325 mg and clopidogrel 75 mg daily for 90 days after enrollment (with subsequent transition to aspirin 325 mg monotherapy), optimization of primary risk factors (hypertension, elevated LDL), and a directed lifestyle management program to address secondary risk factors (including diabetes, elevated non-HDL cholesterol levels, excess weight, smoking, and insufficient cardiovascular activity).

Dual Antiplatelet Therapy

DAT with aspirin and clopidogrel is thought to reduce ischemic events related to regional thromboembolism. The best clinical evidence of the use of DAT in symptomatic ICAD is found in outcomes data for the SAMMPRIS trial where 30-day recurrent ischemic stroke rates in the aggressive medical management arm were significantly lower than patients treated with aspirin or warfarin.
monotherapy as part of the Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis (WASID) trial. A subgroup of patients enrolled in WASID with similar clinical characteristics to those in SAMMPRIS were found to have a 30-day rate of stroke or death of 10.7% and a collective 1-year rate of ischemic stroke, brain hemorrhage, or vascular death of 25% [2]. The corresponding rates in the SAMMPRIS medical management arm were 5.8% at 30 days and 17.5% at 1 year. Given that the recurrent stroke rates were significantly lower in as little as 30 days, these benefits have been hypothesized to be more likely secondary to the DAT regimen than other risk factor modification [7]. There is some evidence that longer term DAT with aspirin and clopidogrel up to 1 year may be associated with further reduction in stroke, MI, and vascular death with similar bleeding risk, but this needs to be evaluated in prospective studies [8].

Additional evidence of the benefit and potential mechanism from DAT in ICAD comes from CLAIR (Clopidogrel plus Aspirin versus Aspirin alone for Reducing Embolization in Patients with Acute Symptomatic Cerebral or Carotid Artery Stenosis Trial), a multicenter, randomized trial with blinded outcome assessment, with patients recruited at sites in Hong Kong, Singapore, China, Thailand, and Malaysia [9]. Patients were enrolled with an extracranial or intracranial stenosis (greater than or equal to 50%, as diagnosed by carotid duplex, transcranial Doppler, or magnetic resonance angiography) if they had a clinical diagnosis of acute ischemic stroke or transient ischemic attack (TIA) during the 7 days prior to enrollment and were found to have microembolic signals (suggesting microemboli of atherosclerotic origin) detected at baseline assessment with transcranial Doppler ultrasound. Patients were randomized to DAT with aspirin and clopidogrel versus aspirin monotherapy. Patients on DAT had significantly reduced microembolic signals compared with patients on aspirin monotherapy. Asymptomatic embolization with dual antiplatelet therapy may also proffer a reduction in clinical events in these patients with symptomatic ICAD.

### Statin Therapy

Statin therapy is an integral part in the prevention of recurrent ischemic events in the symptomatic ICAD cohort. Post-hoc analyses from the WASID trial found that total cholesterol greater than 200 mg/dL was associated with an increased risk of ischemic stroke, myocardial infarction, or vascular death.

In 2013, the American Heart Association released new guidelines regarding the treatment of cholesterol to reduce atherosclerotic cardiovascular risk in adults [10]. Clinical atherosclerotic cardiovascular disease (ASCVD) is the manifestation of systemic atherosclerotic disease

### Table. Optimal Medical Therapy for Symptomatic Intracranial Stenosis

<table>
<thead>
<tr>
<th>Antithrombotic therapy</th>
<th>Dual antiplatelet therapy with aspirin 325 mg and clopidogrel 75 mg PO daily x 90 days followed by aspirin 325 mg daily thereafter</th>
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</table>
| High-potency statin therapy | For patients ≤ 75 years of age, therapy should include atorvastatin 40-80 mg or rosuvastatin 20 or 40 mg  
For patients > 75 years of age, use moderate-intensity statin therapy (atorvastatin 10 or 20 mg, rosuvastatin 5 or 10 mg, pravastatin 40 mg, or simvastatin 20 or 40 mg)  
Goal LDL < 70 |
| Blood pressure management | Goal BP < 140/90 mm Hg in non-diabetic patients  
Goal BP < 130/80 mm Hg in diabetic patients |
| Blood glucose control | Goal hemoglobin A1c < 7.0% in diabetic patients  
Smoking cessation. Support for maintenance of cessation with educational courses, nicotine replacement products, varenicline (nicotine agonist) or bupropion |
| Lifestyle modification | Aerobic exercise with goal of at least 30 minutes of moderate-intensity activity at least 5 days per week or at least 25 minutes of vigorous activity at least 3 days per week  
Dietary modifications should be modeled toward the Mediterranean diet  
Weight loss should be targeted toward a body mass index < 25 kg/m² |
and defined as acute coronary syndromes, a history of myocardial infarction, stable or unstable angina, a history of coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin. Recommendations for secondary prevention in patients with clinical ASCVD include the use of high-intensity statin therapy (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg) for patients less than 75 years of age or moderate-intensity statin therapy (atorvastatin 10 or 20 mg, rosuvastatin 5 or 10 mg, pravastatin 40 mg, or simvastatin 20 or 40 mg) for patients > 75 years of age. In the SAMMPRIS trial, an LDL cholesterol level less than 70 mg/dL was targeted [7].

**Blood Pressure Management**

Post-hoc analysis of data from WASID demonstrated a statistically significant increase in recurrent stroke risk with increasing mean systolic and diastolic blood pressure (BP) [11]. This was particularly true in patients with mean SBP > 160 mm Hg. This is contrary to the common perception that BP should be maintained higher in patients with intracranial stenosis. In multivariable analysis, systolic BP greater than 140 mm Hg was associated with an increased risk of ischemic stroke, myocardial infarction, or vascular death. In the SAMMPRIS trial, the recommended BP goals for patients with symptomatic ICAD were less than 140/90 mm Hg in non-diabetic patients and less than 130/80 mm Hg in diabetic patients [7]. The timing and pace of blood pressure normalization for a recently symptomatic patient with ICAD is still unclear and needs further study.

**Lifestyle Modification and Secondary Risk Factors**

The SAMMPRIS protocol incorporated a lifestyle coach for all patients enrolled in the study. Lifestyle modification to achieve smoking cessation, regular physical activity, weight reduction for overweight patients, and glucose control in diabetes (goal hemoglobin Alc < 7.0%) were complementary to the pharmacotherapy (aspirin, clopidogrel, statin, and antihypertensive regimen) prescribed [7].

Patients should be encouraged to participate in aerobic exercise for at least 30 minutes at least 3 times weekly. Dietary modifications modeled after the Mediterranean diet should be encouraged. These should be coupled with additional efforts to address excessive weight as needed.

Successful smoking cessation proves one of the most challenging lifestyle modifications for this group of patients and may require the employment of an extended support system with both family and medical providers. Nicotine supplementation is a common first-line aid for cessation, which may be provided in the form of gum or transdermal patches. Additional pharmacotherapy to address central mechanisms of addiction may be necessary. Many patients benefit from the addition of an antidepressant therapy such as bupropion or an adjunctive medication such as varenicline (a nicotine receptor partial agonist that helps with breaking nicotine addiction). It is important to establish a quit date and detailed, multistep plan for cessation [12].

**Exceptions and Other Considerations**

These evidence-based recommendations are directed toward a specific group of patients with high-grade stenosis (70%–99%), a single symptomatic vessel, and relatively short segments of stenosis (<14 mm) based on the inclusion and exclusion criteria for the SAMMPRIS trial [7]. Additionally, these patients were not enrolled during the immediate period following an acute ischemic event. There is less evidence on the management of patients who present with <70% symptomatic ICAD but we can infer that therapy with DAT, statins, and risk factor modification are still of benefit for patients with 50%–69% stenosis or those requiring treatment during the acute evaluation [13]. Additionally, some of these SAMMPRIS exclusion criteria were included to select patients who could be considered intracranial stenting candidates (eg, short segment stenosis, single vessel disease, etc) and are not considered to impact on the benefits of the aggressive medical management regimen.

**Further Evaluation**

The patient was initiated on antithrombotic therapy on hospital day 2 (24 hours after IV tPA administration) with aspirin 325 mg daily and clopidogrel 300 mg oral load followed by 75 mg daily, ranitidine 150 mg twice a day to reduce gastroesophageal reflux and atorvastatin 80 mg daily. On hospital day 3, his neurological exam remained stable and he was initiated on losartan 25 mg daily with a plan to titrate the dose up as an outpatient to achieve target blood pressure. The patient and his wife were advised to maintain a blood pressure log and provide it to his physicians at follow-up and was provided smoking cessation counseling with a plan to remain off tobacco after discharge utilizing nicotine patches. The patient was discharged from the
hospital 4 days after admission with a diagnosis of acute ischemic stroke secondary to symptomatic ICAD from regional thromboembolism. Early outpatient follow-up was scheduled with his primary physician within 1 week after discharge to evaluate BP and a vascular neurologist within 1 month after discharge.

**What factors predict recurrent stroke in patients with symptomatic ICAD?**

As evidenced in the WASID post-hoc analysis, female sex, prior ischemic stroke (versus TIA), time from qualifying event to enrollment (<17 days after ischemic event), severity of stenosis (≥70% stenosis) of the symptomatic vessel, and history of diabetes were identified as independent risk factors for recurrent stroke in this population [14].

**How do we manage patients who continue to have symptoms despite optimal medical therapy?**

When evaluating symptomatic ICAD patients with recurrent neurologic symptoms, several important factors should be considered:

- Do the recurrent neurologic symptoms localize to the original ICAD location?

Patients with symptomatic ICAD often have multiple risk factors that put them at risk for other subtypes of ischemic stroke including lacunar stroke. Repeat neuroimaging with brain MRI is recommended to confirm the localization of a recurrent stroke is inside or outside of the territory of the ICAD.

- Were the recurrent neurologic symptoms provoked?

Patients with ICAD can be uniquely sensitive to fluctuations in cerebral blood flow and oxygenation. Diabetic patients with ICAD can develop autonomic neuropathy that results in orthostatic hypotension. If patients have recurrent transient ischemic events associated with postural changes, adequate treatment of orthostasis can reduce recurrent ischemic events. Other provoked circumstances include patients who develop anemia and patients with untreated severe obstructive sleep apnea who may awake with recurrent ischemic events due to hypoxemia.

**Is the patient adhering to the medication regimen?**

Patients with symptomatic ICAD frequently have multiple medications to take for treatment of their comorbidities. Discussion of the number of missed doses of medications over the prior month is important to ascertain adherence. Patients should also be counseled to avoid concomitant medications that may cause drug interactions; given the known drug interactions between nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, specific counseling on the avoidance of NSAIDs should be encouraged.

**Are the patient’s risk factors optimally managed?**

Risk factor control should be assessed on a routine (eg every 3-6 months) basis and again if an ICAD patient has recurrent ischemic symptoms. Regular review of blood pressure logs, interval assessment of lipids, optimization of glucose control with serial hemoglobin A1c, tobacco cessation, and attention to weight management are paramount.

**Does the patient have an appropriate metabolic response to antiplatelet therapy?**

If risk factors are optimized and the patient reports adherence to their medication regimen, aspirin and clopidogrel response should be evaluated. Aspirin resistance can be assessed by measuring the urinary level of 11-dehydrothromboxane B2 [15]. A urine level >1500 pg/mg creatinine should be expected in healthy, aspirin-free individuals; however, if this level is identified in a patient who is prescribed aspirin, aspirin resistance can be diagnosed. Various causes of aspirin resistance have been reported including inadequate adherence to aspirin therapy, concomitant use of a NSAID, genetic mutations in the COX-1 gene, non-platelet sources of thromboxane A2, and high platelet turnover [15]. Aspirin dosage adjustments should be made in consultation with a hematologist.

Resistance to clopidogrel has been less widely evaluated, but one meta-analysis estimated a mean preva-
ence of clopidogrel non-responsiveness at 21% [16]. While there is limited data on the optimal assessment of clopidogrel responsiveness in stroke patients, on-treatment platelet reactivity has been measured in parallel by means of light transmittance aggregometry, Veriftynow P2Y12 and Platelet works assays, and the IMPACT-R and PFA-100 system in one study of patients undergoing coronary stent implantation [17]; of the platelet function assays assessed, only light transmittance aggregometry, Veriftynow, and Platelet works assays were significantly associated with clinical outcomes in patients undergoing coronary stent implantation. Various causes of clopidogrel resistance have been reported including inadequate adherence to clopidogrel therapy, concomitant use of medications that interfere with clopidogrel prodrug conversion in the liver to its active metabolite, and genetic mutations in the cytochrome p450 3A4 gene [18,19]. Clopidogrel dosage adjustments should be made in consultation with a hematologist.

While the majority of patients will have no recurrent ischemic symptoms on aggressive medical therapy, some patients may continue to experience recurrent ischemic stroke or TIA secondary to ICAD despite optimal medical management. Patients who have hypoperfusion resulting in borderzone infarctions may be at higher risk for recurrent ischemic symptoms despite optimal medical therapy [20]. The risks of intracranial stenting, including stroke and death, must be weighed against the potential benefits. In the angioplasty plus stenting arm of the SAMMPRIS trial, the risk of stroke or death at 30 days was 14.7% [7]. In the angioplasty plus stenting arm of the VISSIT clinical trial evaluating symptomatic ICAD patients, the 30-day risk of stroke or death was 24% [21]. While intracranial angioplasty without stenting has been proposed as an alternative, there have been no randomized clinical trials to evaluate its efficacy beyond medical therapy alone in symptomatic ICAD patients. If endovascular treatment is considered, neuro-interventionists with high volume experience appear to have lower peri-procedural complications than those with low volume experience [22].

Another strategy that may be considered in symptomatic ICAD patients who have recurrent ischemic cerebral events due to symptomatic intracranial stenosis despite optimal medical therapy is indirect revascularization via encephaloduroarteriosynangiosis (EDAS). A single center retrospective study of 36 patients with ICAD and recent (< 30 days) TIAs or nondisabling strokes in the territory of the stenotic vessel (degree of stenosis not stated) and evidence of hypoperfusion and poor collateral flow on MR perfusion and/or conventional angiography underwent EDAS [23]. Over a 2-year follow-up period, 5.6% of patients had ischemic strokes (1 stroke was peri-procedural), compared with the estimated 17.2% risk of stroke in the SAMMPRIS cohort.

While endovascular and surgical techniques for revascularization of symptomatic ICAD are options for cases with medically refractory ischemic events due to hypoperfusion, further studies are needed to determine the safety of and optimal timing for these treatments.

**Post-Discharge Follow-up Evaluation**

At 1 month after discharge, the patient denied any new or recurrent signs or symptoms of stroke. Home blood pressure logs showed that BP was at target. Orthostatic BPs were assessed and no evidence of hypotension on standing was identified. Repeat laboratory evaluation was remarkable for hemoglobin A1c of 6.8% and LDL cholesterol of 64 mg/dL. The patient and his wife have been walking briskly 3 times per week for 45 minutes and continue to work on dietary modifications modeled after the Mediterranean diet. He is scheduled to follow up with his vascular neurologist 3 months after the stroke to discuss transition from DAT to aspirin monotherapy.

**Conclusion**

Intracranial atherosclerotic disease is a common cause of ischemic stroke, particularly amongst Asian, black, and Hispanic patients. Identification of ICAD can be performed with noninvasive arterial imaging including CT angiography or contrast-enhanced MR angiography as part of an ischemic stroke workup. Optimal medical management with early DAT with aspirin and clopidogrel along with aggressive risk factor and lifestyle modification has emerged as an effective first-line therapy. In patients with recurrent ischemic symptoms while optimally medically managed, endovascular therapy with angioplasty with or without stenting may be considered.

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References


