Inpatient Management of Acute Stroke and Transient Ischemic Attack

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KEYWORDS

• Acute ischemic stroke • Transient ischemic attack • Antithrombotics
• Quality metrics

KEY POINTS

- Quality metrics standardize inpatient management of acute stroke to improve stroke care and related outcomes.
- TIA and stroke are medical emergencies that require prompt diagnostic evaluation and therapeutic intervention.
- Evaluation and management are guided by suspected etiology.
- Short-term dual antiplatelet therapy is indicated in very specific clinical situations.

FOUNDATIONAL PRINCIPLES

Quality Metrics and Performance Measures

Stroke is a condition with evidence-based diagnostic and treatment strategies. To improve adherence to clinical practice guidelines, numerous organizations in the United States developed initiatives to endorse hospital-based quality metrics; some metrics are additionally endorsed as performance measures for institutional feedback.[1–3] Organizations such as the American Heart Association (AHA)/American Stroke Association (ASA) Get With The Guidelines (GWTG) registry, The Joint Commission, Centers for Disease Control, National Quality Forum, and the Centers for Medicare & Medicaid Services routinely evaluate scientific evidence to reassess quality metric endorsements.

As one example, GWTG is a national registry program that standardizes stroke care. Participating institutions report structured information for each hospitalized patient with a stroke-related diagnosis including demographics, stroke etiology (modeled after Trial of Org 10,172 in Acute Stroke Treatment, or TOAST, subtypes), and

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prespecified quality metrics and performance measures. Harmonized metrics within GWTG and other initiatives include reducing time to intravenous thrombolysis, early antithrombotic initiation, venous thromboembolism prophylaxis, dysphagia screening, antithrombotics prescribed at discharge, intensive statin initiation, smoking cessation counseling, stroke education, and assessment for rehabilitation.[3] Participation in a data repository is additionally endorsed by practice guidelines.[4]

The Importance of Urgent Evaluation for Cerebrovascular Ischemic Events

The primary objectives in acute stroke and TIA care are to identify etiology while initiating treatment to reduce the risk of recurrence. The highest risk period following TIA is within 48 hours; rapid evaluation and treatment are associated with reduced risk of stroke.[5] TIA and stroke are therefore both neurologic emergencies. Patients with TIA should be evaluated and treated emergently; a standard evaluation must be completed definitively within 24 to 48 hours to identify intervenable etiologies. Hospital observation for high-risk TIA patients allows for emergent interventions if symptoms recur or worsen.[5] Most other patients diagnosed with stroke will require hospital admission for structured evaluation and management aligned with quality and performance measures known to improve outcomes.

Stroke Classification Schemes

The TOAST criteria were developed to categorize ischemic stroke into 5 major etiologies[6]: large artery atherosclerosis, cardioembolism, small vessel occlusion (lacune), stroke of other determined etiology, and stroke of undetermined etiology (now cryptogenic stroke, of which half are embolic stroke of undetermined source). Other classification schemes exist, but convenience and moderate interobserver reliability has sustained TOAST as a common research and clinical classification mechanism,[7] including for data registries such as GWTG. Diagnostic methodology improvements are now more likely to identify an etiology in cases that would previously have been categorized as undetermined.

Transient Ischemic Attack and Minor Ischemic Stroke

Transient ischemic attack is transient neurologic dysfunction caused by brain, spinal cord, or retinal ischemia in a vascular distribution without radiographic evidence of infarct. This tissue-based definition is more accurate than time-based endpoints (symptoms lasting <24 hours) in predicting the risk of stroke.[8] The widely used $ABCD^2$ stroke risk calculator was originally intended to identify high-risk patients for hospitalization. $ABCD^2$ has suboptimal predictive performance as its score omits intervenable, high-risk features including atrial fibrillation, carotid stenosis, and infarct. Newer iterations ($ABCD^2$-I, $ABCD^3$-I) include acute infarct in risk estimates[9] though $ABCD^2$ remains ubiquitous in stroke study design for harmonization with prior work. We emphasize that disposition following TIA should be determined clinically given the notable limitations of the $ABCD^2$ score.

Minor stroke is defined as infarct with NIHSS less than 5 and nondisabling deficits.[10] The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial showed decreased risk of recurrent ischemic events with a short course of dual antiplatelet therapy (DAPT) in patients with TIA and minor stroke (defined in POINT as NIHSS $\leq$3) without apparent cardioembolic or carotid disease[11]; subsequent analysis revealed the benefit of DAPT was maximal in the first 21 days.[12] In a higher risk population, the Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death (THALES) trial showed short-course DAPT with ticagrelor with aspirin improved stroke risk reduction

in TIA/minor stroke but with higher rates hemorrhage in the DAPT group.[13] Patients with TIA/minor stroke with NIHSS $\leq$3 and ABCD^2 $\geq$4 presenting early may be treated with a loading dose of clopidogrel (600 mg) followed by 75 mg daily for 21 days in addition to aspirin 81 mg daily indefinitely. DAPT is used only if there are no other identifiable etiologies with specific treatment strategies (carotid stenosis, atrial fibrillation) and if thrombolysis is not administered acutely. Treatment should be implemented as early as possible in addition to other medical therapy described below.

Standard Stroke Evaluation

Evaluation must include brain imaging with computed tomography (CT) or MRI; MR diffusion-weighted imaging is more sensitive than CT for small and/or early infarcts and may be preferred for delayed presentations.[14] Noninvasive vascular imaging of the cervicocephalic vessels via CT or MR angiography or Doppler ultrasound is indicated to query symptomatic stenosis. A 12-lead electrocardiogram, transthoracic echocardiogram (TTE) with shunt evaluation, and telemetry monitoring (with extended cardiac rhythm monitor for 30 days) are indicated to query cardioembolic etiology such as atrial fibrillation or paradoxic embolism. Treating hypertension, insulin resistance, dyslipidemia, and tobacco use is also indicated.[5,14] Evaluation is expanded for patients with cryptogenic stroke, young patients, or patients with atypical presentations suggestive of a genetic disorder or secondary hypercoagulable state.

Prevention of Secondary Brain Injury

Hypoglycemia exacerbates energy failure and hyperglycemia is associated with worse outcomes after stroke.[15,16] Fever is also associated with worse outcomes after stroke and normothermia should be maintained with surface cooling and antipyretics.[17] Following the hyperacute period, blood pressure parameters require additional research; in general, hypovolemia and hypoperfusion are avoided to minimize further ischemia of penumbral tissue, and extreme hypertension with pressures $\geq$220/120 may be lowered cautiously. Antihypertensive treatment for pressures less than 220/120 within the first 48 to 72 hours is not recommended unless there is another indication to do so. Comorbid conditions must be considered when setting blood pressure goals for an individual patient.

Secondary Stroke Prevention

Core strategies to reduce stroke risk include antithrombotic, cholesterol-lowering, and antihypertensive therapies, plus insulin resistance treatment and lifestyle modifications (collectively referred to as medical management herein). Specific antithrombotic strategies will be discussed by stroke etiology below. Long-term blood pressure reduction is a critical modifiable risk factor; for every 10/5 mm Hg reduction, relative risk of stroke is reduced by nearly 30%.[18] Blood pressure can be lowered in the hospital after the 48- to 72-hour acute period with a plan to meet an outpatient target of less than 130/80 over days to weeks. Dyslipidemia therapy includes high-intensity statin with target LDL of less than 70 mg/dL.[19] One quantitative modeling study using stroke prevention strategies revealed relative risk reduction of second stroke by 80% over 5 years with the combination of lifestyle modifications plus aspirin, statin, and antihypertensive treatment.[20] Stroke prevention strategies may require adjustments based on diagnostic study results. Initiating secondary prevention during the hospitalization aligns with required quality metrics and performance measures.

EVALUATION AND MANAGEMENT BY STROKE ETIOLOGY

Intracranial and Extracranial Large Vessel Disease

Important causes of large vessel disease of the intracranial and extracranial arteries include atherosclerosis and dissection. Stroke from in-situ thrombosis or parent vessel thromboembolic events is strongly suspected when there is greater than 50% atherosclerosis in the culprit vascular territory; large vessel atherosclerosis accounts for 15% of stroke.[14] Intensive medical therapy is recommended for all patients with large vessel stroke or TIA. Revascularization may be indicated for some patients with extracranial atherosclerotic disease.

Diagnostic considerations

Digital subtraction catheter angiography is the gold standard for the evaluation of vessel stenosis and other features like collateral hemodynamics. In clinical practice, CT and MR angiography are preferred first-line studies. They are noninvasive with high sensitivity and specificity for stenosis. Carotid Doppler ultrasonography also has high specificity for severe carotid stenosis.[14] More recent revascularization trials (eg, Carotid Revascularization Endarterectomy vs Stenting Trial/CREST series) use noninvasive angiography. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria are used in the United States to measure carotid stenosis through invasive and noninvasive angiography. Diagnostic evaluation for nonatherosclerotic large vessel disease is tailored to the suspected etiology and may include central or systemic evaluation and is not discussed in detail here.

Management

Extracranial large artery atherosclerosis. Extracranial large artery atherosclerosis may affect the carotid and vertebral arteries and intensive medical management is indicated. Patients with carotid disease may be candidates for procedural revascularization with carotid endarterectomy (CEA) or endovascular carotid artery stenting (CAS). Medical management *without* carotid revascularization is preferred in men with symptomatic stenosis but luminal narrowing measuring less than 50% and women with symptomatic carotid stenosis but luminal narrowing measuring less than 70%.[21] Additional contraindications to carotid revascularization include severe medical comorbidities precluding safe procedural intervention, ipsilateral stroke with persistent disabling neurologic deficits, and total or near-total occlusion of the culprit carotid artery.[21] The decision to recommend revascularization should account for baseline stroke risk as well as risks and benefits of the intervention. Intervention should be performed by providers with less than 6% rate of periprocedural morbidity and mortality, between 2 and 14 days of last symptomatic event and ideally during index hospitalization.[22] Benefit of vertebral artery revascularization by any mechanism is not established and not recommended.[23]

Carotid endarterectomy. CEA is indicated in most patients with TIA or nondisabling stroke and severe stenosis (70%–99%) with a surgically accessible lesion, as supported by meta-analysis of the original NASCET, European Carotid Surgery Trial (ECST), and VA CEA trials.[24] CEA should also be considered in men with moderate (50%–69%) stenosis. Patients older than 70 years should undergo CEA over CAS. Contraindications include medical comorbidities that increase risk of perioperative adverse events, prior ipsilateral CEA, and life expectancy less than 5 years.[14,21] Early trials enrolled participants within 2 weeks of the index events, yielding current threshold for intervention during this period. Analysis of 4 randomized controlled trials (RCTs) showed that CEA was associated with lower rates of procedural complications compared to CAS when treatment was performed within 1 week.[25] Medical management with antiplatelet monotherapy remains indicated.

Carotid artery stenting. CAS is considered if the carotid lesion is not surgically accessible, the patient is not a surgical candidate, there is history of radiation-induced stenosis, or if the contralateral ICA is completely occluded.[21] Prior RCTs comparing CAS to CEA in symptomatic patients (International Carotid Stenting Study/ICSS, Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis Trial/EVA-3S, CREST) demonstrated an increased risk of endpoints (stroke and death) with CAS at 30 days and long-term follow-up.[26–29] The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial suggested that CAS was not inferior to CEA but included mostly asymptomatic patients.[30] CREST long-term follow-up analysis revealed similar 10-year endpoints between CAS and CEA; prior subanalyses in symptomatic patients revealed higher rates of 30-day endpoints with CAS, especially in patients aged 70 years or older.[31]

Transcarotid artery revascularization (TCAR) is a hybrid procedure combining surgical exposure of the common carotid artery with stent deployment and concurrent flow reversal to prevent distal embolization. The TCAR surveillance project tracks outcomes, and studies thus far include registry analyses and single-arm safety and efficacy trials.[32] TCAR has not been directly compared to medical management or to CEA in randomized trials but registry analyses suggest comparative risk/benefit profiles to CAS. TCAR may be considered in patients who are not surgical candidates who also have severe vascular or cardiac disease precluding safe catheter angiography.[33] A course of DAPT is indicated for stenting procedures followed subsequently by antiplatelet monotherapy.

Intracranial large artery atherosclerosis. Intensive medical management and specifically daily aspirin 325 mg and systolic blood pressure goal of less than 140 are endorsed by recent guidelines for stroke prevention when the etiology is moderate to severe ICAS (50%–99% stenosis).[14] The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial compared warfarin to aspirin and revealed higher rate of hemorrhage and death with warfarin despite similar rates of stroke.[34] For patients with severe intracranial atherosclerosis (ICAS) (70%–99% stenosis) and related stroke or TIA, Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) showed reduced risk of stroke and death in the medical treatment arm compared to intracranial artery stenting.[35] Medical treatment included daily aspirin 325 mg indefinitely and clopidogrel 75 mg for 90 days. Specific DAPT regimens have not been compared with each other.

Angioplasty and stenting in the absence of intensive medical management is not recommended; there is equipoise for patients with rapid clinical deterioration despite medical management. In summary, aspirin 325 mg daily is indicated for moderate to severe ICAS causing stroke or TIA. For patients with severe ICAS presenting within 30 days of the index event, the addition of clopidogrel 75 mg daily for 90 days is likely of benefit in preventing stroke recurrence.[14]

Cervical vessel dissection. The most common etiology of stroke from nonatherosclerotic large artery disease is arterial dissection. Antithrombotic therapy is indicated for secondary prevention after stroke or TIA.[36] The Cervical Artery Dissection In Stroke Study (CADISS) trial randomized patients with extracranial carotid and vertebral artery dissection and stroke or TIA to anticoagulation or antiplatelet therapy; there was no significant difference in ipsilateral stroke or death within 3 months, and anticoagulation was associated with increased bleeding risk.[36] Recently, the Biomarkers and Antithrombotic Treatment in Cervical Artery Dissection (TREAT-CAD) trial was designed to test noninferiority of aspirin to vitamin K antagonists in patients with cervical artery dissection.[37] Results did not confirm noninferiority of aspirin. Based on expert

consensus, current guidelines recommend antithrombotics for at least 3 months after TIA or stroke from dissection with either aspirin or warfarin.[14]

Small Vessel Disease

Lacunar infarcts (<15 mm in diameter) occur in subcortical structures from occlusion of penetrating arteries and comprise 20% to 30% of ischemic infarcts.[38] Mechanisms for small vessel disease and lacunar infarcts include hypertension-related microangiopathy and microatheroma.[39] Risk factors for small vessel ischemic disease include hypertension, diabetes, dyslipidemia, and tobacco use.

Diagnostic considerations

Classic lacunar syndromes are diagnosed via clinical features, neuroanatomical localization, and presence of vascular risk factors. The standard stroke evaluation is recommended as a minority of subcortical infarcts may be due to cardioembolic or large artery thromboembolism, and early endarterectomy trials included patients with ipsilateral subcortical infarcts (thus identifying ipsilateral carotid stenosis remains of value).

Management

Treatment involves medical management.[40] A common pharmacologic regimen includes aspirin or clopidogrel monotherapy in addition to statin and antihypertensives. Aggressive small vessel risk factor control is important for stroke prevention but also prevention of cognitive impairment and vascular dementia.

Cardioembolism

Proximal sources of embolism account for 20% of ischemic strokes, largely from high-risk conditions of the cardiac structures.[41] Common examples of high-risk conditions include atrial fibrillation or flutter, left atrial thrombus, left ventricular thrombus, valvular vegetations (marantic or infectious), or prosthetic valves (bioprosthetic or mechanical).

Diagnostic considerations

Studies have demonstrated higher rates of atrial fibrillation detection with a longer duration of monitoring.[42,43] TTE is cost-effective and typically sufficient to diagnose significant structural and functional heart disease and some atrial septal defects. Contrast-enhanced echocardiography increases the sensitivity of TTE to identify left ventricular thrombus. Transesophageal echocardiography (TEE) may be useful for patients with cryptogenic stroke or young patients. TEE is used to identify left atrial thrombus, valve disease, and aortic atheromatous disease, and TEE can better characterize atrial septal defects.[14,44]

Management

Many cardioembolic sources of stroke or TIA have indications for anticoagulation, notably atrial fibrillation or flutter. Infarct size and hemorrhagic transformation guide timing of initiation. For small infarcts, anticoagulation can be started 2 days after acute thrombolysis therapy; for TIA due to atrial fibrillation, anticoagulation may be started immediately.[14] Larger infarcts or infarcts with hemorrhagic transformation may necessitate delaying anticoagulation therapy by at least 1 to 2 weeks.[45] Aspirin monotherapy is used until anticoagulation is initiated. Management strategies for select proximal sources of stroke and TIA are discussed below.

Atrial fibrillation or atrial flutter. For nonvalvular atrial fibrillation and atrial flutter, anticoagulants such as direct oral anticoagulants (DOACs) and warfarin are recommended for stroke secondary prevention. In this case, DOACs are as effective or better than warfarin with improved safety profiles including fewer rates of intracranial hemorrhage.[46] Patients who are unable to maintain therapeutic INR with warfarin should

instead be prescribed a DOAC. DOAC dose adjustment or an alternative agent may be necessary for patients older than 80 years, with low weight, and renal impairment based on initial study design and renal clearance of these agents.

Valvular disease. Aspirin is indicated in patients with stroke or TIA who have aortic or nonrheumatic mitral valve disease. Patients with bioprosthetic aortic or mitral valves and history of stroke or TIA are also treated with aspirin following short-term anticoagulation during and after valve replacement. Patients with a history of stroke or TIA and mechanical mitral valve are treated with aspirin plus warfarin with a higher INR target of 3.

Cryptogenic Stroke Including Embolic Stroke of Undetermined Source

Approximately 25% of ischemic strokes do not have a determined etiology despite standard evaluation and are subsequently deemed "cryptogenic."[14] A proportion of cryptogenic strokes meet criteria for embolic stroke of undetermined source (ESUS), or nonlacunar infarct, without $\geq$ 50% stenosis of a parent vessel or high-risk source of proximal embolism and without another specific cause.[47]

Diagnostic evaluation

Standard and expanded diagnostic strategies may help diagnose etiology. CTA and MRA may identify large artery vasculopathy or subclinical atherosclerotic plaques. Transcranial Doppler with emboli detection may detect asymptomatic microemboli from large arteries or cardioembolic sources. TEE often follows nondiagnostic TTE, especially in patients younger than 60 years without vascular risk factors.[44] Extended cardiac event monitoring is indicated.[42] Depending on clinical context, hypercoagulable states from genetic, autoimmune, inflammatory, infectious, or occult malignant causes are considered. Systemic imaging may be useful, and serum studies may include inflammatory markers (ESR, CRP), genetic disorders (protein C/S deficiency, prothrombin gene mutation, factor V Leiden, antithrombin III deficiency[48]), hemoglobinopathies (eg, sickle cell), and other studies indicative of autoimmune (eg, APLS), inflammatory, neoplastic, or infectious states.[14] CSF evaluation can exclude inflammatory or infectious etiologies. Rarely, with recurrent or fulminant presentations despite exhaustive evaluation and intensive medical therapy, brain biopsy is indicated to exclude vasculitis, intravascular lymphoma, and certain infectious diseases.[49]

Management

Antithrombotic therapy. Secondary prevention of cryptogenic stroke may evolve with diagnostic study results. Medical management remains important given similar recurrence rates to established stroke subtypes.[50] Regarding ESUS, the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus Acetylsalicylic Acid to Prevent Embolism in ESUS (NAVIGATE ESUS) trial and the Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with ESUS (RE-SPECT ESUS) trial did not reveal reduction in stroke recurrence rates with DOACs against antiplatelet use[51,52] and DOACs are specifically not recommended for secondary prevention. A single antiplatelet agent (except ticagrelor) is indicated for secondary stroke prevention.[40] Diagnosis of an alternative condition such as occult malignancy or autoimmune condition warrants treatment of the underlying condition and possible adjustments to antithrombotic regimen (eg, anticoagulation for malignancy-associated hypercoagulable state and stroke).

Patent foramen ovale closure. Patients with ESUS and high-risk PFO without alternative etiology of stroke may be diagnosed with PFO-associated stroke. In specific patients, and following interdisciplinary shared decision making, PFO closure can reduce

the risk of recurrent stroke at the expense of 4.9% rate of periprocedural complications and atrial fibrillation. Patients must be younger than 60 years with embolic-appearing stroke without alternative stroke etiology.[53] Patients with a PFO closure device require antiplatelet therapy.[14] Patients who do not meet the criteria for PFO closure should still be treated with antiplatelets.[51,54,55] If the patient has a PFO and evidence of other venous thromboembolism, anticoagulation is indicated and duration is dictated by treatment of the venous thromboembolism.

SUMMARY

Stroke and TIA are medical emergencies and emergent evaluation is indicated to improve outcomes. National quality metrics and stroke registries improve adherence to evidence-based clinical practice guidelines. All patients should receive standard diagnostic studies to determine etiology and guide selection of optimal secondary prevention strategies. Core evidence-based strategies always include antithrombotics, statin, antihypertensives if needed, diabetes treatment, smoking cessation, and other lifestyle modifications. Collectively, core strategies may significantly reduce the risk of stroke. Evaluation and management in the hospital setting with tailored secondary prevention strategies can profoundly reduce the risk of stroke recurrence.

CLINICS CARE POINTS

- Stroke and TIA are medical emergencies. Goals of early evaluation include determining etiology and initiating appropriate secondary prevention strategies.
- Risk of stroke after TIA is highest within 48 hours. Disposition following evaluation and treatment initiation should be determined clinically and not by ABCD2 criteria.
- Dual antiplatelet therapy is indicated in very specific conditions such as TIA (not attributed to specific cause like carotid stenosis or atrial fibrillation), and stroke or TIA due to severe intracranial atherosclerotic disease. The dual antiplatelet treatment course is for a prescribed time and followed by single antiplatelet therapy thereafter.
- Long-term blood pressure management is an extremely valuable modifiable risk factor for stroke and TIA of any etiology. Blood pressure reduction to a goal of <130/80 in most cases reduces risk of secondary events significantly.
- Patients < 60 years of age with ESUS and high-risk PFO may be candidates for PFO closure following shared decision making with the patient and interdisciplinary team.

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