JAMA | Review

Diagnosis and Management of Transient Ischemic Attack and Acute Ischemic Stroke
A Review

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IMPORTANCE Stroke is the fifth leading cause of death and a leading cause of disability in the United States, affecting nearly 800 000 individuals annually.

OBSERVATIONS Sudden neurologic dysfunction caused by focal brain ischemia with imaging evidence of acute infarction defines acute ischemic stroke (AIS), while an ischemic episode with neurologic deficits but without acute infarction defines transient ischemic attack (TIA). An estimated 7.5% to 17.4% of patients with TIA will have a stroke in the next 3 months. Patients presenting with nondisabling AIS or high-risk TIA (defined as a score ≥4 on the age, blood pressure, clinical symptoms, duration, diabetes [ABCD2] instrument; range, 0-7 [7 indicating worst stroke risk]), who do not have severe carotid stenosis or atrial fibrillation, should receive dual antiplatelet therapy with aspirin and clopidigrel within 24 hours of presentation. Subsequently, combined aspirin and clopidigrel for 3 weeks followed by single antiplatelet therapy reduces stroke risk from 7.8% to 5.2% (hazard ratio, 0.66 [95% CI, 0.56-0.77]). Patients with symptomatic carotid stenosis should receive carotid revascularization and single antiplatelet therapy, and those with atrial fibrillation should receive anticoagulation. In patients presenting with AIS and disabling deficits interfering with activities of daily living, intravenous alteplase improves the likelihood of minimal or no disability by 39% with intravenous recombinant tissue plasminogen activator (IV rtPA) vs 26% with placebo (odds ratio [OR], 1.6 [95% CI, 1.1-2.6]) when administered within 3 hours of presentation and by 35.3% with IV rtPA vs 30.1% with placebo (OR, 1.3 [95% CI, 1.1-1.5]) when administered within 3 to 4.5 hours of presentation. Patients with disabling AIS due to anterior circulation large-vessel occlusions are more likely to be functionally independent when treated with mechanical thrombectomy within 6 hours of presentation vs medical therapy alone (46.0% vs 26.5%; OR, 2.49 [95% CI, 1.76-3.53]) or when treated within 6 to 24 hours after symptom onset if they have a large ratio of ischemic to infarcted tissue on brain magnetic resonance diffusion or computed tomography perfusion imaging (modified Rankin Scale score 0-2: 53% vs 18%; OR, 4.92 [95% CI, 2.87-8.44]).

CONCLUSIONS AND RELEVANCE Dual antiplatelet therapy initiated within 24 hours of symptom onset and continued for 3 weeks reduces stroke risk in select patients with high-risk TIA and minor stroke. For select patients with disabling AIS, thrombolysis within 4.5 hours and mechanical thrombectomy within 24 hours after symptom onset improves functional outcomes.

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Multimedia

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Stroke is the fifth leading cause of death in the United States, with annual costs related to stroke care exceeding $70 billion.[1,2] Nearly 800 000 patients experience stroke per year in the US, of which nearly 700 000 are acute ischemic stroke (AIS). If not treated within the first hours to days with antithrombotic therapy (and carotid revascularization in those with severe carotid stenosis), 7.5% to 17.4% of patients with transient ischemic attack (TIA) experience a stroke within 3 months, with half of this risk occurring within the first 48 hours after TIA onset.[3,4] Given absence of recent epidemiologic data and evolving definitions of TIA, the incidence of TIA is less clear than for AIS but may exceed 240 000 patients annually in the US.[5-7]

AIS and TIA occur due to focal cerebral hypoperfusion, typically from embolism and atherosclerotic disease, but can also occur from other conditions such as dissection, moya-moya, reversible cerebral vasoconstriction syndrome, vasculitis, and hypercoagulability. During TIA, arterial flow to brain tissue is temporarily disrupted causing focal neurologic symptoms (eg, hemiparesis), but spontaneous flow restoration results in symptom resolution without permanent tissue injury. If arterial flow is not restored promptly, however, the ischemia progresses to irreversible infarction and the patient experiences an AIS.

The World Health Organization previously defined TIA as focal neurologic symptoms from presumed vascular causes lasting less

than 24 hours. However, even patients whose symptoms rapidly resolve may have radiographic evidence of acute infarction consistent with AIS. Thus, TIA is currently defined as a transient episode of neurologic dysfunction caused by focal brain ischemia without evidence of acute infarction on brain imaging.[8] AIS is defined as sudden neurologic dysfunction caused by focal brain ischemia lasting more than 24 hours or with evidence of acute infarction on brain imaging, irrespective of symptom duration[9] and can be further divided into disabling (major) AIS and nondisabling (minor) AIS based on the severity of presenting neurologic deficits. The American Heart Association/American Stroke Association definition of TIA is tissue based rather than time-based.[8] The difference between TIA and AIS is whether a cerebral infarction occurred. Before magnetic resonance imaging (MRI), symptom duration was used as a surrogate for whether infarct had occurred (**Box**).

This review summarizes current evidence regarding diagnosis of AIS and TIA and early management methods to improve outcomes and prevent recurrent ischemic strokes.

Box. Common Questions and Answers About Transient Ischemic Attack and Ischemic Stroke

What is the difference between a transient ischemic attack (TIA) and an ischemic stroke?

TIA is a temporary episode of neurologic dysfunction caused by focal brain ischemia, which is not associated with evidence of acute infarction on brain imaging. In contrast, an acute ischemic stroke is an episode of sudden neurologic dysfunction caused by focal brain ischemia that is associated with evidence of acute infarction on brain imaging, regardless of symptom duration.

Which patients should receive dual antiplatelet therapy after a transient ischemic attack or minor ischemic stroke?

Randomized clinical trials demonstrated that aspirin at doses ranging from 50 to 325 mg given with clopidogrel 300 to 600 mg within 24 hours of symptom onset followed by aspirin 50 to 325 mg plus clopidogrel 75 mg for 21 days followed by single antiplatelet therapy after high-risk TIA (defined as nondisabling ischemic stroke or score ≥4 on the Age, Blood pressure, Clinical symptoms, Duration, Diabetes [ABCD2] score) or nondisabling minor stroke (defined as a National Institutes of Health Stroke Scale [NIHSS] score ≤3) reduces 90-day stroke risk compared with aspirin alone from 7.8% to 5.2%.

Which acute ischemic stroke patients benefit from endovascular therapy?

Randomized clinical trials have shown that if endovascular mechanical thrombectomy is performed within 6 hours of symptom onset compared with medical therapy alone in patients experiencing an acute ischemic stroke from an anterior circulation (eg, middle cerebral or internal carotid artery) large-vessel occlusion, the probability of a favorable neurologic outcome (score of 0-2 on the modified Rankin Scale), increases from 26.5% to 46.0%. Some patients with an acute ischemic stroke from a large-vessel occlusion of the anterior circulation also benefit from endovascular therapy after 6 hours and up to 24 hours after symptom onset. Patients who may benefit from endovascular therapy during this timeframe are selected based upon advanced perfusion imaging showing a large ratio of perfusion lesion to infarct core volumes that indicates presence of potentially viable ischemic brain tissue that might otherwise progress to irreversibly infarcted tissue.

Methods

A literature search of MEDLINE databases published between January 1, 1995, and November 18, 2020, was performed to identify publications addressing the treatment of patients with TIA and AIS. The search was limited to human studies. Randomized clinical trials, meta-analyses, guideline statements, and prospective observational studies were prioritized (see the Supplement for search terms). The literature search was supplemented by relevant articles not included in our original search but identified from the review of referenced citations.

TIA and Minor Stroke

Diagnosis of TIA

Due to widespread availability and lower costs, computed tomography (CT) is typically the first neuroimaging test performed in patients presenting with possible TIA or stroke (**Figure 1**).[10] However, the probability of detecting acute tissue changes on a noncontrast head CT after ischemic symptoms that resolve within 24 hours is low (approximately 4%).[11,12] Diffusion-weighted imaging MRI, unlike CT-based techniques, can identify brain ischemia within minutes of onset and is highly sensitive (88% sensitivity within 24 hours) and specific (95% specificity) for acute infarction.[13] A meta-analysis of 47 studies of 9078 patients with transient neurologic symptoms showed that 34% had acute infarction on brain MRI.[14] Current American Heart Association/American Stroke Association guidelines recommend that patients with suspected TIA be evaluated within 24 hours of symptom onset and state that MRI is preferred over CT.[8] If MRI is not immediately available, patients should have a CT scan first. If the CT scan shows new infarction, it is reasonable to forgo additional MRI and proceed with further management and evaluation to determine the cause of stroke. Given the insensitivity of CT imaging, absence of infarct on initial head CT should be followed up with a brain MRI.

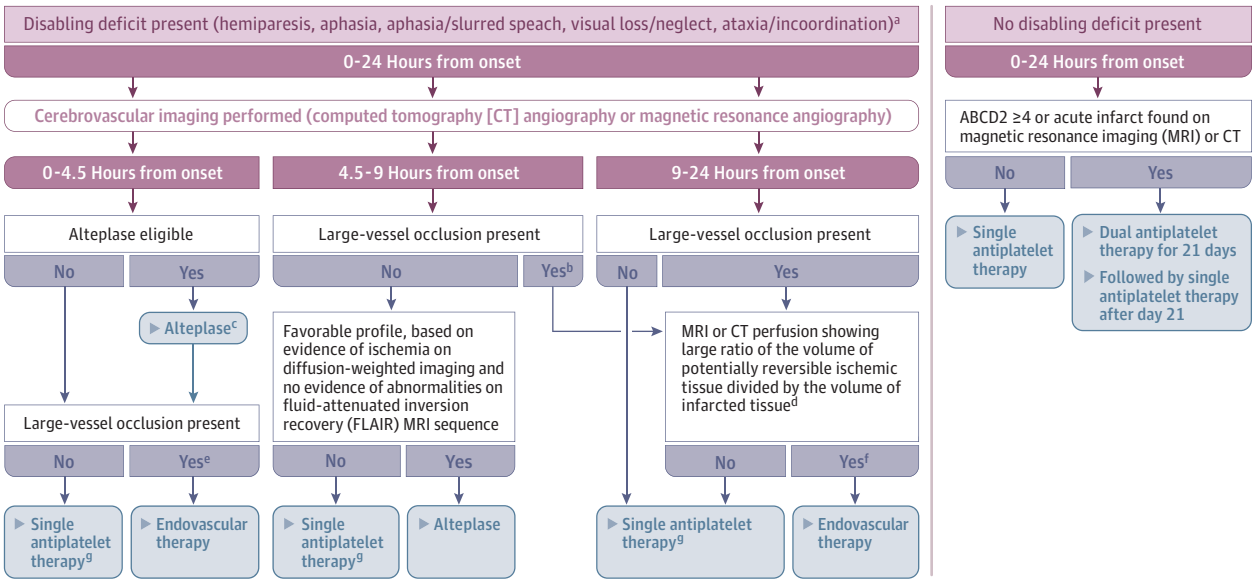
Most patients with TIA do not undergo MRI evaluation,[10] necessitating a clinical diagnosis of TIA that may be limited by the patient's ability to accurately relate TIA symptoms to the evaluating clinicians.[15,16] Nevertheless, clinicians should elicit a detailed history to identify the arterial anatomy corresponding with the clinical presentation and facilitate accurate diagnosis. Specific symptom characteristics (eg, abrupt onset, motor symptoms) may increase the likelihood of TIA rather than nonischemic causes of symptoms.[17-20]

Stroke Risk Stratification After TIA

The age, blood pressure, clinical motor and speech symptoms, duration, diabetes (ABCD2) score (range, 0-7 [7 indicating worst stroke risk]), originally derived and validated in 4 prospective cohorts (2893 patients), was shown to identify 90-day stroke risk in a graded manner (score 0-3 [3.1% risk], score 4-5 [9.8% risk], score 6-7 [17.8% risk]).[3] Subsequent studies applying a score of 4 or greater in the emergency triage of patients with TIA symptoms found that its ability to discriminate risk of stroke was only modest (C statistic 0.6-0.7).[21-23]

Presence of acute infarction on brain imaging, in conjunction with clinical scoring systems such as the ABCD2 score, increases

Figure 1. Treatment Algorithm for Managing Patients With Acute Ischemic Stroke and Transient Ischemic Attack Presenting Within 24 Hours of Symptom Onset



[a] A disabling deficit is defined as impairments that would prevent the patient from performing essential activities of daily living (eg, bathing, ambulating, toileting, hygiene, and eating) or returning to work.

[b] In the presence of large-vessel occlusion, there are insufficient data to recommend alteplase plus endovascular therapy. Currently, endovascular therapy alone should be considered based on imaging selection criteria.

[c] Single antiplatelet therapy (aspirin, clopidogrel, or ticagrelor) should be held for 24 hours following administration of alteplase.

[d] The DEFUSE-3 trial[81] applied a maximum core infarct volume of 70 mL. Patients with greater than this volume were not eligible.

[e] Other criteria for endovascular therapy include a score greater than 5 on the National Institutes of Health Stroke Scale and absence of early infarct signs on CT of the head (ASPECTS score >5).

[f] The American Heart Association acute ischemic stroke guidelines[85] recommend using the criteria in the DEFUSE-3[81] and DAWN[80] trials for mechanical thrombectomy in the extended 6- to 24-hour time window.

[g] Anticoagulants would be appropriate for cardioembolic and hypercoagulable causes of ischemic stroke or transient ischemic attack such as atrial fibrillation.

discrimination (C statistic) of stroke risk from 0.66 to a range of 0.78 to 0.81.[24,25] The presence of large artery severe stenosis or occlusion and/or neurologic symptoms consistent with ischemia in a large artery (eg, carotid stenosis) further improves discrimination of stroke risk.[26,27]

Early Antiplatelet Therapy After TIA and Minor Stroke

A pooled subgroup analysis from 3 clinical trials of aspirin vs placebo in 8561 participants with mild AIS who were randomized within 2 days of symptom onset found that aspirin was associated with lower rates of stroke at 14-day follow-up compared with placebo (0.89% vs 1.74%; hazard ratio [HR], 0.51 [95% CI, 0.34-0.75]).[28] Prospective observational studies in Europe showed that prompt, same-day management (diagnostic evaluation, antiplatelet administration, and risk-factor management) of TIA and minor stroke was associated with 80% relative stroke risk reduction at 90 days compared with standard care (6.0%-10.3% vs 1.2%-2.1%).[29,30]

A meta-analysis of 427 patients with AIS and TIA reported that dual antiplatelet therapy (DAPT) using aspirin plus clopidogrel and initiated within 24 hours of symptom onset reduced stroke risk at 90 days compared with aspirin monotherapy (21.1% vs 13.6%; odds ratio [OR], 0.66 [95% CI, 0.43-1.00]).[31] Subsequently, 3 large randomized clinical trials of DAPT vs aspirin alone in patients with minor nondisabling AIS and high-risk TIA (ABCD2 score ≥ 4) were conducted (**Table 1**).[32-35] Patients with atrial fibrillation, severe stenosis of the internal carotid artery, and other indications for DAPT were excluded from these trials.

In the Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) trial, 5170 participants in China with TIA and minor stroke who presented within 24 hours of symptom onset were randomized to receive DAPT consisting of clopidogrel (300 mg on day 1, followed by 75 mg/d on days 2-90) plus aspirin (75-300 mg on day 1, followed by 75 mg/d on days 2-21) or aspirin monotherapy (75-300 mg on day 1, followed by 75 mg/d on days 2-21). At 90 days, recurrent ischemic and hemorrhagic stroke events occurred in 8.2% of participants in the DAPT group vs 11.7% in the aspirin monotherapy group (HR, 0.68 [95% CI, 0.57-0.81]).[32] The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial enrolled 4881 participants within 12 hours of symptom onset who were randomized to receive DAPT (600 mg of clopidogrel on day 1, followed by 75 mg/d on days 2-90 plus 50-325 mg/d of aspirin on days 1-90) or aspirin monotherapy (50-325 mg/d for 90 days). The POINT trial was stopped early due to greater efficacy of DAPT for preventing stroke at 90 days (5.0% vs 6.5% occurrence; HR, 0.75 [95% CI, 0.59-0.95]), but major bleeding was increased in the DAPT group compared with aspirin alone (0.9% vs 0.4%; HR, 2.32 [95% CI, 1.10-4.87]).[34] Subsequent pooled analysis of these 2 trials showed that DAPT was associated with lower rates of recurrent stroke (6.5% vs 9.1%; HR, 0.70 [95%

Table 1. Randomized Clinical Trials Since 2013 of Acute Antithrombotic Therapy in Patients With Minor Stroke and TIA

Source	Sample size	Enrollment criteria, % of participants[a]	Intervention	Control	Symptom onset to randomization, h	Primary outcome comparing intervention vs control	
						Efficacy	Safety
CHANCE,[32] 2013	5170	TIA (ABCD2 ≥4), 27.9 Minor stroke (NIHSS ≤3), 72.1	Clopidogrel: day 1, 300 mg Days 2-90, 75 mg/d Aspirin: day 1, 75-300 mg Days 2-21, 75 mg/d	Aspirin: day 1, 75-300 mg Days 2-21, 75 mg/d	<24	90-Day stroke risk: 8.2% vs 11.7% HR, 0.68 (95% CI, 0.57-0.81); $P < .001$	Moderate to severe bleeding, 0.4% vs 0.3% HR, 0.84 (95% CI, 0.30-2.31); $P = .73$
SOCRATES,[33] 2016	13 199	TIA (ABCD2 ≥4), 27.2 Minor stroke (NIHSS ≤5), 72.8	Ticagrelor: day 1, 180 mg Days 2-90, 90 mg twice/d	Aspirin: day 1, 300 mg Days 2-90, 100 mg/d	<24	90-Day stroke, myocardial infarction, or cardiovascular death risk: 6.7% vs 7.5% HR, 0.89 (95% CI, 0.78-1.01); $P = .07$	Major bleeding, 0.5% vs 0.6% HR, 0.83 (95% CI, 0.52-1.34); $P = .45$
POINT,[34] 2018	4881	TIA (ABCD2 ≥4), 43.2 Minor stroke (NIHSS ≤3), 56.8	Clopidogrel: day 1, 600 mg Days 2-90, 75 mg/d Aspirin: days 1-90, 50-325 mg/d	Aspirin: days 1-90, 50-325 mg/d	<12	90-Day ischemic stroke, myocardial infarction, or cardiovascular death risk[b]: 5.0% vs 6.5% HR, 0.75 (95% CI, 0.59-0.95); $P = .02$	Major bleeding, 0.9% vs 0.4% HR, 2.32 (95% CI, 1.10-4.87); $P = .02$
THALES,[35] 2020	11 016	TIA (ABCD2 ≥6), 9.4 Minor stroke (NIHSS ≤5), 90.6	Ticagrelor: day 1, 180 mg Days 2-30, 90 mg twice/d Aspirin: day 1, 300-325 mg Days 2-30, 75-100 mg/d	Aspirin: day 1 300-325 mg Days 2-30, 75-100 mg/d	<24	30-Day stroke or death risk[b]: 5.4% vs 6.5% HR, 0.83 (95% CI, 0.71-0.96); $P = .02$	Major bleeding, 0.5% vs 0.1% HR, 3.99 (95% CI, 1.74-9.14); $P = .001$

Abbreviations: ABCD2, age, blood pressure, clinical symptoms, duration, diabetes; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

[a] The ABCD2 scale estimates risk of recurrent stroke (score range, 0 [no symptoms] to 7 [greater stroke risk]); NIHSS assesses stroke-related neurologic deficit (score range, 0 [no stroke] to 42 [severe stroke]).

[b] Outcome indicates a composite end point.

CI, 0.61-0.81]) without an increase in bleeding (0.6% vs 0.4%; HR, 1.59 [95% CI, 0.88-2.86]). This association of DAPT with stroke risk reduction was largest in the first 21 days (5.2% vs 7.8%; HR, 0.66 [95% CI, 0.56-0.77]) but was not observed after 21 days (1.4% vs 1.5%; HR, 0.94 [95% CI, 0.67-1.32]),[36] suggesting that the optimal DAPT duration to maximize benefit and minimize bleeding risk is 3 weeks. The Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death (THALES) trial enrolled 11 016 participants within 24 hours of high-risk TIA or minor stroke symptoms to receive DAPT (180 mg of ticagrelor and 300-325 mg of aspirin on day 1, followed by 90 mg of ticagrelor twice daily and 75-100 mg of aspirin/daily on days 2-30) or matching placebo plus the same dose of aspirin.[35] The ischemic stroke rate at 30 days was 5.0% in the DAPT group and 6.2% in the aspirin only group (HR, 0.79 [95% CI, 0.68 to 0.93). The incidence of severe bleeding was higher in the DAPT group (0.5%) compared with the aspirin plus placebo group (0.1%; HR, 3.99 [95% CI, 1.74 to 9.14]).

The Triple Antiplatelets for Reducing Disability after Ischemic Stroke (TARDIS) trial tested whether the combination of aspirin, clopidogrel, and dipyridamole (triple antiplatelet therapy) reduced recurrent stroke compared with aspirin alone or clopidogrel alone in 1156 participants with ischemic stroke or TIA. Participants were randomized, and treatment was started within 48 hours of symptom onset. The trial was stopped early due to lack of reduction in recurrent stroke (6.0% vs 6.8%; odds ratio [OR], 0.90 [95% CI, 0.67-1.20]) and increased rates of bleeding (19.8% vs 9.0%; OR, 2.54 [95% CI, 2.05-3.16]).[37] The Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial evaluated ticagrelor in 13 199 participants with minor stroke and TIA. Participants were enrolled within 24 hours of symptom onset and randomized to receive ticagrelor (180 mg loading dose on day 1, followed by 90 mg twice daily on days 2-90) vs aspirin (300 mg on day 1 followed by 100 mg daily on days 2-90). The primary end point, a combination of stroke, myocardial infarction, or death, was not different between groups (6.7% vs 7.5%; OR, 0.89 [95% CI, 0.78-1.01]). Ischemic stroke risk was not decreased in the ticagrelor group (5.8% vs 6.7%; HR, 0.87 [95% CI, 0.76-1.00]).[33]

Acute Ischemic Stroke

Diagnosis of AIS

Although MRI is more sensitive for detecting brain infarction than CT,[38] noncontrast brain CT is often the initial imaging study performed in patients presenting with stroke symptoms because of its availability, cost-effectiveness, and high sensitivity and specificity for intracranial hemorrhage (Figure 1).[39-41] Patients with disabling or major deficits from AIS, as assessed by the treating physician,[42] are eligible for thrombolysis within 4.5 hours of symptoms onset. Current guidelines recommend head imaging, either CT or MRI, within 25 minutes of patient presentation to facilitate rapid decision-making regarding thrombolytic therapy.[43] Noncontrast head CT within 3 hours of symptom onset is 47% to 53% sensitive and more than 80% specific for AIS.[44,45] For patients presenting with severe deficits possibly caused by large-vessel occlusions of the internal carotid arteries or proximal

middle cerebral arteries, CT angiogram or MR angiogram of the head and neck can identify the occlusion location and help determine eligibility for mechanical thrombectomy within 24 hours of symptom onset.[46-52] CTA is 92% to 100% sensitive and 82% to 100% specific for large proximal cerebral artery occlusions.[53] In addition to routine CT angiography, multiphase CT angiography, defined as precontrast and postcontrast CT imaging taken during various arterial and venous phases of contrast transit through the brain, can detect the status of the collateral circulation, which may be used to select patients for mechanical thrombectomy.[50] Perfusion imaging with either CT or MRI can be used to assess cerebral blood flow and identify areas of tissue that are likely infarcted vs those likely to recover. Diffusion-weighted MRI, which detects cytotoxic edema, remains the most sensitive measure of the ischemic infarct core.[54] To aid interpretation and facilitate treatment decision making, recent endovascular trials used software for postprocessing of imaging data, which is 100% sensitive[55] and 91% specific for identifying the tissue at risk for infarction in patients with AIS.[56]

Intravenous Thrombolysis

Two randomized clinical trials enrolled 624 patients in the 1990s and tested the benefits of intravenous recombinant tissue plasminogen activator (IV rtPA; alteplase), compared with placebo, for treating AIS within 3 hours of symptom onset.[40] Patients receiving alteplase, compared with placebo, were more likely to attain the favorable primary outcome of a modified Rankin Scale [mRS] score of 0 to 1 or no or minimal disability at 3 months (39% for alteplase vs 26% for placebo; OR, 1.6 [95% CI, 1.1-2.6]) (mRS score range, 0 [no disability] to 6 [more severe disability]). When considering all important changes in health state, the number needed to treat for benefit from tPA was 3.[57,58] The benefits occurred despite the increased risk for symptomatic intracerebral hemorrhage in patients receiving alteplase (6.4% for alteplase vs 0.6% for placebo; $P < .001$). Subsequent analysis of the original trial data determined that the number needed to harm was 35.[59,60]

Following the initial trials of rtPA, pooled individual patient data analysis of 9 randomized clinical trials of rtPA for AIS treatment (1549 patients) demonstrated that thrombolysis was associated with a significant benefit when patients were treated within 3 to 4.5 hours of symptom onset (35.3% for alteplase vs 30.1% for placebo; OR, 1.3 [95% CI, 1.1-1.5]).[61] This benefit was also observed in high-risk groups: patients over 80 years, patients taking warfarin with an international normalized ratio of less than 1.7, and patients with a history of stroke and diabetes.[62-64]

The benefit for alteplase is clear for patients with AIS who have disabling or major neurologic deficits and who present within 4.5 hours from symptom onset. However, alteplase is often not administered to patients presenting with mild symptoms,[65] despite that up to 25% of such patients have functional disability at 90 days.[66] The Potential for rtPA for Ischemic Strokes with Mild Symptoms (PRISMS) trial randomized 313 patients with suspected AIS with mild symptoms (NIHSS ≤5 and nondisabling deficits such as hemisensory syndrome, isolated facial droop, or mild dysarthria) to either thrombolysis or oral aspirin therapy.[67] The study was stopped early due to low enrollment (313 patients of 948 prespecified). There was no significant difference in functional outcomes at 90 days (mRS 0-1: 78% for alteplase vs 81% for aspirin; OR, 0.86 [95% CI, 0.5-1.7]). Five of 154 patients who received alteplase had symptomatic intracerebral hemorrhages compared with 0 of 157 patients treated with aspirin alone (risk difference, 3.3% [95% CI, 0.8%-7.4%]).

Patients who present more than 4.5 hours after symptom onset or who present with an unknown time from symptom onset may still benefit from alteplase. The Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial used MRI to identify patients presenting with AIS symptoms more than 4.5 hours after symptom onset who had evidence of ischemia on diffusion-weighted imaging but no evidence of signal changes on fluid-attenuated inversion recovery (FLAIR) sequence MRI.[68] This pattern of imaging results is consistent with stroke onset within 4.5 hours.[69] Investigators randomized 503 patients with AIS meeting eligibility criteria to either alteplase or standard medical therapy. More patients receiving alteplase achieved a favorable outcome (mRS 0 or 1) at 90 days than those in the control group (53% vs 42%; adjusted OR, 1.61 [95% CI, 1.09-2.36]; $P = .02$). The EXTEND trial used either CT or MR perfusion to identify and randomize 225 patients with AIS who presented 4.5 to 9 hours from symptom onset with infarct cores (ischemic tissue that cannot be restored to preinfarction state regardless of reperfusion) between 10 and 70 ml in size and a perfusion lesion-infarct core mismatch ratio (the volume of potentially reversible ischemic tissue divided by the volume of irreversibly infarcted tissue) greater than 1.2 to receive either alteplase or standard medical therapy.[70] At 90 days, 35.4% of alteplase-treated patients and 29.5% of patients in the control group achieved an mRS of 0 or 1 (adjusted relative risk, 1.44 [95% CI, 0.97-53.5]; $P = .05$). Similarly, the ECASS-4: ExTEND trial used exclusively MR diffusion-weighted imaging and perfusion imaging to select AIS with infarct cores greater than 20 ml and a perfusion lesion-infarct core mismatch ratio greater than 1.2, presenting between 4.5 and 9 hours after symptom onset to receive either alteplase or standard medical therapy.[71] Prior to the trial's early termination because of poor enrollment, 61 patients were randomized to receive alteplase and 58 patients to placebo. There was no significant difference in functional outcome (categorical shift in mRS, an analysis of the distribution of patients over the entire range of functional outcomes as opposed to dichomized comparisons) at 90 days (OR, 1.20 [95% CI, 0.63-2.27]; $P = .58$). A recent meta-analysis of these 3 trials (n = 831 patients in the 4.5- to 9-hour window) found that alteplase improved functional outcome (mRS 0-1, 45.8% vs 36.7%; OR, 1.48 [95% CI, 1.12-1.96]).[72]

Tenecteplase, a longer acting thrombolytic agent that can be administered with a single intravenous bolus and does not require a 1-hour infusion that is required for rtPA, may be a reasonable alternative to rtPA in the treatment of AIS. A meta-analysis of 5 randomized clinical trials (N = 1585 patients) reported that tenecteplase was noninferior to rtPA (57.9% vs 55.4%; 4% risk difference [95% CI, −1% to 8%]) at 3 months.[73] Another study, the EXTEND-IA TNK trial, randomized patients with AIS and large cerebral artery occlusions within 4.5 hours of symptom onset to either rtPA or tenecteplase prior to mechanical thrombectomy. Patients treated with tenecteplase had better 90-day functional outcomes compared with rtPA (90-day median mRS 2 vs 3; common odds ratio, 1.7 [95% CI, 1.0-2.8]) and greater large-vessel territory reperfusion at angiography (22% vs 10% [95% CI, 2%-21% difference]; $P = .002$).[74]

Table 2. All Identified Trials of Endovascular Therapy in Patients With Acute Ischemic Stroke Since 2015

Source[a]	Sample size	Intervention[b]	Median baseline NIHSS score[c]	Time window from symptom onset, h	Patients receiving IV rtPA, %	Favorable 90-d outcome[d]		Symptomatic intracranial hemorrhage	
						Group comparison, %	*P* value	Group comparison, %	*P* value
MR CLEAN,[48] 2015	500	Endovascular therapy plus IV rtPA	Intervention, 17 Control, 18	<6	Intervention, 87.1 Control, 90.6	Intervention, 32.6 Control, 19.1	<.01	Intervention, 7.7 Control, 6.4	.55
EXTEND-IA,[49] 2015	70	Endovascular therapy plus IV rtPA	Intervention, 17 Control, 13	<6	Intervention, 100 Control, 100	Intervention, 71.4 Control, 40.0	<.01	Intervention, 5.7 Control, 0	.31
ESCAPE,[50] 2015	316	Endovascular therapy plus IV rtPA	Intervention, 16 Control, 17	<12	Intervention, 72.7 Control, 78.7	Intervention, 53.0 Control, 29.3	<.01	Intervention, 3.6 Control, 2.7	.75
REVASCAT,[51] 2015	206	Endovascular therapy plus IV rtPA	Intervention,17 Control, 17	<8	Intervention, 68.0 Control, 77.7	Intervention, 43.7 Control, 28.2	.03	Intervention, 1.9 Control, 1.9	1.00
SWIFT PRIME,[52] 2015	195	Endovascular therapy plus IV rtPA	Intervention, 17 Control, 17	<6	Intervention, 100 Control, 100	Intervention, 60.2 Control, 35.3	<.01	Intervention, 1.0 Control, 4.1	.21
THRACE,[77] 2016	412	Endovascular therapy plus IV rtPA	Intervention, 17 Control, 18	<5	Intervention, 100 Control, 100	Intervention, 53 Control, 42	.03	Intervention, 2.0 Control, 2.1	.71
THERAPY,[78] 2016	108	Endovascular therapy plus IV rtPA	Intervention, 17 Control, 18	<5	Intervention, 100 Control, 100	Intervention, 38 Control, 30	.52	Intervention, 9.7 Control, 9.2	>.99
PISTE,[79] 2017	65	Endovascular therapy plus IV rtPA	Intervention, 18 Control, 14	<6	Intervention, 100 Control, 100	Intervention, 51 Control, 40	.20	Intervention, 0 Control, 0	
DAWN,[80] 2018	206	Endovascular therapy	Intervention, 17 Control, 17	6-24	Intervention, 72.7 Control, 78.7	Intervention, 48.6 Control, 13.1	<.001	Intervention, 5.6 Control, 3.0	>.05
DEFUSE-3,[81] 2018	182	Endovascular therapy	Intervention, 16 Control, 16	6-18	Intervention, 68.0 Control, 77.7	Intervention, 44.6 Control, 16.7	< .001	Intervention, 6.5 Control, 4.4	.75

Abbreviations: AIS, acute ischemic stroke; EVT, endovascular therapy; IV rtPA, intravenous recombinant tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

[a] Only prospective randomized open-blinded end point trials were included for comparison.

[b] Control groups were treated with medical therapies alone which included IV rtPA for eligible patients.

[c] NIHSS assesses stroke-related neurologic deficit (score range, 0 [no stroke] to 42 [severe stroke]).

[d] Favorable score indicates participants with a score of 0 to 2 (mRS score range, 0 [no disability] to 6 [more severe disability]).

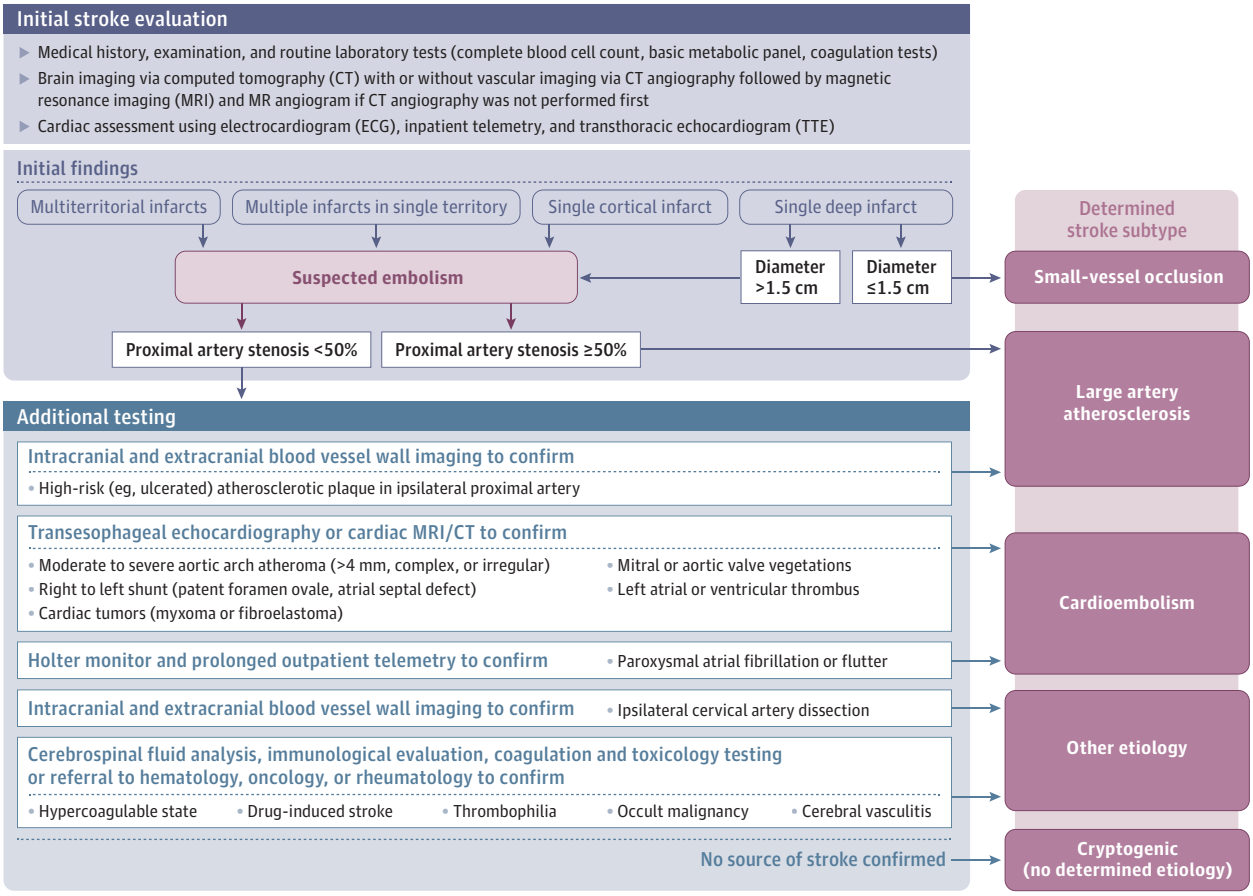
Mechanical Thrombectomy

Patients with AIS due to large-vessel occlusions have poorer outcomes than those without large-vessel occlusions, and only approximately 10%-15% of those with internal carotid artery occlusions and 25% to 50% of those with proximal middle cerebral artery occlusions achieve vessel recanalization after IV rtPA.[75,76] For patients with AIS from proximal large-vessel occlusions in the anterior circulation, the 2 main approaches to remove clots mechanically consist of (1) a stent retriever; and (2) an aspiration catheter. These thrombectomy devices are introduced into the femoral or radial artery via guide catheters and advanced to the occluded cerebral artery using fluoroscopic angiography for guidance. A stent retriever is a wire mesh that is expanded at the site of occlusion, entrapping the clot for removal along with the stent. Aspiration devices use proximal suction to remove the thrombus from occluded arteries.

In 2015, five multicenter randomized clinical trials of endovascular treatment for patients with AIS due to anterior circulation (eg, middle cerebral or internal carotid artery) large-vessel occlusions demonstrated that mechanical thrombectomy improved functional outcomes at 90 days compared with standard medical therapy alone (**Table 2**).[48-52] A patient-level pooled meta-analysis of 1287 patients showed that endovascular treatment was associated with lower 90-day disability compared with medical therapy alone in treated patients (mRS 0-2, 46.0% vs 26.5%; OR 2.49 [95% CI, 1.76-3.53]).[82] This benefit was not associated with an increase in symptomatic ICH or mortality among treated patients. The number needed to benefit from endovascular treatment within 6 hours of symptom onset was 2.6, and a post hoc subgroup analysis favored thrombectomy both in patients eligible and not eligible for alteplase.

The benefit of endovascular treatment for large-vessel occlusions involving the posterior circulation (eg, basilar artery) has been tested in 2 randomized clinical trials: Basilar Artery Occlusion Endovascular Intervention vs Stand Medical Treatment (BEST) and the Basilar Artery International Cooperation Study (BASICS). BEST was terminated early due to poor recruitment (131 participants) and a high crossover rate (22% of control group received mechanical thrombectomy).[83] In the intention-to-treat analysis, there was no difference in favorable outcomes (mRS 0-3 at 90 days) between those treated with thrombectomy vs those treated with standard medical therapy alone (42% vs 32%; OR, 1.74 [95% CI, 0.81-3.74]). The BASICS trial randomized 300

Figure 2. Diagnostic Evaluation of Acute Ischemic Stroke and Determination of Ischemic Stroke Subtype



patients with basilar artery occlusion to receive either mechanical thrombectomy or standard medical treatment. There was no difference in favorable outcome (mRS 0-3 at 90 days) between the 2 groups (44% vs 38%; relative risk, 1.18 [95% CI, 0.92-1.50]).[84] Since patients with posterior circulation vessel occlusions have high mortality and morbidity rates, current guidelines recommend mechanical thrombectomy for carefully selected patients who have AIS in conjunction with occlusion of the vertebral and basilar arteries within 6 hours of symptom onset.[85]

The benefits of treating patients with AIS who present with symptoms after 6 hours with endovascular therapy was supported by 2 large multicenter randomized clinical trials: DAWN (Diffusion weighted imaging or CT perfusion Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke).[80,86] The DAWN trial enrolled 206 patients presenting 6 to 24 hours after symptom onset while DEFUSE 3 enrolled 182 patients presenting 6 to 16 hours after treatment onset (Table 2). Each trial used perfusion imaging (or the addition of diffusion-weighted imaging in the case of the DAWN trial) to select patients with large mismatches between penumbra (tissue at risk of becoming infarcted and potentially salvageable tissue) and ischemic core tissue. Pooled analysis of the 2 trials demonstrated that patients with AIS from anterior circulation large-vessel occlusions and with large ischemic penumbra to infarct core mismatch had improved functional outcomes when treated with mechanical thrombectomy compared with medical management alone (mRS 0-2, 53% vs 18%; OR, 4.92 [95% CI, 2.87-8.44]), without a difference in symptomatic intracerebral hemorrhage between the 2 treatments (6% vs 4%; OR, 1.67 [95% CI, 0.64-4.35]). Mechanical thrombectmy reduced mortality (17% vs 22% with medical management alone; OR, 0.71 [95% CI, 0.34-1.02]).[87] The number needed to benefit from endovascular treatment during the 6- to 24-hour window was 2.8.[80]

Inpatient Stroke Care

In a meta-analysis of 29 randomized clinical trials that included 5902 patients who had experienced a stroke (admission into a stroke unit in which care is delivered by a stroke team of trained physicians, nurses, therapists, and social workers using established evidence-based protocols), there was an association with reduced death or disability when compared with patients not admitted to a stroke unit (52.4% vs 60.9%; OR, 0.75 [95% CI, 0.66-0.85]; $P < .0001$).[88] Patients with large infarctions of the middle cerebral artery territory of brain tissue prone to malignant edema formation and herniation may benefit from a decompressive hemicraniectomy, a surgical procedure that removes a portion of the skull. A meta-analysis of 9 randomized clinical trials of decompressive hemicraniectomy for malignant middle cerebral artery infarction (210 patients) vs standard medical therapy (215 patients) found that receiving surgery improved survival (70.2%

vs 31.4%; relative risk, 1.96 [95% CI, 1.61-2.38]; $P < .001$). Surgery was associated with improved functional outcomes (mRS 0-3) at 6 to 12 months compared with medical therapy alone (26.2% vs 14.9%; relative risk, 1.62 [95% CI, 1.11-2.37]; $P = .01$).[89] In addition to surgical therapy, hyperosmolar therapy (eg, mannitol and hypertonic saline) is reasonable for treating clinical deterioration in patients with malignant infarction.[90]

Determining Stroke Subtype for Targeted Secondary Prevention

Stroke mechanism is often inferred after a obtaining a thorough medical history, physical examination, brain imaging, and targeted ancillary testing (eg, head and neck vessel imaging, cardiac imaging, long-term cardiac monitoring) (**Figure 2**). The most commonly applied classification system of ischemic stroke subtypes was developed for the Trial of Org 10 172 in Acute Stroke Treatment (TOAST).[91] The 5 TOAST subtypes of ischemic stroke in which identified mechanisms are used to guide treatment are large-artery atherosclerosis (eg, carotid artery stenosis), cardioembolism (eg, atrial fibrillation), small vessel occlusion (eg, lacunar stroke), stroke of other determined etiology (eg, vasculitis), and stroke of undetermined etiology (cryptogenic stroke). Alternative classification schema include the Causative Classification System (CCS)[92] and the Atherosclerosis, Small-vessel disease, Cardioembolism, Other causes, and Dissection (ASCOD) system.[93] Compared with the TOAST system, the CSS and ASCOD have higher interrater reliability.[94,95]

After determining stroke mechanism and a patient's risk factors for recurrent stroke, secondary prevention interventions, as recommended by current guidelines, should be initiated (**Table 3**).[85] Besides intensive risk factor and behavioral management, the following specific interventions should be carefully considered in the following subgroups: carotid revascularization for symptomatic moderate or severe extracranial carotid artery stenosis, oral anticoagulation for atrial fibrillation, and closure of patient foramen ovale in select patients with cryptogenic stroke.

Limitations

This review has several limitations. First, scientific advances for acute stroke treatment are evolving rapidly. The evidence described here is current as of the end date of the literature search. Second, there are limited high-quality data to guide optimal endovascular treatment for basilar artery thrombosis. Third, this review does not include a comprehensive evaluation of secondary prevention after AIS and TIA.

Table 3. Summary of Secondary Stroke Prevention Recommendations

Stroke risk factor	Recommendation
Hypertension	For patients with TIA or ischemic stroke, resume antihypertensive medications for previously treated patients after 24 hours Initiate antihypertensive medications for patients with established blood pressure greater than or equal to 140/90 mm Hg (>130/80 mm Hg in patients with diabetes)
Dyslipidemia	Initiate high-intensity statin therapy (atorvastatin or rosuvastatin) for all patients with TIA or stroke with a low-density lipoprotein level greater than 100 mg/dL and those with atherosclerotic disease irrespective of low-density lipoprotein level All patients should be counseled on lifestyle and dietary modifications
Diabetes	All patients with TIA or stroke should be screened for diabetes with plasma glucose hemoglobin A_{1c}
Cigarette smoking	All patients with TIA or stroke who have smoked in the past year should be advised to quit and benoffered interventions to facilitate long-term cessation
Extracranial carotid artery stenosis	Patients with symptomatic carotid artery stenosis (>70% by noninvasive imaging or >50% by catheter-based imaging) should be evaluated for carotid endarterectomy or carotid artery stenting
Intracranial atherosclerosis	Dual antiplatelet with clopidogrel (75 mg) and aspirin (81-325 mg) daily should be prescribed for 90 days following stroke or TIA (within 30 days) caused by severe (>70%) intracranial artery stenosis High intensity statin therapy should be started and a set goal of systolic blood pressure below 140 mm Hg (<130 mm Hg in diabetics)
Atrial fibrillation	Vitamin K antagonists, apixaban, or dabigatran have the highest level of evidence for preventing ischemic stroke in nonvalvular atrial fibrillation
Patent foramen ovale	For patients with a cryptogenic ischemic stroke (stroke without a determined mechanism after a thorough diagnostic evaluation), aged 60 years or younger who have a patent foramen ovale with a high-risk feature (eg, large shunt or associated atrial septal aneurysm), patent foramen ovale closure should be considered

Abbreviation: TIA, transient ischemic attack.

Conclusions

Dual antiplatelet therapy initiated within 24 hours of symptom onset and continued for 3 weeks reduces stroke risk in select patients with high-risk TIA and minor stroke. For select patients with disabling AIS, thrombolysis within 4.5 hours and mechanical thrombectomy within 24 hours after symptom onset improves functional outcomes.

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