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Authors
Meisel, KM
Thabet, AM
Josephson, SA

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Acute Care of Ischemic Stroke Patients in the Hospital

Karl M. Meisel, MD, MA 1  Ahmad M. Thabet, MD 1  S. Andrew Josephson, MD 1

1 Department of Neurology, University of California, San Francisco, California

Address for correspondence Karl M. Meisel, MD, MA, Department of Neurology, UCSF, 505 Parnassus Avenue, Box 0114, San Francisco, CA 94143 (e-mail: Karl.meisel@ucsf.edu).

Abstract

Keywords
► acute ischemic stroke
► secondary stroke prevention
► endovascular therapy
► thrombectomy
► thrombolysis
► acute stroke treatment
► anticoagulation
► antiplatelet medications

Ischemic stroke is a leading cause of death and disability worldwide. Recent advances in acute treatment provide hope that the impact of this disease will be reduced. Rapid assessment for large vessel occlusion is now a key element in acute stroke care given advances in endovascular therapy. Because access to acute therapies is limited, development of systems of care to triage appropriate patients to specialized centers is essential. Acute hospitalization management requires multiple strategies including initiation of secondary prevention measures. In addition to preventing further stroke, physicians can also improve long-term survival by preventing the complications of stroke in the hospital and ensuring longitudinal poststroke care and rehabilitation following discharge.

Stroke is a common disorder leading to 1 in every 20 deaths in the United States. Approximately 57% of stroke mortalities occur outside of the hospital.1 It is estimated that by 2030, stroke prevalence will increase by over 20% from 2012, and 3.4 million more people over the age of 18 will have experienced a stroke. The most effective therapies for acute ischemic stroke are emergent thrombolysis with intravenous (IV) recombinant tissue plasminogen activator (rtPA), endovascular mechanical thrombectomy in proximal vessel occlusions, and comprehensive hospital care, often within primary stroke centers.

Prehospitalization

Stroke education in the community is an essential component of timely treatment, reducing mortality and morbidity. Despite these efforts, only approximately 3% of stroke patients receive thrombolytic therapy because patients often present outside of the treatment window for thrombolysis. Recent efforts toward treating ischemic stroke in the prehospital setting have focused on increasing the proportion of patients eligible to receive IV rtPA. Some researchers have placed a computed tomography (CT) scanner in an ambulance with both a neurologist and radiologist, allowing thrombolysis to occur in the field prior to hospital arrival.2 This approach provides more rapid reperfusion and therefore likely improved outcomes.3

Emergency Evaluation

Emergency services should contact the nearest primary stroke center when transporting a patient who is potentially a candidate for acute stroke therapies. In some municipalities, ambulances may bypass nonstroke centers to better facilitate these rapid treatments. Paramedics have been shown to reliably identify stroke symptoms and thus can prepare emergency staff and neurologists at the receiving hospital.
Once the stroke patient arrives in the emergency department, rapid evaluation should confirm stroke symptoms and establish the last time known normal. A “code stroke” order set, which includes coagulation studies, complete blood count, emergent head CT (HCT), and electrocardiogram, is then initiated. Recent advances in mechanical thrombectomy for anterior circulation proximal large vessel occlusions suggest that a CT angiogram (CTA) of the head and neck can rapidly select eligible patients for this intervention. Therefore, it is likely that CTA will become an increasingly common element of stroke center initial imaging protocols.

Blood-pressure management is essential in the care of acute ischemic stroke patients, as both significant hypertension and hypotension are associated with poor outcomes. A study of 17,398 acute ischemic stroke patients from the International Stroke Trial found a U-shaped relationship between baseline systolic blood pressure (SBP) and death or dependency. Systolic blood pressure should be kept < 185 mm Hg and diastolic blood pressure < 110 mm Hg before administering IV rtPA, in theory to reduce the risk of hemorrhagic conversion. Acute IV medications like labetalol, enalapril, or nicardipine may be used to lower elevated blood pressures into this range. After IV rtPA is given, blood pressure then must be checked every 15 minutes for 2 hours, then every 30 minutes for 6 hours, and then every 60 minutes for 24 hours. If IV rtPA is not given, then “permissive hypertension” is allowed to enhance perfusion to ischemic tissue with a goal blood pressure of less than 220/110 mm Hg.

The initial neurologic examination should include the National Institutes of Health Stroke Scale (NIHSS), allowing for easy communication of stroke severity between health care providers. Baseline NIHSS score has some predictive value for eventual functional outcomes, with a score of 16 or more predicting a higher probability of severe disability or death, and a score of 6 or less predicting a good recovery. It is also likely that a NIHSS of 12 or greater predicts the presence of a large vessel occlusion, which may prompt early activation of mechanical thrombectomy protocols.

Noncontrast HCT is used primarily to exclude intracerebral hemorrhage (ICH). However, it may also reveal early ischemic signs such as loss of gray white matter differentiation, sulcal effacement, or a hyperdense vessel sign. An area of hypodensity greater than one-third of the middle cerebral artery territory should generally serve as a contraindication to thrombolysis. The significance of these early signs on prognosis has been assessed in a prospective study of 203 stroke patients treated with IV rtPA within 3 hours of symptom onset, using the Alberta Stroke Program Early CT score (ASPECTS) to evaluate pretreatment CT scans (the score divides the middle cerebral artery territory into 10 regions). The sensitivity and specificity of the score for predicting poor functional outcomes were 78 and 96%, respectively. Perfusion studies can be helpful in identifying an area of mismatch (penumbra), which may be theoretically salvageable. Mismatch patients who have early reperfusion with endovascular therapy have favorable outcomes, but no correlation between early reperfusion and favorable outcomes was found in those without target mismatch. At this time, perfusion imaging remains experimental, but it is likely to develop a role in the future of acute stroke care (Fig. 1).

**Acute Therapy: IV rtPA**

Thrombolysis with IV rtPA remains the standard therapy for acute ischemic stroke patients who present within 3 hours since last seen normal. Patients should meet the inclusion and exclusion criteria outlined in Table 1. An informed consent discussion is usually attempted within this 3-hour window, but should not delay treatment. In the seminal NINDS (National Institute of Neurological Disorders and Stroke) trial, patients who were less than 75 years old and those with a NIHSS score less than 20 had a better chance of a favorable outcome. Patients older than 75 still benefit from IV rtPA across multiple trials; therefore, there is no maximal age exclusion in the 3-hour treatment window. Intravenous rtPA was associated with symptomatic ICH in the NINDS trial in 6.4% of the treated patients, but it was associated with similar mortality rates compared with the placebo group, with a number needed to treat of three for an improved outcome at 3 months.

Time remains the most important predictor of success with IV rtPA. In the NINDS trial, patients treated within 90 minutes from symptom onset had an odds ratio (OR) of 2.11 for a favorable outcome at 3 months, while patients treated between 90 and 180 minutes had an OR of 1.69. For every 15-minute reduction in door-to-needle time, a 5% improvement of in-hospital mortality is realized.

The use of IV rt-PA in the 3- to 4.5-hour window is not Food and Drug Administration approved, but is recommended. There are additional exclusion criteria for this extended time window, found in Table 1. Consent to treatment is typically discussed with the patient or family and is documented given its off-label use. This extended treatment time recommendation is based largely on the European Cooperative Acute Stroke Study III (ECASS III) trial, which included 821 acute ischemic stroke patients who were treated with IV rtPA or placebo within 3 to 4.5 hours of symptom onset and demonstrated a significantly greater chance of excellent functional outcomes. In an analysis of several clinical trials administering IV rtPA between 4.5 to 6 hours, no benefit was found, suggesting further time window extensions will likely not occur.

Mild or resolving neurologic deficits (NIHSS ≤ 4) are used by some as relative exclusion criteria for IV rtPA. However, multiple studies have shown that patients not treated with IV rtPA because of these criteria suffered poor outcomes. Patients presenting with a disabling symptom such as aphasia, hemianopia, or gait problems, or those who have a large artery occlusion found on imaging are highly likely to benefit from IV rtPA, and therefore should not be excluded.

Patients taking novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban present a new challenge because the effect of these medications is not easily measured in most emergency settings. It is suggested that testing for thrombin time (TT) or ecarin clotting time (ECT) is an accurate measure of dabigatran effect, but this test
is not rapidly available in most emergency departments. The other NOACs are direct factor Xa inhibitors, and measuring factor Xa levels may be helpful to determine if the patient is actively taking these medications, although again availability for rapid results is limited at most centers. Currently, if a stroke patient is taking NOAC medications within the last 48 hours caution is advised when giving IV rtPA.

Hypoglycemia can produce symptoms that mimic an acute ischemic stroke, and if severe enough, can cause permanent brain damage. Hypoglycemia should be treated before considering IV rtPA. Platelet count and coagulation tests in patients with hemorrhagic history, hepatic disease, or current use of anticoagulants are important to check before administering IV rtPA. However, these tests should not delay IV rtPA use in patients not suspected of having coagulopathy. A retrospective study of 1,752 acute ischemic stroke patients found an unsuspected platelet count of less than 100,000 in only 0.3% of patients at presentation.

If the stroke patient develops new neurologic deficits after IV rtPA is initiated, the infusion should be immediately stopped and HCT repeated. If ICH is found, fresh frozen plasma (FFP) should be initiated. Cryoprecipitate and amicaproic acid can also be considered, although protocols vary per institution and little evidence-based data guide treatment choice. A neurosurgeon should be consulted for potential surgical management, although this is rare in the setting of IV rtPA.

### Acute Therapy: Endovascular Techniques

Success with IV rtPA is limited in large vessel occlusions involving the internal carotid artery terminus, proximal middle cerebral artery, and the basilar artery. In response, endovascular therapies have been developed to improve recanalization rates and clinical outcomes in these patients.

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**Fig. 1** Normal noncontrast head computed tomography (CT) scan (A) of a 72-year-old woman presenting 90 minutes after the onset of expressive aphasia and moderate right-sided weakness and sensory loss. CT Angiography (B) demonstrated a left middle cerebral artery (MCA) occlusion (arrow) and CT perfusion showed prolonged mean transit time in the left MCA territory (C) with preserved cerebral blood volume (D), consistent with tissue at risk. Intravenous tissue plasminogen activator followed by mechanical thrombectomy led to recanalization and nearly full resolution of symptoms.
Mechanical thrombectomy using the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) retriever demonstrated improved recanalization rates in observational studies. The desire to confirm the clinical efficacy of these approaches then led to three negative randomized trials (Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke [SYNTHESIS], Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE], Interventional Management of Stroke III [IMS III]). These trials were criticized due to later intervention times, lack of pretreatment vascular imaging to select appropriate patients, and use of older devices instead of newer stent retrievers.

Multiple subsequent trials of endovascular therapy have demonstrated positive results using imaging selection to identify patients with anterior circulation proximal occlusions, treating mainly with stent retrievers. The multicenter MR CLEAN trial randomized 500 patients to either endovascular therapy or standard of care. Intravenous rtPA was given to eligible patients in both groups (89%). An independent functional outcome at 90 days was achieved in 33% of the endovascular therapy group and 19% of the standard care group. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial was discontinued early because it showed similar efficacy as MR CLEAN; in this trial, a mortality benefit was also demonstrated in the endovascular therapy group. The Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND IA) and Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trials also confirmed these positive results in short order, setting the stage for widespread acceptance of this therapeutic approach. The accepted time window for these endovascular therapies is now considered to be less than 6 hours since last time seen well and up to 12 hours in selected cases.

Acute evaluation for endovascular therapy is extremely important given these results, and CTA of the head and neck is typically used to select patients. Disparities between rural and urban stroke patients, which show a 10-fold difference in the likelihood of receiving IV rtPA, will become even more important to address with appropriate ambulance-based triage and transport protocols in the era of endovascular treatment. The development of stroke networks may accelerate based on the limited availability of interventionalists.

### Table 1 Acute ischemic stroke patient inclusion and exclusion criteria for treatment with IV rtPA

<table>
<thead>
<tr>
<th>Criteria for treatment with IV rtPA within 3 h from time of onset</th>
<th>Additional criteria for treatment with IV rtPA within 3 to 4.5 h from time of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td>Ischemic stroke diagnosis with persistent deficits</td>
<td>Time of onset &lt; 3 h</td>
</tr>
<tr>
<td>Time of onset &lt; 3 h</td>
<td>≥ 18 y old</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td><strong>Time of onset from 3 to 4.5 h</strong></td>
</tr>
<tr>
<td>Stroke or significant head trauma within 3 mo</td>
<td>Relative exclusion criteria</td>
</tr>
<tr>
<td>Potential subarachnoid hemorrhage</td>
<td>&lt; 80 y old</td>
</tr>
<tr>
<td>History of intracranial hemorrhage</td>
<td>NIHSS &gt; 25</td>
</tr>
<tr>
<td>Intracranial aneurysm, AVM, or cancer</td>
<td>Current use of an oral anticoagulant</td>
</tr>
<tr>
<td>Recent intracranial or spinal surgery</td>
<td>History of both ischemic stroke and diabetes</td>
</tr>
<tr>
<td>&gt; 1/3 hemispheric infarct on CT</td>
<td></td>
</tr>
<tr>
<td>Noncompressible arterial puncture within 7 d</td>
<td></td>
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<tr>
<td>Active internal hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Systolic BP &gt; 185 mm Hg or diastolic BP &gt; 110 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia &lt; 50 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Acute hemorrhage tendency (platelets &lt; 100,000/mm³, use of heparin within 48 h with an elevated aPTT, current use of warfarin with INR &gt; 1.7 or PT &gt; 15 s, current use of direct thrombin or factor Xa inhibitors)</td>
<td></td>
</tr>
<tr>
<td>Relative exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Mild or resolving neurologic deficits</td>
<td></td>
</tr>
<tr>
<td>Seizure at onset</td>
<td></td>
</tr>
<tr>
<td>Major surgery or significant trauma within 14 d</td>
<td></td>
</tr>
<tr>
<td>GI or urinary hemorrhage within 21 d</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction within 3 mo</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aPTT, activated partial thromboplastin time; AVM, arteriovenous malformation; BP, blood pressure; C T , computed tomography; GI, gastrointestinal; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale.

### Acute Blood Pressure Management without rtPA

Ischemic stroke patients commonly present with hypertension in the acute phase; however, there is possible harm (and
no clear benefit to lowering blood pressure acutely.\textsuperscript{24} Patients who are not given IV rTPA are allowed permissive hypertension; no treatment should be initiated unless the blood pressure exceeds 220/110 mm Hg. It is hypothesized that hypertension is needed to maintain adequate perfusion beyond the area of vessel stenosis and may also allow collateral vessels to be recruited to preserve at-risk ischemic penumbral tissue. In patients with other systemic reasons to maintain a lower blood pressure (e.g., concurrent acute myocardial infarction), a careful balance must be struck between brain perfusion and end-organ preservation. It is not common practice to use vasopressor medications to achieve a higher goal blood pressure in acute stroke, although this strategy may be considered in cases of cardiomyopathy with inadequate perfusion or in patients with iatrogenic-induced hypotension (e.g., from anesthetic agents used in endovascular procedures). After 72 hours, antihypertensive therapy is gradually introduced, typically starting with an angiotensin-receptor inhibitor or thiazide diuretic unless home medications or other comorbidities suggest other alternatives.

**Malignant Cerebral Edema**

Cerebral edema may become life threatening in some cases of ischemic stroke. This “malignant edema” is more common in young adults, those with large areas of ischemia, posterior fossa strokes, and following hemorrhagic transformation. Patients at risk are often monitored in an intensive care setting to allow for early detection of clinical deterioration. Somnolence and new neurologic signs are the most common first indications of evolving edema. Rapid action to prevent herniation is required by elevating the head of the bed, hyperventilation, and the infusion of hyperosmolar agents such as mannitol or hypertonic saline. Emergent HCT is advised to assess for hemorrhage, hydrocephalus, or early herniation. Neurosurgical consultation is necessary to evaluate for the need for cerebrospinal fluid (CSF) diversion in the setting of hydrocephalus and for consideration of decompressive hemispherectomy in cerebellar stroke. Randomized controlled trials of malignant middle cerebral artery ischemic stroke treated with decompressive hemispherectomy have demonstrated a clear benefit to early surgery, both to reduce morbidity and mortality.\textsuperscript{25} Although initial studies included only younger patients aged < 60 years, recent data support the use of this therapy in older individuals as well, although functional outcomes in this older age group are still often poor.\textsuperscript{26}

**Hospital-Based Complications**

Approximately 25% of stroke patients experience a medical complication during their hospitalization.\textsuperscript{27} Fever is common in stroke patients and often reflects a systemic infection that can lead to worsening of neurologic outcomes. In some cases, a benign central cause for fever is suspected after a thorough workup, but should be viewed as a diagnosis of exclusion. Hyperthermia, regardless of etiology, typically requires the use of oral antipyretics (e.g., acetaminophen, ibuprofen), external cooling, or (rarely) intravascular cooling. Although therapeutic hypothermia has not been proven to be beneficial in ischemic stroke patients, fever should be aggressively treated to achieve normothermia.\textsuperscript{28} Antibiotic therapy is commonly delayed until infection is confirmed; however, if there is a high suspicion of infection with clinical deterioration, empiric antibiotics can be considered.

The most common infections in stroke patients are urinary tract infections (UTIs) and pneumonia (15 and 9%, respectively).\textsuperscript{27} Stroke patients in intensive care units have a particularly elevated risk, with a nearly 45% infection rate.\textsuperscript{29} Acute stroke patients who present with a decreased level of consciousness or cranial nerve dysfunction are at highest risk for pneumonia in the first week of hospitalization due to an increased incidence of aspiration.\textsuperscript{30} A dysphagia screen should be performed by trained staff before patients are allowed an oral diet to reduce the risk of aspiration. A nasogastric tube is typically required for both nutrition and oral medications if patients fail this screen. Because UTIs occur more commonly in patients with bladder catheterization, Foley catheters should be avoided or maintained for only a duration of < 24 hours, especially in women, the elderly, and those with impaired immunity.\textsuperscript{30,31}

Treating hyperglycemia requires careful management to avoid complications of both high and low glucose levels. Hyperglycemia is present in about half of stroke patients and is associated with an increased risk of cerebral edema, hemorrhagic transformation, and lower recanalization rates postthrombolysis.\textsuperscript{32} Hyperglycemia also predicts increased mortality and reduced functional recovery poststroke.\textsuperscript{33} Hypoglycemic complications are also associated with increased mortality, emphasizing the need to balance tight glucose control with the risk of overtreatment.\textsuperscript{34} It is reasonable to target normal blood glucose levels initially in the acute poststroke period, although ongoing studies hope to better define optimal treatment goals.

Stroke patients with restricted mobility should be placed on intermittent pneumatic compression devices, and prophylactic doses of low molecular weight heparin (LMWH) should be started within 48 hours of hospitalization to prevent venous thromboembolism. Antithrombotic therapy should not be used for 24 hours following thrombolytic therapy. Most hemorrhagic stroke patients should be started on chemical prophylaxis within 2 to 4 days, provided there is stability of the hemorrhage.\textsuperscript{35}

Stroke patients should be assessed for rehabilitation needs within the first 2 days after a stroke. Physical, occupational, and speech therapists evaluate the patient’s safety and current level of deficits, determining rehabilitation services that will be required at discharge. Typical physical therapy interventions include ankle foot orthoses to help achieve safe ambulation by preventing foot drop, as well as other gait-assist devices that allow improved mobility and prevent falls. Occupational therapists evaluate the ability of patients to perform their individualized activities of daily living safely. The entire treatment team should evaluate for poststroke depression, which occurs in
approximately 30% of patients and may impact long-term outcome and their ability to rehabilitate. Treating with an antidepressant such as fluoxetine has been shown to help upper-extremity motor recovery poststroke; therefore, these medications should considered in all stroke survivors.\textsuperscript{36} Patients are often discharged to inpatient rehabilitation hospitals for further comprehensive treatment, although prescribing these types of rehabilitation services improves the odds of independence even in patients who are discharged to home.\textsuperscript{37}

**Stroke Evaluation and Secondary Prevention**

Stroke etiology classification includes large vessel disease causing artery-to-artery embolism; cardioembolic, small vessel disease; and cryptogenic and defined other etiology. Routine evaluation typically includes urgent carotid imaging with ultrasound, CT, or MRA, as well as evaluation of the intracranial circulation. All ischemic stroke patients should undergo continuous cardiac rhythm monitoring to screen for atrial fibrillation. In cases where cardioembolic etiology is highly suspected after initial negative workup, prolonged ambulatory monitoring should be performed.\textsuperscript{38} Laboratory testing for fasting glucose or hemoglobin A1c and a fasting lipid panel should be routinely performed to assess for vascular risk factors. Echocardiography is used to examine valvular function, exclude intracardiac thrombus, and evaluate for right-to-left shunting. Additional stroke risk factors include chronic kidney disease and sleep apnea, both of which are potentially modifiable.\textsuperscript{39,40}

**Stroke in the Young**

Young adults aged 20 to 44 are an increasing proportion of ischemic stroke patients. Stroke disability burden is higher in this age group despite decreased overall mortality rates.\textsuperscript{51} The causes of stroke in the young include a higher prevalence of cervical arterial dissections, cardioembolism, and thrombophilies.\textsuperscript{42} A CT or MRA of the neck and head vessels should be obtained in all young patients to evaluate for dissection. Recent evidence suggests that antiplatelet therapy may be equally effective as anticoagulation in preventing second events after symptomatic dissection, although randomized trials are ongoing.\textsuperscript{43} If a transesophageal echocardiogram is unrevealing, transesophageal echocardiography can be obtained. Additional serum testing for thrombophilias can be considered in this population. If an arterial coagulopathy is suspected, antiphospholipid antibodies, lupus anticoagulant, homocysteine, and methylenetetrahydrofolate reductase genetic analysis should be performed. If a venous coagulopathy is suspected, investigations can include Factor V Leiden analysis, protein C and S activity, antithrombin III activity, Factor VII levels, and prothrombin genetic analysis. If a vasculopathy or vasculitis is suspected, lumbar puncture, rheumatologic studies, conventional angiography, and brain biopsy should be considered. An increasing proportion of young adult stroke patients have traditional vascular risk factors given the increasing incidence of metabolic syndrome in the young.

**Antiplatelet Agents**

Antiplatelet agents, including aspirin, clopidogrel, and dipyridamole in combination with aspirin, remain the standard therapy for secondary stroke prevention when there is no indication for anticoagulation as discussed below. Acute ischemic stroke patients that do not receive thrombolysis should receive 81 to 325 mg of aspirin in the acute setting.\textsuperscript{44} Following thrombolytic therapy, a HCT is commonly obtained at around 24 hours poststroke to exclude hemorrhagic transformation (earlier if there is any clinical deterioration) before starting aspirin, which reduces the risk of recurrent stroke by 15%.\textsuperscript{45} If the patient’s event occurred while taking aspirin, a transition from aspirin to clopidogrel or to dipyridamole-aspirin often occurs prior to hospital discharge, although evidence supporting this practice is weak.\textsuperscript{35} The Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events (CHANCE) trial conducted in China suggested that in transient ischemic attack (TIA) and minor ischemic stroke, the combination of aspirin and clopidogrel for 90 days reduced the number of recurrent strokes compared with aspirin alone without an increased risk of hemorrhage.\textsuperscript{46} However, the results of the ongoing Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial are needed to further address the safety and efficacy of this approach in a diverse patient population prior to this strategy becoming standard. Patients with large-vessel intracranial stenosis of atherosclerotic origin (> 70% stenosis in the symptomatic vessel) are sometimes treated with the combination clopidogrel and aspirin for 90 days. The long-term (> 90 days) use of both aspirin and clopidogrel is not commonly recommended for secondary prevention as it may increase hemorrhagic risk with little benefit.\textsuperscript{35,44,45}

Clopidogrel is more effective than low-dose aspirin for secondary stroke prevention. It is important to avoid most proton-pump inhibitors while taking clopidogrel. The combination of dipyridamole 200 mg and aspirin 25 mg twice daily also reduced the risk of stroke when compared with aspirin 25 mg twice daily alone.\textsuperscript{47} Headaches and gastrointestinal upset are common side effects of this combination. Dipyridamole plus aspirin was compared directly to clopidogrel in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial and both therapies were found to have similar rates of recurrent stroke at 2.5 years; therefore, either medication is a reasonable alternative to aspirin.\textsuperscript{48}

**Anticoagulation**

Atrial fibrillation is the most common indication for anticoagulation following stroke.\textsuperscript{49} Transient ischemic attack or stroke patients with atrial fibrillation may have up to a fivefold increased risk of stroke, stratified based on CHADS2-VASc score. Treatment with oral anticoagulation should begin within 1 to 2 weeks in these patients and even earlier in those with TIA or nondisabling stroke.\textsuperscript{35} In all cases of anticoagulation after stroke with warfarin, bridging with heparin is not recommended except perhaps in the setting of venous sinus thrombosis.
Novel oral anticoagulants offer a newer, effective alternative to warfarin, although data in the acute period following stroke are lacking. Dabigatran is a direct thrombin inhibitor and was found to be superior to warfarin in nonvalvular atrial fibrillation in the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial, with a lower rate of life-threatening and intracranial bleeding. Dabigatran is not recommended in patients with renal insufficiency. Factor Xa inhibitors such as apixaban and rivaroxaban offer additional therapeutic options and trials have similarly demonstrated their superiority to warfarin. \(^{51}\) Ischemic stroke patients with rheumatic heart disease, cardiac thrombus, inherited thrombophilias, and mechanical heart valves should continue to be treated with warfarin instead of NOACs given limited data as to their efficacy and safety outside of nonvalvular atrial fibrillation.\(^{44}\)

Patients with deep venous thrombosis and acute ischemic stroke should be transitioned to warfarin therapy. A patent foramen ovale or ischemic cardiomyopathy by itself is not an indication for anticoagulation.\(^{35,44}\) Rarely, LMWH is used for secondary prevention of ischemic stroke in patients with adenocarcinoma-related hypercoagulability. Pregnant women who experience a TIA or ischemic stroke are treated with LMWH given the teratogenicity of warfarin.\(^{54}\)

In patients who experience an ICH while anticoagulated, for example in the setting of atrial fibrillation, the initial treatment is emergent reversal followed by avoidance of full-dose anticoagulation for at least 1 week. Aspirin is often used 24 hours following hemorrhage and continues until anticoagulation is resumed.\(^{44}\) The decision as to whether to restart anticoagulation is difficult and should be individualized on a patient-by-patient basis, but can be informed by risk–benefit calculations using the CHADS2-VASc and HAS-BLED formulas.\(^{52}\)

### Carotid Stenosis

Symptomatic carotid stenosis is an important risk factor for recurrent stroke.\(^{53}\) Patients with symptomatic ipsilateral carotid stenosis of 70% or greater should undergo revascularization performed as soon as safely possible, usually < 2 weeks from a nondisabling stroke. Carotid stenting has been shown in some settings to be equivalent to carotid endarterectomy, but is typically reserved for those patients < 70 years of age or those with high surgical risk or difficult surgical anatomy.\(^{54}\)

### Additional Stroke Prevention

Stroke education should be performed in all hospitalized patients. Counseling should include recommendations to initiate a healthy diet (e.g., Mediterranean-type), routine exercise (20–30 minutes daily), and smoking cessation. Intensive lipid-lowering with atorvastatin 80 mg daily is used to achieve a low-density lipoprotein goal below 70 mg/dL in patients with diabetes and less than 100 mg/dL in all other ischemic stroke patients; it is likely that acute effects of statin therapy are beneficial independent of their lipid-lowering effects.\(^{44,55}\)

Because two-thirds of Medicare patients die or are hospitalized within 1 year of their initial stroke, continued posthospital care and counseling are an important focus of treatment.\(^{56}\) Nearly one-third of patients discontinue more than one of their prescribed secondary stroke prevention medications within 1 year following discharge.\(^{57}\) Implementing all indicated secondary stroke prevention therapies provides about a 60% risk reduction, emphasizing the need for good continuity of care with outpatient providers as a key element of treatment in the hospital.\(^{58}\)

### References


