Stroke and Transient Ischemic Attack

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1. Prevention

Identify risk factors for stroke and attempt to modify them.

1.1 Identify risk factors for stroke.

Recommendations

- Identify patients with the following nonmodifiable risk factors:
  - Age >50 years
  - Family history of CAD, CVD, or PVD before age 60 years
  - Black or Hispanic
  - Male

- Identify patients with the following modifiable risk factors:
  - Clinical manifestations of CAD or PVD
  - Hypertension
  - Diabetes mellitus
  - Elevated LDL cholesterol or low HDL cholesterol
  - Smoking
  - Hyperhomocysteinemia
  - Carotid bruit/carotid stenosis
  - History of TIA
  - Paroxysmal or persistent AF
  - Postmenopausal hormone therapy
  - Physical inactivity
  - Obesity
  - Sickle cell disease

- Order electrocardiography to document AF in patients with CAD or irregularity of pulse by history or exam.

- Obtain carotid ultrasonogram if patient has a carotid bruit or vascular risk factors and may be a candidate for carotid endarterectomy.

- See table Contribution of Selected Risk Factors to Stroke Incidence.

Evidence

- The 2006 AHA/American Stroke Association Guidelines on Prevention of Stroke reviewed each risk factor and made recommendations regarding prevention. The guidelines reported that cerebral embolism of cardiac origin is responsible for about 20% of ischemic strokes. Both persistent and paroxysmal AF were important risk factors for initial and recurrent stroke. More than 75,000 cases of stroke per year are attributed to AF (1).

- A systematic review of physical activity and stroke included 18 cohort studies and 5 case-control studies. Combined results from the 23 studies showed that highly active individuals had a 27% lower risk for stroke incidence or mortality (RR, 0.73 [CI, 0.67 to 0.79]) than did less active individuals (2).

- An analysis of the Framingham Heart Study included 5184 men and women with 30 years of follow-up. The proportion of strokes associated with chronic AF without valvular disease was 14.7%, 68 of the total 462 initial strokes. This proportion increased steadily with age from 6.7% for ages 50 to 59 years, to 36.2% for ages 80 to 89 years (3).
• A 2003 systematic review of the association between physical activity and stroke included 23 studies. Overall, high levels of physical activity were associated with lower risk for stroke (RR, 0.73 [CI, 0.67 to 0.79]) (2).

• A 2008 review compared the predictive performance of 12 clinical instruments to assess risk for thromboembolism in AF based on clinical features (4).

• A 2001 study validated the CHADS₂ risk-assessment instrument as a predictor of stroke risk in patients with AF. The study compared the performance of CHADS₂ and older risk-assessment instruments in a cohort of 1733 Medicare beneficiaries with nonvalvular AF who were not prescribed warfarin. Over 2121 patient-years of follow-up, the CHADS₂ instrument predicted stroke more accurately (c-statistic, 0.82) than older classification schemes (c-statistic, 0.68 to 0.74). Stroke risks were 1.9 events per 100 person-years (CI, 1.2 to 3.0) for patients with 0 points, 2.8 events per 100 person-years (CI, 2.0 to 3.8) for patients with 1 point, 4.0 events per 100 person-years (CI, 3.1 to 5.1) for patients with 2 points, 5.9 events per 100 person-years (CI, 4.6 to 7.3) for patients with 3 points, and 18.2 events per 100 person-years (CI, 10.5 to 27.4) in patients with the maximum 6 points (5).

• A retrospective cohort study validated the accuracy of the CHA₂DS₂-VASc score and compared it with the CHADS₂ score in 74,000 patients with AF from a national database in Denmark. Patients classified as low-risk (score of 0) with CHA₂DS₂-VASc and CHADS₂ had stroke rates of 0.78 per 100 person-years (CI, 0.58 to 1.04) and 1.67 per 100 person-years (CI, 1.47 to 1.89), respectively. Patients classified as intermediate-risk (score of 1) with CHA₂DS₂-VASc and CHADS₂ had stroke rates of 2.01 per 100 person-years (CI, 1.70 to 2.36) and 4.75 per 100 person-years (CI, 4.45 to 5.07), respectively (6).

• A pooled analysis of patients from five randomized trials assessed risk factors for stroke in patients with AF. In the multivariate analysis, significant risk factors for stroke included previous stroke or TIA (RR, 2.5), hypertension (RR, 1.6), diabetes (RR, 1.7), HF (RR, 1.4), and age (7).

• Carotid stenosis causing greater than 60% reduction of luminal diameter in asymptomatic patients is associated with about a 2% annual risk for stroke (1; 8).

• Population-based studies have shown cigarette smoking increases the risk for ischemic stroke up to two-fold (9).

• Most studies showed an increased risk for stroke with elevated LDL and lower HDL cholesterol levels. The risk for hemorrhagic stroke may be higher with lower LDL levels (10).

• The Women's Health Initiative was a randomized, controlled primary prevention trial that enrolled 16,608 postmenopausal women with intact uteruses, aged 50 to 79 years. Participants received either estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d (n=8506) or placebo (n=8102). The results showed that strokes occurred in 151 patients (1.8%) in the estrogen plus progestin group and 107 (1.3%) in the placebo group (HR, 1.31 [CI, 1.02 to 1.68]) and with adjustment for adherence, the HR was 1.50 (CI, 1.08 to 2.08). Overall, 79.8% of strokes were ischemic. The HR for ischemic stroke was 1.44 (CI, 1.09 to 1.90) and for hemorrhagic stroke, 0.82 (CI, 0.43 to 1.56) (11; 12).

• A retrospective cohort study evaluated the association between elevated homocysteine and stroke risk in a nationally representative sample of U.S. adults. In the multivariate analysis, patients in the highest quartile of homocysteine levels had increased risk for stroke compared with patients in the lowest quartile (adjusted OR, 2.3 [CI, 1.2 to 4.6]) (13).

• Patients with low ankle-brachial indexes as evidence of PVD are at increased risk for stroke and TIA (14).

**Rationale**

• Presence of nonmodifiable risk factors helps identify patients for more aggressive treatment of modifiable risk factors. Most of the risk factors are modifiable.
Recommendations

1. Comments

- Additional risk factors for stroke may include sleep apnea, C-reactive protein, inflammatory disorders, and others. These risk factors require further study before specific recommendations can be made.

1.1 Institute risk reduction measures for primary prevention of stroke.\textsuperscript{AB} Recommendations

- Control hypertension with lifestyle modification and medications with a goal BP <140/90.
- Although overall BP control is better than a specific agent, consider diuretics and ACE inhibitors.
- Counsel smoking cessation.
- In diabetic patients, maintain good BP control (ACE inhibitor or ARB should be considered) and consider a statin, especially if there are other vascular risk factors.
- Implement statin therapy in patients with CAD or other vascular risk factors.
- Provide antithrombotic therapy to patients with nonvalvular AF who are at high risk for embolic events and possibly in patients at moderate risk, which may include:
  - Patients with previous embolization, who are aged over 75 years, with hypertension or diabetes, and with heart failure or decreased left-ventricular function
  - Consider newer medications, such as dabigatran, rivaroxaban, and apixaban, as an alternative to warfarin in patients with nonvalvular AF
- For treatment of nonvalvular AF, choose among the following:
  - Warfarin (target INR, 2.0 to 3.0) in patients with nonvalvular AF
  - Newer medications, such as dabigatran, rivaroxaban, apixaban, and triflusal
  - Aspirin in patients at low risk for embolic events or in patients who cannot be anticoagulated
- Consider starting low-dose every-other-day aspirin in otherwise asymptomatic women aged over 45 years.
- Consider carotid endarterectomy in asymptomatic patients who have greater than 60% reduction in luminal diameter, have no other contraindications for surgery (especially severe cardiopulmonary disease), are aged under 75 years, and are expected to live more than 5 years.
- When referring for carotid endarterectomy, refer to a neurosurgeon or vascular surgeon with a record of low morbidity and mortality.
- Screen children with sickle cell disease using transcranial Doppler; use transfusion therapy to lower stroke risk.
- Counsel lifestyle modification, recommending a reduced sodium diet that is rich in fruits and vegetables; physical activity of at least 150 minutes a week of moderate intensity, or 75 minutes of vigorous intensity; and weight reduction in obese patients.
- See module Essential Hypertension.
- See module Atrial Fibrillation.
- See module Lipid Disorders.

Evidence

- A 2013 Science Advisory from the AHA, ACC, and CDC on effective control of high BP recommended a goal BP of <140 mm Hg systolic and <90 mm Hg diastolic for most patients, noting that lower targets may be appropriate for some populations (15).
- A 2014 guideline from the JNC 8 panel members recommended initiating therapy in patients aged under 60 years with BP ≥140/90 mm Hg and in patients aged 60 years and older with BP ≥150/90
mm Hg. The guideline recommended using the same BP targets in patients with diabetes and CKD (16).

- The executive summary of the 2013 Standards of Medical Care in Diabetes from the ADA recommended a goal BP <140/90 mm Hg in most patients with diabetes (17).
- A 2011 NICE guideline recommended a goal BP <140/90 mm Hg in patients aged under 80 years and a goal of <150/90 mm Hg in patients aged 80 years and older (18).
- The 2012 AHA/American Stroke Association Science Advisory on oral antithrombotic agents for the prevention of stroke in nonvalvular AF recommended adjusted-dose warfarin (target INR, 2.0 to 3.0) for all patients with nonvalvular AF deemed to be at high risk and many deemed to be at moderate risk for stroke who can receive it safely. Antiplatelet therapy was recommended for low-risk and some moderate-risk patients on the basis of patient preference and estimated risk for bleeding if anticoagulated, and access to high-quality anticoagulation monitoring. In addition to warfarin, the guidelines included evidence supportive of dabigatran, apixaban, and rivaroxaban for the prevention of stroke in patients with nonvalvular AF. The selection of antithrombotic agents should be based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics (19).
- A 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce the risk for cardiovascular disease recommended high-intensity statin therapy for patients with known cardiovascular disease, moderate-intensity statin therapy for patients with diabetes, and therapy based on the calculated risk for cardiovascular events in the rest of the population aged 40 to 75 years (20).
- The 2006 AHA/American Stroke Association Guidelines on Prevention of Stroke reviewed each risk factor and made recommendations regarding prevention (1).
- The 2011 AHA/American Stroke Association guidelines for the prevention of stroke in patients with stroke or TIA emphasized and provided specific recommendations for risk factor control regarding hypertension, diabetes, lipids, cigarette smoking, alcohol consumption, obesity, physical activity, and metabolic syndrome. The guidelines also provided recommendations regarding numerous specific cardiac conditions (21).
- A 2011 ACC/AHA/HRS guideline recommended vitamin K antagonists for patients with AF and risk factors for stroke, and recommended dabigatran as an alternative to warfarin for short-term and long-term anticoagulation of patients with nonvalvular AF. The guideline also recommended anticoagulation for atrial flutter (22).
- A 2014 guideline from the American Academy of Neurology on the prevention of stroke in nonvalvular AF recommended informing patients that antithrombotic medication can reduce the risk for stroke and discussing the balance of potential benefits and harms. The guideline recommended using a risk-stratification algorithm to identify patients who need antithrombotic medication, and recommended choosing among warfarin, dabigatran, rivaroxaban, apixaban, and triflusal for patients at higher risk, noting that aspirin or even no therapy may be appropriate for patients at the lowest risk (23).
- A 2005 systematic review of carotid endarterectomy studies by the American Academy of Neurology found that high-quality studies had been performed to address several of the important clinical questions. The reviewers found that carotid endarterectomy reduced the stroke risk compared with medical therapy alone for patients with 70% to 99% symptomatic stenosis. There was a smaller benefit for patients with 50% to 69% symptomatic stenosis and a small benefit for asymptomatic patients with 60% to 99% stenosis if the perioperative complication rate was low. Aspirin in a dose of 81 to 325 mg per day was preferred to higher doses, 650 to 1300 mg per day, in patients undergoing endarterectomy (24).
• A 2009 systematic review of lipid management for the prevention of stroke included trials with over 165,000 participants which compared statins to other strategies. Lipid lowering with statins was associated with lower risk for primary stroke (RR, 21% [CI, 6.3% to 33.5%]) for every 39 mg/dL decrease in LDL and for secondary stroke (RR, 0.84 [CI, 0.71 to 0.99]) (25).

• A 2008 systematic review of the effects of ACE inhibitors and angiotensin-receptor blockers in the prevention of stroke, MI, and death included six trials with 49,924 participants. Angiotensin-receptor blockers resulted in a slightly lower risk for stroke than ACE inhibitors (OR, 0.92 [CI, 0.85 to 0.99]), with no difference in rates of MI or mortality (26).

• A 2008 systematic review of statins for the prevention of stroke included 42 studies with 121,285 participants. Overall, statin use prevented stroke (RR, 0.84 [CI, 0.79 to 0.91]) and all-cause mortality (RR, 0.88 [CI, 0.83 to 0.93]) (27).

• A 2003 network meta-analysis of the effects of different antihypertensive medications on cardiovascular outcomes included 192,478 patients from 42 trials. Diuretics prevented stroke compared with placebo (RR, 0.71 [CI, 0.63 to 0.81]), and none of the other first-line agents (including calcium-channel blockers, ACE inhibitors, and angiotensin-receptor blockers) were superior to diuretics. Low-dose diuretics were superior to ACE inhibitors for the prevention of stroke (RR, 0.86 [CI, 0.77 to 0.97]) (28).

• A 2007 Cochrane review of anticoagulants vs. antiplatelet medication for primary prevention of thrombotic events in patients with nonvalvular AF included eight randomized trials comparing warfarin with aspirin, with a mean follow-up time of 1.9 years. Warfarin was associated with a lower risk for stroke (OR, 0.68 [CI, 0.54 to 0.85]) and ischemic stroke (OR, 0.53 [CI, 0.41 to 0.68]) and a higher risk for intracranial hemorrhage (OR, 1.98 [CI, 1.20 to 3.28]) (29).

• A 2007 systematic review of antithrombotic and antiplatelet therapy for AF included 29 studies with 28,000 participants. Compared with placebo, warfarin (RR, 0.36 [CI, 0.26 to 0.51]; adjusted RR, 2.7% per year) and aspirin (RR, 0.78 [CI, 0.60 to 0.98]; adjusted RR, 0.7% per year) reduced stroke. Warfarin was superior to aspirin (RR, 0.62 [CI, 0.48 to 0.82]). The risk for intracranial hemorrhage was approximately twice as high with warfarin as with aspirin (30).

• A 2006 systematic review of aspirin, warfarin, and ximelagatran for the prevention of stroke in patients with nonvalvular AF included 13 trials with 14,000 participants. Warfarin reduced the risk for stroke or embolism compared with aspirin (RR, 0.59 [CI, 0.40 to 0.86]) and placebo (RR, 0.33 [CI, 0.24 to 0.45]), but the risk for bleeding was lower with aspirin (RR, 0.58) or placebo (RR, 0.45). Ximelagatran was equivalent to warfarin for stroke prevention (RR, 1.04 [CI, 0.77 to 1.40]), with a lower risk for major bleeding (RR, 0.74 [CI, 0.56 to 0.96]). Warfarin reduced mortality compared with placebo (RR, 0.69 [CI, 0.53 to 0.89]) but not compared with other therapies (31).

• A 2005 Cochrane review of CEA for asymptomatic carotid stenosis included three randomized trials with 5223 patients. Overall, 2.9% of patients had perioperative stroke or death. For the outcome of stroke or death, there was a trend toward benefit in the CEA group (RR, 0.92 [CI, 0.83 to 1.02]). CEA reduced stroke or perioperative death (the primary outcome; RR, 0.69 [CI, 0.57 to 0.83]), and the outcome of perioperative stroke or death or ipsilateral stroke (RR, 0.71 [CI, 0.55 to 0.90]) (32).

• In the Framingham Study, stroke risk was decreased 2 years after quitting smoking (9).

• Data from three large randomized studies suggested no benefit from aggressive glycemic control in diabetics with respect to incident stroke (33; 34; 35). One of the studies was stopped early because of increased mortality in patients with intensive therapy (33).

• In a prospective, double-blind study (LIFE study), 1195 patients with diabetes, hypertension, and signs of left-ventricular hypertrophy on electrocardiogram were randomly assigned to receive either losartan-based or atenolol-based treatment. The results showed that angiotensin-receptor blockers
were more effective than β-blockers in reducing the risk for stroke (although this effect may be limited only to white patients) (36).

- In a pooled analysis of five randomized trials, the annual rate of stroke was 4.5% for the control group and 1.4% for the warfarin group (risk reduction, 68%; CI, 50% to 79%). The annual risk for major bleeding while taking warfarin was 1% to 2% (7).

- In a randomized trial, the combination of aspirin and clopidogrel appeared superior to aspirin alone in patients with AF who were deemed unsuitable for anticoagulation; however, this finding was balanced by a significant increase in major bleeding complications (37).

- Randomized trials showed dabigatran, rivaroxaban, and apixaban, were associated with lower rates of stroke and systemic embolism, but similar or lower rates of hemorrhage compared with warfarin in patients with nonvalvular AF (38; 39; 40).

- In a primary prevention randomized trial, 39,876 women aged over 45 years were assigned to alternate-day low-dose aspirin vs. placebo. Results showed that aspirin was effective in lowering the risk for stroke in this population (41).

- A prospective, randomized study enrolled 1662 patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter. Patients received either medical management alone (daily aspirin and medical risk factor management) or medical management and carotid endarterectomy. After a median follow-up of 2.7 years, patients in the carotid endarterectomy group had a lower yearly rate of stroke from 1% vs. 2% compared with medical management only group (8).

- In a prospective study, 3120 asymptomatic patients with substantial carotid narrowing were randomly assigned to immediate carotid endarterectomy (half had the surgery in 1 month, 88% within 1 year) or medical therapy (4% per year had the surgery). The 5-year stroke risks were 3.8% in the immediate carotid endarterectomy group vs. 11% in the medical group (P<0.0001). Overall, the risk for perioperative stroke or death was 2.8% (42).

- A prospective, randomized study enrolled 2502 patients with carotid stenosis (included symptomatic and asymptomatic patients) and randomly assigned them to treatment with either carotid-artery stenting or carotid endarterectomy. The results showed that for symptomatic and asymptomatic patients with carotid stenosis, there was no significant difference between patients who had stent placement vs. carotid endarterectomy in the primary outcome of stroke, MI, or vascular death, but there was a higher periprocedural risk for stroke in the stent group and a higher risk for MI in the endarterectomy group (43).

Rationale

- The benefits of risk-factor modification for primary prevention are well established.

Comments

- Careful selection of a surgeon with low surgical morbidity is critical, because in the Asymptomatic Carotid Stenosis (ACAS) trial and the Asymptomatic Carotid Surgery Trial (ACST), the perioperative rate of stroke or death was only 2.3%.

- Prophylactic carotid endarterectomy before CABG for asymptomatic incidental carotid stenosis is not supported by evidence; good prospective data on this clinical problem are lacking.

- Stroke risk with arteriography is 0.5% to 1.0%; carotid endarterectomy is possible with two confirmatory noninvasive tests, such as carotid ultrasonography and MR angiography or CT angiography.

- Carotid stenting may be considered in select asymptomatic patients, but effectiveness compared with maximal medical therapy is not well established.
• Aggressive glycemic control in diabetic patients has not been shown to lower the risk for stroke, but the ADA recommends glycated hemoglobin goal <7.0% to prevent microvascular complications of diabetes.

• Healthy postmenopausal women who take estrogen and progestin are at increased risk for ischemic stroke (12).
2. Diagnosis

Confirm stroke in patients with abrupt onset of focal neurologic signs and symptoms.

2.1 Look for elements of the history and physical exam that suggest the type, extent, and anatomical location of the lesion.

Recommendations
- Look for:
  - Abrupt or sudden onset of focal neurologic symptoms
  - Aphasia, visual-field defect, contralateral neglect (imply cortical lesion)
  - Pure motor or sensory symptoms involving face, arm, and leg (usually imply subcortical location)
  - Cranial nerve involvement, diplopia, vertigo, imbalance, and bilateral motor or sensory symptoms, especially perioral tingling (imply posterior circulation)
  - Intracerebral hemorrhage presents with same symptoms and signs as ischemic stroke and cannot reliably be differentiated from ischemic stroke on clinical grounds. Brain imaging is necessary
  - Sudden "worst headache of my life," usually without focal symptoms or signs, suggests subarachnoid hemorrhage
- See table Focal Neurologic Symptoms of Cerebrovascular Accident.
- See figure Cholesterol Embolus.
- See figure Subhyaloid Hemorrhage.

Evidence
- Consensus.

Rationale
- Determining the type, extent, and anatomical location of the lesion helps guide management.

Comments
- A special writing group of the Stroke Council of the American Heart Association published Guidelines for the Management of Spontaneous Intracerebral Hemorrhage (44).

2.2 Perform an urgent head CT or MRI to differentiate ischemic from hemorrhagic stroke and to determine the location, extent, and etiology of ischemic lesions.

Recommendations
- Perform cranial CT or MRI, within 20 minutes of arrival in emergency department, if possible.
- Obtain urgent consultation with a neurosurgeon to guide further testing and treatment if subarachnoid hemorrhage is suspected.
- Obtain vascular studies, typically within 1 to 3 days of initial stroke.
- Obtain an echocardiogram if vascular study results are inconclusive and embolism is suspected.
- Place patient on telemetry for at least 24 hours.
- Obtain other lab studies to define potential underlying conditions.
- See table Classification of Subtypes of Acute Ischemic Stroke.
- See table Features of Subtypes of Ischemic Stroke.
See table Lab and Other Studies for TIA/Stroke.
See table Vascular Studies to Define the Nature and Severity of Stroke.
See table Classification of High- and Medium-Risk Sources of Cardioembolism.
See figure Hemorrhagic Stroke.
See figure Head CT Findings in Acute Ischemic Stroke.

Evidence
• Consensus.

Rationale
• Diagnostic studies are done in patients with symptoms of CVD to determine cerebral localization and subtype of CVD event. These studies, especially brain imaging and vascular studies, must be performed immediately.
• Ischemic stroke can be classified as large-vessel, cardioembolic, small-vessel, other, or undetermined, on the basis of the above diagnostic tests according to the paradigm in the table Classification of Subtypes of Acute Ischemic Stroke (45).

Comments
• TIA and stroke require the same urgent diagnostic evaluation. TIA is a transient event typically lasting <1 hour and without infarct on imaging.
• In children, stroke is most commonly associated with congenital cardiac conditions, coagulopathy, or hemoglobinopathy (sickle-cell disease).

2.3 Consider other underlying disease processes that can present with acute neurologic dysfunction.

Recommendations
• Consider the following factors in the differential diagnosis of stroke or TIA:
  • Seizure
  • Hypoglycemia
  • Complicated migraine
  • Toxic or metabolic insult unmasking previous CNS injury
  • Brain tumor or other rapidly growing mass lesion (e.g., subdural hematoma)
  • Functional illness
• See table Differential Diagnosis of TIA/Stroke.

Evidence
• Consensus.

Rationale
• Correct diagnosis is crucial for management.
3. Consultation

Obtain appropriate consultation. Consultation can help with management of complicated TIA or stroke and maximize long-term function.

3.1 Obtain neurology consultation when the diagnosis is unclear.

Recommendations
- Obtain neurologic consultation to:
  - Confirm diagnosis in patients with stroke when patient risk factors, symptoms or signs, or cranial imaging do not support a clear diagnosis.
  - Assess stroke severity.
  - Institute appropriate therapy.
  - Determine the cause of stroke.
  - Use telemedicine for acute management in community hospitals without onsite stroke expertise.

Evidence
- Consensus.

Rationale
- Accurate diagnosis and determination of etiology influence management and prognosis.

3.2 Consider consultation for various aspects of management.

Recommendations
- Obtain neurologic consultation in managing recurrent TIA and stroke before these events cause significant deficit, and to assist with acute management and help design secondary prevention strategies.
- Obtain consultation with an immunologist or rheumatologist when an autoimmune or vasculitic or connective-tissue mechanism seems likely.
- Obtain consultation with a cardiologist to manage cardiac complications of stroke or to help treat underlying cardiac causes of stroke.
- Obtain consultation with a nephrologist for patients with difficult-to-control hypertension.
- Obtain consultation with an endocrinologist for patients with severe dyslipidemia or for management of diabetes.

Evidence
- Consensus.

Rationale
- Specialists have experience and expertise in management of complicated stroke.

3.3 Obtain rehabilitation consultation to maximize long-term function after stroke.

Recommendations
- Consider specific consultation for rehabilitation:
  - Physical therapy
  - Occupational therapy
• Speech and swallowing
• Psychiatry
• Social service
• Homecare (as needed)

**Evidence**
• Care in a stroke unit, close attention to maintaining stable BP, and an early multidisciplinary approach to rehab has been shown to decrease morbidity, mortality, and costs (46; 47). The NNT for admission to a stroke unit to prevent 1 patient from dying or requiring long-term institutional care is 11, while the NNT is 15 to prevent death and dependency.

**Rationale**
• Rehab is important in the recovery of the patient with stroke.
4. Hospitalization

Hospitalize all patients with suspected stroke.

4.1 Hospitalize patients with suspected stroke for at least 24 hours for initial diagnostic studies, stabilization, and institution of therapy.

Recommendations

- Hospitalize the patient in a dedicated stroke unit when available.
- Triage patients with acute stroke to a designated Primary Stroke Center.
- Arrange for patients to be managed by a multidisciplinary stroke team rather than by using a standardized integrated-care pathway.
- Admit the patient to the intensive care unit if he or she has signs of respiratory or cardiovascular instability or decreased consciousness.

Evidence

- Admission to a stroke unit, maintenance of stable BP, and an early multidisciplinary approach to rehab have been shown to decrease morbidity, mortality, and costs (46; 47; 48; 49). The NNT for admission to a stroke unit to prevent 1 patient from dying or requiring long-term institutional care is 11; the NNT is 15 to prevent death and dependency.
- According to a study done by the New York State Stroke Center Designation Project, patients at primary stroke centers compared with nondesignated hospitals had a shorter time to treatment with tPA and were more likely to be admitted to a stroke unit (50).
- Care by a multidisciplinary stroke team results in better quality of life than standardized care as dictated by a care pathway (51).

Rationale

- Proper care in an inpatient stroke unit or by a multidisciplinary stroke team improves prognosis.

4.2 Hospitalize high-risk patients with TIA.

Recommendations

- Hospitalize patients with high risk for stroke, such as patients aged over 60 years; patients with weakness, speech disturbance, or diabetes; and patients with TIA lasting longer than 10 minutes.
- Stratify risk using the ABCD2 score (see Evidence for details).
- Obtain an urgent evaluation, including carotid ultrasound (or alternative vascular imaging) and an echocardiogram.
- Observe the high-risk patient with frequent neurologic evaluations for recurrence for at least 24 hours.
- Obtain a rapid evaluation for lower risk patients who are not admitted to the hospital within 12 to 24 hours, including:
  - Brain imaging (CT or MRI)
  - Vascular imaging (carotid ultrasound, MR angiography, or CTA)
  - Cardiac studies (electrocardiogram/echocardiogram)

Evidence

- 2006 Consensus guidelines from the National Stroke Association recommended rapid evaluation for all TIA patients (52).
• A cohort study found that patients with TIA have a 10.5% risk for stroke in the next 90 days, and half of those strokes occur in the first 48 hours. The risk for stroke following TIA is associated with age >60 years, weakness, speech disturbance, diabetes, and TIA duration >10 minutes. These risks are additive. The risk for stroke following TIA is greatest for those patients with large-vessel stenosis (53).

• An ABCD2 score of 4 suggests moderate to high risk for recurrent stroke (54).
  • A: Age: ≥60 y = 1
  • B: Blood pressure: systolic BP >140 mm Hg or diastolic BP >90 mm Hg = 1
  • C: Clinical features:
    o Weakness = 2
    o Speech disturbance without weakness = 1
    o Other = 0
  • D: Duration:
    o >60 minutes = 2
    o 10-59 minutes = 1
    o <10 minutes = 0
  • D: Diabetes = 1

• A prospective, population-based, before-and-after study that instituted rapid evaluation and treatment of patients with TIA with early initiation of aspirin, statin, and BP control found the 90-day risk for recurrent stroke dropped from 10% to 2% (55).

Rationale
  • There is a significant risk for stroke in patients who present with TIA.
5. Therapy

Institute drug therapy within 3 hours of stroke onset, and take adjunctive measures to improve prognosis after acute stroke. Consider carotid endarterectomy in appropriate patients.

5.1 In patients seen within 3 hours of suspected stroke onset, consider immediate therapy with iv rtPA to reverse cerebrovascular damage. In select patients in the 3- to 3.5-hour window, consider treatment with iv tPA.

Recommendations

- Do not give thrombolytics if:
  - Mean arterial pressure is >130 mm Hg
  - Systolic BP is >185 mm Hg
  - Diastolic BP is >110 mm Hg
- If tPA is being considered, use conservative measures, such as iv labetalol, nitropaste (1 to 2 inches), or nicardipine infusion, to reach these BP goals.
- Perform the following diagnostic studies before administering rtPA:
  - CT or MRI of the brain within 20 minutes of emergency department arrival (to exclude hemorrhage)
  - ECG
  - Hematocrit, platelet count, and glucose measurement
  - Prothrombin time (INR); partial thromboplastin time if the patient is taking anticoagulants
- Although patients in the 3- to 4.5-hour window should meet all criteria for the 3-hour window, apply the following additional exclusions: age >80, any oral anticoagulant use (even if INR <1.7), National Institutes of Health Stroke Scale score >25, and history of previous stroke and diabetes mellitus.
- Do not give iv tPA to patients on direct thrombin inhibitors unless specific lab testing is normal and the patient has not taken the drug for over 2 days if renal function is normal.
- Do not delay treatment because of the extended time window.
- To administer iv rtPA, give a total dose of 0.9 mg/kg, 10% in first minute as a bolus and remainder as an infusion over 1 hour (maximum dose 90 mg) if inclusion and exclusion criteria are met.
- If iv rtPA is given:
  - Withhold aspirin and anticoagulants for 24 hours.
  - Monitor patients closely for changes in vital signs or neurologic status in a stroke unit or intensive care unit.
  - Control systolic BP and diastolic BP to remain <180 mm Hg and <105 mm Hg, respectively.
  - Monitor for bleeding and angioedema.
- Intra-arterial acute stroke therapy may be considered in select patients not eligible for iv tPA and who have large-artery occlusion.
- See table Blood Pressure Management.
- See table Drug Treatment for TIA/Stroke.
- See table Inclusion and Exclusion Criteria for Intravenous rtPA Therapy.
- See table Follow Before and After Intravenous rtPA Therapy.
- See figure Carotid Artery Thrombolysis.
Evidence

- The 2013 AHA/American Stroke Association guidelines for the early management of patients with acute ischemic stroke recommended iv rtPA for selected patients who may be treated within 3 hours of onset of ischemic stroke. Physicians should review the inclusion and exclusion criteria to determine the eligibility of the patient. Patients may be treated 3 to 4.5 hours after onset of ischemic stroke if they meet the eligibility criteria for treatment within 3 hours and additional inclusion and exclusion criteria (56).

- A 2008 guideline from the American College of Chest Physicians for antithrombotic and thrombolytic therapy for acute stroke recommended rtPA (0.9 mg/kg; maximum dose, 90 mg) for selected patients who may be treated within 3 hours of onset of ischemic stroke (57).

- A 2009 Cochrane review of thrombolysis for acute ischemic stroke included 26 trials with 7152 participants; in most trials, treatment was administered up to 6 hours after stroke. Overall, thrombolysis decreased rates of patient death or dependence at 3 to 6 months (OR, 0.81 [CI, 0.73 to 0.90]) compared with control, but increased rates of death (OR, 1.31 [CI, 1.14 to 1.50]) and symptomatic intracranial hemorrhage (OR, 3.49 [CI, 2.81 to 4.33]). In the subgroup of patients who received treatment within 3 hours of stroke, thrombolytic therapy decreased death or dependency (OR, 0.71 [CI, 0.52 to 0.96]) with no increase in mortality (OR, 1.13 [CI, 0.86 to 1.48]) (58).

Rationale

- Thrombolytic therapy may reverse neurologic dysfunction in patients with acute stroke.

Comments

- Other than rtPA and antiplatelet agents, no therapy has been shown to definitively improve outcome in acute ischemic stroke.

- The relatively smaller benefit of tPA therapy in the 3- to 4.5-hour window compared with the less than 3-hour window reflects the fact that time to treatment with tPA is one of the most important factors in the probability of having a good outcome. Treatment should not be delayed to see whether the patient is going to improve without therapy.

- The 2013 AHA/American Stroke Association guidelines for the early management of patients with acute ischemic stroke reviewed and made recommendations regarding the use of intra-arterial thrombolytic therapy and mechanical thrombectomy. The guidelines indicated that the usefulness of emergent angioplasty or stenting was not established (56).

- Except for evidence of hemorrhage, no exclusion criteria on CT have been established for treatment within 3 hours (59).

- All subtypes of ischemic stroke respond to iv rtPA therapy (60; 61).

- Streptokinase is ineffective and harmful (62; 63; 64).

- Intra-arterial administration of thrombolytics directly into the clot may improve recanalization and allow treatment up to 6 hours in selected patients. This effect has been shown for pro-urokinase treatment in patients with middle cerebral artery trunk occlusion (65; 66).

- In a double-blind, randomized, controlled trial, steroids for brain edema following stroke did not improve outcome and were associated with an increased risk for infection (67).

- The IMS 3 trial did not show benefit of additional mechanical thrombectomy after iv tPA (68).

- MR RESCUE, a randomized trial of mechanical thrombectomy vs. medical therapy in patients treated within 8 hours of onset did not show benefit of mechanical thrombectomy in patients with ischemic penumbra on CT or MR perfusion studies (69).
5.2 Begin adjunctive antiplatelet therapy in patients with acute stroke within the first 48 hours, but generally do not anticoagulate.

**Recommendations**

- Administer aspirin (initial dose is 325 mg) for most patients with acute ischemic stroke.
- Consider the following alternative therapies:
  - Aspirin, 25 mg, plus dipyridamole
  - Clopidogrel for patients who cannot tolerate aspirin
- Delay antiplatelet or anticoagulant therapy if patient has received rtPA until 24 hours after rtPA is given.
- Consider treating with the combination of aspirin plus clopidogrel for 90 days if it can be started within 24 hours of the event.
- Do not provide anticoagulation with heparin or low-molecular-weight heparin in most ischemic strokes except for subcutaneous heparin for prophylaxis against DVT.
- Consider heparin therapy (weight adjusted, without bolus dosing) in the following emergency situations:
  - Suspected cerebral venous thrombosis
  - Basilar occlusion or stenosis in patients who are not candidates for rtPA therapy
  - Suspected extracranial arterial dissection or atherosclerotic occlusion
- See table [Classification of Subtypes of Acute Ischemic Stroke](#).

**Evidence**

- A 2014 guideline from the American Heart Association and the American Stroke Association for the secondary prevention of stroke recommended the use of antiplatelet agents for patients with stroke or TIA. The guideline recommended either aspirin alone or aspirin, 25 mg, plus dipyridamole as first-line agents. The guideline recommended considering treating patients who present within 24 hours of a TIA or minor stroke with the combination of aspirin and clopidogrel for 90 days. The guideline also stated that the value of adding antiplatelet therapy to anticoagulation in patients with stroke or TIA with AF and CAD was not clear (70).
- The 2013 AHA/American Stroke Association guidelines for the early management of patients with acute ischemic stroke recommended oral administration of aspirin within 24 to 48 hours after stroke onset for most patients. However, aspirin is not recommended as a substitute for other acute interventions for treatment of stroke, including iv rtPA (56).
- A 2008 Cochrane review of antiplatelet therapy for acute ischemic stroke included 12 trials with 43,000 participants and follow-up times of up to 6 months. Compared with control, antiplatelet therapy was associated with lower rates of death or dependency at the end of follow-up (OR, 0.95 [CI, 0.91 to 0.99]; NNT, 79), with a small increase in intracranial hemorrhage (71).
- A 2003 Cochrane review of anticoagulants compared with antiplatelet agents for acute stroke included four trials with 16,558 participants. Anticoagulants and aspirin resulted in similar rates of death or dependency (OR, 1.07 [CI, 0.98 to 1.15]) but anticoagulants were associated with higher rates of death (OR, 1.10 [CI, 1.01 to 1.29]) and intracranial hemorrhage (OR, 2.35 [CI, 1.49 to 3.46]) (72).
- A 2002 Cochrane review of anticoagulants compared with antiplatelet agents for acute stroke included four trials with 16,558 participants. Anticoagulants and aspirin resulted in similar rates of death or dependency (OR, 1.07 [CI, 0.98 to 1.15]) but anticoagulants were associated with higher rates of death (OR, 1.10 [CI, 1.01 to 1.29]) and intracranial hemorrhage (OR, 2.35 [CI, 1.49 to 3.46]) (72).
Rationale

- Antithrombotic therapy may help retard thrombosis in these situations and may decrease risk for subsequent stroke.

Comments

- Trials have been conducted using low-molecular-weight heparin, synthetic heparinoids, and unfractionated heparin for management of acute thrombotic cerebrovascular accident. The evidence does not support the use of anticoagulants in this setting, although some subgroups of patients may benefit, such as those with stroke due to large-artery atherosclerosis (73; 74).
- Other than rtPA and antiplatelet agents, no therapy has been shown to improve outcome in acute ischemic stroke.
- The 2013 AHA/American Stroke Association guidelines for the early management of patients with acute ischemic stroke found that the usefulness of anticoagulation for treatment of acute stroke was not established (56).

5.3 Implement critical adjunctive measures to improve prognosis after acute stroke or TIA and admit patients to a specialized stroke unit if available.

Recommendations

- Admit patients to a specialized stroke unit and arrange for care by a multidisciplinary team, if available.
- Provide airway support and ventilator assistance in appropriate patients.
- Monitor vital signs, heart rhythm, oxygenation, and glucose.
- For patients with elevated BP who are otherwise eligible for treatment with iv rtPA, carefully lower BP to systolic <185 mm Hg and diastolic <110 mm Hg. BP pressure should be stable at the lower level before beginning fibrinolytic therapy.
- For patients not receiving fibrinolytic therapy, do not treat BP unless the patient has:
  - Systolic BP >220 mm Hg
  - Mean arterial pressure >140 mm Hg
  - Evidence of coronary or renal insufficiency
  - Aortic dissection is suspected
  - Brain imaging indicates cerebral bleeding
- Administer easily titrated drugs, such as iv labetalol or nicardipine, if necessary, and decrease mean arterial pressure in 10- to 15-mm Hg decrements while monitoring neurologic status in patients with elevated BP.
- Treat body temperature >38°C.
- Maintain greater than 94% oxygen saturation with supplemental oxygen, if necessary.
- Ensure that patients consume nothing by mouth until swallowing has been assessed, usually at least for the first 24 hours after admission.
- Give iv normal saline to maintain euvolemia; avoid glucose-containing solutions, if possible.
- Treat hyperglycemia to achieve blood glucose levels in range of 140 to 180 mg/dL.
- Hypoglycemia (blood glucose <60 mg/dL) should be treated.
- Insert bladder catheter if necessary.
- Perform frequent positioning and suctioning if indicated.
- Within the first 48 hours:
To prevent DVT, apply graduated or pneumatic compression stockings and initiate therapy with subcutaneous heparin, 5000 units every 12 hours, or subcutaneous enoxaparin, 40 mg every 24 hours.
Place nasogastric feeding tube if patient is at risk for aspiration with standard oral feeding.
Institute early physical, occupational, and speech therapy and rehab planning.

Evidence

- The AHA/American Stroke Association 2013 guidelines for the early management of patients with acute ischemic stroke provided recommendations regarding general supportive care and treatment of acute complications (56).
- A 2013 Cochrane review of stroke units in the care of patients with acute stroke included 28 studies with 5855 participants. Compared with care on the general wards, care in a stroke unit reduced mortality at 1 year (OR, 0.87 [CI, 0.69 to 0.94]) and death or dependency (OR, 0.79 [CI, 0.68 to 0.90]) (75).

Rationale

- These measures are designed primarily to prevent complications immediately after acute stroke.

Comments

- Supplemental oxygen is not recommended in nonhypoxic patients.
- There is some evidence, although controversial, suggesting that early (24- to 48-hour) use of an angiotensin-receptor blocker improves morbidity and mortality after stroke (76). However, 2029 patients participated in a randomized, placebo-controlled, double-blind trial of early BP lowering with an angiotensin-receptor blocker, which showed no benefit and possibly worse outcomes (77).

5.4 Institute antiplatelet therapy for secondary stroke prevention in patients with TIA or stroke.

Recommendations

- Treat all patients with ischemic stroke or TIA with antiplatelet therapy: aspirin, 50 to 325 mg/d, aspirin plus extended-release dipyridamole, or clopidogrel.
- Consider clopidogrel, 75 mg/d, in patients who cannot tolerate or are allergic to aspirin.
- Be aware that the combination of clopidogrel, 75 mg/d, and aspirin, 75 mg/d, should not be used routinely for stroke prevention.
- Avoid ibuprofen and other NSAIDs within 8 hours before and 30 minutes after taking an antiplatelet agent.

Evidence

- A 2014 guideline from the American Heart Association and the American Stroke Association for the secondary prevention of stroke recommended the use of antiplatelet agents for patients with stroke or TIA. The guideline recommended either aspirin alone or aspirin, 25 mg, plus dipyridamole as first-line agents. The guideline recommended considering treating patients who present within 24 hours of a TIA or minor stroke with the combination of aspirin and clopidogrel for 90 days. The guideline also stated that the value of adding antiplatelet therapy to anticoagulation in patients with stroke or TIA with AF and CAD was not clear (70).
- A 2012 Cochrane review of antiplatelet agents compared with vitamin K antagonists in patients with minor stroke or TIA due to arterial disease included eight trials with 5762 participants. Overall, anticoagulation and antiplatelet agents led to similar rates of recurrent events (RR from high-intensity anticoagulation, 1.02 [CI, 0.49 to 2.13]) with increased rates of bleeding with high-intensity anticoagulation (RR, 1.93 [CI, 1.27 to 2.94]) (78).
- A 2013 systematic review of dual compared with single antiplatelet therapy in patients with ischemic stroke included seven trials with 39,574 participants. Rates of recurrent stroke were similar in patients receiving dual therapy compared with aspirin alone (RR, 0.89 [CI, 0.78 to 1.01]) and clopidogrel alone (RR, 1.01 [CI, 0.93 to 1.08]). Rates of intracranial hemorrhage were higher.
in patients receiving dual therapy than in patients receiving clopidogrel (RR, 1.46 [CI, 1.17 to 1.82]) but were similar in the dual therapy group and the aspirin alone group (RR, 0.99 [CI, 0.70 to 1.42]) (79).

• A 2008 Cochrane review of antiplatelet agents for acute stroke included 12 randomized trials with 43,041 participants. Overall, aspirin at doses of 160 mg to 300 mg daily reduced rates of death or dependency (OR, 0.95 [CI, 0.91 to 0.99]) (71).

• In a 2013 randomized, controlled study of 5170 patients in China were randomly assigned to receive either combination therapy of clopidogrel plus aspirin, or placebo plus aspirin, within 24 hours after the onset of a minor ischemic stroke or high-risk TIA. All patients received a dose of aspirin on day 1. The results showed that stroke occurred in 8.2% of clopidogrel- and aspirin-treated patients compared with 11.7% of patients in the aspirin-only group (HR, 0.68 [CI, 0.57 to 0.81]; P<0.001). The rate of hemorrhage or hemorrhagic stroke was similar in the two groups (80).

Rationale

• Stroke risk is 4% to 8% in the first month after a TIA and can be modified with antiplatelet agents.

• Clopidogrel is similar to aspirin plus extended-release dipyridamole, and both are likely modestly more effective than aspirin alone.

Comments

• The FDA has concluded that ibuprofen, and potentially other NSAIDs, can interfere with the antiplatelet effects of low-dose aspirin, although studies showing a difference in clinical outcomes are lacking.

5.5 Consider carotid endarterectomy in eligible patients with TIA or nondebilitating stroke.  

Recommendations

• Strongly consider referring patients with nondisabling stroke or TIA in the past 6 months due to internal carotid stenosis greater than 70% for carotid endarterectomy.

• Also consider endarterectomy if the stenosis is 50% to 69% and if the patient is likely to live 5 years, although the benefit is not clearly established in women.

• Do not recommend endarterectomy if the stenosis is less than 50%.

• In general, refer for endarterectomy within 2 weeks following a stroke and as soon as possible following a TIA if ipsilateral carotid stenosis is greater than 70%.

• When referring for carotid endarterectomy, refer to a neurosurgeon or vascular surgeon with a record of low morbidity and mortality.

• Consider stenting as an alternative to carotid endarterectomy:

  • In patients with low risk for complications from endovascular intervention (anticipated periprocedural risk for stroke or death less than 6%)
  • In patients with surgically unapproachable stenosis

Evidence

• A 2014 guideline from the American Heart Association and the American Stroke Association for the secondary prevention of stroke recommended carotid endarterectomy for patients within 6 months of TIA or stroke who have ipsilateral severe carotid stenosis (70% to 99%) if perioperative morbidity and mortality are estimated to be <6%. The guideline recommended considering carotid endarterectomy for patients with lesser degrees of ipsilateral stenosis (50% to 69%) based on patient factors, and recommended against carotid endarterectomy for patients with <50% ipsilateral stenosis. The guideline stated that carotid artery stenting is reasonable in patients at low risk of complications whose carotid artery diameter is reduced by 50% to 70% (70).
• A 2005 Cochrane review of carotid endarterectomy for asymptomatic carotid stenosis included three trials with 5223 participants. Compared with medical management, carotid endarterectomy led to lower rates of the combined endpoint of perioperative stroke or death, or subsequent stroke (RR, 0.69 [CI, 0.57 to 0.83]) and a trend toward lower rates of stroke or death (RR, 0.92 [CI, 0.83 to 1.02]) (32).

• A 2012 Cochrane review of percutaneous angioplasty and stenting compared with endarterectomy or medical management for carotid stenosis included 16 trials with 7572 participants. Compared with endarterectomy, stenting led to increased rates of death or stroke at 30 days (OR, 1.72 [CI, 1.29 to 2.31]), with no increase in rates of death or major disabling stroke (OR, 1.28 [CI, 0.93 to 1.77]) and more risk in patients aged over 70 years. Among patients who were not candidates for surgery, the rate of death and stroke was similar with stenting and medical management (OR, 0.22 [CI, 0.01 to 7.92]) (81).

Rationale
• With medical therapy alone, annual stroke risk is as high as 15% to 20%.

Comments
• A prospective, randomized, open-label (blind adjudication) trial enrolled 195 patients with arteriographically confirmed, symptomatic atherosclerotic internal carotid artery occlusion and hemodynamic cerebral ischemia identified by ipsilateral increased oxygen extraction fraction measure by PET. Patients were treated with either extracranial-intracranial bypass surgery plus best medical therapy, or best medical therapy alone. The study was terminated early for futility as surgery plus medical therapy did not reduce the risk for recurrent stroke at 2 years compared with medical therapy alone (82).

• The CLOSURE trial suggested that percutaneous patent foramen ovale closure did not lower risk for recurrent stroke or TIA compared with medical therapy (83). Further trials are ongoing.

5.6 Consider early hemicraniectomy in younger patients with large middle cerebral artery infarcts at risk for cerebral edema and herniation.

Recommendations
• Strongly consider obtaining a hemicraniectomy and duraplasty within 48 hours of the onset of symptoms in patients aged younger than 60 years with a large MCA infarct.

• Risk factors for malignant MCA infarction with edema and herniation include:
  • High initial NIH Stroke Scale value
  • Younger age
  • Early signs of swelling
  • Greater than 50% MCA hypodensity

Evidence
• The 2013 AHA/American Stroke Association guidelines for the early management of patients with acute ischemic stroke recommended decompressive surgery for malignant edema of the cerebral hemisphere. This surgery is effective and potentially lifesaving. Advanced age and patient and family valuations of achievable outcome may affect decisions regarding surgery (56).

Rationale
• With medical therapy alone, malignant MCA infarct has a mortality of 80%.

Comments
• The 2013 AHA/American Stroke Association guidelines for the early management of patients with acute ischemic stroke recommended decompressive surgical evacuation of a space-occupying cerebellar infarction. This surgery is effective in preventing and treating herniation and brain stem compression (56).
5.7 Provide anticoagulation for secondary stroke prevention in patients after TIA or completed stroke due to high risk sources of cardioembolism but not due to most other causes of stroke.  

Recommendations

- Consider high-risk cardioembolic etiologies of stroke and TIA to include AF, left-atrial appendage thrombus, left-ventricular thrombus, and dilated cardiomyopathy with a significant reduction in ejection fraction.
- Defer anticoagulation for 48 to 96 hours after established stroke if it is to be used.
- Repeat brain imaging to exclude hemorrhagic changes in the infarct.
- Start anticoagulation with weight-adjusted heparin without bolus dosing.
  - Anticoagulate more urgently with heparin to a partial thromboplastin time of 60 to 70 s in ‘crescendo’ TIA (TIA increasing in frequency or duration).
  - Anticoagulate with warfarin to an INR of 2.0 to 3.0 once the patient is stable in cases of AF, the sick sinus syndrome, recent anterior MI, mural thrombus, left-ventricular aneurysm or akinetic segment, mechanical valve, usually after 48 hours.
  - Consider a direct thrombin inhibitor, dabigatran or rivaroxaban, or the factor Xa inhibitor, aphixiban, as an alternative to warfarin in eligible patients with nonvalvular AF and stroke.
- Consider warfarin therapy in patients with cerebrovascular symptoms due to confirmed hypercoagulable state.
- Consider short-term anticoagulation lasting 3 to 6 months in patients with cervicocephalic arterial dissection.

Evidence

- A 2014 guideline from the American Heart Association and the American Stroke Association for the secondary prevention of stroke recommended warfarin, apixaban, or dabigatran for the prevention of stroke in patients with AF and stated that use of rivaroxaban is reasonable. For patients receiving warfarin, the guideline recommended a target INR of 2 to 3. The guideline recommended warfarin for patients with LV thrombi, cardiomyopathy, and valvular heart disease (70).
- A 2012 Cochrane review of antiplatelet agents compared with vitamin K antagonists in patients with minor stroke or TIA due to arterial disease included eight trials with 5762 participants. Overall, anticoagulation and antiplatelet agents led to similar rates of recurrent events (RR from high-intensity anticoagulation, 1.02 [CI, 0.49 to 2.13]), with increased rates of bleeding with high-intensity anticoagulation (RR, 1.93 [CI, 1.27 to 2.94]) (78).
- A 2004 Cochrane review of anticoagulation compared with antiplatelet agents for patients with nonrheumatic AF and history of stroke or TIA included two studies. Overall, anticoagulants prevented vascular events (OR, 0.67 [CI, 0.50 to 0.91]) and recurrent stroke (OR, 0.49 [CI, 0.33 to 0.72]) compared with antiplatelet agents, but increased major extracranial bleeding (OR, 5.16 [CI, 2.08 to 12.83; absolute difference 1% to 2% per year) (84).
- A randomized, double-blind, controlled trial (ARISTOTLE trial) compared the direct factor Xa inhibitor apixaban, 5 mg twice daily, to warfarin (target INR, 2.0 to 3.0) in 18,201 patients with AF and at least one additional risk factor for stroke. The mean duration of follow-up was 1.8 years. The results showed that ischemic or hemorrhagic stroke or systemic embolism occurred at a rate of 1.27% per year in the apixaban group, compared with 1.60% per year in the warfarin group (HR with apixaban, 0.79 [CI, 0.66 to 0.95]; P<0.001 for noninferiority; P=0.01 for superiority) (40).
- A randomized, double-blind, controlled trial (ROSKET AF trial) compared the direct factor Xa inhibitor rivaroxaban, 20 mg once daily, to dose-adjusted warfarin in 14,264 patients with AF who were at increased risk for stroke. The planned analysis was to determine whether rivaroxaban was noninferior to warfarin. In the per-protocol analysis, the stroke or embolism occurred in 188
patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (HR in the rivaroxaban group, 0.79 [CI, 0.66 to 0.96]; P<0.001 for noninferiority). In the intention-to-treat analysis, stroke or embolism occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (HR, 0.88 [CI, 0.74 to 1.03]; P<0.001 for noninferiority; P=0.12 for superiority) (39).

Rationale
- Full anticoagulation is sometimes useful to treat underlying disease processes that predispose to stroke.

Comments
- The role of anticoagulation in patients with other stroke mechanisms, including antiphospholipid antibodies and aortic arch plaque, remains uncertain.
- Short-term anticoagulation for dissection is often recommended given the high risk for thromboembolic infarct, although there is a lack of comparative date.

5.8 Make secondary risk-factor modification a priority among patients with TIA or cerebrovascular accident.

Recommendations
- Encourage smoking cessation.
- Maintain optimal glycemic control in patients with diabetes.
- Treat all patients who have had a stroke or TIA with intensive statin therapy.
- Discontinue combination estrogen and progestin treatment in postmenopausal women.
- Maintain long-term BP control, with a goal BP of <140/90 mm Hg for most patients.

Evidence
- A 2014 guideline from the American Heart Association and the American Stroke Association for the secondary prevention of stroke recommended treating hypertension in patients with prior stroke or TIA and BP ≥140/90 mm Hg, with a goal BP <140/90 mm Hg for most patients and systolic blood pressure <130 mm Hg in those with a recent lacunar stroke, and did not recommend specific drugs. The guideline also recommended intensive statin therapy for most patients with history of stroke or TIA, and recommended screening for diabetes and obesity (70).
- A 2013 Cochrane review of β-blockers compared with placebo for the secondary prevention of stroke included two randomized trials with 2193 participants. There were no differences between the groups in rates of recurrent stroke (RR, 0.94 [CI, 0.75 to 1.17]) or other clinical outcomes (85).
- A 2003 systematic review of BP reduction for the secondary prevention of stroke included seven randomized trials. BP lowering reduced recurrent stroke (OR, 0.76 [CI, 0.63 to 0.92]) and other vascular events (86).
- A randomized trial compared atorvastatin, 80 mg, to placebo in 4731 patients with stroke or TIA and LDL cholesterol between 100 and 190 mg/dL. After a median follow-up time of 5 years, the rate of recurrent stroke was lower in the atorvastatin group (11.2% vs. 13.1%; P=0.03) and mortality rates were similar in both groups (87).
- Following a stroke, all patients benefit from a statin, regardless of cholesterol level (88; 87).

Rationale
- Risk-factor modification can prevent recurrent stroke.
6. Patient Counseling

Inform patients at risk about ongoing therapy, monitoring, and prevention of recurrence.

6.1 Inform at-risk patients and families about the signs and symptoms of stroke and the immediate need for hospital care should they occur.

Recommendations
- Review symptoms of stroke with patients and their families and ensure that they have an action plan, including the need to call for emergency assistance.
- Emphasize the critical need to begin treatment within 3 hours of the onset of symptoms.
- Emphasize the importance of secondary prevention.
- See Prevention.

Evidence
- Consensus.

Rationale
- Most people are unaware of the symptoms of CVD. It is critical to identify high-risk patients and inform them about symptoms because imminent damage can be prevented or reversed if treated early.
- Thrombolytic therapy must be started within 3 hours of symptom onset to be effective.
7. Follow-up

Follow all patients by monitoring signs and symptoms, cardiovascular risk reduction, and functional status.

7.1 Continue management to maximize function and reduce risk for recurrence.

Recommendations

- Perform frequent neurologic exam (at least daily) during the first week after cerebrovascular accident, then usually on a monthly basis once the patient is discharged from the hospital (depending on need) until signs and symptoms are stable.
- Review regularly the status of risk-factor reduction and secondary prevention measures.
- Assess progress of rehabilitation weekly during hospitalization, then monthly after discharge.
- Consider intensive therapist-based rehabilitation programs to improve function after stroke either at a rehabilitation facility or at home.
- Recognize that in persons with spasticity of the wrist or fingers after a stroke, local injections with botulinum toxin type A reduce spasticity and the associated disability.
- Recognize and treat depression after stroke.
- Understand that caregivers for stroke patients should be trained in personal-care techniques and basic nursing care if possible.
- Consider treatment with vitamin B₁₂ and folic acid or a bisphosphonate in stroke patients to prevent hip fracture.

Evidence

- A 2003 Cochrane review of therapy-based rehabilitation services for stroke patients living at home compared with either no therapy or usual care included 14 trials involving 1617 patients. Therapy-based rehabilitation services decreased poor outcomes (OR, 0.72 [CI, 0.57 to 0.92]) and improved independence with activities of daily living (89).
- A randomized trial enrolled 100 patients with stroke who were living in the community. Patients were randomly assigned to either usual care or intervention of 36 structured, progressive, physiologically based, therapist-supervised, in-home program of 90-minute sessions over 12 weeks, targeting flexibility, strength, balance, endurance, and upper-extremity function. The results showed that intensive rehabilitation therapy at home for 12 weeks improved balance, endurance, mobility, and aerobic capacity (90).
- Formalized training of caregivers during patients' rehabilitation improves outcomes and reduces caregiver burden (91).
- Botulinum toxin type A reduces spasticity and disability of the wrist and fingers after stroke (92).
- A 2002 meta-analysis of randomized trials comparing acupuncture with no acupuncture in the 6 months after a stroke included 14 trials including 1213 patients. The results showed that acupuncture does not affect motor recovery after stroke, although it may improve functional ability (93).
- In a case-control study of 290 patients, those without post-stroke depression were nearly two times as likely to have a good recovery in activities of daily living and mobility than patients with depression. Although treatment with fluoxetine improved depressive symptoms in the latter group, it did not improve functional outcomes (94).
• In a 2002 two-part systematic review, post-stroke depression was found to be common, and such instruments as the Beck Depression Inventory, Hamilton Depression Rating Scale, and Zung Self-rating Depression Scale were found to be valid instruments in stroke patients, except those with aphasia. Controlled trials of antidepressant therapy suggested that tricyclics and serotonin reuptake inhibitors were both useful. The latter agents had fewer side effects (95; 96).

• Stroke patients have a greater than seven-fold increased risk for fracture within the first year after hospitalization. Risedronate alone and folate and vitamin B<sub>12</sub> in combination have both been shown to reduce hip fracture in stroke patients (97; 98; 99).

Rationale
• The goals are to maximize function after stroke and to prevent recurrence.

Comments
• It remains unproven whether aggressive prophylaxis or treatment of post-stroke depression will improve recovery or overall prognosis.

• A randomized study compared usual care of rehabilitation services with a caregiver at home. The results showed that providing care at home may be cost-effective and may reduce the burden on the caregiver (100).

• See also evidence in Prevention.
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**Glossary**

**ACE**
angiotensin-converting enzyme

**AF**
atrial fibrillation

**AV**
atroventricular

**AVM**
arteriovenous malformation

**bid**
twice daily

**BP**
blood pressure

**CABG**
coronary artery bypass graft(ing)

**CAD**
coronary artery disease

**CKD**
chronic kidney disease

**CNS**
central nervous system

**CT**
computed tomography

**CTA**
computed tomography angiography

**CVD**
cerebrovascular disease

**CYP**
cytochrome P<sub>450</sub> isoenzymes

**DVT**
deep venous thrombosis

**GI**
gastrointestinal

**HDL**
high-density lipoprotein

**ICH**
intracranial hemorrhage

**INR**
international normalized ratio

**iv**
intravenous

**LDL**
low-density lipoprotein

**MAP**
mean arterial pressure
MCA
middle cerebral infarct

MI
myocardial infarction

min
minutes

MR
magnetic resonance

MRA
magnetic resonance angiography

MRI
magnetic resonance imaging

NNT
number needed to treat

OR
odds ratio

PET
positron emission tomography

PT
plasma thromboplastin

PTT
partial thromboplastin time

PVD
peripheral vascular disease

qd
once daily

qid
four times daily

rtPA
recombinant tissue plasminogen activator

TIA
transient ischemic attack

tPA
tissue plasminogen activator

TTP
thrombotic thrombocytopenic purpura
### Tables

#### Lab and Other Studies for TIA/Stroke

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain CT</td>
<td>90-100 for ICH; &lt;50 for infarct in first 24 hours, but 50-90 for infarct after 24 hours</td>
<td>90-100 for ICH; poor (&lt;50) for infarct in first 24 hours, good (50-90) for infarct after 24 hours</td>
<td>Operating characteristics dependent on etiology</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>90-100 for ICH; 90-100 for infarct</td>
<td>90-100 for ICH; 90-100 for infarct</td>
<td>Operating characteristics dependent on etiology</td>
</tr>
<tr>
<td>Carotid ultrasonography</td>
<td>50-90 for carotid bifurcation stenosis of &gt;70</td>
<td>50-90 for carotid bifurcation stenosis of &gt;70</td>
<td>Operating characteristics dependent on etiology</td>
</tr>
<tr>
<td>Arteriography</td>
<td>90-100 for any stenosis of &gt;50</td>
<td>90-100 for any stenosis of &gt;50</td>
<td>Operating characteristics dependent on etiology</td>
</tr>
<tr>
<td>MRA, CTA</td>
<td>80 for any stenosis of &gt;50</td>
<td>80 for any stenosis of &gt;80</td>
<td>Operating characteristics dependent on etiology</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>50-90 for cardiac lesions</td>
<td>50-90 for cardiac lesions</td>
<td>Operating characteristics dependent on etiology</td>
</tr>
<tr>
<td>Complete blood count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotting studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood cultures</td>
<td></td>
<td></td>
<td>Obtain baseline prothrombin/partial thromboplastin time in anticipation of possible need for anticoagulation; other studies only as dictated by the clinical setting. Routine testing for antiphospholipid antibodies in patients with ischemic stroke is probably not warranted</td>
</tr>
<tr>
<td>Antinuclear and related serologic studies</td>
<td></td>
<td></td>
<td>Obtain if vasculitis is suspected</td>
</tr>
<tr>
<td>VDRL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocysteine</td>
<td></td>
<td></td>
<td>Additional risk factor for arteriosclerotic cardiovascular disease</td>
</tr>
<tr>
<td>Hemoglobin electrophoresis</td>
<td></td>
<td></td>
<td>To define hemoglobinopathies causing CNS infarction</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td></td>
<td></td>
<td>Useful in defining lymphoproliferative diseases predisposing to CNS hemorrhage</td>
</tr>
<tr>
<td>Chromosomal analyses</td>
<td></td>
<td></td>
<td>Useful only to confirm some rare inherited diseases associated with stroke</td>
</tr>
</tbody>
</table>

CNS = central nervous system; CT = computed tomography; CTA = computed tomographic angiography; ICH = intracranial hemorrhage; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; TIA = transient ischemic attack.
## Differential Diagnosis of TIA/Stroke

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Abrupt onset; fixed focal findings referable to arterial distribution (i.e., hemiparesis of face, arm, or leg ± aphasia)</td>
</tr>
<tr>
<td></td>
<td>Cannot distinguish stroke subtypes or infarct from hemorrhage without brain imaging and other tests as described previously. Diffusion MRI abnormal within minutes and is useful in questionable cases</td>
</tr>
<tr>
<td>TIA</td>
<td>Same as for stroke but typically lasting &lt;1 hour and without infarct on imaging</td>
</tr>
<tr>
<td></td>
<td>Originally defined as lasting &lt;24 hours</td>
</tr>
<tr>
<td>Seizure</td>
<td>Abrupt onset and termination of ictus; usually decreased responsiveness during ictus; often involuntary movements during ictus; usually postictal lethargy or confusion; sometimes postictal focal findings that resolve over 24 hours</td>
</tr>
<tr>
<td></td>
<td>May accompany stroke</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>May look like stroke or TIA; almost always in diabetic patients taking hypoglycemic medications; may or may not be accompanied by seizure</td>
</tr>
<tr>
<td></td>
<td>Only way to diagnose is by measuring blood glucose</td>
</tr>
<tr>
<td>Complicated migraine</td>
<td>Similar onset and focal findings as stroke; usually severe headache preceding or following attack; sensory and visual disturbances often prominent; sensory symptoms often spread over affected area</td>
</tr>
<tr>
<td></td>
<td>Suspect in younger patients, more often women with history of severe headache; MRI usually normal; stroke may accompany migraine</td>
</tr>
<tr>
<td>Mass lesion (tumor, abscess, herpes encephalitis, subdural hematoma)</td>
<td>Focal symptoms occur over days, not minutes; may not be in 1 vascular territory; primary cancer, fever, immunosuppression, and history of trauma often present</td>
</tr>
<tr>
<td></td>
<td>Can be distinguished from stroke by brain imaging with CT or MRI</td>
</tr>
<tr>
<td>Functional</td>
<td>May look like stroke; often not in a vascular territory; findings often nonanatomical or inconsistent; MRI usually normal</td>
</tr>
</tbody>
</table>

CT = computed tomography; MRI = magnetic resonance imaging; TIA = transient ischemic attack.
## Drug Treatment for TIA/Stroke

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombolytic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alteplase, tPA (Activase)</td>
<td>0.9 mg/kg iv total dose, with 10% administered over 1 minute and the remainder over 60 minutes. Maximum dose is 90 mg</td>
<td>Bleeding, hypotension</td>
<td>Avoid with severe hypertension. Caution with: severe hepatic disease, CKD</td>
<td>Within 3-4.5 hours of stroke onset in eligible patients</td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>160-325 mg qd initially, then 50-325 mg qd</td>
<td>GI side effects, hypersensitivity reactions, minor bleeding</td>
<td>Avoid with severe hepatic disease or severe CKD. Caution with: asthma, GI disease</td>
<td>Begin within first 48 hours; delay initial aspirin dose until 24 hours after rtPA is given</td>
</tr>
<tr>
<td>Ticlopidine (Plavix)</td>
<td>75 mg qd</td>
<td>Bleeding, diarrhea, rare TTP</td>
<td>Diminished effect in poor metabolizers. Avoid use of omeprazole or esomeprazole. Caution with hepatic disease</td>
<td>If aspirin is contraindicated</td>
</tr>
<tr>
<td>Dipyridamole (Persantine)</td>
<td>75-100 mg qid</td>
<td>Headache, dizziness, hypotension, abdominal distress</td>
<td>Caution with severe hepatic disease</td>
<td>In combination with aspirin</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>250 mg bid with meals</td>
<td>Diarrhea, nausea, elevated hepatic enzymes, bleeding, hypercholesterolemia, hypertriglyceridemia</td>
<td>Life-threatening hematological adverse reactions. Avoid with severe hepatic disease. Caution with moderate hepatic disease. Not preferred in elderly. Inhibitor of CYPs 2C19, 2B6, 1A2</td>
<td>If necessary to decrease BP, decrease MAP in 10-15 mm Hg decrements while monitoring neurologic status</td>
</tr>
<tr>
<td><strong>iv antihypertensives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine (Cardene)</td>
<td>iv: 5 mg/hr iv infusion. If needed, increase by 2.5 mg/hr q15min, up to 15 mg/hr. Once BP goal achieved, decrease to 3 mg/hr</td>
<td>Headache, edema</td>
<td>Caution with: severe bradycardia, HF, hepatic disease, reflux esophagitis, aortic stenosis, CKD</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>Intermittent iv: 20 mg iv over 2 min. Every 10 min, may give 40 mg or 80 mg iv over 2 min until desired supine BP achieved or 300 mg has been given. iv infusion: 2 mg/min infusion. Adjust rate to BP response. Usual total dose is 50-200 mg iv</td>
<td>Orthostatic hypotension, bradycardia, bronchospasm, AV block, nausea, vomiting</td>
<td>Avoid with asthma. Caution with: CKD, hepatic disease, hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Combination agent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipyridamole/aspirin (Aggrenox)</td>
<td>200/25 mg extended-release, dosed 1 capsule bid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- = first-line agent; ■ = black box warning; AM = morning; AV = atrioventricular; bid = twice daily; BP = blood pressure; CKD = chronic kidney disease; CNS = central nervous system; CrCl = creatinine clearance; CYP = cytochrome P450 isoenzymes; GI = gastrointestinal; HF = heart failure; iv = intravenous; MAP = mean arterial pressure; min = minutes; PM = evening; qd = once daily; qid = four times daily; TTP = thrombotic thrombocytopenic purpura.
PIER provides key prescribing information for practitioners but is not intended to be a source of comprehensive drug information.
### Contribution of Selected Risk Factors to Stroke Incidence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3.0–5.0</td>
<td>25–56</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>2.0–4.0</td>
<td>10–20</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5.0–18.0</td>
<td>1–2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.5–3.0</td>
<td>4–8</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.5–3.0</td>
<td>20–40</td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>1.0–4.0</td>
<td>5–30</td>
</tr>
</tbody>
</table>
### Focal Neurologic Symptoms of Cerebrovascular Accident

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness; paresthesia; loss of sensation in face, arm, or leg</td>
</tr>
<tr>
<td>Loss of speech</td>
</tr>
<tr>
<td>Loss of vision in one eye or in one visual field</td>
</tr>
<tr>
<td>Vertigo, with dysarthria, diplopia, paresthesia, imbalance</td>
</tr>
</tbody>
</table>
## Classification of Subtypes of Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis (embolus/thrombosis)*</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism (high risk/medium risk)*</td>
<td></td>
</tr>
<tr>
<td>Small-vessel occlusion (lacuna)*</td>
<td></td>
</tr>
<tr>
<td>Stroke of other determined etiology*</td>
<td></td>
</tr>
<tr>
<td>Stroke of undetermined etiology</td>
<td></td>
</tr>
<tr>
<td>Two or more causes identified</td>
<td></td>
</tr>
<tr>
<td>Negative evaluation</td>
<td></td>
</tr>
<tr>
<td>Incomplete evaluation</td>
<td></td>
</tr>
</tbody>
</table>

* Possible or probable, depending on results of ancillary studies.

### Features of Subtypes of Ischemic Stroke*

<table>
<thead>
<tr>
<th>Features</th>
<th>Large-Artery Atherosclerosis</th>
<th>Cardioembolism</th>
<th>Small-Artery Occlusion (Lacuna)</th>
<th>Other Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>Cortical or cerebellar dysfunction</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical, cerebellar, brain stem, or subcortical infarct &gt;1.5 cm</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>Subcortical or brain stem infarct &lt;1.5 cm</td>
<td>–</td>
<td>–</td>
<td>+/−</td>
<td>+/-</td>
</tr>
<tr>
<td>Tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis of extracranial internal carotid artery</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac source of emboli</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other abnormality on tests</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

### Classification of High- and Medium-Risk Sources of Cardioembolism*

<table>
<thead>
<tr>
<th>High-risk sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical prosthetic valve</td>
</tr>
<tr>
<td>Mitral stenosis with AF</td>
</tr>
<tr>
<td>Atrial fibrillation (other than lone AF)</td>
</tr>
<tr>
<td>Left-atrial/atrial appendage thrombus</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
</tr>
<tr>
<td>Recent myocardial infarction (&lt;4 weeks)</td>
</tr>
<tr>
<td>Left-ventricular thrombus</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Akinetic left-ventricular segment</td>
</tr>
<tr>
<td>Atrial myxoma</td>
</tr>
<tr>
<td>Infective endocarditis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medium-risk sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Mitral annulus calcification</td>
</tr>
<tr>
<td>Mitral stenosis without AF</td>
</tr>
<tr>
<td>Left-atrial turbulence (smoke)</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>Atrial flutter</td>
</tr>
<tr>
<td>Lone AF</td>
</tr>
<tr>
<td>Bioprosthetic cardiac valve</td>
</tr>
<tr>
<td>Nonbacterial thrombotic endocarditis</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Hypokinetic left-ventricular segment</td>
</tr>
<tr>
<td>Myocardial infarction (&gt;4 weeks, &lt;6 months)</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation.  
### Inclusion and Exclusion Criteria for rtPA Therapy

<table>
<thead>
<tr>
<th><strong>Inclusion criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥18 years, clinical diagnosis of ischemic stroke and a measurable neurologic deficit, and time of symptom onset well established to be &lt;270 minutes before start of possible treatment*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Exclusion criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of intracranial hemorrhage on pretreatment CT</td>
</tr>
<tr>
<td>Clinical presentation suggestive of SAH, even with normal CT</td>
</tr>
<tr>
<td>CT shows multilobar infarction (hypodensity &gt;1/3 cerebral hemisphere)</td>
</tr>
<tr>
<td>Active internal bleeding</td>
</tr>
<tr>
<td>Known bleeding diathesis, including but not limited to:</td>
</tr>
<tr>
<td>→ platelet count &lt;100,000 cells/mm³</td>
</tr>
<tr>
<td>→ heparin treatment last 48 hours, with an abnormally elevated aPTT</td>
</tr>
<tr>
<td>→ current use of oral anticoagulants or recent use, with elevated INR &gt;1.7 or PT &gt;15 s</td>
</tr>
<tr>
<td>Significant head trauma or previous stroke (within previous 3 months)</td>
</tr>
<tr>
<td>Recent intracranial or intraspinal surgery</td>
</tr>
<tr>
<td>Arterial puncture at a noncompressible site in previous 7 days</td>
</tr>
<tr>
<td>Elevated BP (systolic &gt;185 mm Hg or diastolic &gt;110 mm Hg)</td>
</tr>
<tr>
<td>History of intracranial hemorrhage</td>
</tr>
<tr>
<td>Abnormal blood glucose (&lt;50 mg/dL)</td>
</tr>
<tr>
<td>Known intracranial neoplasm, AVM, or aneurysm</td>
</tr>
</tbody>
</table>

**Relative exclusion criteria (carefully consider risk vs. benefit)**

- Major surgery or serious trauma, excluding head trauma (in the previous 14 days)
- Pregnancy
- Seizure at stroke onset with postictal residual neurological impairments
- Minor or rapidly improving stroke symptoms
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Recent acute MI (within previous 3 months)

AVM = arteriovenous malformation; CT = computed tomography; MCA = middle cerebral infarct; MI = myocardial infarction; PT = plasma thromboplastin; rtPA = recombinant tissue plasminogen activator.

* Among patients being considered for iv rtPA therapy between 3 and 4.5 hours from symptom onset, exclude those with a NIH Stroke Scale value >25, a history of both diabetes and previous stroke, a history of active anticoagulant use, or more than one third MCA territory hypodensity on CT.

Adapted from the 2013 guidelines for the early management of patients with acute ischemic stroke by the AHA/American Stroke Association (56).
# Procedures to Follow Before and After Intravenous rtPA Therapy

## Before rtPA treatment

<table>
<thead>
<tr>
<th>Step</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine whether time is sufficient to start treatment within 3 hours</td>
<td></td>
</tr>
<tr>
<td>Draw blood immediately to obtain hematocrit, platelet count, blood glucose level, PT, and PTT. Start iv normal saline at 50 mL/hour</td>
<td></td>
</tr>
<tr>
<td>If BP is &gt;185 mm Hg systolic or &gt;110 mm Hg diastolic, administer antihypertensives and continue to record BP</td>
<td></td>
</tr>
<tr>
<td>Neurologic exam</td>
<td></td>
</tr>
<tr>
<td>Perform CT without contrast immediately. Determine whether there is evidence of hemorrhage or lucency suggestive of infarction. If there is lucency, consider the patient's history, since the stroke may have occurred earlier</td>
<td></td>
</tr>
<tr>
<td>Review required test results</td>
<td></td>
</tr>
<tr>
<td>Review patient history for exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Obtain consent. Start second iv infusion</td>
<td></td>
</tr>
<tr>
<td>Initiate iv rtPA therapy: 0.09-mg/kg bolus given over 1 minute, followed immediately by infusion of 0.81 mg/kg over 60 minutes. DO NOT use cardiac dose; DO NOT exceed 90 mg (maximum total dose); DO NOT give aspirin, heparin, or warfarin for 24 hours</td>
<td></td>
</tr>
</tbody>
</table>

## After rtPA treatment

<table>
<thead>
<tr>
<th>Step</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain vital signs and perform neurologic checks every 15 minutes for 2 hours after rtPA infusion, then every 30 minutes for 6 hours, then hourly until 24 hours after rtPA treatment</td>
<td></td>
</tr>
<tr>
<td>Monitor BP closely; follow BP management algorithm</td>
<td></td>
</tr>
<tr>
<td>Delay insertion of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if patient can safely be managed without them</td>
<td></td>
</tr>
<tr>
<td>Monitor neurologic status over next 48 hours</td>
<td></td>
</tr>
<tr>
<td>Repeat CT in 24 hours if heparin or another anticoagulant is indicated after 24 hours. Evidence of intracranial hemorrhage precludes use of aspirin, heparin, or warfarin</td>
<td></td>
</tr>
<tr>
<td>If any acute neurologic deterioration, new headache, acute hypertension, or nausea and vomiting develops, consider possibility of intracranial hemorrhage, stop rtPA infusion, and obtain brain CT immediately</td>
<td></td>
</tr>
</tbody>
</table>

**CT** = computed tomography; **iv** = intravenous; **PT** = plasma thromboplastin; **PTT** = partial thromboplastin time; **rtPA** = recombinant tissue plasminogen activator.
**Blood Pressure Management**

### Before treatment

Monitor BP every 15 minutes

- If systolic BP > 185 mm Hg or diastolic BP > 110 mm Hg, administer:
  - Labetalol, 10-20 mg iv over 1-2 minutes; may repeat ×1
  - Nitropaste, 1-2 inches
  - Nicardipine infusion, 5 mg/hour; titrate up by 2.5 mg/hour at 5- to 15-minute intervals to a maximum dose of 15 mg/hour; when desired BP attained, reduce to 3 mg/hour

- If BP does not decline and remains > 185/110 mm Hg, do not administer rtPA

### During and after treatment with rtPA or other acute reperfusion intervention

Monitor BP every 15 minutes during treatment and then for another 2 hours, then every 30 minutes for 6 hours, and then every hour for 16 hours

- If systolic BP 180 to 230 mm Hg or diastolic BP 105 to 120 mm Hg, administer:
  - Labetalol, 10 mg iv over 1-2 minutes; may repeat every 10-20 minutes; maximum dose, 300 mg
  - Labetalol, 10 mg iv, followed by an infusion at 2-8 mg/minutes

- If systolic BP > 230 mm Hg or diastolic BP 121 to 140 mm Hg, administer:
  - Labetalol, 10 mg iv over 1-2 min; may repeat every 10-20 minutes; maximum dose, 300 mg
  - Labetalol, 10 mg iv, followed by an infusion at 2-8 mg/minutes

- Nicardipine infusion, 5 mg/hours; titrate up to desired effect by increasing 2.5 mg/hours every 5 minutes to a maximum dose of 15 mg/hour

- If BP not controlled, consider sodium nitroprusside

BP = blood pressure; iv = intravenous; rtPA = recombinant tissue plasminogen activator.
# Vascular Studies to Define the Nature and Severity of Stroke

## Excracranial

- Perform carotid ultrasonography in all patients with nondebilitating hemispheric infarction and life expectancy >5 years. MR angiography or CT angiography may be substituted for carotid ultrasonography or used to confirm a carotid lesion suspected on carotid ultrasonography.

- If these noninvasive studies are inadequate, consider catheter angiography to accurately delineate lesions before carotid endarterectomy or stenting.

- These imaging methods can also detect vertebral artery stenosis.

## Intracranial

- Consider transcranial Doppler ultrasonography, MR angiography, or CT angiography in many patients, especially if carotid endarterectomy is being contemplated.

- Perform catheter angiography if other diagnostic tests are insufficient to determine the nature and extent of cerebral vascular disease.

## Cardiac

- Perform cardiac monitoring, 2-D echocardiography, and transesophageal echocardiography if cardiac etiology is suspected.
Figures

Subhyaloid Hemorrhage

Characteristic boat-shaped subhyaloid hemorrhages on funduscopic exam suggesting an aneurysmal subarachnoid hemorrhage.
**Head CT findings in Acute Ischemic Stroke**

Top left, sulcal effacement and loss of the gray-white differentiation (oval circle) in a patient 1.5 hours after the witnessed onset of global aphasia. Top right, hyperdensity (arrow) in the proximal right middle cerebral artery in a patient with left hemiparesis and left hemi-inattention 60 minutes after last being seen well. Bottom left, CT angiogram of the patient from panel B that shows absent contrast in the right internal carotid and proximal middle cerebral arteries (arrow), consistent with a thrombus in the artery. Bottom right, loss of the insular ribbon on the right (arrow) compared with the left where the gray-white differentiation is clearly seen in a patient 2 hours after onset of left hemiparesis.
Cholesterol Embolus

A golden yellow intra-arterial refractile body is characteristic of cholesterol emboli (Hollenhorst plaque).
Hemorrhagic Stroke

Head CT showing changes associated with a hemorrhagic stroke in the basal ganglia.
Carotid Artery Thrombolysis

Left panel shows thrombosis of the right carotid artery and the right panel shows the return of vascular flow following successful thrombolysis.