



Module 6. Preventing and Treating Ischemic Stroke: An Introduction to Therapy

Objectives for Module 6

Knowledge

- List 5 recommendations that you could make to help patients reduce their risk of having a first stroke (primary prevention)
- For a patient who has experienced a recent TIA or ischemic stroke, list 3 appropriate strategies for secondary prevention. What additional measures should be considered when there is (1) an identified source of cardiac emboli or (2) carotid stenosis that's likely related

Clinical Applications and Reasoning

- List immediate diagnostic studies for evaluation of a patient with suspected acute ischemic stroke, and why they are critical for early therapeutic intervention
- Describe time factors and several additional considerations that determine patient eligibility for therapies involving intravenous alteplase (fibrinolytic) and/or mechanical thrombectomy
- Describe additional healthcare measures aimed at improving the clinical outcome of a patient diagnosed with an acute stroke

Clinical Applications to Patient Education

- Develop a plan for discussing the key warning signs of stroke with a 70-year-old patient who has at least 3 major stroke risk factors
- Plan your response to a patient who states: "there's no rush to get help if you think you're having a stroke---you're as good as gone anyway..."

Risk Factor Control to Prevent a First Stroke (Primary Prevention)

RISK FACTOR	Recommendations
Current Cigarette Smoking	Counseling to help patient stop smoking; smoking cessation programs; nicotine replacement
Lack of Regular Physical Activity	As medically appropriate, exercise program providing at least 150 min. of moderate (75 min vigorous) activity per week; strengthening at least 2 days per week.
Excessive Alcohol Consumption	Counseling to reduce alcohol consumption to an average of 1 drink/day (women) or 2 drinks/day (men) and to stop binge drinking; cessation programs if needed
Obesity	Diet and exercise aimed at reducing weight to achieve a body mass index (BMI) < 25 (25-29 is considered 'overweight'; ≥30 is 'obese')

RISK FACTOR	Therapeutic Goal	Recommendations
High Blood Pressure	Decrease build-up of atherosclerotic plaque; reduce direct damage to walls of small arteries and arterioles	Lifestyle modifications and antihypertensive medications reducing blood pressure to <130/80 mm Hg (New guideline)
Acute Myocardial Infarction especially if anterior or septal region of heart wall is damaged	Prevent thrombus from forming on ischemic endocardium	Oral anticoagulants or antiplatelet agents
Any condition, including MI, that reduces motion of the heart wall	Prevent thrombus from forming in ventricle	Oral anticoagulants (preferred) or antiplatelet agents
Atrial Fibrillation	Restore normal rhythm Prevent clot formation in left atrium	Cardioversion, ablation, and/or antiarrhythmic drug therapy Oral anticoagulants (preferred) or antiplatelet agents
Diabetes Mellitus	Decrease rate of atherosclerosis, and its secondary consequences such as hypertension	Diet, oral hypoglycemics, or insulin to reduce or normalize blood glucose levels if possible
High Blood Cholesterol (and other lipids)	Reduce or prevent atherosclerotic plaque formation	Diet limiting saturated fats, increased physical activity, often a statin or related agents
Carotid Artery Stenosis (asymptomatic)	Prevent thrombus formation on existing atherosclerotic plaque	Antiplatelet agents
	Improve blood flow by increasing diameter of lumen	Endarterectomy or stenting; possible plaque reduction by diet or statins

In young patients who may not have traditional vascular risk factors, also consider less common contributing factors such as hypercoagulable disorders, arterial dissection, or drugs (e.g. cocaine)

Areas of Patient Education That Are Important in Prevention

- Realizing that addressing modifiable risk factors can significantly reduce overall stroke risk
- Recognizing the common signs and symptoms of stroke (F.A.S.T.)
- Knowing to call 9-1-1 immediately if warning signs occur (use of EMS generally preferred)
- Understanding that new therapies available only in the ACUTE phase may limit or even reverse deficits
- Seeking immediate medical help for stroke warning signs even if they last for only a few minutes
- Understanding that if a stroke or TIA does occur, aggressive follow-up health care can help prevent future strokes

Treatment of Ischemic Stroke

"My husband and I were having breakfast together. I noticed that he was trying to reach for his coffee mug with his right hand, but now he could barely move his arm. His banana and bagel were falling out of the right side of his mouth. He wasn't talking, just mumbling some sort of gibberish. However he seemed to understand that I was telling him. I knew something was wrong and called 9-1-1. We live just up the street from the hospital, and EMS got him to the ED in about 25 minutes."

NOTE: Use of 911/EMS is recommended as this provides an opportunity for stroke screening, blood glucose determination (finger stick), pre-notification of ED, and potentially rapid transport to closest facility that can capably administer thrombolytic and endovascular therapy if there is suspicion of stroke.

A patient with the abrupt onset of neurologic symptoms arrives in the ED What should happen next?

▪ Therapy 0-6 Hours After Symptom Onset

The INITIAL goals in this early phase are to provide medical support for the patient, establish a clinical diagnosis of stroke, and determine whether the stroke is ischemic or hemorrhagic. The patient's airway, breathing, and circulation are constantly reassessed. The first question to be answered is whether this is a stroke or a stroke mimic (e.g. seizure, migraine, hyperglycemia, hypoglycemia). To establish the clinical diagnosis, physicians consider the patient's history and physical examination, and whether the neurologic symptoms and signs conform to a vascular pattern. A non-contrast head CT scan is obtained as quickly as possible to determine the presence or absence of hemorrhage (the goal is imaging within 20 min of arrival in ED). Recall that a CT study performed in the first hours may not visualize *ischemic regions*, even ones that later will produce large infarcts. CTA of intracranial and extracranial vessels may be simultaneously performed, but this should not delay administration of thrombolytic therapy (IV alteplase) to eligible patients. Various blood tests and an ECG are requested, but only the assessment of blood glucose (to rule out diagnosis of metabolic encephalopathy) must precede initiation of IV alteplase.

Once hemorrhage is excluded the administration of IV alteplase, the FDA-approved recombinant tissue plasminogen activator (r-tPA), may be considered. This fibrinolytic drug opens blocked arteries by dissolving the strands of fibrin that hold together the red blood cells or platelets in an embolus or thrombus. **FDA guidelines for IV alteplase recommend that eligible patients be treated within 3 hours of the time of observed symptom onset; however ACC/AHA guidelines additionally support treatment of selected patients between 3 and 4.5 hours.**

"My husband was examined and had his CT scan right away. The neurologist recommended r-tPA therapy and explained its dangers but also its potential benefits to both of us. She told me getting to the hospital so quickly after his symptoms started improved the chances of success. They started the drug about 1.5 hours after his problem started. As I watched, I could see the strength coming back in his hand. Six months later things have improved but aren't back to normal. For instance, he has to "work" at saying things clearly, and sometimes he struggles to find the word he wants to say."

MORE ABOUT IV alteplase: Over the past ten years, there have been a number of clinical studies examining outcomes of intravenous r-tPA therapy for acute ischemic stroke. While details vary, they collectively demonstrate that *the sooner the treatment is initiated, the better the long-term outcome.* On average, treatment within 90 minutes of symptom onset or last known well is associated with the most favorable outcomes, with favorable outcomes decreasing with time but still demonstrating benefit at 3 to 4.5 hours for selected patients.

Although other tests will certainly have been ordered, the only results that are essential before the time-sensitive decision about IV alteplase therapy is made are the non-contrast head CT scan and blood glucose level (finger stick). The list of exclusion criteria for this therapy includes a number of conditions that would indicate an increased risk of bleeding within the brain or at other sites, for instance uncontrollable hypertension, stroke in prior 3 months, bleeding disorders, recent surgery.

The safety and efficacy of IV alteplase treatment *within 3 hours* of last known normal for eligible adult patients with disabling stroke symptoms regardless of age and stroke severity are well supported. However, one complication of therapy can be severe or even fatal intraparenchymal brain hemorrhage, so the risks and the potential benefits of IV alteplase therapy should be discussed with the patient and/or family, and informed consent obtained prior to administration. However, because of the proven benefit and the critical time factor, IV alteplase treatment is justified even if the patient or proxy cannot immediately provide consent. *Between 3 and 4.5 hours* of last normal, IV alteplase is also recommended but patient selection criteria are more stringent (e.g. the very elderly and those with severe symptoms or large areas of ischemic injury are generally excluded).

Recent clinical trials have demonstrated that mechanical thrombectomy using stent-retriever devices is highly beneficial in eligible patients with causative occlusions of the internal carotid or proximal middle cerebral artery (large-vessel occlusions) up to 6 hours after stroke onset. Patient age, NIH Stroke Scale score, or receipt of IV alteplase do not rule out thrombectomy. Although the benefits are uncertain, new AHA Guidelines indicate that mechanical thrombectomy with stent retrievers may reasonably be considered for patients with M2 or M3 segment MCA, ACA, PCA vertebral or basilar artery occlusions. Vessel imaging with CT angiography (CTA) is required to determine eligibility for thrombectomy. It is helpful that many hospitals now routinely perform rapid CTA at the same time as the initial non-contrast CT.

2019 AHA Guidelines recommend that a patient eligible for IV alteplase should receive it, even if mechanical thrombectomy is being considered.

With mechanical thrombectomy, reduced time between symptom onset and reperfusion is also highly associated with better clinical outcomes. **Time is brain!** However, the time window for clinical benefit is somewhat extended. In an exciting development, recent clinical trials suggest that in selected patients with occlusions in the anterior circulation, mechanical thrombectomy at up to 24 hours after symptom onset may confer functional benefit.

Currently, IV alteplase and/or mechanical thrombectomy using stent retrievers will benefit only those stroke patients who arrive quickly enough to be eligible, and who also meet additional criteria. Furthermore, to take advantage of mechanical thrombectomy the patient must be at a healthcare facility with rapid access to cerebral angiography, neurointerventionalists, and a specialized care team. At this time the outcomes of both these therapies are variable. While a number of patients appear to benefit significantly, others may receive limited benefit, and a small number experience hemorrhagic complications that worsen their deficits or lead to death. Hopefully, future developments in fibrinolytic, endovascular and neuroprotective treatments may provide more powerful or universally helpful alternatives.

More About Testing That Is Part Of The Acute Stroke Work-Up

During the first hours after an ischemic stroke, an important goal is to figure out the cause and the location of the blockage. To establish whether the occlusion involves a large extracranial or intracranial artery, Doppler ultrasound or CT angiography can supplement the history and physical exam. As mentioned previously, some centers now combine CT angiography (and CT perfusion imaging) with the initial non-contrast CT scan to expedite the stroke workup, because CTA images the both the extra and intracranial arterial system to localize any significant stenosis or occlusion causing the stroke. An electrocardiogram may demonstrate presence of intramural (within left atrium or ventricle) thrombus, right to left shunt, regional or global myocardial wall weakness that may predispose to thrombus formation.

During this very early phase, MRI is not commonly used except in major stroke centers. In that setting, diffusion-weighted imaging can be used to detect very early infarcts. MR perfusion studies can be performed using gadolinium contrast. Brain regions showing poor perfusion but no abnormality on diffusion are considered equivalent to the ischemic penumbra -- brain regions that may be at risk of ischemia/infarction but are potentially salvageable if revascularized. Although it is an imperfect approach, the ability to image the ischemic penumbra may be helpful in selecting patients who might benefit from mechanical thrombectomy.

▪ **Therapy Beyond 6 Hours**

If a patient presents more than six hours after symptom onset, physicians ask many of the same diagnostic questions: Is this a stroke? What caused it? What can I do to prevent another stroke?

IV alteplase therapy is not usually an option at this time, because of the increased risk that arteries in the ischemic region of brain will hemorrhage if blood flow is restored. Endovascular therapy with stent retrievers may still be considered, especially in the setting of a clinical trial, if the patient meets criteria and therapy can be initiated with little further delay.

Some of the additional medical issues for physicians in this later phase include:

- Prevention of direct complications of stroke, such as brain swelling and potential herniations
- Control of excessive hypertension, hyperglycemia, dehydration, and fever
- Prevention of secondary complications resulting from the patient's relative immobility, such as deep venous thrombosis, aspiration pneumonia (caused by stroke-related inability to swallow), pressure sores, and contractures (flexion or distortion of joints due to weakness and spasticity).

At this time, physicians provide supportive medical care, prevent and treat any acute complications, determine exactly what caused arterial obstruction, and assess the extent of vascular disease and the need for medical or surgical treatment.

Secondary Prevention After a First TIA or Ischemic Stroke

Patients with TIAs (mini- strokes) should be evaluated very promptly. The risk of stroke after a TIA may be as high as 10-15% in the first 90 days, and a number of the strokes occur in the next 1-2 days. Recently, the number of strokes occurring soon after TIAs has decreased, thanks in part to more timely and effective secondary prevention measures.

A major goal of evaluating patients who have had a TIA or acute ischemic stroke is to determine the *specific etiology (cause)* of the cerebral ischemia, so that the most appropriate therapy can be quickly initiated to prevent recurrence.

Medical and surgical therapies, as well as lifestyle modifications, can help prevent stroke. Strategies for secondary prevention commonly include (1) blood pressure control (however blood pressure control in the acute setting requires caution and expertise), (2) statins, and (3) antiplatelet therapy (except in patients who require anticoagulant therapy). Depending on what the diagnostic evaluation indicates about the most likely cause of the TIA or first stroke, additional medical, endovascular and/or surgical therapies may also be recommended.

(1) High blood pressure is the most important modifiable risk factor for both primary and secondary prevention of stroke. A number of clinical trials indicate benefits of blood pressure reduction in stroke prevention, regardless of the initial blood pressure levels. However the most effective blood pressure target is unclear. Whether any particular class of antihypertensive agents conveys specific benefit in stroke reduction also remains somewhat controversial. A recent clinical

trial suggests the benefit of an angiotensin-converting-enzyme (ACE) inhibitor alone or in combination with a diuretic.

(2) Statins are effective in both primary and secondary stroke prevention. Whether their benefit extends beyond LDL-C level reduction is unclear, although many suspect that this is the case.

(3) Antiplatelet therapy (platelet aggregation inhibitors) is recommended for secondary stroke prevention unless anticoagulation is indicated (see below). These drugs prevent platelets from sticking to each other, and therefore limit the growth of *platelet-rich, relatively fibrin-poor thrombus* on the surface of a damaged atherosclerotic plaque whether in extracranial or intracranial cerebral arteries.

Patients with *carotid stenosis* have a reduced incidence of stroke when they are placed on platelet aggregation inhibitors. Stenosis indicates the presence of atherosclerotic plaque that could become thrombogenic. Presumably antiplatelet drugs reduce the chance of thrombus formation leading to complete vascular occlusion as well as embolization. Antiplatelet therapy is also generally recommended in patients with a patent foramen ovale who have had a stroke or TIA.

The following antiplatelet agents are all acceptable first-line options in secondary stroke prevention:

- **Aspirin** prevents the aggregation of platelets through its irreversible action on an enzyme of prostaglandin metabolism (prostaglandin G/H synthase). *Its effects are rapid.* This is first line (and lowest cost) therapy for patients with TIA and ischemic stroke.
- **Clopidogrel** (Plavix ®) also irreversibly prevents platelet aggregation, but does so by action on the cyclic-AMP pathway. *It takes up to 5 days to become maximally effective.*
- **Aspirin-Extended Release Dipyridamole** (Aggrenox ®) is a combination of aspirin with another platelet aggregation inhibitor (dipyridamole, a phosphodiesterase inhibitor).

ANTICOAGULATION THERAPY is often recommended if a patient has atrial fibrillation (or other cardiogenic sources of thromboemboli) The traditional mainstay of therapy has been **warfarin (Coumadin ®)**. This is an anticoagulant that opposes the formation of fibrin by inhibiting the synthesis of vitamin K dependent clotting factors. It therefore is particularly effective in preventing the extension of large, well-formed cardiac thrombi, which tend to contain a *major component of fibrin with entrapped red blood cells as well as platelets.*

Three of the major conditions leading to thrombus formation in the heart are:

- **Atrial fibrillation** in which asynchronous contraction of the muscle of the left atrium results in failure to empty the chamber and stagnation of blood leading to thrombus formation within the atrium. *At least 15% of ischemic strokes are caused by atrial fibrillation.*
- **Valve abnormalities or prosthetic heart valves**, which are thrombogenic.
- **Abnormally reduced motion of the heart wall**, which may occur after a myocardial infarction or other damage to the heart muscle that decreases its ability to empty the ventricles with each cardiac cycle. Blood becomes stagnant, and thrombus tends to form. Recall that emboli from the left ventricle can travel anywhere in the body, including the brain; however emboli from the right ventricle travel to the lungs unless there is an abnormal right-left shunt in the heart.

In each of these conditions, controlled clinical trials have shown that short-term or long-term treatment with **warfarin** reduces the risk of cardioembolic stroke. Patients on warfarin therapy must be regularly monitored by tests of prothrombin time (a specific coagulation test). Additionally, warfarin can have dangerous side effects and interactions. Because of the risk of hemorrhagic side effects, warfarin is contraindicated in people with bleeding disorders or a history of gastrointestinal bleeding, in people who are at risk for falls (unsteady walking, alcoholic, very elderly), and in people who are unreliable at taking their medications. These individuals are often given aspirin

therapy as an alternative. Aspirin has considerably less efficacy for prevention of cardioembolic stroke than warfarin, because aspirin alters only platelet function and does not affect the humoral clotting system.

Both initiation and management of warfarin therapy are often difficult for physician and patient alike. For this reason, there is a lot of interest in new alternative oral anticoagulant strategies that do not require monitoring: **dabigatran** (a direct thrombin inhibitor) and two direct factor Xa inhibitors (**apixaban** and **ribaroxaban**). Clinical data are still limited, but initial results have shown that all three reduce stroke risk in patients with atrial fibrillation similar to warfarin. These new agents may replace warfarin for many patients, but at present there remain some concerns about a possibly higher risk of systemic bleeding.

SURGICAL OR ENDOVASCULAR THERAPY to improve cerebral blood flow may be recommended if the patient's extracranial internal carotid artery is narrowed by atherosclerosis,

- **Carotid endarterectomy** involves opening the artery and scooping out the accumulated atherosclerotic material, along with any thrombus that has formed. This procedure has demonstrated benefits that must be weighed against its risks, including the chance of a heart attack or stroke that may be fatal. Carotid endarterectomy has been shown to be effective in reducing risk of initial or recurrent stroke *if there is symptomatic high-grade carotid stenosis (70-99%), and if total surgical complication risk for the patient is <6%*. Carotid endarterectomy provides a modest benefit in symptomatic patients with moderate stenosis.
- **Endovascular therapy** Angioplasty with or without stenting is a relatively newer procedure for improving flow in the extracranial carotid artery and in some intracranial vessels that are not accessible surgically. In angioplasty, a catheter is used to position a balloon inside the artery. The balloon is then inflated to enlarge the arterial lumen and restore more normal blood flow. In stenting, the artery is held open by a permanent support after the angioplasty is done. One recently completed randomized trial compared carotid endarterectomy with stenting and found no difference in the primary end point of stroke, MI, or death. However in individuals over age 70, carotid endarterectomy was associated with fewer strokes -- and a somewhat enhanced quality of life.

Surgery in the vertebral-basilar system is relatively less common.

How are things different if the stroke is Hemorrhagic?

Many hemorrhagic strokes initially produce severe or unusual headache and nausea or vomiting, with or without loss of consciousness. Although this presentation increases the clinical suspicion of a hemorrhage, a non-contrast head CT scan is key to confirming the diagnosis. The CT scan not only differentiates hemorrhagic from ischemic stroke in the first 24 hours, it also provides additional critical information about the size and location of hemorrhage, and may sometimes reveal structural abnormalities like aneurysms, arteriovenous malformations, or tumor causing the hemorrhage.

In the case of **intraparenchymal hemorrhage**, there is no clinically-proven, specific medical or surgical therapy, and general medical management is similar to that for patients with ischemic infarction except for relatively more aggressive treatment of hypertension. In addition, any clotting disorders must be corrected. Brain swelling or mass effect of the hemorrhage blocking the flow of CSF, or compressing the brainstem or other structures may require surgical intervention. Evacuation of hematomas above the tentorium does not appear to improve the outcome. However evacuation of large cerebellar hemorrhages to relieve pressure on the brainstem can provide significant benefit.

At present, the prognosis for patients with large or medium size clots is usually grave. However patients with smaller hemorrhages can experience a slow but remarkable return of function. Apparently a small hemorrhage can sometimes push aside brain tissue and disable it temporarily without destroying it. As the clot is slowly reabsorbed, neural function returns.

Prevention: Although there is no conclusive evidence, most stroke experts believe that the treatment of hypertension is probably the most effective means of preventing the majority of intraparenchymal hemorrhages. Reducing excessive alcohol consumption including binge drinking and the use of drugs like cocaine and amphetamines is also important. In addition, careful control of anticoagulation levels in patients receiving warfarin and careful selection of patients for fibrinolytic therapy (whether for acute MI or stroke) should decrease the rate of intraparenchymal hemorrhage.

In the case of nontraumatic **subarachnoid hemorrhage** due to a ruptured saccular aneurysm, an early CT scan will usually detect blood locally or diffusely in the subarachnoid spaces or extending into the ventricular system. In a number of cases, subarachnoid hemorrhage is rapidly fatal in a matter of a few hours. The hemorrhage increases intracranial pressure to a level that approaches arterial pressure, causing a sudden drop in cerebral blood flow and leading to loss of consciousness, coma, and death. If the patient survives the initial period, there is continued danger of rebleeding. Cerebral vasospasm (constriction of cerebral arteries in response to presence of blood in the subarachnoid space), may diminish blood flow to parts of the brain causing an ischemic stroke. Currently most aneurysms are treated by inserting tiny thrombogenic metal coils into the aneurysm using an endovascular (via an angiography catheter) approach. Surgery to occlude the neck of a balloon-shaped aneurysm with a metallic clip is now a far less common approach. Repair is usually undertaken as soon as possible because untreated, ruptured aneurysms will often rebleed.

Prevention: Most aneurysms reflect developmental abnormalities. However their rupture may be associated with smoking or hypertension. If an unruptured aneurysm is detected, it is often recommended that it be repaired although the decision to repair should be individualized depending on the size and location of aneurysm. However, routine screening of at-risk individuals (positive family history or disorders associated with high risk of aneurysms) is not currently recommended.

Stroke Rehabilitation

Rehabilitation of stroke patients begins in the acute care hospital. Patients with mild strokes whose condition is stabilized may leave the hospital for home in less than a week, and may receive outpatient or home physical and occupational therapy. Other patients may be sent to a rehabilitation facility where more extensive and comprehensive care involving physicians, nursing, and therapists is available.

Recovery from an ischemic stroke may begin in a few days although it may be delayed and slow in some patients. Early recovery most likely results from restoration of function in uninfarcted brain. Physical therapy may include constraint-induced movement therapy in patients with arm weakness (immobilizing their *unaffected* side to force the use of the affected side, and requiring use of the affected arm repetitively and intensely for several weeks). This novel therapeutic approach can sometimes improve the functional use of the affected arm to carry out activities of daily living. Over time, apparently other brain areas can take on some of the functions previously carried out by the infarcted regions (neural plasticity). Patients may also “work around” their disabilities by figuring out different ways of doing things.

In a hemorrhagic stroke, brain tissue surrounding the hemorrhage is displaced and compressed but not necessarily infarcted. Therefore in a patient who survives a hemorrhagic stroke, reabsorption of the hematoma is often associated with a return of function in the adjacent tissue – and a remarkable decrease in the patient’s deficits.