



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

Objectives for Module 6

Knowledge

- List 6 recommendations that you could make to help patients reduce their risk of having a first stroke.
- Describe specific measures that can reduce stroke risk after a TIA or initial stroke when there is (1) an identified source of cardiac emboli or (2) carotid stenosis.

Clinical Applications and Reasoning

- Explain why determining whether a stroke is ischemic or hemorrhagic is a critical step in early therapeutic decision-making.
- Explain why only a small percentage of stroke patients are eligible for thrombolytic therapy.

Clinical Applications to Patient Education

- Define 4 points to make in describing the warning signs of stroke to a 70 year-old patient with cardiac disease and medically-treated hypertension and his 65 year-old diabetic wife.
- 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)

LIFESTYLE-RELATED FACTORS	Recommendations
Cigarette Smoking	Counseling to help patient stop smoking; smoking cessation programs; nicotine replacement
Physical Activity	Exercise program providing at least 30 min. of activity most days of week; modifications geared toward medical and physical condition of patient
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’)

MEDICAL CONDITIONS	Therapeutic Goal	Measures
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 <140/90 mm Hg (<120/80 mm Hg desirable)
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 agent
Atrial Fibrillation	Restore normal rhythm Prevent clot formation in left atrium	Cardioversion, ablation, or antiarrhythmic drug therapy Oral anticoagulants (preferred) or antiplatelet agent
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
Dyslipidemia	Reduce or prevent atherosclerotic plaque formation	Diet limiting fats, increased physical activity, possible use of a statin or other agent
Carotid Artery Stenosis (asymptomatic)	Prevent thrombus formation on existing atherosclerotic plaque	Antiplatelet agents
	Improve blood flow by increasing size of lumen	Endarterectomy or stenting; possible plaque reduction by diet or statins

Additional Measures to Change the Risk of Stroke after a Patient has had a first TIA or Stroke (Secondary Prevention)

A major goal of evaluating patients who have had a TIA or mild ischemic stroke is to determine the *specific cause* of the cerebral ischemia, so that the most appropriate therapy can be initiated to prevent recurrence. As a reminder, the most common causes of cerebral ischemia in patients over the age of 50 are:

- Embolus
 - Artery → artery
 - Heart → intracranial vessel (cardiogenic emboli)
- In situ thrombus (usually formed on ruptured plaque)
- Small vessel disease, usually secondary to hypertension or diabetes

Patients with TIAs or mild strokes should be evaluated very promptly. They have a heightened risk of stroke (or a second stroke), especially in the next 48 hours and in the next 90 days. Depending on what the diagnostic evaluation indicates about the most likely cause of the TIA or first stroke, one of the following specific medical and/or surgical therapies may be recommended in addition to general measures to reduce stroke risk.

Patients with atherosclerotic plaque in extracranial or intracranial cerebral arteries have an increased risk for arterial thrombus formation. They are frequently treated with platelet aggregation inhibitors. These drugs prevent the sticking of platelets to each other, and therefore limit the growth of platelet-rich, relatively fibrin-poor thrombus on the surface of a damaged atherosclerotic plaque.

Patients with **carotid stenosis**, either symptomatic (causing TIA or stroke) or asymptomatic, 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 anti-platelet drugs reduce the chance of thrombus formation leading to complete vascular occlusion as well as embolization. There are several accepted options:

- 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 a few days to become maximally effective.
- Aspirin-Extended Release Dipyridamole (Aggrenox ®) is a combination of aspirin with another platelet aggregation inhibitor that appears to have an advantage over aspirin alone in controlled trials.

Antiplatelet agents are also used when atherosclerosis in intracranial arteries has been demonstrated by imaging or is suspected from the medical history.

Statin therapy with intensive lipid-lowering effects is now recommended for patients with atherosclerotic ischemic stroke or TIA and without known coronary heart disease to reduce the risk of recurrent stroke and cardiovascular disease.

Patients with cardiogenic sources of emboli are often treated with 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 and formation of thrombus within the atrium.
- **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. This is particularly a problem if the left ventricle is affected. **Question:** Why?

Answer: 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 situations, controlled clinical trials have shown that 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). 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, alcoholics, 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.

Surgical or Endovascular Therapies may be recommended to improve cerebral blood flow if the extracranial internal carotid artery is narrowed by atherosclerosis.

Carotid endarterectomy This 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 carotid stenosis >70% and, and if total surgical risk for the patient is <6%*. Carotid endarterectomy has also been shown to be better than medical therapy for *asymptomatic carotid stenosis >60% in men, if total surgical risk is <3%*.

Endovascular therapy Angioplasty with or without stenting is a relatively new 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, and there are no randomized controlled trials comparing these procedures with medical therapies. However several small case series suggest that either surgery or angioplasty (with or without stenting) may be beneficial in situations where medical therapy does not relieve symptoms.

Roles of Patient Education in Primary and Secondary Prevention

AREA OF PATIENT EDUCATION	Recommendations for Patients and Families
Understanding that strokes are not inevitable and that many can be prevented	Explain that there are now diagnostic and treatment strategies that can help (1) correct a problem before a full-blown stroke occurs or (2) if a stroke does occur, may restore circulation “before the brain dies”
Reducing Stroke risk by addressing medical or lifestyle factors	Inform and motivate patient to reduce risks
Recognizing the Warning Signs of a TIA or Stroke	Discuss the major stroke warning signs Provide appropriate patient education material
Knowing to seek help quickly if Warning Signs occur	Advise patient or family members to call 911 <i>immediately</i> and tell dispatcher about stroke warning signs. Transport by EMS is preferable to driving the patient to the hospital in most situations. <i>They should not delay in order to consult relatives or to discuss the situation with their physician</i>
Understanding that sometimes stroke warning signs may only last a few minutes and then go away, but that they still need to get immediate medical help	Explain that a TIA (or mini-stroke) is an extremely important warning that the brain is ready to have a stroke – and that treatments can help to lower the risk of having a stroke
Understanding that aggressive follow-up health care can help to prevent future TIA and stroke	Explain what has happened, and how risk modification and medical or surgical treatment can be effective in reducing the chances of a second TIA or stroke

As a reminder, these are the 5 Warning Signs of Stroke as they are described in patient education literature provided by the American Stroke Association:

- Sudden numbness or weakness of face, arm or leg, especially on one side of the body
- Sudden confusion, trouble speaking or understanding
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking, dizziness, loss of balance or coordination
- Sudden, severe headache with no known cause

What should happen when a patient with an acute stroke comes to the ER?

The first step in acute stroke therapy is a precise diagnosis. Therefore the first questions that physicians ask are:

Is this a stroke? If yes, then:

- where is the injured brain tissue located and how much is affected?
- what artery has been affected?
- what is the likely mechanism of the stroke?
- are there any specific treatments that can reverse the effects of the stroke?

The initial diagnosis is usually based on history and physical examination, supported by CT or MRI imaging technology. All this must be done very quickly.

Therapy 0-3 hours after stroke onset

The first goals in this early phase are to provide medical support for the patient and determine whether the stroke is ischemic or hemorrhagic. Physicians consider history, physical examination, and whether the neurologic signs conform to a vascular pattern. A CT scan is usually the quickest way to rule out hemorrhage. Recall that a CT study performed in these first hours does not visualize ischemic lesions, even ones that later produce large infarcts.

Once it is confirmed that the stroke is ischemic, the second goal is to figure out the cause as well as the location of the blockage. Various blood tests and an EKG are done. To establish whether it involves an extracranial or intracranial vessel, Doppler ultrasound or CT angiography can supplement the history and physical exam. During this very early phase MRI is not commonly used except in major stroke centers. However, comparison of diffusion and perfusion-weighted MRI images is now playing a much bigger role in early stroke treatment because it can provide critical information about brain regions that may be non-functional but are potentially salvageable (the stroke penumbra). This information is valuable in selecting patients for thrombolytic therapy.

The possibility of administering **thrombolytic therapy** may be considered. Intravenous recombinant tissue plasminogen activator (r-TPA) is currently the only FDA-approved thrombolytic drug. It opens blocked arteries by dissolving the strands of fibrin that hold together the red blood cells or platelets in an embolus or thrombus.

The results of a large NINDS stroke study show that intravenous r-TPA significantly improves functional outcomes at 3 and 12 months after stroke *when it is given within 3 hours of onset of stroke in carefully selected patients.* The dreaded complication – severe or even fatal intracerebral hemorrhage – tended to occur more often when the drug was given in the last 90 minutes of the 3-hour window than when it was administered in the first 90 minutes. *The narrow time window for reversing ischemia with r-TPA is one of the reasons why teaching patients the warning signs of stroke and how to respond is so important – many wait for the symptoms to resolve and miss the opportunity.*

Patient selection for r-TPA is critical, since it does not improve the outcomes of patients with very large strokes, for example blockage of the MCA stem that reduced flow in both the deep penetrating

and cortical branches. It also is not beneficial in small lacunar strokes, which is why it is important to ascertain quickly just which arteries are blocked. In brief, strict criteria for r-TPA treatment exclude patients with uncontrollable hypertension, intracerebral hemorrhage, bleeding disorders, recent surgery or stroke, or signs of a large infarction. Because of the possibility of major bleeding, both the risks and the potential benefits of r-TPA should be discussed with the patient and/or family, and informed consent must be obtained prior to administration. Unfortunately, the 3-hour window means that these difficult decisions must be made rapidly. A recent European stroke trial suggests that r-TPA given at 3 to 4.5 hours to patients meeting specific criteria may also improve outcomes.

Currently, intravenous r-TPA will benefit only a small percentage of stroke patients who meet criteria, and arrive quickly enough to be eligible. Under the best of circumstances if patients call 911 immediately after symptom onset, perhaps 25% would receive thrombolytic treatment. However, future developments in thrombolytic or neuroprotective therapy (including interventional neuroradiology) may provide more powerful or universally helpful alternatives.

Therapy after the first 3-4 hours

If a patient presents more than three 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?

Some of the major issues for physicians in this phase include:

- Prevention of direct complications of stroke, such as brain swelling and potential herniations
- Prevention of complications of 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)
- Control of excessive hypertension, hyperglycemia, and fever

At this time, physicians provide supportive medical care, prevent and treat any acute complications, confirm the clinical diagnosis, determine exactly what caused arterial obstruction, and assess the extent of vascular disease. Additional imaging techniques including functional MRI, conventional angiography, MR and CT angiography, and echocardiography may be employed. Intravenous r-TPA therapy may not be an option at this point because of the increased risk that vessels in the ischemic region of brain will hemorrhage if their blood flow is restored.

Secondary stroke prevention may be initiated following decisions about whether antiplatelet agents, anticoagulants, or surgical intervention may be appropriate. Physical, occupational, and speech therapy consultations assist in decision-making regarding patient suitability for out patient rehabilitation.

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 therapy. Other patients may be sent to a rehabilitation facility or nursing home where more extensive physician, nursing, and therapist management is available. Recovery from an ischemic stroke may begin in a few days. Early recovery results from restoration of function in uninfarcted brain. However patients continue to improve for at least 6 months, and often even longer. At these times long after injury, functional recovery most often involves learning new ways to accomplish tasks (neural plasticity).

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 clinical suspicion of a hemorrhage, a CT scan is a key element of the initial 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 reveal structural abnormalities like aneurysms, arteriovenous malformations, or tumor that were responsible.

In the case of **intracerebral hemorrhage**, there is no clinically proven specific medical or surgical therapy, and general medical management is similar to that for patients with ischemic infarction. 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. Large cerebellar hemorrhages are evacuated to relieve pressure on the brainstem.

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 blood is slowly reabsorbed, 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 most intracerebral hemorrhages. It is also clear that careful control of anticoagulation levels in patients receiving warfarin and careful selection of patients for thrombolytic therapy (whether for acute MI or stroke) should also decrease the rate of intracerebral hemorrhage.

In the case of **subarachnoid hemorrhage** due to a ruptured saccular aneurysm, an early CT scan will usually detect blood locally or diffusely in the subarachnoid spaces or within the ventricular system. Cerebral angiography using a catheter to place contrast medium directly in the large vessel of interest is currently the standard for diagnosing ruptured cerebral aneurysms as the cause of subarachnoid hemorrhage.

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 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 and ischemic stroke due to cerebral vasospasm. (Cerebral arteries may respond to blood in the subarachnoid space by constricting, thus diminishing blood flow to other parts of the brain). Surgical repair is the treatment of choice for most aneurysms. It may involve occluding the neck of a balloon-shaped aneurysm with a metallic clip, wrapping the outside of the aneurysm, or inserting tiny thrombogenic metal coils into the aneurysm through a catheter. Surgery is usually performed as soon as possible because untreated, ruptured aneurysms have a high risk of rebleeding.

Prevention: Most aneurysms reflect developmental abnormalities. However their rupture is associated with smoking or hypertension. If an unruptured aneurysm is detected, it is often recommended that it be treated surgically. However at this time, screening of at-risk individuals is of unproven value.