Prevention, Pathophysiology and Treatment of Stroke
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Goals/Objectives
1. Describe the major risk factors for stroke and the rationale for primary prevention.
2. Differentiate between occlusive/ischemic stroke, hemorrhagic stroke, transient ischemic attack (TIA).
3. Describe the cellular mechanism of toxicity that occurs in ischemic and hemorrhagic stroke, including the role of various electrolytes and other cerebral mediators.
4. Differentiate in the available treatment options given the diagnosis of occlusive/ischemic or hemorrhagic stroke.
5. Discuss the use and limitations of thrombolytic therapy in the setting of acute stroke.
6. Discuss secondary prevention options in patients with a CVA/TIA history.
7. Understand the mechanism of action and rationale for aspirin, ticlopidine and clopidogrel in stroke prevention.
8. Become familiar with the controversy that exists regarding the proper dose of aspirin for stroke prophylaxis.

References
I. DEFINITIONS

CARDIOVASCULAR ACCIDENT/STROKE
A broad term used to describe the syndrome in which acute vascular and brain tissue changes manifests as one or more focal neurologic deficits that last more than 24 hours. These deficits result from either inadequate blood flow or hemorrhage. Generally a nonspecific term that may be used to describe a number of neurologic events, including:

Transient Ischemic Attack (TIA)
Brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour and without evidence of infarction. Resolves completely within 24 hours of onset. TIAs are important determinant of stroke, with 90-day risks of stroke reported as high as 10.5% and the greatest stroke risk in the first week. Pathophysiology involves the atherosclerotic process, thrombus formation, and low cerebral blood flow.

Occlusive/ischemic cerebrovascular disease
Infarction of brain tissue caused by occlusion of a cerebral blood vessel, which can be classified as either thrombotic or thromboembolic in nature causing permanent damage. The occlusion leads to ischemia in the surrounding cerebral tissue. Approximately 85% of strokes are ischemic. The exact clinical presentation depends on the location of the artery that is affected by diminished blood flow. May be stable (not changing), improving (return of neurologic function over days or weeks) or progressive (status continues to deteriorate).

Thrombotic stroke – Also referred to as large artery/atherosclerotic stroke. Usually occurs when an artery to the brain is blocked by an occlusion that forms over time as the result of atherosclerosis.

Embolic stroke – Usually caused by a dislodged blood clot (embolus) that has traveled through the blood vessels until it becomes wedged in an artery. Most commonly as a result of atrial fibrillation, where the irregular pumping causes pooled blood to form clots, which then travel to the brain as emboli. Emboli can also originate as clots at the site of artificial heart valves/valve disorders, after a heart attack or with heart failure. Emboli more rarely form from fat particles, tumors or air bubbles.

Lacunar disease of penetrating arteries – This is a series of tiny ischemic strokes that cause clumsiness, weakness, and emotional variability. Subtype of thrombotic stroke

Hemorrhagic cerebrovascular disease
Acute bleeding in the brain parenchyma (intracerebral hemorrhage = ICH) or subarachnoid space, usually due to trauma, arteriovenous malformations, or other hematomas, which may cause focal symptoms. Approximately 15% of strokes are hemorrhagic in nature. There are no direct pharmacotherapeutic agents that are effective for treating SAH; only the complications are treated. Most commonly caused by hypertension.

Most frequent sites of arterial and cardiac abnormalities causing ischemic stroke (from Ref 4):
II. RISK FACTORS ASSOCIATED WITH ISCHEMIC STROKE

Most of the data available concerning the risk factors for ischemic stroke is from the Framingham Study, which included 36 years of follow-up of over 5000 males and females age 30-62 years old.

<table>
<thead>
<tr>
<th>Non-Modifiable Risk Factors</th>
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<tr>
<td>• Old age (doubles each successive decade of life after age 45)</td>
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<td>• Male sex (30% higher incidence in men than women)</td>
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<td>• Low birth weight (less than 5 lbs)</td>
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<td>• Race (African American, Asian, Hispanics &gt; whites)</td>
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<td>• Genetic factors</td>
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<td>• Previous TIA or stroke (40% stroke survivors have a subsequent event within 5 yrs)</td>
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<table>
<thead>
<tr>
<th>Modifiable Risk Factors</th>
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<tr>
<td>• Hypertension (systolic and diastolic)</td>
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<tr>
<td>• Atrial fibrillation/flutter</td>
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<td>• Asymptomatic carotid stenosis</td>
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<td>• Left ventricular hypertrophy</td>
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<td>• Valvular heart disease</td>
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<tr>
<td>• Hormone replacement therapy</td>
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<tr>
<td>• Cigarette smoking</td>
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<tr>
<td>• Drug abuse (cocaine, amphetamines, anabolic steroids, caffeine)</td>
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<tr>
<td>• Diabetes mellitus</td>
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<tr>
<td>• Hyperlipidemia</td>
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<tr>
<td>• Coagulopathies/hypercoaguable states</td>
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<tr>
<td>• Heavy alcohol use (&gt; 5 drinks/day)</td>
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<tr>
<td>• Obesity/central body fat distribution</td>
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<tr>
<td>• Oral contraceptive use (esp if &gt;50 mcg estrogen)</td>
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<td>• Physical activity</td>
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<td>• Diet and nutrition</td>
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III. PRIMARY STROKE PREVENTION/RISK FACTOR MANAGEMENT

A. Hypertension

The incidence of stroke increases proportionally to both systolic and diastolic blood pressure. Estimated that approximately 70% of strokes occur due to uncontrolled hypertension. The relationship is direct, continuous and independent of other risk factors. Elevated systolic blood pressure is a more important CVD risk factor than diastolic BP if patients greater than 50 years old. Therefore, the primary goal should be in achieving the systolic BP goal. (JAMA 2003: 289; 2560-2572)

Many large, well-conducted studies have shown that the treatment of hypertension reduces the risk of stroke, and also decreases the associated morbidity and mortality. Reduction of blood pressure should follow the guidelines published in JNC VII.

Current evidence does not readily support any particular agent or class of agents to treat hypertension. Most important is the ability to maintain blood pressure <140/90 mmHg. New evidence is mounting that possibly supports the use of CCB or ARB for treating hypertension:

• ASCOT-BPLA (Lancet 2005) allocated over 19,000 pts to either an amlodipine or atenolol based BP regimen. The amlodipine arm was associated with lower rates of stroke, coronary events and new onset DM. It is unclear whether this is due to the agent itself, or merely the fact that the amlodipine group had lower BP.
• SCOPE study evaluated 4964 patients aged 70-89 yrs old to treatment with candesartan or placebo. Open label antihypertensive therapy (usually thiazide diuretics) was added as needed to control the BP. Patients in the candesartan group had a significant risk reduction of nonfatal strokes and no significant reduction of all strokes. This was achieved with a lower mean BP in the active treatment group. Conclusion at this time is that HTN in the very elderly should be treated to reduce the risk of nonfatal stroke.
B. Carotid Endarterectomy
This is a surgical procedure to clean out and open up the narrowed carotid artery. Used to prevent large artery strokes caused by blockage of the internal carotid artery. The evidence supports this procedure for severe (70-99%) symptomatic stenosis. It is moderately useful for symptomatic patients with 50-69% stenosis and not indicated for symptomatic patients with <50% stenosis. For asymptomatic patients with 60-99% stenosis, individual decisions must be made because the benefit/risk ratio is smaller than with symptomatic patients. Endarterectomy can reduce the future stroke rate if the perioperative stroke/death rate is kept low (< 3%).

C. Atrial fibrillation

AFASAK - Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study (Lancet 1989;1:175-179)
A randomized, controlled trial that compared warfarin (INR 2.8-4.2) or aspirin 75 mg daily versus placebo in patients with nonrheumatic atrial fibrillation. A total of 1007 patients were followed for at least 2 years for the primary endpoint of ischemic stroke, transient cerebral ischemia or systemic embolism or the secondary endpoint of death. A statistically significantly lower rate (2.7 vs 6.2) of thromboembolic complication was seen in the warfarin group (5 patients) than either the aspirin (20) or placebo (21) group. There was no difference between aspirin and placebo. Study was terminated early.

BAATAF - Boston Area Anticoagulation Trial for Atrial Fibrillation (NEJM 1990; 323: 1505-1511)
An unblinded, randomized controlled trial of low-dose warfarin (PT = 1.2-1.5 x control, which corresponded to an INR of 1.5-2.7) compared to a group of patients who could opt for aspirin therapy (47% took aspirin). The 212 patients who received warfarin and 208 controls were followed for an average of 2 years. Two strokes occurred in the warfarin group and 13 in the control group (p = 0.0022); the death rate was 2.25%/year in the warfarin group compared to 5.97% in the control group (p = 0.005). Although not specifically studied, aspirin did not appear to have any protective effect in the control patients who took it.

SPAF - Stroke Prevention in Atrial Fibrillation (Circulation 1991; 84: 527-39)
Study evaluated the occurrence of ischemic stroke or systemic embolism in patients with atrial fibrillation. Patients were divided in 2 groups, categorized as warfarin (INR 2.0-4.5) eligible or noneligible. Did not directly compare warfarin and aspirin, only compared each to the placebo group. Study ended early because found that beneficial effects seen in both the warfarin and aspirin treated groups. Concluded that patients who can tolerate ASA or warfarin should receive prophylactic antithrombotic therapy to decrease their stroke risk.

SPINAF - Stroke Prevention in Non-Valvular Atrial Fibrillation (Circulation 1991; 84: 527-39)
Primary prevention trial of 525 patients with chronic nonvalvular AFib that compared warfarin (INR 1.4-2.8) to placebo. Primary endpoint was cerebral infarction. Concluded that low intensity warfarin prevented infarction in these patients. The incidence of infarction was 0.9% per year compared to 4.3% in the placebo group. Study also terminated early secondary to beneficial effects of warfarin in preventing cerebral infarction associated with AFib.

CAFA - Canadian Atrial Fibrillation Anticoagulation Study (J Am Coll Cardiol 1991; 18: 349-55)
Randomized, double blind placebo controlled trial, which evaluated 383 patients in a primary prevention trial comparing warfarin (INR 2-3) and placebo. A lower rate (44% risk reduction) of thromboembolic complication (stroke or systemic embolism) was seen in the warfarin treated group. Study terminated early due to the results of AFASAK and SPAF. Interim results were consistent with the results of other studies.

SPAF II - (Lancet 1994; 343: 687-91)
Randomized, multicenter trial comparing warfarin (PT 1.3-1.8 x control; INR 2.0-4.5) with aspirin (325 mg/day) for patients with atrial fibrillation. Patients were stratified into two age groups, those 75 years old and less and those greater than 75 years. Primary endpoints were ischemic stroke and systemic embolism. In those less than 75, the event rate was 1.3% vs 1.9% (33% risk reduction), warfarin vs aspirin respectively. In those older than 75, the event rate was 3.6% in warfarin treated patients and 4.8% in aspirin treated patients.
(27% risk reduction). The authors concluded that the younger subset of patients had a low stroke risk on aspirin and that the benefits of warfarin did not outweigh the risk, expense and inconvenience of lifelong anticoagulation. Therefore, they only **recommended warfarin for patients > 75 years old.**

**SPAF III** - (Lancet 1996; 348: 633-38)
This open labeled study compared low-intensity, fixed dose warfarin (INR 1.2-1.5, mean 1.3) and aspirin (325 mg/day) to adjusted dose warfarin (INR 2-3, mean 2.4) in 1044 high-risk patients with atrial fibrillation and at least one other thromboembolic risk factor (CHF, SBP > 160, female >75 yrs or history of thromboembolism). This study was stopped prematurely after a mean follow up period of 1.1 years when the rate of ischemic stroke and systemic embolism in patients given combination therapy was significantly higher than those given adjusted dose warfarin (7.9% vs 1.9%, respectively). Established the need for an INR of 2-3 with warfarin therapy.

**Current Recommendations for Atrial Fibrillation (CHEST 2004; 126: 429S-456S):**

<table>
<thead>
<tr>
<th>Low stroke risk</th>
<th>Intermediate stroke risk</th>
<th>High stroke risk</th>
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<tbody>
<tr>
<td>Less than 65 yr old; no risk factors*</td>
<td>Age 65-75 yrs; no risk factors*</td>
<td>Risk factors* or age &gt; 75 yrs</td>
</tr>
<tr>
<td>Aspirin 325 mg/day</td>
<td>Aspirin 325 mg/day or warfarin INR 2-3</td>
<td>Warfarin INR 2-3</td>
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</table>

*Risk factors include:* prior ischemic stroke, TIA or systemic embolism, age > 75 years, mod-severe left ventricular dysfunction and/or CHF, history of hypertension, diabetes

**D. Hyperlipidemia**
A clear relationship between hyperlipidemia and the risk of ischemic stroke has yet to be definitively identified. However, many coronary artery disease prevention trials and meta-analyses demonstrate and association of statin use with a reduction in stroke risk.

Even though the benefit of statins in stroke prevention in patients with heart disease is supported by several meta-analyses, it is uncertain by what mechanism that statins provide benefit. Some reduction may be due to lipoprotein abnormalities, but may also act via mechanisms unrelated to lipid lowering properties. These might include improved endothelial function, plaque stabilization, and anti-thrombotic, anti-inflammatory, and neuroprotective properties. Management of patients with elevated cholesterol according to the NCEP guidelines should be practiced.

A recently published, well designed, meta analysis of 121,000 patients (Am J Med 2008: 121; 24-33) sought to determine if statins have a role in primary and secondary stroke prevention, and if the benefits are dose dependent.

- Included randomized trials of any statin and any duration
- Studies had to compare statin to placebo or no treatment
- Studies had to report on all cause mortality, all stroke incidence, fatal strokes, hemorrhagic or ischemic strokes
- Studies were excluded if they only included surrogate endpoints, such as LDL levels

**Results**
- Statins play role in preventing all cause mortality, with absolute LDL change being the only significant predictor of effect size. For every unit increase in LDL, mortality risk increase 0.3%.
- There is a relative risk reduction on all stroke types, however significance was not demonstrated with the risk of hemorrhagic stroke incidence.
- Statins provide protection for non-hemorrhagic strokes. It is possible that the pleiotropic effect of statins is more protective in ischemic stroke than LDL reduction alone.
- No difference found between the various statins. Note that no rosuvastatin studies met inclusion criteria.
- Did not examine risk profiles of individual statins.
The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study is a prospective, multi-center, double blind, placebo controlled trial that evaluated the effects of atorvastatin 80 mg/day in patients with stroke or TIA in past 1-6 months with LDL of 100-190 mg/dL, but who have no known CHD. Patients were followed for 5 years. Study evaluates the effect of statin treatment in secondary stroke prevention. Demonstrated a reduction in the overall incidence of stroke and CV events. (NEJM 2006; 355:549-59)

E. Women’s Health Study – ASA for Primary Stroke Prevention in Women (NEJM 2005; 352: 1293-1304)
This study randomized 39,876 asymptomatic women > 45 years of age to receive 100 mg of aspirin on alternate days or placebo. Women were followed for 10 years for the occurrence of a first major vascular event, defined as nonfatal MI, nonfatal stroke or cardiovascular death. Study was negative for the primary endpoint (non-significant 9% reduction), but there was an associated overall reduction in stroke (17% reduction), including a reduction in ischemic stroke. There was an increase in hemorrhagic strokes and GI bleeds requiring transfusions. Subgroup analyses showed a reduction in stroke for women with a history of hypertension*, hyperlipidemia*, diabetes* or 10 yr cardiovascular risk > 10%*. Also, the risk of major cardiovascular events was reduced for patients >65 at study entry. This study supports the use of aspirin in women over the age 65 and who are at increased risk of atherothrombotic events due to these risk factors*.

IV. PATHOGENESIS

A. Thrombi formation – similar to the process of cardiac atherosclerosis
Tissue injury causes the release of ADP, thrombin, and other substances that stimulate platelet adhesion to the exposed collagen of the vessel wall. As the platelets aggregate, phospholipase is activated, which then forms arachidonic acid and ultimately thromboxane A2 (TXA2) and prostacyclin. TXA2 is a potent vasoconstrictor and inducer of platelet aggregation and platelet release. Prostacyclin inhibits platelet aggregation and causes vasodilation. These 2 agents with opposite effects regulate thrombosis formation. The clot can then either embolize or occlude an artery.

B. Autoregulation
Normally the cerebral perfusion pressure is very closely regulated (between 30-70 ml/100 gm per minute) to meet the metabolic demands in different areas of the brain, by changing the cerebral vascular resistance with dilation and constriction (when < 20 ml/100 gm/min). When this autoregulation fails (to less than 12 ml/100 gm/min) and the needs are not met, ischemia occurs. Ischemia involves both vascular and hematologic events that decrease cerebral blood flow such that the normal compensatory mechanisms are ineffective. Initially this regional brain dysfunction is reversible (within 6-8 hours), but if not treated immediately, permanent damage will ensue. This area that suffers reversible damage is referred to as the penumbra. The penumbra receives such a low level of perfusion that neurologic and electrical function is stopped; however the tissue remains viable for a short time (depending on the degree of ischemia). If reperfusion occurs quickly, and the metabolic demands are met, complete neurologic recovery can occur.

C. Cellular injury (The “ischemic cascade”) – occurs when blood flow is reduced, therefore blocking oxygen supply to the brain cells.
The neurons become ischemic and release excitatory amino acids, such as glutamate and N-methyl-d-aspartate (NMDA). These excitatory neurotransmitters excite the nerve cells and when overproduced, can kill them. This causes failure of synaptic transmission, due to rapid and repeated discharge. Also:
- cessation of neurotransmitter synthesis
- release of vasoconstrictors
- intravascular coagulation

When severe ischemia occurs, lactate and hydrogen ions accumulate, contributing to irreversible damage. Other cellular events include:
- ATP depletion
- sodium and potassium depletion
- calcium influx that initiates cell membrane proteolysis
- calcium influx increased reactive metabolites, such as O₂, OH and nitric oxide (oxygen free radicals)
- activation of phospholipase A₂, which hydrolyzes cell membranes
- release of arachidonic acid, which is metabolized to thromboxane A₂, a stimulant of platelet aggregation and vasoconstriction

With these cellular events, ischemic tissue eventually becomes infarcted tissue, which is not salvageable.

Extent of damage dependent on:
- global or focal ischemia
- complete or incomplete (with incomplete causing acidosis secondary to lactate production)
- collateral blood flow (small, penetrating arteries more likely to suffer permanent damage)

D. Clinical presentation of cerebrovascular accident

Regardless of the etiology, the clinical presentation of symptoms in a cerebral ischemic event depends upon:

1. **The location of the vessels**
   - **Lacunar infarcts** – Small cavity infarcts associated with hypertension. May be asymptomatic or most common symptoms are either pure motor or pure sensory deficits.
   - **Middle cerebral artery** – Loss of movement and sensation on contralateral or opposite side of infarction. May be gaze preference to the same side as injury. May be global aphasia if categorical hemisphere (96% left). If representational hemisphere, may be neglect syndrome. Partial occlusion = weakness and partial aphasia.
   - **Posterior cerebral artery** – Memory loss, visual hallucinations, dyslexia, sensory loss, ataxia, altered level of consciousness (LOC)
   - **Anterior cerebral artery** – Weakness and loss of sensation of the contralateral leg and foot
   - **Basilar artery** – Dizziness, double vision, ataxia, hemi-quadriparesis

2. **The presence of collateral circulation** – May gradually develop when there is an alteration in normal blood flow. Most often between major arteries via the Circle Of Willis (internal carotids and vertebral-basilar arteries)

Definitions of most common symptoms
- Sudden weakness, numbness or tingling of the face, arm or leg on one side of the body (hemiparesis, hemiplegia)
- Sudden dimness or loss of vision, particularly in one eye (hemianopia)
- Loss of speech, or trouble talking or understanding speech (aphasia, dysarthria)
- Sudden, severe headaches with no apparent cause
- Unexplained dizziness, unsteadiness or sudden falls, especially with any of the previous symptoms (ataxia)

V. DIAGNOSIS OF STROKE

A. **Brain imaging** – necessary to guide the selection of acute intervention

1. **Computed tomography (CT) scan** – Essential for ruling out hemorrhagic CVA. Should be completed within 25 min of arrival to the emergency department and then interpreted within 20 min of test completion.

2. **Magnetic resonance imaging (MRI) scan** – Recent advances in imaging have enabled the MRI to become an ultra fast imaging method that is able to be used for diagnosis. Images the blood vessels and brain circulation. Can provide additional information as to extent of ischemia and irreversible injury. May help identify patients with previous microhemorrhages who are at increased risk of bleeding secondary to thrombolysis. In future, may be able to distinguish reversible from irreversible
tissue.

**B. Cardiac testing** – to assess cardiac function as cause for embolic phenomena
1. **Electrocardiogram** – To assess cardiac arrhythmias, namely atrial fibrillation.
2. **Cardiac enzymes** – For diagnosis of myocardial infarction.

**C. History and Physical**
1. Neurological deficits: hemiparesis, hemianopia, dysarthria, ataxia, dysphagia, aphasia
   Anatomic localization based on clinical features can help determine the vascular distribution of the ischemic lesion, therefore helping determine the cause of the stroke.

2. Vital signs: heart rhythm, blood pressure, and temperature

3. Stroke severity/prognostic indicator
   - Most common is the National Institutes of Health Stroke Scale (NIHSS):
<table>
<thead>
<tr>
<th>NIH STROKE SCALE ITEM</th>
<th>Scoring Definitions</th>
<th>Score</th>
</tr>
</thead>
</table>
| 1a. LOC | 0=alert and responsive  
1=arousable to minor stimulation  
2=arousable only to painful stimulation  
3=reflex responses or unarousable |       |
| 1b. LOC Questions--Ask pt’s age and month. Must be exact. | 0=Both correct  
1=One correct (or dysarthria, intubated, foreign lang)  
2=Neither correct |       |
| 1c. Commands--open/close eyes, grip and release non-paretic hand, (Other 1-step commands or mimic ok) | 0=Both correct (ok if impaired by weakness)  
1=One correct  
2=Neither correct |       |
| 2. Best Gaze--Horizontal EOM by voluntary or Doll’s. | 0=Normal  
1=partial gaze palsy; abnl gaze in 1 or both eyes  
2= Forced eye deviation or total paresis which cannot be overcome by Doll’s. |       |
| 3. Visual Field--Use visual threat if nec. If monocular, score field of good eye. | 0=No visual loss  
1=Partial hemianopia, quadrantanopia, extinction  
2=Complete hemianopia  
3=Bilateral hemianopia or blindness |       |
| 4. Facial Palsy--If stuporous, check symmetry of grimace to pain. | 0=Normal  
1=minor paralysis, flat NLF, asymmn smile  
2=partial paralysis (lower face=UMN)  
3=complete paralysis (upper & lower face) |       |
| 5. Motor Arm--arms outstretched 90 deg (sitting) or 45 deg (supine) for 10 secs. Encourage best effort. Circle paretic arm in score box | 0=No drift x 10 secs  
1=Drift but doesn’t hit bed  
2=Some antigravity effort, but can’t sustain  
3=No antigravity effort, but even minimal rvt counts  
4=No movement at all  
X=unable to assess due to amputation, fusion, fx, etc. | L or R |
| 6. Motor Leg--raise leg to 30 deg supine x 5 secs. | 0=No drift x 5 secs  
1=Drift but doesn’t hit bed  
2=Some antigravity effort, but can’t sustain  
3=No antigravity effort, but even minimal rvt counts  
4=No movement at all  
X=unable to assess due to amputation, fusion, fx, etc. | L or R |
| 7. Limb Ataxia--check finger-nose-finger ; heel-shin; and score only if out of proportion to paralysis | 0=No ataxia (or aphasic, hemiplegic)  
1=ataxia in upper or lower extremity  
2=ataxia in upper AND lower extremity  
X=unable to assess due to amputation, fusion, fx, etc. | L or R |
| 8. Sensory--Use safety pin. Check grimace or withdrawal if stuporous. Score only stroke-related losses. | 0=Normal  
1=mid-mod unilateral loss but pt aware of touch (or aphasic, confused)  
2=Total loss, pt unaware of touch. Corne, bilateral loss |       |
| 9. Best Language--Describe cookie jar picture, name objects, read sentences. May use repeating, writing, sennegnosis | 0=Normal  
1=mid-mod aphasia (diff but partly comprehensible)  
2=severe aphasia, (almost no info exchanged)  
3=mute, global aphasia, corne. No 1 step commands |       |
| 10. Dysarthria--read list of words | 0=Normal  
1=mid-mod; slurred but intelligible  
2=severe; unintelligible or mute  
X=intubation or mech barrier |       |
| 11. Extinction/Neglect--simultaneously touch patient on both hands, show fingers in both vis fields, ask about deficit, left hand. | 0=Normal, none detected. (vis loss alone)  
1=Neglects or extinguishes to double simultaneous stimulation in any modality (vis, aud, sens, spatial, body parts)  
2=profound neglect in more than one modality |       |

NIHSS < 10 = 60-70% have favorable outcome at 1 year  
NIHSS > 20 = 4-16% have favorable outcome at 1 year + increased risk for ICH
C. Blood Testing
   1. Electrolytes (including BUN/SCr and glucose)
   2. Complete blood count
   3. Blood coagulation studies
   4. Hepatic function tests
   5. Toxicology screen

D. Rule out other causes:
   - Migraine headache
   - Seizures
   - Syncope
   - Transient global ischemia
   - Peripheral nerve disorders
   - Intracranial hemorrhage
   - Other intracranial masses (tumor, abscess)
   - Neuroses (anxiety or panic disorder)
   - Hypoglycemia

VI. Risk Stratification for Stroke after TIA – Statistically, 4-20% of patients who have a TIA will have a stroke within the next 90 days – about half within the next 48 hours. (Lancet 2007: 369; 283-92)

A. **ABCD² Score** – Used to identify TIA patients who are at high risk for stroke within several days.
   Seven point score based on:
   - Age (≥60 years = 1 point)
   - Blood pressure at presentation (≥140/90 mmHg = 1 point)
   - Clinical features (unilateral weakness = 2 points, speech disturbance without weakness = 1 point)
   - Duration of symptoms (≥60 minutes = 2 points, 10-59 minutes = 1 point)
   - Diabetes (1 point)
   Risk for stroke within 2 days of initial presentation: Score 0-3=1%, Score 4-5=4.1%, Score 6-7=8.1%.
   *Seven day and 90 day stroke risk also increased with higher scores.

VII. THERAPY OF ACUTE STROKE
It should be noted that appropriate medical care is often limited by patients’ knowledge and recognition of stroke symptoms. Patients who are at increased risk of stroke should be educated regarding the symptoms and instructed to seek emergent medical attention if these should occur.

A. Acute Supportive Care and Treatment
   1. Airway, Ventilatory Support, and Supplemental Oxygen
   2. Fever
   3. Cardiac Rhythm
   4. Arterial hypertension/hypotension
   5. Hypo/hyperglycemia- avoid glucose > 155 mg/dL
   6. Hydration – avoid hyponatremia

B. Thrombolytic therapy

Multicentre Acute Stroke Trial - Europe (MAST-E)
Recruited persons with acute severe stroke and randomly assigned them to treatment with placebo or 1.5 MU units of streptokinase given over 1 hour. The rate of symptomatic intracranial hemorrhages and deaths was significantly higher in the treatment group and the benefit was marginal. Recruitment was stopped after the safety committee enrolled 270 patients.
Australian Streptokinase Trial (ASK)
Randomized, double blind, placebo-controlled trial of 1.5 MU streptokinase given within 4 hours of stroke onset. The interim analysis of 300 persons revealed that persons treated more than 3 hours after the stroke onset had more adverse reactions. Safety committee recommended that recruitment be halted for patients greater than 3 hours out, but the whole study was stopped.

Multicentre Acute Stroke Trial - Italy (MAST-I)
Controlled, randomized unblinded trial comparing 4 different treatment groups in patients within 6 hours of stroke onset:
- 1.5 MU streptokinase over 1 hour
- 300 mg aspirin QD x 10 days
- combination of the above
- placebo
The safety committee stopped the trial after 622 patients were enrolled because a non-significant reduction in death or disability at 6 months was shown with streptokinase. Mortality and symptomatic intracranial hemorrhage were significantly higher in streptokinase treated group.

European Cooperative Acute Stroke Study
Randomized, double blind, placebo-controlled trial that enrolled persons within 6 hours of stroke. Patients received either TPA or placebo. The TPA was administered as 1.1 mg/kg, or a max of 100 mg. 10% of the total dose was given as a bolus, with the rest infused over 1 hour. 620 patients were enrolled, and statistical analysis included both and intention to treat group and a target population group. Found that thrombolytic therapy was effective in reducing neurologic and functional deficits. However, the benefits of improved neurological, functional and economical outcomes do not outweigh the negative outcomes of a higher mortality rate (due to hemorrhage) at 30 and 90 days in the TPA treated group.

National Institute of Neurological Disorders and Stroke TPA Study (NINDS)
Randomized, double blind placebo controlled trial evaluated endpoints at 2 stages: early response and 3 month outcomes. This study had very stringent exclusion criteria, and patients were all treated within 3 hours of the onset of stroke. TPA was administered in a dose of 0.9 mg/kg (Max = 90 mg), with 10% as a load and the remaining 90% given over 1 hour. The TPA treated group had favorable outcomes at both 24 hours and 3 months after stroke, as well as an increase in the number of patients with minimal or no disability. This study was the basis for the FDA to approve TPA use in acute stroke, based on the strict inclusion and exclusion criteria used in the NINDS study.
TPA Administration to Acute Ischemic Stroke Patients
Recommendations for Clinical Use
(summarized from TPA Stroke Study Group Guidelines)

1. Patients eligible for TPA treatment:
   - Age 18 or older
   - Diagnosis of ischemic stroke with deficit measurable on the NIHSS (National Institutes of Health stroke scale)
   - Onset of symptoms established to be less than 3 hours before treatment would begin
   - Baseline CT scan of the brain without evidence of intracranial hemorrhage

2. Patients in whom TPA treatment NOT recommended based on NINDS (National Institute of Neurological Disorders and Stroke) Study exclusion criteria:
   - Only minor, isolated or rapidly improving neurological symptoms
   - Current users of oral anticoagulants or recent use with PT > 15 seconds (INR=1.7)
   - Use of heparin in previous 48 hours with prolonged aPTT
   - Platelet count < 100,000/mm^3
   - History of stroke or head trauma within preceding 3 months
   - Major surgery within preceding 14 days
   - History of intracranial hemorrhage
   - Pretreatment systolic BP > than 185 mmHg or diastolic > than 100 mmHg
   - Clinical presentation suggestive of subarachnoid hemorrhage, even if CT normal
   - Gastrointestinal or urinary bleeding within preceding 21 days
   - Arterial puncture at non-compressible site within previous 7 days
   - Observed to have seizure at the onset of stroke
   - Blood glucose less than 50 mg/dL or greater than 400 mg/dL
   - Active internal bleeding
   - Recent myocardial infarction

   Note: Symptomatic hemorrhagic transformation of the infarction remains the primary concern with the administration of IV TPA in treating acute ischemic stroke.

3. Recommendations for administration of TPA for ischemic stroke
   Intravenous TPA is administered at a dose of 0.9 mg/kg (maximum dose = 90 mg). A bolus dose of 10% of the total is administered over 1 minute, with the remaining 90% given as an IV infusion over 60 minutes.

4. Ancillary management following TPA administration
   - Admit to a SNF, which permits close observation, frequent neurological assessments and CV monitoring
   - Routine blood pressure monitoring and management for 24 hours following TPA administration to avoid adverse consequences associated with either hypo- or hypertension
   - Avoid placement of central venous access catheters, arterial lines, and NG tubes for the first 24 hours
   - Avoid placement of indwelling bladder catheters for 2 hours after the TPA infusion
   - Avoid anticoagulants or antiplatelet agents for 24 hours after treatment

   a. Management of arterial hypertension as specified by the NINDS study group
      1. Pretreatment
         - Monitor blood pressure every 15 minutes. It should be below 185/110 mmHg.
         - If over 185/110, BP may be treated with nitroglycerin paste and/or 1-2 doses of IV labetalol (10-20 mg over 1 hour). If these measures do not reduce BP below 185/110 and keep it down, the patient should not be treated with TPA.
2. During and After TPA infusion
   - BP monitoring for the first 24 hours after starting treatment
     - every 15 min for 2 hours; then every 30 min for 6 hours; then every hour for 18 hours
   - If diastolic BP > 140 mmHg, start an IV infusion of nitroprusside (0.5-10 ug/kg/min).
   - If systolic BP > 230 mmHg and/or diastolic BP is 121-140 mmHg, give labetalol 20 mg IV over 1-2 min. The dose may be repeated and/or doubled every 10 min, up to 150 mg. Alternatively, following the first bolus of labetalol, an IV infusion of 2-8 mg/min labetalol may be initiated and continued until the desired BP is reached. Use nitroprusside if desired response is not obtained.
   - If systolic BP is 180-230 mmHg and/or diastolic BP is 105-120 mmHg on 2 readings 5 min apart, give labetalol 10 mg IV over 1-2 min. The dose may be repeated or doubled every 10-20 min, up to 150 mg. Alternatively, following the first bolus of labetalol, an IV infusion of labetalol 2-8 mg/min may be initiated and continued until the desired BP is reached.
      * Monitor blood pressure every 15 min during treatment. Hypotension must be avoided, as it may be as detrimental as hypertension.
      * Alternative therapy to nitroprusside may be desired for patients with renal dysfunction
b. Management of intracranial hemorrhage
   Suspect intracranial hemorrhage following TPA infusion if there is any onset of acute neurological deterioration, new headache, acute hypertension, or nausea/vomiting
   If intracranial hemorrhage is suspected:
   a. Discontinue TPA infusion
   b. Obtain CT scan to assess for the presence of hemorrhage
   c. Obtain blood tests: hematocrit, PT, aPTT, platelets, fibrinogen, type/cross
   d. Prepare for the administration of platelets and cryoprecipitate (Factor VIII)
   e. Consult neurosurgeon, neurologist, and/or hematologist as indicated
   f. Assess patient condition for further medical/surgical treatment

5. Overview of events surrounding TPA administration for acute ischemic stroke
A. Determine patient eligibility based on the NINDS inclusion/exclusion data
   a. Patient presentation within critical 3-hour window
   b. CT scan without contrast
   c. Blood draw for hematocrit, PT, aPTT, platelets, Blood glucose
   d. Review past medical history
      f. Blood pressure monitoring
   B. Administer TPA at a dose of 0.9 mg/kg (Max = 90 mg), with 10% as bolus and 1 hour infusion
   C. Adjunctive therapy
      a. Routine blood pressure monitoring for first 24 hours
      b. Routine neurological assessments for first 24 hours
      c. No anticoagulants for first 24 hours after symptom onset
      d. Restrict procedures that may induce bleeding for 24 hours after TPA
      e. Follow guidelines for mgmt. of BP and suspected intracranial hemorrhage
      f. Begin multidisciplinary rehabilitation as patient condition allows
Other thrombolytic therapy:

Desmoteplase in Acute Ischemic Stroke (DIAS trial) – Desmoteplase is highly fibrin specific thrombolytic agent that may allow a longer treatment window (up to 9 hours) following onset of an acute stroke. Current dose ranging studies appear promising, but this agent is still in the early phases of clinical study. Phase III studies began summer 2005.

C. Platelet Glycoprotein Inhibitors
1. Abciximab (Reopro®) – The safety of abciximab was evaluated in a dose escalation study. Patients received one of 4 abciximab regimens within 24 hours of the onset of stroke symptoms. Found to be safe when administered up to 24 hr after stroke onset. Doses ranged from 0.15 mg/kg bolus to a 0.25 mg/kg bolus + 0.125 mcg/kg/min infusion. Since this was only a dose-ranging safety study, the only conclusion that can be drawn is that abciximab deserves further evaluation in the treatment of acute ischemic stroke.

**Abciximab in Emergent Stroke Treatment trial-II**
As a result of the above dose escalation study, abciximab is being investigated in an ongoing trial using bolus dose of 0.25 mg/kg followed by a 12-hour infusion of 0.125 mcg/kg/min with 10 mcg/min maximum dose. Patients are randomized to either abciximab or placebo. Intervention may be made up to 6 hours following onset of symptoms. Patients with symptoms upon awakening are included if treatment is initiated within 3 hours of awakening.

D. Intra-Arterial Thrombolysis
1. Thrombolytic therapy
   - No studies exist directly comparing outcomes of intravenous and intra-arterial administration of thrombolytics. However, physicians with experience in endovascular therapy (interventional radiologists) are using intra-arterial techniques to treat acute ischemic stroke due to occlusion of large intracranial arteries such as the basilar or middle cerebral arteries. There is limited data of this procedure. Usually performed only if presentation is less than 6 hours from onset of symptoms. Not FDA approved therapy.
   - Currently no drugs are approved by FDA for intra-arterial treatment of acute ischemic stroke.
   - Clinical trials are ongoing for combination of intravenous and intra-arterial therapy.
   - May be used if excluded from IV tPA or if not recanalized with IV therapy
   - Difficult to assess effectiveness because well-designed trials are lacking
   - Potential advantages include: longer time window for therapy (up to 12 hrs depending on involved artery), lower dose of fibrinolytic minimizing risk for hemorrhage, improved efficacy.
   - Potential limitations include: limited facilities with expertise and equipment for treatment, delay in treatment to transfer to these facilities, need for ancillary diagnostic testing, unavailability of studied drug in the United States.

E. Antiplatelet/Anticoagulant Therapy
1. Heparin Therapy
   Current use is based on studies from the 1960’s and 70’s, which were not randomized and in general poorly designed. Reportedly, these studies showed up to a 50% reduction in stroke progression. Current studies have shown high rates of progression despite anticoagulation. Also associated with increased bleeding complications (which neutralize any potential benefit) and possibly neurologic worsening. Use is controversial. If used, recommended that:
   - Obtain CT prior to initiation to exclude patients with hemorrhagic complications
   - No loading dose should be administered
   - Goal aPTT should be 1.2-1.5 x control (vs 1.5-2x for VTE)
   - Treatment should be limited to 3-5 days
   - Restrict use in patients with mod-lg infarction who are most likely to have intracranial hemorrhage
   - Heparin use should be considered in patients at high risk for DVT/PE secondary to immobility

**Note:** There is no data demonstrating reduction in mortality or morbidity with subcutaneous or dose-adjusted IV unfractionated heparin. Nor does it reduce the rate of early recurrent strokes.
International Stroke Trial (Lancet 1997; 349: 1569-1581)
19,436 patients randomized within 48 hr of stroke onset to ASA 300 mg/day, SQ heparin (5000 U BID or 12,500 U BID) or both ASA and heparin.
- No significant difference in 14 day mortality or death/dependency at 6 months
- At 14 days, recurrent ischemic strokes decreased in heparin group, but increased hemorrhagic stroke
- Subgroup of Afib + stroke, 14 day recurrence reduced but with increased hemorrhagic stroke
- Blood transfusion or fatal extracranial hemorrhage were significantly more frequent with heparin
- Higher dose heparin associated with more bleeding, hemorrhagic strokes, and inc risk death or nonfatal stroke at 14 days
- Low dose regimen reduced early death or nonfatal stroke with only slight excess of bleeding
- Low dose heparin and aspirin had lowest rate of stroke recurrence, PE and no increase in bleeding risk

2. Antiplatelet agents (See also IST above)
CAST (Chinese Acute Stroke Trial) (Lancet 1997; 349: 1641-9)
21,106 patients randomized to ASA or placebo within 48 hrs after stroke onset and continued up to 4 weeks. Small but significant reductions in 4-week mortality (3.3 vs. 3.9%; p=0.04), recurrent ischemic stroke (1.6 vs. 2.1%; p=0.01), and trend toward decreased death/dependence in the ASA treated group. Consistent with results seen in IST.

Recommendation is that patients who present within 48 hours of symptom onset should be given aspirin (160-325 mg/day) to reduce stroke mortality and decrease morbidity, unless contraindicated due to allergy or administration of tPA is planned. May be combined with low dose SQ heparin for prophylaxis.

3. Low Molecular Weight Heparin/Heparinoids
No data showing reduction in mortality, morbidity or early stroke recurrence.

TOAST trial (JAMA 1998; 279: 1265-72)
1,281 patients with ischemic stroke treated within 24 hours of onset received LMWH danaparoid as 7-day IV infusion or placebo. Overall, no significant difference in proportion of patients with favorable outcomes at 3 months in the danaparoid group compared with placebo.

F. Other acute supportive therapy
1. Nutrition and hydration – Correct nutritional deficiencies to improve 6 month outcomes
2. DVT prevention – Unfractionated or LMWH may be used for prophylaxis
3. Hypertension:

<table>
<thead>
<tr>
<th>Approach to Elevated Blood Pressure in Acute Ischemic Stroke</th>
<th>Blood pressure, mmHg</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not eligible for TPA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic &lt; 220 or Diastolic &lt; 120</td>
<td></td>
<td>Observe unless other end organ involvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat other symptoms and complications</td>
</tr>
<tr>
<td>Systolic &gt; 220 or diastolic 121-140</td>
<td></td>
<td>● Labetalol 10-20 mg over 1-2 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● May repeat or double every 10 min</td>
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<tr>
<td></td>
<td></td>
<td>● Or</td>
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<tr>
<td></td>
<td></td>
<td>● Nicardipine 5mg/hr infusion; titrate by increasing 2.5 mg/hr q 5 min to max of 15 mg/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Aim for 10-15% reduction in blood pressure</td>
</tr>
<tr>
<td>Diastolic &gt; 140</td>
<td></td>
<td>● Nitroprusside infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Aim for 10-15% reduction in blood pressure</td>
</tr>
</tbody>
</table>

**TPA eligible**

Pretreatment | | ● Labetalol 10-20 mg IV over 1-2 min |
| | | ● May repeat x 1 or give 1-2 inch nitropaste |

**During/after treatment:**

Monitor blood pressure | | Every 15 min for 2 hr, then every 30 min for 6 hr, then every hr |
### G. Chronic management following cerebrovascular accident

1. **Spasticity** – drug therapy may relieve spasticity following stroke. Agents that have been tried include: dantrolene (Dantrium), baclofen and botulism toxin (Botox) for nerve block.

2. **Speech** – bromocriptine (Parlodel) may help for pronunciation and sentence formation

3. **Intractable hiccups** – baclofen or chlorpromazine may be useful

4. **Speech/motor skills** – amphetamines (methylphenidate and dextroamphetamine) may help recover function

5. **Depression and/or post-stroke crying** – treatment with antidepressants may help both conditions

6. **Polypharmacy** – drugs taken for conditions associated with stroke may actually slow recovery. Examples are clonidine and prazosin for hypertension, anticonvulsants, haloperidol and benzodiazepines used for anxiety.

### VIII. SECONDARY STROKE PREVENTION (Prevention of recurrent event)

#### A. Control of Risk Factors
- Hypertension, Diabetes, Hyperlipidemia, Alcohol intake, Obesity, Physical Activity, Atrial Fibrillation, Myocardial infarction, Cardiomyopathy

#### B. Antiplatelet agents

**ASPIRIN THERAPY** MOA: Antiplatelet effects of aspirin are responsible for the beneficial antithrombotic effects in the treatment of ischemic cerebral disease. ASA irreversibly inhibits cyclooxygenase, which prevents the conversion of arachidonic acid to thromboxane A$_2$ (TXA$_2$). Thromboxane is a powerful vasoconstrictor and stimulator of platelet aggregation. Platelets are irreversibly impaired, so the effect lasts about 1 week, the lifespan of the platelet. Aspirin also inhibits prostacyclin (PGI$_2$), which has a dose dependent effect on platelet aggregation; the lower the aspirin dose, less inhibition of prostacyclin occurs. Therefore, theoretically the optimal dose of aspirin is one that inhibits thromboxane with the lowest effects on prostacyclin.

A. **Aspirin in Transient Ischemic Attack Study** (Stroke 1977; 8: 301-306)
   Multicenter study compared the use of 650 mg aspirin daily with placebo in patients with carotid system TIA's. Significant difference seen in the aspirin treated group in prevention of stroke.

B. **Canadian Cooperative Study Group** (NEJM 1978; 299: 53-59)
   Compared aspirin 325 mg QID (1300 mg/day), sulfinpyrazone 200 mg QID and placebo in 585 patients with one or more cerebral or retinal ischemic attacks. Average follow up was 26 months. Aspirin reduced the risk of TIA, stroke or death by 19%. If only stroke or death were considered, the risk was decreased by 31%. No benefit in women, or with sulfinpyrazone.

C. **Dutch TIA Trial Study Group** (NEJM 1991; 325: 1261-1266)
   A double blind, randomized controlled trial of patients who had suffered a TIA or minor stroke,1555 patients received ASA 30 mg/day and 1576 received ASA 283 mg/day. After a mean follow-up of 2.6 years, the groups did not differ with respect to death from vascular causes, stroke, or myocardial infarction (14.7% and 15.2% with the 30 mg and 283 mg doses, respectively). Significantly fewer adverse effects occurred in the 30 mg group, however, including minor bleeding and gastrointestinal symptoms.
D. **UK-TIA - United Kingdom Transient Ischemic Attack/Aspirin Trial** *(J Neurol Neurosurg Psychiatry 1991; 54: 1044-54.)*

Evaluated low dose versus high dose aspirin. 2435 patients with a TIA or mild ischemic stroke within 3 months of entry were randomized to receive aspirin 600 mg BID, 300 mg QD or placebo. Patients were followed an average of 4 years. The risk of cerebral infarction was 11% higher in the placebo group, but was not statistically significant. The placebo group experienced fewer side effects. First study to evaluate low dose versus high dose aspirin; demonstrating no important difference in the daily aspirin dose..

E. **SALT - Swedish Aspirin Low-Dose Trial** *(Lancet 1991; 338: 1345-49).*

Double-blind placebo controlled trial of 1360 patients within 3 months of TIA or minor stroke compared 75 mg/day of aspirin to placebo. Demonstrated a decrease in stroke death by 18%. Suggests that low-dose aspirin therapy is effective, but gives no comparative information against higher doses.

F. **ACE trial** *(Lancet 1999; 353: 2179-2184)*

Compared low dose (81 or 325 mg) to high dose (650 or 1300 mg) in 2804 patients undergoing carotid endarterectomy; pts treated for a total of 3 months. There were no differences between high and low doses for any end point at 30 days. Patients who received low doses had a significantly lower rate of stroke, MI and death at 3 months. Lends support to low dose ASA being as effective as high dose.

**TICLOPIDINE THERAPY**

MOA: Inhibits the adenosine diphosphate pathway of platelet aggregation, causing an alteration in platelet membrane and interfering with the membrane interaction with fibrin that causes aggregation. May take 1-2 weeks to see the full effect and the effects may last up to 2 weeks following discontinuation of therapy.

A. **CATS - Canadian-American ticlopidine study in thromboembolic disease** *(Lancet 1989; 1: 1215-1220)*

The efficacy of ticlopidine (525 patients) was compared to that of placebo (528 patients) in reducing the risk of subsequent stroke, myocardial infarction, or vascular death in patients who recently had a moderate-severe (most ASA studies done in minor stroke/TIA) thromboembolic stroke (between 1 week and 4 months previously). During the follow up period there were 118 events/773 patient years in the placebo group and 74 events/683 patient years in the ticlopidine group. This represents a 30% risk reduction in events with ticlopidine. Neutropenia was a severe adverse experience of ticlopidine, occurring in 4 patients.

B. **Ticlopidine vs aspirin in stroke prevention** *(NEJM 1989; 321: 501-507).*

Ticlopidine 500 mg daily was compared to aspirin 650 mg bid in the prevention of stroke and death in 3069 patients who had a TIA or minor stroke. At 3 years, patients treated with ticlopidine had a 9% reduction in their risk of stroke or death from any cause and a 21% reduction in the risk of stroke compared with the aspirin treated group. Women and patients with diabetes may have had a greater reduction in ischemic stroke. These were small, but statistically significant differences. Ticlopidine caused diarrhea (20%), skin rashes (14%) and a severe, reversible neutropenia* (<1%).

*Recommended monitoring is a CBC every 2 weeks for the first 3 months of therapy.


Enrolled 1800 black patients with ischemic stroke to receive aspirin 650 mg/day or ticlopidine 250 mg bid. No difference in the risk of stroke, MI or vascular death at 2 years.

**CLOPIDOGREL THERAPY**

A thienopyridine derivative similar to ticlopidine that is approved for the secondary prevention of MI, stroke and other vascular events. Interferes with adenosine diphosphate-mediated platelet aggregation. Daily dose of 75 mg per day is similar to 250 mg BID of ticlopidine.

A. **CAPRIE Trial** *(Lancet 1996; 348: 1329-39)*

Approval based on this trial of over 19,000 patients with history of atherosclerotic event randomized to ASA 325 mg/day or clopidogrel 75 mg/day and followed for 1-3 years. Clopidogrel patients were found to have a
5.32% combined risk of event (ischemic stroke, MI or vascular death), as compared to 5.83% with ASA. This is an 8.7% relative risk reduction with clopidogrel. For each 1000 patients treated for 1 year, ASA would prevent 19 events, while clopidogrel would prevent 24 events. Side effect profile desirable over ticlopidine.

B. MATCH trial (Lancet 2004; 364: 331-7)
Patients with prior stroke or TIA plus additional risk factors were allocated to clopidogrel 75 mg daily or clopidogrel + aspirin 75 mg daily of each. No significant benefit of combo therapy on composite of ischemic stroke, MI, vascular death or rehospitalization secondary to ischemic events. Data does not support dual therapy.

DIPYRIDAMOLE (extended release)/ASPIRIN THERAPY (Aggrenox®) 200 mg/25 mg
Dipyridamole is an antiplatelet agent that inhibits platelet aggregation via inhibition of adenosine uptake, therefore increasing cAMP. Also may cause vasodilation and stimulate the release of prostacyclin.

A. European Stroke Prevention Study 2 – ESPS-II (J Neurol Sci. 1996; 143: 1-13)
This agent became available in January 2000. It was approved based on the results of the ESPS2 study, a double blind, placebo controlled 24-month study in 6602 patients who had had a previous ischemic stroke or TIA. Patients were randomized to one of four groups: 1.) Aggrenox bid, or 2.) ASA 50 mg, or 3.) dipyridamole 400 mg or 4.) placebo Aggrenox reduced the risk of stroke by 22% compared to ASA, by 24% compared to dipyridamole, by 36% compared to placebo, all of which were statistically significant findings. The combined endpoints of either stroke or death were also examined, and found that Aggrenox reduced this risk by 12% compared to ASA, by 10% compared to dipyridamole, and by 24% compared to placebo. Findings were consistent across all age groups. All cause mortality was similar between treatment groups.

Antiplatelet Trialists’ Collaboration (BMJ 1994; 308: 81-106)
Meta-analysis of trials involving any antiplatelet agent and their effect on various CV endpoints, including ischemic stroke, TIA, MI and total mortality. Reviewed 145 randomized trials with over 100,000 patients with high-risk vascular conditions (unstable angina, MI, TIA, and stroke) and on antiplatelet therapy for at least 1 month. Showed an overall odds reduction of 25% for vascular events (stroke = 39%, nonfatal MI = 31%, vascular death = 15%). Found the benefit of antiplatelet therapy was independent of age, gender and ASA dose. Also independent of hypertension and diabetes. This has established the use of these agents for patients with stroke or TIA.

RECOMMENDATION:
The current recommendation for patients who have suffered a TIA or minor stroke is for initial treatment with aspirin. The effective dose is still debatable, as doses ranging from 75 - 1300 mg/day have been shown to be effective. Clopidogrel (recommended over ticlopidine) and Aggrenox® are recommended only for those patients who are intolerant to aspirin, patients with recurrent ischemic events during aspirin therapy and for those whom close hematologic monitoring is possible (ticlopidine). Warfarin therapy may be considered for patients who continue to have ischemic episodes despite antiplatelet therapy. Evidence is not strong enough to support routine long-term anticoagulation with warfarin for patients with completed stroke. Must examine each patient individually, assess his or her risk factors, and perform a risk/benefit analysis to customize therapy.