INTERNAL MEDICINE
GRAND ROUNDS

UPDATES ON STROKE PREVENTION AND MANAGEMENT
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Introduction
- Cerebrovascular disease is the third leading cause of death in the U.S.
- Number 1 cause of long-term major disability
- There are 795,000 incident strokes in the U.S. each year
- 1 of every 17 deaths in the U.S. is due to stroke.
- There are more than 4.8 million stroke survivors alive today
- There was a 60% decline in stroke mortality over the 29-year period between 1968 and 1996
- The rate of decline began to slow in the 1990s and has plateaued in several regions of the country
- High-incidence “stroke belt” centered on southeastern and south central states
- Cost ~$55 billion annually


Stroke Age-Adjusted Death Rates by State, 2005


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Definition of TIA and Ischemic Stroke Subtypes

- TIA is an important predictor of stroke.
- The 90-day risk of stroke after a TIA has been reported as being as high as 17% (Highest in the first week).
- TIA: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction, symptoms <24h.
- Most TIA’s last 5-20 minutes, if >1hr usually small infarction on MRI.
- Ischemic stroke or brain infarction: when the O2 supply is inadequate to support tissue viability.

Stroke, American stroke Association, Oct 21, 2010; ISSN: 1524-4628

Stroke subtypes

- One must be aware of the mechanisms of disease underlying the clinical stroke syndrome.
- Preventive measures must be tailored to the disease mechanism.
- 87% of strokes are ischemic.
- 9% are due to intracerebral hemorrhage (ICH).
- 4% are due to subarachnoid hemorrhage.


Etiology of AIS

- Atheroemboli from aortic or carotid plaque rupture (Atherosclerosis).
- Carotid or vertebral artery dissection.
- Cardiac valve or heart chamber-related emboli. (LA thrombus in A. Fib, LV thrombus in MI, paradoxical embolus with PFO).
- Hypercoagulable states, sickle cell disease.
- Cryptogenic.

Pathophysiology of AIS

- Ischemia depletes neuronal energy stores causing energy dependent membrane ion pumps to fail.
- This results in increased extracellular glutamate concentration.
- Release of excitotoxic Glutamate & Aspartate open up calcium channels resulting in influx of calcium, sodium and chloride and out flux of potassium causing irreversible neuronal damage.
- This process results in free radicals and nitrous oxide.
- The amount of collateral flow can influence the size of the infarct.
- Temperature and glucose metabolism have effects on cell death and tissue injury.

Risk factor control

Hypertension

- 72 million Americans have hypertension.
- BP>140/90 mm Hg.
- BP lowering is associated with a 30% to 40% reduction in risk of stroke.
- BP reduction is recommended for both prevention of recurrent stroke and prevention of other vascular events in persons who have had an ischemic stroke or TIA and are beyond the first 24 hours (Level 2, Level of Evidence A).

Diabetes

- Affects 8% of adults in US.
- Prevalence is 15-33% with ischemic stroke.
- 3 major RCT of intensive glucose management (HbA1c<6.5%): all have failed to demonstrate a reduction in CV events or death in stroke patients.
- Glycemic targets should not be lowered to HbA1c<6.5%.
- Worse outcomes associated with aggressive glycemic control.
- Use of existing guidelines for glycemic control is recommended.
Lipids

• Statins reduce LDL-cholesterol
• With each 10% reduction in LDL→15% decrease in risk for stroke
• Statins recommended in patients with ischemic stroke/TIA with LDL-C goal<100 mg/dl (No CAD)
• LDL-C goal <70 mg/dl in patients with stroke/TIA and CAD.
• Use niacin or fibrates in patients with low HDL-C.

SPARCL study

• Stroke Prevention by Aggressive Reduction in Cholesterol Levels
• 4,731 patients with prior strokes or TIA’s
• Randomized to placebo or atorvastatin 80mg/day
• Median follow up period 5 years
• 16% reduction with atorvastatin treatment for fatal or nonfatal stroke (p=0.03)
• 23% reduction in risk for TIA or stroke (p=0.001)
Smoking / Alcohol

- Cigarette smoking is a strong independent risk factor for ischemic stroke.
- Risk reduction after smoking cessation: 50% within 1y, baseline after 5y.
- Healthcare providers should advise every patient with stroke/TIA to quit.
- Chronic alcoholism and heavy drinking are risk factors for all stroke subtypes (alcohol-induced hypertension, hypercoagulable state, reduced cerebral blood flow, AF or cardioembolism due to cardiomyopathy).
- Protective effect from light or moderate alcohol consumption (increase in HDL, decrease in platelet aggregation, lower concentration of plasma fibrinogen).
- Light or moderate (no more than 2 drinks/day for men and 1 drink/day for women).
- Nondrinkers should not be counseled to start drinking.

Obesity/physical activity

- No study has demonstrated that weight reduction reduces risk of stroke recurrence.
- Physical activity tends to lower BP and weight, enhance vasodilation, improve glucose tolerance, and promote cardiovascular health.
- For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise may be considered to reduce the risk factors and comorbid conditions that increase the likelihood of recurrent stroke (Class IIb; Level of Evidence C).
- The utility of screening patients for the metabolic syndrome after stroke has not been established.

Initial management

- A,B,C,D
- Neuro assessment
- Brain imaging
- Evaluation for thrombolytics

Airway and ventilatory support

- High risk for respiratory failure from aspiration pneumonia/pneumonitis, due to inability to protect the airways and clear secretions as a result of facial weakness, bulbar weakness and altered level of consciousness.
- Hypoxemia may worsen the injurious effects of cerebral ischemia.
- The goal is to keep O2 Sats>95%.
- Excessive PEEP (>10) should be avoided (increase ICP).
- Mechanically ventilated patients frequently require sedation and frequent discontinuation of sedatives is indicated to monitor carefully for any neuro changes.
Blood pressure and fluid management

- In AIS, patients often have high BP (Physiologic response to increase cerebral perfusion, increased ICP, pain, worsening of long-standing HTN).
- Advantages of treating HTN in AIS: Prevent hemorrhagic transformation.
- Disadvantages: cerebral blood flow compromise and worsening ischemia.

American stroke Association guidelines: recommend that antihypertensive agents should be withheld unless SBP>220 mm Hg or diastolic BP>120 mmHg.
- If patients have received thrombolytics, SBP should be <180 and diastolic BP<105 mmHg.
- Avoid hydralazine and Na nitroprusside (may increase ICP secondary to cerebral vasodilation).
- May use labetalol (Alpha and Beta adrenergic blocker), ACEI, CCB (Nicardipine).
- Do not use ACEI for BP lowering in patients eligible for IV t-PA since serious allergic reaction (angioedema) is more likely to occur when ACEI are given with IV t-PA.

- If patients with AIS are hypotensive, they may benefit from induced HTN.
- Typically MAP is increased 20-25% from baseline, using IVF (isotonic), vasopressors.
- The impact of this therapy is still being evaluated in clinical trials.
- In dehydrated patients hypotonic fluids should be avoided (worsen cerebral ischemia and increased ICP).
Neurologic examination

• Serial neurologic testing should be done.
• Designed to assess the patient’s level of alertness, comprehension, motor/sensory/visual and language function.

Diagnostic workup

• Brain imaging.
  • Non contrasted CT to exclude hemorrhage.
  • CT may be normal in the first 24 hours.
  • MRI detects early cytotoxic edema by measuring the random diffusion of water molecules, which is restricted almost immediately in ischemic brain injury owing to failure of the energy-requiring active sodium and water transport mechanism.
  • MRI shows an abnormal signal within minutes of ischemic onset and also in other conditions (brain tumors, seizures, brain infections, CJK, toxic-metabolic disorders).

Emergent laboratory evaluation and other tests

• Evaluate whether the patient is candidate for tPA.
• CBC, coagulation parameters, serum glucose.
• An EKG is indicated in all patients with acute stroke to detect myocardial ischemia, cardiac arrhythmias such as A. Fib.
• Bun/Creatinine should be checked, in particular in patients who will be exposed to contrast agents.
• In selected patients some other tests should be obtained.
• ABG, troponins, LFT’s and ammonia (unexplained AMS), CXR (aspiration, AMS, Dyspnea), blood cultures in febrile patients raising a concern for septic emboli, UDS (for patients with possible substance abuse), EEG for suspected seizures, LP for suspected meningitis or SAH, Echocardiogram, carotid doppler.
Stroke Management
Intravenous thrombolitics

- Restores cerebral perfusion by clot lysis
- Converts plasminogen to plasmin, an enzyme responsible for fibrin dissolution and maintaining coagulation homeostasis
- Studied in the NINDS study: National Institute for Neurologic Disorders and Stroke
- Randomized, double-blind placebo-controlled trial
- 624 patients received either rt-PA (0.9 mg/kg IV) or placebo
- Favorable outcomes reported in 31-50% of rt-PA treated subjects vs 20-38% in placebo group
- Patients who received t-PA were 30% more likely to have minimal or no disability at 3 months
- Incidence of symptomatic ICH was 6.4%

Neurology 26 (2008) 943-961

Intravenous thrombolysis with tissue plasminogen activator (t-PA) remains the only FDA approved acute therapy for acute ischemic stroke.
- Approved in 1996, for ischemic stroke within 3 h of symptom onset
- The incidence of symptomatic ICH within 36 h after symptom onset was significantly higher in the t-PA group (6.4%), 0.6% in non-t-PA group
- This explains in part the reluctance of some physicians to administer t-PA
- 20-25% of stroke patients arrive at the hospital within 3 h of symptom onset, but t-PA is used only in a small fraction of these patients
- After IV t-PA, risk factors for hemorrhagic conversion include a large area of established infarction, increasing age, hyperglycemia, uncontrolled hypertension, congestive heart failure, did prior treatment with aspirin.

Contraindications to IV rt-PA

- Presentation beyond 3 hours of symptom onset
- Mild neurologic impairment or rapidly resolving neurologic symptoms
- Intracranial hemorrhage on initial head-CT scan
- History of intracranial hemorrhage
- Symptomatic or subarachnoid bleeding
- Stroke or head trauma within the last 3 months
- Systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg
- History of seizure with the presenting stroke
- History of recent myocardial infarction
- Major surgery within the last 3 weeks
- Gastrintestinal or genitourinary hemorrhage within the last 3 weeks
- Current use of warfarin
- International normalized ratio (INR) > 1.7
- Heparin treatment within the last 48 hours
- Elevated activated partial thromboplastin time (aPTT)
- Platelet count < 100,000/ml
- Blood glucose < 50 mg/dl

Neurology 26 (2008) 943-961
Intravenous recombinant tissue plasminogen activator administration protocol

- Total dose of rt-PA: 0.9 mg/kg (maximum dose 90 mg)
- Give 10% as initial IV bolus
- Infuse remainder over 1 hour
- Admit patient to an ICU or stroke unit for monitoring
- Neurologic assessments: every 15 minutes during infusion, then every hour until 24 hours after treatment
- BP monitoring: every 15 minutes for 2 hours, then every hour until 24 hours after treatment
- Administer antihypertensive medication to maintain systolic BP less than or equal to 180 mm Hg and diastolic BP less than or equal to 105 mm Hg
- Delay placement of nasogastric tubes, indwelling bladder catheters, or IA pressure catheters
- Follow-up CT or MRI scan at approximately 24 hours after rt-PA, before starting anticoagulation or antiplatelet agents
- Delay antithrombotic agents for 24 hours after rt-PA

ECASS III study

- European Cooperative Acute Stroke Study
- Showed that the window could be extended up to 4.5 h
- This trial excluded patients with severe stroke (NIHSS score>25) and those with diabetes who had previous strokes, age >80 years, oral anticoagulation therapy.
- More patients had favorable outcomes as assessed by a modified Rankin Scale score of 0 or 1, with IV t-PA than with placebo (52.4% vs. 45.2%)
- The incidence of symptomatic ICH was higher in the t-PA group compared to placebo (2.4% vs. 0.2%)
- The death rate did not differ between the 2 groups.
- AHA/ASA published a science advisory with a class I, level of evidence B recommendation for t-PA administration within 3-4.5 h.

Neuroprotection

- Goal is to minimize ischemic brain injury and prevent reperfusion injury
- Therapeutic hypothermia useful after cardiac arrest to decrease metabolic demands and O2 consumption
- Preclinical data from animal models of stroke suggest a beneficial role of hypothermia
- Magnesium infused 4 gm load in the field, followed by 16 gm over 24 h in the hospital
- ( Mg2+ functions as NMDA receptor blocker and VGCC blocker).
- Caffeine and ethanol ( reduced infarct size by 83% in animal models).
- Statins (atorvastatin) administered within 24 h ( beneficial effect on endothelial function, CBF, inflammation and homeostasis), more studies needed.
- Thiazolidinediones, in vitro can prevent neuronal apoptosis in response to oxidative injury (Decrease COX-2 expression), more studies needed.
- Due to lack of compelling clinical data, the 2007 AHA/ASA have assigned a class III recommendation to administer neuroprotective agents in AIS.

Currently in Europe, IV thrombolysis is performed up to 4.5 h from the time of symptom onset.
FDA has not approved yet the use of t-PA between 3 and 4.5 h in US.
But many stroke centers have updated their treatment algorithms with the new time frame, a practice that has been recently recommended by AHA.
The earlier thrombolysis is performed, the more likely it is to be efficacious.
Practitioners should make every effort to administer t-PA soon after onset within the window.
Intra-Arterial thrombolysis

- IA thrombolysis uses a catheter to selectively deliver a thrombolytic drug to the culprit vessel during AIS. Allows for a lower tPA dose and a decreased risk of hemorrhage.
- PROACT II trial: the Prolyse in Acute Cerebral Thromboembolism II
  - Prospective, randomized, placebo-controlled trial
  - Provided efficacy data supporting the IA administration of recombinant prourokinase in patients with MCA strokes who presented within 6 hours.
  - At 90 days, 40% of treated patients had a modified Rankin Scale score of 0-1 (minimal or no neuro deficit), compared to only 25% of control patients.
  - IA thrombolysis resulted in an increased incidence of ICH compared to placebo (11% vs 3%).
  - Prourokinase has not been approved for clinical use in the US.
  - However, the PROACT II data as well as the results of small trials and case series have been extrapolated to support the off-label use of IA urokinase and rt-PA in AIS.
  - IA thrombolysis may be a treatment for selected patients: presentation between 3-6 h, major cerebral artery occlusion, severe neuro deficit, high risk of systemic hemorrhage with IV t-PA.
  - Disadvantage: Time, expertise required for catheterization, restricted to medical centers that have interventional neuroradiologists and critical care services available 24 h a day.

Mechanical thrombectomy

- Several devices are being studied
  - FDA-approved Merci device in the MERCI trial (Mechanical Embolus removal in Cerebral Ischemia)
  - Multi MERCI trial investigated the role of the Merci device in patients with AIS within 8 h of symptoms.
  - The Multi MERCI trial allowed mechanical embololysis to be performed on patients who had already received IV t-PA and had persistent large vessel occlusion.
  - IA thrombolysis was permitted in patients in whom mechanical intervention failed to achieve arterial patency (at least TIMI flow 2).

IA thrombolysis resulted in an increased incidence of ICH compared to placebo (11% vs 3%).

Recanalization was achieved in 55% of 164 patients in whom the device was deployed and in 68% of the same cohort when adjuvant IA thrombolysis was used.

Symptomatic ICH occurred in 9.8% of patients.

When recanalization occurred, good neurological outcomes at 90 days were observed in 49% of patients compared with 9.6% of patients who did not recanalize (p < 0.001).

Similarly, in the same groups, 90-day mortality was observed in 25% and 52%, respectively (p < 0.001).

Mechanical thrombectomy remains an area of active clinical investigation.

Endovascular mechanical thrombectomy may be employed, either alone or as an adjunct to IV tPA, and has several potential advantages, including a wider time window (up to 8 h), the capacity for use in coagulopathic patients and higher recanalization rates (up to 82%).

Nonetheless, mechanical thrombectomy has engendered controversy because no randomized trials have yet been performed to support its use.

Stent placement

The success of coronary stents in opening infarct-related coronary arteries has led to trials of stents for the treatment of stroke.

The primary advantage of using direct stent placement is the speed of reperfusion. However, unlike myocardial infarction, in which the IRA often contains in situ thrombus, in ischemic stroke patients a cerebral artery is frequently obstructed by an organized thrombus that formed elsewhere and embolized to an intracranial location.

Three stent systems are currently FDA-approved for intracranial aneurysm treatment in the US: Neuroform (Boston Scientific, Natick, MA, USA), Wingspan (Boston Scientific) and Enterprise (Codman Neurovascular/ Cordis, Raynham, MA, USA).

Seems to be promising but in-stent restenosis is a major concern.

As of yet, there is no published data regarding the in-stent restenosis incidence of stents placed for acute stroke treatment.

Medical therapy for mass effect from edema after stroke

Absolute avoidance of free water and hypotonic solutions.

Maintenance of normal or mildly elevated serum osmolarity, initiate immediately. Osmotic gradient favors efflux of interstitial and intracellular fluid into capillaries.

CPP optimization, prevents reflex vasodilation and elevated ICP, requires ICP monitoring.

Bed positioning < 30 degrees, minimizes ICP.

Avoidance of hypovolemia, prevents brain hypoperfusion.

Avoidance of fever, T < 38.3°C, fevers increase ICP, aggravate ischemia, and are associated with poor outcome.
Medical therapy for mass effect from edema after stroke

- 20% mannitol 1 g/kg IV if clinical signs of herniation: LOC attributed to edema, papillary abnormalities. Cerebral edema, Do not give to dehydrated patients: use 23.4% NaCl instead. Can cause electrolyte depletion.
- 23.4% NaCl 1-2 mL/kg IV push over 5 min, Osmotic agent and intravascular volume expander, Volume overload, may cause pulmonary edema.
- Hyperventilation in acute herniation syndromes, critical elevated ICP, extremely rapid cerebral vasoconstriction reduces ICP by reducing CBF. Excessive hyperventilation (PCO2 <30 mm Hg) may aggravate brain ischemia.
- Hypertonic hypertonic, in refractory elevated ICP and/or herniation, decreases cerebral metabolism, reduces secondary brain injury.

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Carotid endarterectomy

- 2 studies examined the potential benefit of CEA in patients with symptomatic carotid stenosis.
- NASCET (North American Symptomatic Carotid Endarterectomy Trial) and ECST (European Carotid Surgery Trial)
- For symptomatic subjects, CEA benefitted those with 50% to 99% stenoses.
- The landmark ACAS (Asymptomatic Carotid Atherosclerosis Study) established that for patients with 60% to 99% stenosis who could be operated on with very low perioperative risk for stroke or death, CEA produced more favorable outcomes than best medical therapy (relative risk reduction: 53%, p = 0.004).


Current recommendation for CEA

- For symptomatic patients with a >5-year life expectancy and 50% to 99% stenoses, perioperative mortality risk <6%, CEA should be considered (I A)
- For asymptomatic patients with a >5-year life expectancy and 50% to 99% stenoses, it is reasonable to consider CEA.
- There is good evidence that patients with more severe stenoses (but not subtotal or total occlusions) are more likely to benefit from CEA than those with less severe stenoses.
- When the degree of stenosis is <50%, there is no benefit from CEA.


Timing for CEA

- Historically, literature has suggested that the optimal timing to perform CEA is 6 weeks after an acute stroke.
- High risk of cerebral hemorrhage with early intervention, hyperperfusion syndrome.
- Recent studies recommend earlier intervention, 2 weeks, to minimize the risk of recurrent strokes especially in the following patients with:
  1. Stable neurologic deficit
  2. Normal LOC
  3. Significant midline shift on brain imaging

Stoke recurrence is approximately 10-15% while waiting for CEA after acute stroke.

Patients with unstable deficits, who have steadily progressive clinical deterioration, profound deficit and not appropriate for early CEA.

Carotid angioplasty/stenting

- Less invasive compared to CEA
- Causes less discomfort to the patient.
- Shorter recuperation period
- Its durability is unproven.
- Reserved for high risk patients (cardiac conditions that precludes open surgery, severe lung or renal disease, challenging technical/anatomical factors: prior neck operation, neck irradiation, post CEA restenosis, contralateral carotid occlusion, presence of tracheostomy).

The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

- CAS, when done by experienced and skilled interventionalists, has patient outcomes similar to those of CEA.
- During the perioperative period, more strokes occur after CAS and more MI's occur after CEA.
- Younger patients have slightly better outcomes with CAS.
- Older patients have better outcomes with CEA.

Treatment for stroke in patients with specific conditions: Cardiogenic embolism

- 20% of ischemic strokes
- Atrial Fibrillation: >75,000 cases of stroke per year
- Warfarin: relative risk reduction of 68%
- Absolute reduction in annual stroke rate from 4.5% in control patients to 1.4% in warfarin treated patients
- ASA: 21% relative RR compared to placebo
- ACTIVE W study (atrial fibrillation Clopidogrel Trial with Irbesartan): safety and efficacy of ASA and clopidogrel vs. warfarin in AF patients with at least 1 risk factor for stroke → study stopped prematurely, clear superiority of warfarin.
No evidence supports combining ASA to warfarin. Increased bleeding risk.

- Percutaneous implantation of a device to occlude the left atrial appendage (WATCHMAN device). In patients with contraindication to anticoagulation.

- Periprocedural complications.

- More data required. Good option if contraindication to anticoagulation.

- Dabigatran, recently approved by FDA, thrombin inhibitor.

- Tested in the RE-LY study (Randomized evaluation of Long Term anticoagulation Therapy), randomized open-label trial, >18,000 AF patients 150 mg twice a day, associated with lower rates of stroke or systemic embolism, and rates of major hemorrhage similar to warfarin.

- Bridging therapy required for AF patients at high risk for stroke (TIA or stroke within 3 months, CHADS2 score of 5 or 6, or mechanical or rheumatic valve disease.

- INR goal 2-3, target 2.5

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Acute MI and LV thrombus

- 1/3rd of patients within 2 weeks after anterior MI.

- Cerebral infarction occurs in 10% with LV thrombus.

- Anticoagulation reduces the risk of embolism from 3 to 1% compared with no anticoagulation.

- No consensus regarding the duration of anticoagulation, but at least 3 months is reasonable. (IB)

- INR goal 2-3, target 2.5

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Cardiomyopathy

- 10% of stroke patients have LVEF<30%

- Benefit of warfarin has not been established (unless patient has A. Fib, prosthetic valve or other indication for anticoagulation).

- Dosing trial (WARCEF). Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction, comparing the efficacy of warfarin (INR 2.5-3.0) and ASA 325 mg daily, and point of death or stroke in patients with EF<35%.

- Warfarin, ASA 81mg daily, clopidogrel 75mg daily, or combination of ASA 25 mg BID and SR dipyridamole 200 mg BID may be considered to prevent recurrent stroke/TIA in patients with cardiomyopathy. IIB

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Native valvular heart disease

- Rheumatic MV disease: recurrent embolism occurs in 30-65% of patients

- 60-65% in the first year.

- Mitral valveplasty does not eliminate the risk and the need for anticoagulation.

- Long term warfarin, INR goal 2.0-3.0, target 2.5

- Antiplatelet agents should not be added to avoid additional bleeding risk.

- In patients with mitral annular calcification, MVP, nonrheumatic MV disease, native aortic disease, antiplatelet therapy may be reasonable.
Prosthetic heart valves

- Warfarin recommended; INR goal 2.5-3.5, target 3.0 with mechanical valves
- Add ASA 75-100 mg daily for recurrent strokes while on warfarin. (if bleeding risk not high)
- For bioprosthetic valves: Warfarin therapy is recommended for patients with stroke/TIA if no other source of thromboembolism is identified, INR 2.0-3.0

Antithrombotic therapy for noncardioembolic stroke

- Antiplatelet agents
- FDA approved for prevention of vascular events among patients with strokes/TIA
- ASA, ASA/Dipyridamole, clopidogrel, ticlopidine.
- On average, these agents reduce the RR of stroke, MI or death by 22%
- Important differences exist between these agents.

Aspirin

- RR reduction 15%
- Magnitude of benefit is similar for doses ranging from 50-1500 mg
- More GI bleed with higher doses.
- With doses <325 mg daily, annual risk of GIB is 0.4%, 2.5 times the risk for nonusers.

Ticlopidine

- Adenosine diphosphate receptor antagonist. Evaluated in 3 randomized trials
  - CATS (Canadian American Ticlopidine Study) compared ticlopidine 250 mg BID with placebo for stroke prevention, MI or vascular death in 1053 patients followed over 2 years.
  - Relative RR 11.3% placebo and 14.8% ticlopidine.
  - TASS (Ticlopidine Aspirin Stroke Study) compared ticlopidine 250mg BID with ASA 650 mg daily in 3069 patients followed over 3 years.
  - Primary outcome of stroke / death lower with ticlopidine 17% vs 19%, RRR 12%
  - The African American Antiplatelet Stroke Prevention Study: 1809 black patients. Ticlopidine 250 mg BID vs ASA 325 mg daily.
  - No difference between 2 groups.
  - Side effects of ticlopidine: diarrhea, rash, severe neutropenia in <2% almost always reversible after discontinuation. TTP described.
Clopidogrel

- ADP receptor antagonist
- Tested in 2 trials as single agent for secondary stroke prevention, one comparing it with ASA alone and one comparing it with ASA/dipyridamole.
- In each trial rates of primary outcomes were similar
- Has not been compared with placebo.
- Safety comparable to ASA with minor differences: diarrhea and rash more common than with ASA, GIB less common, few cases of TTP.

Dipyridamole and Aspirin

- Dipyridamole inhibits phosphodiesterase and augments prostacyclin-related platelet aggregation inhibition.
- Dipyridamole combined with ASA has been examined in 4 large randomized trials.
- ESPS-1 (European Stroke Prevention Study). 2500 patients assigned to placebo or ASA 325 mg plus 75 mg IR dipyridamole TID. After 2 years, rate of stroke/death 16% with asa/dipyridamole vs 25% for placebo.
- ESPS-2: 6602 patients with prior strokes, 4 groups 1-asa 25 mg BID + ER dipyridamole 200 mg BID, 2-asa 25 mg BID, 3-ER dipyridamole alone, 4-placebo.
- Compared to placebo, rate of stroke/death reduced by 25% with asa, 16% with dipyridamole, and 37% with the combination. Headache and GI symptoms more in dipyridamole group, bleeding not significantly increased.
- ESPRIT (European/Australian Stroke Prevention in Reversible ischemia Trial), prospective, randomized, open label, blinded end point evaluation to compare asa alone vs asa+dipyridamole for stroke/MI/vascular death/hemorrhage in patients with TIA/stroke within 6 months. After 3.5 years, primary end point (stroke, MI, vascular death) was 13% of patients on combination therapy vs 16% on asa alone.
- PRoFESS study, compared clopidogrel with asa/dipyridamole

Combination clopidogrel and Aspirin

- MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke)
- Clopidogrel 75mg plus asa 75mg compared with clopidogrel 75mg alone.
- No significant benefit of combination therapy compared with clopidogrel alone.
- Risk of bleeding increased with combination group.
- ASA/clopidogrel recommended over asa alone for ACS.

Summary on oral antiplatelet therapy

- Evidence indicates that ASA, Ticlopidine, ASA+dipyridamole, are each effective for secondary stroke prevention.
- Combination ASA/Dipyridamole may be more effective than ASA alone.
- Ticlopidine may be more effective than ASA but safety concerns limit its use.
- Risk for D2 listed or other major hemorrhage may be greater with ASA or ASA/Dipyridamole than for clopidogrel.
- Combination ASA/Dipyridamole is well tolerated better than either ASA or clopidogrel alone, primarily GI related bleeding.
- Patient characteristics may affect the choice of agents and coadministration
- Ticlopidine is a good choice in patients who are allergic or cannot tolerate ASA.
- If intolerance to dipyridamole (headache), ASA or clopidogrel are appropriate.
- Combination ASA/Clopidogrel may be appropriate for patients with ACS or recent vascular event.
- In patients who present with a first or recurrent stroke while on aspirin therapy, consider clopidogrel in patients for whom switching to another antiplatelet agent would be beneficial.
**Recommendations on antiplatelet therapy**

- Antiplatelet agents rather than anticoagulation in noncardioembolic stroke.
- ASA 50-325mg/d monotherapy.
- Combination ASA 25 mg/ER Dipyridamole 200 mg BID.
- Clopidogrel 75mg/d monotherapy.
- Addition of ASA to Clopidogrel increases the risk of hemorrhage and is not recommended.
- For patients allergic to ASA, clopidogrel is reasonable.
- For recurrent stroke while on ASA, no evidence exists to support increasing the dose.

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**Arterial dissections**

- Young patients with stroke.
- Carotid, vertebral arteries.
- 50% after head and neck trauma.
- 50% spontaneous or after trivial injury.
- Congenital tissue disorders (Finn dysplasia, Marfan syndrome, Ehlers-Danlos syndrome type IV, von Recklinghausen neurofibromatosis, other genetic conditions).
- Treatment options include anticoagulation, antiplatelet therapy, angioplasty with or without stenting or observation without specific therapy.
- Optimal strategy is controversial.
- Recommended: antithrombotic treatment for at least 3-6 months (time for the dissection to heal), some authors support to repeat imaging studies to confirm recanalization of the dissected vessel before a change in therapy.
- Relative efficacy of antiplatelets vs. anticoagulation is unknown.
- If there is recurrence despite optimal medical therapy, stenting may be considered.
- Surgical treatment in patients who are not candidates for endovascular treatment.

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**Patent foramen ovale, PFO**

- Right to left passage of embolic material to the brain.
- Embryonic defect in interatrial septum.
- Common, in up to 15 to 25% of adult population.
- Antiplatelet therapy is reasonable.
- Insufficient data to establish whether anticoagulation is equivalent or superior to ASA.
- Insufficient data to make a recommendation regarding PFO closure in stroke patients with PFO.

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**Hypercoagulable states**

- Hypercoagulable state: Protein C and S deficiency, AT III deficiency, factor V leiden, prothrombin G20210 mutation rarely contribute to adult stroke.
- Play a major role in pediatric stroke.
- Mostly venous events.
- Little is known about inherited thrombophilias and the risk of recurrent stroke.
- Stroke and inherited thrombophilias: treat with warfarin if + DVT.
- If no DVT, antiplatelets or anticoagulants, reasonable.
- APS, antiphospholipid syndrome: positive and stroke/thrombosis with antiplatelet. If APA syndrome diagnosed heparin with INR goal 2.0-3.0.
- Hyperhomocysteinemia: 2- fold risk of stroke, folate supplementation reduced levels but may not prevent stroke recurrence.
Sickle cell disease

- Sickle cell disease: risk of stroke 11% by age 20, 15% by age 30, 24% by age 45. More common with SS genotype, greater degree of anemia, prior acute chest syndrome.
- Due mainly to large artery arteriopathy, due to intimal hyperplasia related to repeated endothelial injury.
- Antithrombotic agents, Transfusion therapy to reduce Hgb S levels<30%, hydroxyurea, BMT may help for secondary prevention.

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• Fabry’s disease: X-linked deficiency of the enzyme alpha-galactosidase → lipid deposition in vascular endothelium → progressive vascular disease in brain, heart, skin, kidneys.
• Treat with enzyme replacement.
• Postmenopausal HT is not recommended in women who have had a stroke/TIA.

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Conclusion

1. The cost in quality of life and financial terms of acute stroke at both the individual and population levels is enormous.
2. Contemporary treatment of acute stroke is severely under-utilized.
3. Successful treatment of acute ischemic stroke requires early recognition by patients so that treatment is not delayed.
4. The appropriate treatment of acute ischemic stroke requires a multidisciplinary approach from emergency personnel, stroke neurologists, advanced neurological imaging specialists, and neurovascular interventionalists.
5. These resources must be readily deployable, and available around the clock, 7 days a week, in order to provide consistent high-quality care for stroke patients.
6. Data regarding the pharmacologic and mechanical treatment of acute stroke demonstrate a strong correlation between recanalization and good clinical outcomes.
7. As technology evolves for diagnosing and treating stroke, ongoing research must adhere to uniform standards for quantifying severity of illness as well as procedural and clinical outcomes.