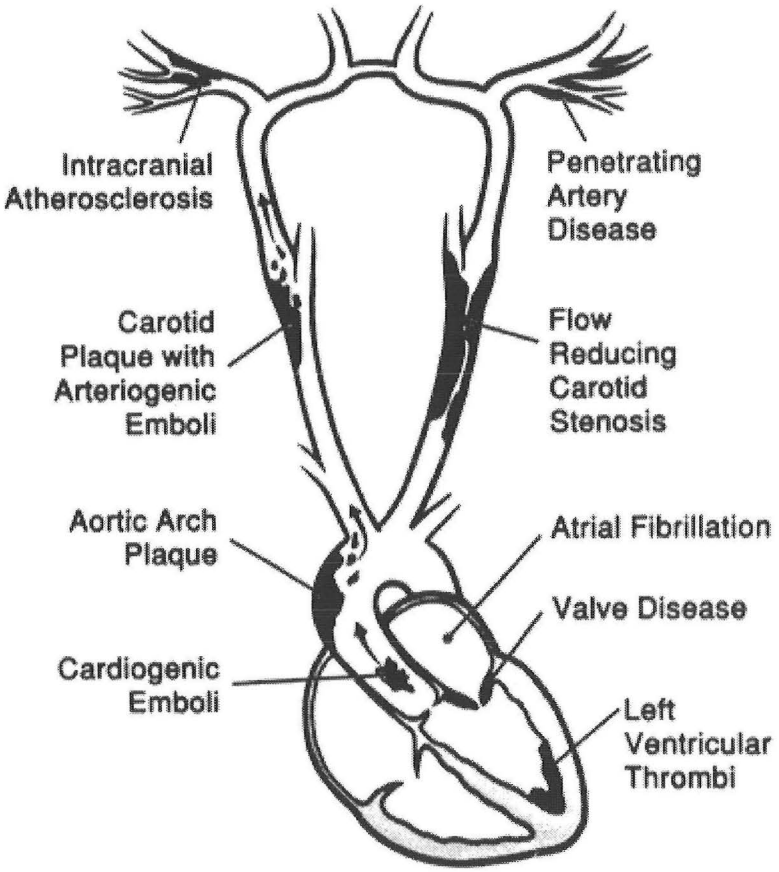
Brain Attack: An Update on Therapy for Acute Stroke



Hari Raja, M.D.

Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
October 10, 2002

Dr. Raja has no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Raja will not be discussing off-label uses in his presentation.

Name: Hari Raja, M.D.

Rank: Assistant Professor

Division: General Internal Medicine
UT Southwestern Medical Center

Interests: Medical education
Nutrition
Treatment of obesity
Preventative Medicine

Note: The figure on the title page is courtesy of Dr. Robert Hart from UT San Antonio.

Dr. Raja would like to thank both Dr. Hal Unwin and Dr. Dion Graybeal for reviewing the protocol and providing some of the information in the lecture.

Background

Acute stroke is one of the leading causes of mortality and morbidity in the world. It is estimated to be the 3rd most common cause of death in the U.S. leading to 150,000 deaths per year. Some estimates place a cost of $40 billion for health care expenditures and lost productivity due to strokes. It is also a common cause of patients being placed in institutions. There are many possible ways to discuss this topic, but this lecture will focus mainly on acute therapies and prevention of strokes.

Classification of Stroke

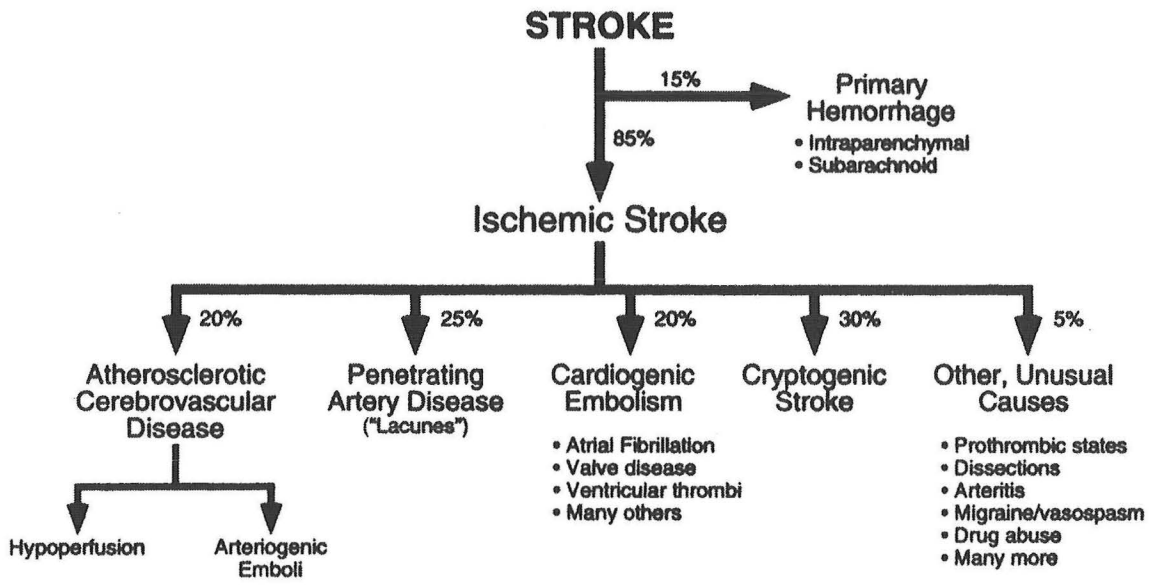


Figure 1. Stroke classification by mechanism with estimates of frequency of various categories by abnormalities. [1]

The first division in the classification is between hemorrhagic and ischemic. Hemorrhagic strokes are defined as either intraparenchymal or subarachnoid and occur in about 15% of acute strokes. This lecture will focus mainly on the therapy of ischemic stroke, which occurs the remaining 85% of the time. Figure 1 shows the various etiologies of ischemic stroke and their frequency [1].

Atherosclerotic disease of either large or small arteries is the most common cause. Large artery disease is usually due to occlusion by an atherosclerotic plaque, which can cause arterial stenosis or lead to artery-to-artery emboli. Small artery disease in the penetrating vessels of the brain is the most common cause of the "lacunar" infarcts. Embolic strokes most commonly result from atrial fibrillation leading to mural thrombi and subsequent cardiac embolism.

Nearly 30% of strokes fall into the cryptogenic category after a negative work-up. Cerebral angiography within a few hours of the stroke usually shows occlusions of intracranial arteries that then resolve within a few days. The hypothesis in these cases has been that there is transient embolic or thrombotic obstruction. It is particularly challenging in these patients to determine the optimal therapy.

Initial Assessment & Management

The patient with an acute stroke must be recognized as a medical emergency in the emergency room or acute care facility setting. It is imperative to perform a quick history, physical, and obtain the pertinent diagnostic tests to classify the stroke between hemorrhagic and ischemic. The following discusses individual parameters that need to be assessed thoroughly prior to initiating treatment. Care after admission is best done in the setting of either an ICU or a designated stroke unit for intensive nursing care and monitoring.

Emergent diagnostic tests

CT scan is a great test that is reliable to distinguish between hemorrhagic and ischemic stroke. Some studies have shown that CT can show signs of ischemia as early as 2 hours after the onset of symptoms [2], but it may take more time in some cases. If an extensive infarct is seen, there is a higher chance of secondary hemorrhage or edema formation. CT is readily available in many centers and should be the first test of choice in the evaluation of a stroke patient. CT can also be useful in diagnosing other illnesses that are frequently confused with stroke.

MRI is more sensitive than CT but is not readily available in many centers as a stat study. MRA, diffusion MRI, and perfusion MRI are excellent techniques and may replace CT in the future if they become cost effective. EKG should be done to look for arrythmias, as these are frequently associated with embolic stroke. Basic laboratory tests such as CBC, electrolytes, LFTs, and PT/PTT should be obtained at baseline.

Airway protection

Adequate oxygenation is key in stroke management. It is thought that adequate oxygenation is important to preserve metabolic turnover in the penumbra, the marginal zone of insult. It is also important to make sure that the airway is patent, especially in patients who have a seizure due to the stroke. Intubation is also an option in patients with large hemispheric infarcts and unconscious patients who are at risk for aspiration pneumonia. One study showed that the 1-year survival of patients requiring intubation was nearly 33% [3].

Cardiac care

EKG is important to recognize any cardiac arrythmias, changes in ST segments, or even deep T wave inversions that can be seen in significant CNS disease. Cardiac enzymes can also be elevated in a stroke [4], and this is frequently a secondary cardiac event. However, a patient can have both a stroke and a MI in the same setting [5]. Hypotension can be managed with either dobutamine or dopamine, depending on the patient's heart rate and volume status.

Blood pressure management

As the cerebrum becomes infracted, blood flow regulation in the area can be defective. As a result, flow to the infracted area becomes dependent on mean arterial pressure. The blood pressure usually becomes elevated to maintain this flow to the infracted area. It is critical not to lower the blood pressure too much as this will decrease the cerebral blood flow. In patients with established hypertension, one should target a systolic BP of 180 and a diastolic BP of 100-105 mm Hg. In patients without established hypertension, one should target a systolic BP of 160-180 and a diastolic of 90-100 mm Hg. If the systolic is greater than 220 or the diastolic is greater than 120, the following regimens are some that are used and recommended [6, 7].

1.) Captopril 6.25-12.5 mg orally
2.) IV regimens
   a.) Labetalol 5-20 mg IV followed by drip if needed
   b.) Hydralazine 5 mg IV
   c.) Metoprolol 10 mg IV
   d.) Nitroglycerin 5 mg IV followed by drip if needed
   e.) Sodium nitroprusside 1-2 mg IV

Labetalol and Metoprolol should be used cautiously in patients with asthma, CHF, severe conduction abnormalities, and bradycardia. Oral nifedipine has a rapid effect and is discouraged as initial therapy to lower blood pressure.

Glucose metabolism

Diabetes is often diagnosed newly during a stroke, but diabetes is a major risk factor. The serum glucose tends to increase markedly with the stress of a stroke, and one should avoid D5W infusions [8]. The hyperglycemia enhances anaerobic metabolism with resultant lactic acidosis, worsens tissue damage, and increases risk of reperfusion hemorrhage. Insulin can be administered in the acute setting to lower the glucose if needed.

Body temperature

Patients are more susceptible to infection after a stroke [9] with causes such as aspiration pneumonia, etc. Experimental studies have shown that fever can increase the infarct size and can lead to a poor outcome [10]. It is important to not only treat the cause of the fever but also to lower the body temperature itself with antipyretics.

Specific treatment

The choice of therapies for acute stroke has been somewhat controversial and challenging. The following section will describe the various therapies available and the supporting evidence for each therapy.

Thrombolytic therapy

Thrombolytic therapy was studied for stroke treatment on the premise that angiograms have shown occlusive clot in nearly 80% of ischemic strokes [11]. Early experimental studies had shown evidence that thrombolytics could lyse the clot, but the

main concerns were risk of hemorrhage. There was renewed hope in this therapy after it was shown that thrombolytics were quite beneficial in the treatment of MI. von Krummer et al [12] reported three cerebral hematomas and seven hemorrhagic transformations in 33 patients treated with tPA and heparin. Another open study (part of it done at UTSW) by Wolpert & Greenlee et al [13] of 104 patients given IV tPA within 8 hours of stroke onset had an 11% incidence of parenchymal hematomas. Hemorrhagic transformation was more likely if the patients received tPA after 6 hours of stroke onset, had hypertension, or received large doses of tPA. Based on these and other pilot studies, large-scale trials were done using 0.9 mg/kg at 90 minute and 180 minute therapeutic windows. The following summarizes the results from the 4 trials.

				Symptomatic ICH		Mortality	
Study	**# Patients**	**Dose (mg)**	**Time given (hours)**	**tPA (%)**	**Placebo (%)**	**tPA (%)**	**Placebo (%)**
NINDS	624	0.9	<3	6.4	0.6	17.4	20.6
ECASS-I	620	1.1	<6	19.8	6.5	22	15.6
ECASS-II	800	0.9	<6	8.8	3.4	10.5	10.7
ATLANTIS-B	547	0.9	3-5	7.0	1.1	11.0	6.9

Large scale trials of tPA

1.) **NINDS rt-PA study** [14]

This was a randomized, double blind, placebo-controlled study that enrolled 624 patients to receive tPA within 3 hours of symptom onset. Each patient received a pretreatment CT scan to rule out hemorrhage. Eligible patients received 0.9 mg/kg tPA or placebo treatment given as 10% bolus over 1 minute with subsequent infusion over the next hour. Systematic algorithms were developed to maintain the blood pressure at <180 mm Hg systolic and <110 mm Hg diastolic. There were 2 parts to the study with different outcome measures. Part 1's primary endpoint looked at 24-hour improvement of neurological deficits. Part 2's primary endpoint looked at 3-month complete neurological recovery.

Part 1 enrolled 291 patients while part 2 enrolled 333 patients. The results were reported together and showed that t-PA patients had a17% mortality at 3 months compared to 21% for placebo. The 24-hour improvement in neurological deficit was not statistically significant between the 2 groups, but the tPA group did have an improved neurological exam and score. The incidence of hemorrhage was 6.4% in the tPA group and 0.6% in the placebo group. However, the trial did show that tPA offered a benefit when given in a 3-hour window from symptom onset.

2.) **ECASS-I trial** [15]

This trial was a multi-center, double-blind, placebo-controlled trial randomizing 620 patients to IV tPA at a dose of 1.1 mg/kg or placebo within 6 hours of symptom onset. The primary endpoint was neurological function at 90 days. Patients with infarcts affecting >33% of the MCA territory were excluded as were patients with very severe strokes. The study included 511 patients because 109 were eliminated due to protocol violations. The results showed no significant difference in 30-day mortality between the

two groups, but major parenchymal hemorrhages occurred in 19.8% in the tPA group compared to 6.5% in the placebo group. The study concluded that tPA might be effective when given within 6 hours of stroke onset.

3.) **ECASS- II trial** [16]

This trial was a double-blind and placebo-controlled trial randomizing 800 patients to either 0.9 mg/kg IV tPA vs. placebo. Low-dose subcutaneous heparin was allowed in this study. The primary endpoint was neurological function at 90 days, defined as either favorable or unfavorable. Overall, 40.3% of tPA patients had a favorable outcome vs. 36.3% of the placebo group. Mortality was 10.3% in tPA vs. 10.5% in placebo. Intracranial hemorrhage occurred in 8.8% of tPA patients vs. 3.4% of placebo patients. The investigators concluded that tPA again is likely effective when given within a 6-hour window.

4.) **ATLANTIS trial** [17]

This trial was initiated in 1991 to evaluate the safety and efficacy of IV recombinant tPA in patients with ischemic stroke <6 hours in duration. The study was then changed to 0-5 hours of onset because of safety concerns in the 5-6 hour group. When the FDA approved tPA for ischemic stroke in 1996, the study was modified to 3-5 hour window. There were 547 patients randomized to 2 groups with the primary endpoint being 3 month outcomes. The trial was terminated early in July 1998 because an interim analysis suggested that tPA was unlikely to be beneficial. The 3 month improvement was seen in 34% of tPA patients compared to 32% of placebo patients. The 90-day mortality was 6.9 % in placebo vs. 11% in tPA. Intracranial hemorrhage occurred in 7% of tPA patients and 1.1% of placebo patients. As a result, the investigators concluded that tPA was not beneficial when given past 3 hours of symptom onset.

Conclusion: The data from these trials indicate that tPA is beneficial in ischemic stroke when given within 3 hours of symptom onset.

Large scale trials of streptokinase

1.) **MAST-Italy** [18]

This study randomized 622 patients to 1.5 million units of IV streptokinase over 1 hour, aspirin 300 mg/d for 10 days, both drugs, or placebo. The 10-day mortality and hemorrhage rates are listed below. There was no significant difference in death or disability in the groups given streptokinase.

	10 Day Mortality Rate	**Intracranial hemorrhage**
Streptokinase	27%	6%
Aspirin	10%	2%
Aspirin + Streptokinase	34%	10%
Placebo	12%	0.6%

2.) **MAST- Europe** [19]

This study randomized 270 patients with stroke of <6 hours duration to streptokinase 1.5 million units vs. placebo. The trial was halted early when the results

showed a hemorrhage risk of 17.5 % in streptokinase vs. 3% for placebo. The 10-day mortality was 35% with streptokinase vs. 18% with placebo.

3.) **ASK trial** [20]

The study randomized 340 patients within 4 hours of stroke onset to either 1.5 million units of streptokinase vs. placebo. The trial was also stopped after an increase in mortality and disability was seen in the streptokinase group.

Conclusion: Given the data from these 3 trials, it was concluded that streptokinase caused an increase in mortality and intracranial hemorrhage when given during a 6-hour window of symptom onset. The outcomes were worse when streptokinase was combined with aspirin.

Intra-arterial thrombolysis studies

Intra-arterial thrombolytics therapy is delivered either by local or regional infusion by a catheter. The advantage of this technique is that the drug can be delivered to a selective site with a lower total dosage. The disadvantage is that there are few centers trained in this technique in an efficient manner.

1.) **PROACT trial** [21]

The study randomized 40 patients with MCA occlusions to either intra-arterial rpro-UK or placebo. Both groups received IV heparin with the drugs given an average of 5 hours after symptom onset. The study group had a recanalization rate of 58% compared with 14% in the placebo group. Hemorrhage and mortality rates were not statistically significant between the 2 groups.

2.) **PROACT II trial** [22]

The study randomized 180 patients with MCA occlusion by angiogram to receive 9 mg intra-arterial rpro-UK plus IV heparin vs. IV heparin alone. The results are summarized below. The primary outcome was 3 month improvement in function, which was seen in 40% of the UK group and 25% of the heparin group.

	UK + Heparin	**Heparin**
Improved neurologic deficits	40%	25%
Mortality	25%	27%
Intracranial hemorrhage	10%	2%
Recanalization rate (TIMI grade 2 or 3)	66%	18%

Conclusion: The FDA has still not approved intra-arterial thrombolysis, and this is still being studied in future clinical trials. However, this appears to be a promising therapeutic alternative in the future in select patients similar to primary angioplasty in CAD.

Who should receive thrombolytics? [1]

1.) Age >18 years
2.) Clinical diagnosis of stroke < 3 hours from symptom onset

3.) Baseline CT showing no evidence of either intracranial or subarachnoid hemorrhage

Who should not receive thrombolytics? [1]

1.) CT showing hemorrhagic stroke
2.) Minor or rapidly improving symptoms or signs
3.) Seizures
4.) Previous stroke or head injury within past 3 months
5.) Minor surgery or serious trauma within past 2 weeks
6.) GI bleed or urinary tract hemorrhage within past 3 weeks
7.) Systolic BP >185, diastolic BP > 110 mm Hg
8.) Glucose <50 or >400 mg/dL
9.) LP within past week
10.) Platelets < 100,000
11.) Heparin therapy within past 48 hours or current use of oral anticoagulants with INR > 1.7
12.) Pregnancy or lactating women
13.) Arterial puncture at a noncompressible site within the past 7 days

Antithrombotic and Antiplatelet Therapy

For patients who are not eligible for thrombolytics, the options have included several antithrombotic therapies. This also applies to patients with embolic strokes from both carotid and heart disease, or to patients with less common disorders such as antiphospholipid antibody syndrome and cerebral venous sinus thrombosis. The rationale for use of anithrombotic therapy has been to reduce the risk of stroke progression or recurrent cerebral thromboembolism and prevent DVT/PE. The following will discuss the different treatment options and the evidence supporting them.

Heparin

1.) **IV Heparin trials**

There has only been 1 randomized trial investigating the effect of IV Heparin on acute ischemic stroke [23]. The study randomized 225 patients to IV Heparin vs. placebo to maintain the PTT to 1.5-2.5 times control. The Heparin could be given up to 48 hours after symptom onset and excluded patients with progressing stroke or stroke from a presumed cardioembolic source. There was no difference in any of the outcomes between the 2 groups. There have been other small trials using open administration of IV heparin, but the data shows similar findings. These studies even prompted the AHA to make the following statement in 1994 [24]:

> "Until more data are available, the use of heparin remains a matter of preference of the treating physician. It should be understood that the use of heparin (or the lack of its administration) may not alter the outcome of a patient with acute ischemic stroke."

The American Stroke Association and the American Academy of Neurology further modified this statement in a joint report in July 2002 [70]:

> "IV, unfractionated heparin, or high-dose LMW heparin/heparinoids are not recommended for any specific subgroup of patients with acute ischemic stroke that is based on any presumed stroke mechanism or location (e.g. cardioembolic, large vessel atherosclerotic, vertebrobasilar, or "progressing" stroke) because data are insufficient (Grade U). Although the LMW heparin, dalteparin, at high doses may be efficacious in patients with atrial fibrillation, it is not more efficacious than aspirin in this setting. Because aspirin is easier to administer, it, rather than dalteparin, is recommended for the various stroke subgroups (Grade A)."

2.) **Subcutaneous Heparin trial**

The **International Stroke Trial** (IST) [25] was an unblinded trial that randomized 19,435 patients from multiple centers with suspected acute ischemic stroke to aspirin, SQ heparin, both, or neither. The treatment was given within 48 hours of symptom onset, 300 mg of aspirin, and 2 different doses of SQ heparin (5000 U or 12,500 U). Half of the patients received 300 mg of aspirin while the other half received none. The primary outcomes were 14 day and 6 month mortality. Secondary outcomes included recurrent ischemic stroke, hemorrhagic stroke, PE, or fatal extracranial hemorrhage. The results were analyzed by combining the heparin groups and no heparin groups together and showed a 14 day mortality of 9% in heparin group, 9% aspirin group, 9.3% no heparin group, and 9.4% no aspirin group. The 6-month mortality or dependency rate was 62.9% in both groups.

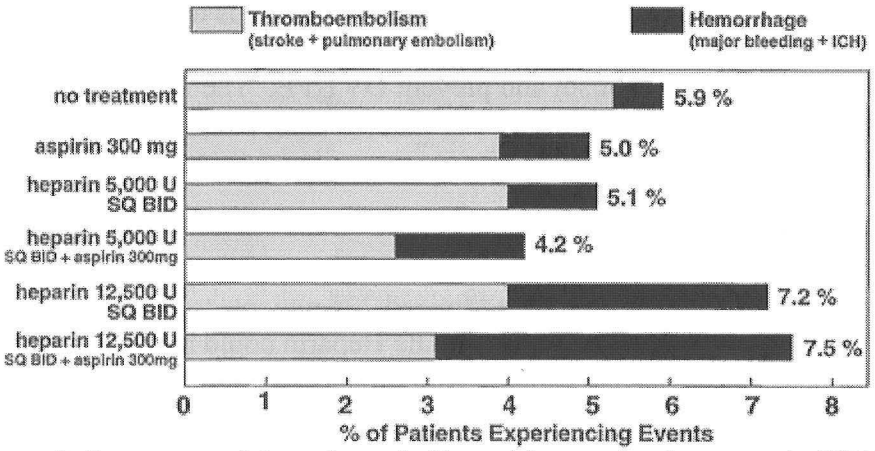


Figure 2. Summary of thromboembolic and hemorrhagic events in IST [1]

The complications of the treatments are shown above. Heparin did provide some benefit to patients with atrial fibrillation, but this was negated by the increased risk of hemorrhage. The investigators concluded that SQ heparin likely reduced early stroke recurrence but led to an increased risk of hemorrhage. In European centers, CT scan was not required prior to giving heparin and some of the hemorrhages may have been present prior to heparin administration.

3.) **Low Molecular Weight Heparin**

a.) **Hong Kong Trial** [26]- This study randomized 308 patients to either high-dose (4100 anti-Xa U BID), low-dose (4100 anti-Xa IU daily) nadroparin (fraxiparin), or placebo within 48 hours of symptom onset. There was no significant effect noted between the 3 groups at 3 months, but the heparin groups had a higher risk of death or dependency at 6 months.

b.) **FISS trial** [27]- This study randomized 767 patients with acute ischemic stroke within 24 hours of symptom onset to high-dose or low-dose fraxiparin and placebo. The 6 month risk of death or dependency was 59.2% in the high-dose group, 57.2% in the low-dose group, and 56.8% for the placebo group.

c.) **TOAST trial** [28]- This study randomized 1281 patients within 24 hours of symptom onset to danaparoid (ORG 10172) or placebo. The patients were given 7 days of IV infusion and had daily dose adjustments based on antifactor Xa units. The primary endpoint was 3 month outcomes and the results are shown in Figure 3. The results were similar in both groups. Subgroup analysis showed that the heparin had a beneficial effect in patients with large artery atherosclerosis.

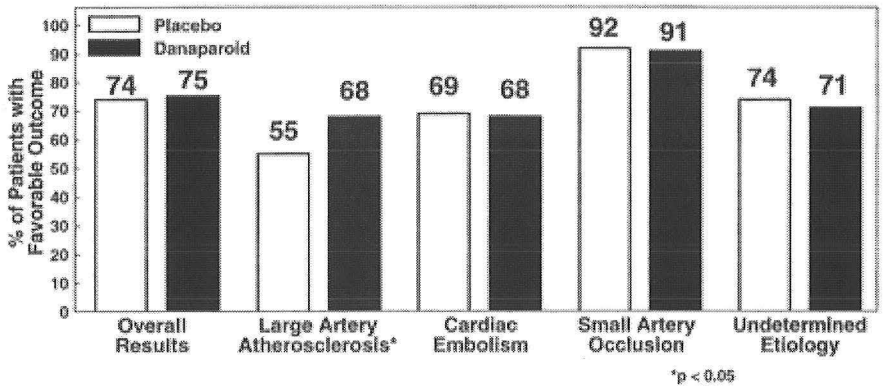


Figure 3. TOAST trial outcomes

d.) **HAEST trial** [29]- This study looked at effect of dalteparin in patients with suspected embolic stroke due to atrial fibrillation. 449 patients were randomized to aspirin 160 mg vs. high dose dalteparin within 30 hours of onset of symptoms. There was no difference in outcomes or recurrence of ischemic stroke between the 2 groups.

e.) **TOPAS trial** [67]- This was a prospective, non-placebo controlled trial that randomized 400 patients to receive 4 different doses of SQ certoparin within 12 hours of symptoms onset. The patients received either 3000 U QD, 3000 U BID, 5000 U BID, or 8000 U BID. There was no benefit shown in the short term or at 3 months in stroke outcome between the low or high dose groups.

f.) **TAIST trial** [68]- This double-blinded study randomized 1486 patients with acute ischemic stroke within 48 hours of onset to either high dose tinzaparin (175 anti-Xa IU/kg), low dose tinzaparin (100 anti-Xa IU/kg), or aspirin 300 mg/day for 10 days. The outcomes were 6-month disability, death, and neurologic recovery. There was no statistical difference between the 3 groups, but there were 9 DVTs in the aspirin group and none in the tinzaparin group.

Conclusion: The studies above seem to indicate that low molecular weight heparin is not beneficial for improvement of stroke symptoms when started within 24-48 hours of symptom onset. There is a benefit in DVT prevention but an increased risk in hemorrhage. Future studies will need to better address this question. Until then, the use of heparin is up to the treating physician's preference.

Aspirin

Aspirin is the only antiplatelet agent that has been evaluated for treatment of acute ischemic stroke. There have been 3 trials that have looked at the effect of aspirin.

1.) **IST trial** [25]- described previously. The trial showed no difference between the groups treated with aspirin, heparin, or neither for the combined endpoint of severe disability or death. Secondary analysis showed that aspirin did decrease the rate of recurrent ischemic stroke at 2 weeks (2.8% in aspirin group vs. 3.9% in no aspirin group).

2.) **CAST trial** [30]- This study randomized 21,106 patients with acute ischemic stroke within 48 hours of symptom onset to aspirin 160 mg or placebo for 4 weeks. The primary endpoint was death from all causes at 1 month and at hospital discharge. There was no major difference between the 2 groups in mortality (3.3% in aspirin vs. 3.9% in placebo) or recurrent ischemic strokes (1.6% in aspirin vs. 2.1% in placebo). Combining the IST and CAST trials did show that aspirin can prevent 1 early death, recurrent stroke, or late death for every 111 patients treated.

3.) **MAST-Italy**- described previously. This trial showed no major difference between aspirin and streptokinase.

Conclusion: Aspirin (160 mg or 325 mg daily) results in a small but statistically significant reduction in death and disability when given within 48 hours after ischemic stroke.

Ancrod

Ancrod is a thrombin-like defibrinogenating agent derived from a purified snake venom fraction. It converts fibrinogen into soluble fibrin products with a subsequent decrease in plasma concentrations of fibrinogen and depletion of the substrate needed to form a thrombus. This also leads to decreased platelet aggregation, reduces blood viscosity, and increases cerebral blood flow. It is also thought that the fibrinogen breakdown products indirectly stimulate plasminogen activators, which may enhance clot lysis [31].

The **STAT** trial [32] randomized 500 patients to ancrod vs. placebo within 3 hours of symptom onset. The ancrod was given as a 72 hour infusion followed by 1 hour infusions at 96 and 120 hours. The dose was adjusted to keep plasma fibrinogen levels between 40-69 mg/dL. Ancrod improved the outcome in 42.2% of the patients compared to 34.4% in the placebo group. There was no difference in mortality, but the incidence of CNS hemorrhage was 5.2% in the ancrod group compared to 2% in the placebo group.

Conclusion: Ancrod has still not approved by the FDA and it is still being investigated. It appears promising as an effective therapy for acute ischemic stroke. The **European Stroke Treatment with Ancrod Trial** (ESTAT) [1] is in progress and will evaluate 1680 patients randomized to either ancrod or placebo within 6 hours of symptom onset.

Abciximab

There has been one small trial looking at the effect of abciximab in acute ischemic stroke. The study [69] was a phase II, randomized, double blind, and placebo-controlled where 74 patients (54 abciximab, 20 placebo) were randomized to receive either abciximab or placebo within 24 hours of stroke onset. There was a trend toward a higher rate of recovery in the abciximab group, but the trial did not have sufficient power to detect differences in functional outcome assessments. The 3-month mortality rate was not statistically different between the 2 groups (15% placebo vs. 17% abciximab).

Conclusion: Abciximab appears to improve short-term recovery but does not appear to improve outcome or mortality. Future larger studies will need to be done to evaluate the full effect of the drug.

Stroke Prevention

The key to preventing any disease is the early detection and treatment in addition to prevention. In the case of stroke, there have been many studies looking at the different therapies for both primary and secondary prevention. The following will discuss the different treatments and the supporting evidence for them.

Primary Prevention

Primary prevention implies that treatment of a general population at risk would significantly decrease the incidence of a disease. The following table shows the major risk factors for stroke, prevalence, and the relative increase in risk [71].

Factor	Prevalence (%)	Increased Risk
Hypertension	25-40	5-10 times
Diabetes mellitus	5-10	2 times
Hypercholesterolemia	6-40	1.5 times
Smoking	25	2 times
Obesity	18	1.5 times
Asymptomatic carotid stenosis (>50%)	2-8	2 times
Atrial fibrillation	1	5 (nonvalvular) 17 (valvular)

Hypertension

Hypertension is probably the most prevalent and easiest modifiable risk factor for stroke. Several studies have looked at the benefit of lowering blood pressure and the optimal blood pressure for prevention.

The **SHEP** trial [33] looked at management of isolated systolic hypertension greater than 160 mm Hg in patients over 60. The results showed that lowering the systolic below 160 mm Hg reduced the total incidence of stroke by 36%, and it was estimated that the 5-year benefit would be a prevention of 30 events per 1000 patients. The main classes of drugs used were β-blockers and diuretics, but ACE inhibitors [34] and ARBs [74] have also been shown to be beneficial. A recent further analysis of the SHEP trial [35] showed that lowering blood pressure reduced the incidence of both hemorrhagic and ischemic strokes.

Other meta-analysis trials [36] have shown a significant reduction of 42% in stroke with a decrease of 5-6 mm Hg in the diastolic pressure and 9-10 mm Hg in systolic pressure. Although a target had not been established in these studies, it was accepted to lower the systolic to <150 mm Hg and the diastolic to <90 mm Hg. The **HOT** study [37] did show a decrease in the incidence of stroke by lowering the BP to 135-140/85-90.

Diabetes mellitus

Although diabetes is clearly an independent risk factor for stroke, there has not been much evidence to support that control of diabetes prevents the macrovascular complications. Diabetics have a higher incidence of hypertension and atherosclerotic disease, and this likely leads to the increased incidence of strokes. Intensive therapy in Type 2 diabetics with either sulfonylurea and/or insulin decreased the microvascular complications but not macrovascular complications [38].

Hypercholesterolemia

Hypercholesterolemia has been well linked to CAD through many trials, but the link to stroke is less established. Many of the studies were done with statins looking at the effect on CAD, and stroke was measured in subanalysis of the data. Sheperd et al. found 31% relative risk reduction in stroke in patients treated with pravastatin [39]. The **CARE** study [40] showed a 32% relative risk reduction of stroke in patients treated with pravastatin. Meta-analysis of nearly 16 trials [41] showed a 29% relative risk reduction in stroke and 28% relative risk reduction in deaths in patients treated with statins. There has not been a published randomized trial looking at direct effect of statins in stroke prevention as a primary outcome. However, the **SPARCL** study has completed randomization and the results are expected within a year. Most of the data has been extrapolated from the cardiovascular trials. From this data, it appears that lipid lowering with statins to levels recommended by NCEP would be beneficial in preventing stroke as secondary prevention and likely primary prevention.

Smoking

The risk of cigarette smoking has been evaluated in both men and women and is as high as 6 times that of nonsmokers [42, 43]. The true risk depends on the number of cigarettes the patient smokes, but both of the studies found that smoking cessation can reduce the risk by up to 50% of stroke.

Obesity

Obesity has been linked to many cardiovascular and pulmonary diseases partly through the insulin resistance syndrome. The Physician Health Study [44] showed that exercise is associated with a decreased risk of stroke mainly by lowering body weight, blood pressure, serum cholesterol, and blood sugar.

The following table summarizes the effectiveness of primary prevention strategies [71].

Strategy	**Relative Risk Reduction**	**Number needed to treat to prevent 1 stroke a year**
HTN therapy if BP increased	42 %	7,937
Statin therapy if LDL elevated	25 %	13,333
Aspirin	RR increase	N/A
Aspirin after MI	36 %	400
ACE inhibitor	30 %	11,111

Conclusions: Treating hypertension, reducing weight, and quitting smoking can greatly prevent strokes. Lowering the LDL in patients with risk factors also seems to lower the incidence of strokes. Treatment of diabetes does not directly prevent strokes but does improve the patient's general health.

Aspirin

1.) **British male physician study** [45]- This study randomized (in an unblended fashion) 5139 male physicians to receive no treatment vs. 500 mg aspirin daily. There was no difference in the incidence of MI, but the aspirin group had a higher incidence of disabling strokes. There was limited data on whether the strokes were thrombotic or hemorrhagic, but it is presumed to be hemorrhagic.

2.) **Physician's Health Study** [46]- This study was a randomized, double-blinded, placebo-controlled trial that randomized 22,071 male physicians to either 325 mg aspirin vs. placebo every other day. There was a 44% relative risk reduction of MI, but there was a slight increase in stroke (likely hemorrhagic) that was not statistically significant.

3.) **Nurses' Health Study** [47]- This was a prospective study that looked at the incidence of stroke in women taking aspirin. The aspirin group had a lower relative risk of MI, but there was no difference in the risk of stroke.

Conclusion: Aspirin does not seem to confer a benefit in primary prevention of stroke in asymptomatic individuals and led to an increased risk of hemorrhage.

Atrial Fibrillation and embolic stroke

Many studies have estimated that the risk of embolic stroke in patients with atrial fibrillation is approximately 5% a year. Many studies [48-53] have shown that coumadin can reduce the relative risk of stroke by up to 70% down to an incidence of 1-2% per year. The **European Atrial Fibrillation Study Group** study [54] showed that coumadin therapy in patients with atrial fibrillation was most effective when the INR was between 2.0- 3.0. This had a relative reduction of 80% of ischemic and hemorrhagic strokes when compared to an INR less than 2.0. If the INR was above 5.0, there was a higher risk of

bleeding complications that outweighed the benefits. As a result, coumadin is the mainstay of therapy in patients with atrial fibrillation to prevent embolic stroke.

There have been four randomized trials looking at the effect of aspirin in patients with atrial fibrillation. The pooled data from these trials [55] found that there was a relative risk reduction of 21% of strokes with 300 mg/day of aspirin when compared to placebo. Aspirin has become the recommended therapy for patients with lone atrial fibrillation under the age of 65. Patients over 65 may be considered for coumadin or aspirin therapy depending on their other risks. Otherwise, aspirin is an alternative therapy in any patient with atrial fibrillation who cannot take coumadin.

Although atrial fibrillation is the major cause of embolic stroke, the table [1] below lists some of the other causes. These would all be considered possible indications for chronic anticoagulation.

Major risk	**Minor or Uncertain Risk**
Atrial fibrillation	Mitral valve prolapse
Mitral stenosis	Mitral annular calcification
Prosthetic mechanical valves	Patent foramen ovule (PFO)
Recent MI	Atrial septal aneurysm
Left ventricular thrombus	Calcific aortic stenosis
Atrial myxoma	Mitral valve strands
Infective endocarditis	
Dilated cardiomyopathy	
Marantic endocarditis	

The table below summarizes the current recommendations for aspirin vs. coumadin therapy in patients with atrial fibrillation for primary prevention of stroke [71].

Biannual Stroke Risk	**Patient Features**	**2001 ACCP Recommendations**	**NNT to prevent 1 stroke**
Low (~2%)	Age <65, no major risk factors	Aspirin	227
Low moderate (3%)	Age 65-75, no major risk factors	Aspirin or coumadin (INR 2-3)	ASA: 152 Coum: 54
High moderate (5%)	Age 65-75 with DM or CAD	Coumadin (INR 2-3)	32
High (12%)	Age <75 with HTN or CHF Age > 75, no major risk factors	Coumadin (INR 2-3)	14
Very high (20%)	Age >75 with HTN, CHF, or prior CVA, TIA, or embolic	Coumadin (INR 2-3)	8

Conclusion: Coumadin is the recommended therapy for stroke prevention in patients with atrial fibrillation (especially in patients over the age of 65) unless the patients are a fall risk or have complications from coumadin. Aspirin is an alternative therapy in these patients and in patients with lone atrial fibrillation.

Asymptomatic Carotid Stenosis and Carotid Endarterectomy (CEA)

The role of CEA as primary prevention for asymptomatic carotid disease has been controversial. There have been many small trials showing equivocal or conflicting results. The largest trial was the **Asymptomatic Carotid Atherosclerosis Study**, which compared the 5-year survival in 1662 patients undergoing CEA vs. standard therapy [56]. The study found that patients with greater than 60% carotid stenosis have a 5-year relative risk reduction of 53% of ipsilateral stroke when they had a CEA. The absolute risk reduction was only 5.9% in 5 years, and the incidence of stroke in the medically treated group was only 11% in 5 years or 2.3% annually.

Conclusion: CEA does seem to confer some benefit as primary prevention in asymptomatic patients with carotid stenosis > 50% if the operative risk is low (<3%). This data has left the physician to treat each patient on a case-by-case basis.

Secondary Prevention

Secondary prevention implies the prevention of a disease recurrence in a patient who has already manifested the disease. The following section looks at the evidence supporting the various therapies.

Aspirin

1.) **Swedish Aspirin Low-Dose Trial (SALT)** [57] - This study randomized 1360 patients with minor stroke/TIA to 75 mg/day of aspirin vs. placebo. There was an 18% relative risk reduction in stroke plus all death in the aspirin group and a 17% relative risk reduction in stroke, MI, or vascular death. These results were statistically significant and agreed with a previous study that found benefit in patients taking aspirin at any dose above 30 mg/day [58].

2.) **Dutch TIA Trial** [59] - This study randomized 3131 patients with minor stroke/TIA to either 30 mg/day or 273 mg/day of aspirin. The primary endpoint was incidence of stroke, MI, or vascular death. There was no difference between the 2 groups, and there were fewer bleeding events at the 30 mg dose.

3.) **ESPS-II** [60]- This study randomized 6602 patients to one of four arms: aspirin 25 mg BID, extended-release dipyridamole 200 mg BID, aspirin + dipyridamole, or placebo with a 2 year follow-up. The results are summarized below.

Treatment	Relative risk reduction of stroke recurrence compared to placebo
Aspirin	18 %
Dipyridamole	16 %
Aspirin + Dipyridamole	37 %

When compared to aspirin alone, the combination of dipyridamole and aspirin relatively reduced the risk of stroke by 23%.

4.) **ACE trial** [61] - This study looked at the effects of different doses of aspirin for stroke prevention in patients undergoing CEA. The 2804 patients were randomized to aspirin at 4 doses: 81 mg, 325 mg, 650 mg, or 1300 mg a day for a total of 3 months. The endpoints were 30 day incidence of stroke or death and 3 month incidence of ipsilateral stroke or death. There were no major differences between the low and high dose groups for all endpoints at 30 days. However, the aspirin group did have a statistically lower rate of stroke, MI, and death at 3 months. This led to the recommendation to use 325 mg aspirin for the first 3 months after a CEA.

Conclusion: There is still no consensus on the recommended dose of aspirin for stroke prevention. The FDA published their guidelines in 1998 stating that aspirin can be used between 50 mg/day to 325 mg/day for stroke prevention. The American Heart Association and Stroke Council recommended in 1999 that aspirin can be used between 30 mg/day to 1300 mg/day for stroke prevention. Ultimately, the choice is left up to the clinician and the risks vs. benefits for the patient.

Clopidogrel

Clopidogrel is a thienopyridine derivative of the same chemical family as ticlopidine. It inhibits platelet aggregation by inhibiting the action of adenosine diphosphate. The **CAPRIE** study [62] evaluated the effects of clopidogrel in three groups: recent ischemic stroke, recent MI, and symptomatic peripheral arterial disease. The 19,185 patients (6431 of which had ischemic stroke) were randomized to either clopidogrel 75 mg/day or aspirin 325 mg/day for nearly 2 years. The primary outcome was the composite risk of ischemic stroke, MI, or vascular death.

The aspirin group had a 5.83% annual risk for the endpoints vs. 5.32% risk for clopidogrel. This 0.5% absolute risk reduction translated to 8.7% relative risk reduction and was not statistically significant. The number needed to treat for this difference is 200 patients to save one event between the 2 groups, but the investigators concluded that clopidogrel was at least as safe and effective as aspirin. Clopidogrel is safer than Ticlopidine and has replaced it as the drug of choice for prevention if aspirin is not an alternative. Adverse effects of clopidogrel include case reports of neutropenia, TTP, and hemorrhage.

Conclusion: Clopidogrel does seem to confer some benefit in secondary prevention of stroke.

Dipyridamole

Dipyridamole is another anitplatelet drug that inhibits platelet aggregation by inhibiting phosphodiesterase. There have been ten trials comparing dipyridamole to placebo, and they showed a 23% odds reduction for stroke with dipyridamole. The **Antiplatelet Trialists** [63] performed a meta-analysis of 14 trials that compared dipyridamole, aspirin, and the combination of the two. The data suggests that aspirin was slightly more beneficial than the combination of dipyridamole and aspirin or dipyridamole alone. However, this benefit was not statistically significant. The **ESPS-2**

study described earlier also showed that the combination of the two has more benefit than aspirin alone in preventing stroke.

Once again, there are no direct trials comparing all 3 antiplatelet therapies of clopidogrel, aspirin, and dipyridamole. The data from various trials suggests that all 3 are effective and have different risk/benefit ratios. The cost of the drug is also an important consideration. It is again up to the clinician to select the appropriate antiplatelet agent for r prevention. Most physicians choose aspirin first and save clopidogrel either for patients who fail aspirin or cannot tolerate aspirin.

Conclusion: The data is somewhat conflicting for dipyridamole, but it is still a viable option for secondary prevention.

Anticoagulation

1.) **European Atrial Fibrillation Study Group trial** – This study was described earlier and showed that coumadin (target INR of 2-3) is the preferred therapy in patients with recurrent embolic stroke and atrial fibrillation.

2.) **SPIRIT trial** [72]- This study randomized 1316 patients with nonembolic stroke to coumadin with a target INR of 3.0-4.5 vs. aspirin 30 mg/day. The study was stopped prematurely because there were 27 intracranial hemorrhages in the coumadin group and overall excess bleeding in the coumadin group. The comparative data between aspirin and coumadin could not be determined.

3.) **WARSS trial** [73]- This study randomized 2206 patients with previous nonembolic stroke to receive either warfarin to an INR of 1.4-2.8 vs. aspirin 325 mg/day for a 2 year period. The primary endpoint was death or recurrent ischemic stroke, which was seen in 17.8% of the coumadin group vs. 16.0% of the aspirin group. The rate of hemorrhage was low in both groups (2.22/100 patient years in coumadin group vs. 1.49/100 patient years in aspirin group). The investigators concluded that there was no statistical difference between aspirin and coumadin for prevention of recurrent ischemic stroke, but coumadin was less cost-effective and required more monitoring than aspirin.

Conclusion: There is inadequate data to support the use of anticoagulation in nonembolic stroke. However, anticoagulation is the recommended therapy in patients with atrial fibrillation for secondary stroke prevention.

CEA

There have been 2 major trials evaluating the role of CEA in patients with symptomatic ipsilateral carotid stenosis greater than 70%. The **ECST** trial [64] found that patients undergoing CEA for carotid stenosis greater than 70% had an absolute risk reduction of ipsilateral stroke of 6.5% and a relative risk reduction of 39%. This benefit was offset in some cases with a 7.5% perioperative risk of complications (death, disabling stroke, or stroke symptoms for > 7 days).

The **NASCET** trial [65] found an absolute risk reduction of 17% of ipsilateral stroke at 2 years in patients undergoing a CEA for symptomatic carotid stenosis >70%. A

further analysis of symptomatic patients with 50-69% stenosis who underwent CEA revealed an absolute risk reduction of 6.5% and a relative risk reduction of 29% of stroke.

Conclusion: Most physicians would reserve CEA for patients with significant stenosis >50% and symptoms of TIA or stroke as secondary prevention. Patients undergoing CEA should receive aspirin 81-325 mg before and after the surgery.

Angioplasty

Percutaneous transluminal angioplasty (PTA) of the carotid artery could be a feasible alternative in the future when this technique becomes more widely available. PTA with stenting appears to be a promising technique, and the **CAVATAS** [75] trial is the first randomized comparison of angioplasty and CEA. This study randomized 504 patients with carotid artery stenosis to CEA vs. PTA with 3- year follow-up. Both groups received aspirin and the PTA group also received heparin prior to angioplasty. The PTA group also received stenting as per the treating physician. The outcomes are shown below.

Outcomes	Endovascular treatment	Endarterectomy	RRR (95% CI)	NNT
Nondisabling stroke at 30 d	3.6%	4.0%	9% (−114 to 62)	Not significant
			RRI (CI)	NNH
Death or disabling stroke at 30 d	6.4%	5.9%	8% (−45 to 110)	Not significant
Death or disabling stroke at 3 y	14.3%	14.2%	0.8% (−34 to 54)	Not significant

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

Figure 4. CAVATAS trial outcomes [76]

This study had too small a power to completely answer the questions, but the data showed that both CEA and PTA were equally effective for treatment of carotid stenosis. Further studies need to address this question.

The following table summarizes the effectiveness of secondary prevention strategies [71].

Strategy	Relative Risk Reduction	NNT to prevent 1 stroke
HTN therapy if BP elevated	28 %	51
Statins if LDL elevated	25 %	57
Coumadin for nonrheumatic atrial fibrillation	62 %	13
Smoking cessation	33 %	43
Aspirin	28 %	77
Clopidogrel vs. aspirin	13 %	64
CEA for symptomatic stenosis >50%	44 %	26

Summary of recommendations for stroke treatment

Acute ischemic stroke within 3 hours of symptom onset

1.) IV tPA at dose of 0.9 mg/kg with 10% as initial bolus and the remainder infused over 60 minutes for eligible patients as noted by inclusion and exclusion criteria after screening head CT or MRI is obtained to rule out hemorrhagic stroke.

2.) Thrombolytic therapy should be withheld if CT shows clear evidence of extensive brain edema or mass effect.

Acute ischemic stroke within 3-6 hours of symptom onset

1.) IV tPA and streptokinase are not recommended and are investigational.
2.) In patients where angiogram shows MCA occlusion and no CT signs of major infarction, intra-arterial thrombolysis is a feasible treatment option.

Acute ischemic stroke not eligible for thrombolytics

1.) IV Heparin, SQ heparin, and LMW heparin have not been shown to improve mortality or outcomes in acute ischemic stroke and are not recommended.
2.) Clinicians may consider anticoagulation for treatment of acute cardioembolic stroke and large artery ischemic strokes or progressing strokes where the mechanism is suspected to be thromboembolic in nature.
3.) Aspirin 160 mg/day to 325 mg/day is recommended for patients not receiving thrombolytics or IV heparin within 48 hours of symptom onset. Aspirin may be given safely in combination with SQ heparin (for DVT prophylaxis).

Summary of recommendations for stroke prevention

Antiplatelet agents

For nonembolic strokes or TIA, the following are acceptable options for secondary prevention.

1.) Aspirin 50 mg to 325 mg PO QD
2.) Aspirin 25 mg BID + Dipyridamole 200 mg PO BID
3.) Clopidogrel 75 mg PO QD

Anticoagulants

1.) There is inadequate data to recommend anticoagulation for nonembolic stroke.
2.) Long-term anticoagulation is recommended as primary and secondary prevention for embolic stroke in patients with atrial fibrillation with a goal INR of 2.0-3.0.
3.) Patients who are unable to tolerate anticoagulation or have risks for anticoagulation may be given aspirin 325 mg/day.

Carotid stenosis

1.) CEA is beneficial for some patients with asymptomatic carotid stenosis depending on the operative risk.
2.) CEA is beneficial for patients with symptomatic stenosis of >70% and may be beneficial for patients with symptoms and 50-69% stenosis.

3.) Aspirin 81 mg to 325 mg/day should be given to patients undergoing CEA before and until 3 months after the procedure.

Abbreviations

Abbreviation	Trial	Page #
ACAS	Asymptomatic Carotid Atherosclerosis Study	17
ACE	ASA and Carotid Endarterectomy trial	18
ASK	Australian Streptokinase trial study group	8
ATLANTIS	Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke	7
CAPRIE	Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events	18
CARE	Cholesterol and Recurrent Events study	14
CAST	Chinese Acute Stroke Trial	12
CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study	20
ECASS	European Cooperative Acute Stroke Study	6,7
ECST	European Carotid Surgery Trial	19
ESPS	European Stroke Prevention Study	17
ESTAT	European Stroke Treatment with Ancrod Trial	13
FISS	Fraxiparine in Ischemic Stroke Study	11
HAEST	Heparin in Acute Embolic Stroke study	11
HOT	Hypertension Optimal Therapy study	14
IST	International Stroke Trial	10,12
MAST	Multicentre Acute Stroke Trial	7,12
NASCET	North American Symptomatic Carotid Endarterectomy Trial	19
NINDS	National Institute of Neurological Disorders and Stroke	6
PROACT	Prolyse in Acute Cerebral Thromboembolism	8
SALT	Swedish Aspirin Low-dose Trial	17
SHEP	Systolic Hypertension in the Elderly Program	14
SPARCL	Stroke Prevention with Atorvastatin to Reduce Cholesterol Levels	14
SPIRIT	Stroke Prevention in Reversible Ischemia Trial	19
STAT	Stroke Treatment with Ancrod Trial	12
TAIST	Tinzaparin in Acute Ischemic Stroke Trial	11
TOAST	Trial of ORG 10172 in Acute Stroke Treatment	11
TOPAS	Therapy of Patients with Acute Stroke	11
WARSS	Warfarin Aspirin Recurrent Stroke study	19

References

1.) Albers G.W., et al. Sixth ACCP Consensus Conference on Antithrombotic Therapy. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke. Chest 2001; 119:300S-320S.

2.) Kummer R von, et al. Acute stroke: usefulness of early CT findings before thrombolytics therapy. Radiology 1997; 205: 327-333.

3.) Grotta J, et al. Elective intubation for neurologic deterioration after stroke. Neurology 1995; 45: 640- 644.

4.) Kaste M, et al. Heart type creatinine kinase isoenzyme in acute cerebral disorders. Br Heart J 1978; 40: 802-805.

5.) Furlan A. The heart and stroke. 1994; Springer, Berlin Heidelberg New York.

6.) Ringleb PA, et al. Hypertension in patients with cerebrovascular accident. To treat or not to treat? Nephrol Dial Transplant. 1998; 13: 2179-2281.

7.) Hacke W, et al. European Stroke Initiative: recommendations for stroke management. Organisation of stroke care. Journal of Neurology. 2000; 247(9): 732-748.

8.) Pulsinelli W, et al. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med. 1983; 74: 540-544.

9.) Grau A, et al. Recent infection as a risk factor for cerebrovascular ischemia. Stroke. 1995; 26: 373-379.

10.) Reith J, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet. 1996; 347: 422-425.

11.) Fieschi C, et al. Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours. J Neurol Sci. 1989; 91: 311-322.

12.) von Kummer R, et al. Recanalization, infarct volume, cerebral hemorrhage and clinical outcome after recombinant tissue plasminogen activator and heparin in acute carotid stroke. In: del Zoppo GJ, Mori E, Hacke W, eds. Thrombolytic therapy in acute ischemic stroke. Berlin, Germany: Springer-Verlag, 1993; 53-58.

13.) Wolpert SM, et al. Neuroradiological evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. Am J Neuroradiol. 1993; 14: 3-13.

14.) The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995; 333: 1581-1587.

15.) Hacke W, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: The European Cooperative Stroke Study (ECASS). JAMA. 1995; 274: 1017-1025.

16.) Hacke W, et al. Randomized double-blind placebo controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II): Second European-Australian Acute Stroke Study Investigators. Lancet. 1998; 352: 1245-1251.

17.) Clark WM, et al. The rtPA (alteplase) 0 to 6 hour acute stroke trial, part A (A0276g): results of a randomized, double blind, placebo-controlled, multicenter study. Thrombolytic therapy in acute ischemic stroke study investigators. Stroke. 2000; 31: 811-816.

18.) Multicenter Acute Stroke Trial- Italy (MAST-I) Group. Randomized controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischemic stroke. Lancet. 1995; 346: 1509-1514.

19.) Multicenter Acute Stroke Trial- Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. N Engl J Med. 1996; 335: 145-150.

20.) The Australian Streptokinase (ASK) Trial Study Group. Streptokinase for acute ischemic stroke with relationship to time of administration. JAMA. 1996; 276: 961-966.

21.) del Zappo GJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct delivery in acute middle cerebral artery stroke. Stroke. 1998; 29: 4-11.

22.) Furlan AF, et al. A randomized trial of intra-arterial prourokinase for acute ischemic stroke of less than 6 hours duration due to middle cerebral artery occlusion. JAMA. 1999; 282: 2003-2011.

23.) Duke RJ, et al. Intravenous heparin for the prevention of stroke regression in acute partial stable stroke: a randomized controlled trial. Ann Intern Med. 1986; 105: 825-828.

24.) Adams HP, et al. Guidelines for the management of patients with acute ischemic stroke. American Heart Association Medical/Scientific Statement.1994: 1-23.

25.) International Stroke Trail Collaborative Group. The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, or neither among 19,435 patients with acute ischemic stroke. Lancet. 1997; 349: 1569-1581.

26.) Kay R, et al. Low-molecular-heparin for the treatment of acute ischemic stroke. N Engl J Med. 1995; 333: 1588-1593.

27.) Hommel M, et al. Fraxiparine in Ischemic Stroke Study (FISS bis). Cerebrovasc Dis. 1998; 8(Suppl 4): 19

28.) Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. JAMA. 1998; 279: 1265-1272.

29.) Berge E, et al. Low molecular-weight heparin versus aspirin in patients with acute ischemic stroke and atrial fibrillation: a double-blind randomized study. Lancet. 2000; 355: 1205-1210.

30.) Chinese Acute Stroke Trial (CAST) Collaborative Group. CAST: a randomized placebo-controlled trial of early aspirin use in 20,000 patients with acute ischemic stroke. Lancet. 1997; 349: 1641-1649.

31.) Atkinson RP, et al. Ancrod in the treatment of acute ischemic stroke: a review of clinical data. Cerebrovasc Dis. 1998; 8: Suppl 1: 23-28.

32.) Sherman DG, et al. Intravenous ancrod for the treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. JAMA. 2000; 282: 2395-2403.

33.) SHEP Cooperative Research Group (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 265(24): 3255-3264.

34.) Yusuf S, et al. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcome Prevention Evaluation Study Investigators. N Engl J Med. 2000; 342: 145-153.

35.) Perry HM, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of strokes: the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 2000; 284(4): 465-471.

36.) Collins R, et al. Blood pressure, stroke, and coronary heart disease II. Short term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. Lancet. 1990; 335: 827-838.

37.) Hansson L, et al. Effects of intensive blood-pressure lowering and low dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet. 1998; 351: 1755-1762.

38.) UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352: 837-853.

39.) Sheperd J, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med. 1995; 333: 1301-1307.

40.) Plehn J, et al. Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. Circulation. 1999; 99: 216-233.

41.) Blaw G, et al. Stroke, statins, and cholesterol: a meta-analysis of randomized, placebo-controlled, double blind trials with HMG-CoA reductase inhibitors. Stroke. 1997; 28: 946-950.

42.) Abbott R, et al. Risk of stroke in male cigarette smokers. N Engl J Med. 1986. 315: 717-720.

43.) Colditz G, et al. Cigarette smoking and the risk of stroke in middle-aged women. N Engl J Med. 1988; 318: 937-941.

44.) Lee I, et al. Exercise and the risk of stroke in male physicians. Stroke. 1999; 30: 1-6.

45.) Peto R, et al. Randomized trial of prophylactic daily aspirin in British male doctors. BMJ. 1988; 296: 313-316.

46.) Steering Committee of the Physicians' Health Study Research Group. Final report of the ongoing physicians health study. N Engl J Med. 1989; 321: 129-135.

47.) Manson J, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. JAMA; 1991. 266: 521-527.

48.) Petersen P, et al. Placebo-controlled, randomized, trial warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the AFASAK study. Lancet. 1989; 1(8631): 175-179.

49.) Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation: final results. Circulation. 1991; 84: 527-539.

50.) Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. N Engl J Med. 1990; 323: 1505-1511.

51.) Ezekowitz MD, et al. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med. 1992; 327: 1406-1412.

52.) Laupacis A, et al. Antithrombotic therapy in atrial fibrillation. Chest. 1998; 114: 579-589.

53.) Connolly SJ, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. J Am Coll Cardiol. 1991; 18: 349-355.

54.) European Atrial Fibrillation Study Group. Optimal oral anticoagulation therapy with nonrheumatic atrial fibrillation and recent cerebral ischemia. N Engl J Med. 1995; 333: 5-10.

55.) hart R, et al. Prevention of stroke in patients with nonvalvular atrial fibrillation: views and reviews. Neurology. 1998; 51: 674-681.

56.) Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS). Endarterectomy for asymptomatic carotid artery stenosis. JAMA. 1995; 273: 1421-1428.

57.) The SALT Collaborators Group. Swedish Aspirin Low-dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events. Lancet. 1991; 338: 1345-1349.

58.) Algra A, et al. Aspirin at any dose above 30 mg offers only modest protection after cerebral ischemia. J Neurol Neurosurg Psychiatry. 1996; 60: 197-199.

59.) The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 273 mg a day) in patients after transient ischemic attack or minor ischemic stroke. N Engl J Med. 1991; 325: 1261-1266.

60.) Diener HC, et al. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke: European Stroke Prevention Study 2. J Neurol Sci. 1996; 143: 1-13.

61.) Taylor DW, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid Endarterectomy: a randomized controlled trial: ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Lancet. 1999; 353: 2179-2184.

62.) CAPRIE Steering Committee. A randomized, blinded, trial of Clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). Lancet. 1996; 348: 1329-1339.

63.) Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ. 1994; 308: 81-106.

64.) European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet. 1991; 337: 1235-1243.

65.) North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid Endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991; 325: 445-453.

66.) Barnett H, et al. Benefit of endarterectomy inpatients with symptomatic moderate or severe stenosis. N Engl J Med. 1998; 339: 1415-1425.

67.) Diener HC, et al. Treatment of acute ischemic stroke with the low-molecular weight heparin certoparin. Results of the TOPAS Trial. Stroke. 2001; 32: 22-29.

68.) Bath PMW, et al. Tinzaparin in acute ischemic stroke (TAIST): a randomized aspirin-controlled trial. Lancet. 2001; 358: 702-710.

69.) The Abciximab in Ischemic Stroke Investigators. Abciximab in acute ischemic stroke: a randomized, double-blind, placebo-controlled, dose escalation study. Stroke. 2000; 31: 601-609.

70.) Coull BM, et al. Anticoagulants and antiplatelet agents in acute ischemic stroke. Report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association(a Division of the American Heart Association). Neurology. 2002; 59: 13-22.

71.) Strauss SE, et al. New Evidence for Stroke Prevention. JAMA. 2002; 288(11): 1388-1395.

72.) The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trail of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. Ann Neurol. 1997; 42: 857-865.

73.) Mohr JP, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001; 345:1444-1451.

74.) Dahlöf B, et al. LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002; 359: 995-1003.

75.) CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet. 2001 Jun 2;357:1729-37.

76) Percutaneous transluminal coronary angioplasty and endarterectomy were both effective for carotid stenosis. ACP Journal Club. 2001; 135(3): 91.