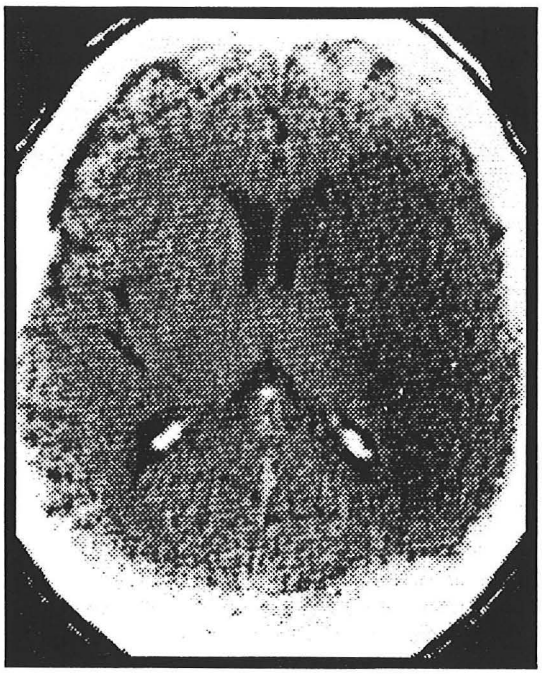
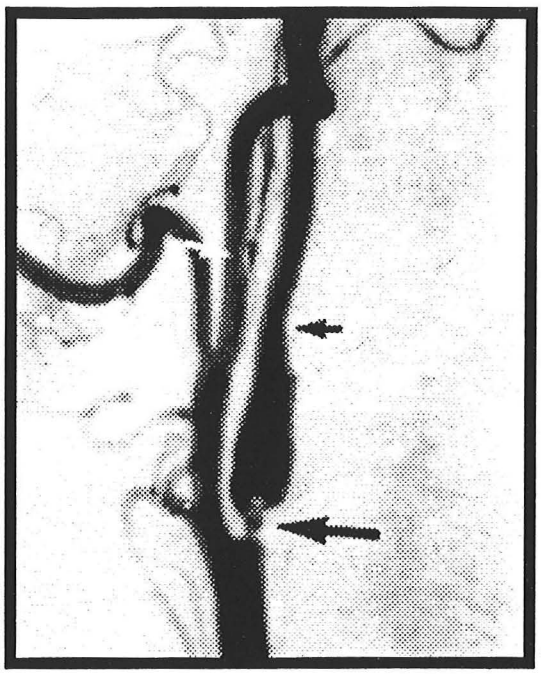
Controversies in Antithrombotic Therapy of Cerebrovascular Disease





Internal Medicine Grand Rounds

University of Texas Southwestern Medical School

SOUTHWESTERN

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Controversies in Antithrombotic Therapy of Cerebrovascular Disease

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Controversies in Antithrombotic Therapy of Cerebrovascular Disease

I. Introduction and Background

A. Epidemiology

Despite recent gains in control of risk factors for cerebrovascular accidents, approximately 500,000 new strokes occur in the United States each year, with indications that the declines in incidence from 1950-1975 may be leveling off.[I.A.1]

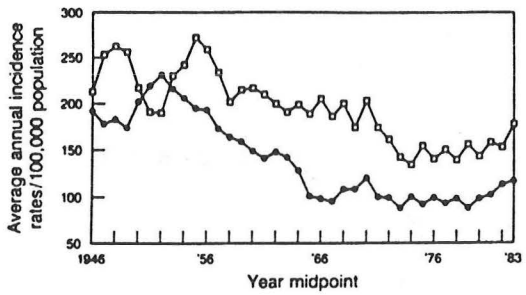


FIGURE 1. *Overlapping 3-year average annual incidence rates of first stroke in Rochester, Minnesota, 1945–1984. Rates were age-adjusted to 1970 US white population.* □, *men;* ●, *women.*

Broderick et al, Ref I.A.1

Stroke currently ranks as the third leading cause of mortality in the United States, resulting in some 150,000 deaths per year.[III.D.1] Some 20% of hospital admissions for stroke result in death, and about 40% of persons suffering a stroke die within one month of occurrence.[III.C.1] Approximately 25-40% of persons experience a transient ischemic attack (TIA) prior to a cerebral infarction.[III.B.1] Stroke is also a leading cause of disability in adults, leading to 140,000 nursing home admissions annually.[III.D.1] Moreover, the economic burden of stroke is enormous, with estimates of costs, including those related to chronic care of some 2-3 million stroke survivors at about $25 billion.[I.A.2]

B. Risk Factors

Several general risk factors for stroke[V.1] have been identified:

1) Hypertension (including isolated systolic HTN)
2) Cigarette smoking
3) Diabetes mellitus
4) Heavy ethanol consumption
5) Older age
6) Hypercholesterolemia

Hypertension remains the most significant risk factor. Based on data from the Framingham study, persons with blood pressure (BP) over 160/95 have a four-fold relative risk for

cerebrovascular events.[I.A.3] However, the good news for patients is that a reduction of 5 mm in diastolic BP results in a 42% reduction in the rate of such events,[I.A.4,5] and that control of isolated systolic hypertension results in a 2 to 4 fold reduction in the stroke incidence.[I.A.6] Cigarette smoking carries a relative risk of 1.9 for ischemic stroke overall, with a larger RR for persons < age 55.[I.A.7] A Cox proportional hazards regression model for predicting an individual's risk of stroke has been derived from the Framingham data.[I.A.3]

TABLE 5. Probability of Stroke Within 10 Years for Men Aged 55–84 Years and Free of Previous Stroke: Framingham Study

	Points										
Risk factor	0	1	2	3	4	5	6	7	8	9	10
Age (yr)	54–56	57–59	60–62	63–65	66–68	69–71	72–74	75–77	78–80	81–83	84–86
SBP (mm Hg)	95–105	106–116	117–126	127–137	138–148	149–159	160–170	171–181	182–191	192–202	203–213
Hyp Rx	No		Yes								
DM	No		Yes								
Cigs	No			Yes							
CVD	No			Yes							
AF	No				Yes						
LVH	No						Yes				

Points	10-yr probability	Points	10-yr probability	Points	10-yr probability
1	2.6%	11	11.2%	21	41.7%
2	3.0%	12	12.9%	22	46.6%
3	3.5%	13	14.8%	23	51.8%
4	4.0%	14	17.0%	24	57.3%
5	4.7%	15	19.5%	25	62.8%
6	5.4%	16	22.4%	26	68.4%
7	6.3%	17	25.5%	27	73.8%
8	7.3%	18	29.0%	28	79.0%
9	8.4%	19	32.9%	29	83.7%
10	9.7%	20	37.1%	30	87.9%

SBP, systolic blood pressure; Hyp Rx, under antihypertensive therapy; DM, history of diabetes mellitus; Cigs, smokes cigarettes; CHD, history of myocardial infarction, angina pectoris, or coronary insufficiency; CVD, history of intermittent claudication or congestive heart failure; AF, history of atrial fibrillation; LVH, left ventricular hypertrophy on electrocardiogram.

Wolf et al, Ref I.A.3

Specific predisposing factors for cardioembolic strokes include atrial fibrillation, prosthetic heart valves, and cardiomyopathy with severely reduced ejection fraction. For nonembolic stroke, the presence of an asymptomatic carotid bruit results in a fourfold higher risk, TIA or prior stroke in a fivefold risk (annual risk 4.5-6.6%,[I.A.8,9] with the highest risk during the first several months after the index event), and

significant carotid stenosis in a tenfold risk elevation; occurrence of a retinal TIA (amaurosis fugax) carries a lower risk for stroke than does a carotid TIA.[VI.1] However, the risks associated with vertebrobasilar and carotid TIAs are probably equivalent.[I.A.8]

There are two major categories of stroke, namely hemorrhagic and ischemic, and cerebral imaging studies are the criterion (gold) standard for distinguishing them. Clinical prediction rules for distinguishing ischemic from hemorrhagic infarction have been evaluated and found lacking in overall sensitivity.[I.A.10] Ischemic stroke may be further divided into embolic, thrombotic and miscellaneous (uncommon) causes[V.2] as follows:

Etiology of Ischemic Stroke		
Cardioembolic		15-20%
Thrombotic		
	Large artery	60-65%
	Small artery	15%
Miscellaneous (rare)		
	Hypercoagulable states	<1%
	Aortic arch disease	<1%
	Arterial dissection	<1%

Many questions in the area of appropriate treatment for patients with cerebrovascular disease remain unanswered. This discussion will deal with the following controversial issues:

- Is anticoagulation effective in the treatment of acute ischemic stroke?
- What is the role of newer antithrombotic therapies, including thrombolysis and angioplasty?
- What is the optimal dose of aspirin (ASA) for preventing ischemic cerebrovascular events (secondary prevention)?
- Is there a gender-based difference in response to ASA used for secondary prevention?
- What is the role of the newer antiplatelet agent ticlopidine as compared to aspirin?
- What is the optimal methodology for investigating and treating (if indicated) asymptomatic carotid artery disease?

While a brief overview of cardioembolic stroke will follow, the remainder of this discussion will focus on primary thrombotic disease of the cerebral vessels.

A WORD ABOUT RISK

Before embarking on further analysis of studies involving risk factors for stroke, it is important to establish an understanding of the basic epidemiologic concepts of risk. The odds ratio (OR) or relative odds is used primarily in retrospective studies and generally refers to the ratio of the odds of exposure to a putative risk factor among diseased individuals compared to the odds of exposure to the same factor

among healthy persons ($OR=O_D/O_H$). Relative risk (RR) is properly used in studies involving actual incidence rates in longitudinal cohort analyses and is defined as the ratio of disease occurrence in an interventional study cohort relative to that in a control group ($RR=R_I/R_C$). Relative risk reduction (RRR) is the ratio of the decrease in occurrence rate of disease among an intervention group compared to the rate in the control group ($RRR=[R_C-R_I]/R_C=1-RR$). Absolute risk reduction (risk difference) is the difference in incidence rates between the intervention and control groups ($ARR=R_C-R_I$). The number needed to treat (NNT) is a more recently defined concept and refers to the number of patients at risk of a disease outcome who must be treated to prevent one person from developing that outcome. Mathematically, NNT is simply the reciprocal of the ARR (NNT=1/ARR).

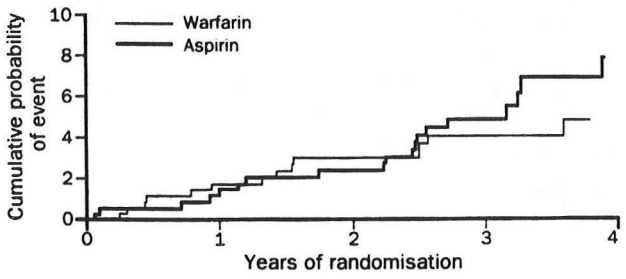
As an example, consider two disease processes A and B. For disease A, the rate of disease occurrence found in a controlled clinical trial among the control group was 0.04 (4%) and among the intervention group was 0.02 (2%). Therefore, the RRR is 0.04-0.02/0.04=50%, the ARR is 0.04-0.02=0.02, and the NNT is 1/.02=50. For disease B, the incidence of disease in the control group is 0.50 (50%) and in the intervention group is 0.25 (25%). The RRR, then, is 0.50-0.25/0.50=0.50 (50%) and the ARR is 0.50-0.25=0.25 (25%), and the NNT=1/.25=4. While the RRR is identical in the two groups, the impact in the population is much greater in the case of the intervention for disease B, in which only 4 patients need be treated to prevent one case of disease compared to 50 patients for disease A.

	Disease A	Disease B
Rate in control group (R_C)	0.04	0.50
Rate in intervention group (R_I)	0.02	0.25
RRR (R_C-R_I/R_C)	50%	50%
ARR (R_C-R_I)	0.02	0.25
NNT (1/ARR)	50	4

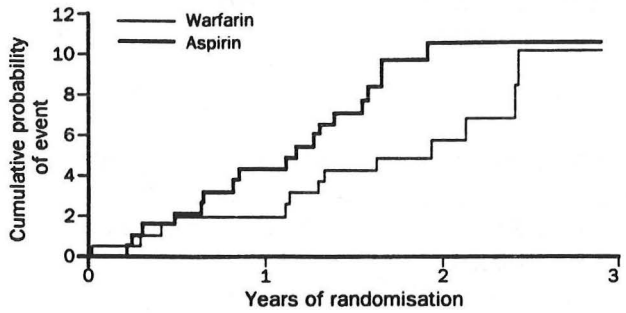
I.B. Cardioembolic Stroke

The majority of studies performed which relate to cardioembolic stroke focus on two risk states: atrial fibrillation and the immediate post-myocardial infarction period. Atrial fibrillation, whether continuous or paroxysmal, and whether occurring in or outside the context of valvular heart disease increases the risk of stroke. However, persons under the age of 60 with no evidence of valvular disease, normal left ventricular function, and normal left atrial size have a much lower average risk of about 1%.[I.B.1]

There have now been five Level I or Level II studies (randomized controlled trials) of stroke reduction using warfarin compared to placebo among patients with atrial fibrillation,[I.B.2-6] each of which showed a relative risk <1.0 favoring warfarin, with



Warfarin	358	326	299	164	92
Aspirin	357	327	302	164	81



Warfarin	197	177	99	10
Aspirin	188	170	96	11

Figure 1: **(Top) cumulative probability of ischaemic stroke or systemic embolism in patients ⩽75 years old at entry and (bottom) >75 years old at entry**

No of patients after randomisation shown. Two events in aspirin-assigned patients ⩽75 years occurred after >4 years of follow-up and are not shown. One event in a warfarin-assigned patient >75 years occurred after >3 years of follow-up and is not shown. Warfarin vs aspirin; ⩽75 years p=0·24, >75 years p=0·39 (p values include all data).

SPAF II, Ref I.B.7

four of the five having statistically significant differences. A meta-analysis of efficacy studies reveals an overall RR of 0.33 (relative risk reduction of 67%) for stroke while on warfarin.[V.1] Comparisons of antiplatelet agents vs placebo have shown a RR for stroke of 0.56 for ASA in the SPAF I study, and no apparent benefit of ASA in the AFASAK study, which enrolled older patients and used a smaller ASA dose of 75 mg/day. The recently published results of the SPAF II trial showed no apparent difference in the efficacy of ASA and warfarin;however, a trend for warfarin superiority was noted among those over age 75, especially persons having specific risk factors (hypertension, recent heart failure, or prior thromboembolism).[I.B.7]

However, about 40% of events in the warfarin arm of this study occurred while patients were not actually taking the medication, and the balance of cumulative evidence still favors the use of anticoagulation in this setting when feasible.[I.B.8]

About 3-4% of patients sustaining a myocardial infarction experience an embolic stroke, mostly during the peak risk period of 3 days to 3 weeks after the event. A detailed discussion of antithrombotic therapy post myocardial infarction is beyond the scope of this protocol; however, the combined results of aspirin usage in this setting show a RR=0.67.[V.1]

II. Management of Acute Ischemic Stroke

The rationale for antithrombotic treatment of acute ischemic stroke centers on the prevention of two processes: 1) deep

venous thrombosis of the lower extremities with resultant pulmonary embolism and 2) ongoing thrombosis of involved cerebral vessels. Based on a meta-analysis of heterogeneous conditions, the use of antithrombotic agents may reduce the risk of DVT by 40-50% and PE by 70%.[II.1] Specifically, low-dose subcutaneous heparin (5000 units every 8 hrs) has been found to reduce the risk of DVT and PE by about 60% in perioperative studies, with comparable levels of risk reduction shown in a small study of acute stroke (75% vs 13%).[II.2]

Many patients with stroke deteriorate neurologically after hospital admission, some of which has been attributed to propagation of thrombosis.[II.3] A study from the Karolinska Institute revealed evidence of neurologic deterioration in 43% of stroke patients following hospital admission, with half of these occurring in the first 24 hours.[II.4] However, there has been no demonstration of the efficacy of heparin in this setting.

A randomized controlled clinical trial by Duke et al[II.5] of heparin vs. placebo in the setting of partial stroke showed equivalent rates of neurologic progression: The study enrolled 225 patients (84% with symptoms in the carotid and 16% with symptoms in the vertebral circulation) and administered continuous IV heparin or placebo infusions for 7 days. There were no differences found in the degree of neurologic change (27% improved on heparin and 24% with placebo), stroke progression after 7 days (17% with heparin and 20% on placebo, 95% CI for difference of -9% to 14%), or in functional status after 7 days, 3 months, or 1 year ($p>0.01$). At 1 year, there was a higher total death rate among the heparin treated patients. Although no statistically significant difference was found, this study was designed with 80% power to detect a difference of at least 30% between the two groups.

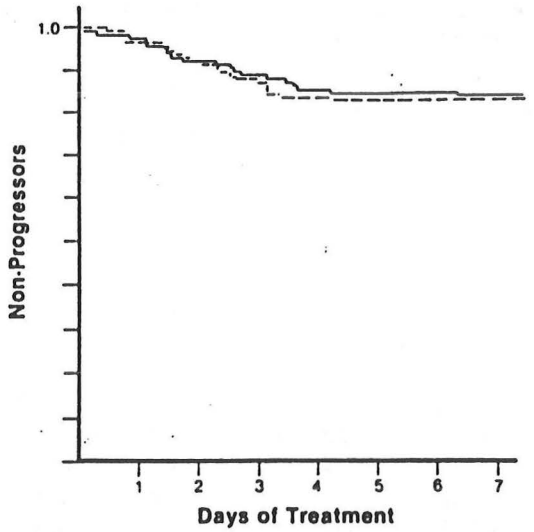


Figure 1. Percentage of patients who had no stroke progression during 7 days of treatment with either heparin (*solid line*) or placebo (*broken line*). The difference is not significant.

Duke et al, Ref II.5

While there are obvious concerns about the risk of inducing cerebral hemorrhage with heparin, especially since about 40% of cerebral infarcts undergo some degree

of spontaneous hemorrhagic transformation,[II.6] there has been no confirmation of such a risk in empiric studies.[II.1,7]

Due to the uncertainty which lingers over the use of heparin for acute stroke, the International Stroke Trial has been established to compare, in a 2x2 factorial design, the safety and efficacy of heparin alone, aspirin alone, both or neither for acute therapy. The goal of the study is to enroll some 20,000 patients who will be treated within 48 hours of symptom onset. Moreover, a multicenter randomized controlled trial of low molecular weight heparin in this setting is also in progress.[V.2]

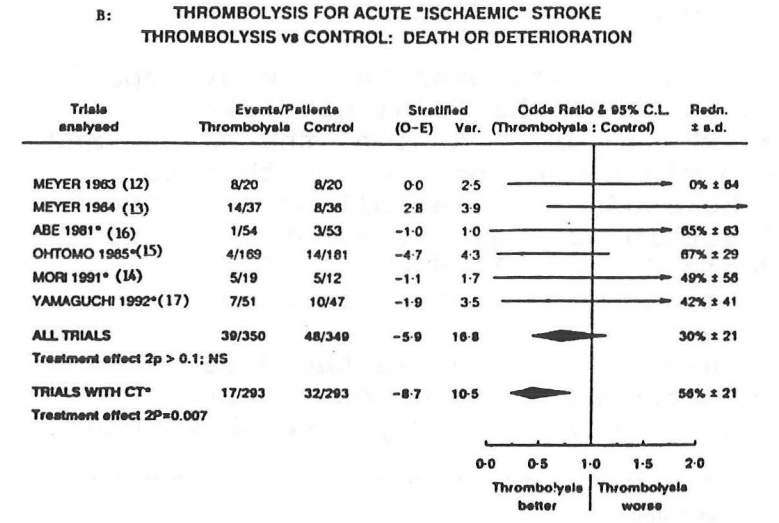
Another approach with mechanistic appeal is the direct dissolution of thrombi in the cerebral circulation. Rabbit studies using tissue plasminogen activator (tPA) have shown clot

Table 1. "Controlled" Trials of Thrombolysis for Acute "Ischemic" Stroke

Author	Drug	Route	Dose	Time from onset	Outcome measure	Results: Treated No.	Treated %	Control No.	Control %
Randomized									
Meyer[13]	Fib/Pla	IV	2.5–11.5 $\times 10^5$ units	<72 hours	Clinical improvement at 10 days	20	45	20	45
Meyer[13]	SK	IV	2.5–17.5 $\times 10^5$ units	<72 hours	Clinical improvement at 10 days	37	43	36	58
Mori[14]	t-PA	IV	34–50 mg	<6 hours	Recanalization	19	47	12	25
Ohtomo[15]	UK	IV	6×10^4 units per day for 7 days	<5 days	Clinical improvement at 4 weeks	169	56	181	42
Abe[16]	UK	IV	6×10^4 units per day for 7 days	<30 days	Clinical improvement at 1 and 4 weeks	54	63	53	43
JTSG[17]	t-PA	IV	34 mg	<6 hours	Clinical improvement at 4 weeks	51	72	47	55

Wardlaw et al, Ref II.12

dissolution and reduced morbidity, with no apparent associated risk of increased bleeding when the tPA is given as late as 45 minutes after experimental embolization.[II.8,9] One small safety trial in humans have shown a 34% recanalization rate using thrombolytic agents, with a concurrent risk of cerebral hemorrhage if tPA was started more than 6 hours after the onset of symptoms.[II.10] Another has shown improvement in neurologic outcome among patients receiving tPA within 6 hours of stroke despite no difference in recanalization rates.[II.11]



Wardlaw et al, Ref II.12

There have been 6 small randomized trials of thrombolysis for acute stroke which have been published. Two of these were conducted before the modern era of CT scanning, and 4 others are more recent Japanese studies. The combined results of the CT-based trials shows a 37% RRR for death (95% CI, -74% to 47% excess) and 56% RRR for the combined endpoints of death or deterioration (95% CI, 20-76% reduction).[II.12]

It may be noted that thrombolysis for acute myocardial infarction was almost mistakenly rejected after many small trials failed to show its benefit. Only overviews and very large trials corrected this initial misimpression. There is clearly no point in further small studies, and two large randomized controlled clinical trials of the efficacy of tPA and other thrombolytics are now underway.[II.12]

III. Management of TIAs and Completed Strokes (Secondary Prevention)

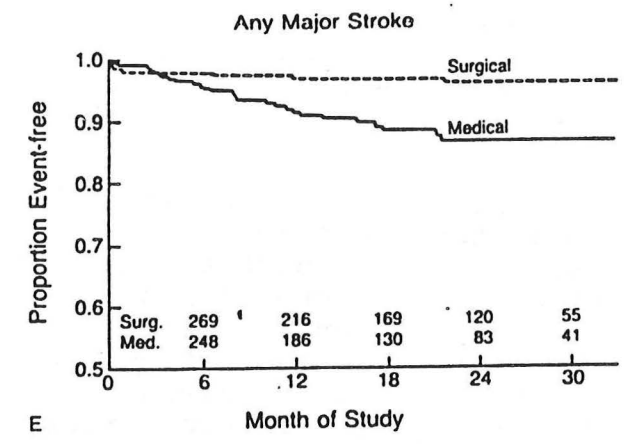
A. Invasive: Surgery and Angioplasty

The procedure known as carotid endarterectomy was introduced in 1954 and gradually gained popularity, rising from 15,000 procedures in 1971 to 107,000 procedures (exclusive of VA-based surgery) in 1985.[III.A.1] The modern era of surgical management of cerebrovascular disease has been entered with the publication of three large randomized controlled clinical trials, namely the NASCET (North American Symptomatic Carotid Endarterectomy Trial),[III.A.1] the European Carotid Surgery Trialists Collaborative Group,[III.A.2] and the Department of Veterans Affairs Cooperative Studies Program 309 Trialists Group studies.[III.A.3] These trials have demonstrated that CEA is indeed better than medical therapy in preventing stroke following a TIA or nondisabling stroke. Among persons with carotid stenosis of ≥70%, a 60% reduction in the risk of stroke over 2 years was shown.

The **European Carotid Surgery Trialists Collaborative Group**[III.A.2] enrolled three categories of patients after a nondisabling stroke or TIA: those with carotid stenosis of 0-29%, 30-69%, and 70-99%. The low range patients showed no benefit from surgery. At 3 years, the primary endpoint of death or stroke among the high-grade stenosis group was seen in 12.3% of those having CEA and 21.9% of controls, for an ARR=9.6% ($p<0.01$).

The **VA Cooperative Studies Program 309 Trialist Group**[III.A.3] enrolled patients with a history of TIA or small strokes and at least 50% ipsilateral carotid stenosis. All patients received 325 mg of ASA daily, and half were allocated to surgery or observation. Follow-up at 12 months revealed that stroke or crescendo TIA occurred in 7.7% of patients having surgery but 19.4% of those receiving medication only, for an ARR=11.7% ($p<0.01$). Among those with stenoses >70%, the ARR was 18% ($p=0.004$). There was no overall difference in mortality.

The largest study was the **North American Symptomatic Carotid Endarterectomy Trial (NASCET)**,[III.A.1] enrolling 659 patients with hemispheric or retinal TIAs or nondisabling stroke and at least 70% carotid stenosis. All patients received 1300 mg of ASA daily. After 2 years, any ipsilateral stroke occurred in 26% of the medicine only group and 9% of the CEA group (RRR=65%, ARR=17%), and stroke or death occurred in 18% of the medicine group and 8% of the surgical group (RRR=56%, ARR=10%, $p<0.001$).



NASCET, Ref. III.A.1

The operating characteristics of various approaches to the diagnosis of carotid stenosis have been further analyzed, and the performance of Doppler studies is as follows. The sensitivity of Doppler studies for high grade stenosis confirmed by angiography was 88% (false negative rate=12%), and the specificity for high grade stenoses was 60% (40% false positive rate).[III.A.4] Therefore, unless some combination of newer technologies, such as magnetic resonance angiography and color flow duplex sonography or 3-D ultrasound proves to be satisfactory, reliance must still be placed on angiography to establish candidacy for carotid surgery.[III.A.5]

While the efficacy of carotid surgery for prevention of stroke has been upheld by these studies, another surgical approach has since been abandoned. The use of extracranial-intracranial bypass (superficial temporal to middle cerebral artery), first performed in 1967 and evaluated in an international randomized trial of 1,377 persons begun in 1977, has been demonstrated to be ineffective in the prevention of stroke. The final report of this study found that strokes occurred earlier and more frequently in the surgical group, with a point estimate of the RR of all strokes over the 5 year study of 1.14. Multiple analyses failed to pinpoint any subgroups for whom surgical benefit was evident.[III.A.6]

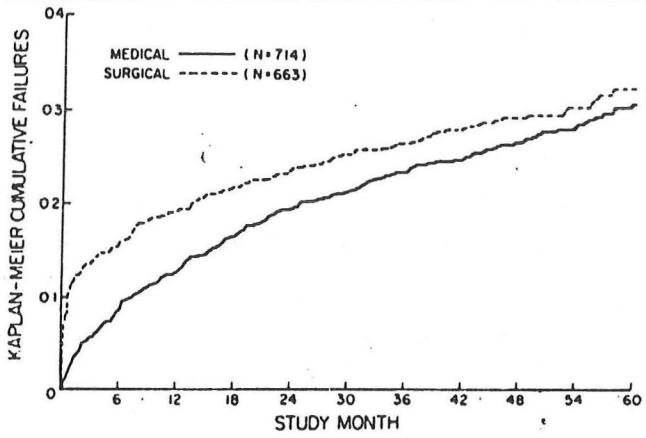


Figure 1. Results of the Primary Analysis (All Strokes, Both Fatal and Nonfatal), Showing the Failure of Bypass between the Superficial Temporal Artery and the Middle Cerebral Artery to Reduce Stroke in the Surgical (663 Patients) as Compared with the Medical Cohort (714 Patients) after an Average Follow-up of 55.8 Months.
The analysis uses Kaplan–Meier cumulative-failure curves.

EC/IC Bypass Study, Ref III.A.6

Angioplasty is perhaps the newest interventional approach to the therapy of symptomatic carotid artery disease. An ongoing large scale multicenter study (of which UT Southwestern is a member) designed to demonstrate the safety, efficacy, and economic feasibility of this procedure, known as the North American Cerebral Percutaneous Transluminal Angioplasty Register, began in 1991. Enrolled patients all must have had a stroke or TIA, demonstrated carotid stenosis of at least 70%, and be deemed a poor surgical candidate for CEA. CPTA, so named to distinguish itself from angioplasty of the coronary arteries, involves introduction of a 2-5 French catheter through the femoral artery into the carotids, with balloon inflation twice for a total of less than 10 seconds. Evidence to date suggests that the procedure is safe, prompting investigators to consider making it an outpatient procedure. It also has a low reocclusion rate of 8%, compared to 30-35% or higher for PTCA. Requiring about one hour to perform, CPTA costs $4,000-$8,000, compared to $10,000 to $15,000 for CEA surgery.[III.A.7]

III.B. Anticoagulation

There is very scant medical evidence upon which to base the use of chronic anticoagulation for the prevention of cerebrovascular thrombosis. Although three recent randomized

trials have been performed, including a direct comparison of ASA vs anticoagulation and ASA plus dipyridamole versus anticoagulation,[III.B.1-3] none has shown any benefit of warfarin over antiplatelet agents. However, none has been of sufficient size to definitively determine the possible efficacy of this strategy.

Randomized Trials of ASA vs Anticoagulation after TIA

	N	Mean F/U	Stroke Incidence (%)	Stroke or Death (%)
Olsson et al, ASA + DP	67	13	4	7
Anticoagulant	68	12	1	10
Buren & Ygge, ASA + DP	65	24	3	8
Anticoagulant	60	24	2	3
Garde et al ASA	127	20	3	4
Anticoagulant	124	20	4	5
Aggregate:	Patient-yrs	Strokes, N	Strokes or Deaths, N	
ASA	409	13	24	
Anticoagulant	384	10	20	

From Sherman et al, Ref V.2

III.C. Aspirin and Older Antiplatelet Agents

Aspirin's effect on platelet functional activity, manifest clinically as a prolongation of the bleeding time, appears to be exclusively related to permanent inactivation of prostaglandin G/H synthase, the enzyme catalyzing the initial step in prostaglandin synthesis, the conversion of arachidonic acid to PG G_2 and PGH_2. This enzyme is involved in the first step of the eventual production of other prostaglandins and thromboxane A2. The type I enzyme is expressed consitutively in platelets and most other tissues and is permanently suppressed by administration of aspirin, as platelets lack the capability to synthesize new protein, and the defect cannot be repaired during their 8-10 day life span. Thus, a drug with only a 20 minute half-life is fully effective when administered only once every 24 hours. Aspirin acetylates the hydroxyl group of a serine residue at position 529 in the polypeptide chain of platelet prostaglandin G/H synthase I and causes irreversible loss of its cyclooxygenase activity. This decreases formation of PGG_2 and the downstream products PGH_2 and thromboxane A_2, which induces irreversible platelet aggregation. A single dose of 100 mg virtually completely suppresses thromboxane A_2 production in normal subjects. Large doses of aspirin may diminish the resistance to thrombosis which is mediated by endothelial prostacyclin production.[III.C.2]

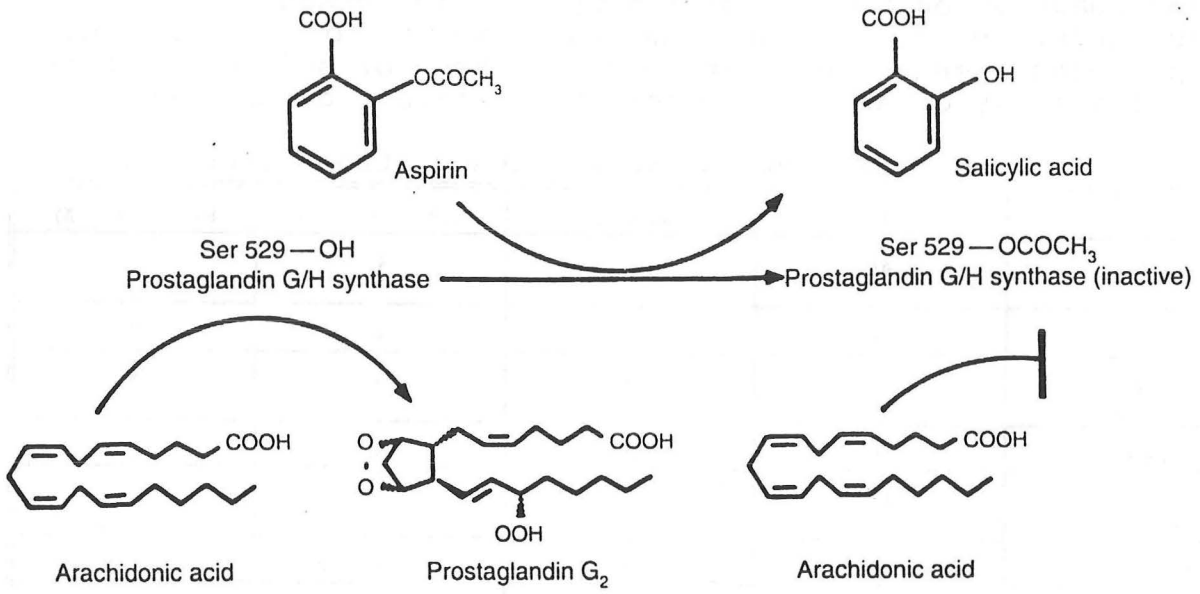


Figure 1. Mechanism of the Antiplatelet Action of Aspirin.

Aspirin acetylates the hydroxyl group of a serine residue at position 529 (Ser529) in the polypeptide chain of human platelet prostaglandin G/H synthase, resulting in the inactivation of cyclooxygenase catalytic activity. Aspirin-induced blockade of prostaglandin G_2 synthesis will result in decreased biosynthesis of prostaglandin H_2 and thromboxane A_2.

Patrono, Ref III.C.2

There have been eight Level I or II studies[III.C.3-11] directly comparing the use of aspirin vs placebo for the prevention of stroke following TIA or minor stroke. By themselves, none of these eight showed a statistically significant reduction in the risk of stroke or death. Aggregated, data from these eight trials show that ASA usage carries a RR for stroke of 0.84 (95% CI 0.72-0.99). However, there is also and indication that aspirin perhaps has an increased associated risk for more nonfatal major complications compared to placebo (RR=1.7, 95% CI=0.86-3.2). Combining the results of studies using aspirin with other antiplatelet agents yields a higher protective efficacy (RR=0.76, 95% CI=0.64-0.90).[V.1] However, substantial controversy remains over the optimal effective dose of aspirin as well as the possible differential effect of aspirin among men vs women.

The largest study which addresses the issue of optimal dosing of ASA in the standard range is the UK-TIA trial[III.C.9] of 2,345 patients with TIA or minor stroke who were randomized to receive either placebo, 300 mg of ASA, or 1200 mg of ASA per day. Among the combined treatment groups, there was a 15% reduction in the primary endpoint of MI, stroke, or vascular death. While there was a trend for the superiority of the 1200 mg dose, the

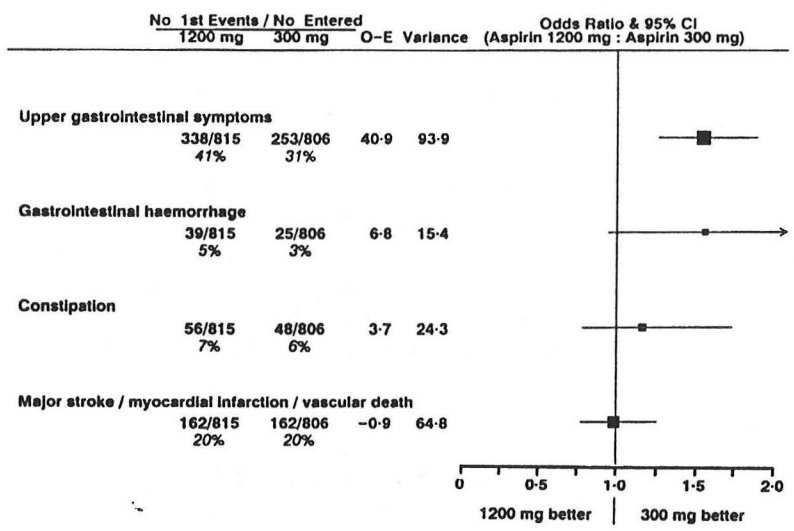


Figure 2 Comparison of 1200 mg versus 300 mg daily aspirin: main adverse effects and main vascular events; "intention-to-treat" analysis of proportion of patients experiencing at least one event. In the log rank analysis of time to "major stroke, myocardial infarction, vascular death", this small difference is reversed yielding an odds ratio of 1·03, see table 13. The filled boxes are proportional to the amount of information (that is, number of events) contained in the analysis.

UK-TIA Trial, Ref III.C.9

difference was not statistically significant. However, there was a low overall event rate of 3.2% in this study, vs a 7% event rate in comparable trials, such that a difference between the two treatment arms could have been missed due to inadequate statistical power. While the 1200 mg group showed a higher rate of GI bleeding than the 300 mg group, they had no higher rate of transfusions, indicating an equivalent rate of major bleeding episodes.

The Dutch TIA Trial and Swedish SALT studies evaluated the effect of even lower dose aspirin therapy. The Dutch trial[III.C.12] enrolled 3,131 patients who were followed for a mean of 2.6 years and were given either 30 mg or 283 mg of ASA daily. At the end of the study, the combined endpoints of death, nonfatal stroke, and nonfatal MI occurred in about 15% of each group, with fewer GI side effects noted in the 30 mg group. The Swedish Aspirin Low Dose Trial (SALT) study[III.C.10] compared 75 mg of ASA vs placebo in 1,360 patients over a median of 32 months follow-up, noting a RR=0.82 for stroke or death in the intervention group. To explore the ASA dosing issue further, Matchar and colleagues[V.1] plotted the log odds of stroke while on ASA vs placebo for these 8 trials

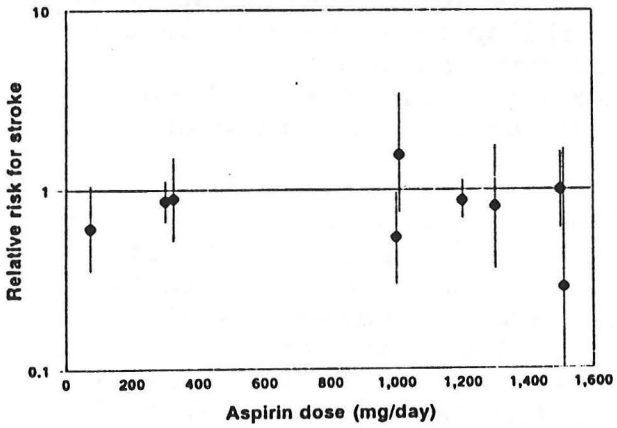


Figure 1. The relative risk for stroke estimated from eight randomized controlled trials of aspirin as compared with placebo, plotted against the target aspirin dose in that trial.

Matchar et al, Ref V.1

against aspirin dosage. There was no evidence for a trend favoring higher doses for efficacy nor one linking higher doses to a greater risk of major nonfatal complications. The confidence intervals are wide and do not completely exclude the possibility of a dose-response effect.

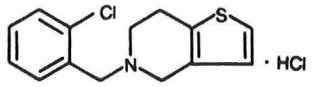
The existence of a possible gender difference in the protective effect of aspirin has been raised by two studies. The Canadian Cooperative Study Group[III.C.6] followed 526 patients over an average of 26 months using a 2x2 factorial design of 325 mg ASA QID, 200 mg sulfinpyrazone QID, both, or neither. They found an overall RR for stroke or death which was sex dependent, being 0.52 for males ($p<0.005$) and not significant ($RR=1.42$, $p=0.35$) for females. This helped to create a storm of controversy about the efficacy of aspirin for vascular event reduction among women. The UK-TIA Study[III.C.9] found a diminished protective effect of aspirin among females for certain outcomes in the study. However, given the existence of a lower overall event rate among females, the power to detect a difference in outcome is limited. The European Stroke Prevention Study,[III.C.13] which found a 37% RRR in stroke and death, found no difference in the effect of aspirin among women and men. The French AICLA Study[III.C.7,14] similarly found no gender difference in the effect of aspirin.

A number of studies address the effect of other (non-salicylate) antiplatelet agents for the prevention of stroke. The European Stroke Study[III.C.13] found a 34% relative reduction for the combined endpoint of stroke and death, a somewhat higher rate of protection than the average rate of 25% in all other studies combined, using ASA (975 mg) together with dipyridamole. The French Toulouse study,[III.C.15] the French AICLA study,[III.C.7] and the Canadian-American Study[III.C.16] found no benefit with the use of dipyridamole in addition to aspirin. Other studies investigating the effect of dipyridamole alone in doses up to 800 mg per day for up to 25 months vs placebo,[III.C.17] sulfinpyrazone alone in doses of 400 mg BID vs ASA 500 mg BID or in combination with aspirin[III.C.6,18] failed to show a superior or enhanced effect on stroke, and suloctidil[III.C.19] proved to be both ineffective and hepatotoxic in routine use.

In summary, the weight of medical evidence supports the use of 325 mg to 975 mg per day as the standard aspirin dose, if tolerated. There are no individual study data which indicate that aspirin doses of <325 mg per day are equivalent to 975 mg per day or more. However, the Antiplatelet Trialist Collaborators overview found no difference in net effect between higher dose and intermediate dose ASA therapy (75-160 mg).[III.C.21] Though the risk of gastrointestinal hemorrhage may be increased with higher doses, risk benefit assessment would favor doses of at least 325 mg if even minimally more effective.[V.2] There are no data which definitively support the existence of a gender effect

in response to aspirin, and discrepancies noted to date may be accounted for by the diminished power to demonstrate an effect among women. There is no support for the use of dipyridamole[III.C.20] or other older nonsalicylate agents.

III.D. Ticlopidine



Ticlopidine

Ticlopidine, a thienopyridine derivative, is a relatively new antiplatelet agent. While its pharmacologic actions are not completely understood, ticlopidine inhibits the ADP-induced pathway of platelet aggregation, by inhibiting ADP-induced exposure of the fibrinogen binding site of the glycoprotein IIb-IIIa complex, with the clinical effect of prolonging the bleeding time. Ticlopidine also inhibits aggregation by a number of other platelet agonists, including arachidonic acid, collagen, thrombin, and platelet activating factor. It has no effect on synthesis of thromboxane in platelets or prostacyclin in the endothelium. However, it decreases platelet deposition on atheromatous plaques and reduces fibrinogen levels and blood viscosity. After oral dosing, 80-90% is absorbed and rapidly metabolized, with one metabolite more active than the parent compound. It reaches maximum effect after 3-5 days, with a terminal elimination half life of 96 hours and duration of effect of up to 10 days.[III.D.2]

There are two large scale randomized controlled trials addressing the effects of ticlopidine in humans. The Canadian American Ticlopidine Trial (CATS)[III.D.3] evaluated the effect of ticlopidine compared to placebo and the Ticlopidine Aspirin Stroke Study (TASS)[III.D.4] directly compared the efficacy of these two drugs.

CATS revealed that ticlopidine was superior to placebo among patient with completed (major) stroke in preventing the combined endpoints of stroke, myocardial infarction, or vascular death, as well as the secondary endpoint of all strokes.

Outcome	Placebo		Ticlopidine		RRR(%)	p
	No. of Events	Event rate/yr	No. of events	Event rate/yr		
Stroke, MI, vascular death	118	15.3	74	10.8	30.2	0.006
Stroke or stroke death	89	11.4	54	7.8	33.5	0.008

CATS, Ref III.D.3

The only Level I study to compare directly aspirin with ticlopidine in the setting of minor stroke or TIA is TASS, which was designed to evaluate the primary endpoint of nonfatal stroke and all deaths and the secondary endpoint of all strokes. TASS showed superiority for ticlopidine in reducing the rate of stroke (RR=0.82, 95% CI=0.67-1.0) and in accounting for fewer major complications (RR=0.34, 95% CI=0.14-0.76). Results were essentially the same in a subgroup analysis involving only patients with minor strokes.[III.D.5] However, ticlopidine also had a higher rate of patient intolerance.

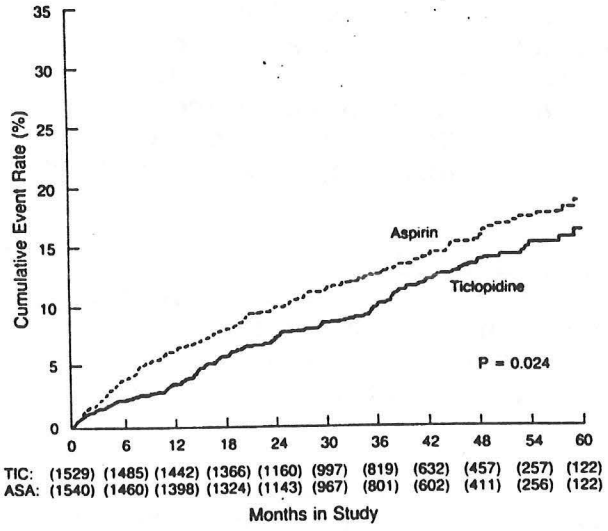


Figure 2. Cumulative Event-Rate Curves for Fatal or Nonfatal Stroke.

TASS, Ref III.D.4

In TASS, ticlopidine was discontinued due to adverse effects in 21% of patients, vs 15% of those taking ASA over an average of 3 years of follow-up. However, these data may overestimate the true difference between these two drugs, as persons with any prior aspirin intolerance or contraindications to its use were not eligible for the ASA arm in TASS. On the other hand, ASA caused more frequent hemorrhage (RR=3.0, 95% CI=1.3-7.0), transfusion (RR=12, 95% CI=1.6-92), gastrointestinal ulceration (RR=3.7, 95% CI=2.0-7.0), and hospitalization (RR=16, 95% CI=2.1-120). The most frequent adverse effect of ticlopidine was diarrhea, noted by 21% of patients, though most GI side effects of the drug disappeared by taking it with food. Skin rash and urticaria occurred in 12% and 2%, respectively, compared to 5% and 0.3% in the ASA group. Ticlopidine increased total cholesterol levels by 9% vs 2% with

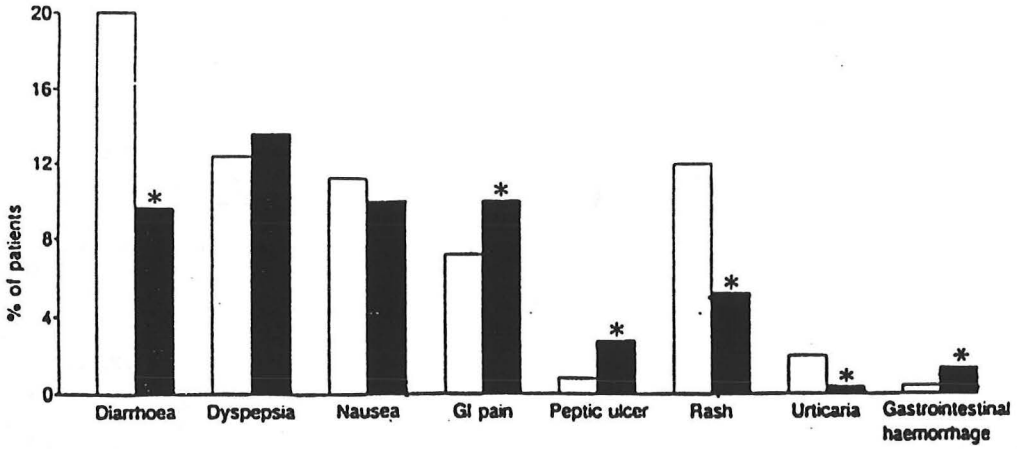


Fig. 6. Percentage of patients reporting adverse effects during 2 to 6 years' treatment with ticlopidine 500 mg/day (n = 1529, □) or aspirin 1300 mg/day (n = 1540, ■); * $p < 0.05$ statistically significant difference from ticlopidine (after Hass et al. 1989).

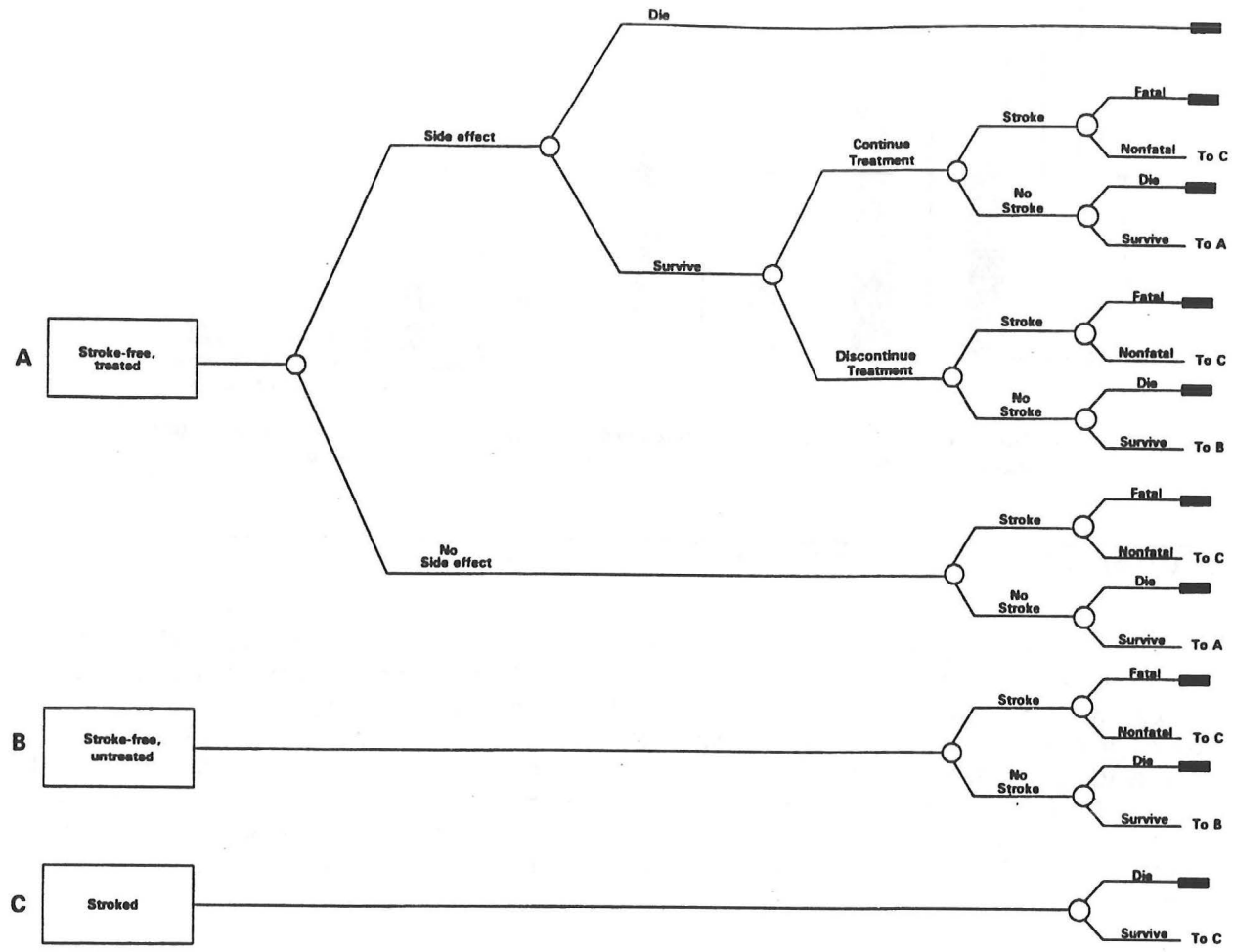
McTavish et al, Ref III.D.2

ASA, but HDL/LDL ratios were similar with the 2 drugs. The most widely discussed side effect of ticlopidine is neutropenia, which occurred infrequently in TASS. The overall frequency of neutropenia (absolute neutrophil count [ANC] $<1.2 \times 10^9$/L) was 2.4% and of severe neutropenia (ANC $<0.45 \times 10^9$/L) was 0.9%. All cases of severe neutropenia were reversible and occurred during the first 3 months of therapy, leading to the recommendation to monitor the ANC every other week for the first 12 weeks after starting this medication.

To put the net effect of these antiplatelet agents in proper perspective, it is useful to consider the net effect of treatment among a large cohort of patients at risk for ischemic stroke. The number of patients needed to treat (NNT) with ticlopidine instead of aspirin for one year, to prevent one nonfatal stroke or death is 28. By doing so, 3 more of the patients would have an adverse effect (compared to aspirin), one of which would be severe.[III.D.6] The NNT for ticlopidine compares very favorably with that of other treatments used to prevent cardiovascular endpoints.

While claims have been made that ticlopidine may have higher efficacy among women, and that it may be superior to aspirin for treatment of vertebrobasilar symptoms, symptoms occurring while on aspirin or warfarin, or among patients with renal insufficiency, diabetes mellitus, or hypertension, such

statements are based on subgroup (post hoc) analyses which have not been further substantiated.[III.D.7,8]



Model of monthly outcomes of primary stroke prevention.

Oster et al, Ref III.D.1

In order to determine whether the apparent advantage in efficacy translates into improved cost-effectiveness for ticlopidine, Oster and colleagues[III.D.1] performed a highly detailed decision analysis using a variety of strictly defined assumptions. Starting out with a hypothetical cohort of men and women with recent TIAs, all of whom were 65 years of age, they

assigned half to aspirin (1300 mg/d) and half to ticlopidine (500 mg/d) and projected outcomes for all until age 100 or predicted patient death, as shown in the decision tree.

A daily cost of $0.13 for aspirin and $2.75 for ticlopidine was used in the model. The overall results were as follows:

	Aspirin	Ticlopidine
Average Life Expectancy (yrs)	10.71	10.76
Quality Adjusted Life Expectancy (yrs)*	9.93-10.53	10.04-10.60
Quality Adjusted Life Expectancy (yrs)* (discounted)	7.18-7.54	7.25-7.58
Cost Effectiveness per Quality Adjusted Life Year*		$31,200-$55,500 Mean: $39,900

*Varying utility of life after stroke from 0.75-0.95

Overall, the average life expectancy of the ticlopidine group was increased by just over 18 days, at an average cost of about $40,000 per quality adjusted life year gained. While this gain seems small, it would, of course be distributed unequally among recipients, with some obtaining large benefits and others experiencing none. The cost-effectiveness is favorable in comparison with many interventions currently accepted in medical practice.

IV. Asymptomatic Cerebrovascular Disease (Primary Prevention)

The amount of reliable information available on the topic of asymptomatic cerebrovascular disease is far less than that for symptomatic involvement. However, asymptomatic disease of the carotid carries important risks. The presence of an asymptomatic carotid bruit is associated with a 1.5% to 4% annual risk of stroke; however, only half of persons with bruits have carotid stenosis of ≥70%.[V.1] In addition, 7% of asymptomatic patients with significant stenosis have CT evidence of prior ipsilateral stroke.[IV.1] A fifty percent reduction in carotid artery diameter, which is equivalent to a 75% reduction in cross sectional area, translates into a 2.5% annual risk for ipsilateral stroke.[IV.2]

Unfortunately, there are no Level I or II studies which address medical therapy of this clinical entity. The Physicians Health Study,[IV.3] a multi-year follow up of 22,071 male physicians treated with either 325 mg of aspirin or placebo every other day

was designed to measure difference in the occurrence of coronary endpoints. In fact, the study showed a definite decrease in the incidence of myocardial infarction, but the rate of strokes overall was not different. There was no evident reduction in the occurrence of ischemic stroke, and a trend toward increased risk of hemorrhagic stroke was noted with RR=2.14 (95% CI 0.96-4.77).

Physicians Health Study

Stroke Type	ASA Group	Placebo	RR	95% CI
Ischemic: Mild	69	61	1.13	0.80-1.60
Mod-Severe	21	20	1.05	0.57-1.95
Unknown	1	1		
Total	91	82	1.11	0.82-1.50
Hemorrhagic: Mild	10	6	1.67	0.61-4.57
Mod-Severe	13	6	2.19	0.84-5.69
Total	23	12	2.14	0.96-4.77

Hennekens, Ref IV.3

However, recent reports appear to show a benefit from surgical intervention. The VA Cooperative Study of carotid endarterectomy for asymptomatic carotid stenosis found a highly significant decrease in the combined endpoints of hemispheric or retinal TIA plus stroke in the surgical vs medical groups (20.6% vs 8.0%, with a RR of 0.38 (95% CI 0.22-0.67). There was no statistically significant difference between groups with regard to all strokes (4.7% surgical, 9.4% medical group) or in the combined endpoints of all strokes and deaths.[IV.4]

The **Asymptomatic Carotid Atherosclerosis Study (ACAS)** Group[IV.5] announced its results (Clinical Advisory, National Institute of Neurological Disorders and Stroke, 1994) before the scheduled end of the trial when a review committee decided that a statistically significant difference had already arisen in favor of surgery. ACAS was designed to determine whether receipt of CEA affected the 5 year risk of fatal and nonfatal ipsilateral strokes among asymptomatic persons with at least 60% carotid artery stenosis. Patients were excluded if they had prior stroke or TIA, prior CEA, unstable angina, severe diabetes, and other high risk conditions. All patients received 325 mg of ASA daily. Half of the 1,662 patients enrolled were assigned to surgery, and using Kaplan-Meier analysis for 5 year outcomes, the rate was 4.8% for the surgical group and 10.6% for the medical group, with an ARR=5.8% and RRR=55%, 95% CI=23%-73%). The aggregate risk for stroke or death in the perioperative period was 2.3%. The

importance of low morbidity and surgical mortality rates in demonstrating efficacy is shown by the CASANOVA trial, which found no difference between groups, but had complication rates of angiography plus surgery of 7%.[IV.6] The importance of routine ASA use for all study members is highlighted by the Mayo Clinic trial of surgery vs low dose ASA, which was terminated early due an increased frequency of myocardial infarctions and TIAs in their surgical group, which was not given ASA.[IV.7]

V. Consensus Recommendations for Stroke Prevention

In all cases, primary risk factors for stroke, namely hypertension, smoking, diabetes mellitus, heavy ethanol intake, and hypercholesterolemia should be addressed and controlled whenever possible. The following recommendations were adapted from the Third American College of Chest Physicians Consensus Conference on Antithrombotic Therapy,[V.2] the review article by Rothrock and Hart,[V.3] and the most recent American Heart Association Guidelines for TIA management.[V.4]

•Cervical Bruits/Asymptomatic Carotid Stenosis

If reliable imaging studies indicate at least 60% stenosis of the involved carotid artery, recent studies indicate that carotid endarterectomy in addition to ASA 325 mg per day may become the treatment of choice.

•Symptomatic Carotid Stenosis

If ≥70% carotid stenosis and good operative risk with an excellent surgical team on site, carotid endarterectomy is preferred. The role of CEA for lesser degrees of stenosis among symptomatic patients is currently being evaluated.

•TIA and Minor Ischemic Strokes

IF NOT A SURGICAL CANDIDATE:
Aspirin in doses of at least 325 mg daily or Ticlopidine 250 mg BID. Ticlopidine is clearly the preferred agent for patients with intolerance or contraindications to ASA or who are refractory to therapy with aspirin. Use of warfarin has not been proven to be an effective alternative, and prolonged anticoagulation therapy with warfarin is not recommended.

•Acute Ischemic Stroke (stable)

Subcutaneous heparin to prevent DVT/PE is advised in the situation of severe lower extremity weakness. Systemic heparin for vertebrobasilar strokes may be considered.

•Ischemic Stroke in Progress

Heparin anticoagulation for 3-5 days is a reasonable therapeutic option, especially for patients with symptoms in the vertebrobasilar circulation. Head CT should be performed to exclude hemorrhage as a cause for deterioration prior to

treatment. Some experts recommend aspirin only due to the absence of conclusive clinical data.

•Acute Cardioembolic Stroke

For small to moderate sized infarcts:
•with negative CT for hemorrhage at ≥48 hours and
•absence of severe hypertension:
Start heparin intravenously, then switch to warfarin to achieve an INR of 2.0 to 3.0. Due to low risk of early recurrence in the case of non-valvular atrial fibrillation, heparin need not be given and warfarin alone may be administered.

For large strokes or if significant hypertension present:
•Postpone anticoagulation therapy for 5 to 14 days.

VI. The Future: The Stroke Prevention PORT

One of 15 Patient Outcomes Research Teams (PORT) funded by the Agency for Health Care Policy and Research (AHCPR) focuses on treatment and prevention of cerebrovascular disease. This Stroke-PORT has an overall goal of "identifying the most appropriate and effective clinical strategies for stroke prevention for high risk individuals and by designing and testing an intervention to disseminate the information to providers and the public." Its specific aims include the following:

1) To critically review the evidence regarding benefits and risks of stroke prevention practices.

2) To identify variations in diagnosis, treatment, and management practices directed at prevention of stroke.

3) To explain these observed variations with predictive models.

4) To develop recommendations for stroke prevention in high risk populations using formal consensus development methods as well as decision and cost-effectiveness analyses.

5) To disseminate these recommendations to clinicians and the general public.

6) To determine the effect of the foregoing on physician attitudes and behaviors.[VI.1]

As mentioned earlier, the results of several trials involving stroke are eagerly anticipated. These include:

1) Two multicenter randomized trials of tPA in acute ischemic stroke;

2) The International Stroke Trial comparing heparin, ASA, both, or neither in the setting of acute ischemic stroke;

3) Multicenter randomized placebo controlled trial of low molecular weight (LMW) heparin in acute stroke;

4) Final results of the Asymptomatic Carotid Atherosclerosis Trial; and

5) The North American CPTA Register.

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