DRUG THERAPY

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DRUGS AND SURGERY IN THE PREVENTION OF ISCHEMIC STROKE

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ISCHEMIC and hemorrhagic strokes are among the principal causes of death and disability in older people, although the incidence of such strokes is lower than in the past.[1,2] Control of blood pressure, decreased cigarette smoking, and possibly altered dietary habits are among the important but unconfirmed reasons proposed for this decline.[3-5] This review addresses the antithrombotic and surgical measures to prevent ischemic stroke that have been rigorously evaluated in randomized clinical trials.

USE OF ANTICOAGULANT AGENTS TO PREVENT ISCHEMIC STROKE

Since the introduction of anticoagulant agents 50 years ago, their use has varied widely, which is to be expected for a treatment based on anecdotal evidence, case studies, and imperfect early clinical trials.[6] Recent studies allow some firm recommendations for the use of warfarin to prevent stroke, but areas of uncertainty persist.

Cardiac Disorders

Prospective studies have established nonrheumatic atrial fibrillation as a common cause of stroke, increasing in incidence and prognostic importance with age. Six randomized clinical trials have shown a benefit from the administration of warfarin as compared with placebo (Fig. 1).[7-12] With the results of these trials combined in a meta-analysis, the overall reduction in the relative risk (1 minus the relative risk) of stroke among patients treated with warfarin as compared with placebo was 64 percent (95 percent confidence interval, 51 to 74; $P<0.001$). Data from trials and case–control studies indicate that patients with nonvalvular atrial fibrillation who are less than 60 years old and have no other risk factors do not have an increased risk of stroke as compared with normal subjects.[13,14] The risk of stroke is also low if the fibrillation is paroxysmal and the patient has no recent history of congestive heart failure and no history of hypertension or thromboembolism. The value of warfarin remains unclear for patients older than 75 years of age, a group at higher risk for hemorrhagic complications of anticoagulation.[15,16] Maintenance of an international normalized ratio between 2.0 and 3.0 may make age a less important factor.[15,17]

The overall reduction in the relative risk of stroke among patients with nonvalvular atrial fibrillation treated with aspirin as compared with placebo was 22 percent (95 percent confidence interval, −1 to 39; $P=0.06$).[7,10,12] Although warfarin is superior to aspirin (Fig. 1), aspirin is an acceptable alternative to lifetime therapy with warfarin for younger patients who have low risk profiles and for patients in whom warfarin cannot be administered safely.

In early trials of less rigorous design, warfarin proved useful in the prevention of stroke among patients with rheumatic valvular heart disease, whether or not they had atrial fibrillation.[18] The decline in the prevalence of rheumatic heart disease makes the repetition of these trials unlikely.

Anticoagulant agents, more recently combined with platelet inhibitors, have long been administered to patients with artificial heart valves. For patients who receive bioprosthetic heart valves, the customary practice is to recommend the use of warfarin for three to six months, unless a patient has atrial fibrillation, in which case the drug is continued indefinitely.[19,20] For patients with mechanical valves, who have a higher risk of cerebral thromboembolism, warfarin is given indefinitely. The risk of thromboembolism among patients with mechanical valves who are treated with warfarin may be minimized with the maintenance of an international normalized ratio between 3.0 and 4.5.[21]

Case–control studies suggest that in patients with a recent myocardial infarction complicated by cerebral embolism, heparin and warfarin reduce the risk of recurrence,[22] and the results of a randomized trial that was stopped after only 44 patients had been enrolled indicate a similar benefit.[23] The results of several large studies and meta-analyses favor the use of heparin and warfarin to prevent stroke after myocardial infarction.[22,24-27]

Arteriosclerotic Lesions of the Cerebral Arteries

The value of warfarin is unknown in patients who have transient ischemic attacks, strokes related to arteriosclerotic disease of the major cerebral arteries, or lacunar disease. Fewer than 200 patients with transient ischemic attacks or minor strokes have received placebo or warfarin in randomized clinical trials,[6] but patients with ischemic events that are apparently arterial in origin are often treated empirically with warfarin if platelet inhibitors are ineffective or cannot be tolerated. Large trials examining the benefit of warfarin and heparin in patients with acute or progressing stroke are under way. In the Warfarin–Aspirin Recurrent Stroke Study, warfarin and aspirin are being compared in patients with recent strokes; the study includes patients

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with only transient ischemic attacks provided there is computed tomographic evidence of brain infarction (Mohr JP: personal communication).

Prevention of Ischemic Stroke with Platelet Inhibitors

Sulfinpyrazone, aspirin, and dipyridamole all inhibit platelet aggregation in vitro.[28-30] On the basis of studies that demonstrated the presence of white platelet–fibrin thrombi in the retinal arterioles in patients with amaurosis fugax,[31,32] these drugs were given to patients with recurrent transient monocular blindness and found to be beneficial.[33,34] Similar white platelet–fibrin material was subsequently observed in cortical arteries exposed for bypass surgery (Fig. 2), linking hemispheric and brain-stem transient ischemic attacks of seemingly arterial origin to platelet–fibrin thromboembolism. Clinical trials of platelet inhibitors were then launched.

Clinical Trials of Platelet-Inhibiting Drugs

The first clinical trial in which aspirin was used as a platelet inhibitor in patients with any form of vascular disease was the Canadian Cooperative Study[35] of aspirin, sulfinpyrazone, and placebo. The study involved 585 patients (406 men and 179 women) with transient ischemic attacks or minor strokes in the region of the carotid or vertebrobasilar arteries (excluding patients with recognizable cardiac sources of embolism). The combined incidence of stroke and death was reduced by 31 percent among the patients who took 1300 mg of aspirin per day alone or with sulfinpyrazone, as compared with the combined incidence in the placebo group. Sulfinpyrazone alone was ineffective. A subgroup analysis showed a statistically significant reduction in the relative risk of stroke or death (48 percent) among the men but no significant reduction in the relative risk of these outcomes among the women. This difference in responsiveness according to sex was not confirmed in later trials.[36,37] Among the several shortcomings of this trial, the sample was small and the question of the optimal dose was not addressed.

A total of approximately 14,400 patients with transient ischemic attacks or minor strokes of noncardiac origin have subsequently been enrolled in 15 randomized studies evaluating five platelet-inhibiting drugs.[38-52] Stroke was not prevented by sulfinpyrazone, dipyridamole, or suloctidil,[35,49,50] and neither dipyridamole plus aspirin nor sulfinpyrazone plus aspirin proved more beneficial than aspirin alone in four trials.[35,39,40,46] A limitation of all these trials is that most of the patients were not evaluated sufficiently to determine the probable cause of the cerebral ischemia. Most of the studies excluded patients with an identifiable po-

Trial	Time since Last Event (mo)	INR Range (daily aspirin dose)	Sample Size and Person-Years	No. of Strokes
Warfarin vs. placebo				
AFASAK[7]	1	2.8–4.2	W: 335 (250) P: 336 (382)	5 18
BAATAF[8]	6	1.5–2.7	W: 212 (487) P: 208 (435)	3 13
CAFA[9]	12	2.0–3.0	W: 187 (235) P: 191 (239)	7 11
SPAF I[10]	24	2.0–4.5	W: 210 (260) P: 211 (244)	7 18
VA[11]	No event (91% of patients)	1.4–2.8	W: 281 (489) P: 290 (483)	9 24
EAFT[12]	Recent event required	2.5–4.0	W: 225 (507) P: 214 (405)	21 54
Overall	—	—	—	—
Warfarin vs. aspirin				
AFASAK[7]	1	2.8–4.2 (75 mg)	W: 335 (250) A: 336 (364)	5 17
SPAF I[10]	24	2.0–4.5 (325 mg)	W: 210 (260) A: 552 (720)	7 27
EAFT[12]	Recent event required	2.5–4.0 (300 mg)	W: 225 (507) A: 404 (838)	21 94
SPAF II[16]	24	2.0–4.5 (325 mg)	W: 555 (1493) A: 545 (1460)	41 44
Overall	—	—	—	—

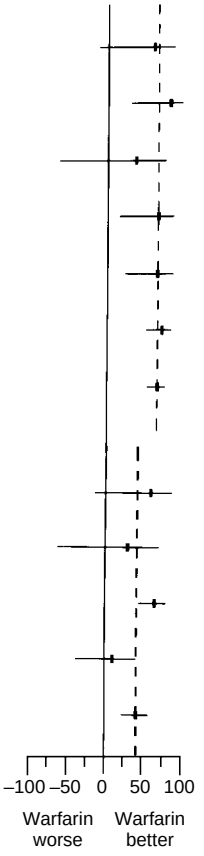

Figure 1. Reduction in the Relative Risk of Stroke Associated with Warfarin as Compared with Placebo or Aspirin among Patients with Nonvalvular Atrial Fibrillation.

Each tick mark represents the reduction in the relative risk of stroke, and each horizontal line the corresponding 95 percent confidence interval. The overall relative-risk reduction, represented by the broken vertical line, was 64 percent (95 percent confidence interval, 51 to 74; $P<0.001$) for warfarin (W) as compared with placebo (P) and 40 percent (95 percent confidence interval, 21 to 55; $P<0.001$) for warfarin as compared with aspirin (A). All P values are two-tailed. The result of a test for heterogeneity in the relative-risk reduction for each group of trials was not statistically significant. The reduction in relative risk, defined as 1 minus the relative risk, was calculated on the basis of the estimated number of person-years of follow-up (shown in parentheses after sample size). All fatal and nonfatal strokes, intracranial hemorrhages, and systemic embolisms were counted as strokes. INR denotes international normalized ratio; AFASAK Atrial Fibrillation, Aspirin, Anticoagulant trial; BAATAF Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA Canadian Atrial Fibrillation Anticoagulation trial; SPAF Stroke Prevention in Atrial Fibrillation trial; VA Veterans Affairs trial; and EAFT European Atrial Fibrillation Trial. Aspirin use was allowed in the BAATAF trial.

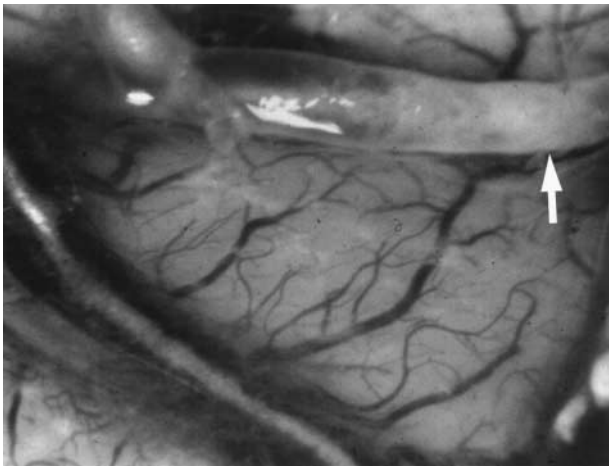

Figure 2. White Platelet–Fibrin Material (Arrow) in the Cortical Branch of the Middle Cerebral Artery Flowing from Left to Right and Exposed at Craniotomy in a Patient Undergoing Superficial Anastomosis between the Temporal and Middle Cerebral Arteries (×10).

The patient had symptoms related to intracranial stenosis of the internal carotid artery. The platelet–fibrin origin of some transient ischemic attacks in the hemisphere due to proximal major vascular disease is confirmed by such chance observations. (Photograph kindly provided by Dr. H. Reichman, Loyola University.)

tential cardiac source of thromboembolism, and none of the studies attempted to distinguish between lacunar and nonlacunar strokes. The value of platelet inhibitors for these specific causes of stroke is therefore not known.

Concern about the potential disadvantages of simultaneously inhibiting the production of platelet thromboxane A_2[53] and the production of endothelial prostacyclin[54] has led to trials of lower doses of aspirin (75 to 300 mg daily). Low doses of aspirin, which cause less gastrointestinal discomfort than higher doses,[55] have proved effective in reducing the incidence of recurrent myocardial infarction and stroke among patients with angina, unstable angina, or acute myocardial infarction.[56] The benefit of low doses of aspirin in patients with transient ischemic attacks or minor strokes of arterial origin is less certain.[57,58]

Meta-Analyses of Trials of Platelet-Inhibiting Drugs

The first meta-analysis from the Antiplatelet Trialists' Collaboration reported on vascular events in 25 trials involving some 29,000 patients with histories of transient ischemic attacks, minor strokes, unstable angina, or myocardial infarction.[59] The main analysis, which considered all platelet inhibitors and treatment regimens of equal value, reported an overall 25 percent odds reduction for vascular events (stroke, myocardial infarction, or death from a vascular cause) and a 27 percent odds reduction for nonfatal stroke. (The odds reduction is defined as 1 minus the odds ratio, where the odds ratio is the ratio of the odds of an unfavorable outcome among patients receiving one treatment to the corresponding odds among patients receiving another treatment. The odds reduction is analogous to the relative-risk reduction but slightly larger.) The benefit of the antiplatelet therapy was similar regardless of the agent and dose used and did not vary according to whether the patient had a history of cerebral or cardiac disease.

The second meta-analysis from the same group involved over 100,000 patients in 145 trials.[60] Data on platelet inhibitors of all types and patients with vascular disease or other conditions associated with an increased risk of occlusive vascular disease were aggregated. The overall odds reduction for vascular events was 25 percent. Among patients with previous minor strokes or transient ischemic attacks, the odds reduction was 22 percent for vascular events and 23 percent for nonfatal strokes.

We performed a meta-analysis of all trials in which aspirin was compared with placebo in patients with transient ischemic attacks or minor strokes of noncardiac but presumably arterial origin. The outcome events were stroke, fatal stroke, or death from a vascular cause; nonfatal myocardial infarctions were not counted. In previous meta-analyses, the investigators assumed that the mechanisms of production and inhibition of platelet–fibrin thrombi in patients at high risk were identical in all vascular beds. However, an agent that is effective in reducing the risk of myocardial infarction due to coronary artery disease may not be equally effective in reducing the risk of stroke due to cerebral artery disease, because of differences in vascular reactivity and thrombus formation in various circulatory beds.[61-63]

No single trial has demonstrated that aspirin in high doses (900 to 1300 mg daily) or low doses (75 to 300 mg daily) is significantly more effective than placebo in preventing strokes in this group of patients (Fig. 3). The meta-analyses show that the overall reduction in the relative risk of stroke associated with high-dose or low-dose aspirin was modest and not statistically significant. Aspirin combined with dipyridamole or sulfinpyrazone (Fig. 4) was significantly more effective than placebo, but there was no difference between combined therapy and aspirin alone (Fig. 4).

These indirect comparisons raise the question of a possible synergistic effect between aspirin and other antiplatelet agents, but meta-analyses cannot directly test for a statistically significant drug interaction. A large randomized trial should be conducted to establish the optimal dose of aspirin and the role of aspirin combined with other platelet inhibitors in patients with transient ischemic attacks or strokes of arterial origin.

Ticlopidine

Ticlopidine is the only other platelet-inhibiting drug that has been proved beneficial in clinical trials. It is a thienopyridine derivative and, unlike aspirin, does not affect the cyclooxygenase pathway. Ticlopidine inhibits platelet aggregation induced by adenosine diphosphate and other agonists, apparently by altering the platelet membrane and interfering with the membrane–fibrinogen interaction, thereby blocking the platelet glycoprotein IIb/IIIa receptor.[64,65] The antiplatelet effect is max-

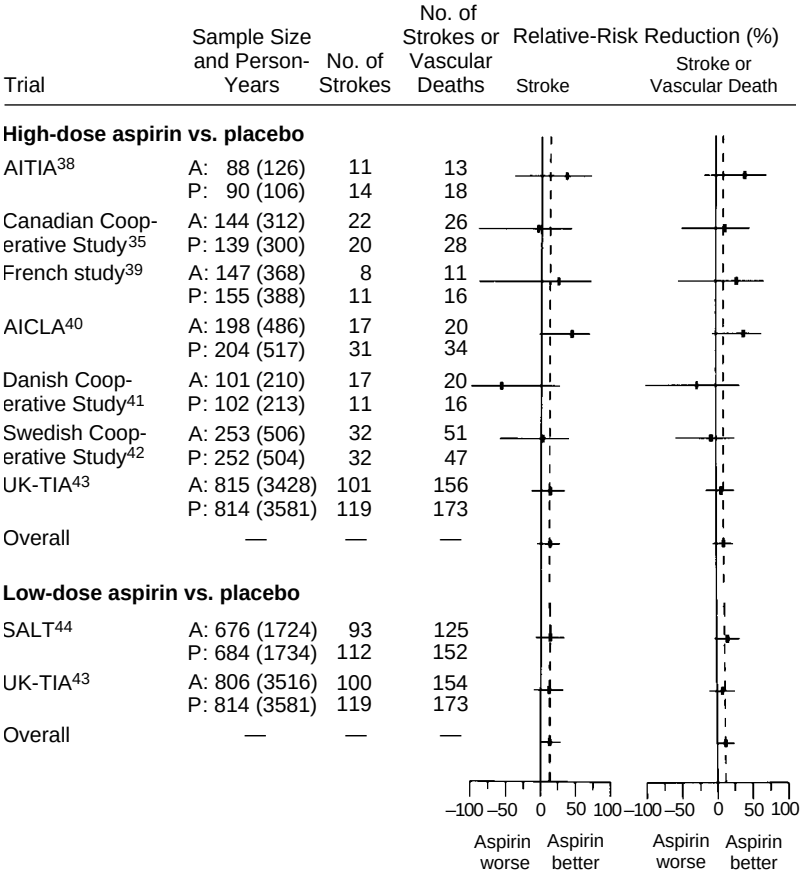

Figure 3. Reduction in the Relative Risk of the Combined Outcome of Fatal or Nonfatal Stroke and Death from a Vascular Cause Associated with High-Dose or Low-Dose Aspirin as Compared with Placebo in Patients with Transient Ischemic Attacks or Strokes of Noncardiac Origin.

High doses of aspirin ranged from 900 to 1300 mg daily, and low doses from 75 to 300 mg daily. Each tick mark represents the reduction in the relative risk of stroke or vascular death, and each horizontal line the corresponding 95 percent confidence interval. The broken vertical lines represent the overall relative-risk reduction. The overall reduction in the relative risk associated with high-dose aspirin was 11 percent (95 percent confidence interval, −7 to 26; P = 0.20) for stroke and 9 percent (95 percent confidence interval, −6 to 22; P = 0.23) for stroke or vascular death; the overall reduction in the relative risk associated with low-dose aspirin was 15 percent (95 percent confidence interval, −2 to 30; P = 0.08) for stroke and 13 percent (95 percent confidence interval, −1 to 26; P = 0.08) for stroke or vascular death. A negative number indicates an increase in risk. All P values are two-tailed. The result of a test for heterogeneity in the relative-risk reduction for each group of trials was not statistically significant. The numbers in parentheses are estimated person-years of follow-up. AITIA denotes Aspirin in Transient Ischemic Attacks trial, A aspirin, P placebo, AICLA Accidents Ischémiques Cérébraux Liés à l'Atherosclerose, UK-TIA United Kingdom Transient Ischaemic Attack trial, and SALT Swedish Aspirin Low-Dose Trial.

imal in 24 to 48 hours, as compared with a maximal effect in 20 minutes for aspirin. The effect is associated with a twofold to fivefold prolongation of the bleeding time, is not reversible, and dissipates within a week after the drug has been discontinued.

Ticlopidine has been studied in two large trials of stroke prevention in patients with no evidence of cardiac disease. In the Ticlopidine Aspirin Stroke Study, 3069 patients with transient ischemic attacks or minor strokes received ticlopidine (500 mg daily) or aspirin (1300 mg daily).[51] The risk of nonfatal stroke or death from any cause at three years was 17 percent in the ticlopidine group and 19 percent in the aspirin group (relative-risk reduction with ticlopidine, 12 percent). The three-year risk of fatal or nonfatal stroke was 10 percent in the ticlopidine group and 13 percent in the aspirin group (relative-risk reduction with ticlopidine, 21 percent). The investigators concluded that "ticlopidine was somewhat more effective than aspirin," but more patients in the ticlopidine group had side effects. Subgroup analyses suggested that ticlopidine was more effective than aspirin in women, in patients with completed stroke, and in patients with ischemia in the posterior cerebral circulation.[66-68]

In the Canadian American Ticlopidine Study, 1072 patients received ticlopidine (500 mg daily) or placebo within 1 to 16 weeks after a major stroke.[52] The combined yearly rate of strokes, myocardial infarctions, and deaths from vascular causes was 15 percent in the placebo group and 11 percent in the ticlopidine group (relative-risk reduction with ticlopidine, 30 percent). This trial was the first in which patients with major strokes were studied. An exclusive benefit in patients with strokes cannot be claimed for ticlopidine, because aspirin has also proved beneficial in patients with minor strokes.[40,43,45]

The side effects of ticlopidine therapy include suppression of bone marrow, diarrhea, and rash. Neutropenia, reported in 2 percent of patients in the Ticlopidine Aspirin Stroke Study, occurs early but is reversible after the cessation of therapy; patients must be monitored regularly for at least three months after the start of therapy. Transient diarrhea is common (with a frequency of 22 percent in the Canadian American Ticlopidine Study), and persistent diarrhea necessitating the cessation of therapy occurs in about 5 percent of patients.[51,52]

Aspirin in Healthy Middle-Aged Subjects

In two studies of aspirin therapy for primary prevention, 22,071 American male physicians received 325 mg every other day, and 5139 British male physicians received 500 mg daily.[69,70] In the American trial, which included a placebo group, there was a marked reduction in the incidence of first myocardial infarctions (relative-risk reduction, 44 percent) but no reduction in the

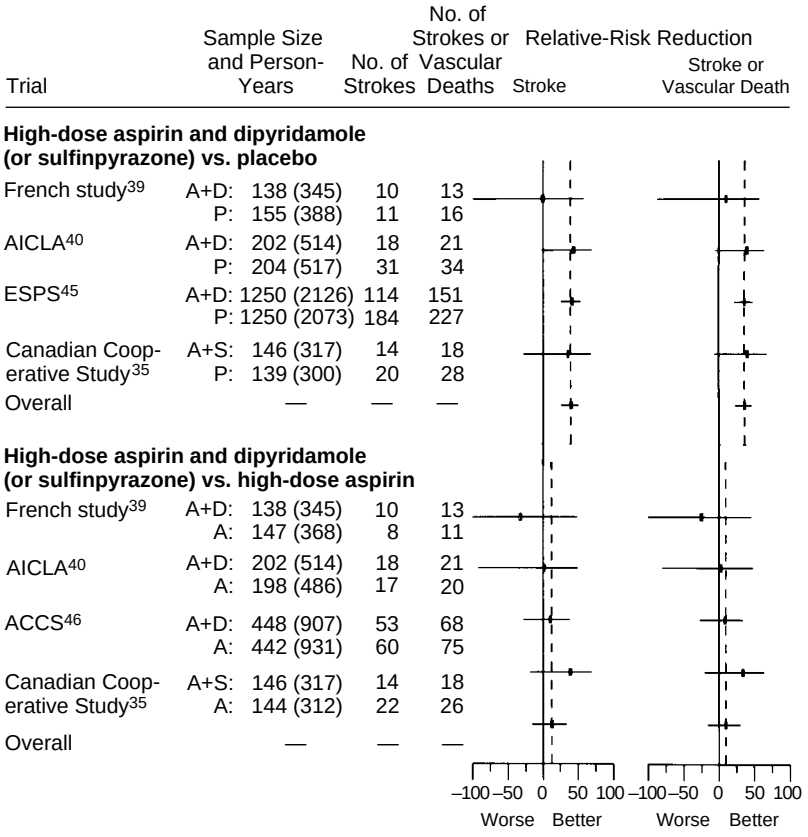

Figure 4. Reduction in the Relative Risk of the Combined Outcome of Fatal or Nonfatal Stroke and Death from a Vascular Cause Associated with High-Dose Aspirin and Dipyridamole (or Sulfinpyrazone) as Compared with Placebo or High-Dose Aspirin Alone in Patients with Transient Ischemic Attacks or Strokes of Noncardiac Origin.

The doses used were 900 to 1300 mg of aspirin daily, 150 to 300 mg of dipyridamole daily, and 800 mg of sulfinpyrazone daily. Each tick mark represents the reduction in the relative risk of stroke or vascular death, and each horizontal line the corresponding 95 percent confidence interval. The broken vertical lines represent the overall relative-risk reduction. The overall relative-risk reduction associated with high-dose aspirin and dipyridamole as compared with placebo was 38 percent (95 percent confidence interval, 24 to 49; $P<0.001$) for stroke and 35 percent (95 percent confidence interval, 22 to 45; $P<0.001$) for stroke or vascular death; the overall relative-risk reduction associated with high-dose aspirin and dipyridamole as compared with high-dose aspirin alone was 11 percent (95 percent confidence interval, −17 to 32; $P=0.42$) for stroke and 8 percent (95 percent confidence interval, −17 to 28; $P=0.48$) for stroke or vascular death. A negative number indicates an increase in risk. All P values are two-tailed. The result of a test for heterogeneity in the relative-risk reduction for each group of trials was not statistically significant. The numbers in parentheses are estimated person-years of follow-up. A denotes aspirin, D dipyridamole, P placebo, AICLA Accidents Ischémiques Cérébraux Liés à l'Atherosclerose, ESPS European Stroke Prevention Study, S sulfinpyrazone, and ACCS American–Canadian Co-Operative Study.

incidence of deaths from vascular causes or strokes. In the smaller British trial, there was no reduction in any of these events. In a prospective cohort study involving 87,678 women, regular use of aspirin (one to six 325-mg tablets daily), as compared with no use of aspirin, reduced the risk of a first myocardial infarction by 32 percent but did not reduce the risk of stroke.[71]

Recommendations for Administering Platelet Inhibitors

On the basis of imperfect data, aspirin is the drug of first choice for patients with cerebral ischemia (transient or persistent) of an apparently noncardiac origin. Aspirin may not be better than or even as effective as warfarin, but the potential benefit of the latter drug has not yet been evaluated properly. The combination of aspirin with another antiplatelet agent may confer an additional benefit.

The preferred dose of aspirin is still uncertain. A dose as low as 40 mg daily reduces the incidence of fatal and nonfatal myocardial infarction in patients with unstable angina. This low dose will completely inhibit cyclooxygenase activity in most people. If the inhibition persisted for the life of all platelets in all patients, whatever the type of threatened thrombosis, and if no other thrombotic mechanisms were affected by aspirin, there would be less uncertainty about the best dose to prevent stroke. In some patients, however, the antiplatelet effect of a low dose is incomplete, and the effect increases when the dose is increased.[72,73] In addition, platelet aggregation in response to collagen may vary according to the dose of aspirin.[74]

In one trial a low dose of aspirin (50 to 100 mg) was no more effective than placebo in preventing stroke after carotid endarterectomy, which exposes collagen to platelets,[47] but in another trial the administration of 75 mg of aspirin beginning 12 hours before endarterectomy was beneficial.[48] In a third trial, a dose of 1000 mg daily reduced the incidence of postoperative death.[75] Among the patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), a daily dose of 650 mg or more was superior to a daily dose of 325 mg or less in preventing stroke during the first 30 days after surgery (unpublished data). A randomized trial has been started to determine the most effective postoperative dose.

At this time, we favor an initial dose of no less than 650 mg daily for patients with symptoms indicating the possibility of a stroke of arterial origin. The evidence that lower doses may result in fewer thrombotic events is not firm. Furthermore, the chief complications of aspirin therapy are not related to the dose.[76] An enteric-coated preparation reduces gastrointestinal distress. For patients with an intolerance to aspirin, gastrointestinal side effects, or continuing ischemic events, we recommend 250 mg of ticlopidine twice daily. For patients who are taking 650 mg or more of aspirin daily and have less severe side effects, the dose may be reduced.

Table 1. Randomized, Controlled Trials of Carotid Endarterectomy to Prevent Stroke in Patients with Carotid Artery Disease.

TRIAL*	ENROLLMENT CRITERIA	INCIDENCE OF PERIOPERATIVE STROKE OR DEATH FROM ANY CAUSE (%)†	% RELATIVE-RISK REDUCTION (95% CI)‡	SIGNIFICANT BENEFIT	COMMENTS
Fields et al.[77]	Vertebrobasilar or carotid symptoms, internal-carotid-artery stenosis			No	Excess of 30-day complications from bilateral or occluded-artery surgery
Surgical group					
Unilateral endarterectomy (n = 169)		7.1	1.5 (−70.8 to 43.8)		
Bilateral or occluded-artery endarterectomy (n = 56)		19.6			
Medical group (n = 147)					
Shaw et al.[78]	Ipsilateral carotid symptoms, internal-carotid-artery stenosis	35.0	−14.3 (−178.1 to 53.0)	No	Excess of 30-day complications, surgical group not given aspirin
Surgical group (n = 20)					
Medical group (n = 21)					
NASCET[79]	Ipsilateral carotid symptoms, internal-carotid-artery stenosis ≥70 percent§	5.8 (disabling stroke, 2.1)	52.5 (27.6 to 69.3)	Yes	
Surgical group (n = 328)					
Medical group (n = 331)					
ECST[80]	Ipsilateral carotid symptoms, internal-carotid-artery stenosis ≥82 percent§	7.5 (disabling stroke, 3.7)	36.3 (12.7 to 53.5)	Yes	
Surgical group (n = 455)					
Medical group (n = 323)					
Mayberg et al. (VA trial)[81]	Ipsilateral carotid symptoms, internal-carotid-artery stenosis ≥50 percent	6.6	−7.8 (−260.1 to 67.7)	No	Trial discontinued
Surgical group (n = 91)					
Medical group (n = 98)					
CASANOVA[82]	Asymptomatic, ≤90 percent carotid-artery stenosis	3.0	22.0 (−81.7 to 67.1)	No	Serious problems with study design
Surgical group (n = 122)					
Medical group (n = 111)					
MACE[83]	Asymptomatic, ≥50 percent carotid-artery stenosis	8.3	Indeterminate	No	Trial discontinued (8 myocardial infarctions in surgical group and none in medical group); surgical group not given aspirin
Surgical group (n = 36)					
Medical group (n = 35)					
Hobson et al. (VA trial)[84]	Asymptomatic, ≥50 percent carotid-artery stenosis	4.4	9.9 (−27.7 to 36.6)	No	Sample too small
Surgical group (n = 211)					
Medical group (n = 233)					

*NASCET denotes North American Symptomatic Carotid Endarterectomy Trial; ECST European Carotid Surgery Trial; VA Veterans Affairs; CASANOVA Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin trial; and MACE Mayo Asymptomatic Carotid Endarterectomy trial.

†Includes all fatal and nonfatal strokes (defined as a neurologic deficit persisting for more than 24 hours).

‡Reduction in relative risk of stroke or death from a vascular cause. Relative-risk reduction due to surgical treatment was calculated as 1 minus the relative risk. A negative number indicates an increase in risk. CI denotes confidence interval.

§According to a type of measurement used in NASCET.

Whether patients who have gastrointestinal bleeding with aspirin can tolerate ticlopidine is unknown.

SURGICAL PROCEDURES TO PREVENT STROKE

Randomized clinical trials have evaluated two surgical procedures (carotid endarterectomy and extracranial–intracranial anastomosis) to prevent stroke in patients with arteriosclerotic disease of the carotid arteries. Transluminal angioplasty is a third procedure currently being studied. Table 1 summarizes the results of the completed trials of carotid endarterectomy.[77-84]

Carotid Endarterectomy

The surgical correction of a symptomatic carotid lesion was first reported in 1954.[85] Surgeons were quick to learn the technique. The records from the National Hospital Discharge Survey in the United States indicate the subsequent growth, decline, and resurgence of interest in the procedure (Fig. 5). The fluctuating enthusiasm for carotid endarterectomy has several explanations. The procedure quickly gained popularity because many surgeons developed the skill required to perform the operation, and it was used for both symptomatic and asymptomatic occlusive disease detected by noninvasive imaging techniques. In a large survey, 44 percent of patients who underwent the procedure were asymptomatic.[86] The reports of two randomized studies with negative results did not detract from the popularity of carotid endarterectomy, perhaps because the operation seemed such a logical way to treat carotid arterial disease.[77,78]

The rising popularity of carotid endarterectomy in the early 1980s suggested that the number of procedures performed annually would soon reach 150,000. Unexpected developments then intervened, and the number of procedures declined. The perioperative complications reported by the experts in their case studies were not matched by the experience in most hospitals in the United States; data from the National Hospital Discharge Survey and other sources revealed that the average rate of stroke and death in the perioperative period was about 10 percent.[58,86] Questions about the safety, as well as the benefits, of the operation led to several clinical trials.

Symptomatic Carotid Artery Disease

In three multicenter studies, patients with transient focal retinal or cerebral symptoms associated with arteriosclerotic stenosis of the carotid artery were randomly assigned to receive medical care (regulation of treatable risk factors and aspirin) alone or combined with surgery. Patients with major strokes were exclud-

ed, as were patients with nonspecific symptoms, such as dizziness, lightheadedness, confusion, fainting, and drop attacks. In NASCET and the European Carotid Surgery Trial (ECST), interim analyses indicated that for symptomatic patients with stenosis of 70 percent or more, medical care alone was inferior to carotid endarterectomy at two and three years, respectively.[79,80] Further follow-up of patients in the surgical group in NASCET affirmed the durability of the benefit (Fig. 6). The absolute difference between the risk of stroke among patients receiving medical care alone and the risk among those undergoing surgery was unequivocal. In NASCET the risk of ipsilateral stroke at two years was 26 percent for patients treated medically and 9 percent for those treated surgically. The benefit was smaller in ECST; at three years the absolute difference was 14 percent, as compared with 17 percent at two years in NASCET. The explanation for this discrepancy in results is that the two trials used different methods to measure the degree of stenosis.[87,88]

The third study, conducted within the Department of Veterans Affairs, was stopped when the benefit of surgery for patients with severe stenosis in NASCET and ECST became evident. This study of 189 patients who had carotid stenosis of at least 50 percent revealed no benefit of surgery unless transient ischemic events during or after treatment were considered along with stroke in the analysis of outcome events.[81]

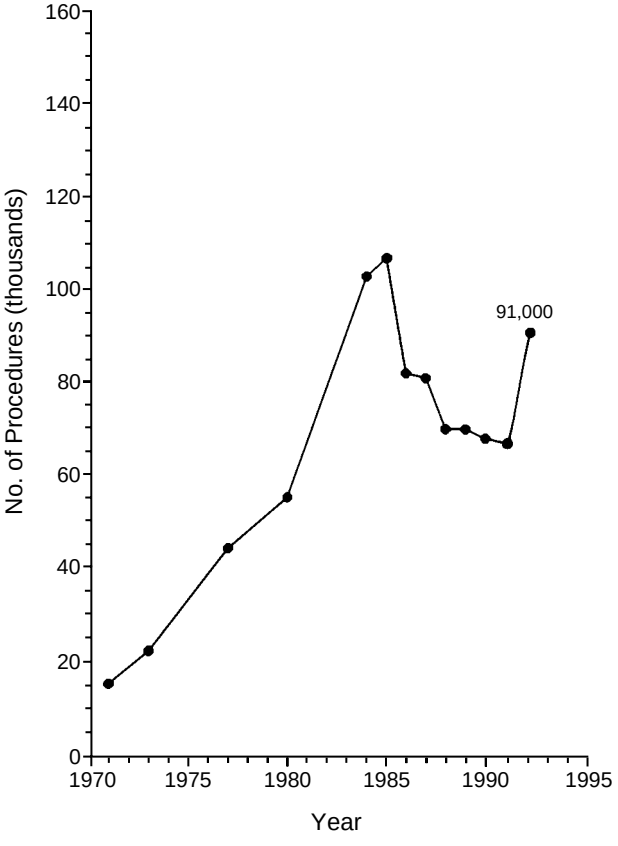

Figure 5. Number of Carotid Endarterectomies Performed in the United States from 1971 to 1992.

Data are from the National Hospital Discharge Survey (Dyken M, Pokras R: personal communication).

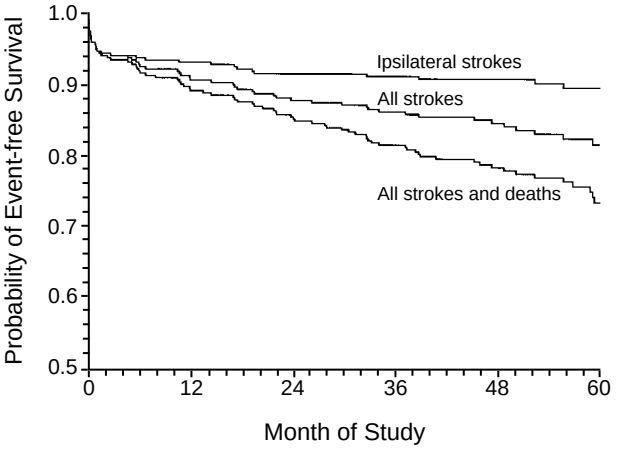

Figure 6. Kaplan–Meier Curves for Event-free Survival after Carotid Endarterectomy in Symptomatic Patients with Severe Stenosis.

The mean duration of follow-up was 47 months. At five years, the risk of an ipsilateral stroke was 10 percent, the risk of any stroke (ipsilateral, contralateral, or vertebrobasilar) was 18 percent, and the risk of any stroke or death was 27 percent.

In both NASCET and ECST surgery was not beneficial in patients with less than 70 percent stenosis. Both trials continue to enroll symptomatic patients in this category, with the goal of studying approximately 2000 patients each.

It should be noted that the results of these trials apply only to patients with symptoms associated with severe carotid stenosis (70 to 99 percent, as measured on angiograms with the use of a jeweler's eyepiece).[89] The extrapolation of the results from NASCET and ECST to patients evaluated with ultrasonography remains a challenge. A comparison of ultrasonography and arteriography in NASCET showed that ultrasonography had a disappointingly low sensitivity (67 percent) and a specificity of 78 percent for detecting severe stenosis (unpublished data). However, ultrasound technology has been improved, so that closer agreement can now be achieved with the use of color-coded Doppler and B-mode ultrasonography. Nevertheless, correlations between ultrasonographic and arteriographic measurements remain imprecise.[90-92]

If endarterectomy is to be recommended, the rate of perioperative complications must be similar to that in NASCET. Although symptomatic patients with severe carotid stenosis have a poor prognosis if they are not treated with endarterectomy, a perioperative incidence of 10 percent or more for stroke or death negates the benefit of surgery. Hospital and departmental audits must ensure that patients do not face unduly high surgical risks.

Ultrasonography as a Prelude to Carotid Endarterectomy

Even in expert hands, conventional carotid arteriography poses a minimal but definite risk of stroke. Ultrasonography is being used by some as the sole method to quantify the degree of stenosis, but it has not been used alone in any randomized trial evaluating carotid endarterectomy. Several factors related to the condition of the artery argue against replacing arteriography

with any of the methods of noninvasive imaging that are currently available. NASCET reported a reduction in the benefit of endarterectomy in patients with declining degrees of carotid stenosis. The absolute difference (benefit) in two-year survival free of ipsilateral stroke between the medically and surgically treated patients was 26 percent in patients with stenosis of 90 to 99 percent, 18 percent in those with stenosis of 80 to 89 percent, and 12 percent in those with stenosis of 70 to 79 percent. The results of ECST were similar.[87]

This decline in the benefit of endarterectomy underscores the importance of calculating precisely the degree of stenosis in order to determine the risk of stroke. The presence of vessel-wall ulceration adds to the risk, as does the presence of an intraluminal thrombus and coincidental stenosis of the intracranial portion of the carotid artery.[93,94] These features are imperfectly detected by ultrasonography.

The possibility of an unsuspected intracranial aneurysm is another reason for eschewing dependence on ultrasonography alone as a prelude to endarterectomy. Of the 2193 patients enrolled in NASCET, 66 (3 percent) had intracranial aneurysms (unpublished data). Six of these patients had aneurysms larger than 6 mm in diameter and underwent clipping operations; one of the six had a subarachnoid hemorrhage after the endarterectomy had been performed but before the aneurysm had been clipped. Neurosurgeons disagree about which aneurysms are likely to rupture, but most suggest clipping aneurysms that are 6 to 7 mm in diameter or larger as soon as feasible after a carotid endarterectomy has been performed for severe symptomatic stenosis (Drake CG: personal communication).

Improvement in ultrasonography, so that the results correlate more closely with those of arteriography, or in magnetic resonance arteriography should make conventional arteriography unnecessary. At present, the degree of stenosis is overestimated by magnetic resonance arteriography, and the problem of signal void related to turbulence has not been resolved. Until these other methods have been improved, ultrasonography should be used as a screening test with confirmation of the results by arteriography in patients with severe or moderate stenosis who appear to be candidates for endarterectomy or for enrollment in a trial evaluating the benefit of the procedure for moderate stenosis.[95]

Asymptomatic Carotid Artery Disease

Asymptomatic arteriosclerotic disease of the carotid artery is common, and its incidence increases with age. Thirty percent of people over 50 years of age have some evidence of carotid artery disease. The incidence of carotid stenosis of more than 50 percent has been estimated, on the basis of ultrasonography, to be 4 percent among middle-aged and older people; less than 1 percent of people in these age groups have stenosis of 80 percent or more.[96]

Two large follow-up studies of asymptomatic patients who underwent carotid ultrasonography have been reported.[97,98] In an eight-year Canadian study of 696 patients, the annual rate of ipsilateral stroke was 2.5 percent among the patients with at least 75 percent stenosis of one carotid artery. In a 12-year German study of 500 patients with at least 80 percent stenosis, the annual rate of ipsilateral stroke was 2.4 percent (Hennerici M: personal communication). For patients with less than 75 percent stenosis, the annual rate of stroke was 1 percent in both studies. The risk of fatal coronary artery disease increases with the degree of carotid stenosis; in the Canadian study the annual rate of death (in most cases from myocardial infarction) was 6.5 percent.

The results of three randomized trials of endarterectomy in patients with asymptomatic carotid disease have been published. In the Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin (CASANOVA) trial, patients with stenosis of more than 90 percent were excluded, and those with bilateral disease who were randomly assigned to medical treatment underwent endarterectomy for the more severely affected carotid artery.[82] Only 25 percent of the 440 patients in the trial received medical treatment alone. No benefit was found for endarterectomy. The Mayo Asymptomatic Carotid Endarterectomy study was discontinued after 71 patients had been enrolled,[83] because myocardial infarctions and cerebral ischemic events had occurred in 8 and 3 patients, respectively, in the endarterectomy group, as compared with none in the aspirin group. The third trial with negative results was the Department of Veterans Affairs study of 444 patients.[84] The 30-day rate of postoperative stroke or death in the 203 patients who underwent endarterectomy was 4.4 percent. The stroke-free–survival curves for the medical and surgical groups overlapped both during the early weeks of follow-up and thereafter. The incidence of transient ischemic attacks, especially amaurosis fugax, was reduced in the surgical group. Prevention of transient ischemic attacks without a reduction in the number of strokes, at the risk of perioperative stroke and death, does not warrant endarterectomy.

An interim analysis from a fourth, just concluded, trial, the Asymptomatic Carotid Atherosclerosis Study,[99] found a benefit from endarterectomy as compared with medical treatment in 1662 patients followed for an average of 2.7 years. The five-year risk of stroke was 10.6 percent in the medical group and 4.8 percent in the surgical group.[100] This reflects only a 5.8 percent absolute risk reduction in five years, which is just above 1 percent per year.

Asymptomatic Carotid-Artery Stenosis and Coronary-Artery Bypass Surgery

The gravest complication of coronary-artery bypass grafting has been ischemic stroke.[101] Cognitive impairment is a more recently recognized neurologic sequel.[102] The frequent coexistence of coronary and carotid artery disease has led to the assumption that the circulatory changes, including hypotension, resulting from the cardiac procedure cause cerebral hemodynamic insufficiency. Carotid endarterectomy is therefore being performed in patients with asymptomatic carotid stenosis before, simultaneously with, or soon after coronary-artery bypass grafting. Patients with asymp-

tomatic carotid stenosis or with carotid bruits are prone to ischemic strokes after major surgical procedures, and the risk of this complication is higher after coronary-artery bypass grafting than after other surgical procedures equally capable of disrupting the circulation,[103,104] but the complicating ischemic events are not necessarily ipsilateral to the carotid disease. It is not possible to state how often asymptomatic carotid stenosis of any degree of severity contributes to the incidence of ischemic stroke after coronary-artery bypass grafting. A reasonable conclusion is that an embolism emanating from the cardiopulmonary bypass or a diseased aorta, not the carotid stenosis, causes the stroke in most of these cases.

The voluminous literature on a variety of retrospective case series and procedures for managing coronary artery disease and asymptomatic carotid stenosis is full of conflicting results and opinions.[105,106] The American Heart Association's consensus statement on carotid endarterectomy (Moore W: personal communication) concludes that this is an area of sufficient uncertainty that a clinical trial must be conducted to settle the issue. Until a trial is done, the benefit of a carotid endarterectomy performed before, during, or after coronary-artery bypass grafting in patients with asymptomatic carotid stenosis should be regarded as unconfirmed.

Symptomatic Carotid-Artery Stenosis and Coronary-Artery Bypass Surgery

Patients occasionally present with recent symptoms related to severe carotid-artery stenosis and a compelling reason for coronary-artery bypass grafting. The simultaneous performance of coronary-artery bypass grafting and carotid endarterectomy carries a high risk[106] but is warranted in patients with recent symptoms of both severe coronary disease (unstable angina) and severe carotid stenosis. Otherwise, a stepwise approach is indicated. For example, a patient with a near-occlusion of the carotid artery or frequent cerebral ischemic events and angina should undergo carotid endarterectomy first, followed 30 days later by coronary-artery bypass grafting. For patients with moderate symptoms of carotid stenosis, no treatment of the carotid lesion has been proved to be of value.

Extracranial-to-Intracranial Anastomosis

A randomized trial involving 1377 patients examined the potential benefit of microvascular anastomosis between the superficial temporal and middle cerebral arteries to prevent ischemic stroke.[107] The procedure was not beneficial.

Percutaneous Transluminal Angioplasty for Cerebral-Artery Stenosis

Several small series of patients with symptoms related to stenosis in either the vertebrobasilar or carotid arteries and their major branches have been treated with percutaneous transluminal angioplasty.[108] This procedure carries the risk of dislodging emboli that can then be carried to the brain or retina. A trial in Europe is comparing angioplasty with carotid endarterectomy in patients with symptomatic extracranial carotid disease.[109] Angioplasty should be avoided until well-designed trials have affirmed its usefulness.

Summary

Randomized clinical trials have proved that warfarin therapy decreases the risk of stroke in patients with nonvalvular atrial fibrillation and in those who have had a myocardial infarction. In patients who are not candidates for long-term anticoagulant therapy, aspirin is beneficial, but the reduction in risk is smaller with aspirin than with warfarin. In patients with cerebral ischemic symptoms of noncardiac origin, aspirin and ticlopidine reduce the risk of stroke, but the benefit is modest. Given alone, neither dipyridamole nor sulfinpyrazone prevents stroke. The question remains whether either of these drugs plus aspirin is better than aspirin alone. The optimal dose of aspirin for stroke prevention has not been established.

Carotid endarterectomy reduces the risk of stroke in symptomatic patients with at least 70 percent stenosis, as determined by arteriography. Current trials are addressing the question of whether endarterectomy is beneficial for patients with moderate degrees of carotid stenosis. The benefit of endarterectomy for patients with asymptomatic carotid lesions remains unclear.

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CORRECTION

Prevention of Ischemic Stroke

To the Editor: Barnett et al. (Jan. 26 issue)[1] state that ``neutropenia occurs early but is reversible after the cessation of [ticlopidine].´´ Unfortunately, this is not always true. Six patients who died of irreversible ticlopidine-induced bone marrow failure have been reported to the Canadian Health Protection Branch. In four of the patients (one man and three women; age, 70 to 86 years), agranulocytosis developed (granulocyte count, <500 per cubic millimeter) 15 to 74 days (mean, 38) after ticlopidine was begun. Two women, 72 and 84 years old, had aplastic anemia that first presented as agranulocytosis 27 and 41 days after ticlopidine was begun.

We used information from the adverse-reaction forms completed by the reporting physicians and two analytic methods to determine the relation between the ticlopidine and the hematologic toxicity. First, evaluation according to the World Health Organization definitions of causality (certain, probable or likely, possible, and likely) suggested there was a ``probable or likely´´ association in each case because the timing was appropriate for drug-induced agranulocytosis and it could not be attributed to another cause. Second, using a computer-based method of probabilistic differential diagnosis to calculate whether the drug was responsible for the agranulocytosis,[2,3] we found that the probability that ticlopidine was responsible for the hematologic toxicity was greater than 90 percent in each patient — that is, nine times more likely than any alternative cause.[2,3]

These case reports indicate that ticlopidine can cause irreversible agranulocytosis and aplastic anemia.

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The authors reply:

To the Editor: Drs. Shear and Appel have drawn attention to previously unpublished information that clearly indicates that bone marrow suppression related to the use of ticlopidine is not always reversible. Using the records of the Canadian Health Protection Branch, they report that six fatalities have occurred in Canadian patients who received this drug. Dr. Robert Pless, head of the Adverse Drug Reaction Evaluation Section, Bureau of Drug Surveillance, has allowed us access to their data on these six patients and on a seventh death possibly associated with ticlopidine therapy. In three of the seven patients there is documentation of adequate monitoring of blood counts. The records of another three make it uncertain whether there was monitoring, and in the last case the record states ``blood counts were monitored.´´

At our request Dr. Peter Glasner, head of Roche Global Pharmacoepidemiology, has done a preliminary search of the records for adverse hematologic events associated with ticlopidine therapy based on worldwide reports through the end of 1994. He writes: ``There were a total of 645 cases of aplastic anemia, bone marrow suppression, pancytopenia and agranulocytosis, of which 102 (16%) had been coded as being fatal as a result of the primary reported adverse event term.´´

These records chronicle an estimated 10 million patient-years of ticlopidine treatment (Dorey G, Sanofi Pharma, Gentilly, France: personal communication). It is not known which patients in this data base were monitored according to the guidelines. Nor is it possible to be certain that none of them had another reason for the agranulocytosis or aplastic anemia. It is also not certain that the voluntary reporting of complications in the post-marketing period is complete. Thus, an exact estimate of these complications is not possible.

Clearly, Shear and Appel are correct: ticlopidine can cause fatal bone marrow suppression. The risk is low. There were no deaths from bone marrow suppression among the approximately 8000 patients who were studied either in the closely monitored studies[1,2] or during the post-marketing monitoring surveillance (Glasner P: personal communication). The risk of this complication is probably less than the risk of stroke and fatal stroke in properly selected patients. No one should receive ticlopidine without a proved indication, without an understanding of the potential complications, and without careful drug and hematologic monitoring. The manufacturer recommends blood-count monitoring every other week for the first three months after therapy is instituted.

There was an unrelated error in the article.[3] In the entry in Table 1 on the ECST study (European Carotid Artery Surgery Trial), the enrollment criterion for internal-carotid-artery stenosis was given as >82 percent; the correct value is >70 percent.

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