AJNR

Cerebral intraarterial fibrinolysis at the crossroads: is a phase III trial advisable at this time?

R D Ferguson and J G Ferguson

AJNR Am J Neuroradiol 1994, 15 (7) 1201-1216
http://www.ajnr.org/content/15/7/1201

Cerebral Intraarterial Fibrinolysis at the Crossroads: Is a Phase III Trial Advisable at This Time?

Robert D. G. Ferguson and John G. Ferguson

PURPOSE: To describe the rationale for fibrinolysis, review the state of the art in cerebral fibrinolysis, and discuss whether it is time for phase III studies of cerebral intraarterial fibrinolysis.
METHODS: Critical review of the literature with statistical reevaluation of significant clinical data.
RESULTS: There are abundant phase III data supporting the use of thrombolysis in the cardiovascular system. However, there are no published phase III trials of intraarterial fibrinolysis in stroke. All reports of cerebral intraarterial fibrinolysis are case series. The studies are typically small with variable treatment protocols and designs that are susceptible to bias. The only analysis comparing cerebral intraarterial fibrinolysis with conventional therapy is based on nonconcurrent controls.
CONCLUSIONS: Stroke is common and costly. Acute stroke intervention with fibrinolytic drugs is theoretically justified. Studies done to date have significant, inferential limitations. The data suggest an association between thrombolysis, recanalization, and prognosis. However, imprecision and inadequate control of systematic error preclude conclusions regarding clinical outcomes. Randomized, controlled trials are needed to establish the clinical value of cerebral local intraarterial fibrinolysis. However, cerebral local intraarterial fibrinolysis availability, the cerebral local intraarterial fibrinolysis learning curve, anticipated technological advances, unresolved procedural controversies, and ethical and fiscal considerations make a large phase III trial impractical and ill-advised at the present time. Additional basic research is needed to set the stage for a successful clinical trial.

Index terms: Thrombolysis; Brain, infarction; Drugs, intraarterial injection; Interventional neuroradiology

AJNR Am J Neuroradiol 15:1201–1216, Aug 1994

There appears to be a consensus in the neurointerventional community that intraarterial fibrinolysis may benefit patients who have an evolving thromboembolic stroke. However, there are divergent opinions regarding the best way to evaluate this proposition. We will describe the rationale for fibrinolysis, review the state of the art in cerebral fibrinolysis, and discuss whether it is time for phase III studies of cerebral local intraarterial fibrinolysis. The Glossary defines terms that may be unfamiliar to clinicians.

Stroke is the third most common cause of death in North America (1, 2). There are approximately 500 000 strokes per year in the United States (3). Seventy-five percent of these occur in the distribution of the carotid arteries (3). The 30-day and 5-year mortality rates for stroke occurring in the carotid distribution are 17% and 40%, respectively (1). There were 150 300 stroke-related fatalities in 1988 (3). These facts translate into an enormous expenditure in both human and financial terms. The American Heart Association estimates that stroke will cost the United States $18 billion in 1993 (4). The majority of ischemic strokes are attributable to reduced cerebral perfusion, caused by thromboembolic arterial occlusion (5). Cerebral local intraarterial fibrinolysis is designed to restore blood flow to ischemic tissue by delivering clot-lysing drugs directly to the site of thromboocclusion. Timely reperfusion may limit the extent of infarction and the severity of residual neurologic deficits.

Received August 18, 1993; accepted after revision January 3, 1994.
From the Memphis Vascular Research Foundation.

Address reprint requests to Robert D. G. Ferguson, MD, Memphis Vascular Research Foundation, 910 Madison Ave, Suite 710, Memphis, TN 38103.

AJNR 15:1201–1216, Aug 1994 0195-6108/94/1507–1201

The role of thrombus in stroke, combined with the clinical and angiographic efficacy of thrombolytics in acute myocardial infarction, has fostered renewed interest in cerebral fibrinolysis research. Thrombotic arterial occlusion is the proximate cause of irreversible ischemia in both acute myocardial infarction and stroke. DeWood et al (6) reported compelling evidence for an association between thrombosis and acute myocardial infarction in 1980. They observed total occlusion of the infarct-related artery in 87% of patients undergoing coronary angiography within 4 hours of onset of symptoms of acute myocardial infarction. Several independent studies confirmed this association (7, 8). In general, stroke, like myocardial infarction, is caused by arterial thromboocclusion. Angiographic studies done in stroke patients within 8 hours of symptom onset show complete occlusion of the primary vessel in more than 80% of patients (9). When angiography is done within 12 hours, it shows atherothrombotic stenoses or occlusions appropriate to the neurologic deficit in 80% to 90% of patients (10).

Phase III trials involving thousands of patients have demonstrated that fibrinolytics dissolve thrombi and save lives in acute myocardial infarction. Spontaneous reperfusion is demonstrated by coronary angiograms in about 10% after an acute myocardial infarction (11, 12). This figure increases to approximately 35% by 24 hours (6) and reaches 67% by 2 weeks (13). In contrast, the average results of studies using conventional dosing regimens show 90-minute patency rates of 53%, 68%, and 72% for intravenous streptokinase, alteplase (rt-PA), and anistreplase (APSAC), respectively (14). The late patency rate, after 24 hours, is over 90% with nearly all thrombolytic drugs in acute myocardial infarction (15).

Coronary recanalization is associated with higher survival rates. The combined results of major randomized trials of intravenous streptokinase versus placebo yield a pooled odds reduction for mortality of 27% (confidence interval 21% to 33%, $P < .00001$) for patients randomized within 6 hours of acute myocardial infarction onset. Based on the results of six trials of alteplase versus placebo, the pooled odds reduction of mortality for alteplase is 29% (confidence interval 14% to 41%, $P = .0003$). In the AIMS trial, the odds reduction of 30-day mortality for anistreplase was 50.5% (confidence interval 26% to 67%, $P = .0006$) (16).

In summary, stroke is common and costly, and is frequently caused by cerebrovascular thrombosis. Renewed interest in thrombus-lysing drugs for stroke is attributable in part to their angiographic and clinical effectiveness in coronary thrombosis.

The Evolution of Cerebral Fibrinolysis

Systemic Thrombolysis

Early experiments with intravenous administration of fibrinolytics in the treatment of acute stroke attempted to demonstrate efficacy related to arterial recanalization and clinical outcome, as well as to estimate the risk of inducing cerebral hemorrhage. In general, the results were interpreted to suggest that systemic administration was risky and of little overall benefit.

From the late 1950s to the late 1970s, multiple studies, mostly uncontrolled, used one or more intravenous fibrinolytic agents in patients with either clinical or angiographic evidence of symptomatic, cerebral thromboocclusion. In general, mortality was high, hemorrhage was not uncommon, and there was no clear therapeutic benefit.

However, the efficacy of coronary thrombolysis, development of new thrombolytic agents, recognition of the methodologic weaknesses of early studies, and the advent/availability of an accurate screening procedure (computer-assisted tomography) for intracranial hemorrhage, rekindled interest in central nervous system thrombolysis. In 1981, Abe et al (17, 18) reported a randomized controlled double-blind study of intravenous urokinase. There was no significant therapeutic effect attributable to urokinase. However, the investigators used a very low urokinase dose of 60 000 to 100 000 U per day, for 3 to 10 days. This may explain, in part, the absence of a detectable therapeutic effect as well as the occurrence of only one intracranial hemorrhage in the urokinase group.

The National Institutes of Health Very Early rtPA Study (19) evaluated three separate intravenous dose regimens and required pretreatment computed tomography (CT) scanning but not angiography. Seventy-four patients were treated within 90 minutes of symptom onset. The recombinant tissue-type plasminogen acti-

vator dose ranged from 10 to 87 mg. Increased dosage was not associated with improved clinical outcome. A total of 6 (8%) patients developed intracranial hemorrhage, with one death. Using the same protocol, albeit with a different time window for patient inclusion (90 to 180 minutes from symptom onset), Haley et al observed fatal intracerebral hemorrhage in 2 of 21 patients (20).

In 1992, Mori et al (21) reported a double-blind placebo-controlled randomized study of intravenous alteplase in 31 patients with acute carotid territory stroke and occlusion of the internal carotid artery or its main branches. Patients with deep coma, CT abnormality related to the ischemic event, hemorrhage, serious comorbidity, and/or age greater than 80 were excluded. The randomization process was compromised. One patient, allocated to the alteplase group, was treated with the placebo. Analysis was not done according to the principle of intention to treat. Angiography was done before treatment as well as 30 and 60 minutes after the initiation of alteplase. All patients received 5000 U of intravenous heparin before and during angiography. Additional anticoagulants and antiplatelet agents were delayed for 24 hours and thereafter were administered at the discretion of the physician in charge. Serial neurologic assessment was based on a modified Hemispheric Stroke Scale. There was no indication that the modified Hemispheric Stroke Scale was validated. Angiograms and CT scans were interpreted blindly. It is unclear whether neurologic assessment was blinded.

There was no statistically significant difference in the 1-month mortality rate between the placebo and the alteplase groups. Although reperfusion was more common in the alteplase group, the effect was not statistically significant. Successful reperfusion, defined as angiographic grade 2 or better (grade 2 indicates branch recanalization with reperfusion in less than 50% of the ischemia-related area), at 60 minutes occurred in 5 (50%) of 10 of those treated with 30 mIU alteplase, 4 (44%) of 9 of those treated with 20 mIU alteplase, and 2 (17%) of 12 patients receiving placebo (placebo versus alteplase, $P = .08$). The authors reported a significant difference in Hemispheric Stroke Scale score change between the patients receiving 20 mIU alteplase and patients receiving placebo ($P < .05$). However, proper analysis of these data requires simultaneous comparison of all three treatment groups, followed by multiple, pairwise comparisons, only if the overall test is statistically significant. Moreover, the pairwise tests must be adjusted to control for multiple comparisons. In addition, the placebo versus Hemispheric Stroke Scale analysis was based on a statistical test intended for use with interval scale data. Appropriate analysis with a nonparametric test could inflate the probability value to a nonsignificant level. Hemmorhagic conversion occurred in 4 (33%) of 12 of the placebo group, 5 (56%) of 9 of the 20 mIU recombinant tissue-type plasminogen activator group, and 3 (30%) of 10 of the 30-mIU alteplase group (placebo versus 20 mIU versus 30 mIU, $P = .46$). A moderate parenchymal hematoma was observed in 1 patient in each group ($P = .98$). There were no large, parenchymal hematomas.

The most recent report of a systemic fibrinolysis study, by del Zoppo et al (9) in July 1992, examined the effect of intravenous alteplase on cerebral arterial recanalization in patients with acute focal cerebral ischemia and arterial occlusion as defined by the Thrombolysis in Myocardial Infarction trial (TIMI grade 0) (22). Twenty-four hours after treatment, 4 (4.3%) of 93 patients had complete recanalization, and 28 (30.1%) of 93 had some degree of recanalization. Intracranial hemorrhage occurred in 30.8% of patients.

In summary, studies of intravenous cerebral fibrinolysis have lacked statistical power to detect a bona fide treatment effect, and in general they have been devoid of internal controls. No study has demonstrated an unbiased treatment effect that was both clinically and statistically significant. However, the following observations are noteworthy. First, the placebo-controlled data from Mori et al (21) suggest that recanalization rates with urokinase may, in selected patients, exceed the rate of spontaneous recanalization in stroke. Second, recanalization estimates are relatively low in some studies, which is disturbing given that the benefits of thrombolysis depend, in theory, on recanalization. Third, recanalization rates from different studies cannot be compared, because they are based on different definitions of recanalization. Fourth, although the rate of intracranial hemorrhage varies widely across studies, it is disquietingly high in the largest and most recent reports.

Summary of cerebral local intraarterial fibrinolysis studies

Author	Agent	N	Patency rate	Outcome	Intracranial hemorrhage
del Zoppo et al 1988 (23)	urokinase/streptokinase	20	15/20	better 12/20	4/20
Maiza et al 1988 (24)	streptokinase/urokinase	16	16/16	better 15/16	1/16
Mori et al 1988 (25)	urokinase	22	10	. . .	4/20
Hacke et al 1988 (26)	urokinase/streptokinase	43	19/43	favorable 10/43	4/43
Zeumer et al 1989 (27)	urokinase	7	7/7	better 4/7	1/7
Theron et al 1989 (28)	streptokinase/urokinase	12	. . .	better 10/12	3/12
Bockenheimer et al 1991 (29)	urokinase	18	. . .	good 6/18	0/18
Sugawara et al 1992 (30)	urokinase	11	9/11	favorable 7/11	2/11
Casto et al 1992 (31)	urokinase	5	4/5	favorable 4/5	1/5
Zeumer et al 1992 (32)	urokinase/tissue plasminogen activator	59	33/59*	. . .	8/59

* Based on complete recanalization.

Intraarterial Thrombolysis

Cerebral intraarterial fibrinolysis may be local or regional. In 1987, del Zoppo et al (23) reported evidence suggesting a higher reperfusion rate with local than with regional infusion in middle cerebral artery occlusion. All five patients treated with local urokinase experienced recanalization. Another two patients were given regional (cervical intracarotid) infusion. Neither of these patients experienced recanalization, although they developed a systemic fibrinolytic effect. Reperfusion rates in recent studies have been consistently higher with local infusion.

Local Intraarterial Fibrinolysis. All local intraarterial fibrinolysis reports are case series involving regional or local infusion of three fibrinolytic agents, alone or in combination, into the following vessels: vertebral, internal carotid, basilar, and/or anterior, middle, or posterior cerebral arteries. Studies reported before 1989 generally refer to regional therapy without microcatheter technology. Important local intraarterial fibrinolysis studies by Maiza et al (24), Mori et al (25), Hacke et al (26), Zeumer et al (27), Theron et al (28), Bockenheimer et al (29), Sugawara et al (30), Casto et al (31), and Zeumer et al (32) are summarized in the Table.

In 1988, Mori et al (25) reported their initial 3-year experience with acute middle cerebral artery and middle cerebral artery branch occlusions. The series included 22 patients younger than 80 years of age who presented to the hospital within 12 hours of onset of symptoms of acute middle cerebral artery ischemia without CT hypodensity attributable to the ischemic event and who consented to angiography and intraarterial fibrinolysis with urokinase. Two additional patients were excluded because of failure of selective catheterization. Of the patients who received urokinase, 82% were treated within 6 hours of symptom onset (mean, 4.5 hours; range, 0.83 to 12 hours). The mean urokinase dose was 927 000 U (range, 80 000 to 1 320 000). Duration of infusion ranged from 10 to 30 minutes. If reperfusion was not established by 30 minutes, the infusion was stopped. In addition, all patients received low-molecular-weight dextran. Angiography was repeated every 10 to 15 minutes in some and only after 30 minutes in others. Recanalization was achieved in 10 (45%) of 22 patients included in the study. Because calculation of recanalization rates in intraarterial fibrinolysis should include eligible patients who cannot be selectively catheterized, the true recanalization rate was 10 (42%) of 24 patients. Recanalization was considered complete in 4 (17%) of 24. Mild and severe residual stenoses were found in 4 and 2 patients, respectively. There was rapid, symptomatic improvement in 8 of the 10 patients who recanalized. In addition, there was a statistically significant association between recanalization and outcome. Patients who recanalized had a better outcome than those who did not; however, the clinical significance of the association is questionable because no adjustment was made for differences in the baseline prognostic status of the groups. None of the patients who recanalized died, whereas 3 (25%) of 12 of those who did not recanalize died ($P = .28$). Patients who were relatively healthy at the time of presentation did well, and patients who were relatively sick at the time of presentation did poorly. Of the patients who presented with stupor or severe deficits, 3 (27%) of 11 died, and only 2 (18%) of 11 were deemed capable of having a productive life (good outcome) at the time of final examination. On the other hand, of those who presented

with mild or moderate deficits, none died and 11 (92%) of 12 experienced a good or excellent outcome. No correlation was found between the interval from symptom onset to treatment, or urokinase dose, and prognosis. Hemorrhagic transformation occurred in 4 (18%) of 22 within 24 hours. The rate of hemorrhagic transformation in the recanalized group was 1 (10%) of 10, compared with 3 (25%) of 12 in the nonrecanalization group. All brain hemorrhages occurred in patients treated within 5 hours of symptom onset; 4 (18%) of the 22 patients were treated more than 5 hours after symptom onset.

In 1988, del Zoppo et al (23) reported a two-center series of consecutive cases with angiographically documented complete occlusion of the internal carotid artery, middle cerebral artery, anterior cerebral artery, or posterior cerebral artery, and no evidence of intracranial hemorrhage on pretreatment CT scan. There were 8 women and 12 men, ranging from 21 to 80 years of age. All patients had stable symptoms in the appropriate distribution, with acute onset less than 24 hours before initiation of fibrinolytic treatment. Seventeen (85%) of 20 had onset of symptoms within 8 hours. Patients received either urokinase or streptokinase by either regional or local infusion. The investigators administered urokinase at a dose of 40 000 to 300 000 IU over 1 to 4 hours and streptokinase at either 6000 to 7000 IU over 0.5 to 2.0 hours or 250 000 IU over 1.0 hour. Some patients received intravenous heparin at 500 IU/h, along with hydroxymethyl starch, initiated 1 to 5 hours after completion of infusion of the fibrinolytic agent. Complete recanalization occurred within 24 hours of the baseline angiographic study in 15 (75%) of 20. Overall, 10 (50%) of 20 patients had partial to near-complete resolution of motor deficits. However, of the patients who had complete recanalization, 10 (67%) of 15 had near-complete resolution of motor deficits. On the other hand, 0 (0%) of 5 patients who had partial or no recanalization had near-complete resolution of motor deficits ($P = .04$). Three (15%) of 20 patients died: 1 (7%) of 15 with complete recanalization, and 2 (40%) of 5 with partial or no recanalization ($P = .28$). Three (15%) patients had embolic complications in the carotid territory. Four other patients suffered CT-documented intracranial hemorrhage within 24 hours after intraarterial infusion. None of the 4 patients with intracranial hemorrhage experienced clinical deterioration. All of the patients with intracranial hemorrhage received ancillary treatment with heparin and hydroxymethyl starch. It is noteworthy that 2 patients with M1 occlusions in whom the fibrinolytic was infused at the carotid bifurcation did not recanalize despite development of a systemic fibrinolytic state, whereas 5 patients with M1 occlusions infused near the origin of the middle cerebral artery recanalized.

Hacke et al (26) reported a retrospective analysis of patients with angiographically documented vertebrobasilar occlusions treated with fibrinolysis compared with nonconcurrent control patients treated with platelet antiaggregant agents or anticoagulants. Of the 65 patients reported, 43 were treated with either urokinase or streptokinase from 1983 to 1986, and 22 were treated with 500 mg/d of acetylsalicylic acid or anticoagulants between 1975 and 1982. The anticoagulant regimen comprised either low-dose heparin (3×5000 U) or full-dose heparin followed by warfarin (3000 to 6000 U bolus and 1000 U/h infusion). Patients were excluded if prefibrinolysis CT showed a hypodense lesion in the brainstem or cerebellum. Patients undergoing fibrinolysis received urokinase or streptokinase by either intermittent or continuous infusion. Infusion rate varied from 10 000 U/h to 100 000 U/h. In general, the infusion was administered for up to 4 hours, but in some patients for up to 48 hours. In addition, all patients in the fibrinolysis group were treated with intravenous heparin and hemodilution therapy with hydroxyethyl starch. The time interval from onset of symptoms to treatment was less than 24 hours in 29 (67%) of 43 and less than 6 hours in 6 (14%) of 43. At least 1 patient received treatment 3.2 days after symptom onset. The recanalization rate was 19 (44%) of 43 in the fibrinolysis group. Fourteen (33%) of 43 patients in the fibrinolysis group survived, whereas only 3 (14%) of 22 historical controls survived. However, the level of consciousness at baseline was significantly better in the fibrinolysis group ($P = .02$), and the unadjusted difference in survival was not statistically significant ($P = .14$). For example, only 1 (5%) of 22 patients in the acetylsalicylic acid/heparin group were awake at baseline compared with 16 (37%) of 43 patients in the fibrinolysis group, and 11 (50%) of 22 acetylsalicylic acid/heparin patients were comatose at baseline versus 11 (26%) of 43 in the fibrinolysis group. On the other hand, survival was strongly associated with recanaliza-

tion in the fibrinolysis group, despite the absence of detectable differences in level of consciousness ($P = .39$) and motor abilities ($P = .53$) at baseline in the patients who recanalized versus those who did not. Fourteen (74%) of 19 patients who recanalized survived, whereas the mortality rate was 100% in the patients who did not recanalize ($P = .001$). Hemorrhagic conversion occurred in 4 (9.3%) of 43 fibrinolysis patients: 2 in the group that recanalized and 2 in the group that did not recanalize.

Bockenheimer et al (29) reported their 2-year experience with local intraarterial urokinase in 18 patients who presented with occluded cerebral vessels. Five of 18 had internal carotid/middle cerebral artery occlusions. Three (60%) of the 5 patients left the hospital with minor deficits and 2 (40%) of 5 died. The other 13 patients had acute vertebrobasilar occlusions. Three (23%) of the 13 patients survived the treatment in good general condition, 6 (46%) of 13 died, and 2 (15%) of 13 were left with locked-in syndrome. Inclusion/exclusion criteria, baseline patient characteristics, treatment protocol, and detailed clinical results were not available at the time of writing.

Two papers coauthored by Maiza and Theron (24, 28) do not provide additional insight because of inconsistent data duplication. It is impossible to discern the full extent of duplication; however, the papers contain at least two replicate cases. For example, case 1 in Theron et al's paper and case 5 in Maiza et al's paper have identical angiograms. Both were 54-year-old men with recurrent right brachial monoplegia. The case descriptions differ on the number of streptokinase boluses given (4 versus 5), the size of the boluses (25 000 U versus 20 000 U), and the results of thrombolysis. Theron et al (28) reported that the patient's angiogram showed complete recanalization, and thereafter the neurologic exam and CT remained normal, before endarterectomy 1 week later. Maiza et al (24), on the other hand, specified that during a fifth injection the patient experienced sudden complete right hemiparesis with aphasia. Moreover, they indicated that repeat arteriography showed thrombus fragmentation and myriad emboli in some middle cerebral artery branches before achieving arterial patency and regression of deficits. Three days later the CT showed multiple hemorrhages, and 5 days after that the patient underwent endarterectomy and bypass of the internal carotid artery origin. The discrepancies were never reconciled. There is no way to determine which account is correct without going beyond the published reports.

Zeumer et al's 1993 paper (32) probably includes cases described in a previous report (27). This analysis was conducted to compare the efficacy of urokinase and alteplase in achieving thrombus resolution in vivo. The report describes 59 consecutive patients who were allocated nonrandomly to treatment with local intraarterial urokinase or alteplase for acute vertebrobasilar and carotid stroke. Enrollment began in 1987. Patients enrolled before 1989 were treated with urokinase. Patients treated with alteplase were enrolled after 1989 and comprised 40 of the 59 study subjects. It is not clear whether any patients received urokinase after 1989. Patients with vertebrobasilar stroke were included if they had stroke in progress with incomplete neurologic deficits and basilar or bilateral vertebral occlusion, deep coma for more than 6 hours, or loss of brain stem reflexes. Patients with carotid territory stroke were included if they had occlusion in the carotid artery territory with dense hemiplegia and if a 2-hour treatment could be completed within 6 hours of symptom onset. Drug doses were up to 750 000 IU of urokinase or 20 mg of alteplase. The drugs were administered over 2 hours by infusion. Complete recanalization occurred in 33 (56%) of 59: 14 (74%) of 19 urokinase patients, and 19 (48%) of 40 alteplase patients. Hemorrhagic conversion occurred in 8 (14%) of 59 patients; none of these experienced clinical deterioration. Twenty-six (44%) of 59 died. The authors did not classify death by treatment.

Zeumer et al drew several conclusions, some of which were based on data from studies other than the one under review. They concluded that local intraarterial fibrinolysis can improve clinical outcome in acute vertebrobasilar occlusion. In the present study, local intraarterial fibrinolysis was associated with an overall mortality in acute vertebrobasilar stroke of 18 (64%) of 28. Even if we assume that the mortality in acute vertebrobasilar stroke without thrombolysis is 80% to 100%, this represents a relative risk of 1.25 to 1.55. Confounding in a nonrandomized analysis without internal controls can easily produce relative risks of this magnitude; therefore, the study merely suggests that local intraarterial fibrinolysis can improve outcome in acute vertebrobasilar occlusion. The authors

also conclude that the earlier a stroke in progress is treated, the better; however, they did not do an analysis of outcome versus time to presentation of stroke in progress. The third conclusion, regarding the relative angiographic efficacy of superselective catheterization, does not follow from this study because all patients were treated by the superselective approach.

The two conclusions that stem from Zeumer's data are that local application of alteplase does not seem to be superior to urokinase for reducing recanalization time and that a favorable outcome seems possible in certain types of occlusion. With regard to the first, it is impossible to tell from the analysis whether the difference in recanalization rates was caused by the drugs, the recalcitrance of the lesions treated with alteplase, or some other factor. The comparison groups were not concurrent, and there may have been confounding factors. For example, all patients with M-type occlusions were treated with alteplase, accounting for 14 (70%) of 20 alteplase patients in the study. Recanalization was particularly slow and infrequent in this type of lesion. Although the exact rate of complete recanalization for M-type occlusions is uncertain, based on their Table 3 it was no greater than 3 (21%) of 14. The authors noted that this lesion type was associated with a relatively large burden of thrombus. Hence the difference in recanalization observed for urokinase versus alteplase may have been caused by patient factors. Nevertheless, Zeumer et al observed an association between lesion type and neurologic deficit ($P < .01$); however, the analysis was based on 33 subjects when there were only 31 patients with carotid occlusion. Moreover, the sparseness of the data undermines the reliability of the evidence. Although this analysis does not address treatment-effect modification by lesion type, it does provide the kind of information that can improve the design of future cerebral local intraarterial fibrinolysis studies, such as phase III trials (eg, if confirmed, it suggests the need to consider stratifying treatment allocation by lesion type).

Impact of Intraarterial Studies on the State of the Science in Cerebral Fibrinolysis

There are no comparative studies of the recanalization rate in intraarterial thrombolysis versus in conventional stroke therapy. Cross-study comparisons are limited by varying definitions of recanalization and differences in the timing of repeat angiography. Nonetheless, there is provisional evidence for higher recanalization rates with intraarterial thrombolysis. Recanalization rates measured within minutes to hours of therapy in the two largest series were 42% and 75%, respectively. Overall, the recanalization rate with intraarterial therapy is in the range of 40% to 100%. This compares with: i) a rate of 17% (95% confidence interval, 2% to 48%), at 60 minutes, in the placebo group of a small randomized controlled trial of intravenous cerebral fibrinolysis (21), and ii) spontaneous recanalization rates between 40% and 80%, days (as opposed to hours) after therapy (33).

Four intraarterial studies address the prognostic significance of recanalization (23, 25, 26, 31). All four support the notion that recanalization after administration of thrombolytics is associated with a favorable prognosis. Mori et al's data (25) show a trend toward lower mortality in urokinase-treated patients who recanalized than in those who did not (mortality 0% versus 25%, $P = .28$). However, their analysis was not adjusted for baseline prognostic differences. The need to consider adjustment is underscored by their data, which suggest that prognosis may depend on baseline consciousness level. The report also stipulates that patients who recanalized experienced relatively rapid symptomatic improvement. This observation should increase the credibility of the mortality findings, because it is consistent with the putative, therapeutic action of thrombolytics. However, there are no objective data in the report supporting the authors' clinical impression. Indeed, the impression may have been purely subjective.

Del Zoppo's (23) report bolsters the notion that recanalization is a marker for improved prognosis in stroke. However, the same inferential limitations apply. Ten (67%) of 15 patients with complete recanalization had near-complete resolution of motor deficits. On the other hand, 0 (0%) of 5 patients who had partial or no recanalization had near-complete resolution of motor deficits ($P = .04$). In addition, only 1 (7%) of 15 with complete recanalization died, compared with 2 (40%) of 5 with partial or no recanalization ($P = .28$).

The report by Hacke et al (26) provides the strongest evidence for an association between recanalization and prognosis. Despite lack of a detectable difference in baseline consciousness

(P = .39) and motor abilities (P = .53), the authors found a strong association between survival and recanalization in the fibrinolysis group: 14 (74%) of 19 patients who recanalized survived, whereas the mortality rate was 100% in the 24 patients who did not ($P <= .001$).

No study clearly demonstrates the clinical effectiveness and safety of intraarterial fibrinolysis. Indeed, there is only one small nonrandomized comparative study of intraarterial and conventional therapy (26). The control subjects in this study were nonconcurrent, and the mortality analysis was not adjusted for apparent differences in baseline prognosis. Moreover, the difference in mortality was not statistically significant. Currently, there is no valid basis for comparing intraarterial thrombolysis with other stroke therapies. By the same token, there is no compelling evidence that intraarterial thrombolysis is less effective than existing alternatives. Nor is there strong evidence that intraarterial thrombolysis is associated with an unacceptable incidence of clinically important intracranial bleeds. Because the prognosis of stroke syndromes is highly variable, appropriately timed, randomized, controlled trials are needed to evaluate the relative clinical effectiveness of intraarterial fibrinolysis. Several cerebral local intraarterial fibrinolysis protocols are currently being planned, debated, and, in at least in one instance, actively pursued.

The Crossroads—Has the Time Come for a Phase III Trial of Cerebral Local Intraarterial Fibrinolysis?

Phase III trials are clinical studies that are large enough and control systematic error well enough to support definitive conclusions regarding the clinical effectiveness of cerebral local intraarterial fibrinolysis. Most phase III studies involve randomization of patients to experimental and control therapies. Conventional wisdom dictates that investigators and patients remain unaware of treatment assignment for maximal control of systematic error. The majority of clinical scientists, with some noteworthy exceptions (34, 35), regard randomized controlled studies as the standard of reference for assessing therapeutic effectiveness. We subscribe to the conventional point of view; however, phase III randomized controlled studies are a major undertaking, and the decision to proceed to phase III is complex. The following discussion delineates elements of the decision pertinent to the design of contemporary cerebral local intraarterial fibrinolysis research.

Implications of the Neurointerventional Learning Curve

Some argue that studies of new therapy should randomize the first patient (36). Even they will recognize the need for exceptions. There is a learning curve in the development of endovascular surgical treatments. Brown (37) states: "It is clear that a certain amount of development and practice with a new surgical technique [read new neurointerventional technique], in patients, is absolutely necessary before the potential value of the new technique can be put to a fair test." In addition, there is no statistical technique that can take a learning curve into account (38).

For example, there was a 20-fold difference (range, 0.3% to 6.4%) in the surgical mortality between participating hospitals in the coronary artery surgery study (39). According to a Rand corporation publication (40):

> Operative mortality is related to the number of cases performed per year in a hospital or by an individual surgeon. A study in California hospitals found 68% higher operative mortality for [coronary artery bypass graft] performed in hospitals with fewer than 100 cases per year compared to those with 350 cases per year. In a recent study in New York State, hospital volume was found to be less significant than physician volume. Surgeons who performed fewer than 116 procedures per year had adjusted mortality rates that were 22 percent higher than surgeons who performed more than 116 procedures annually. However, low volume surgeons in high-volume hospitals (greater than 650 operations/yr) had lower adjusted mortality rates than high-volume surgeons in low volume hospitals.

The same appears to be true of transluminal angioplasty. According to a second Rand analysis (41):

> [a major] contributing factor to the angioplasty primary success rate is the experience of the operator performing the procedure [42–48]. Hamad et al [43] observed a 91% clinical success rate among three operators performing at least 100 procedures and an 84% clinical success rate among 14 operators performing an average of 25 procedures from May 1986 to April 1987. Complication rates in this study were 1.8 percent for experienced operators and 3.2 percent for less experienced operators when dilating simple lesions. Corresponding rates for complex lesions were 3.1 percent and 7.5 percent, respectively. Finci observed a 93% success rate among high-volume (average 14.9 PTCAs/month) operators and an 85% success rate among low-volume (1.3 PTCAs/month) operators performing single-vessel percutaneous transluminal

coronary angioplasty (PTCA) [42]. Kelsey et al, reporting on findings from the initial National Heart Lung and Blood Institutes (NHLBI) registry, examined individual physician success rates for left circumflex artery PTCA and observed a 41% success rate among the first 50 patients, a 54% success rate among the next 50, and a 75% success rate for patients after the first 100 [44]. Although overall success rates have increased since the initial NHLBI registry, this study demonstrates, as do others, that operator experience is an important component of PTCA success.

Many beneficial surgical therapies never would have been adopted had they been required, from the first patient, to undergo randomized clinical evaluation (38). Because the results of trials of endovascular surgery depend on the degree to which the technique has evolved, as well as on operator skill, experience, and caseload, the same can be said for endovascular surgical techniques. When there is a learning curve, the results may be unduly influenced by operator experience (49, 50). If a randomized trial were done today, it would probably underestimate the effectiveness of intraarterial fibrinolysis because of changing techniques, a paucity of experienced operators, the operator learning curve, and rapidly evolving technology. A recent survey of potential cerebral local intraarterial fibrinolysis research sites in the United States indicated that only 12 centers had performed 10 or more intraarterial thrombolyses. Surprisingly, centers with less experience have been recruited to participate in a proposed randomized clinical trial. Would the North American Symptomatic Carotid Endarectomy Trial have demonstrated the effectiveness of carotid endarterectomy had study organizers enlisted inexperienced surgeons? Accepting unseasoned operators into an intraarterial thrombolysis study is rational only if the operators' learning curve is inconsequential (ie, if the procedure of selective intracranial intraarterial infusion of a thrombolytic agent into an occluded artery can be performed with little or no experience). Otherwise, it must be acknowledged that the act of catheter placement and drug delivery may impact on the estimated therapeutic effect.

State of the Science and Initiation of Phase III Cerebral Local Intraarterial Fibrinolysis Trials

Levy and Sondik (51), writing on behalf of the NHLBI, state: "Another facet of the decision is the timing of the trial. The time may be such that the state of the science is not stable and rapidly changing concepts cannot underlie or buttress the trial." It is just such a time in the field of cerebral intraarterial fibrinolysis. Among other things, catheter and guide wire technology, drug delivery systems, procedural technique, and dosing regimens are in a state of flux.

Technology can alter practice so dramatically that it may antiquate therapeutic maneuvers. The 1986 release of the Tracker microcatheter is a prime example. This device increased accessibility of distal neurovascular lesions and decreased the risk of treating them, virtually overnight. Consequently, it reduced the experience and skill required to perform neurointerventions. A significant increase in the number of centers capable of endovascular surgery ensued. Recent refinements in guide wire technology have had a similar impact. Several products under development are likely to have a major impact on delivery techniques. Two of these products were recently released in Europe and are awaiting regulatory approval in the United States. Their emergence could invalidate the results of a contemporary phase III trial.

There are several drug delivery systems and procedural techniques. Controversy surrounds the choice of catheter (end hole versus multiside hole), optimum catheter position (prethrombus, intrathrombus, or postthrombus or some combination of these), drug delivery method (pulsed spray versus continuous drug infusion), advisability of mechanical thrombus disruption, and usefulness of initial mechanical reperfusion. A consensus is also lacking concerning the optimal fibrinolytic agent(s), as well as dose and rate of drug administration. At this time, there is little evidence to suggest that one dosing regimen is superior to another. Additional data concerning drug delivery and adjunctive maneuvers are needed before intraarterial fibrinolysis can be properly assessed in phase III trials.

Catheter and guide wire technology, delivery systems, procedural technique, and dosing regimens are the elements of cerebral intra-arterial fibrinolytic treatment. As noted by Weiss et al (52), "A common criticism directed at controversial studies is that inappropriate or questionable treatment strategies were employed to test laudable study objectives. Study planners must anticipate peer criticisms of all proposed treatment regimens and choose the study regimens with the awareness that unless they are perceived as appropriate and generalizable the

study results may not be accepted." In short, it is premature to undertake phase III studies until the treatment in question is well defined. Moreover, if active research is likely to make aspects of the intervention outmoded in a short time, studying such an intervention may be inappropriate. If a trial is started while a procedure is evolving rapidly, the success and complications do not reflect the ultimate performance of the technique (49, 50). The state of the science must be ready to buttress the results of the trial. If the time is such that the state of the science is not stable, the trial can be postponed or abandoned, or additional clinical research or a small pilot study might be tried (53).

Ethics of Cerebral Local Intraarterial Fibrinolysis and Randomized Controlled Trials

Although randomization is the most reliable way to eliminate bias in analytical research, its use has ethical ramifications. Randomization limits choice. In particular, it limits the treating physician's and, more importantly, the patient's choice of therapy. According to Lebascqz (54), "Most commentators agree that randomization is justified only where there is reason to believe that the two treatments are potentially medically equivalent." In theory, this is the case for fibrinolysis. That is to say, despite the grave consequences and prevalence of stroke, there is currently no accepted specific medical therapy for acute, focal brain ischemia (55), and intraarterial fibrinolysis *appears* to have an acceptable risk profile. However, as mentioned above, there are few centers with the experience required to perform intraarterial fibrinolysis safely and effectively. Yet a randomized trial of intraarterial fibrinolysis in the carotid distribution and its intracranial tributaries would require hundreds of patients to show a biologically and statistically significant reduction in stroke mortality. This is primarily a consequence of the fact that many anterior circulation territory strokes are associated with good recovery or are of a nature that does not cause massive injury at ictus. For example, the North American Symptomatic Carotid Endarectomy Trial enrolled 659 patients and included 50 centers (56). Although studies of posterior circulation stroke require fewer subjects because of the poor outcome associated with strokes in this territory, recruiting patients can be daunting. For example, a recently completed acute stroke intervention study (9) that accrued patients over a 4-year period at a total of 17 centers enrolled only 1 patient with a vertebrobasilar stroke. Thus, a phase III trial of intraarterial thrombolysis in the anterior and or posterior circulation requires so many centers that it would include operators with questionable skill. This is tantamount to ignoring the primary ethical dictum of clinical research (57): *primum non nocere* ("first do no harm"). Alternatively, the trial would take so long that the costs would be prohibitive, the trialists would lose interest, the techniques and medications used would become outmoded, or the trial would be too small to provide a definitive result.

Another ethical consideration is that sufficient testing has been performed to ensure that the likelihood of toxic effects of therapies is minimized (51). This is not the case for intraarterial thrombolysis, given the procedure's development curve and the operator learning curve and given that we are probably on the steep, ascending portion of both curves. Thus, both patients and treating physicians should be completely free to choose between conventional therapy and thrombolysis at this point in cerebral local intraarterial fibrinolysis development.

Specifying the Experimental Maneuver

There is an emerging consensus that optimal intra-arterial thrombolysis requires impaling the thrombus with the drug delivery system. Peripheral fibrinolysis experience provides direct evidence for the superiority of this type of maneuver from the point of view of angiographic efficacy; the data from del Zoppo (23) provide preliminary evidence for the value of a similar strategy in the cerebral circulation. However, there is considerable disagreement about the optimal approach to breaching the thrombus. Some advocate traversing it with a guide wire; others have suggested merely advancing the catheter into the thrombus. Still others advocate embedding the catheter tip at the proximal thrombus/blood interface. One of the most curious proposals suggests placing the catheter tip one third of the way into the thrombus, while proscribing the technique used to determine the length of the thrombus (ie, traversing the thrombus).

Specifying the Control Maneuver

Specifying the control maneuver is a vexing issue in the design of a definitive phase III trial of cerebral local intraarterial fibrinolysis. The need to limit bias is counterbalanced by practical and ethical considerations. On the one hand, angiography is needed to identify potential candidates for thrombolysis accurately. However, angiography entails risk, and it is not a component of standard acute stroke therapy. On the other hand, it is an absolute prerequisite to intraarterial thrombolysis. A design that requires angiography in the control subjects exposes them to an unconventional risk, and thereby creates a bias favoring intraarterial thrombolysis. In effect, it compares intraarterial thrombolysis with combined conventional therapy and angiography, not with conventional therapy alone.

Blinding therapy is complicated if, as noted in the previous section, optimal intraarterial thrombolysis requires impaling the thrombus with the drug delivery system. Blinding the investigator to this procedure requires masking fluoroscopy, the catheterization log, the angiogram, and the angiogram report. Because this may be impossible, some investigators have suggested impaling the thrombus in the control group as well as in the active treatment group. However, impaling the thrombus without administering a fibrinolytic drug is untested and potentially dangerous (known complications include thrombus fragmentation with distal embolization and neurologic deterioration). There is no precedent in clinical research for such a control maneuver. Critics can legitimately argue that the placebo is, in fact, an active and untested therapeutic option. Hence, such a proposal requires compelling justification. We agree with Dr Richard Latchaw, who recently stated in a letter to potential cerebral local intraarterial fibrinolysis investigators, that intraarterial fibrinolysis for stroke "should be compared to best medical therapy."

Sample Size and Feasibility

As noted by Freiman et al (58), most of the trials performed are too small to answer the questions they were designed to address. Often, the preliminary estimate of patient availability is much higher than the actual number of eligible subjects willing to participate. It is sobering to remember that the NHLBI-funded Multiple Risk Factor Intervention Trial screened a total of 361 662 men and, of these, randomized 12 866. The time required for planning and recruitment was 44 months (59). Despite the large sample size, Multiple Risk Factor Intervention Trial had inadequate power to test the primary hypothesis at the level of significance stipulated in the study protocol (60, 61). Sample size is a particular concern in the design of any acute stroke intervention trial. Mori et al (21) required 2 years and three participating centers to enroll 31 patients with acute carotid territory stroke in an intravenous alteplase study; del Zoppo et al (9) enrolled only 1 patient with a vertebrobasilar stroke during a 4-year recruitment period in a 17-center study; Casto et al (31) enrolled only 5 of 615 consecutive carotid territory stroke patients presenting within 5 hours of the onset of symptoms in their local intraarterial urokinase study. In short, the number of patients required to establish a biologically and statistically significant therapeutic effect exceeds the current potential for patient enrollment (62) as a result of a paucity of sites with CLIF capability and limited potential for patient recruitment at these sites.

In addition, one must consider the role of the patient and the primary physician in determining sample size. What evidence do we have that patients and referring physicians will accept randomization on the scale required to ensure adequate statistical power? What proportion of referring physicians know anything about cerebral local intraarterial fibrinolysis? Referring physicians must be cognizant of the merits of the competing therapies, and they must be convinced that there is no satisfactory evidence to differentiate the effectiveness of the study treatments or treatments available outside the trial. As Holland pointed out (63), the success of randomized controlled clinical trials in health care is heavily dependent on the cooperation of those who provide services (64). Failure to recognize this can easily lead to a trial that is too small to address the primary hypothesis.

End Points

In theory, thrombolysis must effect recanalization to produce a beneficial clinical effect. One group attempting to mount a blinded study of intraarterial thrombolysis has advocated a fixed infusion duration, instead of individual

dosing based on the degree of angiographic recanalization. This design ignores a potential advantage of the intraarterial route, ie, drug titration guided by serial angiographic measurements. This proposal may have been formulated to ensure a blind comparison because it is illogical and futile to titrate a placebo to an angiographic end point. Nevertheless, although blinding is highly desirable, it is not always practical to blind all aspects of a study. A dogmatic approach to blinding is counterproductive when it leads to an unrealistic therapeutic comparison, like that involving a placebo that is potentially active yet bears no conceptual resemblance to conventional therapy.

As Brown (37) states, "It is clear that there can be such a thing as a premature randomized trial, a trial of a therapy with great but undeveloped potential, which fails on test because it was not ripe for test." Recall that in 1912, Herrick related acute myocardial infarction to acute coronary thrombosis, and the view that thrombosis was responsible for this condition was widely accepted. The first published trial of thrombolytic therapy in acute myocardial infarction occurred in 1959 (8). Over the next 25 years, 24 randomized studies of intravenous, thrombolytic therapy were conducted primarily in Europe. However, only 5 of these showed a statistically significant reduction in mortality (8). Not until the mid-1980s, a full 25 years later, was the profound beneficial impact of intravenous thrombolytic therapy on mortality in acute myocardial infarction finally recognized.

Merit of Registries in Preliminary Research

We believe that in general, randomized controlled trials are needed to establish therapeutic effectiveness. However, randomized controlled trials are not the only way of gaining knowledge, and clinical trials cannot be substituted for fundamental research (51, 53). Respected statisticians have even questioned the statistical arguments on which conventional randomized controlled trials are based (34, 35). Despite this, some investigators discount nonrandomized designs. Others are more circumspect. Bunker et al (65) conclude, "the study of a new therapy need not always be randomized, but all study of the new therapy should be carefully planned and monitored and the principles of design should be used in the plans so as to maximize the speed with which persuasive and useful information can be generated and made available as a basis for further study." Brown (37) concurs and emphasizes that early uncontrolled pilot studies, phase I studies and phase II studies (as defined by the Food and Drug Administration), have an important place in the development of new therapies. In particular, pilot studies can be used to obtain information and work out the logistics and management deemed necessary for further clinical trials (66). Pilot studies can have a variety of designs. The appropriate design depends on the context.

Registries are a cost-effective approach to obtaining preliminary information in health care evaluations. The NHLBI has used registries effectively. According to Levy and Sondik of the NHLBI Office of Program Planning and Evaluation (51), "The Institute must also consider alternative approaches to obtain the information desired from the clinical trial; it may be possible to establish a registry to develop information on the effects of alternative treatments. . . . Since a registry does not require the extensive control of a clinical trial, it may prove to be a considerably less expensive endeavor." Registries can be used to increase the awareness of physicians regarding new therapies; establish data-gathering and quality control procedures, clinical working groups, and patient recruitment networks; identify hospital centers capable of multicenter collaboration; and estimate patient/physician acceptance of therapeutic alternatives and patient dropout rates. In short, registries can be used to obtain information and establish procedures, at relatively low cost, that are essential for phase III research at a relatively low cost.

For example, the founders of the NHLBI Percutaneous Transluminal Coronary Angioplasty Registry anticipated that registry data would be used to design a randomized controlled clinical trial to compare the clinical effectiveness of percutaneous transluminal coronary angioplasty with medical and surgical therapy for atherosclerotic coronary artery disease. However, when the results of the registry were reviewed in 1981, it was concluded that a controlled trial would be premature because of the continuing evolution of angioplasty (67). Several years later, however, the experience from the registry was used to design the ongoing NHLBI multicenter-controlled Bypass Angioplasty Revascularization Investigation. Moreover, the data center, which was developed for the registry,

became the data center for the Bypass Angioplasty Revascularization Investigation (68).

Observational databases have provided useful information at a relatively low cost. The NHLBI Percutaneous Transluminal Coronary Angioplasty Registry (69, 70) was used to study a large, diverse sample of patients and percutaneous transluminal coronary angioplasty operators. The database contains 3079 patients enrolled between 1979 and 1982 plus 2500 patients recruited since it reopened in 1985 to evaluate new trends. Registry data established the immediate success rate of percutaneous transluminal coronary angioplasty—78% overall, 73% in patients with multivessel disease. It also demonstrated the restenosis rate after percutaneous transluminal coronary angioplasty—angiographic restenosis occurs in approximately 35% and symptomatic restenosis in approximately 25% of patients within 8 months of percutaneous transluminal coronary angioplasty. Other databases have been used successfully to study the incidence/prevalence of disease and risk factors (71), the natural history of disease (72), and prognosis (73, 74), and to develop diagnostic tests (75, 76).

In addition, observational databases can suggest hypotheses for and improve the quality of randomized clinical trials. For instance, they can be used to ameliorate clinical experiments by suggesting important subgroup hypotheses, by providing parameters for sample-size estimates, and by identifying potential confounders that require statistical control. They can also assist in pretrial standardization of terminology and provide a ready-made data management system for the trial itself, thereby reducing administrative problems, helping to ensure protocol compliance, and improving communication between different sites. Finally, they can be used to evaluate eligible nonrandomized patients (77) after the trial and thereby help to delimit the generalizability of the results.

The registry approach can be used for a fraction of the cost of a phase III trial. Prospective, randomized, long-term clinical trials are tedious and costly (78). Large-scale trials at the NHLBI have involved more than 10 000 subjects and required up to 10 years to complete at costs of more than $100 million (51). At a cost of nearly $2000 per patient per year for clinical trials funded by the National Institutes of Health before 1978 (79) (Meinert CL, Cost Profiles of Data Coordinating Centers: Coordinating Centers Model Project, presented at the fifth Annual Symposium on Coordinating Clinial Trials, Arlington, Va, May 1978), we cannot afford the luxury of starting a phase III trial prematurely. More phase II data are needed to design proper phase III cerebral local intraarterial fibrinolysis protocols. Let's make sure we get it right the first time (80). Patients may suffer needlessly if we do not.

Summary

Stroke is common and costly. Acute stroke intervention with fibrinolytic drugs is theoretically justified. Studies done to date have significant inferential limitations. The data suggest an association between thrombolysis, recanalization, and prognosis. However, imprecision and inadequate control of systematic error preclude conclusions regarding clinical outcomes. Randomized controlled trials are needed to establish the clinical value of cerebral local intraarterial thrombolysis. However, cerebral local intraarterial fibrinolysis availability, the cerebral local intraarterial fibrinolysis learning curve, anticipated technological advances, unresolved procedural controversies, as well as ethical and fiscal considerations make phase III trials impractical and ill-advised at the present time. Additional basic research is needed to set the stage for a successful clinical trial and prevent a costly mistake.

Glossary

Phase I trial: The first stage in testing a new drug in humans. The studies usually are done to generate preliminary information on the chemical action and safety of the drug using healthy volunteers. Usually done without a comparison group (81).

Phase II trial: The second stage in testing a new drug in humans. It is generally carried out on patients with the disease or condition of interest. The main purpose is to provide preliminary information on treatment efficacy and to supplement information on safety obtained from phase I trials. Usually, but not always, designed to include a control treatment and random allocation of patients to treatment (81).

Phases I and II seek to answer questions such as (82): *a)* Is it worth subjecting this treatment to an expensive phase III trial? Does toxicity clearly rule out therapeutic use? If not, is there

any sign of efficacy? *b)* What dose of a drug should be used in a subsequent phase III trial? *c)* What procedural technique should be used in a subsequent phase III trial?

Phase I and II studies are not designed to prove that toxicity is low and efficacy is high. This type of research is exploratory, can be carried out in small samples, and does not demand an internal control group.

Phase III trial: The third and usually final stage in testing a new drug in humans. Concerned primarily with assessment of dosage effects and efficacy and safety. Usually designed to include a control treatment and random allocation to treatment (81). Phase III trials seek to establish efficacy of specific therapeutic regimens. They are objective, definitive, require control groups, and in general entail large samples (82).

Principle of intention to treat: The approach to data analysis whereby all patients are counted in the treatment group to which they were randomly assigned whether or not they completed or even received the assigned treatment. Analysis by intention to treat is needed to maintain the baseline comparability afforded by randomization (83, 84).

Interval scale: A scale on which measurements are ordered and separated by units of known size (eg, temperature in degrees Celsius).

References

1. Chambers BR, Norris JW, Shurvell BL, Hachinski V. Prognosis of acute stroke. *Neurology* 1987;37:221–225
2. Wolf PA, Kannel WB, McGee DL. Epidemiology of strokes in North America. In: Barnett HJM, Stein BM, Mohr JP, Yatsu FM, eds. *Stroke: Pathophysiology, Diagnosis and Management.* New York: Churchill Livingstone; 1986:19–29
3. Feussner JR, Matchar DB. When and how to study the carotids. *Ann Intern Med* 1988;109:805–818
4. *1993 Heart and Stroke Facts Statistics.* Dallas: American Heart Association; 1992:18
5. Zeumer H, Freitag HJ, Knospe V. Intravascular thrombolysis in central nervous system cerebrovascular disease. *Neurol Clin North Am* 1992;2(2):359–369
6. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;303:897–902
7. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;326(4):242–250
8. Cairns JA, Collins R, Fuster V, Passamani ER. Coronary thrombolysis. *Chest* 1989;95(suppl 2):73S–87S
9. del Zoppo GJ, Poeck K, Pessin M, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol* 1992;32(1):78–86
10. Solis OJ, Roberson GR, Taveras JM, et al. Cerebral angiography in acute cerebral infarction. *Rev Interam Radiol* 1977;2:19–25
11. Khaja F, Walton JA, Brymer JF, et al. Intracoronary fibrinolytic therapy in acute myocardial infarction: report of a prospective randomized trial. *N Engl J Med* 1983;308:1305–1311
12. Leiboff RH, Katz RJ, Wasserman AG, et al. A randomized, angiographically controlled trial of intracoronary streptokinase in acute myocardial infarction. *Am J Cardiol* 1984;53:404–407
13. Rentrop KP, Feit F, Blanke H, et al. Effects of intracoronary streptokinase and intracoronary nitroglycerin infusion on coronary angiographic patterns and mortality in patients with acute myocardial infarction. *N Engl J Med* 1984;311:1457–1463
14. Bates ER. Is survival in acute myocardial infarction related to thrombolytic efficacy or the open artery hypothesis? A controversy to be investigated with GUSTO. *Chest* 1992;101(suppl 4): 140S–150S
15. Bassand JP, Schiele F, Bernard Y, Anguenot T. Arterial permeability, objective of thrombolytic therapy [in French]. *Arch Mal Coeur Vaiss* 1992;85(suppl 5):677–687
16. Cairns JA, Fuster V, Kennedy W. Coronary thrombolysis: Third ACCP Consensus Conference on Antithrombotic Therapy. *Chest* 1992;102(4):482S–507S
17. Abe T, Kazawa M, Naito I, et al. Clinical evaluation for efficacy of tissue culture urokinase (TCUK) on cerebral thrombosis by means of multicenter double-blind study. *Blood Vessels* 1981;12: 321–341
18. Abe T, Kazawa M, Naito I, et al. Clinical effect of urokinase (60,000 U/d) on cerebral infarction: comparative study by means of multicenter double-blind test. *Blood Vessels* 1981;12:342–358
19. Brott TG, Haley EC, Levy D, et al. Safety and potential efficacy of tissue plasminogen activator (tPA) for stroke [abstr]. *Stroke* 1990; 21:181. Abstract
20. Haley EC, Levy D, Sheppard G, et al. A dose-escalation safety study of intravenous tissue plasminogen activator in patients treated from 90 to 180 minutes from onset of acute ischemic stroke [abstr]. *Ann Neurol* 1990;28:225
21. Mori E, Yoneda Y, Tabuchi M, et al. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology* 1992;42:976–982
22. TIMI study group. *N Engl J Med* 1985;312:932–936
23. del Zoppo GJ, Ferbert A, Otis S, et al. Local intra-arterial fibrinolytic therapy in acute carotid territory stroke: a pilot study. *Stroke* 1988;19(3):307–313
24. Maiza D, Theron J, Pelouze GA, et al. Local fibrinolytic therapy in ischemic carotid pathology. *Ann Vasc Surg* 1988;2(3):205–214
25. Mori E, Tabuchi M, Yoshida T, Yamadori A. Intracarotid urokinase with thromboembolic occlusion of the middle cerebral artery. *Stroke* 1988;19(7):802–812
26. Hacke W, Zeumer H, Ferbert A, Brückman H, del Zoppo GJ. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebrobasilar occlusive disease. *Stroke* 1988;19(10): 1216–1222
27. Zeumer H, Freitag HJ, Grzyska U, Neunzig HP. Local intraarterial fibrinolysis in acute vertebrobasilar occlusion: technical developments and recent results. *Neuroradiology* 1989;31:336–340
28. Theron J, Courtheoux P, Casasco A, et al. Local intraarterial fibrinolysis in the carotid territory. *AJNR Am J Neuroradiol* 1989; 10:753–765
29. Bockenheimer ST, Reinhuber F, Mohs C. Intraarterielle thrombolyse hirnversorgender Gefaße. *Radiologe* 1991;31:210–215
30. Sugawara Y, Ueda T, Mogami H, Tanada S, Hamamoto K. Intraarterial urokinase infusion therapy with superselective catheterization for acute occlusive cerebrovascular disease [in Japanese]. *Nippon Igaku Hoshasen Gakkai Zasshi* 1992;52(8):1083–1091

31. Casto L, Moschini L, Camerlingo M, et al. Local intraarterial thrombolysis for acute stroke in the carotid artery territories. *Acta Neurol Scand* 1992;86(3):308–311
32. Zeumer H, Freitag HJ, Zanella F, Thie A, Arning C. Local intraarterial fibrinolytic therapy in patients with stroke: urokinase versus recombinant tissue plasminogen activator (rt-PA). *Neuroradiology* 1993;35:159–162
33. Brott TG. Thrombolytic therapy for stroke. *Cerebrovasc Brain Metab Rev* 1991;3:91–113
34. Urbach P. The value of randomization and control in clinical trials. *Stat Med* 1993;12(15/16):1421–1441
35. Berry DA. A case for Bayesianism in clinical trials. *Stat Med* 1993;12(15/16):1377–1404
36. Chalmers TC. Randomized clinical trials in surgery. In: Varco RL, Richard L, Delaney JP, eds. *Controversy in Surgery*. Philadelphia: W B Saunders, 1976
37. Brown BW. Statistical controversies in the design of clinical trials: some personal views. *Controlled Clin Trials* 1980;1:13–27
38. Fisher LD, Kennedy JW. Randomized surgical clinical trials for treatment of coronary artery disease. *Controlled Clin Trials* 1982; 3:235–258
39. Kennedy J, Kasier G, Fisher L, et al. Clinical and angiographic predictors of operative mortality from the collaborative study in coronary artery surgery (CASS). *Circulation* 1981;63:793–802.
40. Leape LL, Hilborne LH, Kahan JP, et al. *Coronary Artery Bypass Graft: A Literature Review and Ratings of Appropriateness and Necessity*. Santa Monica: Rand Corp (prepared for the Cardiac Advisory Committee of the State of New York), 1991:41–42
41. Hilborne LH, Leape LL, Kahan JP, Park RE, Kamberg CJ, Brook RH. *Percutaneous Transluminal Coronary Angioplasty: A Literature Review and Ratings of Appropriateness and Necessity*. Santa Monica: Rand Corp (prepared for the Cardiac Advisory Committee of the State of New York), 1991:7
42. Finci L, Meier B, Steffinino G, et al. Percutaneous transluminal coronary angioplasty by high-volume and low-volume operators. *Clin Cardiol* 1987;10:355–357
43. Hamad N, Pichard AD, Lyle HRP. Results of percutaneous transluminal coronary angioplasty by multiple, relatively low frequency operators: 1986–1987 experience. *Am J Cardiol* 61:1229–1231
44. Kelsey S, Mullin S, Detre K, et al. Effect of investigator experience on percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1984;53:56C–64C
45. Mews G. Percutaneous transluminal coronary angioplasty in Australia. *Med J Aust* 1984;140:693–695
46. Roubin G, Douglas JJ, King S III. Percutaneous coronary angioplasty: influence of operator experience on results. *Am J Cardiol* 1986;57:873–874
47. Simpfendorfer C, Raymond R, Schraider J, et al. Early and long-term results of percutaneous transluminal angioplasty in patients 70 years of age and older with angina pectoris. *Am J Cardiol* 1988;62:959–963
48. Timmis A, Crick J, Griffin B, et al. Factors predictive of early angiographic and functional success following percutaneous transluminal coronary angioplasty. *Eur Heart J* 1986;7:602–608
49. Friedman LL, Furberg CD, De Mets DL. *Fundamentals of Clinical Trials*. 2nd ed. Littleton, Mass: PSG Publishing Inc; 1985:5
50. Pocock SJ. *Clinical Trials: A Practical Approach*. Chichester, NY: John Wiley and Sons; 1983:59
51. Levy RI, Sondik EJ. Initiating large-scale clinical trials. *Controlled Clin Trials* 1982;3:29–46
52. Weiss DG, Willford WO, Collins JF, Bingham SF. Planning multicenter clinical trials: a biostatistician's perspective. *Controlled Clin Trials* 1983;4:53–64
53. *Issues in Research With Human Subjects*. Washington, DC: Public Health Service; 1980:12, US Department of Health, Education and Welfare. NIH Publication 80-1858
54. Lebascqz K. Controlled clinical trials: some ethical issues. *Controlled Clin Trials* 1980;1:29–36
55. Biller J. Medical management of acute cerebral ischemia. *Neurol Clin* 1992;63–85
56. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325(7):445–453
57. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: US Dept of Health, Education and Welfare; 1978 (#(05) 78-0012)
58. Freiman JA, Chalmers TC, Smith H, et al. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 1978;299:690–694
59. Neaton JD, Grimm RH Jr, Cutler JA. Recruitment of participants for the multiple risk factor intervention trial (MRFIT). *Controlled Clin Trials* 1987;8(suppl 4):41S–53S
60. Patterson RR, Lewis C. Results of the multiple risk factor intervention trial. *Md Med J* 1984;33(1):13–14
61. Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial: risk factor change and mortality results. *JAMA* 1982;248(12):1465–1477
62. Taylor DW, Scakett DL, Haynes RB. Sample size for randomized trials in stroke prevention: how many patients do we need? *Stroke* 1984;15(6):968–971
63. Holland WW. Randomized controlled trials in health care. In: Sackett DL, Baskin MS, eds. *Methods of Health Care Evaluation: Readings and Exercises Developed for the National Health Grant, Health Care Evaluation Seminar*. Hamilton, Ont: McMasters University Publ, 1978
64. Stein REK, Jones Jessop D. An ethics committee to aid in implementing a randomized clinical trial. *Controlled Clin Trials* 1983;4: 37–42
65. Bunker JP, Hinkley D, McDermott WV. Surgical innovation and its evaluation. *Science* 1978;200:937–941
66. Spilker B. *Guide to Clinical Trials*. New York: Raven Press, 1991:8
67. Levy RI, Mock MB, William VL, Passamani ER, Frommer PL. Percutaneous transluminal coronary angioplasty: a status report. *N Engl J Med* 1981;305:399–400
68. Mock MB, Smith HC, Mullany CJ. The 'Second Generation' NHLBI percutaneous transluminal coronary angioplasty registry: have we established the role for PTCA in treating coronary artery disease? *Circulation* 1989;80:700–702
69. Kent KM, Bentivoglio LG, Block PC, et al. Percutaneous transluminal angioplasty: report from the registry of the National Heart Lung and Blood Institute. *Am J Cardiol* 1982;49:2011–2020
70. Detre K, Holubkov R, Kelsey S, et al. Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981: the National Heart Lung and Blood Institute Registry. *N Engl J Med* 1988;318: 265–270
71. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham study. *Am J Cardiol* 1976;38:46–51
72. Friedman JM, Birch P, Greene C. National Neurofibromatosis Foundation international database. *Am J Med Genet* 1993;45(1): 88–91
73. Harrel FE Jr, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modeling strategies for improved prognostic prediction. *Stat Med* 1984;3:143–152

74. Califf RM, McKinnis RA, McNeer JF, et al. Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patients studied with cardiac catheterization for suspected ischemic heart disease. *J Am Coll Cardiol* 1983;2:1060–1067
75. Hlatky MA, Pryor DB, Harrel FE Jr, Califf RM, Mark DB, Rosati RA. Factors affecting the sensitivity and specificity of the exercise electrocardiogram: a multivariable analysis. *Am J Med* 1984;77: 64–71
76. Pryor DB, Califf RM, Harrel FE, et al. Clinical data bases: accomplishments and unrealized potential. *Med Care* 1985;23(5):623–647
77. Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery surgery: comparability of entry characteristics and survival in randomized patients and non-randomized patients meeting randomization criteria. *J Am Coll Cardiol* 1984;3:114–128
78. Klimt CR. The conduct and principles of randomized clinical trials. *Controlled Clin Trials* 1981;1:283–293
79. *NIH Inventory of Clinical Trials,* Fiscal Year 1975, Volumes I and II, Bethesda, Md: National Institutes of Health, 1978
80. Ferguson R. Getting it right the first time. *AJNR Am J Neuroradiol* 1990;11:875–877
81. Meinert CL. *Clinical Trials: Design, Conduct, and Analysis.* New York: Oxford University Press; 1986:281–308
82. Whitehead J. The case for frequentism in clinical trials. *Stat Med* 1993;12(15/16):1405–1413
83. Meinert CL. *Clinical Trials: Design, Conduct, and Analysis.* New York: Oxford University Press; 1986:185
84. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *Int J Epidemiol* 1992;21(5):837–841

Please see the commentary on page 1217 in this issue.