The Canadian American Ticlopidine Study (CATS) in Thromboembolic Stroke
Design, Organization, and Baseline Results

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The Canadian American Ticlopidine Study is a randomized, placebo-controlled, double-blind, multicenter study to assess the efficacy and safety of ticlopidine hydrochloride in patients who have suffered a thromboembolic stroke no less than 1 week and no more than 4 months before entry into the study. The primary assessment of efficacy will be based on the cluster of outcome events recurrent stroke, myocardial infarction, or vascular death. Twenty-five clinical centers, 12 in Canada and 13 in the United States, entered a total of 1,072 patients during a 3-year recruitment period; these patients were randomly allocated to receive either 250 mg ticlopidine or identical-appearing placebo tablets twice daily for up to 3 years. Patient recruitment was completed in December 1986. Patients were followed for a maximum of 3 years or until the close of the study in December 1987; at that time an average follow-up of 25 months had been achieved. We summarize the protocol and organization of the study and document the methods of execution and analysis, with corresponding criteria, before disclosure of the treatment code to any of the study investigators. We also provide a clinical description of the patients at entry into the study. (Stroke 1988;19:1203-1210)

The majority of disabling and fatal strokes are thromboembolic1-2 and are sometimes preceded by transient ischemic attacks (TIAs).3 This, together with the established role of platelets in arterial thrombosis, has provided the rationale for numerous randomized trials of platelet-inhibiting drugs in patients with TIAs or minor strokes. A recent comprehensive overview analysis based on these studies4 has established the efficacy of acetylsalicylic acid (ASA) in patients with TIAs or mild strokes, with the estimated benefit of a 22% reduction in the risk of subsequent stroke, myocardial infarction, or vascular death. However, this approach of treating patients with TIAs deals with only a small part of the problem of ischemic stroke since <20% of thromboembolic strokes are preceded by TIAs.5 Prophylaxis for patients surviving a thromboembolic stroke is still not established and remains a major concern since such patients have a high risk of subsequent stroke, myocardial infarction, or vascular death over the ensuing year.6 Notwithstanding the efficacy of ASA in patients with TIA or mild stroke, it may not be appropriate to extrapolate the beneficial effect to these patients, who are at the severe end of the spectrum of cerebral ischemia. Indeed, in the only reported randomized study of ASA restricted to patients with a completed thromboembolic stroke, the observed rate of recurrent stroke or death was slightly higher in the ASA group than in the placebo group.6

For these reasons, we carried out a randomized clinical trial to assess the potential benefit of ticlopidine, one of the newer antiplatelet drugs, in reducing the incidence of recurrent stroke, myocardial infarction, or vascular death in patients surviving a thromboembolic stroke. Ticlopidine strongly inhibits ADP-induced platelet aggregation and moderately inhibits aggregation induced by collagen, epinephrine, platelet activat-
ing factor, and several other physiologically important inducers. Ticlopidine prolongs the bleeding time, inhibits adhesion of platelets to glass beads, and blocks the platelet-release reaction; it most likely interferes with the ADP and fibrinogen receptor pathways on the platelet membrane; it does not inhibit cyclooxygenase or cAMP phosphodiesterase. Ticlopidine’s antiplatelet activity is irreversible and persists for the life of the platelet.

**Study Organization**

Like most large, multicenter clinical trials, the Canadian American Ticlopidine Study (CATS) had a fairly complex study organization and included 25 clinical centers, a Coordinating and Methods Center, a Clinical Monitoring Center, and appropriate committees responsible for policy, adjudication, safety, and monitoring. We describe the centers and committees and list corresponding memberships in Appendix 1.

Twenty-five clinical centers, 12 in Canada and 13 in the United States, participated in CATS. The principal investigator at each clinical center was responsible for the conduct of the study at that center, and a designated clinical coordinator at each center played a key role in the day-to-day activities of patient recruitment and follow-up.

The Coordinating and Methods Center was located at McMaster University, Hamilton, Canada. Its main responsibility was the day-to-day administration and execution of CATS, including the collection, checking, editing, processing, and analysis of all study data. Staff from the Coordinating and Methods Center were responsible for providing 1) a general status report, including information relating to patient recruitment, follow-up assessments, overdue reports, and projected follow-up schedules for individual patients; 2) a formal presentation, providing information relating to the quality and discipline of study execution, the deliberations of the Central Adjudication Committee, and any methodologic problems arising, to the Steering Committee every 6 months; 3) a presentation, relating to study progress, protocol adherence, and logistic problems, at the annual meeting of investigators and annual workshops with clinical coordinators; and 4) a comprehensive computer data tape every quarter to the Interim Analysis Group, which in turn prepared appropriate summaries to allow the Safety Committee to fulfill its responsibilities.

The Steering Committee had the overall responsibility for the design, execution, analysis, and reporting of CATS. The Steering Committee comprised the principal investigators from five of the clinical centers, three individuals from the Coordinating and Methods Center, and one individual from each of the two sponsors. The Steering Committee met every 6 months to address and resolve policy issues encountered during the course of CATS and to assure the timely and accurate completion of study documentation based on detailed reports from the Coordinating and Methods Center.

The responsibility of the Central Adjudication Committee was validation of the eligibility of patients entered into CATS and of the outcome events reported by the clinical investigators. The Central Adjudication Committee comprised a neurologist, an internist, and a nonclinical methodologist, all of whom were active investigators in CATS. To discharge their responsibilities, the Central Adjudication Committee met on approximately 30 occasions during the course of the study; details of the validation process are given below.

Statistical analyses were performed quarterly by an Interim Analysis Group, the Statistics and Epidemiology Research Corporation, Seattle, Washington, the director of which was also a member of the Safety Committee. The Interim Analysis Group prepared interim summaries, including outcome events and adverse drug reaction data as well as verification that the randomization procedure was properly executed, for the Safety Committee. No data or resulting analysis was disclosed to anyone not a member of the Interim Analysis Group or the Safety Committee, all of whom were directed to maintain the strictest confidence.

The primary responsibility of the Safety Committee was protection of the welfare of the patients who participated in the study. The Safety Committee was independent and had no formal association with members of the CATS Group or with Syntex/Sanofi representatives and, other than the Interim Analysis Group, the members of the Safety Committee were the only people aware of the treatment assigned to individual patients. The Safety Committee received quarterly summaries relating to drug toxicity and efficacy from the Interim Analysis Group and met every 6 months for a formal review. The Safety Committee did not share this information with anyone but issued a brief annual statement, which simply said there was no reason for the study to come to an early close at that time, to the CATS Group. The Safety Committee also received drug experience reports from the Clinical Monitoring Center and forwarded this information to federal regulatory agencies (the Health Protection Branch in Canada and the Food and Drug Administration in the United States) within 15 days after adding the drug identity to the report. The CATS Safety Committee also served as the Safety Committee for TASS, a complementary study of ticlopidine versus ASA in patients with TIA or mild stroke; the committee thus had a much expanded data base for monitoring safety.

The Ticlopidine Policy Committee served the same sort of function in relation to other multicenter trials with ticlopidine that are planned by Syntex as did the Steering Committee for CATS. The Ticlopidine Policy Committee’s sole responsibility for CATS was to act as an intermediary between the Safety Committee and the Steering Committee in the event that the Safety Committee...
recommended that CATS be stopped for unacceptable drug toxicity or spectacular efficacy.

The sponsors of CATS were Syntex Research, a division of Syntex (USA) Inc., Palo Alto, California, and Sanofi, Paris, France. Staff from Syntex played an important role in the design and execution of CATS, particularly in routine monitoring and site visits to the clinical centers, and as the Clinical Monitoring Center.

**Design and Methods**

**Subjects and Eligibility**

Eligible patients must have experienced a thromboembolic stroke no less than 1 week and no more than 4 months before entry into CATS. Atherothrombotic strokes including retinal and lacunar infarctions qualified, but strokes thought to be cardioembolic did not. There must have been the sudden onset of a new neurologic deficit with residua persisting at the time of randomization. The diagnosis of thromboembolic stroke was based on an appropriate neurologic evaluation and assessment of the clinical course; a brain computed tomogram (CT scan) was required before randomization, primarily to rule out disease processes other than cerebral infarction. For atherothrombotic stroke, the deficit had to involve one or more of the following: 1) weakness of the face, arm, or leg; 2) numbness or sensory impairment of the face, arm, or leg; 3) speech impairment; 4) temporospatial impairment; 5) vision loss, either monocular or binocular; and 6) two or more of incoordination, cranial nerve abnormality, and dysarthria. For lacunar infarction, the deficit had to involve one or more of the following: 1) pure motor hemiplegia affecting the face, arm, or leg; 2) pure sensory stroke affecting the face, arm, or leg; 3) motor sensory stroke affecting the face, arm, or leg; 4) ataxic hemiparesis; and 5) dysarthria-clumsy hand syndrome. In addition, the CT scan had to be either compatible with a small deep infarct or normal.

The stroke was judged to be cardioembolic and therefore to disqualify the patient if any one of the following were present: mitral stenosis, prosthetic valve, endocarditis, myocardial infarction within 6 weeks before the stroke, myocardial aneurysm, intracardiac clot or mass, or mitral valve prolapse in a person <45 years of age with no reasonable alternative explanation for the event. The stroke was also judged to be cardioembolic if any two of the following were present: chronic or paroxysmal atrial fibrillation, sick sinus syndrome, recent involvement of more than one vascular territory, seizure at onset, hemorrhagic infarct, or cerebral artery branch occlusion(s) without overt evidence of extracranial or intracavernous carotid artery disease on arteriography. Patients considered by their physicians to have cardiac embol, regardless of these criteria, were ineligible.

Patients were also ineligible 1) if they were likely to remain bedridden or were demented and thus were unlikely to be rehabilitated to any extent, 2) if they had severe comorbid condition(s) that may have limited survival during the course of the study, 3) if they had contraindications to the use of ticlopidine (e.g., renal or hepatic insufficiency, history of hemostatic disorder or pathologic bleeding, history of thrombocytopenia or neutropenia, or any other drug-induced hemato logical abnormalities), 4) if they had significant laboratory test abnormalities, 5) if the qualifying stroke was secondary to carotid endarterectomy or angiography, 6) if carotid endarterectomy was performed after the qualifying stroke but before randomization, 7) if long-term anticoagulant or antiplatelet therapy was required, 8) if there was a history of alcohol or drug abuse, or 9) if they were participating in another drug trial.

Any patient fulfilling the inclusion criteria and passing the screen of exclusion criteria was eligible for CATS. Following discussion with the clinical investigator, those patients giving informed consent were entered into the study.

It was judged important to keep a log of patients who met the inclusion criteria but failed to pass the screen of exclusion criteria since this would provide valuable information describing the population of patients considered for CATS. To increase study discipline and completeness of logging exclusions, a rotation system was used in which each clinical center documented carefully all patients excluded in a particular month, and then the clinical center did not have to record exclusions for the next 4 months. This systematic 20% sampling for each clinical center was expected to provide not only a sample of adequate size but also one of greater consistency and accuracy and hence representativeness than might be expected from attempting the much more demanding complete log throughout the study. Within this rotation system, a log was kept of eligible patients who refused to take part in CATS.

Each Initial Clinical Assessment form accompanied by appropriate documentation, including diagnostic information, hospital summaries, baseline laboratory data, etc., was reviewed by a clinical member of the Central Adjudication Committee without knowledge of treatment allocation or any clinical outcomes, and each patient was classified as eligible, technically ineligible, or truly ineligible. Technically ineligible patients had the disease of interest (i.e., thromboembolic stroke) but had failed one of the exclusion criteria unrelated to safety (e.g., time since the qualifying stroke was <7 days or >4 months). Truly ineligible patients were judged not to have the disease of interest (e.g., the patient had cardiac embolism). Any apparent discrepancies or questions regarding the available documentation were discussed at a meeting of the Central Adjudication Committee, and if the matter could not be resolved additional documentation was sought from the clinical investigator. Investigators were notified
in writing of any patients considered ineligible with reasons given by the Central Adjudication Committee; the investigator then had the opportunity to challenge this decision and to provide further information. All patients judged to be technically or truly ineligible were presented to the Steering Committee for final approval.

As will be discussed later, technically ineligible patients will be included in all analyses of efficacy and safety even though the investigators were not generally aware of this policy decision during the course of CATS. Truly ineligible patients will be reported and their outcomes will be described, but these patients will not be included in any analysis of efficacy and safety.

Eligible patients were allocated to treatment with either ticlopidine or placebo according to a prescribed randomization arrangement generated separately for each clinical center; no other stratification was used.

The treatment code was known only to the Interim Analysis Group and the Safety Committee. In this way potential biases during patient entry and in the adjudication of patient eligibility and outcome events should have been avoided. A special tablet packaging and shipment procedure was used so that the sponsors were also blind to specific patient treatment assignments. In each of the 4 years of CATS, Syntex was responsible for preparing several cartons, each containing individually labeled patient packages that would accommodate the needs of any clinical center for 1 year. The Safety Committee was then responsible for randomly allocating these cartons to specific clinical centers so that only the Safety Committee knew the randomization code for any particular clinical center.

Treatment and Follow-up

Ticlopidine was supplied as 125-mg film-coated tablets in plastic bottles containing 140 tablets (1 month's supply). Placebo tablets were identical in appearance and packaging. The intended dosage of ticlopidine was two 125-mg tablets b.i.d. (500 mg total daily dose). The tablets were to be taken with the morning and evening meals to minimize gastric irritation and abdominal discomfort. If a patient was unable to tolerate this regimen, it could be modified for short periods to try to reduce intolerance. Every effort was made to stay as close to the full dosage as possible.

Each bottle was clearly labeled with the patient's study number and dosage instructions. In addition, attached to each box of bottles for an individual patient there was a sealed, tear-off label that contained the treatment identity. The sealed labels were attached to the Drug Accountability Form and returned unopened to the Safety Committee at the end of each year, immediately following receipt of the new cartons. In an emergency, the sealed label could be opened to break the treatment code for an individual patient. This should rarely have been necessary and should have been done only after consultation with the senior principal investigator or the Clinical Monitoring Center.

The initial clinical assessment required information relating to demography, medical history, concomitant medications, general physical examination, cerebrovascular history, neurologic history of the qualifying stroke, complete neurologic examination at the time of entry into CATS, functional status, results of investigations, and site and type of stroke. Follow-up clinical assessments were made at 1 and 4 months and every 4 months thereafter to a maximum of 3 years. At these follow-up visits, changes in demographic data, hospitalizations, newly developed medical conditions or episodes, study drug and other medications, general physical and neurologic examinations, and adverse drug experiences were recorded. Outcome events were also identified and documented.

Laboratory investigations were carried out both locally and at a central laboratory. Since ticlopidine has been associated with occasional cases of neutropenia and thrombocytopenia, safety considerations dictated that a complete blood count and platelet count be done every 2 weeks for the first 3 months of administration of the study medication. The risk of hematologic reactions is thought to lessen subsequently, and a reduced frequency of follow-up blood counts was considered justified. Blood counts were made at entry into CATS; every 2 weeks for the first 12 weeks; at months 4, 5, 6, and 8; and every 4 months thereafter. For those patients who had to travel a great distance to their clinical center, it was permissible to have some of the laboratory investigations done by their personal physician or at a laboratory other than that at their clinical center.

Laboratory Services, San Jose, California, was contracted as the central laboratory facility to allow standardized results across clinical centers, and the laboratory investigations were scheduled to be performed at entry into CATS; at months 1, 4, and 8; and every 8 months thereafter.

Diagnostic information that had to accompany the Initial Clinical Assessment form and hospital summary (if appropriate) to the Coordinating and Methods Center included the CT scan report, electrocardiogram (ECG) tracings and report, a chest x-ray report, an echocardiogram report (if done), and the angiography report (if done). These investigations did not need to be repeated during the course of CATS except in the course of appropriate clinical care.

Compliance was assessed simply by counting tablets from the bottles of study medication returned by the patient at routine follow-up visits; platelet aggregation testing was strictly forbidden as this could have broken the treatment code. Patients were provided with a list of common over-the-counter ASA-containing products and were specifically instructed to avoid them. A supply of acetaminophen was provided at no cost to each patient to be used for minor aches and pains when necessary. Each patient and the family physician was
given printed information about CATS, emphasizing the importance of avoiding concomitant use of anticoagulants and antiplatelet drugs. Essential medications for comorbid conditions were allowed, and their use was recorded systematically.

Clearly, patients could decide to stop taking their study medication at any time. However, this decision could also have been made by a clinical investigator if it was considered to be in the patient’s best interest; ordinarily, this should have been done only after consultation with the Clinical Monitoring Center. Clinical events for which permanent discontinuation of study medication was mandatory included death, subarachnoid hemorrhage, primary intracerebral hemorrhage, and serious adverse experiences. In all instances, the reason(s) for permanent discontinuation of study medication was documented on a termination form.

**Outcome Events**

The principal outcome events for the assessment of efficacy were nonfatal stroke, nonfatal myocardial infarction, and vascular death. Since the primary focus of CATS was on events due to atherosclerotic arterial disease, subarachnoid hemorrhage and primary intracerebral hemorrhage were not included in the assessment of efficacy. However, it was recognized that these were potentially adverse outcomes due to the intervention as were other major bleeding complications.

The criteria for the outcome event nonfatal stroke were identical to those for the qualifying stroke except that the deficit had to last a minimum of 24 hours if in a new location or > 1 week if it was accompanied by an appropriate new CT finding. Strokes thought to be cardioembolic were also legitimate outcome events.

The diagnosis of the outcome event nonfatal myocardial infarction required at least two of the following: 1) typical symptoms of pain occurring anywhere in the anterior chest, back, epigastrium, jaw, neck, or upper extremity; 2) compatible ECG changes or a positive pyrophosphate radionuclide scan; and 3) appropriate serum enzyme changes. Serial serum concentrations of serum glutamicoxaloacetic transaminase, lactic dehydrogenase, creatine phosphokinase (or CPK-MB, if performed) were considered compatible with an acute myocardial infarction if the peak values of one of the three exceeded twice the upper limit of normal for the laboratory in which they were measured and if these peaks occurred within 72 hours of the onset of symptoms.

Deaths were classified as vascular or nonvascular, but within each classification more specific determinations were made. Among vascular deaths were new cerebral infarction, myocardial infarction, sudden death, and congestive heart failure. Most nonvascular deaths were expected to be either primary pneumonia, respiratory failure, pulmonary embolism, or cancer. Deaths due to subarachnoid hemorrhage, primary intracerebral hemorrhage, or to the qualifying stroke will not be included in the primary assessment of efficacy.

If a patient had surgery for any reason and then suffered a vascular outcome event, such events will be considered in the primary assessment of efficacy even if they were considered to be a consequence of the surgery.

Patients experiencing a nonfatal stroke should have been seen by a neurologist, if possible, and their medical records were reviewed to verify the event. Similarly, nonfatal myocardial infarctions should have been reviewed and verified by an internist or cardiologist at that clinical center. The underlying cause of any death was to be determined by independent review of all available medical records by two or more physicians. In all instances, the reviewing physicians were unaware of the study medication given to individual patients.

Outcome events were reviewed independently by both clinical members of the Central Adjudication Committee provided with the Outcome Event form and all available support documentation and were subsequently discussed in committee. When appropriate, relevant baseline data were also provided to confirm change in neurologic status in the reporting of nonfatal strokes. Disagreements about the outcome events were communicated to the investigators, who had the opportunity to provide further information to support their initial judgments. Any significant changes in the classification of outcome events proposed by the Central Adjudication Committee were presented to the Steering Committee for final approval.

**Analysis**

Information regarding the risk of major clinical events after recovery from a thromboembolic stroke is meager and variable. The report by Gent et al provided the most recent and, in view of the similarity of patient eligibility criteria and study objectives, the most relevant estimates. Gent et al reported a rate of subsequent stroke, myocardial infarction, or vascular death of nearly 20% at 1 year and approximately 25% after 2 years. Based on these estimates, it was proposed to recruit 1,000 patients over 2½ years and to follow them to a common termination point at 3 years. This would result in a 90% chance of demonstrating a significant difference in outcomes between the two treatment groups, at a one-sided significance level of 5%, if the true benefit of ticlopidine was a relative risk reduction of 30% in the subsequent occurrence of nonfatal stroke, nonfatal myocardial infarction, or vascular death (i.e., from 25% to 17.5%).

The main assessments of drug efficacy will be in terms of the outcome events nonfatal stroke, nonfatal myocardial infarction, or vascular death and in terms of the composite outcome events stroke, myocardial infarction, or death from any cause;
Amendments to Protocol

The respective survival curves for the two treatment groups can be estimated using the Kaplan-Meier method.14 Analysis are appropriate for summarization and comparison of event rates. The proportion of patients remaining event-free at any time after randomization can be represented as a survival curve and can be estimated using the Kaplan-Meier method.14 The respective survival curves for the two treatment groups will be compared using the Mantel-Haenszel test.15

Since both prorandomization patient eligibility decisions and the 28-day rule have been implemented blindly with respect to treatment and outcomes, no bias should result and a considerable potential gain in statistical sensitivity should be achieved. There will be full disclosure in the CATS final report of all outcome events in truly ineligible randomized patients and in the post–28-day periods among eligible patients.

Since the duration of follow-up of individual patients will vary and since an outcome event can occur at any time, the techniques of survival data analysis are appropriate for summarization and comparison of event rates. The proportion of patients remaining event-free at any time after randomization can be represented as a survival curve and can be estimated using the Kaplan-Meier method.14 The respective survival curves for the two treatment groups will be compared using the Mantel-Haenszel test.15

The primary efficacy analysis will be based on the time to occurrence of the first outcome event with the 28-day rule applied. Secondary analyses will consider the composite outcomes of 1) stroke, myocardial infarction, or death from any cause; 2) nonfatal stroke or stroke death; 3) vascular death; and 4) death from any cause, all with the 28-day rule applied. In addition, corresponding analyses, including all outcome events that occur during follow-up, will be carried out on an intention-to-treat basis. Randomized patients who were ruled truly ineligible will not be included in any analysis of efficacy or safety, but all events in such patients will be reported separately.

Amendments to Protocol

During the course of CATS the Steering Committee made three formal amendments to the protocol.

The original protocol had a lower limit of 2 weeks relative to the qualifying stroke, but experience during the first year indicated that a number of potentially eligible patients were discharged from the hospital between 1 and 2 weeks after their stroke, and most of these patients were lost to CATS. The decision was made, therefore, to lower the qualifying time limit to 1 week after the qualifying stroke, thus facilitating both patient enrollment and in-hospital supervision.

The original protocol also called for patient recruitment over 30 months, with a planned common study termination after 3 years. In two subsequent changes, the recruitment period was extended by 6 months to achieve the required number of patients, and the minimum patient follow-up was also extended by 6 months based on a recommendation from the Safety Committee, the reason for which will not be disclosed to the Steering Committee until release of the final data base and breaking of the treatment code. As a result the total study period became 4 years rather than 3.

The Steering Committee also made the criteria and eligibility rules for both patients and outcome events as they related to the proposed analyses of efficacy and safety more specific.

Results

The original group of 11 clinical centers was expanded in two distinct stages to a total of 25 centers.
and the planned recruitment period of 30 months was extended to 3 years. The number of patients entered from individual clinical centers ranged from four to 108, with the total being 1,072 patients.

Of these 1,072 randomized patients, 19 were ruled truly ineligible by the Steering Committee: 11 were considered to have had cardioembolic stroke, six were judged to be misdiagnosed and were reclassified as having venous angioma, dissection of the right internal carotid artery, middle cerebral artery aneurysm, hydrocephalus, sarcoidosis, and glioblastoma; and two were judged to have had insufficient evidence to support the diagnosis of stroke. Of the remaining 1,053 patients, 26 were ruled technically ineligible by the Steering Committee: 17 fell outside the entry window (13 being >4 months and four being <1 week since the qualifying stroke), six did not have a neurologic deficit at the time of randomization, two had a carotid endarterectomy between the qualifying stroke and randomization, and for one patient the qualifying stroke was a complication of angiography. In accordance with CATS policy, all 26 technically ineligible cases will be included in all analyses of efficacy and safety.

The demographic and general clinical characteristics of the study cohort at entry into CATS are shown in Table 1, details of the qualifying stroke are given in Table 2, and cerebrovascular history is summarized in Table 3. Comparing the CATS patients with those in the sulocitidil stroke study\textsuperscript{5} or the Swedish study,\textsuperscript{6} the CATS patients are similar with respect to mean age (65 years), sex distribution (62% men), and cardiovascular comorbidity except for diabetes mellitus (32%) and history of hypertension (67%), which were more frequent in CATS patients. We included 26% lacunar infarctions, which proportion is much higher than the 11% reported in the sulocitidil study,\textsuperscript{5} but the vascular distribution was similar as was the cerebrovascular history. The mean time from stroke onset to randomization was 42 days, which is appreciably less than the 59 days reported in the sulocitidil study.\textsuperscript{5}

A total of 122 center-months of exclusion monitoring was reported, with most clinical centers contributing 6 months; this represented approximately a 20% sampling. This 122 center-months of reporting identified 1,161 patients who fulfilled the inclusion criteria, of whom 394 (34%) passed the screen of exclusion criteria and were thus eligible for CATS. However, only 201 (51%) of these 394 eligible patients were successfully recruited into the study, the remainder being unwilling or unable to give informed consent.

**Discussion**

We believe that CATS has been designed with care and executed with discipline and that it represents a sterling effort from many colleagues across North America. The principal features of CATS that should maximize the acceptance and credibility of the subsequent findings is that it is randomized, that it has a large patient base, and that no investigator, adjudicator, or representative of the sponsors had access to the treatment code at any time during the study. Indeed, the disclosure of the treatment
code to the principal investigator will not be made until a computer tape of the final data base is handed over to the Safety Committee to ensure that no further modifications of key data can be made after receiving the treatment code.

The process of making decisions about the eligibility of patients and the validity of outcome events is demonstrably unbiased, and this publication of the study rules and procedures before disclosure of the treatment code should rule out any suggestion of bias in the classification of outcome events or in the selection of analyses to be carried out and presented in our next report.

Appendix 1.


References

Key Words: cerebrovascular disorders • clinical trials • ticlopidine
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