Design Paper

Design of the Trial of Org 10172 in Acute Stroke Treatment (TOAST)

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ABSTRACT: TOAST is a multicenter, randomized, placebo-controlled clinical trial testing the usefulness of a new antithrombotic drug in improving the outcome of persons with acute ischemic stroke. Until recently, no clinical trial testing a treatment for ischemic stroke had demonstrated efficacy in outcome. Design problems of previously conducted trials with inconclusive results may partly explain their failures. During the design of TOAST, the investigators addressed several issues so the trial could test the treatment accurately. We report the strategies used in designing, implementing, and coordinating the trial.

KEY WORDS: Ischemic stroke, antithrombotic therapy, acute treatment, clinical trials, design

Ischemic stroke is a leading cause of death and disability in the United States and most other industrialized countries. Thus, the care of persons who have ischemic stroke remains critical. Several treatments improve outcome after stroke by prevention or control of medical or neurological complications [1]. Unfortunately, until recently, no treatment had established efficacy in improving outcome after stroke [2–3]. Acute treatment to stop worsening is important because progression of neurologic deficits is seen in 25–40% of patients, most commonly within the first few days [4,5]. Neurologic deterioration can result from the development of brain edema, seizures, progression of the cellular consequences of ischemia, or medical complications such as hypoxia or electrolyte disturbances. In addition, worsening also may result from recurrent embolism, progression of the thrombosis, or failure of the collateral circulation.
Antithrombotic drugs, heparin in particular, are widely prescribed to persons with acute ischemic stroke [6–8]. These drugs may halt the progression of the thrombosis, prevent recurrent embolism, and maintain collateral flow. Acutely administered antithrombotic drugs also lessen the risk of deep vein thrombosis and possibly forestall pulmonary embolism, a leading cause of death after stroke [9]. In the future, antithrombotic drugs also may be important adjuncts to treatment with thrombolytic drugs. Although antithrombotic drugs are used extensively, data about their usefulness in stroke are not available [1,9]. The uncertainty about the value of this therapy means that clinical trials are needed to test the usefulness of these drugs.

Low molecular weight (LMW) heparins and heparinoids are new antithrombotic drugs that have more selective effects on coagulation than conventional heparin [3,10,11]. Their longer duration of action means less variability in therapeutic response. These agents prevent thrombosis in a number of settings. Hopefully, the LMW compounds have a lower associated risk of hemorrhage than conventional heparin. These drugs also have little effect on platelets, and thus the risks of thrombocytopenia, white clot syndrome, and arterial thrombosis are expected to be less than with unfractionated heparin. Org 10172 (danaparoid sodium/Orgaran), a LMW glycosaminoglycuran derived from biological sources, inhibits the activation of Factor Xa. It lessens the risk of deep vein thrombosis in bedridden patients, including those who have had a recent stroke [12–14]. It has been used to prevent thrombosis in other situations, including in persons who have heparin-induced thrombocytopenia [15].

Because of its potential usefulness, pilot studies of Org 10172 in the treatment of acute ischemic stroke were performed at the University of Iowa and Duke University [16,17]. The promising results of these studies were used to design a clinical trial to test the efficacy and safety of Org 10172 in improving outcome after stroke. The resulting Trial of Org 10172 in Acute Stroke Treatment (TOAST), which was funded by the National Institute of Neurological Disorders and Stroke (NINDS), completed recruitment in December 1996. In this report, we described the design of TOAST and discuss several methodologic issues commonly occurring in acute ischemic stroke therapeutic trials.

DESIGN OF TOAST

TOAST is a multicenter, randomized, double-blind, placebo-controlled clinical trial that compares the outcomes of persons who receive the best medical care for acute ischemic stroke to those who receive the best medical care with the addition of Org 10172. The primary hypothesis is that Org 10172 is more efficacious than placebo in improving the likelihood of a favorable outcome at 3 months after acute ischemic stroke. Secondary hypotheses include the ability of Org 10172: to reduce mortality at 7 days and 3 months after stroke, to halt progression of stroke within 7 days, to improve outcome at 7 days, and to prevent recurrent stroke or other ischemic events during the first 7 days after stroke.

The trial is designed to detect a 20% relative improvement with treatment at 3 months from an estimated base rate of 50% in the placebo-treated group to 60% in the actively treated patients with 90% power and a 5% significance using two-sided tests and intention-to-treat analyses. The size of the sample
to test the primary hypothesis is 1076 persons divided into two treatment
groups of equal size. To compensate for cases who are lost to follow-up, the
planned sample size was increased to 1300 persons; this allowed a 20% loss
to follow-up.

Responses are assessed during the acute treatment period, at 7 days, and at
3 months (Table 1). Validated rating instruments, including the NIH Stroke
Scale, Modified Barthel Index, and Glasgow Outcome Scale [18–21] are used.
In addition, we used a classification system that we described previously [22]
to attribute the cause (subtype) of ischemic stroke. All assessments are made
by study-certified physicians or nurse coordinators.

Organization

TOAST, which is funded by two grants from NINDS, has two principal
investigators. One of the principal investigators (HPA) is responsible for the
overall conduct of the trial and is masked to treatment of allocation. The
other principal investigator (RFW) is aware of assignments of therapy and is
responsible for data management and analyses. Organon Inc. (West Orange,
NJ) holds the investigational new drug (IND), donates the study drugs, and
provides additional funding to the trial to help ensure compliance with all
requirements of the Food and Drug Administration.

The trial has 13 organizational components: (1) participating clinical centers
at major medical centers across the United States (see Appendix for the list of
sites), (2) clinical coordinating center, (3) data management center, (4) radiology
center, (5) central laboratory, (6) operations committee, (7) adjudication commit-
tee, (8) publications committee, (9) advisory committee, (10) financial manage-
ment group, (11) in-house safety committee, (12) NINDS-appointed safety and
monitoring committee, and (13) Organon Inc. The clinical coordinating center,
data management center, radiology center, central laboratory, financial manage-
ment group, and in-house safety committee are located at the University of Iowa.

The participating clinical centers were selected on the basis of past perfor-
mance in clinical studies in stroke, expertise, and interest in the treatment of
persons with cerebrovascular disease, as well as evidence of a large number
of persons with acute ischemic stroke who are seen annually. Some centers
have more than one hospital. Personnel at the centers include a local principal
investigator, collaborating physicians (coinvestigators), and a study coordina-
tor, all of whom are unaware of treatment allocation. They enroll, treat, and
assess the patients, maintain local records, collect and transmit data to the data
management center, and assist in data monitoring and auditing procedures.
They also interact with their respective institutional review boards to ensure
that the trial remains in compliance with local human research regulations.
Each center keeps a log of patients screened for participation in the trial. A
limited amount of information about all persons seen within 7 days of onset
of stroke is recorded on these logs to assess the impact of inclusion and exclusion
criteria, and to provide information about the generalizability of the trial’s
results. The logs are forwarded to the data management center monthly. At
most centers, a pharmacist handles the study drug. All centers have a laboratory
that performs the local measurements of anti–Factor Xa levels. Each site has
an unmasked local safety monitor who is not involved actively in the care of
### Table 1  Assessments of Participants

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Medical history and examination, screening general medical history and examination; NIH Stroke Scale, National Institutes of Health Stroke Scale; Motor, supplemental motor examination; Medical Evaluation, medical evaluation, including vital signs and ancillary care; Barthel, Modified Barthel Index; Glasgow, Glasgow Outcome Scale; Subtype, stroke subtype; CT, computed tomography; ECG, electrocardiogram; Anti Xa, anti-Factor Xa level; CBC, complete blood count; PTT, partial thromboplastin time; ProT, prothrombin time; Guaiac, stool guaiac; UA, urinalysis.
the participating patients. The local safety monitor recommends adjustments in the infusions of study drugs to the masked treating physicians.

The clinical coordinating center administers the trial on a day-to-day basis and closely interacts with the trial's other components. It assists the participating clinical centers in recruiting, treating, and assessing the patients. The financial management group handles the fiscal aspects of the trial, including reimbursement to the centers. The central laboratory measures anti-Factor Xa levels in samples obtained from all actively treated patients to standardize laboratory data. The central laboratory also assists the local laboratories in maintaining high-quality data at the centers. The radiologists in the radiology center interpret the results of computed tomographic (CT) examinations of the brain at the end of treatment. They assess the images for the presence, extent, and location of ischemic stroke, and they examine for complications, especially brain hemorrhage.

The data management center is in charge of the randomization process, as well as receiving, editing, and managing the data. Its staff prepares reports for the in-house safety committee and the NINDS safety and monitoring committee, as well as quarterly updates for the trial's NINDS project officer. The data management center performs interim and final analyses, and assists in the development of additional projects and reports from the trial.

Organon Inc. holds the IND for the study drug, and its personnel are responsible for ensuring that the trial meets all regulatory requirements. In particular, Organon Inc. advises investigators about the reporting of serious adverse experiences and notifications of the respective institutional review boards per the regulations of the Food and Drug Administration. Personnel from Organon Inc. also perform on-site audits of all patient records and case report forms to confirm the accuracy of the collected information in preparation for regulatory review.

The operations committee, which supervises the conduct of the trial, consists of Dr. Adams, Dr. Woolson, and several local principal investigators who serve staggered and rotating terms. The adjudication committee is composed of several investigators who address questions about eligibility, responses to treatment, and outcome. Several investigators also sit on the publications committee, which oversees the development of manuscripts and abstracts that emanate from the trial. An advisory committee of five experienced clinicians and researchers provides recommendations to the principal investigators. The in-house safety committee consists of five physicians at the University of Iowa who regularly review data for issues related to safety. This group independently reports to the NINDS safety and monitoring committee, which oversees the progress of the trial.

Patient Selection

Patients who meet all inclusion criteria and have no reason that excludes entry are asked to participate in the trial (Table 2). The upper age limit was temporarily lowered to 79 from September 1, 1993 to July 1, 1994, while a potential age-related safety issues was examined. Beginning March 1, 1995,
Table 2  Inclusion and Exclusion Criteria for Participant Selection

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<th>Inclusion Criteria</th>
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<tr>
<td>1. Age $\geq 18$ and $\leq 85$</td>
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<td>2. Clinical criteria of acute ischemic stroke</td>
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<td>3. Symptoms present more than 1 but $\leq 24$ hr</td>
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<td>4. Diagnosis by an investigating physician</td>
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<td>5. Pre-stroke Barthel Index at least 12 (scale 0–20)</td>
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<th>Exclusion Criteria</th>
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<td>1. Complete or substantial resolution of neurologic symptoms</td>
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<td>2. Minor stroke resulting in an isolated, mild neurological deficit</td>
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<td>3. Coma</td>
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<td>4. Signs of mass effect on baseline CT</td>
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<td>5. Illness that requires anticoagulation</td>
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<td>6. Currently receiving heparin for this stroke</td>
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<td>7. Woman who is pregnant or lactating (before March 1, 1995, any woman of childbearing potential was excluded)</td>
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<td>8. Stroke present $&gt;24$ hr, even if progression in the last 24 hr</td>
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<td>9. CT evidence of nonvascular cause of neurologic symptoms</td>
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<td>10. Evidence of intracranial blood on CT</td>
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<td>11. Active bleeding or severe, unexplained anemia</td>
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<td>12. Major operative procedure in the previous 24 hr</td>
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<td>13. Abnormal baseline coagulation studies</td>
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<td>14. Mean blood pressure sustained $&gt;130$ torr</td>
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<td>15. Renal, hepatic, respiratory, or cardiac failure</td>
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<td>16. Terminal illness</td>
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<td>17. Complex medical illness that confounds treatment</td>
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<td>18. Known or suspected infective endocarditis</td>
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<td>19. Known or suspected vasculitis</td>
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<td>20. Currently receiving warfarin for any indication</td>
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<td>21. Thrombolytic therapy in the previous 24 hr</td>
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<td>22. Severe confounding neurologic disease</td>
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<td>23. Adverse reaction or hypersensitivity to heparin, sulfites, or bisulfites</td>
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<td>24. Previously in TOAST or currently in another clinical trial</td>
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<td>25. Inmate of a state institution</td>
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<td>26. Patient refuses to participate or is unable to give written informed consent, and next-of-kin is unavailable or refuses to give consent</td>
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<tr>
<td>27. Baseline NIH Stroke Scale score $&gt;15$ (implemented September 1, 1993)</td>
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</table>

Women of childbearing potential were permitted to enter the trial; before enrollment, they must have a negative urine or serum test for pregnancy. An operations manual includes definitions for all inclusion and exclusion criteria. Patients are randomized only after consent is obtained. When necessary, an interpreter is used. When permitted by state law, consent is obtained from the next-of-kin when an aphasic patient is unable to give permission. All consent forms are approved by the individual centers’ institutional review boards and the regulatory officers of Organon Inc.

Baseline screening assesses the patient’s past medical history, including demographic and risk factors, history of stroke, and the history of the qualifying event (Table 1). The baseline examination involves measurement of the vital signs, a general medical examination, and a neurological examination. Physicians score the NIH Stroke Scale and a supplemental motor examination, and
they diagnose the most likely cause of stroke. The results of the baseline screening and diagnostic studies, except for the anti-Factor Xa level, must be known before the patient is randomized. Other diagnostic studies, such as those to determine the likely etiology of stroke, are performed after the patient enters the trial and are selected at the discretion of the treating physician.

Randomization and Study Drugs

A permuted blocks randomization schedule developed by the data management center maintains the masking of the investigators at each site. Randomization is stratified by the time of entry into the trial by individual hospitals so that equal number of persons are in each treatment group within a specified number of patients. The ratio of persons treated with Org 10172 or placebo is 1:1. A unique eight-digit patient identification (ID) number is paired with the randomization sequence to determine which patients receive active drug and which receive placebo. The ID numbers and treatment assignments are forwarded to Organon Inc., where labels are printed and applied to boxes and ampules of study drug for each of the two groups. The study drugs are packaged in identically appearing 2-ml ampules that contain either placebo or 2500 anti-Factor Xa units of Org 10172. All the ampules needed to treat an individual participant through the 7-day course of therapy are placed in an individual box. A sealed envelope, which contains the identity of the study drug, is prepared by the data management center and placed inside each box before sealing and shipping. The sealed envelope remains in the hospital's pharmacy and is not opened unless an emergency requires knowledge of treatment allocation.

After the treating physician decides that a patient is eligible, and after the person has given consent, the physician sends an order to the pharmacy. The writing of an order to administer the study drug is considered the time of randomization for the purpose of the intention-to-treat analyses. The pharmacist dispenses the study drug with the next sequential ID number to the patient. The ID number appears on all infusion labels, is recorded in the patient's medical record, and appears on all case report forms.

Treatment Regimen and Adjustment of Dosages

Several assumptions were made during the design of the treatment regimen (Table 3). The desired levels of inhibition of Factor Xa (antithrombotic effect) are postulated to be higher for arterial occlusions, such as stroke, than for venous thrombosis. A bolus dose is given so that maximal antithrombotic actions can be immediate. The drug is given intravenously in a continuous infusion to avoid wide fluctuations in blood levels. The drug is given for 7 days to cover the period of risk for early neurologic worsening or early recurrent stroke.

Orders for the study drug are included on the patients' regular hospital medication order forms. To expedite the writing of orders and to ensure their accuracy, each center is encouraged to prepare preprinted order forms. Instructions for the preparation of the study drug are detailed in a pharmacy protocol included in the operations manual.
Table 3  Treatment Regimen

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<th>Loading Dose</th>
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<td>1. 2.0 ml of study drug containing either placebo or 2500 anti–Factor Xa units or Org 10172 is added to 25 ml of normal or half-normal saline.</td>
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<td>2. Drug is given over 10 minutes.</td>
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<th>Rapid Phase Infusion</th>
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<td>1. 1.9 ml of study drug containing either placebo or 2400 anti–Factor Xa units or Org 10172 is added to 100 ml of normal or half-normal saline.</td>
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<td>2. Immediately follows loading dose and is given over 4 hr for an approximate dose of 600 anti–Factor Xa units/hr.</td>
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<th>Slower Phase Infusion</th>
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<td>1. 3.8 ml of study drug containing either placebo or 4800 anti–Factor Xa units of Org 10172 is added to 300 ml of normal or half-normal saline.</td>
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<td>2. Immediately follows rapid phase infusion and is given over 12 hr for an approximate dose of 400 anti–Factor Xa units/hr.</td>
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<th>Maintenance Infusion</th>
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<td>1. 1.9 ml of study drug containing either placebo or 2400 anti–Factor Xa units or Org 10172 is added to 200 ml of normal or half-normal saline.</td>
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<td>2. Immediately follows slower phase infusion and is given over 8 hr for an approximate dose of 300 anti–Factor Xa units/hr.</td>
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<th>Daily Infusion (Days 2–7):</th>
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<td>1. 5.8 ml of study drug containing either placebo or 7200 anti–Factor Xa units of Org 10172 is added to 500 ml of normal or half-normal saline</td>
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<td>2. Immediately follows the previous day’s maintenance infusion, and is given over 24 hr for an approximate dose of 300 anti–Factor Xa units/hr.</td>
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Blood levels of anti–Factor Xa activity are measured at regular intervals during treatment to monitor biologic responses to the infusion and to follow compliance with the protocol (Table 1). Because knowledge of the test results would unmask the treating physicians and coordinator, the levels are sent to the local safety monitor, who is unblinded. The desired goal for treatment is 0.6–0.8 anti–Factor Xa units/ml. If blood levels are above 0.8 but not more than 1.0 anti–Factor Xa units/ml, the dose of study drug is reduced by 10% from the previous dose. If blood levels are above 1.0 anti–Factor Xa units/ml, the infusion is discontinued for 12 hr and then reinstituted at a 10% lower dose. If blood levels are below 0.6 anti–Factor Xa units/ml, the drug is increased by 10% from the previous dose. To maintain the masking of the study, dosage adjustments and temporary interruptions in the infusion occur in both groups. The changes in the actively treated patients happen in response to the blood tests; alternations in the placebo-treated group follow instructions provided to the local safety monitor by the data management center. Premature termination of the study drug is avoided, but the infusion may be stopped if the patient or personal physician withdraws consent, if a major adverse experience possibly associated with the study drug occurs, or if an intercurrent illness necessitates the use of treatments that might interact with Org 10172.

Ancillary and Subsequent Care

Participating patients are hospitalized for the 7-day course of treatment. During the first 24 hr, nursing assessments are performed frequently, and bed rest is encouraged. Thereafter, patient activities are increased as tolerated.
Evaluation of swallowing is advised before a patient eats or drinks. Intravenous fluids, using half-normal or normal saline, are given to maintain adequate urinary output. Pneumatic compression stockings are applied to prevent deep vein thrombosis among bedridden patients. Medications that were prescribed before the stroke are continued, except those that might interact with Org 10172. Prohibited medications include oral anticoagulants, aspirin, dipyridamole, ticlopidine, nonsteroidal anti-inflammatory drugs, heparin, LMW heparins, volume expansion drugs, nimodipine, nicardipine, and thrombolytic drugs. Acetaminophen, nonacetylated salicylates, or narcotics are used to treat headache or other pain. Medical therapies such as mannitol, corticosteroids, antihypertensive drugs, antibiotics, insulin, cardiac medications, or ventilatory assistance are prescribed at the direction of the treating physician. Rehabilitative services such as speech therapy, physical therapy, occupational therapy, or psychological or behavioral assessments are encouraged.

Care after the acute treatment period, including selection of medical or surgical interventions to prevent recurrent ischemic events, is at the discretion of the treating physician. Referral of appropriate persons to a rehabilitation service or hospital for additional therapy is recommended.

Assessments and Rating Instruments

Medical and functional disability examinations are scheduled during the treatment period and at 3 months (Table 1). Additional examinations are aimed at detecting adverse experiences, including intercurrent illnesses, complications of stroke, or side effects of treatment. Laboratory studies are performed during the acute treatment period to monitor for adverse experiences. CT scans of the brain are done at baseline and at day 7 or if the study drug is terminated prematurely. Each scan is read locally by an investigator who is masked to the treatment. To determine the most likely cause of ischemic stroke, additional diagnostic studies are ordered on a case-by-case basis. The results of these studies are recorded on separate case report forms.

Patient Safety

Several components of the trial are directed at ensuring the safety of its participants. Many exclusion criteria are aimed at safety. Clinical and laboratory assessments are scheduled at regular intervals throughout the treatment period. The local safety monitor receives daily reports of the anti-Factor Xa levels and makes adjustments in the treatment regimen in an effort to lower the risk of adverse experiences. Drugs that might interact with Org 10172 and increase the risk of bleeding are avoided.

Adverse experiences that develop from the time of randomization until the 3-month follow-up examination, regardless of cause, are recorded on case report forms. Serious adverse experiences, including all deaths, are reported on an emergent basis to Organon Inc. A medical monitor at Organon determines whether the adverse experience is serious and unexpected, and notifies the Food and Drug Administration. The local investigators and local institutional review boards are also notified.
The in-house safety committee, composed of physicians at the University of Iowa who are aware of treatment allocation, independently monitors data related to patient safety and examines adverse experiences. When appropriate, the committee interacts with the NINDS safety and monitoring committee.

Annually, the investigators meet with the NINDS safety and monitoring committee to review the trial's progress, including issues related to safety. The recommendations from these meetings are reported at the annual TOAST investigators' meetings and in the TOAST Times, a quarterly informational publication for TOAST sites.

Quality Control Measures and Monitoring

Each center receives a detailed operations manual that includes sections for the investigating physicians, study coordinator, local safety monitor, local pharmacy, and local laboratory. All data are entered on case report forms. Coordinators are trained, tested, and certified in the handling of the forms and in computerized data entry. Monitoring of the accuracy of the data begins during the data entry at the sites. Intrinsic range and logic checks are included. Data are further examined for accuracy by the staff of the data management center. Discrepancies and questionable items are returned to the site for correction. On-site audits of data are performed by personnel of the clinical coordinating center. In addition, monitors from Organon Inc. compare all data with the clinical records, and identified inconsistencies are resolved and forwarded to the data management center for correction. A summary of collected data from each participant is forwarded to masked physicians at the clinical coordinating center who examine the data for any discrepancies.

The Glasgow Outcome Scale has been tested and used in a number of clinical trials (2,19,21,23). The Modified Barthel Index, which measures disability among persons with neurological illnesses, is reliable and reproducible [2,18, 21]. The NIH Stroke Scale is based on the neurological examination; it measures the seriousness of the stroke and detects changes in a patient's neurological impairments [20]. The scale is valid and reproducible, and has a high inter-observer reliability [20,24]. A certification process for the physicians' use of the NIH Stroke Scale, Glasgow Outcome Scale, and the supplemental motor examination ensures compatibility of clinical assessments at sites across the country [25].

Investigators and coordinators attend an annual study-wide meeting, during which issues related to the conduct of the trial are discussed. Members of the clinical coordinating center are on call 24 hr a day to answer questions about eligibility, adverse experiences, or treatment from the local investigators and coordinators. A member of the data management center also is on call 24 hr a day to address inquiries from the local safety monitors.

Local laboratory measurements of anti–Factor Xa activity are examined for quality by regular testing using control samples. If differences between the local and central values are found, remediation is performed. In addition, samples from all actively treated participants are re-examined independently at the central laboratory at the University of Iowa. The values obtained at the central laboratory will be used in the data analysis, thus avoiding inter-laboratory differences in values. In addition to local interpretation of the CT, a copy
of the CT obtained at the end of treatment is forwarded to the University of
Iowa, where a neuroradiologist who is unaware of treatment allocation inter-
prets these scans. These interpretations will be used in the data analyses.

**Data Transmission, Management, and Analyses**

Data are entered onto case report forms that are compiled in individual
patient binders. Within one working day of randomization, the study coordina-
tor notifies the data management center that the patient has been randomized.
The data management center verifies the patient’s ID number and enters it into
a database that is designed to track data through all stages of processing. A
calendar, generated from the date of randomization, identifies deadlines by
which the data are expected.

Each center has a personal computer that is configured with a 20-megabyte
fixed disk drive, color monitor, printer, and modem. The configuration uses
RODE/PC data entry software from DPX Inc. (Palo Alto, CA). This software
requires double data entry of all forms, and performs range and logic checks
of data fields as they are entered. Data are then extracted from the system into
a form that is suitable for transmission to the data management center. The
data entry screens resemble the case report forms; each item on the form is
identified with a similar field name on the screen. The coordinator completes
each field as the cursor moves over the screen. Electronic data transmission is
via standard telephone lines using modems. The data may be transmitted 18
hr/day, 7 days/week at the coordinator’s convenience. The RODE/PC software
automatically extracts all available data, dials the data management center,
and transfers the data. A personal computer at the data management center is
dedicated to receive incoming data. The contents of each transferred file are
electronically logged at the local site and at the data management center.
Passwords protect against unauthorized access.

The data management center loads data into an Oracle database and runs
computer edit programs. If errors are identified, the coordinator is notified,
problem fields are corrected, and the forms are re-edited. After all forms from
an individual participant are received, the data become available for on-site
monitoring by Organon Inc. The database values for every variable are com-
pared with the clinical records and the case report forms. Corrections are
recorded on the case report forms, and these corrected forms are sent via mail
to the data management center. Each time a form is corrected, it is re-edited
by computer to ensure that no new errors have been made. All transactions
are maintained in a transaction file database.

The primary outcome measure is the 3-month rate of favorable outcome,
which is defined as having a Glasgow Outcome Scale score of I or II (no-to-
moderate impairment) and a Modified Barthel Index score of 12 or more (out
of 20 possible points rating activities of daily living). Rates of favorable outcome
and the secondary outcome measures, including mortality, will be compared
between the active- and placebo-treated groups. The primary analyses for
efficacy of treatment are based on intention-to-treat; all randomized participants
with at least one post-baseline outcome assessment will be included regardless
of the duration of treatment, survival, withdrawal due to adverse experiences,
or the occurrence of secondary events. Analyses for safety will be performed
using data collected only from those persons who received at least some study drug. Secondary analyses excluding truly ineligible participants or other subgroups will also be done.

Comparisons of favorable outcome rates and mortality between the two treatment groups will be performed using the Cochran-Mantel-Haenszel procedure \[26\]. Homogeneity of treatment rate odds ratios across sites will be assessed using the Breslow-Day procedure \[27\]. Secondary hypotheses require comparisons of other outcome variables. Similarities of outcomes for the Glasgow Outcome Scale and Modified Barthel Index utilize the generalized Cochran-Mantel-Haenszel procedure \[26\], with the numeric value of the variable used as a score. This nonparametric method compares mean values after adjusting for center differences. Analysis of covariance (ANCOVA)—including covariate terms for baseline values, center, and center by treatment interaction \[28\]—will be performed for the Modified Barthel Index, NIH Stroke Scale, and the supplemental motor examination. Treatment effects will be estimated from the full ANCOVA model, adjusting for baseline and center differences \[28\]. Analyses will be performed both at the primary endpoint time of 3 months and at 7 days.

Because the TOAST randomization stratifies only for center and does not include prestratification, additional follow-up analyses will be performed stratifying for important risk factors and potentially confounding variables. Certain prognostic characteristics, such as severity of stroke or duration from onset of symptoms until initiating treatment, as well as important demographic features such as age, race, and sex of the patient, will be used as covariables or stratification variables in these secondary analyses.

Formal interim statistical analyses are performed approximately annually. To preserve a 5% significance level, the Lan and DeMets method \[29,30\] with the O'Brien-Fleming spending function \[31\] is used to compute interim stopping rule cut points. The results of interim analyses are released only to the NINDS safety and monitoring committee. Interim and final analyses include the generation of confidence intervals.

**DISCUSSION**

One of the possible explanations for the lack of proven treatments for ischemic stroke is problems in designing clinical trials to test promising therapies \[32,33\]. Several issues should be addressed for a trial to test a promising intervention accurately and successfully. Epidemiologic variables, the heterogeneous nature of stroke, its natural history and potential complications, the nature of the drug being tested, and desired outcomes must be considered in study design. Stroke is a potentially fatal or disabling disease that affects persons of all ages and those who have a number of co-morbid diseases. Conversely, most stroke victims spontaneously improve, and many can recover rapidly, dramatically, or nearly completely \[2,34,35\]. Ischemic stroke can implicate different vascular beds that produce a variety of neurological deficits, and it is the result of a number of diseases that cause arterial occlusion. Although antithrombotic drugs are widely prescribed for management of acute ischemic stroke, their usefulness is uncertain \[1,3,6-9\]. Thus, TOAST is investigating an issue of importance to patients and physicians. If TOAST determines that this
LMW heparinoid is useful, an important advance in care will result. On the other hand, if the trial does not demonstrate a benefit from treatment, new alternative approaches to care can be examined.

Neither the treating physicians, study coordinators, nor the enrolled participants in TOAST are aware of treatment allocation. Although double-masking adds considerably to the complexity of a trial such as TOAST, it can be achieved and patient safety can be protected. We rejected the paradigm of a managing physician who is aware of treatment and a rating physician who is masked to allocation because of our concern that knowledge of therapy can influence ancillary care or the response to a minor bleeding event. Rather, we incorporated an unmasked local safety monitor at each site who is not involved in the patient's care. This person receives the results of laboratory tests and recommends adjustments in dosage for the active group and the control group. This technique was used in the Veterans Affairs study of oral anticoagulants in person with atrial fibrillation [36]. It does maintain and enhance the scientific integrity of the trial, but its implementation is both logistically cumbersome and fiscally costly.

Any multicenter trial that spans a continent is complicated. TOAST has several organizational components that closely interact; the data management and clinical coordinating centers are very important. Although financially and physically separate and with differing responsibilities, the two groups at the University of Iowa closely oversee the progress and jointly deal with issues daily. Other components of the trial, such as the central laboratory and radiology center, help maintain the quality of the data by minimizing inter-center variability. Several other aspects of the trial help protect the participants' safety and ensure that the trial meets all regulatory requirements. These efforts are vigorous and expensive, but they add to the validity of the data.

TOAST is testing straightforward hypotheses. The sample size is large enough to ensure a small type II statistical error [32,33]. The planned analyses, based on the intention-to-treat method, are appropriate for a clinical trial such as TOAST. TOAST is designed to test the hypotheses that the addition of Org 10172 to conventional care improves outcome after ischemic stroke.

We selected 3 months after stroke as the time to judge effects of treatment. This period corresponds to the time when persons in the United States are usually determined to be disabled after stroke. Persons often have considerable improvement during the first 3 months after stroke, and this period of observation allows the investigators to assess whether responses to treatment are sustained. A trial needs to show that any favorable effects from treatment result in improved outcomes of clinical relevance. The 3-month period also permits detection of any serious sequelae of stroke that lead to death or disability. Conversely, a prolonged period of follow-up is not advisable because survivors of stroke often have recurrent vascular events, such as myocardial infarction, that lead to death. One trial of heparin in care of stroke included follow-ups to 1 year and found more deaths in the actively treated group than in the controls [38]. Most deaths were late and were probably unrelated to either the stroke or its treatment. The 3-month period of follow-up observation means that care after the acute treatment period should be as uniform as possible. TOAST encourages prescription of medical or surgical therapies of established
values to prevent recurrent stroke. These treatments, selected on a case-by-case basis by the attending physician, are initiated after the completion of the infusion. In addition, the trial promotes the use of rehabilitation in an attempt to maximize recovery from stroke.

All clinical trials have limitations; none can replicate practice completely. The need to define inclusion and exclusion criteria carefully and to follow responses to treatment make a trial much different from customary practice. As a result, outcomes among persons enrolled in clinical trials are often better than in the general population. Still, a trial should be as close to usual practice as is possible. Because TOAST is entering persons across a wide age range at multiple institutions throughout the United States, it should provide information about responses across important demographic variables, including gender, ethnicity, and age. The inclusion and exclusion criteria are as broad as possible. Patients are enrolled regardless of the presumed vascular territory of the stroke, the nature of the presenting signs, or the presumed cause of stroke. We elected not to treat persons with very severe strokes because their prognosis is very poor, and it is possible that no therapy would be beneficial. To exclude these cases, we initially used the surrogates of coma or a shift of midline structures on baseline CT. In 1993, we also added the exclusion criterion of an aggregate NIH Stroke Scale Score above 15 to improve safety. Conversely, we are not entering persons with very mild strokes because their prognosis is good regardless of treatment; however, because one reason for early administration of antithrombotic drugs is to prevent recurrent embolism or progression of stroke, we are enrolling persons with mild to moderate strokes. These people would have the most to lose if their strokes worsened. TOAST excludes persons with recognized contraindications for acute antithrombotic therapy or those who have severe concomitant diseases that likely will confound care or assessments. Such restrictions are clinically relevant and replicate the practice of most physicians.

Confining treatment to persons with a specific subtype of stroke (e.g., cardiogenic) is problematic. Using TOAST data, Madden et al [39] recently reported that the etiologic diagnoses at baseline and at 1 week differed in approximately one third of cases. If the trial had restricted entry to one group, we would have entered ineligible persons and excluded patients who were truly eligible. In addition, our data suggest that the diagnosis of the cause of ischemic stroke is difficult in an emergency setting—a situation that is clinically important. Even when strict criteria are used and when a larger number of ancillary diagnostic studies are available, specialists will disagree about the cause of stroke [40]. We therefore decided not to consider presumed etiology when developing the TOAST inclusion/exclusion criteria.

TOAST requires randomization within the first 24 hr after stroke onset. Experimental studies demonstrate that therapeutic effects of many drugs for management of acute ischemic stroke require treatment within a very short period. These data have stimulated the concept of the "brain attack," which promotes emergent evaluation and treatment [41]. Several clinical trials testing therapies such as thrombolytic drugs are restricting entry to persons seen within a few hours of onset of stroke [2,42,43]. While our goal is to treat persons as quickly as possible, there are several reasons to study the efficacy of treatment in a relatively broad window. The goals of treatment with acutely administered
antithrombotic drugs are to prevent recurrent stroke or subacute progression; thus, the therapeutic window for these drugs may be longer than for other treatments. In addition, many persons do not seek medical attention quickly or have their strokes during sleep; they cannot be treated with hyperacute therapies such as thrombolytic drugs [2]. These persons often have serious strokes and deserve treatments of proven efficacy.

Our primary hypothesis involves testing the utility of Org 10172 in improving the likelihood of a variable outcome, a finding that is relevant to patients and their physicians. We are using valid, reliable, and reproducible outcome rating instruments. Inclusion and exclusion criteria were developed to ensure safety while offering treatment to a broad range of stroke patients. The sample size is large enough to detect a meaningful treatment effect with high probability. Numerous quality control and monitoring procedures are in place. While TOAST is a costly trial with its own limitations, the methodologic rigor in its design should lead to widespread acceptance of its ultimate findings by the neurologic community.

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REFERENCES


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Trial of Heparinoid in Ischemic Stroke

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