Low Molecular Weight Heparinoid, ORG 10172 (Danaparoid), and Outcome After Acute Ischemic Stroke

A Randomized Controlled Trial

The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators

Context.—Anticoagulation with unfractionated heparin is used commonly for treatment of acute ischemic stroke, but its use remains controversial because it has not been shown to be effective or safe. Low molecular weight heparins and heparinoids have been shown to be effective in preventing deep vein thrombosis in persons with stroke, and they might be effective in reducing unfavorable outcomes following ischemic stroke.

Objective.—To test whether an intravenously administered low molecular weight heparinoid, ORG 10172 (danaparoid sodium), increases the likelihood of a favorable outcome at 3 months after acute ischemic stroke.

Design.—Randomized, double-blind, placebo-controlled, multicenter trial.

Setting and Participants.—Between December 22, 1990, and December 6, 1997, 1281 persons with acute stroke were enrolled at 36 centers across the United States.

Intervention.—A 7-day course of ORG 10172 or placebo was given initially as a bolus within 24 hours of stroke, followed by continuous infusion in addition to the best medical care. Doses were adjusted in response to anti–factor Xa activity.

Main Outcome Measures.—Favorable outcome rated as the combination of a Glasgow Outcome Scale score of I or II and a modified Barthel Index of 12 or greater. A favorable outcome was defined as follows: (1) a Glasgow Outcome Scale score of I or II and a modified Barthel Index of 19 or greater; (2) a Glasgow Outcome Scale score of I or II and a modified Barthel Index of 12 or greater, with an improvement in favorable outcome at 3 months.

Results.—At 3 months, 482 (75.2%) of 641 persons assigned to treatment with ORG 10172 and 457 (71.5%) of 634 persons assigned to placebo had favorable outcomes (P=.49); 49.5% and 47%, respectively, of patients in each group had very favorable outcomes at 3 months after acute ischemic stroke.

Conclusion.—Despite an apparent positive response to treatment at 7 days, emergent administration of the antithrombotic agent, ORG 10172, is not associated with an improvement in favorable outcome at 3 months.
Patients with acute ischemic stroke. The design of the trial has been reported elsewhere.13,14 Based on the results of these projects, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) was performed to test the efficacy of the drug in improving outcomes among persons with acute ischemic stroke.

**METHODS**

**Design**

TOAST was a randomized, double-blind, placebo-controlled multicenter trial conducted from December 1990 to December 1996 that treated persons within 24 hours of the onset of acute ischemic stroke. The design of the trial has been reported elsewhere.15

**Patient Population**

Patients were eligible for the trial if their age was 18 to 85 years, if they had evidence of acute or progressing ischemic stroke with symptoms present more than 1 hour but less than 24 hours, if they were diagnosed by 1 of the investigators in the trial, and if they had an estimated prestroke modified Barthel Index of 12 or more.

Patients were excluded if they had the following: resolution of neurologic symptoms, an isolated mild neurologic deficit, a stroke less than 24 hours old with recent progression, coma, mass effect (shift of midline structures) on baseline computed tomogram (CT), intracranial blood on a CT, CT evidence of a nonvascular cause of symptoms, active bleeding, major surgery in the previous 24 hours, another illness that required anticoagulation, were currently receiving heparin or warfarin, received thrombolytic therapy in the previous 24 hours, active bleeding, abnormal baseline coagulation studies, mean blood pressure greater than 130 mm Hg, major organ failure, known vasculitis or infective endocarditis, a complex medical illness or terminal illness, confounding neurologic disease, allergy to heparin, prior participation in TOAST, or were participating in another clinical trial. Women of childbearing potential were excluded at the beginning of the trial but, subsequently, women who were not pregnant or lactating and who had a negative pregnancy test were enrolled.

**Outcome Measures**

Patients were assessed daily during the acute treatment period and had a follow-up examination at 3 months. Investigators who rated the patients were certified in use of the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Outcome Scale using a videotape testing system.16

The primary outcome was a favorable outcome at 3 months after stroke, defined as a score of 1 or II on the Glasgow Outcome Scale and a score of 12 to 20 on the modified Barthel Index.17-19 The intention-to-treat (ITT) analysis required that the patient have at least 1 postbaseline assessment of the Glasgow Outcome Scale and Barthel Index. The study was designed to detect an improvement of 20% with treatment (from an assumed base rate of 50%) with 90% power.

Prespecified secondary hypotheses included a favorable outcome at 7 days, reducing recurrent stroke within 7 days, halting worsening of neurologic deficits within 7 days, and reducing mortality at 7 days and 3 months. After a trial of thrombolytic therapy demonstrated a benefit in improving very favorable outcomes after stroke,20 the TOAST investigators added analyses evaluating similar responses (defined as a combination of a Glasgow Outcome Scale score of I and a Barthel Index score of 19 or 20) at 7 days and 3 months. Neurologic worsening was assessed by evaluating differences between the day 7 and baseline scores of the NIHSS.21 Patients whose day 7 NIHSS score was 4 or more points less than baseline or was 0 were classified as improved, a score that was within 3 points of baseline was considered unchanged, and a score of 4 or more additional points or death was rated as worse.

Subtypes of acute ischemic stroke were also a prespecified end point. Classification was based on a central-blinded evaluation assessing the clinical findings and the results of brain imaging and ancillary diagnostic tests, such as carotid duplex or echocardiography. Categories were large-artery atherosclerosis, cardioembolism, small-artery occlusion, other determined cause, or undetermined cause.22

Safety analyses assessed events experienced by any treated patient subcategorized by the time of onset and included adverse experiences that occurred (1) during treatment with the study drug, (2) during the first 10 days after entry, and (3) during the follow-up period. Major adverse events included deaths, symptomatic hemorrhagic transformation of the infarction, other intracranial bleeding, other major hemorrhages, myocardial infarction, recurrent ischemic stroke, systemic embolism, clinically diagnosed deep vein thrombosis, pulmonary embolism, and thrombocytopenia. A panel of 3 physicians who were not aware of treatment allocation assessed the most likely cause of death.

Two amendments were added to the protocol during the trial to assure patient safety. Because an increased risk of...
hemorrhage among persons with severe strokes was observed in September 1993, as discussed in the “Results” section, persons with an NIHSS score greater than 15 were excluded at the direction of the trial's National Institutes of Health–appointed Performance and Safety Monitoring Board. In May 1996, patients who weighed less than 56.2 kg (<125 lb) were excluded after high levels of anti–factor Xa activity and excess bleeding were observed.

Institutional review boards at the participating centers approved the project and periodically reviewed the progress of the study. Informed consent was obtained directly from the patients or from the next-of-kin.

Randomization

Patients were randomized 1:1 to treatment with ORG 10172 or placebo using permuted blocks with randomly ordered sizes of 6, 6, and 4 balanced for every 16 consecutive patients entered.

Treatment

An intravenous bolus dose was administered within 24 hours of onset of stroke symptoms to rapidly reach desired levels followed by a continuous infusion for 7 days. Rates of the infusion were adjusted after 24 hours to maintain the anti–factor Xa activity at 0.6 to 0.8 anti–factor Xa U/mL. Dosage adjustments were recommended by a local unblinded safety monitor. Based on preprinted instructions, the local safety monitor also recommended “sham” dose adjustments for selected patients receiving placebo. The study agent could be stopped prematurely for safety reasons, if the patient required potentially confounding therapy, or if the patient’s discharge was mandated by third party payers. Ancillary care to treat medical and neurologic complications of stroke was permitted, but heparin, warfarin, aspirin, ticlopidine, and nonsteroidal anti-inflammatory drugs were prohibited during the 7-day treatment period. After the completion of the treatment period, attending physicians remained unaware of the treatment arm. They selected medical or surgical therapies aimed at preventing recurrent stroke and rehabilitation.

Statistical Analyses

Analyses were ITT. All tests were 2-sided and an α level of .05 was used to assess statistical significance. No adjustments were made for multiple comparisons. The primary analysis examined the rates of favorable outcomes using the Cochran-Mantel-Haenszel test stratified by the participating site. The day 7 evaluation was used in the analysis for persons who did not have a 3-month follow-up evaluation for any reason other than death (last observation carried forward). Deaths were assigned the worst-case score for each scale. Mortality also was assessed using the Cochran-Mantel-Haenszel test stratified by site. In addition, survival curves for each treatment group were estimated using the Kaplan-Meier method and compared using the log-rank test. The Cochran-Mantel-Haenszel test stratified by site also was used to test rates of stroke progression during the first 7 days. Four interim analyses for the Performance and Safety Monitoring Board were performed approximately yearly during the course of the study. The procedure of Lan and DeMets for interim analyses was used utilizing the O’Brien-Fleming spending function. Incidence rate differences between drug groups for each adverse experience were evaluated using the Fisher exact test.

RESULTS

A total of 1281 persons were enrolled from a screened group of 25,624 (Figure). The reasons for exclusion of the screened group were consent could not be obtained in 623 cases; 8345 patients arrived after 24 hours of stroke onset; 2448 persons were outside the age range; 1186 patients did not have an acute stroke; 222 had severe preexisting disability; 379 were not enrolled because an investigator was unavailable; intracranial bleeding or baseline CT was detected in
Table 2.—Outcomes at 7 Days and 3 Months After Stroke

<table>
<thead>
<tr>
<th>TOAST Subtype</th>
<th>F. Outcome</th>
<th>F. Outcome P Val</th>
<th>ORG 10172 (%)</th>
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<th>Odds Ratio 95% CI</th>
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<tr>
<td>Atherosclerosis</td>
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<td>Small vessel†</td>
<td>144/158 (91.1)</td>
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<td>Other cause</td>
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*Primary hypothesis tested in the trial.
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‡Other cause refers to large-artery atherosclerosis and small vessel to small-artery occlusive disease (lacuna).

Table 3.—Influence of Stroke TOAST Subtype on Rates of Favorable and Very Favorable Outcomes at 3 Months After Stroke

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2505 persons; symptoms resolved in 1766 persons; a minor stroke with isolated signs occurred in 1367; coma was present in 254; active bleeding was present in 272; and 1066 were receiving heparin or warfarin. After September 1, 1993, 316 persons were excluded because their baseline NIHSS score was greater than 15. Other exclusion criteria were cited in 5432 instances.

No differences were seen in the baseline characteristics of patients enrolled randomized to the 2 groups (Table 1). Of those enrolled, 3-month follow-up data were available from 591 patients treated with ORG 10172 and 583 patients treated with placebo (Figure). Past treatment interventions did not differ between groups: 460 patients in the ORG 10172 group (81.3%) received antiplatelet agents; 174 patients in the ORG 10172 group (91.1%) received anticoagulants, and 17 patients in each group had a carotid endarterectomy.

Primary Efficacy Analysis: Favorable Outcome at 3 Months

No significant difference in the rate of favorable outcomes at 3 months after stroke was noted between the 2 treatment groups (Table 2). Approximately 75% of patients in both groups achieved favorable outcomes by the end of the observation period.

Secondary Efficacy Analyses

Favorable Outcome at 7 Days and Very Favorable Outcomes at 7 Days and 3 Months.—At 7 days, 376 patients receiving ORG 10172 (59.2%) and 344 control patients (54.3%) had reached a favorable outcome (Table 2). The rates of very favorable outcomes at day 7 were 33.9% and 27.5% among persons administered ORG 10172 and placebo, respectively (Table 2). By 3 months, approximately 48% of patients in each group had very favorable outcomes (Table 2).

Neurologic Worsening or Improvement During the First 7 Days.—Twenty persons (ORG 10172, 99; placebo, 11) had their study drug stopped prematurely because of neurological deterioration. By 1 week, 63 patients given ORG 10172 (10.0%) and 62 persons given placebo (9.5%) had worsening of 4 points or more. During the same interval, 261 patients receiving ORG 10172 (41.3%) and 223 placebo-treated patients (35.6%) (P = .09) had an improvement of 4 points or more or reached a score of 0.

Effects of Stroke Subtype and Baseline Severity of Stroke on Favorable or Very Favorable Outcomes at 3 Months.—The effects of the severity of stroke on admission or the cause of stroke on outcomes at 3 months are listed in Table 3. For strokes due to large-artery atherosclerosis, the rates of favorable and very favorable outcomes were significantly higher among persons who received ORG 10172. No treatment effect was noted in the other stroke subtypes. While the severity of baseline neurologic deficits strongly predicted outcomes at 3 months, it did not influence outcomes between the 2 treatment groups.

Adverse Experiences

Approximately 14% of patients in the trial had their study drug stopped prematurely (Figure). Significantly more participants receiving ORG 10172 had adverse experiences, primarily bleeding, that prompted premature termination of therapy (Table 4). Symptomatic hemorrhagic transformation of the stroke prompted stopping of the study drug in 9 patients receiving ORG 10172 and in 3 who were given placebo (P = .14). Three patients in each group had the study drug stopped because of asymptomatic hemorrhagic transformation of the stroke. Four patients administered ORG 10172 and 2 receiving placebo had the study drug stopped because of new ischemic strokes.

Bleeding.—Minor and more severe hemorrhages were more frequent among persons receiving ORG 10172 (Table 5). In the entire trial, 80 patients with an NIHSS score greater than 15 received ORG 10172 and 80 patients received placebo. Eleven patients who had a baseline NIHSS score greater than 15 had serious bleeding within 10 days; 10 patients received ORG 10172 (P = .01). By 3 months, serious brain hemorrhages were noted in...
11 patients and 3 patients, respectively \( (P = .06) \). Differences in the rates of major bleeding events within 10 days of starting therapy were significant \( (P < .005) \) (Table 5). By 3 months after entry, 14 patients receiving ORG 10172 had 16 intracranial bleeding events and 8 events were reported among 7 patients assigned placebo. By 3 months, 3 of the 14 patients in the ORG 10172 group and 1 of the 7 placebo-treated patients had favorable outcomes. Hemorrhagic transformation of ischemic stroke was found by brain imaging within 10 days of enrollment in 61 persons receiving ORG 10172 (9.6%) and in 55 placebo-treated patients (8.6%) \( (P = .69) \). By 3 months, among persons who weighed less than 56.2 kg \((< 125 \text{ lb})\), serious bleeding occurred in 6 of 59 patients (7 events) given ORG 10172 and 0 of 47 patients administered placebo \( (P = .03) \).

**Recent Ischemic Events.**—Recent ischemic strokes were diagnosed during the treatment period in approximately 1.2% of patients (Table 5). The rates of early recurrent stroke (first 7 days) as influenced by etiologic subtype were as follows: large-artery atherosclerosis (ORG 10172, 3 of 113 and placebo, 3 of 117), cardioembolism (ORG 10172, 0 of 143 and placebo, 2 of 123), small-artery occlusion (ORG 10172, 1 of 158 and placebo, 2 of 148), other cause (ORG 10172, 1 of 13 and placebo, 1 of 17), and undetermined cause (ORG 10172, 3 of 210 and placebo, 1 of 226). By 3 months, the total of ischemic events, including systemic embolism, myocardial infarction, deep vein thrombosis, and pulmonary embolism, was higher among persons treated with placebo (Table 5). By the end of the follow-up, recurrent stroke as influenced by stroke subtype were large-artery atherosclerosis (ORG 10172, 7 of 113 and placebo, 13 of 117), cardioembolism (ORG 10172, 4 of 143 and placebo, 9 of 123), small-artery occlusion (ORG 10172, 5 of 158 and placebo, 7 of 148), other cause (ORG 10172, 1 of 13 and placebo, 1 of 17), and undetermined cause (ORG 10172, 9 of 210 and placebo, 6 of 226).

**Mortality.**—Overall, 44 patients assigned to treatment with ORG 10172 and 38 patients given placebo died by 3 months (Table 6). At 7 days, 12 persons in the ORG 10172 cohort and 9 patients in the placebo group had died. Two deaths in the ORG 10172 group occurred in persons who did not receive any study medication; 1 had a fatal brain hemorrhage after randomization but before the infusion could begin. These 2 deaths are not listed in Table 6.

**COMMENT**

TOAST is the largest trial of an intravenously administered antithrombotic drug for treatment of acute ischemic stroke; it demonstrated no treatment effect in achieving either a favorable or very favorable outcome at 3 months after stroke, although higher rates of neurologic improvement, favorable outcome, and very favorable outcome were shown at day 7. Approximately 75% of persons in both cohorts had reached favorable outcomes at the end of the period of observation, a rate that is higher than reported in other clinical trials. Because of our concern of a risk of symptomatic hemorrhagic transformation, we did not enroll patients with severe deficits and, as a result, our patients had less severe neurologic deficits than those reported in the recent trial of rt-PA (recombinant tissue-type plasminogen activator). Our trial demonstrates that neurologic worsening during the first week is approximately 10%, regardless of treatment assignment. As a whole, the risk of early recurrent stroke in TOAST was only 1.5% within 1 week. Our data at 1 week are comparable to the 14-day rates de-
scribed by the International Stroke Trial and the 30-day rates reported by the Chinese Acute Stroke Trial. The experience of TOAST suggests that the risk of early recurrent ischemic stroke is relatively low. Thus, immediate administration of anticoagulants to prevent recurrent stroke may be unnecessary within the first days after a stroke.

Many physicians consider persons with cardioembolic stroke to be at particularly high risk for recurrent ischemic events. Still, past data about the efficacy of emergent antithrombotic therapy in preventing early recurrent cardioembolic stroke are minimal. Our therapy in preventing early recurrent ischemic stroke is particularly low, which lessens the urgency for early antithrombotic treatment. In addition, the findings of TOAST, we encourage a prospective study evaluating such an approach to treatment of persons with acute ischemic stroke.

Although our trial demonstrates no efficacy of ORG 10172 in improving outcomes at 3 months after stroke, TOAST provides other information that hopefully will influence patient care. Our data suggest that antithrombotic drugs administered as late as 24 hours after onset of stroke might improve outcomes of persons whose strokes are secondary to large-artery atherosclerosis. Our data imply that the likelihood of early recurrent stroke is relatively low, which lessens the urgency for early antithrombotic treatment. In addition, the findings of TOAST mean that the emergent administration of antithrombotic drugs is associated with major bleeding and an increased risk of intracranial hemorrhage, especially among persons with major stroke.

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Yale University School of Medicine, New Haven, Conn (enrolled patients, 12): P. B. Fayad, MD; L. M. Brasel, RN, coinvestigators; F. J. Pavalkis, PA, study coordinator.

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Rhode Island Hospital, Providence (enrolled patients, 32): E. Feldmann, MD, principal investigator; J. L. Wiltener, MD; J. L. Saver, MD; K. Furie, MD; J. Stamosulis, MD, coinvestigators; E. Baldwin, RN; L. Rice, BSN, study coordinator.

Columbia-Presbyterian Medical Center, New York, NY (enrolled patients, 31): J. P. Mohr, MD, principal investigator; R. L. Sacco, MD, coinvestigator; M. Clavijo, LPN, study coordinator.

Northwestern University Medical School, Chi- cago, Ill (enrolled patients, 28): J. Miller, MD, principal investigator; J. L. Saver, MD; J. I. Frank, MD; J. T. Patrick, MD; E. Fernandez-Duarte, MD, coinvestigators; L. R. Chaulkin, RN, study coordinator.

The University of South Carolina, Columbia (enrolled patients, 26): T. L. Hwang, MD, principal investigator; W. L. Brannon, MD; A. C. Trujillo, MD, coinvestigator; R. L. Frank, PhD, study coordinator.

University of Missouri Health Sciences Center, Columbia (enrolled patients, 26): G. A. Banet, RN, MSN, study coordinators.

University of California at Los Angeles (enrolled patients, 24): T. L. Hwang, MD, principal investigator; M. J. U. Park, MD; G. A. Yegyan, MD; S. J. U. Park, MD; M. H. Garabedian, MD; R. F. Macko, MD; M. A. Kelly, MD; A. Bijari, MD; J. W. Plyler, MD, coinvestigators; B. K. Muntzinger, PA, study coordinator.

University of Illinois Medical Center, Chicago (enrolled patients, 5): J. M. Weinberger, MD, principal investigator; G. B. Schubert, MPH, study coordinator.

Boston University School of Medicine, Boston, Mass (enrolled patients, 3): C. S. Kase, MD, principal investigator; P. A. Wechsler, MD, coinvestigators; B. Neely, MD, coinvestigator; J. Carpenter, RN, MSN, study coordinator.

Evans Hospital, Evansston, Ill (enrolled pa- tients, 19): D. B. Mirza, MD, principal investigator; S. Neely, MD, coinvestigator; J. Carpenter, RN, MSN, study coordinator.

References


