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 on a scale of 0 to 20 at 3 months or 7 days; very favorable outcome was recorded for the combination of a Glasgow Outcome Scale of I and a Barthel Index of 19 or 20 at 3 months or 7 days.

Results.—At 3 months, 482 (75.2%) of 641 persons assigned to treatment with ORG 10172 and 467 (73.7%) of 634 patients treated with placebo had favorable outcomes (P=.49); 49.5% and 47%, respectively, of patients in each group had very favorable outcomes at 3 months. At 7 days, 376 (59.2%) of 635 persons given ORG 10172 and 344 (54.3%) of 633 receiving placebo had favorable outcomes (P=.07). For the same interval, 215 (33.9%) of 635 persons given ORG 10172 and 176 (27.8%) of 633 persons administered placebo had very favorable outcomes (P=.01; odds ratio, 1.36; 95% confidence interval, 1.06-1.73). Within 10 days of onset of treatment, serious intracranial bleeding events occurred in 14 patients given ORG 10172 (15 events) and in 4 placebo-treated patients (5 events) (P=.05).

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.

JAMA. 1998;279:1265-1272

ANTICOAGULATION with unfractionated heparin commonly is used to treat persons with acute ischemic stroke.[1] However, the use of heparin remains controversial because it is not established as safe or effective.[2-6] A recent open trial demonstrated a modest effect from subcutaneously administered heparin in preventing recurrent stroke within 14 days but no improvement in outcomes.[7] Thus, whether an intravenously administered anticoagulant that would act more rapidly would be effective remains unanswered. The search for alternative medications that possess the antithrombotic characteristics of heparin but have a lower propensity for bleeding or thrombocytopenia led to the development of low molecular weight heparins and heparinoids. A clinical trial recently showed a lower rate of unfavorable outcomes at 6 months after stroke following the administration of the low molecular weight heparin, nadroparin, but no significant differences were noted at 10 days or 3 months.[8]

ORG 10172 (danaparoid sodium [Orgaran]) is a mixture of glycosaminoglycans with a mean molecular weight of 5500 d that is isolated from porcine intestinal mucosa. The anti–factor Xa activity of ORG 10172 is attributed to its heparan sulfate component,[9] which has a high affinity for antithrombin III. It is not inactivated by endogenous heparin-neutralizing factors such as histidine-rich glycoprotein or platelet factor 4, and it has virtually no effect on platelet function. It has minimal effects on the activated partial thromboplastin time, prothrombin time, or thrombin time.[10] The drug has low cross-reactivity to antibodies correlated with heparin-induced thrombocytopenia, and it is used to treat persons at high risk for thrombosis who have a history of heparin-induced

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

A complete list of the local principal investigators and coordinators and members of study committees appears at the end of this article.

Presented in part at the Sixth European Stroke Conference, Amsterdam, the Netherlands, May 29, 1997, and at the 23rd International Joint Conference on Stroke and Cerebral Circulation, Orlando, Fla, February 7, 1998.

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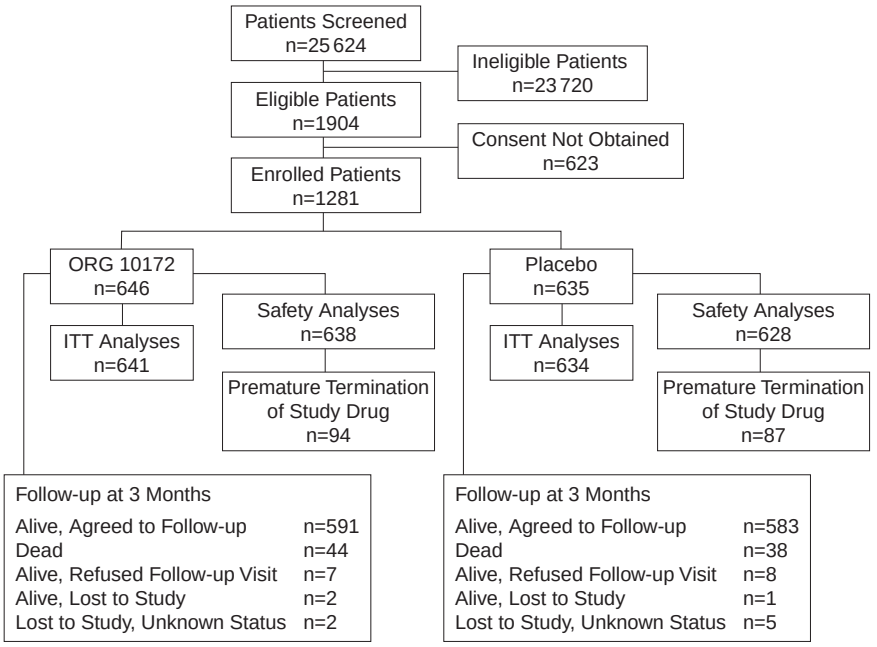

The populations were reported in TOAST (Trial of ORG 10172 [(danaparoid sodium, low molecular weight heparinoid] in Acute Stroke Treatment). The ITT (intention-to-treat) data were collected from persons who had at least 1 postbaseline outcome assessment. Postbaseline primary efficacy (Glasgow Outcome Scale and Barthel Index scores) data were not provided by 5 patients assigned to treatment with ORG 10172 and 1 patient treated with the placebo. These 6 patients were excluded from the ITT analysis. The safety analyses involve data collected from persons who received any amount of the study drug or placebo.

thrombocytopenia.[11] It is also used for prophylaxis against deep vein thrombosis.[12] Pilot studies examined the safety and potential utility of ORG 10172 in persons with acute ischemic stroke.[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 even 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 I 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 ascertained 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.[14,15] 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 withdrew consent, 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 nonsteroid 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.[23,24] 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.[24] In addition, survival curves for each treatment group were estimated using the Kaplan-Meier method and compared using the log-rank test.[25] The Cochran-Mantel-Haenszel test stratified by site also was used to test rates of stroke progression during the first 7 days.[24] 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[26] for interim analyses was used utilizing the O'Brien-Fleming spending function.[27] Incidence rate differences between drug groups for each adverse experience were evaluated using the Fisher exact test.[28]

Table 1.—Baseline Characteristics of Enrolled Patients With Intention-to-Treat Analyses

Characteristic	No. (%) of Patients Treated With ORG 10172* (n = 641)	No. (%) of Patients Treated With Placebo (n = 634)
Mean (SD) age, y	65.7 (11.29)	65.2 (11.44)
Men	391 (61.0)	382 (60.3)
White	394 (61.5)	403 (63.6)
African American	148 (23.1)	142 (22.4)
Hispanic American	73 (11.4)	60 (9.5)
Other ethnic groups	26 (4.1)	29 (4.5)
History of hypertension	430 (67.1)	415 (65.5)
Diabetes mellitus	184 (28.7)	187 (29.5)
Hypercholesterolemia	146 (22.8)	145 (22.9)
Tobacco use	254 (39.6)	243 (38.3)
Alcohol use <24 h	81 (12.6)	62 (9.8)
Claudication	46 (7.2)	39 (6.2)
Myocardial infarction	130 (20.3)	102 (16.1)
Atrial fibrillation	47 (7.3)	52 (8.2)
Cardiac operation	55 (8.6)	57 (9.0)
Previous transient ischemic attack	89 (13.9)	93 (14.7)
Previous stroke	123 (19.2)	106 (16.7)
Carotid endarterectomy	10 (1.6)	12 (1.9)
Aspirin use <7 d	259 (40.4)	250 (39.4)
Mean (SD) interval to treatment, h	15.6 (5.77)	15.8 (5.85)
Presentation of stroke		
Headache	59 (9.2)	63 (9.9)
Focal signs	625 (97.5)	625 (98.6)
Decreased alertness	66 (10.3)	56 (8.8)
Mean (SD) NIHSS score†	8.8 (6.20)	8.9 (5.98)
NIHSS score		
0-6	301 (47.0)	284 (44.8)
7-15	258 (40.2)	270 (42.6)
16-42	82 (12.8)	80 (12.6)
TOAST subtypes of stroke‡		
Large-artery atherosclerosis	113 (17.6)	117 (18.5)
Cardioembolism	143 (22.3)	123 (19.4)
Small-artery occlusion	158 (24.5)	148 (23.3)
Other cause	13 (2.0)	17 (2.6)
Undetermined cause	210 (32.7)	226 (35.6)
Mean (SD) blood pressure, mm Hg		
Systolic	154.8 (20.13)	153.1 (20.92)
Diastolic	85.0 (11.85)	84.1 (12.53)
Recent stroke on computed tomogram	162 (25.3)	167 (26.3)
Mean (SD) hematocrit	0.42 (0.04)	0.42 (0.05)

*ORG 10172 (danaparoid sodium) is the low molecular weight heparinoid.
†NIHSS indicates National Institutes of Health Stroke Scale. The untestable items received worst-case scores before summating the items.
‡The TOAST (Trial of ORG 10172 in Acute Stroke Treatment) subtype was based on data available at 3 months as determined by the Clinical Coordinating Center. Four patients receiving ORG 10172 and 3 placebo-treated patients did not have their subtype assessed.

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; 1196 patients did not have an acute stroke; 252 had severe preexisting disability; 379 were not enrolled because an investigator was unavailable; intracranial blood on baseline CT was detected in

Table 2.—Outcomes at 7 Days and 3 Months After Stroke*

No. (%) of Patients Treated With ORG 10172	No. (%) of Patients Treated With the Placebo	*P* Value	Odds Ratio (95% CI)
Favorable Outcome at 3 Months†			
482/641 (75.2)	467/634 (73.7)	.49	1.09 (0.85-1.41)
Favorable Outcome at 7 Days			
376/635 (59.2)	344/633 (54.3)	.07	1.23 (0.98-1.54)
Very Favorable Outcomes at 3 Months			
317/641 (49.5)	298/634 (47.0)	.35	1.11 (0.89-1.39)
Very Favorable Outcomes at 7 Days			
215/635 (33.9)	176/633 (27.8)	.01	1.36 (1.06-1.73)

*Title of the scheduled visit performed at the end of observation. ORG 10172 (danaparoid sodium) is the low molecular weight heparinoid. CI indicates confidence interval.
†Primary hypothesis tested in the trial.

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

TOAST Subtype	No. (%) of Patients Treated With ORG 10172	No. (%) of Patients Treated With Placebo	*P* Value	Odds Ratio (95% CI)
Favorable Outcome				
Atherosclerosis†	77/113 (68.1)	64/117 (54.7)	.04	1.77 (1.04-3.03)
Cardioembolism	97/143 (67.8)	85/123 (69.1)	.82	0.94 (0.56-1.59)
Small vessel†	144/158 (91.1)	134/148 (90.5)	.86	1.07 (0.49-2.34)
Other cause	11/13 (84.6)	14/17 (82.4)	.87	1.18 (0.16-8.60)
Undetermined	150/210 (71.4)	167/226 (73.9)	.56	0.88 (0.58-1.35)
Very Favorable Outcomes				
Atherosclerosis†	49/113 (43.4)	34/117 (29.1)	.02	1.87 (1.08-3.22)
Cardioembolism	69/143 (48.3)	58/123 (47.2)	.86	1.04 (0.64-1.69)
Small vessel†	93/158 (58.9)	93/148 (62.8)	.48	0.85 (0.53-1.34)
Other cause	7/13 (53.8)	10/17 (58.8)	.79	0.82 (0.19-3.59)
Undetermined	97/210 (46.2)	101/226 (44.7)	.75	1.06 (0.73-1.55)

*The TOAST (Trial of ORG 10172 [danaparoid sodium, the low molecular weight heparinoid] in Acute Stroke Treatment) subtypes are determined by the Clinical Coordinating Center. CI indicates confidence interval.
†Atherosclerosis refers to large-artery atherosclerosis and small vessel to small-artery occlusive disease (lacuna).

2505 persons; symptoms resolved in 1976 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 (77.8%) and 474 patients in the control group (81.3%) received antiplatelet agents; 174 patients in the ORG 10172 group (29.4%) and 177 patients in the placebo-treated group (30.4%) 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 27.8% 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 (9.9%) 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.

Table 4.—Reasons for Premature Termination of Study Drug

Reasons	No. (%) of Patients Treated With ORG 10172* (n = 638)	No. (%) of Patients Treated With Placebo (n = 628)
Any reason	94 (14.7)	87 (13.9)
Adverse experiences	54 (8.5)	34 (5.4)†
Death	3 (0.5)	4 (0.6)
Major bleeding	22 (3.4)	6 (1.0)‡
Minor bleeding	14 (2.2)	5 (0.8)
Major nonbleeding	8 (1.3)	7 (1.1)
Minor nonbleeding	12 (1.9)	14 (2.2)
Neurological worsening	9 (1.4)	11 (1.8)
Need for other therapy	18 (2.8)	23 (3.7)
Misrandomization	6 (0.9)	7 (1.1)
Patient withdrew consent	9 (1.4)	17 (2.7)
Other reason	25 (3.9)	23 (3.7)

*ORG 10172 (danaparoid sodium) is the low molecular weight heparinoid.
†P<.05.
‡P<.005.

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

Table 5.—Major Bleeding and Ischemic Adverse Experiences Among Patients Who Received the Study Drug*

	During Treatment		Within 10 Days		End of Observation	
	No. of Events in ORG 10172 Group (n = 638)	No. of Events in Placebo Group (n = 628)	No. of Events in ORG 10172 Group (n = 638)	No. of Events in Placebo Group (n = 628)	No. of Events in ORG 10172 Group (n = 638)	No. of Events in Placebo Group (n = 628)
All serious adverse experiences	41 (38)	24 (23)	54 (46)	35 (31)	82 (69)	83 (67)
Serious bleeding†	26 (25)	7‡	33 (32)	11‡ (10)	37 (34)	18§ (17)
Gastrointestinal	2	1	3	2	6	6
Urinary	2	2	2	2	2	2
Retroperitoneal	3	0	3	0	3	0
Musculoskeletal	3	0	3 (2)	1	3	1
Multisystem	2	0	3	0	3	0
Serious brain bleeding	11 (10)	3	15 (14)	5§ (4)	16 (14)	8 (7)
Symptomatic hemorrhagic transformation of infarction	9	3	11	3	11	4
Minor bleeding	201 (154)	133‖ (112)	253 (190)	187‡ (152)	324 (229)	245 (177)
Serious nonbleeding†	15	17 (16)	21 (20)	24 (22)	45 (42)	65 (56)
Recurrent stroke	7	8 (7)	10	11 (10)	26	37 (36)
Myocardial infarction	6	4	7	4	11	7 (6)
Deep vein thrombosis	0	2	0	3	2	10§
Pulmonary embolus	0	1	1	2	2	4
Thrombocytopenia	2	1	3	2	4	5

*In categories in which patients experienced more than 1 event, the number of patients affected is provided in parentheses. ORG 10172 (danaparoid sodium) is the low molecular weight heparinoid.
†Not all bleeding events are subcategorized.
‡$P<.005$.
§$P<.05$.
‖$P<.001$.

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 lb), serious bleeding occurred in 6 of 55 patients (7 events) given ORG 10172 and 0 of 47 patients administered placebo ($P=.03$).

Recurrent Ischemic Events.— Recurrent 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.

Table 6.—Causes of Death Among Patients Who Received the Study Drug

Causes	No. of Patients Treated With ORG 10172* (n = 638)	No. of Patients Treated With Placebo (n = 628)
Stroke itself	8	8
Hemorrhagic transformation	6	1
Stroke and medical complications	9	7
Recurrent ischemic stroke	1	4
New hemorrhagic stroke	0	1
Myocardial infarction	2	3
Sudden death	5	8
Other cardiovascular	1	2
Other vascular condition	1	0
Nonneurologic bleeding	1	1
Nonvascular condition	6	0
Undetermined	2	3
Total Deaths	**42**	**38**

*ORG 10172 (danaparoid sodium) is the low molecular weight heparinoid.

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 neurological deficits than those reported in the recent trial of rt-PA (recombinant tissue-type plasminogen activator).[20] 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.[7,29] 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.[1] Still, past data about the efficacy of emergent antithrombotic therapy in preventing early recurrent cardioembolic stroke are minimal.[4] Our data show that the risk among persons with cardioembolism is not much different than for persons with strokes due to other causes. Our data suggest that early administration of intravenous antithrombotic drugs may have a limited impact when compared with long-term anticoagulation in lowering the overall risks of recurrent cardioembolic stroke.

Drugs that affect coagulation are associated with an inherent risk of bleeding, and intracranial hemorrhage is the most life-threatening complication. The likelihood of symptomatic intracranial hemorrhage may be particularly high following ischemic brain injury and many physicians have been reluctant to give antithrombotic drugs because of the risk of bleeding.[1] Asymptomatic hemorrhages often are found by brain imaging performed after ischemic stroke, and symptomatic hemorrhagic transformation of an infarction can occur spontaneously.[30] However, the recent experience with thrombolytic therapy highlights the importance of intracranial hemorrhage as a potential complication.[20,31] Studies of heparin report intracranial bleeding as an adverse reaction to treatment and correlate the complication with the severity of the stroke, the patient's age, and the level of anticoagulation.[32,33] Our experience confirms the conclusion that emergent administration of antithrombotic drugs to persons with severe strokes increases the chance of symptomatic intracranial bleeding.

Serious hemorrhages in other parts of the body are associated with the level of anticoagulation and the presence of other diseases that predispose to bleeding. During TOAST, we detected higher rates of anti–factor Xa activity and more bleeding events among persons who weighed less than 56.2 kg (<125 lb). At the time TOAST was designed, weight-based nomograms had not been developed for emergent administration of antithrombotic drugs; such regimens now are available for heparin.[34] A weight-based nomogram for the use of ORG 10172 might result in improved safety and efficacy in management of persons with acute ischemic stroke.

We examined the influence of the cause of stroke on responses to treatment. We previously showed that determining stroke subtype can be difficult and such diagnoses often change as the results of ancillary tests become available.[35,36] In order to maintain uniformity in subtype diagnoses, we developed a system of central determination of diagnoses of subtype using the previously defined TOAST criteria for subtype.[21] These diagnoses were made when the results of ancillary tests were available. This situation is different from the one that a physician faces in an emergency room. Such qualification of our data is important because TOAST shows a significant response to treatment at 7 days and 3 months among persons who had stroke secondary to large-artery atherosclerosis. The positive response to treatment among patients with stroke secondary to occlusion of a major extracranial or intracranial artery or artery-to-artery embolism is intriguing. Antithrombotic drugs might help maintain collateral flow or halt progression of thrombosis in this group of seriously ill persons. Our data should prompt further testing of antithrombotic drugs in persons with ischemic stroke secondary to large-artery atherosclerosis. However, if this treatment is to be effective, early and accurate determination of this subtype will mandate the use of ancillary tests, such as duplex ultrasound of the carotid artery, transcranial Doppler, magnetic resonance angiography, or CT angiography. Based on the results 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.

This study was funded by the US Public Health Service, the National Institutes of Health, and the National Institute of Neurological Disorders and Stroke grants R0-1-NS-27863 and R01-NS-27960. Additional support, including a supply of the study drug, was given by Organon Inc, West Orange, NJ. The principal investigator for the randomized Trial of ORG 10172 in Acute Ischemic Stroke was Harold P. Adams, Jr, MD, and the principal investigator for the data management component of the trial was Robert F. Woolson, PhD. The project officer for the National Institute of Neurological Disorders and Stroke was John R. Marler, MD.

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