

LOW-MOLECULAR-WEIGHT HEPARIN FOR THE TREATMENT OF ACUTE ISCHEMIC STROKE

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Abstract Background. Despite doubts about their efficacy and concern about their safety, antithrombotic agents are often used to treat acute ischemic stroke. Recent experience in patients with other thromboembolic disorders suggests that low-molecular-weight heparin, which requires only subcutaneous administration once or twice daily, may be more effective and safer than standard (unfractionated) heparin.

Methods. We conducted a randomized, double-blind, placebo-controlled trial comparing two dosages of low-molecular-weight heparin with placebo in the treatment of ischemic stroke. Patients were randomly assigned within 48 hours of the onset of symptoms to receive high-dose nadroparin (4100 anti-factor Xa IU twice daily), low-dose nadroparin (4100 IU once daily), or placebo subcutaneously for 10 days. The primary measure of outcome was death or dependency regarding activities of daily living six months after randomization. Secondary outcomes

were death, hemorrhagic transformation of the infarction, and other complications at 10 days, and death or dependency at 3 months.

Results. A total of 2750 patients were screened for the study. Among 312 patients randomized, 306 had outcomes that were analyzed at six months. Forty-five patients (45 percent) in the high-dose group, 53 patients (52 percent) in the low-dose group, and 68 patients (65 percent) in the placebo group died or became dependent. There was a significant dose-dependent effect among the three study groups in favor of low-molecular-weight heparin ($P = 0.005$ by the chi-square test for trend). No significant differences among the groups in the occurrence of secondary outcomes were observed at 10 days.

Conclusions. For patients with ischemic stroke treated within 48 hours of the onset of symptoms, low-molecular-weight heparin was effective in improving outcomes at six months. (N Engl J Med 1995;333:1588-93.)

ISCHEMIC stroke accounts for approximately 85 percent of all strokes in Europe and North America and for 70 percent of those in the Far East.¹ Established methods of preventing such strokes in patients at high risk include treatment with antiplatelet agents, oral anticoagulants, or carotid endarterectomy.² For acute episodes, however, no specific treatment has been shown in randomized, controlled trials to improve functional status or reduce mortality.^{3,4} Antithrombotic agents, particularly heparin, have been a popular choice of many physicians for decades, but their benefit is unproved and their use remains controversial.⁵⁻¹¹

Recent clinical studies in patients with venous thrombosis suggest that low-molecular-weight heparin may be more effective than standard unfractionated heparin, with no increase in the risk of bleeding,¹²⁻¹⁵ as well as being more bioavailable and simpler to administer.¹⁶ In an open pilot study reported previously,¹⁷ we gave low-molecular-weight heparin subcutaneously to 55 patients with acute ischemic stroke and found the treatment well tolerated. In this randomized, double-blind, placebo-controlled study, we sought to test the hypothesis that in the treatment of patients with acute ischemic stroke, low-molecular-weight heparin is superior to placebo in reducing death or dependency

with regard to activities of daily living six months after a stroke.

METHODS

Patients and Study Design

Patients admitted to the four hospitals participating in the study who had clinical diagnoses of acute stroke were screened for eligibility. They were included in the study if their symptoms of stroke had started during the previous 48 hours (counted from the time of awakening, if the symptoms had been noted on waking from sleep) and if the patient or the patient's family members provided written informed consent. Patients were excluded from the study if any of the following were present: age over 80 years; computed-tomographic (CT) evidence of intracranial hemorrhage; transient neurologic deficits; sustained hypertension, with systolic blood pressure above 180 mm Hg or diastolic blood pressure above 120 mm Hg; major confounding neurologic or systemic illness (including a previous disabling stroke); a recent major operation or known tendency toward bleeding; current anticoagulant therapy or valvular heart disease necessitating such therapy; and known hypersensitivity or any other adverse reaction to heparin. Patients with strokes of all degrees of severity were enrolled, except those with no motor deficit and patients in whom death was considered to be imminent.

Individual investigators at each hospital were responsible for the recruitment, medical treatment, and follow-up assessment of patients. Case-record forms were faxed to the study coordinator for immediate entry into a computerized data base (FileMaker Pro, Claris, Santa Clara, Calif.). All personnel involved in the study remained unaware of the treatment assignments until the completion of follow-up for the last patient. No interim analyses were undertaken. The study protocol was approved by the ethics committees of the Chinese University of Hong Kong and the University of Hong Kong.

Treatment Schedule

Patients were randomly assigned to one of three treatments (high-dose low-molecular-weight heparin, low-dose low-molecular-weight heparin, or placebo) in blocks of six according to a computer-generated randomized schedule. These treatments were administered subcutaneously twice daily for 10 days by means of identical syringes filled with 4100 anti-factor Xa IU of nadroparin calcium (Frax-

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iparine, Sanofi-Winthrop, Gentilly, France) in 0.4 ml of solution, or the same volume of placebo. The syringes were contained in sequentially numbered boxes that were assigned to the patients consecutively. Patients in the high-dose group received the active drug every 12 hours. Patients in the low-dose group received the active drug in alternation with placebo every 12 hours (the first dose was always the active drug). The patients in the placebo group received injections of placebo every 12 hours.

Nonstudy medications, such as antihypertensive agents, steroids, and osmotic diuretics, were allowed, but the use of other antithrombotic agents, including aspirin, was discouraged. At the end of the 10-day treatment period, all the patients were given oral aspirin (100 mg daily) unless it was contraindicated.

Base-Line Assessment and Definitions of Infarct Subtypes

At the base-line assessment, the sex and age of each patient were recorded and information was collected on the following variables: any history of hypertension, diabetes mellitus, angina or myocardial infarction, stroke or transient ischemic attack, or smoking during the previous year; the patient's level of consciousness; the time of onset of symptoms; blood pressure; and other clinical data used to diagnose the subtype of the infarct¹⁸ and whether it had a cardioembolic cause.¹⁹

The definitions of the subtypes of cerebral infarction were adapted, with modifications, from Bamford et al.,¹⁸ with the precondition that a motor deficit had to be present before a patient could be enrolled in the study. A total infarct of the anterior circulation was defined as an ischemic stroke involving a combination of (1) higher cerebral dysfunction (dysphasia or visuospatial disorder), (2) homonymous hemianopia, and (3) hemiparesis in at least two of three areas (the face, an arm, and a leg). If the level of consciousness was impaired and formal testing of higher function or the visual field was impossible, a deficit was assumed to be present. A partial infarct of the anterior circulation was defined as an ischemic stroke involving two of the three components of the total anterior-circulation infarct or hemiparesis of the face, an arm, or a leg (only one of the three areas). A lacunar infarct was defined as an ischemic stroke involving hemiparesis in at least two of these areas (the face, an arm, and a leg). Patients with impaired consciousness were considered not to have lacunar infarctions but rather to have total or partial infarcts of the anterior circulation. An infarct of the posterior circulation was defined as an ischemic stroke involving hemiparesis or tetraparesis and brain-stem or cerebellar signs. The validity of this classification system has been studied by Anderson et al.,²⁰ and its interobserver reliability has been evaluated by Lindley et al.²¹

Initial Study Assessment

The initial study assessment was made 10 days after randomization. The causes of any deaths during the first 10 days were documented. Any complication that led to early discontinuation of the study medication or that was noted at the end of the treatment period and any use of nonstudy medication during that period were recorded.

Initially, the study protocol did not require CT to be performed a second time at the end of the treatment period. After the 49th patient, the protocol was modified to include CT at this point so that the risk of hemorrhagic transformation of the infarct, defined as an area of bleeding within infarcted brain tissue, could be measured objectively among patients whose symptoms might not worsen. Both the first and second CT scans were read by a participating radiologist who was unaware of the treatment assignment and the patient's degree of progress. At the conclusion of the trial, the CT films were reviewed by another blinded observer. Disagreements were resolved by a panel comprising the second observer and two participating neurologists.

Assessment of Outcome

The primary, prespecified study outcome was "poor outcome," defined as either death from any cause or dependency with respect to daily activities during the six months after randomization. The method of assessing dependency in the International Stroke Trial was employed.²² Briefly, patients or their care givers were asked whether the

patient had needed help in performing activities of daily living in the previous two weeks and whether the patient considered that he or she had recovered completely from the stroke. Patients were interviewed either in person or over the telephone and were considered to be dependent if they said they required help in performing activities of daily living and that they had not recovered completely from the stroke. Patients who said they did not need help with activities of daily living or considered themselves to have recovered fully were not regarded as dependent. To validate this measure of dependency in our cohort of patients, we compared it with the assessments obtained with the Barthel index²³ three months after randomization.

Secondary study outcomes were death, hemorrhagic transformation of the infarct, and the occurrence of any other complication within the 10 days of treatment, and poor outcome 3 months after randomization.

Statistical Analysis

Since the study design involved three groups of patients receiving dosages of active drug (0.8, 0.4, and 0 ml per day) that differed by the same amount, the chi-square test for trend with one degree of freedom was used to test the significance of group differences with respect to the primary and secondary outcomes.²⁴ To test the association between treatment and outcome, we estimated risk ratios and 95 percent confidence intervals. To determine whether other factors influenced outcomes, we performed a logistic-regression analysis that incorporated the base-line characteristics of the patients. All the tests were two-tailed, and computations were made with SAS software (SAS Institute, Cary, N.C.). To assess the validity of our measure of dependency, we calculated its sensitivity and specificity²⁵ with respect to the assessments obtained with the Barthel index.

RESULTS

Characteristics of the Patients

From October 1992 through July 1994, 2750 patients were screened for the study, 312 of whom (11 percent) were randomized. All were Chinese. Four patients were found to be ineligible for the study before the randomization code was broken (three patients in the high-dose group because of meningioma, parkinsonism, and hypoglycemia, and one in the low-dose group because of a nasopharyngeal carcinoma); these patients were excluded from all subsequent analyses.

The base-line characteristics of the 308 patients included in the study were similar in the three groups, as shown in Table 1.

Events during the 10 Days of Treatment

During the 10-day treatment period, 23 patients (7.5 percent) died, and 28 had complications leading to early discontinuation of the study medication. The causes of death and the types of complications are listed in Table 2. There were no significant differences among the three groups in numbers of either deaths ($P=0.84$) or complications ($P=0.14$). Nonstudy medications administered during this period that could affect the outcome of stroke are also shown in Table 2.

Except for the first 49 patients, for whom a second CT study was not required, such a study was performed routinely at the end of the treatment period. Twelve patients died without a second CT scan, and in three patients scanning was not done a second time because the patient refused to participate or was discharged early from the hospital (Table 3). Among the 245 patients

who had second scans, 22 (9.0 percent) had evidence of hemorrhagic transformation of their infarcts, which was asymptomatic in all but one patient (in the placebo group) and did not immediately lead to death in any. There were no significant differences among the three groups in the proportion of patients who had hemorrhagic transformation ($P=0.19$).

Outcome at Three Months

By the end of three months after randomization, 42 patients (13.6 percent) had died. Two patients in the high-dose group could not be located. The causes of death and the functional status of the remaining 264 patients are shown in Table 4. The risk ratio for a poor outcome in the high-dose group as compared with the placebo group was 0.83 (95 percent confidence interval, 0.66 to 1.05), corresponding to a reduction of 17 percent in the relative risk (95 percent confidence interval, -5 percent to 34 percent). The risk ratio for a poor outcome in the low-dose group as compared with the placebo group was 0.95 (95 percent confidence interval, 0.76 to 1.17). An observed trend favoring the effect of low-molecular-weight heparin on the outcome at three months was not statistically significant ($P=0.12$).

Outcome at Six Months

By the end of six months after randomization, 50 patients (16.2 percent) had died. One patient who could

Table 1. Base-Line Characteristics of the Study Patients According to Treatment Group.

CHARACTERISTIC	HIGH-DOSE GROUP (N=102)	LOW-DOSE GROUP (N=101)	PLACEBO GROUP (N=105)
Mean age (yr)	66.5	66.8	67.6
Sex (M/F)	62/40	55/46	63/42
Medical history (no. of patients)			
Hypertension	58	46	44
Diabetes mellitus	25	29	22
Angina or myocardial infarction	14	8	8
Stroke or transient ischemic attack	13	14	11
Smoking (no. of patients)	39	37	36
Infarct subtype (no. of patients)			
Anterior circulation, total	14	18	21
Anterior circulation, partial	40	42	39
Lacunar	41	29	40
Posterior circulation	7	12	5
Level of consciousness (no. of patients)			
Alertness	78	83	85
Drowsiness or coma	24	18	20
Cardioembolic cause of stroke (no. of patients)	17	10	16
Time to first dose (no. of patients)			
0-24 hr	40	37	35
25-48 hr	62	64	70
Mean no. of hr to first dose	27.4	27.7	27.0
Symptoms first noted on waking (no. of patients)	41	32	41
Mean blood pressure (mm Hg)			
Systolic	156	155	153
Diastolic	87	86	86

Table 2. Deaths, Complications, and Use of Nonstudy Medications during the 10-Day Treatment Period, According to Treatment Group.

VARIABLE	HIGH-DOSE GROUP (N=102)	LOW-DOSE GROUP (N=101)	PLACEBO GROUP (N=105)
<i>no. of patients</i>			
Deaths			
Initial stroke	6	8	8
Myocardial infarction	1	0	0
All*	7	8	8
Complications			
Causing early discontinuation of study drug	10	7	11
Minor gastrointestinal bleeding	5	4	3
Major gastrointestinal bleeding†	0	0	1
Hematuria	1	0	1
Dizziness	1	0	0
Perforated peptic ulcer	1	0	0
Disseminated intravascular coagulopathy	0	0	1
Deep venous thrombosis	0	0	1
Rash at injection site	0	0	1
Recurrent ischemic stroke	2	1	1
Hemorrhagic transformation‡	0	2	1
Patient's refusal to continue study	0	0	1
Noted after 10 days of treatment	7	10	15
Minor gastrointestinal bleeding	1	1	1
Major gastrointestinal bleeding†	0	1	0
Perforated peptic ulcer	0	1	0
Recurrent ischemic stroke	1	2	5
Hemorrhagic transformation‡	5	5	9
All§	17	17	26
Nonstudy medications			
Nifedipine	28	32	24
Other antihypertensive agents	8	10	13
Unfractionated heparin or antiplatelet drug	2	0	2
Glycerol or steroids	2	4	7

* $P=0.84$ by the chi-square test for trend.

†Bleeding that necessitated transfusion.

‡As observed on the second CT scan.

§ $P=0.14$ by the chi-square test for trend.

not be located at three months was found, but another patient in the high-dose group was lost to follow-up at six months. Of the 256 remaining patients, 191 were seen in person, 63 were contacted by telephone, and 2 were contacted by letter. The causes of death and the functional status of these patients are shown in Table 4. Forty-five patients (45 percent) in the high-dose group, 53 patients (52 percent) in the low-dose group, and 68 patients (65 percent) in the placebo group had poor outcomes. The risk ratio for a poor outcome in the high-dose group as compared with the placebo group was 0.69 (95 percent confidence interval, 0.54 to 0.90), corresponding to a reduction of 31 percent in the relative risk (95 percent confidence interval, 10 percent to 46 percent). The risk ratio for a poor outcome in the low-dose group as compared with the placebo group was 0.81 (95 percent confidence interval, 0.64 to 1.02). There was a significant favorable, dose-dependent effect of low-molecular-weight heparin on the outcome at six months ($P=0.005$) (Fig. 1). When the two patients lost to follow-up were included and assumed to have had poor outcomes, the P value was 0.007.

Between three and six months after randomization,

Table 3. Incidence of Hemorrhagic Transformation of the Infarct as Detected on a Second CT Scan at 10 Days, According to Treatment Group.

VARIABLE	HIGH-DOSE GROUP	LOW-DOSE GROUP	PLACEBO GROUP
	(N = 102)	(N = 101)	(N = 105)
	<i>no. of patients (%)</i>		
No second CT (n = 63)	21	20	22
None required by initial protocol*	15	17	16
Omitted; patient refused or was discharged†	1	0	2
Not done; patient died in 1st 10 days‡	5	3	4
Second CT (n = 245)	81	81	83
No hemorrhagic transformation seen			
Patient survived	75	72	70
Patient died	1	2	3
Hemorrhagic transformation seen‡	5 (6.2)	7 (8.6)	10 (12.0)

*Numbers shown do not include one patient who was excluded from the study.

†The group studied began with the 50th patient, as described in the Methods section.

‡P=0.19 by the chi-square test for trend.

the functional status of 11 patients in the high-dose group, 9 in the low-dose group, and 6 in the placebo group improved, whereas in 2, 1, and 7 patients in the respective groups the outcomes worsened. The patient who could not be located at three months but was found at six months was alive but dependent. Of the 10 patients whose conditions deteriorated, none had a change of medication between three and six months: 8 were taking aspirin, 1 in the high-dose group was taking ticlopidine because of intolerance to aspirin, and 1 in the placebo group received no antithrombotic prophylaxis because of a hemorrhagic transformation of the infarction. Eight patients died between three and six months after randomization, all of whom had been considered dependent at three months; for that reason, they did not contribute to the difference among the three groups in the percentage of poor outcomes at six months.

Effect of Patients' Characteristics

Logistic regression was used to determine which of the patients' characteristics listed in Table 1 were significant predictors of the outcome at six months, to adjust the effect of treatment for any imbalance in prognostic factors, and to study the degree to which the effect of treatment was modified by prognostically important factors. This process indicated that age ($P<0.001$), a history of diabetes mellitus ($P=0.005$), the patient's level of consciousness ($P<0.001$), and two of the four infarct subtypes (total infarct of the anterior circulation [$P=0.002$] and lacunar infarct [$P=0.01$]) had a significant predictive influence. Including the effect of treatment in a model that contained these factors decreased the P value for treatment to 0.003. Thus, the effect of treatment was slightly increased after adjustment for imbalances in prognostic factors created by randomization. In a subsequent analysis, product terms representing the interaction between each prog-

nostic factor and treatment were considered for inclusion in the model. The P value for each interaction was large, indicating that there was no real evidence that any of these factors affected the size of the treatment effect.

The effects of treatment are shown according to infarct subtype in Table 5.

Validation and Compliance

Validation of Functional Outcome

At three months, 263 of the 264 patients who were still alive were available for validation of their functional status. Among the 116 patients who had scores of 16 or less on the Barthel index, 109 were classified as dependent, whereas among the 147 patients with scores of more than 16 on that index, 118 were classified as independent. Thus, our measure of dependency had a sensitivity of 94 percent and a specificity of 80 percent as compared with a score of 16 or less on the Barthel index, a level above which the majority of patients

Table 4. Mortality and Functional Status, According to Treatment Group.*

VARIABLE	HIGH-DOSE GROUP	LOW-DOSE GROUP	PLACEBO GROUP
	(N = 100)	(N = 101)	(N = 105)
	<i>no. of patients (%)</i>		
Outcomes at 3 mo			
Died	12	15	15
During the 10-day treatment period	7	8	8
Initial stroke	4	4	1
Recurrent stroke	0	1	4
Myocardial infarction	0	0	1
Perforated peptic ulcer	1	1	0
Gastrointestinal bleeding	0	1	0
Chronic renal failure	0	0	1
Survived			
Independent			
Complete recovery	21	22	13
Incomplete recovery	26	17	22
Dependent			
Complete recovery	0	1	3
Incomplete recovery	41	46	52
All poor outcomes†	53 (53)	61 (60)	67 (64)
Outcomes at 6 mo			
Died	13	17	20
During 1st 3 mo	12	15	15
Initial stroke	1	1	3
Recurrent stroke	0	1	1
Peripheral vascular disease	0	0	1
Survived			
Independent			
Complete recovery	28	25	19
Incomplete recovery	26	22	17
Dependent			
Complete recovery	1	1	1
Incomplete recovery	32	36	48
All poor outcomes‡	45 (45)	53 (52)	68 (65)

*The number of patients with poor outcomes was calculated for each study interval by adding the number who died to the number who remained dependent and had incomplete recoveries.

†P=0.12 by the chi-square test for trend.

‡P=0.005 by the chi-square test for trend.

would be considered independent with respect to activities of daily living.²⁶

Compliance

As Table 2 shows, 10 patients in the high-dose group, 7 in the low-dose group, and 11 in the placebo group did not complete the full 10 days of treatment. At three months, 87 percent of the patients still alive were taking aspirin, and at six months 81 percent of those still alive were doing so. Five patients were taking other antithrombotic drugs at three months, and seven patients were doing so at six months. These patients were equally distributed among the three groups. No patient underwent carotid endarterectomy.

DISCUSSION

Antithrombotic therapy is commonly prescribed without a clear justification for patients with acute ischemic stroke. This clinical trial suggests that low-molecular-weight heparin may have benefits beyond the prevention of deep venous thrombosis. In a meta-analysis of randomized trials of antithrombotic therapy in patients with ischemic stroke (including four trials of low-

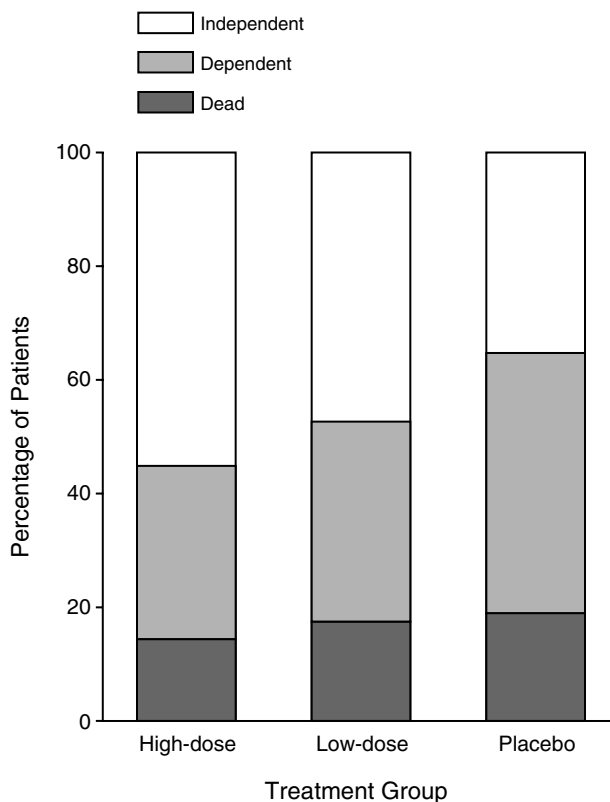


Figure 1. Outcomes of Patients in Each Treatment Group Six Months after Randomization.

There was a significant, dose-dependent reduction in the risk of death or dependency at six months among the patients treated with low-molecular-weight heparin (chi-square for trend = 8.066; $P = 0.005$).

Table 5. Effect of Treatment at Six Months According to Subtype of Infarct.

INFARCT SUBTYPE AND TREATMENT GROUP	OUTCOME	
	POOR (N = 166)	FAVORABLE (N = 140)
	<i>no. of patients</i>	
Total anterior-circulation infarct (n = 53)		
High-dose	11	3
Low-dose	17	1
Placebo	18	3
Partial anterior-circulation infarct (n = 121)		
High-dose	21	19
Low-dose	22	20
Placebo	26	13
Lacunar infarct (n = 108)		
High-dose	8	31
Low-dose	9	20
Placebo	21	19
Posterior-circulation infarct (n = 24)		
High-dose	5	2
Low-dose	5	7
Placebo	3	2

molecular-weight heparin or heparinoid in a total of 268 patients),²⁷ a significant reduction in deep venous thrombosis was found, but no reduction in pulmonary embolism or mortality. There were no data on survival free of severe disability. In this study, in contrast to previous trials, we primarily attempted to determine whether treatment reduced mortality and lessened morbidity. We used modern methods of study design, randomization, blinding, and outcome analysis. Telephone interviews, regarded as reliable means of assessing stroke outcomes,^{28,29} ensured that only two patients were lost to follow-up.

The results of this study are consistent with the hypothesis that low-molecular-weight heparin is helpful in reducing the risk of death or dependency six months after a stroke. A trend favoring an effect of low-molecular-weight heparin was found at three months, but the trend was not statistically significant at that point. Between three and six months, more treated patients than patients given placebo had improvement, and fewer treated patients had a worsening of their condition. We speculate that antithrombotic treatment may have reduced the volume of the infarct by limiting the extension of thrombus to the ischemic penumbra, which could exist for up to 48 hours after ischemic stroke,³⁰ and by maintaining blood flow in that region. Treated patients would thus have more potential for survival and recovery.

In this study, base-line characteristics, including all that were prognostically important, were distributed evenly among the three groups. Because all the personnel involved were unaware of the study assignments, the ancillary care provided during and after the treatment period was similar in the three groups. The secondary prophylaxis prescribed was equivalent in the three groups, and subsequent compliance with therapy was balanced. Hence, the only explanation for the favorable responses we observed was the effect of treat-

ment — which, incidentally, became more significant when it was adjusted for imbalances in prognostic factors created by randomization. However, the study sample was too small to allow any meaningful analysis of the effect among subgroups.

The dosage of low-molecular-weight heparin given to the high-dose group corresponded to the dose recommended to treat deep venous thrombosis. The treatment was safe; there was no significant difference between the treated patients and those given placebo in rates of hemorrhagic transformation of the infarct or other complications. Further advantages of low-molecular-weight heparin as compared with conventional unfractionated heparin include the opportunity to administer only one or two subcutaneous doses daily, a more predictable anticoagulant response to fixed doses,¹⁶ and a lower incidence of heparin-induced thrombocytopenia.³¹ Without the need for continuous infusion or laboratory monitoring, earlier mobilization of the patient and even home treatment become possible.

We conclude that low-molecular-weight heparin, given as nadroparin at a dosage of 4100 anti-factor Xa IU twice daily for 10 days, was superior to placebo in treating patients with acute ischemic stroke. Our data suggest that for every five patients so treated, one death or case of dependency may be avoided. Further clinical trials are needed to determine the optimal dosage and duration of treatment and to see whether our results can be generalized to other populations.

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