Are There Patients With Acute Ischemic Stroke and Atrial Fibrillation That Benefit From Low Molecular Weight Heparin?

Martin J. O’Donnell, MB; Eivind Berge, MD, PhD; Per Morten Sandset, MD, PhD

Background and Purpose—Treatment doses of heparins are not recommended for acute ischemic stroke. Despite this, their use in this setting is widespread. We investigated whether subgroups of patients with acute ischemic stroke and atrial fibrillation, identified by clinical, hemostatic (d-dimer, prothombin fragments [F1+2], soluble fibrin monomer), or inflammatory (C-reactive protein [CRP]) variables might have a differential response to low molecular weight heparin (LMWH) over aspirin. In addition, we sought to identify factors associated with a poor clinical outcome at 3 months.

Methods—We conducted a post hoc subgroup analysis of a randomized, placebo-controlled, double-blind trial (Heparin in Acute Embolic Stroke Trial) designed to test the hypothesis that treatment doses of LMWH (dalteparin; 100 IU/kg BID) would be superior to aspirin (160 mg per day) in patients with acute ischemic stroke and atrial fibrillation. For the current analysis, 431 participants were included. The primary outcome measure was a poor outcome at 3 months, defined as death or dependency in activities of daily living. Using regression analysis, we determined whether any of the chosen variables were associated with a differential response to dalteparin (treatment interaction) or with poor outcome.

Results—in the multivariable logistic regression model, none of the clinical, hemostatic, or inflammatory variables were associated with a significant treatment interaction. Stroke severity (odds ratio [OR], 1.09 [95% CI, 1.07 to 1.12]), increasing age (OR, 1.09 [CI, 1.05 to 1.14]), CRP level (OR, 1.32 [CI, 1.04 to 1.66]), and F1+2 level (OR, 1.77 [CI, 1.07 to 2.91]) were independently associated with a poor outcome at 3 months.

Conclusions—Our study does not support the use of treatment doses of LMWH in any of the studied subgroups of patients with acute ischemic stroke and atrial fibrillation. Age, stroke severity, CRP, and F1+2 were predictive of poor outcome at 3 months. (Stroke. 2006;37:452-455.)

Key Words: heparin ■ stroke, ischemic ■ atrial fibrillation

Numerous clinical trials have failed to demonstrate an overall benefit of treatment doses of heparin in acute ischemic stroke,1-7 and current antithrombotic guidelines do not recommend their use.8 Despite this, many clinicians continue to prescribe heparins for selected patients with acute stroke.9 In part, this practice likely reflects a belief that some patients, not adequately represented in clinical trials, may benefit from acute anticoagulant therapy.9-12 One such patient group is that with atrial fibrillation.

In the Heparin in Acute Embolic Stroke Trial (HAEST), treatment-dose low molecular weight heparin (LMWH) was compared with aspirin in patients with acute ischemic stroke and atrial fibrillation.4 This study reported no overall reduction in the frequency of recurrent stroke, death, or dependency with LMWH over aspirin therapy. The objective of the current post hoc analysis was to determine whether selected patient subgroups, identified by clinical, hemostatic or inflammatory markers, would benefit from LWMH over aspirin. Identification of such subgroups may provide information to guide further research. In addition, we sought to identify factors associated with a poor outcome at 3 months.

Materials and Methods

Heparin in Acute Embolic Stroke Trial

The HAEST study was a randomized, placebo-controlled, double-blind, trial of LMWH (dalteparin; 100 IU/kg subcutaneously, twice daily) versus aspirin (160 mg per day) among 449 patients with acute ischemic stroke and atrial fibrillation.4 Treatment was started within 30 hours of stroke and given for 14 days. The primary outcome measure was recurrent ischemic stroke during the first 14 days, or until discharge, whichever occurred first. Additional outcome measures included intracranial hemorrhage, death, and functional outcome, as measured by the Barthel index, the modified Rankin scale, and the International Stroke Trial (IST) scale at 14 days. The IST scale score was also assessed at 3 months by mail or telephone interview.

Outcome Measures and Predictor Variables

The primary outcome measure for the current analysis was an IST scale score of 3 or 4 (dependent or dead) at 3 months. This outcome
measure is clinically meaningful and was the chosen measure of functional outcome at 3 months in HAEST. Secondary outcome measures in the current analysis were recurrent ischemic stroke, progression of ischemic stroke, and death or disability at 2 weeks (modified Rankin scale score 4 to 6). D-dimer, prothrombin fragments 1+2 (F1+2), soluble fibrin monomer (s-FM), and C-reactive protein (CRP) were all collected at the time of randomization. Additional baseline clinical variables included age, gender, baseline Scandinavian Stroke Scale (SSS) score, premorbid Rankin scale score, stroke subtype (lacunar versus nonlacunar), history of diabetes mellitus, hypertension, coronary heart disease, stroke/transient ischemic attack (TIA), heart failure, previous aspirin therapy, admission glucose, and creatinine. For the current analysis, eligible participants were required to have ischemic stroke without evidence of hemorrhagic transformation and treated according to treatment allocation.

### Blood Sampling and Analysis

Whole blood was collected before randomization in 5-mL vacuum tubes (Becton-Dickinson) containing 0.5 mL buffered sodium citrate (0.129 mol/L). Plasma was prepared within 1 hour by centrifugation at 2000 × g for 15 minutes at ambient room temperature and pipetted off in plastic tubes and stored in aliquots at −70°C. Samples were subsequently transferred for analysis to Hematological Research Laboratory, Ullevål University Hospital. D-Dimer, F1+2, and s-FM were assayed with commercial enzyme immunoassays (Asserachrom D-Di from Stago; Enzygnost F1+2 from Behringwerke; and Enzymune test FM from Boehringer Mannheim).

### Statistical Methods and Analysis

We sought to determine whether certain patient subgroups might preferentially respond to LMWH. Clinical response to LMWH was defined as evidence of a statistical interaction between treatment and each of the baseline variables that favored LMWH. Therefore, we evaluated whether individual subgroup variables might significantly alter the effect of treatment, termed treatment interaction. To test for treatment interaction (univariate analysis), we generated separate models for each of the baseline variables. Each of these 19 models included the individual predictor variable (eg, previous stroke/TIA), treatment variable (ie, LMWH or aspirin), and a treatment–variable interaction term. Subsequently, individual variables and interaction terms were included in a multivariable stepwise binary logistic regression analysis if the probability was < 0.2 on univariate analysis. A probability of 0.2 was chosen to improve our ability to detect a treatment interaction, such that we would avoid excluding a potentially important interaction at the preliminary stage of the analysis. Baseline variables included in the final model were those that were significant on univariate analysis and those previously shown to predict poor outcome after stroke. Two-way interaction terms (excluding treatment variable) were sought. For all significant (P < 0.2) 2-way interactions, 3-way interactions with treatment were sought to increase our power to detect associations. Collinearity between hemostatic variable were sought, and, if present, variables were evaluated in the model separately. Finally, individual variables and interaction terms with probabilities of < 0.05 were retained in the final logistic regression model. Hemostatic and inflammatory markers were log transformed before analysis. The Hosmer-Lemeshow test for goodness of fit was performed. All analyses were performed using SPSS 11.0 for Windows.

### Results

Of 449 patients randomized in HAEST, 18 subjects were excluded from the current analysis for the following reasons: 9 patients were not treated according to treatment allocation; 3 transpired not to have a stroke; 2 subjects had hemorrhagic transformation of stroke at presentation; and 4 had parenchymatous intracranial hemorrhage. Therefore, data from 431 subjects were used in this analysis. Each of the clinical variables was available for 99% of subjects. Hemostatic/biochemical variables were available for the majority (84%) of participants with ischemic stroke. We were unable to identify a systematic reason to account for missing data, that is, participants with missing data were similar with respect to baseline variables and outcome, to the remainder of the cohort. Baseline clinical and laboratory parameters are shown in Table 1.

Of the 431 participants, 149 (34.6%) were either independent or mildly dependent (good outcome), and 282 (65.4%) were dead or dependent (poor outcome) at 3 months. Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (dalteparin vs aspirin)</td>
<td>0.95 (0.64–1.41)</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>1.09 (1.06–1.12)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Male</td>
<td>1.81 (1.21–2.71)</td>
<td>0.004*</td>
</tr>
<tr>
<td>SSS (Baseline)</td>
<td>0.91 (0.89–0.93)</td>
<td>&lt;0.004*</td>
</tr>
<tr>
<td>Lacunar vs nonlacunar stroke</td>
<td>0.73 (0.42–1.24)</td>
<td>0.2</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>1.55 (0.96–2.51)</td>
<td>0.07*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.71 (0.93–3.12)</td>
<td>0.08*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.07 (0.71–1.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Previous aspirin</td>
<td>0.96 (0.64–1.43)</td>
<td>0.8</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.41 (1.42–4.1)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.11 (0.73–1.68)</td>
<td>0.6</td>
</tr>
<tr>
<td>Systolic blood pressure (on admission)</td>
<td>1.0 (0.99–1.01)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diastolic blood pressure (on admission)</td>
<td>1.0 (0.98–1.01)</td>
<td>0.8</td>
</tr>
<tr>
<td>Premorbid Rankin scale score</td>
<td>1.97 (1.07–3.6)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Ln d-dimer (ng/mL)</td>
<td>2.25 (1.64–3.1)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Ln CRP (mg/L)</td>
<td>1.49 (1.24–1.8)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Ln F1+2 (mmol/L)</td>
<td>2.05 (1.32–3.17)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Ln s-FM (mg/L)</td>
<td>1.56 (1.28–1.89)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

*Significant P value; to be included in logistic regression model; †age variable coded in yearly increments; Ln indicates natural log.
illustrates the results of univariate analysis for individual variables. Overall, treatment was not predictive of outcome, as reported in the main publication.4 Age, gender, stroke severity (SSS), premorbid modified Rankin, previous stroke/TIA, heart failure, and the natural log of D-dimer, CRP, F1/F2, and s-FM were all associated with poor outcome at 3 months. The Figure shows the interaction terms for treatment and each of the variables in the analysis. Past history of heart failure, prerandomization aspirin therapy, and coronary heart disease showed interaction (\( P < 0.02 \)) with treatment allocation and were all associated with a better outcome in the aspirin arm in univariate analysis. When these variables were included in a stepwise multivariable regression model, none of these variables showed a significant interaction with treatment allocation. No significant treatment interaction terms were identified for each of the secondary outcome measures, that is, recurrence or progression of ischemic stroke and poor outcome (modified Rankin 4 to 6) at 2 weeks (data not shown). In the final stepwise regression model, which included 362 participants, 16 variables were included, of which 3 were treatment interaction terms. Stroke severity (odds ratio [OR], 1.09 [95% CI, 1.07 to 1.12]), age (OR, 1.09 [CI, 1.05 to 1.14]), natural log of CRP (OR, 1.32 [CI, 1.04 to 1.66]), and F1/F2 (OR, 1.77 [CI, 1.07 to 2.91]) were independently associated with a poor outcome at 3 months (Table 3). A goodness-of-fit test demonstrated no significant departure of model prediction from observed data (Hosmer and Lemeshow test; \( P = 0.8 \)).

**Discussion**

Our study failed to identify any patient subgroup that did better with treatment doses of LMWH compared with aspirin. Stroke severity, age, CRP, and F1/F2 were independently associated with a poor outcome at 3 months. A recent survey of neurologists in North America reported that the majority of those surveyed continue to prescribe treatment doses of intravenous heparin in patients with acute stroke and atrial fibrillation.9 It has been suggested that the failure of most clinical trials to demonstrate a benefit from heparins/heparinoids in acute stroke reflects discordance between patients in real life and those included in clinical trials.9,10,12 In particular, there may be concern that certain subgroups, not adequately represented in clinical trials, may benefit from anticoagulant therapy. In this study, we hypothesized that the presence of clinical factors would be associated with a preferential response to LMWH. Such factors

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**TABLE 3. Association of Baseline Variables With Poor Outcome at 3 Months (final multivariate model)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln CRP (mg/L)</td>
<td>1.32 (1.04–1.66)</td>
</tr>
<tr>
<td>ln F1/F2 (mmol/L)</td>
<td>1.77 (1.07–2.91)</td>
</tr>
<tr>
<td>SSS</td>
<td>1.09 (1.07–1.12)</td>
</tr>
<tr>
<td>Age</td>
<td>1.09 (1.05–1.14)</td>
</tr>
</tbody>
</table>

Ln indicates natural log. Hosmer and Lemeshow test \( P = 0.8 \).
include hypertension, diabetes mellitus, congestive cardiac failure function, and coronary heart disease. Similarly, we proposed that hemostatic markers, reflecting active thrombogenesis, would identify a group most likely to respond to anticoagulant therapy. Adding strength to this hypothesis, recent studies have reported that elevated levels of D-dimer appeared to discriminate cardioembolic from other stroke subtypes, and elevated hemostatic markers were associated with an increased risk of recurrent stroke and stroke progression. However, in univariate and multivariate analysis, we were unable to identify any group that did better with LMWH for any outcome measure.

The presence of atrial fibrillation is associated with greater mortality and morbidity after ischemic stroke. In this study, two thirds of patients were dead or disabled at 3 months. As expected, increasing baseline stroke severity and age was associated with a poor outcome. Elevated levels of F$_1$+$_2$ and CRP were also associated with a poor outcome at 3 months. This latter observation is, in part, consistent with previous research. A recent study reported that elevated levels of CRP are predictive of recurrent vascular events in the first year after ischemic stroke. To our knowledge, this analysis is the first to report on the relationship between CRP and short-term prognosis. Recently, a number of studies have reported an association between D-dimer levels and risk of stroke recurrence and progression. Although all 3 hemostatic variables appeared as predictors in the univariate analysis, F$_1$+$_2$ was a much stronger predictor of outcome in the final regression model than either D-dimer or FM. Overall, there is convincing evidence that hemostatic and inflammatory markers may allow identification of “high-risk” populations, which may have important implications for future research.

The main limitation of our study is reduced statistical power because of a relatively small sample size and a relatively high number of predictor variables. As a consequence, the study may have failed to detect smaller but potentially meaningful differences in treatment effect. Also, because patients already on anticoagulants were excluded from the study, there remains the possibility that there exists a particularly high-risk population of patients who were not represented in this study. The main strength of our study is that it included a homogenous sample of patients with acute ischemic stroke and atrial fibrillation, that all predictor variables were collected at baseline, and that few patients were lost to follow-up at 3 months. The baseline characteristics and the high proportion of participants with a poor outcome at 3 months suggest that they are representative of patients with acute stroke and atrial fibrillation in clinical practice.

In conclusion, our study does not support the use of treatment doses of LMWH in any subgroup of patients with acute ischemic stroke and atrial fibrillation. Age, stroke severity, CRP, and F$_1$+$_2$ are independent prognostic factors of poor outcome at 3 months.

Acknowledgments

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References

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