Prophylaxis of Thrombotic and Embolic Events in Acute Ischemic Stroke With the Low-Molecular-Weight Heparin Certoparin

Results of the PROTECT Trial

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Background and Purpose—Patients with stroke are at substantial risk of thromboembolic complications and therefore require antithrombotic prophylaxis. To show the noninferiority of the low-molecular-weight heparin certoparin to unfractionated heparin (UFH) for the prevention of thromboembolic complications, we performed a randomized, double-blind, active-controlled multicenter trial in patients with acute ischemic stroke.

Methods—Overall, 545 patients were randomized within 24 hours of stroke onset to treatment with certoparin (3000 U anti-Xa OD; n = 272) or UFH (5000 U TID; n = 273) for 12 to 16 days. Patients with paresis of a leg and an National Institutes of Health Stroke Scale score of 4 to 30 points were included. The primary end point was a composite outcome of proximal deep vein thrombosis, pulmonary embolism, or death related to venous thromboembolism during treatment. Computed tomography was performed at trial entry, after 7 days, and when clinical deterioration occurred.

Results—The per-protocol analysis revealed 17 (7.0%) primary events in the certoparin group compared with 24 (9.7%) in the UFH group, thereby demonstrating noninferiority (P = 0.0011), confirmed by intention-to-treat analysis (6.6% versus 8.8%; P = 0.008). Major bleeding occurred during treatment in 3 patients allocated to certoparin (1.1%) and 5 patients allocated to UFH (1.8%).

Conclusions—Certoparin (3000 U anti-Xa OD) is at least as effective and safe as UFH (TID) for the prevention of thromboembolic complications in patients with acute ischemic stroke. (Stroke. 2006;37:139-144.)

Key Words: cerebrovascular accident ■ heparin ■ venous thrombosis

Venous thromboembolic complications occur frequently in patients with acute ischemic stroke, in particular in patients with leg weakness or patients who are confined to bed. Without prophylaxis, deep vein thrombosis (DVT) occurs in 20% to 75% of stroke patients, and 2% of the patients experience pulmonary embolism (PE). In 1984, when heparin was used only sporadically, PE was diagnosed in 52% of the patients on postmortem examination; in 1988, only 27% of the patients who died after stroke had PE. In recent studies investigating the use of aspirin versus no aspirin or placebo in the acute phase of stroke, the rate for symptomatic PE was 0.1% to 0.8%. Over the last decade, it has been clearly shown that stroke patients who are managed in an organized stroke unit are less likely to die, require institutional care, or have long-term dependency when compared with general ward management. Stroke unit care may also reduce DVT frequency.

Prophylaxis of thrombosis is performed with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). A few trials have compared either UFH or LMWH with a control group without anticoagulation, but only the trial of Hillbom et al performed a head-to-head comparison of UFH versus LMWH. This trial showed promising results for the LMWH. In the past, heparins or heparinoids were given on the assumption that they improved the outcome after stroke and not primarily for the prevention of thromboembolic complications. However, the concept of improved outcome after stroke by inhibiting thrombus growth and preventing early stroke recurrence has been disproved in a number of studies.
The rationale for using LMWH compared with UFH is the easier use (one dose per day) and the well-known tendency for fewer bleeding complications. The primary objective of the PROphylaxis of Thromboembolic Events by Certoparin Trial (PROTECT) was to compare the LMWH certoparin with UFH standard prophylaxis for the prevention of thromboembolic complications in acute ischemic stroke. The dose of certoparin was chosen on the basis of the safety trial Therapy of Patients with Acute Stroke (TOPAS).\textsuperscript{17} TOPAS suggested that a dose of 3000 U anti-Xa of certoparin was safe in patients with stroke and effective in preventing venous thromboembolism (VTE).

### Patients and Methods

#### Study Design

PROTECT was a randomized, double-blind, active-controlled, parallel group multicenter trial. PROTECT was performed in 37 centers in the European Union. The study was approved by all local institutional ethics committees and was undertaken in accordance with the Declaration of Helsinki. All patients gave written informed consent. The study was sponsored by Novartis (Nürnberg, Germany). Novartis was responsible for site monitoring, data management, and statistical planning and analysis. The study was supervised by a steering committee. An independent Safety Committee monitored safety to recognize any unacceptable risks for continuation of the trial. The members of all committees had full access to the data and had full control over the right to publish.

#### Patients and Treatment

PROTECT included men and women 18 to 85 years of age who had a clinical diagnosis of acute ischemic stroke. The severity of the underlying stroke was defined by a score on the National Institutes of Health Stroke Scale (NIHSS) of 4 to 30 with a mild to severe paresis of a leg. Patients had to be treated within 24 hours of symptom onset. Exclusion criteria were: indication for thrombolysis, no availability of computed tomography (CT), CT-documented signs of intracerebral or subarachnoidal hemorrhage, current bleeding or thrombosis, history of bleeding or thrombosis within the last 12 months, recurrent gastrointestinal ulcerations, post-thrombotic syndrome, acute or unstable cardiovascular disease, major infection, currently active, recurrent or metastatic cancer within the last 5 years, platelet count $<$ 75 000/μL at baseline, known hypersensitivity to heparin, known severe diabetic retinopathy, and an estimated body weight $<$ 55 kg. Pregnant or breastfeeding women were not included.

Eligible patients were randomized to certoparin (3000 U anti-Xa subcutaneously injected once daily plus 2 injections of placebo) or UFH (5000 U UFH 3 times daily) according to computer-generated lists provided by Novartis and allocated to the lowest available randomization number. Randomization data were kept strictly confidential, accessible only to authorized persons until the time of unblinding. Duration of treatment was 12 to 16 days. A follow-up visit was performed after 3 months. Administration of ticlopidine, clopidogrel, or aspirin alone ($\geq 325$ mg daily) or in combination with dipyridamole was allowed.

#### Computed Tomography

CT was performed at baseline before randomization, routinely at days 7 to 8, and anytime in the case of clinical deterioration or suspicion of intracranial hemorrhage. An independent neuroradiologist blinded to clinical information, time of stroke onset, and treatment allocation evaluated all CT scans. Hemorrhagic transformation of brain tissue was classified by radiological criteria according to Pessin et al\textsuperscript{18} as either hemorrhagic infarction or parenchymal hemorrhage.

#### Outcome Measures

The primary end point was a composite outcome consisting of symptomatic or asymptomatic proximal DVT, symptomatic PE, or death related to VTE occurring during treatment. Patients were screened for DVT by duplex and compression ultrasonography at baseline, at days 3 to 4, at days 7 to 8, and at days 12 to 16, or when clinical symptoms occurred. Compression sonography was performed for both legs by a certified sonographer according to a standardized protocol. Documentation of the paretic leg included cross-sectional views of the respective veins with and without compression. For the common femoral vein also, a longitudinal view...
including breath-modulated blood flow was documented. Sonography was also performed for the nonparetic leg, but documentation was only required if thrombosis was found. An independent end point committee consisting of 2 external experts blinded to treatment allocation evaluated sonograms of all patients and decided if DVT had occurred or not. PE had to be diagnosed by ventilation/perfusion lung scan, pulmonary angiography, spiral CT, or other appropriate tools. NIHSS ratings were performed by the local investigators at baseline, at days 7 to 8, at days 12 to 16, and after 3 months.\(^{19,20}\)

Bleeding was classified as major if it was intracranial (only if parenchymal), retroperitoneal or gastrointestinal, resulted in death, was clinically overt and led to transfusion of \(\geq 2\) U of packed red cells/whole blood, or was associated with a fall in hemoglobin level of \(\geq 2\) g/dL. Bleedings that did not meet the criteria above were classified as minor.

**Statistical Analysis**

The primary objective was to demonstrate noninferiority of certoparin versus UFH in the rate of thromboembolic events occurring during treatment. This limit was derived from a pooled analysis of trials investigating the efficacy of heparin versus placebo.\(^ {21}\) All confirmatory testing was performed using the per-protocol approach; however, for sensitivity reasons, intention-to-treat results were also considered. \(P\) values and their corresponding CIs were based on the method of Blackwelder.\(^ {22}\)

Assignment of patients to the populations analyzed was performed before data bank lock, unblinding of the treatment code, and start of data analysis. The safety population (identical to the intention-to-treat population) included all randomized patients who received \(\geq 1\) dose of study medication. The per-protocol population included all intention-to-treat patients who had a final assessment after double-blind treatment without major protocol violation or who experienced a primary end point before a major protocol violation occurred. Protocol violations were determined in detail by a review committee before unblinding. The sample size of 500 evaluable patients was based on expected incidence rates of thromboembolic events of 7.4\% under LMWH and 9.3\% under UFH, which would result in a power of \(>80\%\) to reject the hypothesis of inferiority of LMWH at a one-sided significance level of 2.5\% with a noninferiority margin of 5\%. Demographic data and NIHSS scores were presented as mean±SD.

**Results**

Between January 2001 and September 2003, a total of 545 patients were randomized, 272 patients were allocated to certoparin, and 273 to UFH (Figure). A total of 490 patients were available for per-protocol analyses: 242 patients in the certoparin group and 248 patients assigned to UFH.

Baseline characteristics were well balanced between the 2 treatment groups (Table 1). However, with respect to the medical history, significantly more patients with cardiac failure were allocated to certoparin compared with UFH (2\% \(P\) = 0.013; Fisher exact test). Additionally, there was a tendency for more patients with myocardial infarction or severe respiratory disorders within the certoparin group. Duration of treatment with study medication was 13.6±3.2 days. Patients received platelet aggregation inhibitors as concomitant medication as follows: aspirin, certoparin group 77.2\% versus UFH group 78.4\%; aspirin in combination with dipyridamole, 12.1\% versus 11.7\%; clopidogrel, 16.9\% versus 17.6\%; and ticlopidine, 2.9\% versus 4.4\%.

As shown in Table 2, the primary efficacy end point occurred in 17 patients in the certoparin group (7.0\%) and 24 patients in the UFH group (9.7\%; per-protocol population). This result demonstrates the one-sided equivalence of certoparin to UFH for the predefined limit of noninferiority of 5\% \(P\) value = 0.0011; 97.5\% CI, –100.0, 2.2) as well as up to a limit of noninferiority of 3\% \(P\) value = 0.0117; 97.5\% CI, –100.0, 2.2). The hypothesis of noninferiority was confirmed by the intent-to-treat analysis: 6.6\% of the patients allocated to certoparin and 8.8\% of the patients allocated to UFH had an efficacy end point (limit of noninferiority of 5\%; \(P\) value = 0.0008; 97.5\% CI, –100.0, 2.3; limit of noninferiority of 3\%; \(P\) value = 0.0117; 97.5\% CI, –100.0, 2.3). Nonfatal PE did not occur in any group. For 1 patient, the investigator suspected PE as the most likely cause of death because increased D-dimers were measured, but no signs for a cardiac etiology were found. However, an autopsy was not performed. The end point committee (blinded to treatment allocation) decided to count this case as an end point because PE as a cause of death could not be definitely excluded.

There were no differences in the absolute improvement of NIHSS over time between the treatment groups (mean±SD): certoparin/UFH, 8.7±4.0/8.2±3.6 at baseline, 6.6±4.7/6.0±4.1 at day 7 to 8, 5.5±4.7/5.0±4.1 at day 12 to 16, and 3.5±3.8/3.4±3.4 after 3 months. There were also no differences in the NIHSS item “Motor leg,” indicating a similar recovery of paresis in both treatment groups. Progressive or recurrent ischemic strokes were diagnosed in 4.8\% of patients in each treatment group during the entire study up to the 3-month visit.

Bleeding complications occurred during treatment in 3.7\% of patients of each treatment group (Table 3). Major bleeding occurred in 3 patients allocated to certoparin (1.1\%); two of

**TABLE 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Certoparin n=272</th>
<th>UFH n=273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.3±10.9</td>
<td>67.3±10.6</td>
</tr>
<tr>
<td>Men</td>
<td>149 (54.8%)</td>
<td>164 (60.1%)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>77.9±14.1</td>
<td>78.4±13.3</td>
</tr>
<tr>
<td>Body mass index, kg/m^2</td>
<td>27.4±4.6</td>
<td>27.1±3.9</td>
</tr>
<tr>
<td>NIHSS</td>
<td>8.7±4.0</td>
<td>8.2±3.6</td>
</tr>
<tr>
<td>Leg paresis†</td>
<td>2.1±0.9</td>
<td>2.0±0.9</td>
</tr>
<tr>
<td>Grade 1</td>
<td>86 (31.6%)</td>
<td>91 (33.3%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>108 (39.7%)</td>
<td>110 (40.3%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>55 (20.2%)</td>
<td>55 (20.1%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>23 (8.5%)</td>
<td>17 (6.2%)</td>
</tr>
<tr>
<td>Time-to-treatment, h</td>
<td>15.4±7.2</td>
<td>15.4±6.2</td>
</tr>
<tr>
<td>Infarction in carotid territory</td>
<td>256 (94.1%)</td>
<td>251 (91.9%)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>42 (15.4%)</td>
<td>37 (13.6%)</td>
</tr>
<tr>
<td>Previous transient ischemic attack</td>
<td>10 (3.7%)</td>
<td>7 (2.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>210 (77.2%)</td>
<td>207 (75.8%)</td>
</tr>
<tr>
<td>Previous cardiac failure</td>
<td>21 (7.7%)</td>
<td>8 (2.9%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>23 (8.5%)</td>
<td>15 (5.5%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>81 (29.8%)</td>
<td>71 (26.0%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>51 (18.8%)</td>
<td>48 (17.6%)</td>
</tr>
<tr>
<td>Previous severe respiratory disorders</td>
<td>20 (7.4%)</td>
<td>13 (4.8%)</td>
</tr>
<tr>
<td>Previous thrombosis</td>
<td>6 (2.2%)</td>
<td>9 (3.3%)</td>
</tr>
</tbody>
</table>

Mean±SD. †Motor leg score of NIHSS: grade 0, no drift; grade 1, leg drifts, but does not hit bed; grade 2, some effort against gravity; grade 3, no effort against gravity; grade 4, no movement.
these were parenchymal hemorrhages. Another patient experienced hematuria with a drop of hemoglobin of 2 g/dL. For the UFH group, overall, 5 hemorrhages were classified as major ones (1.8%): 3 patients with parenchymal hemorrhages (1 patient’s bleeding was not revealed by routinely performed CT, but massive intracerebral bleeding was shown by autopsy 2 days later); and 2 patients with gastrointestinal hemorrhages from duodenal ulcer. Intracranial bleeding was fatal in 1 patient in each treatment group.

Heparin-induced thrombocytopenia was suspected in 1 patient in the certoparin group (0.4%) and 2 patients in the UFH group (0.7%). However, no measurement of antibodies was performed in any of the cases. One of the patients allocated to UFH experienced proximal and distal DVT after a drop in platelet count to 48 000/μL. Study medication was stopped, and the patient was treated with hirudin.

Altogether, 14 patients died during treatment, 7 patients in each treatment group (2.6%; Table 4). As expected, the most frequent reason was progression or recurrence of stroke. At 3 months, the mortality rate within the certoparin group was 7.7% compared with a rate of 5.5% in the UFH group.

**Discussion**

This is the second randomized, double-blind study to compare efficacy and safety of a LMWH with UFH in the prevention of thromboembolic events in patients with ischemic stroke. It is also the only study performing routine duplex and compression ultrasonography of the legs at the beginning and during treatment. In contrast to previous studies, the dose of certoparin in this trial was selected on the basis of a safety trial in stroke patients. PROTECT shows noninferiority for certoparin compared with UFH, with a nonsignificant trend for superiority. Major intracranial or extracranial bleeding complications as well as thrombocytopenia were slightly less frequent with certoparin than with UFH. PROTECT had no placebo group, a decision that was drawn with respect to the possible severe consequences. We are therefore unable to draw any conclusions as to whether either of the 2 prophylactic drugs would exert any benefit on the functional outcome of stroke.

The only other trial, by Hillbom et al, included 212 patients who were randomized to enoxaparin 40 mg once daily versus 5000 IU of UFH 3× daily. The end point was the occurrence of a thromboembolic event confirmed by venography during treatment. Thromboembolic events occurred in 19.7% of patients with enoxaparin and in 34.7% of patients treated with UFH. It is worthwhile to note that the frequency of thromboembolic events was less in PROTECT compared with the study by Hillbom et al. However, it may be difficult to compare the patient populations of PROTECT and of the study by Hillbom et al, especially regarding the neurological impairment at baseline. In the study by Hillbom et al, more disabled patients were included, explaining the higher rates of thrombosis compared with PROTECT. With respect to bleeding complications, both studies used routine CT scanning after stopping the study treatment or at days 7 or 8, respectively, to investigate the occurrence of parenchymal bleeding.

**TABLE 4. Mortality and Causes of Death**

<table>
<thead>
<tr>
<th></th>
<th>Certoparin</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=272</td>
<td>n=273</td>
</tr>
<tr>
<td>Treatment period</td>
<td>7 (2.6%)</td>
<td>7 (2.6%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up</td>
<td>14 (5.1%)</td>
<td>8 (2.9%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>4 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Pneumonia/sepsis</td>
<td>4 (1)</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>1</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*(n) autopsy was performed and confirmed cause of death.*
Hemorrhage rates were similar in both trials. It should be considered that nearly all patients received aspirin, aspirin plus dipyridamole, or clopidogrel for secondary prophylaxis. It is unknown how the concomitant administration of platelet aggregation inhibitors influences the rate of thrombosis or bleeding.

There are several ways of documenting silent or clinically apparent DVT in stroke patients. We decided to use ultrasound for the diagnosis of proximal DVT, which is noninvasive, and, in contrast to venography, does not carry the burden of x-ray films and allows for blinded evaluation by tape recording. Ultrasound also allows investigating patients repeatedly. The use of this method is in accordance with European guidelines.

In the certoparin group, the mortality rate at 3 months, but not during treatment, was slightly higher compared with the UFH group. No particular cause of death was ascertained, but it should be taken into consideration that more patients in the certoparin group experienced cardiac failure, myocardial infarction, and severe respiratory disorders in their medical history than the patients in the UFH group. The overall mortality rate of 6.6% at 3 months was remarkably low compared with the rate in the study by Hillbom et al (23.1%). The most likely explanation for the difference in mortality is the fact that in PROTECT most patients were treated in a stroke unit, whereas the Hillbom study was performed between 1992 and 1994, at a time when stroke care was less sophisticated than today. Furthermore, the patients of the present study were started with thromboprophylaxis 1 day earlier than in the study of Hillbom et al, the patients were allowed concomitant drug treatment (ticlopidine, clopidogrel, and aspirin alone or in combination with dipyridamole), and more cases with mild and rapidly disappearing leg paresis were perhaps included. Other trials investigating heparins or heparinoids showed mortality rates of 6.6% (Triap of Org 10172 in Acute Stroke Treatment [TOAST]), 11.8% (Tinzaparin in acute ischaemic stroke [TAIST]), 17.9% (Heparin in Acute Embolic Stroke Trial [HAEST]), and 26.9% (Fraxiparine in Ischaemic Stroke Study [FISS] bis). In TOPAS, the mortality rate within the treatment arm with low-dose certoparin (3000 U anti-Xa) was 4.0%. In summary, our data show that VTE remains common in acute stroke patients, even in modern organized stroke management wards. The LMWH certoparin was at least as effective as UFH, with a comparable safety profile. Additionally, thromboprophylaxis with certoparin is easier to use because it is administered only once a day, and dosage is independent of body weight.

Appendix

Committees

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References

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