Emerging Therapies

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Considering the Role of Heparin and Low-Molecular-Weight Heparins in Acute Ischemic Stroke

Majaz Moonis, MD, MRCP, DM; Marc Fisher, MD

Background and Purpose—The utility of parenteral anticoagulation therapy in acute ischemic stroke has engendered much controversy and discussion. Recent studies of low-molecular-weight heparins in multiple acute stroke subtypes have not demonstrated improved outcome or reduced recurrence risk. Beneficial treatment effects may occur in subgroups such as patients with large artery atherothrombotic stroke, but further studies will be needed to prove this possibility.

Summary of Review—The benefits of unfractionated intravenous heparin for reducing early stroke recurrence and improving outcome remain to be established, with the current lack of appropriately powered trials in stroke subgroups at high risk for such early recurrence. To most clinicians, the primary reason to use early intravenous anticoagulation is to prevent early stroke recurrence, not to improve outcome of an established stroke. Unfortunately, effects of reduction of recurrent stroke risk may be counterbalanced by a substantial increased risk of intracerebral hemorrhage with intravenous anticoagulation.

Conclusions—Unfractionated intravenous heparin should therefore not be used routinely in acute ischemic stroke, but it may be considered in select stroke groups at high risk for early recurrent ischemic events (ie, patients with atrial fibrillation or acute myocardial infarction and large mural thrombi). However, even in these select populations, new clinical trials will be needed to define the risk-benefit ratio. (Stroke. 2002;33:1927-1933.)

Key Words: anticoagulants ■ heparin ■ stroke, acute ■ stroke, ischemic ■ warfarin

While the role of oral anticoagulants is clearly established in the prevention of recurrent cardioembolic stroke, anticoagulation with parenteral unfractionated intravenous heparin (UFIH) and low-molecular-weight heparin (LMWH) for acute ischemic stroke remains an area of ongoing controversy with strong proponents and critics.1–6 The use of UFIH and LMWH has been hampered by a lack of knowledge about a number of relevant variables such as the precise risk of early recurrent stroke (RS), the effect of UFIH and LMWH on recurrence risk, the natural history for the risk of secondary hemorrhagic conversion (SHC) and the effect of heparin on this risk, and the effects of UFIH and LMWH on improving stroke outcome. This review will present relevant information about these topics and provide suggestions about the potential use or nonuse of UFIH and LMWH in the setting of acute ischemic stroke.

Risk of Recurrent Stroke After an Acute Ischemic Stroke
The outcome of a stroke study with anticoagulation should compare the risk of stroke recurrence in the treated and placebo group. As was eloquently stated by Albers, “If the end point of a stroke study is not stroke, the real risk of recurrent strokes and the treatment effects tend to be obscured.”7

The precise risk of early recurrence within the first 2 weeks after an initial ischemic stroke remains unclear. This is an important issue, since UFIH is mainly utilized during this time period. Several earlier retrospective studies indicated that the RS risk might be as high as 10% to 20% in the first 2 weeks.8–12 More recently, Sacco et al demonstrated that while the overall risk of early RS within the first 30 days is 3.3%, this increased to 8.5% with the co-existence of hyperglycemia and hypertension.13 Data from large, multicenter studies revealed that the overall risk of RS may have been overstated in the past. In the placebo arm of the International Stroke Trial (IST; n=4859), Trial of ORG 10172 in Acute Ischemic Stroke (TOAST; n=628), and the Chinese Acute Stroke Trial (CAST; n=10 320), the early recurrence risk was 4.4%, 1.1%, and 2.5%, respectively.14,15 In the subgroup of patients with atrial fibrillation (AF) in the placebo arm of the TOAST study, the RS risk in the first week was 4.5%.16 This is similar to the recurrence rate of 4.9% (half of the overall 9.9%) seen in the first 14 days in the Treatment of Patients with Acute Ischemic Stroke (TOPAS) trial.17 These results are consistent with a large, multiethnic study, the...
Northern Manhattan Stroke Study, which observed an RS rate of 6% within the first month. A recently completed double-blind, multicenter study of low-molecular-weight heparin (dalteparin) in acute ischemic stroke and atrial fibrillation (Heparin in Acute Embolic Stroke Trial [HAEST]) found the risk of RS in the placebo group over the first 7 days to be as high as 8.5%.18

Recurrent Stroke After Acute Anticoagulation (UFIH and LMWH)

Even if the incidence of recurrent ischemic strokes is relatively high within subgroups of acute ischemic stroke (cardioembolic stroke, first or recurrent strokes following acute myocardial infarction) within the first 2 weeks of onset, an important issue to consider is whether intervention with UFIH or LMWH is helpful in reducing the risk of recurrent stroke. Data from large, multicenter studies suggests that there may be a significant risk reduction. However, this is counterbalanced by an increased incidence of symptomatic intracerebral and extracerebral hemorrhage. The IST study demonstrated a small overall reduction of recurrent ischemic stroke in patients treated with subcutaneous heparin. This small, statistically significant reduction of 0.9% was counterbalanced by a similar increase in serious extracranial bleeding (0.9%) and a significant increase in the risk of hemorrhagic stroke (0.8%). The nonblinded nature of this study raises the question of a possible systemic bias against heparin. Without a strict requirement for pretreatment CT scans, intracerebral hemorrhages and hemorrhagic infarcts may have been included. Patient monitoring with activated partial thromboplastin time (aPTT) was not required, and this may have been another factor that contributed to the excess bleeding. Finally, patients on heparin may have been more closely observed for signs of bleeding. Interestingly, the low-dose heparin (5000 U twice daily) group was associated with a significant 1.2% reduction in early death or stroke without an increase in the rate of transfused or extracranial bleeds.14,19 Prospective, double-blinded studies of LMWH have revealed a similar incidence of early stroke recurrence in the placebo and treated groups, suggesting that LMWH are not useful in preventing early stroke recurrence (Table 1).

Patients with a recent anterior wall myocardial infarction (AMI), left atrial thrombi, or ventricular thrombi are at a significantly higher risk of embolism in the first 2 weeks following the initial event.20 Mobile or protruding thrombi were associated with a >50% risk of RS. Heparin in the early periods following an AMI reduces the incidence of subsequent cardioembolism. Anticoagulation before detection of thrombi is more effective than its use after thrombus formation.20 Johannessen found a 37% rate of thrombus formation in 150 consecutive patients with acute myocardial infarction within 7 days.21 Anticoagulation initiated after thrombi were detected still resulted in a 33% risk of peripheral emboli, emphasizing that anticoagulation initiated early before thrombus formation may be more effective in stroke prevention in this group.

In a similar study of 53 patients with acute anterior wall myocardial infarction, Johannessen et al anticoagulated 26 patients with UFIH and followed the remaining 27 patients who did not have any intervention. Intraventricular thrombus formation was seen in 7 control patients and in none of the treated group. In another small prospective study, the investigators evaluated the risk of intracardiac thrombus formation and RS in 25 patients with a cardioembolic stroke. Seven were treated with UFIH within 2 days and 18 were not. At 1 week, almost 40% in the control group had developed large intracardiac thrombi and 3 of the 18 patients had developed a recurrent stroke. While this was an unblinded small study, it suggests that the risk of not treating cardioembolic strokes with early anticoagulation may be substantial.26

These observations suggest that the risk of recurrence within the first few days of an ischemic stroke is not uniform across all stroke subtypes and that patients with cardioembolic stroke, especially AF, may be at a higher risk, which

### TABLE 1. Risk of Early Recurrent Stroke Within the First 4 Weeks in Patients With Acute Ischemic Stroke: Results From Prospective Randomized Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, n</th>
<th>Period, d</th>
<th>All Patients RS (%)</th>
<th>Cardioembolic RS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IST (placebo)</td>
<td>4859</td>
<td>14</td>
<td>214 (4.4)</td>
<td>4.9</td>
</tr>
<tr>
<td>TOAST (placebo)</td>
<td>628</td>
<td>7</td>
<td>7 (1.1)</td>
<td>1.6</td>
</tr>
<tr>
<td>CAST (placebo)</td>
<td>10,320</td>
<td>28</td>
<td>258 (2.5)</td>
<td>1</td>
</tr>
<tr>
<td>IST (low dose)</td>
<td>2429</td>
<td>14</td>
<td>78 (3.2)</td>
<td>3.6</td>
</tr>
<tr>
<td>IST (high dose)</td>
<td>2426</td>
<td>14</td>
<td>86 (3.5)</td>
<td>3.6</td>
</tr>
<tr>
<td>TOAST (danaparoid)</td>
<td>638</td>
<td>7</td>
<td>7 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>TOPAS (certoparin)</td>
<td>404</td>
<td>12–16</td>
<td>20 (4.9)</td>
<td>Not described</td>
</tr>
<tr>
<td>HAEST (dalteparin)*</td>
<td>244</td>
<td>14</td>
<td></td>
<td>8.5%</td>
</tr>
<tr>
<td>TAIST (tinzaparin) high dose</td>
<td>487</td>
<td>16 (3.3)</td>
<td>Not described</td>
<td></td>
</tr>
<tr>
<td>TAIST low dose</td>
<td>505</td>
<td>14</td>
<td>22 (4.5)</td>
<td>Not described</td>
</tr>
</tbody>
</table>

RS indicates recurrent stroke; IST, International Stroke Trial; TOAST, Trial of ORG 10172 in Acute Ischemic Stroke; CAST, Chinese Acute Stroke Trial; TOPAS, Treatment of Patients With Acute Ischemic Stroke; HAEST, Heparin in Acute Embolic Stroke Trial; TAIST, Tinzaparin in Acute Ischemic Stroke trial.

*Patients with cardioembolic stroke.

†IST: high dose = 12 500 U twice a day. Low dose included 5000 U twice a day.
may have been masked by the large number of patients with other stroke diagnosis included in these randomized studies. Furthermore, in the larger prospective studies, the presumably higher risk sub-groups of patients with carotid or vertebral artery dissection, severe left ventricular dysfunction, left heart thrombi and intracranial venous strokes were not adequately represented. Therefore in these studies, the risk of recurrent stroke cannot be assessed in patients with these stroke etiologies. Additional, large prospective studies are clearly needed to define the precise risk of RS in a variety of ischemic stroke subtypes. When recurrence risk for these stroke subtypes is more precisely known, then carefully designed and adequately powered acute anticoagulation trials to hopefully determine which stroke subtypes are conclusively benefited by the use of UFIH or LMWH can be designed.

Secondary Hemorrhagic Conversion
The current classification of SHC recognizes 2 main types, hemorrhagic infarction (HI) and parenchymal hematoma (PH). HI appears as a petechial, nonconfluent areas of increased attenuation on CT and is usually confined to the region of the affected ischemic arterial territory. PH occur as a discrete, dense, homogenous collection of blood often associated with mass effect and with clinical deterioration. Several retrospective and prospective studies revealed that up to 6% to 30% of presumed cardioembolic strokes underwent spontaneous acute HI. The incidence in an MRI series was even higher at 50% to 60%. These HI were largely asymptomatic, as suggested by several open, labeled prospective series that demonstrated that the occurrence of HI in most cases was not clinically significant. PH associated with clinical deterioration is less common (1.5% to 7.8%) than HI.

In the 3 large, prospective studies of anticoagulation and antiplatelet therapy—ie, the IST, CAST, and TOAST trials—the risk of symptomatic SHC in non-anticoagulated patients (the placebo arms of these studies) was considerably lower than in the nonclinical trial setting. The IST control group included 4859 patients. Symptomatic intracranial hemorrhage occurred in 15 patients (0.3%). The CAST placebo arm included 10 320 patients with acute ischemic stroke. Ninety-three (0.9%) patients sustained an acute symptomatic SHC. Of the 628 patients randomized to no treatment in the TOAST study, symptomatic SHC occurred in only 0.8%. The incidence of SHC in untreated acute ischemic stroke patients may have been overstated in the past, and evidence from the placebo arms of these 3 large multicenter studies—ie, IST, CAST, and TOAST—suggests a lower incidence (Table 2).

Table 2. Secondary Hemorrhagic Conversion in Acute Ischemic Stroke: Results From Prospective Double-Blinded Placebo Controlled Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Incidence of Spontaneous Symptomatic SHC (placebo arm of the trials)</th>
<th>Symptomatic SHC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IST</td>
<td>4859</td>
<td>14</td>
</tr>
<tr>
<td>CAST</td>
<td>10 320</td>
<td>28</td>
</tr>
<tr>
<td>TOAST</td>
<td>628</td>
<td>7</td>
</tr>
</tbody>
</table>

Symptomatic SHC (heparin trials)

| IST high dose (SC)*    | 2426                                                                   | 14                  |
| IST low dose (SC)*     | 2429                                                                   | 14                  |
| Chamorro et al (UFIH)†‡| 231                                                                    | 5–9                |

Symptomatic Hemorrhage (LMWH)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Incidence of Spontaneous Symptomatic SHC (placebo arm of the trials)</th>
<th>Symptomatic SHC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOAST</td>
<td>638</td>
<td>7</td>
</tr>
<tr>
<td>HAEST†</td>
<td>224</td>
<td>14</td>
</tr>
<tr>
<td>TOPAS§</td>
<td>404</td>
<td>12–16</td>
</tr>
<tr>
<td>TAIST (high dose)</td>
<td>487</td>
<td>14</td>
</tr>
<tr>
<td>TAIST (low dose)</td>
<td>508</td>
<td>14</td>
</tr>
</tbody>
</table>

SHC indicates secondary hemorrhagic conversion; IST, International Stroke Trial; CAST, Chinese Acute Stroke Trial; TOAST, Trial of ORG 10172 in Acute Ischemic Stroke; SC, subcutaneous; UFIH, unfractionated intravenous heparin; LMWH, low-molecular-weight heparin; HAEST, Heparin in Acute Embolic Stroke Trial; TOPAS, Treatment of Patients with Acute Ischemic Stroke; TAIST, Tinzaparin in Acute Ischemic Stroke trial.

†All patients with cardioembolic stroke.
‡Nonblinded, non-placebo-controlled case series.
§Did not include a placebo group.

The incidence of SHC is higher in patients with atrial fibrillation and stroke with early UFH. Twenty-eight percent of patients had an excellent outcome. This improved outcome was associated with younger age, normal baseline CT scan, lower ischemic scores at baseline, and early heparinization. Recurrent strokes occurred more commonly in patients with a less intense partial thromboplastin time (PTT) as compared with the PTT in patients without recurrent ischemic events. The investigators suggested that UFH might have other properties aside from anticoagulation effects that could influence the outcome after an ischemic stroke. The authors concluded that treatment with UFH should not be withheld in patients with stroke and nonvalvular atrial fibrillation. The study was at best inconclusive, in that it was limited to patients with atrial fibrillation, did not have a control group, and was open labeled.

The IST randomized 19 435 patients to subcutaneous heparin in doses of 5000 U and 12 500 U twice daily or no heparin with or without aspirin (325 mg/d) and demonstrated no overall benefit on outcome of acute ischemic stroke with placebo for 7 days within 48 hours after stroke onset, no treatment effect was found. The investigators did not report any symptomatic intracranial or extracranial hemorrhages in the treated groups. In the only study suggesting an improved stroke outcome with UFH, Chamorro et al treated 231 patients with atrial fibrillation and stroke with early UFH. Twenty-eight percent of patients had an excellent outcome. This improved outcome was associated with younger age, normal baseline CT scan, lower ischemic scores at baseline, and early heparinization. Recurrent strokes occurred more commonly in patients with a less intense partial thromboplastin time (PTT) as compared with the PTT in patients without recurrent ischemic events. The investigators suggested that UFH might have other properties aside from anticoagulation effects that could influence the outcome after an ischemic stroke. The authors concluded that treatment with UFH should not be withheld in patients with stroke and nonvalvular atrial fibrillation. The study was at best inconclusive, in that it was limited to patients with atrial fibrillation, did not have a control group, and was open labeled.
subcutaneous heparin. However, an absolute reduction in the end point of death at 14 days and death or dependency at 6 months was noted in the high-dose subcutaneous heparin group, but this was counterbalanced by a similar increase in HI. When the low-dose subcutaneous heparin group alone was compared with the no-heparin group, there was a significant reduction in early death or stroke in the heparin group (10.8% versus 12%, 2P=0.03). This corresponded to 12 fewer deaths per thousand, with only a slight increase of transfused or fatal extracranial bleeds that was not significant. In the subcutaneous heparin groups, there was a lower incidence of pulmonary embolism (0.8%). While this would be consistent with other studies demonstrating reduction of deep vein thrombosis and pulmonary embolism with low-dose subcutaneous heparin, underreporting may have contributed to the observed low incidence. Symptomatic intracranial hemorrhage was seen in 0.65% of the low-dose group (5000 U twice daily) and 1.8% of the high-dose group (12 500 U twice daily). Since the study included 33% of patients treated with heparin before a CT scan was done, the subsequent HI rate may have in part been falsely attributed to the use of subcutaneous heparin because spontaneous HI may have been present in some cases even before the heparin was started. Furthermore, aPTT monitoring was not required in this study and may have resulted in an increased risk of HI.

Overall, prospective outcome studies of LMWH in acute ischemic stroke, including the large TOAST study, failed to show any difference in functional outcome in the treated group compared with placebo. An early study of LMWH, the Fraxiparine in Acute Ischemic Stroke Study (FISS), performed at one center in Hong Kong, compared 2 doses of Fraxiparine given subcutaneously for 10 days to placebo. Dependency or death at 6 months, the primary end point of the study, occurred in 45%, 52%, and 65% of the high-dose, low-dose, and placebo groups, respectively. No significant difference was detected in the rate of hemorrhagic complications among the 3 groups. In the larger, multicenter FISS-bis trial, the previous positive results with Fraxiparine were not duplicated. More recently, in 3 large prospective studies of LMWH, there was no overall benefit on the primary end point (favorable outcome at 3 months [TOAST and HAEST] or 6 months [Tinzaparin in Acute Ischemic Stroke; TAIST]). TOAST randomized 635 patients to treatment with danaparoid and 633 patients to placebo. The primary outcome measure was a combined Glasgow Outcome Scale of 1 and 2 and a modified Barthel of >12 on a scale of 0 to 20. Very favorable outcome was considered with a Glasgow Outcome Scale of 1 and a modified Barthel of 19 or 20. At 7 days, 59.2% in the treated group and 54.3% in the placebo group achieved a comparable favorable outcome. Overall at 3 months, 75.2% of patients in the treated group and 73.7% in the placebo arm had achieved a favorable outcome. Patients in the treatment arm had a statistically significant increased rate of symptomatic intracerebral hemorrhage compared with placebo (2.3% versus 0.8%, P=0.05). Even though overall this was a negative trial, the investigators did find a significant difference in the very favorable outcome in the treatment group at 1 week (33.9% versus 27.8%, P=0.01), the time point when the treatment ended. This was not the primary outcome time point in this study but it might be reasonable to expect a beneficial outcome as long as the drug is given rather than at 3 months from a short-term intervention of acute anticoagulation for 1 week. Furthermore, this study was not designed to assess treatment effects in patients with stroke-in-progression, arterial dissection, or hypercoagulable states, and no inferences can be drawn about these subgroups based on the results of this study. A subgroup analysis of TOAST found that treated patients with severe carotid stenosis showed a favorable outcome at 3 months. The outcome of this study may have been limited by the fact that early on, the investigators excluded patients with more severe strokes (NIH stroke scale >15). Since mild stroke patients tend to have a good outcome, the treatment effect would necessarily have to been very robust to demonstrate significance. This suggestion is supported by the excellent outcome seen in the placebo arm of the study in which 73.7% of untreated patients achieved a favorable outcome. In the TOPAS trial, 404 patients with acute ischemic stroke were randomized within 12 hours to receive certoparin in 1 of the 4 doses: 3000 U anti–factor X (aXa) once daily, 3000 U (aXa) twice daily, 5000 U (aXa) twice daily, and 8000U (aXa) twice daily. There was no placebo group in this study to compare to active treatment. The primary efficacy variable was the proportion of patients reaching a favorable outcome (Barthel Index >90 points) at 3 months. There was no significant difference in the outcome between groups. Again, interestingly, the European Stroke Scale improved in all groups during the treatment period of 14 days, a time period that represented the duration of treatment. Clinical improvement was greatest in the first week in all 4 groups. Death was more frequently seen in the highest dose treatment group. Symptomatic intracranial hemorrhage was seen in 2%, 1%, 2%, and 4%, respectively, in the 4 groups. In the Tinzaparin in Acute Ischemic Stroke (TAIST) study, 1486 patients with acute ischemic stroke were randomized within 48 hours of stroke onset to receive 1 of the 3 treatments: high-dose tinzaparin 175 anti Xa IU/kg (487 patients), low-dose tinzaparin 100 anti Xa IU/kg (508 patients), or aspirin 300 mg (491 patients). Treatment was carried out for 10 days. There was no true placebo arm in the study. The primary outcome measure was assessed by the modified Rankin scale at 6 months as independence (0 to 2), disability or death (3 to 6). Secondary outcomes were median scores on the modified Rankin score and the proportion of patients achieving a modified Rankin score of 0 to 2 and a Barthel Index of >90. Outcomes assessed at the end of the treatment were the proportion of patients with neurological deterioration as assessed by a reduction of 5 points on the Scandinavian stroke scale or a reduction of >2 points on the consciousness portion of the scale, recurrent stroke, symptomatic deep vein thrombosis, or pulmonary embolism. Overall there was no difference in outcome in the 3 treatment arms. The proportion of patients independent at 6 months was similar in the 3 groups (high-dose tinzaparin [41.5%], low-dose tinzaparin [42.4%], and aspirin [42.5%]). At the end of the treatment, stroke recurrence was 3.3%, 4.5%, and 3.1%, respectively, in the 3 groups. Although there were no symptomatic, venous thrombosis, or pulmonary embolism in the high-dose tinzaparin group, this was offset by the increased
TABLE 3. Stroke Functional Outcome: Results of Studies With UFIH and LMWH

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo-Controlled</th>
<th>Patient Population</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamorro et al*</td>
<td>231</td>
<td>No</td>
<td>Proportion of patients with Rankin Score 0 to 1</td>
<td>28% achieved Rankin Score 0 to 1 (γ)</td>
</tr>
<tr>
<td>Haley et al</td>
<td>36</td>
<td>No</td>
<td>Stroke progression</td>
<td>Not effective</td>
</tr>
<tr>
<td>Duke et al*</td>
<td>225</td>
<td>Yes</td>
<td>Stroke progression</td>
<td>Negative</td>
</tr>
<tr>
<td>TOAST†</td>
<td>1261</td>
<td>Yes</td>
<td>Stable or progressing ischemic stroke</td>
<td>Negative</td>
</tr>
<tr>
<td>TOPAS‡</td>
<td>404</td>
<td>No</td>
<td>Functional improvement (Barthel &gt; 90)</td>
<td>Negative</td>
</tr>
<tr>
<td>TAIST high dose</td>
<td>487</td>
<td>Aspirin-controlled</td>
<td>Acute ischemic stroke</td>
<td>Modified Rankin (0–1)</td>
</tr>
<tr>
<td>TAIST low dose</td>
<td>508</td>
<td>Aspirin-controlled</td>
<td>Acute ischemic stroke</td>
<td>Modified Rankin (0–1)</td>
</tr>
</tbody>
</table>

UFIH indicates unfractionated intravenous heparin; LMWH, low-molecular-weight heparin; TOAST, Trial of ORG 10 172 in Acute Ischemic Stroke; GOS, Glasgow Outcome Scale; MB, Modified Barthel Scale; TOPAS, Treatment of Patients with Acute Ischemic Stroke; TAIST, Tinzaparin in Acute Ischemic Stroke trial.

*UFIH subcutaneous.
†RS: Rankin Score.
‡LMWH, TOAST (danaparoid), TOPAS (certoparin), TAIST (tinzaparin).
§(γ) Positive predictors of recovery: Mathew score >74, normal baseline CT scan, early treatment with UFIH.

symptomatic intracerebral hemorrhage rate (1.4%) compared with 0.6% and 0.1% in the low-dose and aspirin groups, respectively (Table 3).37

A large, systemic meta-analysis of more than 23 000 patients anticoagulated with UFIH, subcutaneous heparin, and LMWH within 2 weeks from the onset of symptoms revealed 9 fewer RS in the treated group but a similar number of increased hemorrhages. The groups with the highest bleeding rate were treated with LMWH.39 With the exception of the 1 open-labeled, nonplacebo controlled study of UFIH in patients with AF reported by Chamorro et al,33 no trial has demonstrated an improved outcome with treatment of acute ischemic stroke with heparin or LMWH. A multicenter European study of UFIH randomizing 1400 patients within the first 12 hours of a cardioembolic stroke, Rapid Anticoagulation to Prevent Ischemic Damage (RAPID), is underway and may answer questions about improving outcome and reducing recurrence risks with the use of UFIH. Results should be available in 2002. The study is being done with very close monitoring of the aPTT to minimize hemorrhagic complications.34,40

Clinical Deterioration of Patients With SHC on Continued Heparin Therapy

Most clinicians would consider stopping heparin in patients with radiological evidence of SHC. However, there may be situations where this may place the patient at risk of stroke progression or recurrence. Small retrospective and prospective studies have yielded conflicting results concerning the use of UFIH in this setting. Pessin et al41 found no clinical deterioration in 12 patients with acute ischemic stroke who developed HI while anticoagulated with UFIH. Heparin was continued in most cases. Was the HI in these cases spontaneous or heparin induced?41,42 In an aggregate of 3 retrospective studies of 99 nonanticoagulated patients with SHC, clinical worsening occurred in only 5%.43 Bogousslavsky and Ghika44 observed SHC in 6% of 200 patients with ischemic stroke treated with UFIH within 96 hours of onset of stroke. Of these, 2 patients with presumed cardioembolic stroke died. In other stroke subtypes, only 3 of the 16 patients on anticoagulation with UFIH had clinical deterioration. SHC was related to large infarct size and hypertension. The intensity of anticoagulation was not significantly associated with SHC risk.44 In other small uncontrolled studies, HI was more frequently associated with clinical deterioration and higher morbidity and mortality.9,28,45–49 Factors associated with HI were history of previous transient ischemic attack and radiological evidence of previous silent infarcts.45 In a retrospective study of 44 hospital patients with SHC, Ott et al42 found 73% of the cases to be possibly embolic. Forty-five percent of the patients had been treated with anticoagulants. In 14 patients, anticoagulation was continued despite SHC and clinical deterioration was uncommon. Factors associated with a poor outcome were large infarct size, underlying systemic illness, and PH.47

Although the risk of increased PH with UFIH and LMWH is small, all evidence suggests that PH is associated with a relatively high mortality and morbidity.50 Since PH are more likely to be seen with large anterior circulation infarcts and strokes associated with severe hypertension and with recurrent strokes, the presence of these risk factors would constitute relative contraindication to UFIH.47 Additionally, both heparin and LMWH are associated with an increased risk of fatal and nonfatal extracranial bleeding, and a careful assessment of potential causes of extracranial bleeding should be sought and excluded before initiating therapy.13–16,37
Initiating Anticoagulation Therapy

One of the major problems with using UFH relates to lack of effective control of the intensity of anticoagulation. While most clinicians attempt to keep the aPTT between 1.5 to 2 times the control value, this is difficult to achieve with the present monitoring guidelines. Chamorro et al found the aPTT within an acceptable range only 33% of the time with almost the same percentage found to be excessively anticoagulated.34,40 Bedside monitoring of aPTT may result in fewer hemorrhagic events.51 Patients subjected to excessive heparinization, especially in the presence of hypertension, previous stroke, and leukoaraiosis are at a significantly higher risk of bleeding. One method to achieve better control of the intensity of anticoagulation would be to monitor aPTT more frequently and have more frequent dose adjustments of the UFH.51 Conversely, another approach to anticoagulation is to initiate oral therapy without concomitant intravenous therapy. With warfarin, effective anticoagulation (international normalized ratio [INR] 2.5 to 3) can be achieved in most cases within 5 to 7 days with once-daily dosing. Patients with a protein C deficiency or those exposed to high initial warfarin doses may be at an increased risk for transient hypercoagulability. True protein C deficiency is rare in stroke patients, and unfortunately the determination of protein C levels in acute stroke patients may not be accurate. High warfarin doses can be avoided, and initiating therapy with a lower dose of 5 mg once daily can lead to adequate anticoagulation within an acceptable time period.

Heparinoids or UFH as Initial Therapy in Acute Ischemic Stroke

Is bridging therapy with LMWH safer than UFH as the initial treatment of subgroups of cardioembolic stroke at high risk of early RS? A small study attempted to address this question. Twenty-four consecutive patients with acute stroke treated with enoxaparin were compared with 24 previously treated patients who received UFH. The authors found that fewer patients in the enoxaparin group experienced neurological worsening as compared with the heparin group. The length of stay was reduced in the enoxaparin group without an increase in the recurrent stroke risk.15 Currently, it is hard to draw conclusions based on this one study. All the large prospective studies of LMWH in acute ischemic stroke have been negative, so this treatment does not have any established evidence of efficacy.15,16,35–37 The TOAST study suggested a possible role of heparinoids in large-vessel, atherothrombotic stroke, but this will need to be confirmed in a prospective study with an adequate sample size.15

Conclusions

What implications can be derived from the currently available data concerning the role of UFH and LMWH for acute ischemic stroke patients?

The Risk of Recurrent Stroke

(1) The overall risk of recurrent ischemic stroke in the first 1 to 2 weeks is generally very low in the overall stroke population (<2.2%).14,16,19 (2) The risk appears to be higher in subsets of patients with AF and other cardioembolic stroke mechanism (4.5% to 8%).15,18 (3) In certain subgroups, the risk of recurrence is not clearly established (dissection, venous sinus thrombosis, hypercoagulable states)

Considerations for Acute Treatment With UFH or LMWH

Based on the results of several clinical trials, LMWH cannot be recommended in any type of acute ischemic stroke populations to prevent RS or to improve stroke outcome. UFH is not generally indicated in most patients with an ischemic stroke. However, in certain cardioembolic stroke subgroups, especially AF, presenting with additional risk factors such as mural thrombi and/or recent AMI, the subsequent stroke risk seems to be high. These patients may benefit from UFH and concomitant initiation of warfarin with careful multiple aPTT and INR monitoring during the course of treatment. Further clinical trials are needed to more precisely define the risk benefit ratio of UFH even in these subgroups.

In some situations in which anticoagulation is required for the long term (eg, patients with AF), initiation of treatment with warfarin early after stroke onset is likely safer than beginning treatment with UFH and switching to warfarin. Starting treatment within a few days of stroke onset is not likely associated with an increased risk of early RS as compared with using initial UFH and switching to warfarin. This would also abrogate the associated risk of major bleeding side effects associated with the use of UFH.

References

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