Unfractionated or Low–Molecular Weight Heparin for the Treatment of Cerebral Venous Thrombosis

Jonathan M. Coutinho, MD; José M. Ferro, MD, PhD; Patrícia Canhão, MD, PhD; Fernando Barinagarrementeria, MD; Marie-Germaine Bousser, MD, PhD; Jan Stam, MD, PhD; for the ISCVT Investigators

**Background and Purpose**—There is no consensus whether to use unfractionated heparin or low–molecular weight heparin for the treatment of cerebral venous thrombosis. We examined the effect on clinical outcome of each type of heparin.

**Methods**—A nonrandomized comparison of a prospective cohort study (the International Study on Cerebral Vein and Dural Sinus Thrombosis) of 624 patients with cerebral venous thrombosis. Patients not treated with heparin (n=107) and those who sequentially received both types of heparin (n=99) were excluded from the primary analysis. The latter were included in a secondary analysis, allocated according to the type of heparin given first. The primary end point was functional independency at 6 months (modified Rankin scale score ≤2). Secondary end points were complete recovery (modified Rankin scale score 0 to 1), mortality, and new intracranial hemorrhages.

**Results**—A total of 119 patients received low–molecular weight heparin (28%) and 302 received unfractionated heparin (72%). Significantly more patients treated with low–molecular weight heparin were functionally independent after 6 months, both in univariate analysis (odds ratio, 2.1; CI, 1.0 to 4.2) and after adjustment for prognostic factors and imbalances (odds ratio, 2.4; CI, 1.0 to 5.7). In the secondary analysis, there was a similar, nonsignificant trend (odds ratio, 1.7; CI, 0.80 to 3.6). Low–molecular weight heparin was associated with less new intracerebral hemorrhages (adjusted odds ratio, 0.29; CI, 0.07 to 1.3), especially in patients with intracerebral lesions at baseline (adjusted odds ratio, 0.19; CI, 0.04 to 0.99). There was no difference in complete recovery and mortality.

**Conclusions**—This nonrandomized study in patients with cerebral venous thrombosis suggests a better efficacy and safety of low–molecular weight heparin over unfractionated heparin. Low–molecular weight heparin seems preferable above unfractionated heparin for the initial treatment of cerebral venous thrombosis. *(Stroke. 2010;41:2575-2580.)*

**Key Words:** sinus thrombosis, intracranial stroke, heparin, low–molecular weight

Anticoagulation with heparin is widely considered the standard initial therapy for patients with acute cerebral venous thrombosis (CVT), but there is no consensus on which type of heparin to use: unfractionated or low–molecular weight heparin.1–4 Unfractionated heparin (UFH) is administered intravenously and requires dose adjustments based on activated partial thromboplastin time values. Advantages of UFH are that it may provide a faster therapeutic level of anticoagulation and that it can be antagonized with protamine sulfate in acute situations. However, because of a nonlinear dose–response effect, UFH has an unpredictable anticoagulant effect, which increases the risk of under-dosing and overdosing.5 Low–molecular weight heparin (LMWH) has a longer plasma half-life and a more stable therapeutic effect and therefore can be administered subcutaneously in a fixed, weight-adjusted dose.6 In addition, heparin-induced thrombocytopenia occurs less often after treatment with LMWH.7,8

The efficacy and safety of UFH and LMWH have been compared in several randomized trials in patients with venous thromboembolism (venous thrombosis of the leg and pulmonary embolism).9–11 A meta-analysis of these trials showed that LMWH is associated with less hemorrhagic complications and a lower mortality than UFH.12 For patients with CVT, direct comparisons between UFH and LMWH have not been performed, and it is controversial whether UFH or LMWH is the best initial treatment for CVT. We therefore analyzed data from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) and compared the outcomes of patients treated with UFH and those treated with LMWH.

**Methods**

**Study Design**
The organization of the ISCVT has been described previously.13 Briefly, the ISCVT is a prospective international observational study of 624 patients with cerebral venous thrombosis, intracranial stroke, heparin, low–molecular weight.
A cohort study that included 624 consecutive adult patients with symptomatic CVT between 1998 and 2001. A complete list of participating centers is available in a previous publication. CVT was diagnosed by magnetic resonance venography, CT venography, conventional angiography, surgery, or autopsy. The decision whether or not to treat the patient with heparin, as well as the choice of heparin type, was left to the treating physician. The type of heparin and use of concomitant therapies were registered. Monitoring of anticoagulant therapy was performed according to the local hospital protocol. Baseline characteristics, risk factors, and complications during admission were recorded systematically. Repeated cerebral imaging was performed at the discretion of the local investigators, and documentation of new parenchymal lesions was required. Follow-up visits were performed after 6 months, 12 months, and yearly thereafter. Disability was classified according to the modified Rankin scale (mRS 0=no symptoms at all; 6=dead).

Study Population
Patients who were not anticoagulated with heparin, or who only received prophylactic doses, were excluded from the analysis. A subset of patients initially received UFH followed by LMWH or vice versa. We excluded these patients from the primary analysis. However, changing the type of heparin may be related to the clinical condition of the patient, and thus, exclusion of these patients may introduce an unknown bias. Therefore, we performed a secondary analysis in which we included these patients and allocated them according to the type of heparin they received first. Predefined subgroups for analysis were patients with an intracerebral lesion at baseline (nonhemorrhagic or hemorrhage) and patients with a baseline intracranial hemorrhage.

End Points
We considered an mRS of 0, 1, or 2 (no symptoms, minor symptoms, minor handicap [ie, functional independency], respectively) after 6 months the primary outcome. Secondary end points were complete recovery (defined as an mRS of 0 or 1) at 6 months, all-cause mortality at 6 months, and the occurrence of new intracranial hemorrhages. For patients who missed the 6-month evaluation, we imputed the mRS at discharge (last observation carried forward).

Statistical Analysis
Categorical data were analyzed with the χ² test and continuous data with a Mann–Whitney test. For each of the outcome measures, the unadjusted odds ratio (OR) with 95% CI is provided. In addition, we used logistic regression analysis to calculate adjusted ORs. For the clinical end points (the scores on the mRS), age, gender, thrombosis of the deep cerebral venous system, mental status disorder, coma, intracranial hemorrhage, infection of the central nervous system, malignancy, and focal neurological deficits (motor or sensory deficit, neglect, aphasia, or hemianopia) were forced into the model as independent variables. These variables were chosen because they were significantly associated with outcome in a previous analysis of the ISCVT data or because they are clinically relevant. In addition, we adjusted for significant imbalances at baseline. For multivariate analysis of new intracranial hemorrhages, we used a similar approach and additionally adjusted for nonhemorrhagic lesions. The Hosmer–Lemeshow test was used to determine goodness of fit of the regression model. In view of the explorative nature of this study, we did not correct for multiple comparisons. All data were analyzed with SPSS 16.0.

Role of the Funding Source
The funding source had no involvement in the collection, analysis, or interpretation of the data nor in any part of writing this article.

Results
Of the 624 patients in the original ISCVT cohort, 104 (17%) did not receive any kind of heparin in therapeutic dose and were excluded from the analysis. Ninety-nine patients (16%) sequentialement received both UFH and LMWH during admission and were excluded. Therefore, the primary study group cohort is composed of 421 patients, 119 of whom were treated with LMWH and 302 with UFH.
There was no difference in the frequency of pretreatment intracranial hemorrhagic or nonhemorrhagic lesions. Heparin was started on the day of diagnosis in the majority of patients (Table 1). Thrombolysis was performed in 2% of patients in each group. Further, the proportions of patients who received steroids or anticonvulsants during admission did not differ. There was a trend toward a longer duration of hospital admission in the UFH-treated patients (median 16 versus 17 days; \( P = 0.06 \)). During follow-up, most patients were treated with oral anticoagulants (81% versus 85%).

Approximately a quarter of the patients in each group deteriorated during admission, predominantly within the first 2 days after diagnosis (median 2 days for each group; Table 2). More patients treated with UFH developed a depressed consciousness (11% versus 17%) or an altered mental state (4% versus 8%), whereas new seizures were more common in LMWH-treated patients (10% versus 6%), but none of these differences were statistically significant. One patient in each group had a leg-vein thrombosis, and one patient treated with LMWH experienced a gastrointestinal hemorrhage. Cerebral imaging was repeated during admission in 41% and 44% of LMWH- and UFH-treated patients, respectively. New intracranial hemorrhages were more common among UFH-treated patients (10% versus 6%), but none of these differences were statistically significant. One patient in each group had a leg-vein thrombosis, and one patient treated with LMWH experienced a gastrointestinal hemorrhage. Cerebral imaging was repeated during admission in 41% and 44% of LMWH- and UFH-treated patients, respectively. New intracranial hemorrhages were more common among UFH-treated patients (10% versus 6%), but none of these differences were statistically significant. One patient in each group had a leg-vein thrombosis, and one patient treated with LMWH experienced a gastrointestinal hemorrhage. Cerebral imaging was repeated during admission in 41% and 44% of LMWH- and UFH-treated patients, respectively. New intracranial hemorrhages were more common among UFH-treated patients (10% versus 6%), but none of these differences were statistically significant. One patient in each group had a leg-vein thrombosis, and one patient treated with LMWH experienced a gastrointestinal hemorrhage. Cerebral imaging was repeated during admission in 41% and 44% of LMWH- and UFH-treated patients, respectively. 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with a good outcome (adjusted OR, 2.4; 95% CI, 1.0 to 5.7). If only patients who had a follow-up evaluation at 6 months were analyzed, the results were essentially the same (independency 92% versus 85%; OR, 2.0; 95% CI, 0.92 to 4.2). The rates of complete recovery and mortality at 6 months did not differ between the groups. In the multivariate analysis, there was trend toward fewer new intracranial hemorrhages among LMWH-treated patients (adjusted OR, 0.29; 95% CI, 0.07 to 1.3; Table 3).

Table 4 shows data of the patients who had an intracranial hemorrhage or infarct before treatment with heparin. Similar to the primary study cohort, LMWH was associated with functional independency at 6 months (adjusted OR, 3.0; 95% CI, 1.1 to 8.3). In addition, LMWH-treated patients had significantly fewer new intracranial hemorrhages (adjusted OR, 0.19; 95% CI, 0.04 to 0.99), whereas there was no difference in the rate of repeated cerebral imaging in this subgroup (47% versus 52%). A separate analysis of patients who had an intracranial hemorrhage at baseline yielded similar results (Table 4).

Of the 99 patients who received both UFH and LMWH, 14 were treated first with LMWH, 82 with UFH, and in 3 patients, it was not possible to determine which type of heparin was given first. Differences in baseline characteristics and risk factors were similar to the primary cohort (data not shown). Inclusion of these 96 patients according to the treatment they received first (the secondary analysis; Table 4) indicated that an independent outcome at 6 months was still more common in LWMH-treated patients (91% versus 86%), but the difference was no longer statistically significant (adjusted OR, 1.6; 95% CI, 0.75 to 3.4). New intracranial hemorrhages were identified in 7 patients first treated with LMWH and in 26 patients first treated with UFH (12% versus 15% of patients who underwent repeated cerebral imaging).

**Discussion**

This is the first study in which the relationship between the type of heparin used to treat patients with CVT and clinical outcome is examined. Our data suggest that LMWH results in better outcomes and less hemorrhagic complications than UFH. Significantly more patients treated with LMWH were independent at 6 months, both in univariate analysis and after adjustment for known prognostic variables. New intracranial hemorrhages were less common among LMWH-treated patients, but this was not statistically significant in the primary analysis. We did not find a difference in the rate of complete recovery (mRS 0 to 1), either in the primary analysis or in any of the subgroups. This reflects the general good outcome for the majority of patients with CVT, regardless of the type of heparin used. Nevertheless, LMWH may make a clinically relevant difference for a significant minority of patients.

A minority of patients were sequentially treated with both UFH and LMWH, most with UFH first. The decision to change the type of heparin may have been motivated by

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**Table 3. Primary and Secondary End Points**

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>LMWH n=119</th>
<th>UFH n=302</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted OR (95% CI)</td>
<td>P Value</td>
<td>Adjusted OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Independency (mRS 0–2)</td>
<td>92%</td>
<td>84%</td>
<td>2.1 (1.0–4.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete recovery (mRS 0 or 1)</td>
<td>78%</td>
<td>78%</td>
<td>1.0 (0.61–1.7)</td>
<td>0.94</td>
</tr>
<tr>
<td>Mortality</td>
<td>6%</td>
<td>8%</td>
<td>0.72 (0.30–1.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>New intracranial hemorrhage*</td>
<td>10%</td>
<td>16%</td>
<td>0.61 (0.22–1.7)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*The percentages of patients who underwent repeated CT or MRI are given.
†P value for Hosmer–Lemeshow test was >0.20 and <0.85 for each of the multivariate analyses.
several reasons. For example, if a patient deteriorates, most notably in the case of a hemorrhagic complication, a physician may decide to switch to another type of heparin. In addition, a switch to LMWH can be made if a patient has improved enough to be mobilized or discharged because LMWH does not require intravenous access. Further, some physicians may always start with UFH, based on the idea that an adequate level of anticoagulation is achieved more rapidly with UFH, and then change to LMWH after a few days. Finally, it is possible that the type of heparin changed if a patient is transferred to another department or to the care of another physician. Because the reason to change the treatment regimen was not recorded, we excluded these patients from the primary analysis. In a secondary analysis, we allocated these patients according to the type of heparin they received first. In this analysis, the contrast between LMWH and UFH toward better outcomes for LMWH-treated patients and more intracerebral lesions after UFH treatment.

We were especially interested in the subgroup of patients with intracerebral lesions caused by CVT before treatment. These lesions are caused by thrombosis and occlusion of cortical veins, and the risk of new or increased intracerebral hemorrhage is higher in these patients. Nevertheless, experts and guidelines, supported by evidence from a few small trials, recommend heparin as standard treatment for CVT, even in the presence of intracerebral lesions, because the benefit outweighs this risk.\(^1,15–17\) Interestingly, in the subgroup of patients with pretreatment intracerebral lesions, the number of new intracerebral hemorrhages was essentially the same for patients treated with LMWH as in the entire cohort (11% and 10%, respectively). On the other hand, in patients treated with UFH, the number of new hemorrhages was higher in the subgroups: 21% in the all-lesion subgroup and 28% in the patients with pretreatment hemorrhages, compared with 16% in the entire cohort. Accordingly, the contrast in rates of good outcomes between LMWH- and UFH-treated patients was larger in this subgroup, in favor of LMWH. A plausible explanation for this finding is that LMWH combines a better safety profile with equal or better anticoagulant efficacy, which becomes more conspicuous in patients with baseline intracerebral lesions.

Our results are in complete agreement with data from randomized trials in noncerebral venous thromboembolism. A Cochrane meta-analysis of 22 trials, including nearly 9000 patients, convincingly showed that treatment with LMWH results in significantly less thromboembolic recurrences (OR, 0.68), fewer major hemorrhagic complications (OR, 0.57), a higher recanalization rate (OR, 0.69), and a lower mortality (OR, 0.76) than UFH.\(^12\) The superior safety and efficacy of LMWH in leg-vein thrombosis is probably attributable to its pharmacokinetic properties. Contrary to LMWH, UFH requires frequent activated partial thromboplastin time measurements and dose adjustments, which have proven to be difficult to implement in practice. A British audit of 45 consecutive patients who received UFH during admission showed that patients were adequately anticoagulated less than a quarter of the time.\(^18\) Most of the time, patients were below the therapeutic range, but overdosing also occurred frequently. There is a robust correlation between subtherapeutic activated partial thromboplastin time values and the risk of recurrent thrombosis,\(^19\) and the likely effect of overdosing...
UFH is an increased risk of hemorrhagic complications.20 Other studies have demonstrated that it often takes >24 hours until patients are adequately anticoagulated with UFH, even if a treatment algorithm is used.21,22 Thus, the theoretical advantage of more rapid anticoagulation with intravenous UFH is probably rarely realized in practice.

Our study has several limitations. First, information on which types of LMWH drugs were used, and in which dosages, was not recorded in the ISCVT study. For the same reason, activated partial thromboplastin time values in the UFH-treated patients are not available. Another limitation is that the study is nonrandomized. Although the 2 groups were well balanced regarding most baseline characteristics, and we minimized the risk of bias by adjusting for prognostic factors, we cannot exclude the possibility that the results are in part caused by some unknown confounding variable. A direct comparison between LMWH and UFH in a randomized controlled trial would obviously be superior. However, considering the number of patients that would be required for such a trial, the rarity of CVT, and the good outcome of most patients, it seems unlikely that such a trial is feasible. In the absence of trial data, we believe that our results, derived from the largest prospective cohort study on CVT, provide the best available evidence at this moment.

In conclusion, the results of this nonrandomized study suggest that LMWH leads to better outcomes and fewer hemorrhagic complications than UFH in patients with CVT, especially in those with baseline intracerebral lesions. In combination with data from large randomized trials in extracerebral venous thromboembolism, a plausible pathophysiological basis, and obvious advantages of LMWH in daily practice, LMWH seems preferable over UFH for the initial treatment of patients with CVT.

Acknowledgments
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Disclosures
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虺 경우 목적
뇌혈액혈전증(cerebral venous thrombosis) 치료에 있어 비
분획해파린(unfractionated heparin) 혹은 저분자량해파린
(low-molecular weight heparin) 사용에 대해서는 일치된
의견이 아직 없다. 저자들은 각 해파린 사용에 따른 임상적
효과를 조사하였다.

방법
전향적으로 구축된 624명의 뇌혈액혈전증 코호트에 대하여 비
무작위 배정 연구를 시행하였다(International Study on
Cerebral Vein and Dural Sinus Thrombosis). 해파린 투
여를 받지 않은 환자(n=107) 및 두 가지 해파린을 모두 투여받
은 환자(n=99)는 본 일차 분석에서 제외되었다. 두 가지 해파
린을 모두 투여받은 합자는 이차 분석에 포함되었는데, 먼저
투여받은 해파린군에 포함되었다. 일차 결과 변수는 6개월 시
점에서 측정한 경조직 독립 상태(modified Rankin Scale 점
수 2점 이하)였다. 이차 결과 변수는 완전한 회복(modified
Rankin Scale 점수 0 혹은 1), 사망률 및 새로운 두개내출혈
(intracerebral hemorrhage)의 발생이었다.

결과
총 119명의 환자 중 저분자량해파린을 투여받았으며(28%),
302명이 비분획해파린을 투여받았다(72%). 저분자량해파린을
투여받은 군에서 6개월 시점의 경조직 독립성을 보이는 환자
가, 단변량 분석(대응비, 2:1; 신뢰구간 1.0~4.2)이나 응급 인
자 및 불균형을 보정한 이후(대응비 2.4; 신뢰구간 1.0~5.7)에
도 유의하게 많았다. 저분자량해파린을 투여받은 환자군에서
뇌내출혈(intracerebral hemorrhage)의 신규 발생이 적었는
대(보정 대응비, 0.29; 신뢰구간 0.07~1.3), 특히 초기에 뇌내
혈변이 있는 환자군에서 그 효과가 더욱 투명하였다(보정 대응
비 0.19; 신뢰구간 0.04~0.99). 완전한 회복 및 사망률에 있
어서는 두차량 차이를 보이지 않았다.

결론
뇌혈액혈전증에 대한 본 비무작위 배정 연구는 저분자량해파린
이 비분획해파린에 비하여 더 높은 효능 및 안전성을 가지고
있음을 보여 주고 있다. 저분자량해파린은 비분획해파린에 비
하여 뇌혈액혈전증의 초기 치료 방법으로 적합한 것으로 생각
된다.