Low-Molecular-Weight Heparin and Early Neurologic Deterioration in Acute Stroke Caused by Large Artery Occlusive Disease

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Background: Patients with acute ischemic stroke and large artery occlusive disease (LAOD) have an increased risk for early neurologic deterioration (END) due to progressive stroke, early recurrent ischemic stroke (ERIS), or symptomatic intracranial cerebral hemorrhage (SICH). Low-molecular-weight heparin (LMWH) has been widely advocated to prevent venous thromboembolism, but its risks and benefits in early ischemic stroke are inadequately defined.

Objective: To determine the efficacy and safety of LMWH in treating END in patients with acute ischemic stroke and LAOD.

Design: Post hoc analysis of randomized, controlled trial.

Setting: Academic research.

Patients: Among 603 patients recruited, 353 patients (180 treated with LMWH, 173 with aspirin) had acute ischemic stroke and LAOD.

Interventions: Patients were randomly assigned to receive either subcutaneous LMWH or oral aspirin within 48 hours after stroke onset for 10 days, then all received aspirin once daily for 6 months.

Main Outcome Measures: We assessed whether LMWH was superior to aspirin for the prevention of END within the first 10 days after index stroke. Early neurologic deterioration was defined as a composite end point of progressive stroke, ERIS, and SICH.

Results: Among 353 patients included in the study, END within the first 10 days occurred in 6.7% of LMWH-allocated patients (12 of 180 patients) compared with 13.9% of aspirin-allocated patients (24 of 173). Low-molecular-weight heparin was significantly associated with the reduction of END (absolute risk reduction, 7.2%; odds ratio [OR], 0.44; 95% CI, 0.21-0.92). When individual components of END were examined, LMWH was significantly associated with a lower frequency of stroke progression within the first 10 days compared with aspirin (5.0% [9 of 180] vs 12.7% [22 of 173]; OR, 0.36; 95% CI, 0.16-0.81). Meanwhile, among those taking LMWH vs aspirin, the frequency rates of ERIS were 1.1% (2 of 180) vs 0 (0); 0.6% (1 of 180) vs 1.2% (2 of 173) for SICH; and 2.2% (4 of 180) vs 2.9% (5 of 173) for symptomatic and asymptomatic cerebral hemorrhage, respectively; they showed nonsignificant trends. Early neurologic deterioration was significantly associated with 6-month disability with both LMWH (OR, 12.75; 95% CI, 3.27-49.79 on Barthel Index and OR, 18.15; 95% CI, 2.09-157.93 on modified Rankin Scale) and aspirin (OR, 6.09; 95% CI, 2.44-15.20 on Barthel Index and OR, 7.50; 95% CI, 2.08-27.04 on modified Rankin Scale) groups.

Conclusions: For patients with acute ischemic stroke and LAOD, treatment with LMWH within 48 hours of stroke may reduce END during the first 10 days, mainly by preventing stroke progression. The similar rate of cerebral hemorrhage between LMWH and aspirin demonstrated that LMWH may be safely used in acute ischemic stroke.

Trial Registration: strokecenter.org/trials Identifier: FISS-tris

Anticoagulation is a controversial treatment option for early secondary prevention, as the results of clinical trials remain inconclusive. For patients with symptomatic intracranial stenosis, while retrospective data have suggested that warfarin was superior to aspirin for the prevention of recurrent ischemic stroke, the prospective Warfarin-Aspirin Symptomatic Intracranial Disease study was stopped early owing to safety concerns about excessive adverse events in the warfarin group together with no signal for effectiveness. Likewise, beneficial effects were not observed for low-molecular-weight heparin (LMWH) within 2 weeks of treatment in the Heparin in Acute Embolic Stroke Trial study, a randomized trial for early recurrence in patients with acute ischemic stroke and atrial fibrillation (AF). However, in the International Stroke Trial study, unfractionated heparin reduced ischemic stroke recurrence during the period of treatment. Furthermore, hemorrhagic transformation was also observed in these studies and was associated with antiocoagulation using unfractionated heparin and LMWH, and it may be of importance as both ERIS and hemorrhagic transformation cause END.

We have previously reported that hemorrhagic transformation in patients with LAOD was similar between LMWH-treated and aspirin-treated patients. However, clinical differences between LMWH and unfractionated heparin are likely the results of their distinct pharmacokinetic profiles. To our knowledge, the efficacy of LMWH in preventing END has not been examined, hence we report a post hoc analysis of a randomized aspirin-controlled trial exploring the efficacy and safety of LMWH for END in patients with acute ischemic stroke and LAOD.

METHODS

DESIGN

The design of the Fraxiparin in Stroke Study for the treatment of ischemic stroke (FISS-tris) has been published. In short, the study was a prospective multicenter, randomized clinical trial conducted at multiple trial sites in Hong Kong and Singapore with ethics committee approval, and it was designed to compare LMWH with aspirin for the early treatment of patients with LAOD and acute ischemic stroke. Randomization into the trial was done through the central randomization office at the Clinical Trials and Epidemiology Research Unit in Singapore by means of sealed envelopes or allocation via the Internet. Block randomization was used (block sizes of 4 and 6), stratified by regions (Hong Kong, Kowloon, New Territories, and Singapore), time from onset of stroke (0-24 hours or 24-48 hours), National Institute of Health Stroke Scale (NIHSS) score (0-8 or ≥9), and whether neurovascular investigations were done before randomization (vascular lesion present or status unknown), with a one-to-one treatment allocation. The treatment assignment was generated by computer. Written informed consent was obtained from all participants or their legally acceptable representatives. This study is registered at http://www.strokecenter.org/trials (identifier FISS-tris).

PARTICIPANTS

The target population was defined as patients diagnosed as having acute ischemic stroke and with LAOD who could be treated with either nadroparin calcium, 3800 anti-factor Xa IU/0.4 mL, subcutaneously twice daily (LMWH group) or aspirin, 160 mg, once daily (aspirin group) within 48 hours after stroke onset for 10 days, then all received aspirin, 80-300 mg, once daily for 6 months. All patients underwent a computed tomographic head scan before randomization and a repeat computed tomographic scan at day 10 (or a computed tomographic/magnetic resonance image earlier in case of rapid and severe neurologic deterioration). Vascular imaging was performed to identify moderate or greater stenosis in the internal carotid, vertebrobasilar, middle cerebral, anterior cerebral, and posterior cerebral arteries by carotid duplex scan, transcranial Doppler imaging, or magnetic resonance angiography, according to previously published criteria. Vascular evaluation was done before or within 3 days after randomization, and only patients with symptomatic LAOD were included in the analysis. Other exclusion criteria are as previously described.

FOLLOW-UP, EVENTS, AND OUTCOMES

The patients were randomized following a central randomization code to 2 treatment groups, subcutaneous LMWH or oral aspirin, and baseline data were collected including demographics, medical history, prestroke modified Rankin Scale (mRS) and NIHSS scores. The primary outcome event for this analysis was END defined as an increase of 4 points or more on the NIHSS explainable by the stroke event at 10 days from baseline or death owing to a stroke event during the same period. Early neurologic deterioration was also a composite end point including progressive stroke, ERIS, and symptomatic intracranial cerebral hemorrhage (SICH). Progressive stroke was defined as stroke events of END without evidence of ERIS or SICH. Symptomatic intracranial cerebral hemorrhage was classified to be the cause of END when a parenchymal hematoma was identified on post-treatment computed tomography. Early recurrent ischemic stroke was defined as a sudden and persistent (>24 hours) deficit occurring after index stroke onset, with both clinical and imaging findings of ischemic stroke diagnosed in an independent artery separated from index stroke territory.

At day 10, or earlier if discharged from the hospital, trained personnel performed the NIHSS and Barthel Index. Favorable outcomes were defined as a Barthel Index score of at least 85 points as used in the FISS tris study. The END, progressive stroke, ERIS, and SICH were assessed by physicians who were aware of the treatment assignments. At 6 months after randomization, Barthel Index and mRS scores were assessed by a clinician or a nurse without knowledge of the treatment allocation. Disability was identified as a Barthel Index score of 80 or less or mRS score of 2 or greater in survivors.

STATISTICAL ANALYSIS

All analyses were performed according to the intent-to-treat principle. Frequencies of events and outcomes were compared with the chi-squared test. If the number in any group was less than 5, the Fisher exact test was preferred. The effect of treatment was expressed as odds ratios (ORs) with 95% confidence intervals; OR values of greater than 0 and less than 1 indicated an advantage of LMWH over aspirin for END. Comparisons of baseline characteristics also involved t test and χ2 with 2-sided P values to show significance. For a better identification of patients at risk for END or bad outcome, adjustment for the confounding effect of variables was achieved by logistic regression analysis. The primary model was based on the 5 hypothesized contributors to the risk for END: baseline NIHSS score, age, hypertension, diabetes mellitus, and hyperlipidemia. Additional variables were considered for inclusion in the multivariable model.
if they could be associated with END in univariate analysis at the P < .05 level. Odds ratios and their 95% confidence intervals were used to evaluate the association of END with the risk for death and disability within 6 months of stroke. Descriptive statistics were reported as median values with 25th to 75th percentiles. The analysis was carried out using SPSS version 15.0 (SPSS Inc).

**RESULTS**

In the FISS-tris study, 603 patients with acute ischemic stroke were enrolled in 11 hospitals in Hong Kong and Singapore, of whom 353 patients were confirmed as having LAOD. The location of LAOD was solely intracranial in 300 patients (85%), solely extracranial in 11 patients (3%), and both intracranial and extracranial in 42 (12%). Altogether, 10 patients ended treatment before 10 days owing to death (n = 1), cerebral hemorrhage (n = 3), neurologic deterioration (n = 1), extracerebral hemorrhage (n = 3), esophageal ulcer (n = 1), and elevated liver enzymes (n = 1). Overall compliance with the study medication was 96.7% (174 of 180 patients) in the LMWH group and 97.7% (169 of 173) in the aspirin group. In our study, we included only those whose cause of END was stroke event. We excluded 5 patients who also had an increase of 4 or more points on the NIHSS within the first 10 days, but whose cause of deterioration was not stroke (3 patients in the aspirin group with pneumonia, continuing hematuria, and diarrhea; and 2 in the LMWH group with severe hematoma on the scalp and pneumonia). Among the 5 patients, 1 died from chest infection and the others had transient neurologic worsening that occurred within the first 10 days and the deficit reversed after the condition was controlled.

**PATIENT CHARACTERISTICS**

The baseline characteristics of patients between the LMWH and aspirin groups were well balanced, except for higher levels of triglycerides in the LMWH group (P = .01). Table 1 presents the baseline characteristics of patients with END (more elderly patients in the aspirin group, higher NIHSS scores in the LMWH group) and without END (more patients with hypertension in the aspirin group).

**EVENTS**

There was a significance difference (absolute risk reduction, 7.2%; OR, 0.44; 95% CI, 0.21-0.92) in the frequency of deterioration during the first 10 days of acute ischemic stroke with LAOD (12 of 180 [6.7%] in the LMWH group vs 24 of 173 [13.9%] in the aspirin group, which indicated as an advantage of LMWH over aspirin; Table 2).

Treatment with LMWH was significantly associated with a lower frequency of stroke progression during the first 10 days (9 of 180 [5.0%] vs 22 of 173 [12.7%]; absolute risk reduction, 7.7%; OR, 0.36; 95% CI, 0.16-0.81) (Table 2). Of the patients with progressive stroke, 9 had abrupt courses (2 taking LMWH and 7 taking aspirin) and 22 had progressive courses (7 taking LMWH and 15 taking aspirin).

There was no significant difference in the frequency of ERIS during the first 10 days: 2 patients (1.1%) in the LMWH group and none in the aspirin group (Table 2).

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**Table 1. Baseline Characteristics of Patients With and Without END**

<table>
<thead>
<tr>
<th></th>
<th>LMWH (n = 180), No. (%)</th>
<th>Aspirin (n = 173), No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without END (n = 168)</td>
<td>With END (n = 12)</td>
</tr>
<tr>
<td><strong>Age, median (25th-75th percentile), y</strong></td>
<td>70 (62-75)</td>
<td>69 (64-78)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>99 (59)</td>
<td>7 (58)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td>34 (20)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>20 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>131 (78)</td>
<td>19 (83)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>67 (40)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>77 (46)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>25 (15)</td>
<td>1 (8)</td>
</tr>
<tr>
<td><strong>Fasting glucose levels, median, mmol/L, 25th-75th percentile</strong></td>
<td>5.70 (4.80-7.68)</td>
<td>6.45 (5.30-8.10)</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>5 (3)</td>
<td>1 (8)</td>
</tr>
<tr>
<td><strong>NIHSS score, median (25th-75th percentile)</strong></td>
<td>6 (4-9)</td>
<td>9 (5-13)</td>
</tr>
<tr>
<td>0-8</td>
<td>122 (73)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>≥9</td>
<td>46 (27)</td>
<td>6 (50)</td>
</tr>
<tr>
<td><strong>Previous and ongoing medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antplatelet agents</td>
<td>53 (32)</td>
<td>7 (58)</td>
</tr>
</tbody>
</table>

Abbreviations: END, early neurologic deterioration; LMWH, low-molecular-weight heparin; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.
Also nonsignificantly different was the frequency of SICH during the first 10 days: 1 patient (0.6%) taking LMWH vs 2 (1.2%) taking aspirin (OR, 0.48; 95% CI, 0.04-5.32), as was the frequency of symptomatic and asymptomatic intracranial hemorrhage identified by brain imaging: 4 (2.2%) taking LMWH vs 5 (2.9%) taking aspirin (OR, 0.76; 95% CI, 0.20-2.89). However, extracerebral hemorrhages occurring in the LMWH-allocated patients were more frequent (OR, 2.22; 95% CI, 0.67-7.35) (Table 2).

In the LMWH group, during the first 10 days, 1 patient was diagnosed as having increased intracranial pressure owing to brain edema caused by a middle cerebral artery occlusion and underwent craniectomy, and another patient died of pneumonia.

OUTCOMES

At day 10, there was no significant association between favorable outcomes and LMWH, as assessed by a Barthel Index score of at least 85 points (79 of 180 [43.9%] taking LMWH vs 67 of 173 [38.7%] taking aspirin; OR, 1.24; 95% CI, 0.81-1.89; P = .33, unadjusted, and P = .71, adjusted).

Table 3 shows the frequency of 6-month disability and 6-month death in the FISS-tris cohort according to the presence of END and aspirin/LMWH allocation. The Figure illustrates the ORs for 6-month disability and 6-month death rates according to the presence of END and LMWH/aspirin allocation. Odds ratios were adjusted for baseline NIHSS score, age, hypertension, diabetes mellitus, hyperlipidemia, and National Institutes of Health Stroke Scale score. BI indicates Barthel Index; M-H, Mantel-Haenszel; mRS, modified Rankin Scale; SICH, symptomatic intracranial cerebral hemorrhage.

Abbreviations: BI, Barthel Index; END, early neurologic deterioration; LMWH, low-molecular-weight heparin; mRS, modified Rankin Scale; SICH, symptomatic intracranial cerebral hemorrhage.

Figure. Odds ratios and 95% confidence intervals (CIs) for 6-month disability and 6-month death rates among patients with and without early neurologic deterioration (END) in the low-molecular-weight heparin (LMWH) and aspirin groups. Odds ratios were adjusted for age, hypertension, diabetes mellitus, hyperlipidemia, and National Institutes of Health Stroke Scale score. BI indicates Barthel Index; M-H, Mantel-Haenszel; mRS, modified Rankin Scale.

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disability and the relationship was similar in the LMWH (OR, 12.75; 95% CI, 3.27-49.79 on the Barthel Index and OR, 18.15; 95% CI, 2.09-157.93 on mRS) and aspirin (OR, 6.09; 95% CI, 2.44-15.20 on the Barthel Index and OR, 7.50; 95% CI, 2.08-27.04 on mRS) groups. Patients with END had a nonsignificantly higher risk for death (LMWH: OR, 1.82; 95% CI, 0.21-15.87; aspirin: OR, 4.11; 95% CI, 0.92-18.49). Early neurologic deterioration and progressive stroke led to higher 6-month disability (Barthel Index and mRS scores, 0-2) in the LMWH group vs the aspirin group, but no significant difference was found (Table 3).

**COMMENT**

The FISS-tris trial was designed to evaluate the efficacy of LMWH in the treatment of acute ischemic stroke with LAOD. Although the study showed there was no significant benefit of LMWH over aspirin in patients with LAOD at 6 months,13 early effectiveness was not examined. To date, there is no international consensus on END, and the NIHSS has been widely used in published studies with a high predictive value of worse outcome. A reasonable definition might be to consider END as an increase of 4 or more points in the NIHSS, which has been proven to be valid for cortical and subcortical brain infarction.19-21 As LMWH may play a preventive role on the recurrence and propagation of thrombus, which presents clinically as stroke deterioration or progression, our analysis was performed and the findings suggested that LMWH was superior to aspirin in patients with acute ischemic stroke and LAOD for the prevention of END and in particular stroke progression during the first 10 days. The observed incidence of END in our trial was 10.2% (36 of 353 patients), which was lower than in previous studies.19,23,24 The reasons for the difference may be attributed to different definitions of neurologic deterioration or stroke recurrence, as well as different subtypes of ischemic stroke in patients. In the Tinzaparin in Acute Ischemic Stroke study, the frequency of END was similar at day 10, but there was no difference between LMWH-treated and aspirin-treated groups.14 In the Trial of ORG 10172 in Acute Stroke Treatment study, by 1 week, the incidence of END was 10%, with no difference between the LMWH and placebo groups.13 However, in the Tinzaparin in Acute Ischemic Stroke and Trial of ORG 10172 in Acute Stroke Treatment studies, the rates of stroke subtypes were 485 of 1486 patients (33%) and 230 of 1268 (18%) with large-vessel strokes, 534 of 1486 (36%) and 306 of 1268 (24%) with small-vessel strokes, and 368 of 1486 (25%) and 266 of 1268 (21%) with cardioembolic strokes, respectively. Neither of these studies performed subgroup analysis of END according to large-vessel, small-vessel, or cardioembolic stroke subtypes.13,14 Hence, to our knowledge, FISS-tris is the only acute stroke anticoagulation study that has targeted enrollment of patients with LAOD, most of whom had intracranial atherosclerosis.

The mechanisms of END may include ERIS, progressive stroke, and SICH.19,20 The definition of ERIS differed between studies, hence ERIS may be caused by different pathophysiological processes.1,12,19,20,23 We defined ERIS as not occurring in the original artery of the index stroke because ERIS found in a new territory may be associated with other nonatherosclerosis mechanisms, especially AF.20 Among patients with ERIS in our study, case 1 was owing to newly diagnosed AF causing bilateral cerebral embolism, while multiple-territory infarct also occurred in case 2, which may be attributed to embolism from other sources such as aortic arch atheroma. Electrocardiogram on hospital admission alone is insensitive for AF screening as a result of low sensitivity and specificity. Moreover, echocardiography was not mandatory in our study, hence there may be undocumented sources of cardiac embolism.

In our study, the frequency of stroke progression was 8.8% (31 of 353 patients), which was lower than in previous studies,19 and LMWH was significantly associated with a reduction of progressive ischemic stroke. The causes of progressive stroke were diverse and included reocclusion, distal embolism, poor collateral circulation of the original artery, brain edema, and excitatory amino acids. Common stroke mechanisms in patients with intracranial artery stenosis were the occlusion of a single penetrating artery or an artery-to-artery embolism.25 In the Clopidogrel Plus Aspirin Versus Aspirin Alone for Reducing Embolization in Patients with Acute Symptomatic Cerebral or Carotid Artery Stenosis study, microembolic signals were detected in 62.2% of patients with acute ischemic events and symptomatic intracranial stenosis at baseline,26 suggesting that artery-to-artery embolism may be the leading cause of progressive stroke owing to the original artery. Both anticoagulants and antiplatelet agents can suppress microembolic signals and prevent embolism.20,27 In a FISS-tris substudy, 47 patients were investigated for microembolic signals detection and no difference was identified between LMWH and aspirin.28 Nevertheless, LMWH may be also efficacious in preventing the propagation of red emboli associated with blood flow reduction due to LAOD.20 In our study, there were several methodologic limitations for the assessment of progressive stroke: the collateral blood flow was not evaluated to explore the hemodynamic factors and just 1 patient was identified with obviously increased intracranial pressure owing to edema, while more moderate degrees of brain edema may also cause progressive stroke.

Consistent with our results, in the International Stroke Trial study, patients allocated to heparin had significantly fewer recurrent ischemic strokes within 14 days than patients allocated to aspirin.29 It is difficult to establish whether there is a difference in the prevention of early stroke recurrence between heparin and LMWH. However, the Heparin in Acute Embolic Stroke Trial study reported LMWH did not reduce the risk for early recurrent stroke in patients with acute ischemic stroke and AF who were treated with LMWH compared with those treated with aspirin.12 The reasons for the difference may be ascribed to distinct pathophysiological mechanisms of stroke groups and LMWH may not be efficacious in cardioembolic stroke as opposed to other stroke subtypes.

In line with other studies, the incidence of symptomatic hemorrhage in our study was 0.8% (3 of 353 pa-
pations) and did not differ between LMWH and aspirin, indicating a low risk for cerebral bleeding complications.

In the FISS-tris study, LMWH was not superior to aspirin using the dichotomized Barthel Index outcome measure after 10 days and 6 months. The difference may be attributed to the relatively low sensitivity of the Barthel Index as a measure for mild stroke, with 41% and 71% of patients achieving a score greater than 85 at 10 days and 6 months, respectively.

In our study, patients exhibiting END had a higher risk for 6-month disability compared with patients without END. Hence, END detected within the first 10 days of ischemic stroke may be regarded as a marker of bad outcome. Early neurologic deterioration was also revealed to be an independent predictor of functional outcome in another study. However, as no effective therapy capable of preventing END or reversing its impact on outcome has been developed, our study suggested that LMWH may be a rational choice for patients with LAOD. In the FISS-tris study, LMWH increased good outcome at 6 months, as defined by a mRS (0-1) dichotomy. Our current analysis provides further evidence that the benefit may partly be attributed to the effect of LMWH on the prevention of END. However, other factors may also have impacted early neurologic worsening and outcomes such as fever, hyperglycemia, and swallowing dysfunction in acute stroke stage, hence the implementation of multidisciplinary-supported evidence-based protocols may be a preferred strategy.

Because FISS-tris was not a blinded study, the findings may be affected by bias, which is an important limitation of the study. Other potential limitations of our study are related to statistical power and generalizability owing to the relatively low number of patients with END and the homogenous study population of Asian ethnicity.

Despite these limitations, the results of our study suggest that LMWH treatment may have a positive influence on patients with END and progressive stroke due to acute ischemic stroke caused by LAOD. Our study should create interest in further large double-blind clinical trials with advanced diagnostic aids to access the arterial stenosis site and grade on the early anticoagulant therapy in patients with ischemic stroke because of large-artery atherosclerosis, especially intracranial disease.

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REFERENCES


