Low-Molecular-Weight Heparin or Dual Antiplatelet Therapy Is More Effective Than Aspirin Alone in Preventing Early Neurological Deterioration and Improving the 6-Month Outcome in Ischemic Stroke Patients

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Background and Purpose   Dual antiplatelet therapy (DAT) with clopidogrel and aspirin has been shown to confer greater protection against early neurological deterioration (END) and early recurrent ischemic stroke (ERIS) than aspirin alone in patients who have experienced an acute ischemic stroke. However, few studies have compared the effects of anticoagulation therapy with low-molecular-weight heparin (LMWH), DAT, and aspirin.

Methods   Patients with acute ischemic stroke (*n*=1,467) were randomized to therapy groups receiving aspirin (200 mg daily for 14 days, followed by 100 mg daily for 6 months), DAT (200 mg of aspirin and 75 mg of clopidogrel daily for 14 days, then 100 mg of aspirin daily for 6 months), or LMWH (4,000 antifactor Xa IU of enoxaparin in 0.4 mL subcutaneously twice daily for 14 days, followed by 100 mg of aspirin daily for 6 months). The effects of these treatment strategies on the incidence of END, ERIS, and deep-vein thrombosis (DVT) were observed for 10−14 days after treatment, and their impacts on a good outcome were evaluated at 6 months.

Results   The DAT and LMWH were associated with a more significant reduction of END and ERIS within 14 days compared with aspirin-alone therapy. In addition, LMWH was associated with a significantly lower incidence of DVT within 14 days. At 6 months, DAT or LMWH improved the outcome among patients aged >70 years and those with symptomatic stenosis in the posterior circulation or basilar artery compared with aspirin.

Conclusions   LMWH or DAT may be more effective than aspirin alone for reducing the incidence of END and ERIS within 14 days, and is associated with improved outcomes in elderly patients and those with stenosis in the posterior circulation or basilar artery at 6 months post-stroke.
                                                            J Clin Neurol 2015;11(1):57-65

Key Words   acute ischemic stroke, low-molecular-weight heparin, dual antiplatelet therapy, outcomes, early neurological deterioration.

Introduction

Aspirin is the most commonly used antiplatelet medication for ischemic stroke worldwide, and it has been shown to have ben-

eficial effects on patient outcomes.[1,2] A large trial found clopidogrel to be more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction (MI), and vascular death in patients at risk of ischemic events.[3] However, recent observations have suggested that drug resistance leads to the failure of antiplatelet therapy in patients using aspirin or clopidogrel.[4-6] Therefore, intensive clinical research is still needed to develop more effective and safe interventions in these patients.[7]

Aspirin and clopidogrel can synergistically inhibit platelet aggregation because their pharmacological mechanisms are different.[8,9] In fact, such dual antiplatelet therapy (DAT) has been shown to reduce the risk of recurrent ischemic events in patients with acute coronary syndrome.[10,11] Large-scale trials in patients with ischemic stroke did not reveal a clear prophylactic benefit of DAT for ischemic events.[12-14] However, these trials did not include patients with the highest risks. Three recent small pilot studies have shown trends toward a benefit of DAT in patients with acute ischemic stroke.[15-17] The Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events study has also shown that DAT is superior to aspirin alone for reducing the risk of stroke in the first 90 days.[18] However, the impacts of DAT on other clinical outcomes has yet to be investigated.

Anticoagulation therapy with low-molecular-weight heparin (LMWH) in acute ischemic stroke patients remains controversial. The results of the Fraxiparine in Ischemic Stroke (FISS-tris) trial have shown that LMWH is associated with better outcomes as compared with aspirin treatment in patients with large-artery occlusive disease (LAOD).[19] In addition, it has been suggested that anticoagulation therapy is effective in certain subgroups of patients, such as those with posterior circulation stenosis or vertebrobasilar disease.[20,21] However, these observations were not supported by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) or Tinzaparin in Acute Ischemic Stroke Trial (TAIST) results.[22-24] Asians have a higher prevalence than other populations of atherosclerosis development in the intracranial arteries,[25] which might explain why the beneficial effect of LMWH in Chinese patients was not reproduced in studies of Caucasians.

Early neurological deterioration (END) and early recurrent ischemic stroke (ERIS) are very common events in acute stroke patients.[26,27] Our previous studies have shown that LMWH appears to have advantages over aspirin in reducing END and deep-vein thrombosis (DVT),[28] and that DAT is safer and more effective at reducing ischemic stroke recurrence and neurological deterioration.[29] However, LMWH was not compared with DAT, and longer-term outcomes were not investigated in our previous studies. In the present randomized study, we investigated whether subcutaneous enoxaparin or DAT with clopidogrel plus aspirin is superior to aspirin alone in preventing END and ERIS in acute stroke patients within 14 days of treatment. In addition, their impacts on other clinical outcomes were evaluated at 6 months.

Methods

Ethics statement
This clinical study protocol was reviewed and approved by

the Ethics Committee of the People's Hospital of Deyang City and the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical College. Each of the subjects provided informed consent (in Chinese language) to participate before the commencement of this study.

Study populations
The patients who had suffered their first ever stroke and were admitted into the two aforementioned hospitals within 48 h of symptom onset (*n*=1,467) were prospectively enrolled between August 1, 2010 and October 31, 2013. These two hospitals are large hospitals located in southern China.

The inclusion criteria were as follows: 1) aged 40−80 years; 2) diagnosis of ischemic stroke as defined by the World Health Organization criteria; 3) first dose of trial medication was administered within 48 h after the onset of stroke; 4) presence of motor deficit; 5) intracerebral hemorrhage (ICH) not detected in a brain computed tomography (CT) scan; and 6) presence of stroke categorized as being due to either large-artery atherosclerosis (LAA) or small-artery disease (SAD) according to the TOAST classification system.[30]

The following exclusion criteria were applied: 1) cardiogenic cerebral embolisms or cerebral infarction caused by other etiology or other undetermined etiology; 2) score on the National Institutes of Health Stroke Scale (NIHSS) of >15; 3) history of ICH; 4) isolated sensory symptoms, isolated visual changes, isolated dizziness, or vertigo; 5) treatment with thrombolysis or carotid stenting before randomization or during the follow-up period; 6) known contraindications for the use of enoxaparin, clopidogrel, or aspirin; 7) already on anticoagulation therapy or antiplatelet therapy before the onset of stroke; 8) sustained hypertension (blood pressure >200/110 mm Hg) before randomization; 9) gastrointestinal bleeding or major surgery within the previous 3 months; and 10) coexisting systematic diseases such as a malignant tumor, renal failure, cirrhosis, severe dementia or psychosis, brain tumor, atrial fibrillation on electrocardiogram, chronic rheumatic heart disease, post metallic heart-valve implantation, or thrombocytopenia (platelet count <100×10^9/L, if known).

All patients underwent a brain CT scan before randomization and again during days 10−14 to identify ICH or hemorrhagic transformation (HT). Vascular imaging assessments were performed to identify stenosis of the internal carotid arteries, vertebrobasilar arteries, middle cerebral arteries, anterior cerebral arteries, and posterior cerebral arteries with the aid of a carotid duplex scan, CT angiography, or magnetic resonance angiography; any stenosis was diagnosed according to previously described criteria.[31,32] The vascular evaluation was performed before or within 2 days of randomization. Venous duplex ultrasound examination of both lower limbs was also

performed at day 14 to identify asymptomatic DVTs.

Study design and treatment regimens

Patients fulfilling the enrollment criteria were randomized to one of three treatment groups: 1) aspirin; 2) DAT with aspirin and clopidogrel; or 3) LMWH. Randomization was performed by an independent randomization committee with sealed envelopes and using computer-derived random sequences.

According to the Chinese Acute Ischemic Stroke Management Guidelines,[33] patients allocated to the aspirin group received aspirin at 200 mg daily for 14 days, followed by 100 mg daily for 6 months. Patients in the DAT group received 200 mg of aspirin and 75 mg of clopidogrel daily for 14 days, then 100 mg of aspirin daily for 6 months. The LMWH group received 0.4 mL of 4,000 antifactor Xa IU of enoxaparin via subcutaneous injection twice daily for 14 days, followed by 100 mg of aspirin daily for 6 months. In addition, the other stroke treatments were administered according to the Chinese Acute Ischemic Stroke Management Guidelines,[33] including a similar blood pressure goal after stroke, DVT prophylaxis, statin use, and rehabilitation in the two involved hospitals.

Outcomes

Baseline data were collected, including demographics, medical history, and NIHSS scores. The primary efficacy outcome was the incidence of END, which was defined as an increase in the score on the NIHSS scale of at least 4 points within 10 days after admission, excluding HT of an infarct or a newly formed infarct in another vascular territory.[34] The secondary efficacy outcomes included incidences of ERIS, venous thromboembolism (VTE), MI, and death within 14 days after admission. ERIS was defined as a sudden and persistent (lasting >24 h) deficit, with the presence of both clinical symptoms and a new lesion on the diffusion-weighted image of ischemic stroke diagnosed as an independent artery from the index stroke territory.[35] VTE included symptomatic or asymptomatic DVT, symptomatic pulmonary embolism (PE), or fatal PE.[36] Deaths, regardless of the causes, were also recorded.

The safety outcomes included hemorrhagic episodes that occurred during the 14 days after admission. Hemorrhagic episodes were defined as the presence of any of the following: 1) symptomatic or asymptomatic HT of the cerebral infarct, or symptomatic or asymptomatic ICH, which was not associated with cerebral infarction; 2) extracranial hemorrhages (e.g., gastrointestinal bleeding, hematoma, or hematuria). Serious hemorrhage was defined as any symptomatic intracranial hemorrhage or any hemorrhage requiring a blood transfusion.

At day 14 after admission or at discharge from the hospital (whichever occurred first), trained personnel without knowledge of the patients' treatment allocation determined the NI-HSS and modified Rankin Scale (mRS) scores for each patient. At 6 months after admission, a follow-up assessment was performed by telephone interview and by reviewing the medical charts of each participant; the mRS scores were determined again by a clinician or a nurse without knowledge of the treatment allocation. Favorable outcome was defined as an mRS score of 0−2, and disability was identified as an mRS score of >2 in the survivors. Recurrent ischemic stroke, MI, hemorrhage, VTE, and overall mortality during follow-up were also documented.

All reported efficacy and safety outcomes were confirmed by our central adjudication committee, which was unaware of the study-group assignments.

Statistical analysis

We speculated that a sample size of 1,450 patients would provide a power of 90% in detecting a relative risk (RR) reduction of 15% in the DAT group, with a two-sided type I error of 0.05, assuming an event rate of 10% in the aspirin group and a 5% overall rate of withdrawal (defined as medication nonadherence).[37] SPSS (version 16.0, SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. Categorical variables are presented as frequencies and percentages. For the categorical variables, patient demographics among groups were compared using chi-squared tests or, if the expected frequencies were small, Fisher's exact tests were conducted. Continuous variables are presented as mean±SD values, and were compared using analysis of variance followed by the Student-Newman-Keuls test for three-group comparisons. Cox proportional modeling was used to analyze the potential risk of 6-month disability. The results are reported as RRs and the corresponding 95% confidence intervals (CIs).

Results

Study patients and follow-up

Fig. 1 shows the general profile of the study. In total, 1,467 patients were enrolled, with 489 randomized to the aspirin group, 490 to the DAT group, and 488 to the LMWH group. Thirteen patients were withdrawn by the local investigators (three in the aspirin group, five in the DAT group, and five in the LMWH group) because they did not meet the inclusion criteria for the following reasons: they began treatment >48 h after symptom onset, received carotid stenting after randomization, or experienced cardiogenic cerebral embolisms after extensive cardiac and other laboratory investigations. Thus, 1,454 patients (486 in the aspirin group, 485 in the DAT group, and 483 in the LMWH group) were analyzed. The three groups were well balanced with respect to the baseline characteristics (Table 1).
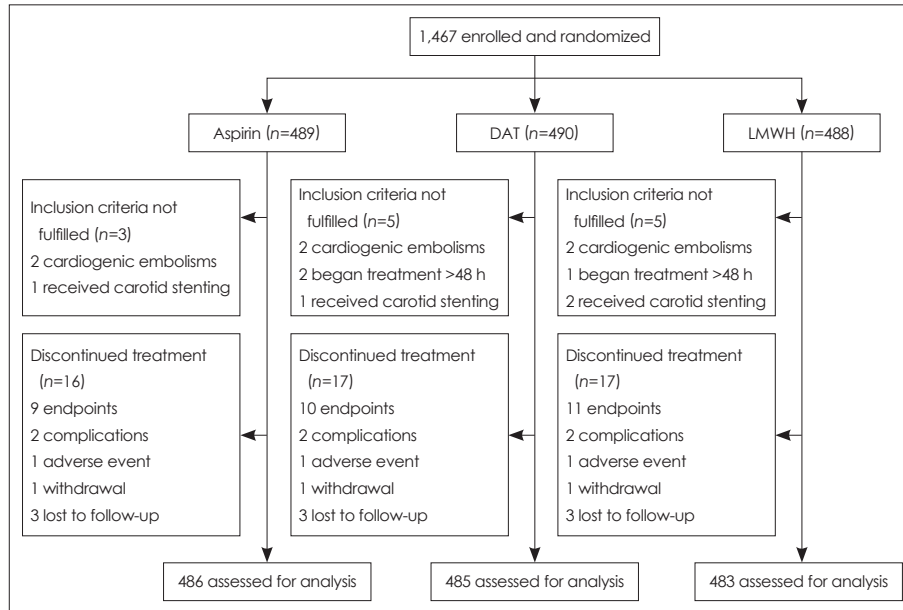
Fig. 1. General profile of the study. DAT: dual antiplatelet therapy, LMWH: low-molecular-weight heparin.

Table 1. Baseline characteristics of the patients in the three treatment groups

	Aspirin, n=486	DAT, n=485	LMWH, n=483	p*
Age (years)	70.1±11.12	69.5±10.14	71.1±10.41	0.18
Gender (female)	218 (44.86)	220 (45.36)	221 (45.76)	0.99
SBP (mm Hg)	134.9±21.26	135.3±20.32	136.4±20.21	0.22
DBP (mm Hg)	83.5±10.91	84.1±11.2	84.2±10.72	0.26
Time between symptom onset and randomization (h)	40.8±8.46	41.1±8.62	40.5±9.13	0.72
Smoking	199 (40.95)	201 (41.44)	192 (39.75)	0.90
Hypertension	345 (70.99)	348 (71.75)	342 (70.81)	0.91
Diabetes	165 (33.95)	160 (32.99)	167 (34.58)	0.93
Previous MI	7 (1.44)	9 (1.86)	8 (1.66)	0.99
Previous angina	10 (2.06)	9 (1.86)	11 (2.28)	0.98
TC (mmol/L)	5.02±1.02	4.98±1.12	4.96±1.21	0.51
TG (mmol/L)	1.82±0.63	1.79±0.71	1.80±0.69	0.80
HDL-C (mmol/L)	1.31±0.37	1.28±0.41	1.27±0.38	0.63
LDL-C (mmol/L)	3.48±1.01	3.26±0.96	3.37±0.83	0.44
NIHSS score at baseline	10.48±3.24	9.96±3.01	9.88±3.11	0.36
Length of stay (days)	17.83±5.85	16.98±4.95	17.10±4.66	0.75
Current medications				
Antihypertensive	267 (54.94)	270 (55.67)	261 (54.04)	0.99
Hypoglycemic	132 (27.16)	140 (28.87)	140 (28.98)	0.98
Stating	49 (10.08)	45 (9.28)	47 (9.73)	0.98
Antiplatelet	0	0	0	
Stroke subtype				
LAA	332 (68.31)	325 (67.01)	334 (69.15)	0.62
SAD	154 (31.69)	160 (32.99)	149 (30.85)	

Except where stated otherwise, the data are mean±SD or n (%) values.
*Statistical significance was based on variance analysis and the chi-squared (χ^2) test. Compared among the three-group comparison, p>0.05.
DAT: dual antiplatelet therapy, DBP: diastolic blood pressure, HDL: high-density lipoprotein, LAA: large-artery atherosclerosis stroke, LDL: low-density lipoprotein, LMWH: anticoagulant therapy with low-molecular-weight heparin, NIHSS: National Institutes of Health Stroke Scale, SAD: small-artery disease, SBP: systolic blood pressure, TC: total cholesterol, TG: triglyceride.

The median age of the patients was 70 years, and 45.32% of them were women. A total of 71.18% of the patients had a history of hypertension, and 33.83% had diabetes. Eight patients (0.55%), including three in the aspirin group, three in the DAT group, and two in the LMWH group, were lost during the follow-up. Sixteen patients (3.29%) in the aspirin group, 17 (3.51%) in the DAT group, and 17 (3.52%) in the LMWH group discontinued the study medication before the end of the study (Fig. 1).

Efficacy outcomes

Of the 1,454 included patients, 7.36% (107/1,454) suffered from END and 1.65% (24/1,454) suffered from ERIS. END occurred in 72 patients (14.81%) in the aspirin group, compared to 20 (4.12%) in the DAT group and 15 (3.11%) in the LMWH group. ERIS was observed in 18 patients (3.7%) in the aspirin group, compared to 3 (0.62%) in the DAT group and 3 (0.62%) in the LMWH group. DAT and LMWH were associated with more significantly reduced rates of END and ERIS within 14 days of treatment compared with aspirin ($p<0.001$) (Table 2). However, the incidences of END and ERIS did not differ significantly between the DAT and LMWH groups (Table 2).

The incidence of DVT within 14 days of treatment was 2.41% (35/1,454), while that for PE was 0.14% (2/1,454). Of the DVT cases, 45.71% (16/35) had no clinical symptoms. LMWH was significantly associated with a lower risk of DVT as compared with either aspirin or DAT [3/483 (0.62%) vs. 17/486 (3.49%) and 15/485 (3.09%); $p=0.008$] (Table 2).

At the 6-month follow-up, the incidence of a favorable outcome did not differ significantly among the three groups (Table 3). However, the patients older than 70 years in the LMWH group and the DAT group were more likely to have a favorable outcome as compared with their counterparts in the aspirin group [63.64% (154/242) and 64.02% (153/239) vs. 43.98% (106/241)]. The incidence of a favorable outcome following DAT or LMWH was also significantly increased in patients with symptomatic stenosis in the posterior circulation artery [72.97% (54/74) and 75.34% (55/73) vs. 42.25% (30/71)] or basilar artery [78.57% (33/42) and 76.74% (33/43) vs. 45.95% (17/37)] (Table 3). However, no difference in the incidence of a favorable outcome among the three groups was observed in patients of the other subgroups, including those with NIHSS scores of 0−9 or 10−15, or patients with LAA or SAD (Table 3).

The occurrence of PE, MI, or all-cause death during the first 14 days of treatment were did not differ significantly among the three groups (Table 2). Furthermore, no significant differ-

Table 2. Incidence of efficacy and safety outcomes in the patients in the three treatment groups

	Aspirin, n=486	DAT, n=485	LMWH, n=483	p*
Efficacy outcome				
END	72 (14.81)	20 (4.12)	15 (3.11)	<0.001†
ERIS	18 (3.70)	3 (0.62)	3 (0.62)	<0.001†
DVT	17 (3.49)	15 (3.09)	3 (0.62)	0.008‡
Symptomatic	9 (1.85)	8 (1.65)	2 (0.41)	0.13
Asymptomatic	8 (1.64)	7 (1.44)	1 (0.21)	0.23
PE	1 (0.21)	1 (0.21)	0 (<0.01)	-
MI	1 (0.21)	1 (0.21)	1 (0.21)	0.99
All-cause death	2 (0.41)	2 (0.41)	2 (0.41)	0.99
Safety outcome				
HT	18 (3.70)	23 (4.74)	24 (4.96)	0.52
Symptomatic	2 (0.41)	2 (0.41)	2 (0.41)	0.99
Asymptomatic	16 (3.29)	21 (4.33)	22 (4.55)	0.67
ICH	2 (0.41)	2 (0.41)	2 (0.41)	0.99
Symptomatic	1 (0.21)	1 (0.21)	1 (0.21)	0.99
Asymptomatic	1 (0.21)	1 (0.21)	1 (0.21)	0.99
Extracranial hemorrhage	7 (1.44)	10 (2.06)	10 (2.07)	0.75
Serious hemorrhage	0	0	0	-

The data are n (%) values.
*Statistical significance was based on the χ^2 test, †Comparison between aspirin group and the DAT and LMWH groups; $p<0.001$, ‡Comparison between the LMWH group and the DAT and aspirin groups; $p=0.008$. All others were compared using the three-group comparison; $p>0.05$.
DAT: dual antiplatelet therapy, DVT: deep-vein thrombosis, END: early neurological deterioration, ERIS: early recurrent ischemic stroke, HT: hemorrhagic transformation of the cerebral infarction, ICH: intracerebral hemorrhage, LMWH: anticoagulant therapy with low-molecular-weight heparin, MI: myocardial infarction, PE: pulmonary embolism.

ences among the three groups in the incidence of recurrent ischemic stroke, DVT, MI, or all-cause death were observed during day 15 to 6 months (Table 4).

Cox proportional regression analyses showed that END (RR=3.145, 95% CI=1.214−7.348; p<0.001) may be an inde-

pendent risk factor for 6-month disability (Table 5).

Safety outcomes

The incidences of HT, ICH, and extracranial hemorrhage did not differ significantly among the three groups at day 14 after

Table 3. Incidence of a favorable outcome in the three groups at 6 months

	Aspirin		DAT		LMWH		p*
	n	n (%)	n	n (%)	n	n (%)	
Total	486	293 (60.29)	485	302 (62.27)	483	299 (61.90)	0.82
Age >70 years	241	116 (48.13)	242	154 (63.64)	239	153 (64.02)	<0.001
Age ≤70 years	245	177 (72.22)	243	148 (60.91)	244	146 (59.84)	0.071
Male	268	176 (65.67)	265	179 (67.55)	262	174 (66.41)	0.78
Female	218	117 (53.67)	220	123 (55.91)	221	125 (56.56)	0.81
LAA patients	332	168 (50.60)	325	169 (52.00)	334	169 (50.59)	0.32
SAD patients	154	125 (81.17)	160	133 (83.13)	149	121 (81.21)	0.32
NIHSS score at baseline							
0–8	330	219 (66.36)	325	224 (67.88)	327	224 (68.50)	0.48
9–15	156	74 (47.44)	160	78 (48.75)	156	75 (48.08)	0.69
Symptomatic artery[†] of LAA patients							
Anterior	218	149 (68.35)	212	146 (68.87)	215	142 (66.05)	0.82
Posterior	71	30 (42.25)	74	54 (72.97)	73	55 (75.34)	<0.001
Internal carotid	59	39 (66.10)	56	37 (66.07)	54	38 (70.37)	0.84
Middle cerebral	114	77 (67.54)	110	72 (65.45)	115	74 (64.35)	0.89
Basilar	37	17 (45.95)	42	33 (78.57)	43	33 (76.74)	0.006
Combination[‡]	66	27 (40.91)	68	28 (41.18)	61	25 (40.98)	0.99

The data are presented as the total number of patients in the subgroup (n) followed by the number and percentage of patients in that subgroup with a favorable outcome, defined as an mRS score of 0–2 [i.e., n, n (%)].
*The χ^2 test was used to compare good outcomes between LMWH and aspirin treatment, [†]The symptomatic artery was identified by cerebral vessel evaluations including transcranial Doppler, carotid duplex, and magnetic resonance angiography, [‡]Combinations include internal carotid artery and middle cerebral artery, middle cerebral artery and anterior cerebral artery, posterior cerebral artery and basilar artery, posterior cerebral artery and vertebral artery, and basilar artery and vertebral artery; bilateral vertebral artery stenosis was identified to be symptomatic at enrollment.
DAT: dual antiplatelet therapy, LAA: large-artery atherosclerosis stroke, LMWH: anticoagulant therapy with low-molecular-weight heparin, SAD: small-artery disease.

Table 4. Incidence of secondary efficacy and safety outcomes in the three treatment groups

	Aspirin, n=486	DAT, n=485	LMWH, n=483	p*
Efficacy outcome				
RIS	10 (2.06)	8 (1.65)	8 (1.66)	0.92
DVT	3 (0.62)	3 (0.62)	3 (0.62)	0.99
PE	0	0	0	-
MI	3 (0.62)	3 (0.62)	3 (0.62)	0.99
All-cause death	4 (0.82)	5 (1.03)	4 (0.83)	0.99
Safety outcome				
HT	3 (0.62)	2 (0.41)	2 (0.41)	0.99
ICH	2 (0.41)	2 (0.41)	2 (0.41)	0.99
Extracranial hemorrhage	4 (0.82)	5 (1.03)	4 (0.83)	0.99
Serious hemorrhage	0	0	0	-

The data are n (%) values.
*Statistical significance was based on the chi-squared (χ^2) test.
DAT: dual antiplatelet therapy, DVT: deep-vein thrombosis, HT: hemorrhagic transformation of the cerebral infarction, ICH: intracerebral hemorrhage, LMWH: anticoagulant therapy with low-molecular-weight heparin, MI: myocardial infarction, PE: pulmonary embolism, RIS: recurrent ischemic stroke.

Table 5. RRs for the prediction of disability at 6 months post-stroke: Cox proportional modeling analysis

Variables	p	RR	95% CI
Gender (female)	0.161	0.913	0.923–1.724
Age (years)	0.124	0.867	0.932–1.629
Hypertension	0.094	1.212	1.011–3.124
Diabetes	0.097	1.032	0.985–2.643
DVT	0.064	1.342	0.969–2.462
END	<0.001	3.145	1.214–7.348
HT or ICH	0.067	1.245	0.986–2.457
LAA stroke	0.284	0.856	0.895–1.428
SAD stroke	0.242	0.901	0.795–1.412

DVT: deep-vein thrombosis, END: early neurological deterioration, HT: hemorrhagic transformation of the cerebral infarction, ICH: intracerebral hemorrhage, LAA: large-artery atherosclerosis stroke, RR: relative risk, SAD: small-artery disease, 95% CI: 95% confidence interval.

randomization (Table 2) or within 6 months (Table 4). Moreover, no major hemorrhagic events were detected in any of the groups (Table 2 and 4).

Discussion

In this randomized controlled study of Chinese patients who had just experienced an acute ischemic stroke, we found that overall 7.36% of patients developed END and 1.65% had an ERIS within 14 days of treatment. More importantly, the results of this study indicate that both DAT and LMWH were more effective than aspirin alone for the prevention of END and ERIS. In addition, neither DAT nor LMWH appeared to increase the risk of hemorrhagic events in these patients as compared with aspirin treatment. Moreover, the benefits of DAT and LMWH appeared to be observed mainly in elderly patients and those with stenosis in the posterior circulation or basilar artery. These results suggest that either DAT or LMWH may be a rational choice for patients who have just experienced an acute ischemic stroke (at least for Chinese patients).

The optional antithrombosis strategy for patients who have experienced an acute ischemic stroke has been studied extensively, but the data are inconsistent. The results of the present study appear to differ from those of previous trials, which did not support a better effect of DAT.[12,14] One possible explanation for this discrepancy is that unlike previous trials, our trial included only patients who had their first acute stroke within 48 h of treatment and an NIHSS score of <15; patients with such an NIHSS score may have a lower risk of hemorrhage. In contrast, previous trials have included patients who had experienced strokes of greater severity, but not in the acute phase. Patients in the first hours after an index stroke, during which the risk of neurological deterioration and recurrent ischemia is particularly high, were not included in those studies. These

differences may mean that the previous trials did not have sufficient statistical power to detect the potential benefits of DAT for the prevention of END and ERIS. Moreover, the treatment duration of DAT was 14 days in the present study, while for the previous two trials[12,14] the duration of combination therapy was much longer (28 months and 18 months, respectively). It can be estimated that a longer duration of DAT may be associated with a greater likelihood of hemorrhagic events, which may overcome their benefits with respect to favorable outcomes.

The value of anticoagulant therapy for acute ischemic stroke remains controversial. In this study, LMWH was superior to aspirin for the prevention of END and ERIS, which is consistent with another study involving Asians.[20] However, the previous FISS-tris trial revealed no significant benefit of LMWH over aspirin in patients with LAOD.[38] However, the FISS-tris trial had a small sample (353 in total, comprising 180 LMWH- and 173 aspirin-treated patients), and it did not examine early effectiveness. The incidences of END and ERIS found in TOAST and TAIST were similar in the present study, but no significant differences regarding the incidences of END and ERIS were detected between the LMWH and the aspirin or placebo groups.[22-24] One potential shortcoming of these two trials is that no attempt was made to determine whether anticoagulant treatment was more effective in certain subgroups of patients who had experienced an acute ischemic stroke. The inclusion of different races in the study population may also have affected the results; for example, atherosclerosis develops more frequently in the intracranial arteries in Asians than in other populations.[25]

In our study, both DAT and LMWH were significantly associated with a favorable outcome at 6 months poststroke in patients older than 70 years, while aspirin was not. Age is well recognized as an independent risk factor for stroke. Previous studies have shown that age is an independent risk factor for intracranial atherosclerosis (ICAS),[39] and that the prevalence of basilar artery lesions increases with age.[40] Age may not only increase the severity of ICAS, but may also influence the distribution of occluded vessels.[39] On the other hand, the consequences of platelet activation, such as platelet aggregation and platelet-leukocyte aggregation, play a crucial role in arterial thrombogenesis and in the pathophysiology of ischemic stroke in the elderly.[29,41] Hence, antithrombotic therapy could reduce the risk of recurrent stroke.[42] Retrospective studies also suggest that anticoagulation can improve the outcome in certain subgroups of patients with severe stenosis (70−99%) or vertebrobasilar disease.[20,21] Thus, the present findings support a potential role of LMWH or DAT as an effective antithrombotic therapy in the elderly.

The results of this study also show that either DAT or

LMWH may be more effective than aspirin alone in patients with posterior circulation stenosis or basilar artery stenosis. These findings are consistent with those of previous retrospective studies.[20,21] Wang et al.[20] showed that LMWH may be more efficacious in patients with posterior circulation stenosis, while it may not be beneficial in patients with basilar artery stenosis. However, their study included only 28 patients with basilar artery stenosis, which limits the power of its findings and resulted in wide CIs, thus further reducing the reliability of the findings. Previous retrospective studies have shown the benefit of warfarin in patients with vertebrobasilar disease;[21] however, no significant difference was identified in the areas of symptomatic arteries between aspirin and warfarin in the Warfarin-Aspirin Symptomatic Intracranial Disease study.[43] It has been suggested that anterior circulation stroke (ACS) differs from posterior circulation stroke (PCS) in terms of the etiology and pathological mechanisms. PCS is most often due to atherosclerosis and local branch occlusion, while ACS is usually due to artery-to-artery embolism, and is merely associated with local branch occlusions.[44,45] These factors are possible reasons for the potential different efficacies of DAT or LMWH, according to the involved vessels.

With regard to the safety outcomes, the risks of HT, ICH, and extracranial hemorrhage also did not differ significantly among the three treatment groups. Furthermore, no serious hemorrhagic events were detected in any of the patients from the three groups. These results indicated that either DAT or LMWH may be safe in patients who have just experienced an acute ischemic stroke.

This study was subject to some limitations, the most important being its nonblinded design. The results of this two-center study, with its relative small sample, may not represent most accurately the disease outcomes after DAT or LMWH in China. The short duration of therapy exposure and outcome assessment, along with the inclusion/exclusion criteria may limit the generalizability of the trial results. Before the proposed drug regime is applied in clinical practice, studies with larger scales are required to validate the advantage of DAT or LMWH in acute ischemic stroke patients. Furthermore, double-blind studies with multiple centers should be performed to confirm the efficacy and safety of DAT and LMWH in patients with acute ischemic stroke.

In conclusion, to the best of our knowledge, few studies have compared the efficacies of LMWH, DAT, and aspirin alone in the prevention of END in acute stroke patients. The findings of this study suggest that either DAT or LMWH is more effective than aspirin alone for reducing the rates of END and ERIS within 14 days of treatment, as well as improving the outcomes in elderly patients and those with stenosis in the posterior circulation or basilar artery at 6 months poststroke. In addition, both DAT and LMWH appear to be associated with fewer hemorrhagic events in these patients as compared with aspirin alone.

Conflicts of Interest

The authors have no financial conflicts of interest.

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