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Efficacy and safety of early anticoagulation after endovascular treatment in patients with atrial fibrillation

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ABSTRACT

Background The timing for initiating anticoagulant therapy in acute ischaemic stroke (AIS) patients with atrial fibrillation who recanalised after endovascular treatment (EVT) is unclear. The objective of this study was to evaluate the effect of early anticoagulation after successful recanalisation in AIS patients with atrial fibrillation.

Methods Patients with anterior circulation large vessel occlusion and atrial fibrillation who were successfully recanalised by EVT within 24 hours after stroke in the Registration Study for Critical Care of Acute Ischemic Stroke after Recanalization registry were analysed. Early anticoagulation was defined as the initiation of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) within 72 hours after EVT. Ultra-early anticoagulation was defined if it was initiated within 24 hours. The primary efficacy outcome was the score on the modified Rankin Scale (mRS) at day 90, and the primary safety outcome was symptomatic intracranial haemorrhage within 90 days.

Results Overall, 257 patients were enrolled, of whom 141 (54.9%) initiated anticoagulation within 72 hours after EVT, including 111 within 24 hours. A significant shift towards better mRS scores at day 90 was associated with early anticoagulation (adjusted common OR 2.08 (95% CI 1.27 to 3.41)). Symptomatic intracranial haemorrhage was comparable between patients treated with early and routine anticoagulation (adjusted OR 0.20 (95% CI 0.02 to 2.18)). Comparison of different early anticoagulation regimens showed that ultra-early anticoagulation was more significantly associated with favourable functional outcomes (adjusted common OR 2.03 (95% CI 1.20 to 3.44)) and reduced the incidence of asymptomatic intracranial haemorrhage (OR 0.37 (95% CI 0.14 to 0.94)).

Conclusions In AIS patients with atrial fibrillation, early anticoagulation with UFH or LMWH after successful recanalisation is associated with favourable functional outcomes without increasing the risk of symptomatic intracranial haemorrhages.

Trial registration number ChiCTR1900022154.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Current guidelines recommend starting anticoagulation 4–14 days after stroke in patients with atrial fibrillation. However, the timing of initiation of anticoagulation after endovascular treatment (EVT) in such patients is uncertain.

WHAT THIS STUDY ADDS

⇒ Our study found that in acute ischaemic stroke patients with atrial fibrillation who recanalised after EVT, starting anticoagulation within 72 hours is associated with favourable functional outcomes without increasing the risk of symptomatic intracranial haemorrhage. This benefit was more pronounced in patients treated with anticoagulation within 24 hours. The mechanism may be that early anticoagulation can improve microcirculation function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ After rigorous selection, it may be feasible to start anticoagulation therapy earlier after stroke in patients with atrial fibrillation. A randomised controlled trial is needed for further study.

INTRODUCTION

In acute ischaemic stroke (AIS) with large vessel occlusion (LVO), endovascular treatment (EVT) has become one of the most effective treatment modalities. Successful recanalisation occurred in 71%–89% of patients, but only 36%–61% of patients were functional independent 90 days after EVT.[1–6]

Strokes caused by cardioembolic events make up 20%–30% of ischaemic strokes,[7] of which atrial fibrillation is the most common cause.[8] Compared with strokes caused by other causes, strokes caused by atrial fibrillation tend to cause more disability and mortality.[9] The recurrence of embolism after the initial recanalisation is one of the reasons for poor outcomes in AIS patients with atrial fibrillation. As a secondary stroke prevention measure, anticoagulant therapy has been routinely administered to lower the incidence of recurrent embolic events. The current guidelines recommend starting anticoagulation 4–14 days following stroke,[10] because of the potential for intracranial haemorrhage transformation.[11]

Another important cause of poor recovery is persistent tissue hypoperfusion due to incomplete microcirculatory reperfusion after macrovascular recanalisation (no-reflow), which mainly occurs in the first 24 hours after recanalisation.[12] Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been proven in experimental tests to dissolve the microthrombi at microvascular level,[13 14] which may improve microcirculatory perfusion in the ischaemic areas. Several studies have explored the effect of early anticoagulation on AIS patient outcomes,[15] but evidence on the optimal time to initiate anticoagulation for AIS patients with atrial fibrillation who recanalise after EVT is still lacking. The objective of this study was to evaluate the efficacy and safety of early anticoagulant therapy after successful recanalisation by EVT in AIS patients with atrial fibrillation.

METHODS

Study population

We used data from the Registration Study for Critical Care of Acute Ischemic Stroke after Recanalization registry, which is a prospective, multicenter cohort study conducted at 18 comprehensive stroke centres across China, aimed to evaluate the outcomes of AIS patients with LVO treated with EVT in clinical practice. This study is registered on the Chinese Clinical Trial Registry (URL: http://www.chictr.org.cn; Unique identifier: ChiCTR1900022154).

Inclusion and exclusion criteria

Patients aged 18 years or older, with LVO in the anterior circulation (internal carotid artery, middle cerebral artery (M1/M2)), and with atrial fibrillation were eligible for inclusion in the current study. We confirmed the LVO by CT angiography. Patients should also have a moderate-to-severe AIS (a score of 6 or more on the National Institutes of Health Stroke Scale (NIHSS, ranging from 0 to 42, with higher scores indicating greater deficits)), must not already have a large core infarction (a score of 6 or more on the Alberta Stroke Programme Early CT Score (ASPECTS)), and have a prestroke modified Rankin Scale (mRS, an ordered scale ranging from 0 (no symptoms) to 6 (dead)) Score of 1 or less. Finally, patients should be able to be successfully recanalised (modified Thrombolysis In Cerebral Infarction Score of 2b to 3) after EVT.

We excluded patients who had parenchymatous haematoma type 2 (haematoma occupying 30% or more of the infarcted tissue, with obvious mass effect[16] or severe subarachnoid haemorrhage (SAH, defined as modified Fisher scale 2–4[17]; grade 2 indicates minimal or thin SAH with intraventricular haemorrhage (IVH); grade 3, thick cisternal clot without IVH; grade 4, cisternal clot with IVH) as confirmed on postprocedure non-contrast computed tomography (NCCT); discharged within 24 hours after EVT; and lost to follow-up at 90 days. If a patient had a 4 point or more increase in NIHSS Score within 24 hours after EVT, while postprocedure NCCT imagings were not available and the cause of the exacerbation was not documented in detail, it was considered that a procedure-related severe intracranial haemorrhage had occurred and this patient's information needed to be excluded.

Anticoagulant therapy administration

Initiation of UFH or LMWH within 72 hours after EVT was defined as early anticoagulation. This group was further subdivided into an ultraearly anticoagulation group that started anticoagulation within 24 hours and a 24–72-hour anticoagulation group. Those who start anticoagulation on or after the fourth day of stroke are defined as the routine anticoagulation group. In the early group, patients were treated with UFH for 24 hours or more, LMWH for two or more times, or UFH bridging LMWH for a cumulative duration of 24 hours or more. The median duration of UFH or LMWH use was 5 days, with UFH doses ranging from 300 to 1000 IU/hour and LMWH doses ranging from 2000 to 4250 IU two times per day. In the routine group, patients were anticoagulated with vitamin K antagonists, NOAC or LMWH.

All patients in the early anticoagulation group had a detailed explanation of the possible benefits and risks of early anticoagulation with UFH or LMWH by the neurologist prior to drug administration. The final decision was made by the patients or their legal representative. The choice of anticoagulant drug and its dose was left to the discretion of experienced neurologist. Depending on the anticoagulant dose, we classify the regimens into minimal dose (initial UFH dose of 300 IU/hour and up to 500 IU/hour, or LMWH dose of 2000 IU two times per day) and low dose (initial UFH dose of 500 IU/hour or maximum dose over 500 IU/hour, or LMWH dose of 4000 or 4250 IU two times per day).

Outcome measures

The score on the mRS at day 90 and symptomatic intracranial haemorrhage (sICH, intracranial haemorrhage on follow-up NCCT with an increase of 4 or more points on the NIHSS) within 90 days were the primary efficacy and safety outcome, respectively. Functional independence (mRS≤2) at day 90, mortality, asymptomatic intracranial haemorrhage (aICH) and new ischaemic stroke within 90 days were secondary outcomes.

The first postprocedure NCCT was used as a reference, and the follow-up NCCT was compared with it. If there was a new hyperdense area in the follow-up NCCT, it was considered a new intracranial haemorrhage. If a new hypointense area appears outside the original infarct lesion, it was considered a new ischaemic stroke. When follow-up NCCT information was missing and the patient's symptoms did not worsen, we assumed the patient had no new intracranial haemorrhage or new ischaemic stroke.

Statistical methods

The Student's t-test or the Mann-Whitney U test was used to analyse continuous variables, which are expressed as

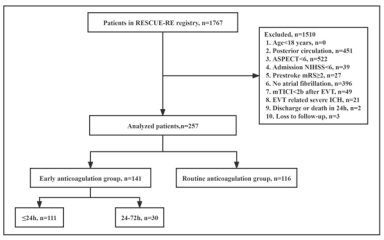

Figure 1 Flowchart. ASPECTS, Alberta Stroke Programme Early CT Score; EVT,endovascular treatment; ICH, intracranial haemorrhage; mRS, modified Rankin Scale; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; RESCUE-RE, Registration Study for Critical Care of Acute Ischemic Stroke after Recanalization.

mean and SD or median and IQR. Categorical variables are expressed as frequency (percentage), and they were analysed using the Fisher's exact test or the χ^2 test. Statistics were considered significant for p values<0.05. Using ordinal and multivariable logistic regression, we compared the outcomes of patients treated with early and routine anticoagulation, adjusted for prognostic factors (age, history of hypertension, baseline NIHSS, baseline glucose level, baseline ASPECTS, treatment with intravenous thrombolysis, heparin during procedure and onset to reperfusion time). These factors were selected based on statistical significance in the univariable analysis and the potential to affect patient outcomes. The functional independence in subgroups were divided by age (≤72 years or >72 years), sex (male or female), stroke severity (NIHSS Score 6 to 16 or >16), baseline ASPECTS (6 to 8 or >8), occlusion site (internal carotid artery, first or second segment of middle cerebral artery) and onset to reperfusion time (≤410 min or >410 min) and were compared between the two groups. IBM SPSS Statistics V.24.0 was used for all statistical analyses.

RESULTS

Patient population

Overall, 257 patients were included for analysis, among them, 141 (54.9%) were treated with UFH or LMWH within 72 hours after EVT, including 111 within 24 hours (figure 1). In the early anticoagulation group, patients had higher admission NIHSS scores (16 (12, 21) vs 15 (12, 18), p=0.02), lower proportion of previous hypertension (64/141 (45.4%) vs 78/116 (67.2%), p<0.01) and higher proportion of preprocedure intravenous thrombolysis (66/141 (46.8%) vs 38/116 (32.8%), p=0.02) and intraprocedure UFH use (64/141 (45.4%) vs 27/116 (23.3%), p<0.01). The median time from symptom onset to arrival in the emergency room was longer in the early anticoagulation group (204 (105, 353) vs 139 (80, 251) min, p=0.01), but the procedure time was shorter (60 (40, 97) vs 85 (50, 135) mins, p=0.01). In terms of other baseline data, there were no significant differences between the two groups (table 1).

Primary and secondary outcomes

Patients in the early anticoagulation group had better and significantly different mRS scores at day 90 than those in the routine anticoagulation group (2 (1–4) vs 3 (1–4); adjusted common OR (acOR) 2.08 (95% CI 1.27 to 3.41); figure 2). Five patients experienced sICH, including 2 (1.4%) and 3 (2.6%) patients from the early and routine anticoagulation groups, respectively. Early anticoagulation and sICH did not show a statistically significant association (adjusted OR (aOR) 0.20 (95% CI 0.02 to 2.18)). Among secondary outcomes, the early anticoagulation group had a higher proportion of functional independence (82/141 (58.2%) vs 53/116 (45.7%), aOR 2.28 (95% CI 1.21 to 4.31)) and lower mortality (7/141 (5.0%) vs 20/116 (17.2%), aOR 0.26 (95% CI 0.09 to 0.71)). The incidence of aICH (24/141 (17.0%) vs 14/116 (12.1%), aOR 1.73 (95% CI 0.78 to 3.88)) and new ischaemic stroke (9/141 (6.4%) vs 7/116 (6.0%), aOR 1.11 (95% CI 0.36 to 3.40), table 2) were comparable between the two groups.

Subgroup analysis

Subgroup analyses for functional independence are presented in figure 3. Its results did not show any characteristics significantly associated with early anticoagulation effects. Patients age >72 years, woman, admission NIHSS 6–16, internal carotid artery occlusion and onset to reperfusion time>410 min had a higher proportion of functional independence in the early anticoagulation group, but without statistically significant.

Different early anticoagulation regimens

Baseline characteristics of patients on different regimens in the early anticoagulation group are described in online supplemental tables 1–3. The favourable shift in the mRS distribution at day 90 was significant for ultraearly anticoagulation (acOR 2.03 (95% CI 1.20 to 3.44)) but not for 24–72-hour anticoagulation (1.95 (0.89–4.30)) compared with those who receive routine anticoagulation (online supplemental figure 1). Compared with 24–72-hour anticoagulation, ultraearly anticoagulation was associated with a decreased incidence of aICH (OR 0.37 (95% CI 0.14 to 0.94)). The various anticoagulant regimens for other categories did not show any statistically significant differences in efficacy and safety outcomes (figure 4, online supplemental tables 4–6).

DISCUSSION

This retrospective study found that early anticoagulation with UFH or LMWH after successful recanalisation is associated with favourable functional outcomes in AIS patients with atrial fibrillation without increasing the risk of sICH. Comparing different early anticoagulation regimens, we further found that ultraearly anticoagulation was more significantly associated with favourable functional outcomes and reduced the incidence of aICH.

For secondary prevention of AIS patients with atrial fibrillation, anticoagulation therapy is recommended,

Table 1 Baseline demographics of patients treated with early versus routine anticoagulation

	Early anticoagulation (n=141)	Routine anticoagulation (n=116)	P value
Common patient characteristics			
Age, years	71 (62–78)	73 (65–79)	0.15
Male	52 (36.9%)	56 (48.3%)	0.07
Admission NIHSS	16 (12–21)	15 (12–18)	0.02*
Ischaemia in left hemisphere	74 (52.5%)	59 (50.9%)	0.80
Treatment with intravenous thrombolysis	66 (46.8%)	38 (32.8%)	0.02*
Premorbid oral antithrombotic use	50 (35.5%)	42 (36.2%)	0.90
Smoke	28 (19.9%)	29 (25.0%)	0.32
Hypertension	64 (45.4%)	78 (67.2%)	<0.01*
Diabetes mellitus	32 (22.7%)	31 (26.7%)	0.46
Previous stroke	16 (11.3%)	22 (19.0%)	0.09
Systolic blood pressure, mm Hg	142.56±23.51	146.49±23.40	0.19
Diastolic blood pressure, mm Hg	83.62±16.26	86.62±16.26	0.15
INR	1.05 (0.99–1.13)	1.06 (0.98–1.12)	0.70
Thrombocyte count, 10^9/L	176 (139–220)	170 (143–224)	0.95
Glucose level, mmol/L	7.50 (6.15–9.20)	7.25 (5.68–9.40)	0.34
CHA2DS2-VASc Score	5 (3–5)	5 (4–6)	0.13
HAS-BLED Score	3 (3–4)	3 (3–4)	0.18
Heparin during procedure	64 (45.4%)	27 (23.3%)	<0.01*
Tirofiban during procedure	36 (25.5%)	38 (32.8%)	0.20
Imaging			
ASPECETS	9 (8–10)	9 (8–10)	0.50
Occlusion site			0.73
ICA	39 (27.7%)	27 (23.3%)	
MCA-M1	77 (54.9%)	67 (57.8%)	
MCA-M2	25 (17.7%)	22 (19.0%)	
Reperfusion before intervention (mTICI)			0.78
0	119 (84.4%)	96 (82.8%)	
1	8 (5.7%)	9 (7.8%)	
2a	5 (3.5%)	6 (5.2%)	
2b	9 (6.4%)	4 (3.4%)	
3	0 (0.0%)	1 (0.9%)	
Workflow, min			
Symptom onset to admission ER	204 (105–353)	139 (80–251)	0.01*
Admission ER to groin puncture	123 (97–162)	138 (95–180)	0.36
Duration procedure	60 (40–97)	85 (50–135)	0.01*
Symptom onset to reperfusion	435 (315–591)	400 (305–544)	0.25

Baseline variables with early versus routine anticoagulation.
*P<0.05.
ASPECTS, Alberta Stroke Programme Early CT Score; CHA2DS2-VASc, (Congestive heart failure, Hypertension, Age ≥75 years [double weight], Diabetes, previous Stroke [double weight], Vascular disease, Age 65–74 years, female Sex category) a tool developed for finding risk factors for thromboembolic events in patients with atrial fibrillation; ER, emergency room; HASBLED, (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly) one risk stratification scheme of several that has been validated to estimate baseline risk of major hemorrhage; ICA, internal carotid artery; INR, international normalised ratio; MCA-M1/M2, the first/second segment of middle cerebral artery; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale.

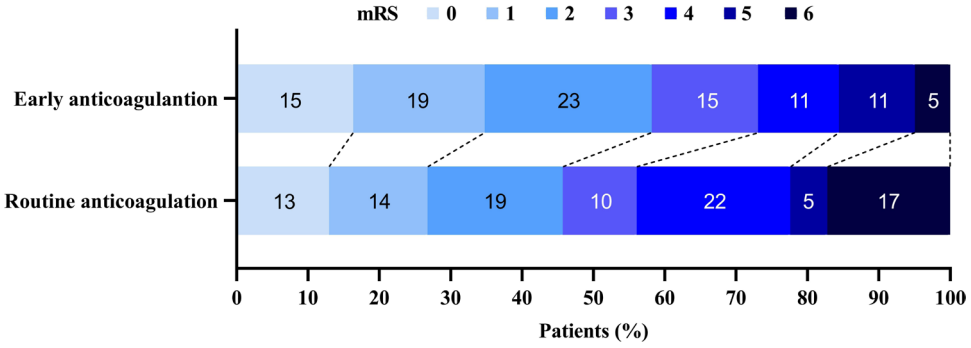

Figure 2 Distribution of modified Rankin Scale (mRS) scores at 90 days for patients allocated to early and routine anticoagulation group (adjusted common OR 2.08 (95% CI 1.27 to 3.41)).

but when to begin it in patients with successful recanalisation after EVT is unclear. Some previous studies have suggested that early anticoagulation after stroke may be feasible. For instance, the Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants (RAF-NOACs) study showed that ICH occurred after 30 days of early anticoagulation, and its association with early anticoagulation was unclear.[18] A registry study found that early initiation of anticoagulation reduces the risk of recurrent stroke and systemic embolism without increasing severe bleeding events.[15] None of these studies analysed patients treated with EVT separately, so it has limited reference value for anticoagulant therapy in patients with recanalisation after EVT.

Neurologist concerns about bleeding complications in the first few days after recanalisation have limited the use of early anticoagulation.[19 20] Patients at high risk of thrombosis events are also at high risk of bleeding events, and no one variable that can consistently separate the two risks.[21] Clinically, the CHA2DS2-VASc (predicting risk for ischaemic events based on the presence of congestive heart failure, hypertension, age ≥75 years [double weight], diabetes, previous stroke [double weight], vascular disease, age 65–74 years and female sex category) and HAS-BLED (predicting risk for major haemorrhage based on the presence of hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years) and drugs/alcohol concomitantly) scores are frequently used to assess the risk of ischaemic or bleeding events in atrial fibrillation patients undergoing anticoagulant therapy.[22 23] All patients in this study had CHA2DS2-VASc scores≥2 and should be on anticoagulants according to the guidelines of antithrombotic therapy for atrial fibrillation.[24] The median HAS-BLED Score was 3 in both groups, indicating that the risk of severe bleeding was not very high. Our findings imply that, following a careful evaluation of the risk of bleeding, early initiation of anticoagulant therapy is safe in patients who had an AIS who should be treated with anticoagulation.

It is important to recognise that the use of UFH in periprocedural periods is not novel. Previous studies on the use of heparin during EVT suggest that it can improve patient outcomes.[25 26] Moreover, patients treated in centres with more experience using heparin had better

Table 2 Primary and secondary outcomes in patients treated with early versus routine anticoagulation

	Early anticoagulation (n=141)	Routine anticoagulation (n=116)	P value	OR (95% CI)	P value*	a(c)OR (95% CI)*
Primary outcomes						
mRS	2 (1–4)	3 (1–4)	0.01	1.81 (1.15 to 2.83)	0.01	2.08 (1.27 to 3.41)
sICH†	2 (1.4%)	3 (2.6%)	0.83	0.54 (0.09 to 3.30)	0.19	0.20 (0.02 to 2.18)
Secondary outcomes						
mRS≤2	82 (58.2%)	53 (45.7%)	0.05	1.65 (1.01 to 2.71)	0.01	2.28 (1.21 to 4.31)
Mortality	7 (5.0%)	20 (17.2%)	<0.01	0.25 (0.10 to 0.62)	0.01	0.26 (0.09 to 0.71)
aICH	24 (17.0%)	14 (12.1%)	0.27	1.50 (0.73 to 3.04)	0.43	1.40 (0.61 to 3.18)
New ischaemic stroke	9 (6.4%)	7 (6.0%)	0.91	1.06 (0.38 to 2.94)	0.86	1.11 (0.36 to 3.40)

Comparison of the outcomes of early and routine anticoagulation.
*Adjusted for age, history of hypertension, baseline NIHSS, baseline glucose level, baseline ASPECTS, treatment with intravenous thrombolysis, heparin during procedure, and onset to reperfusion time.
†Not adjusted for age, history of hypertension, baseline ASPECTS and onset to reperfusion time due to the low incidence of sICH.
a(c)OR, adjusted common OR; aICH, asymptomatic intracranial haemorrhage; ASPECTS, Alberta Stroke Programme Early CT Score; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial haemorrhage.

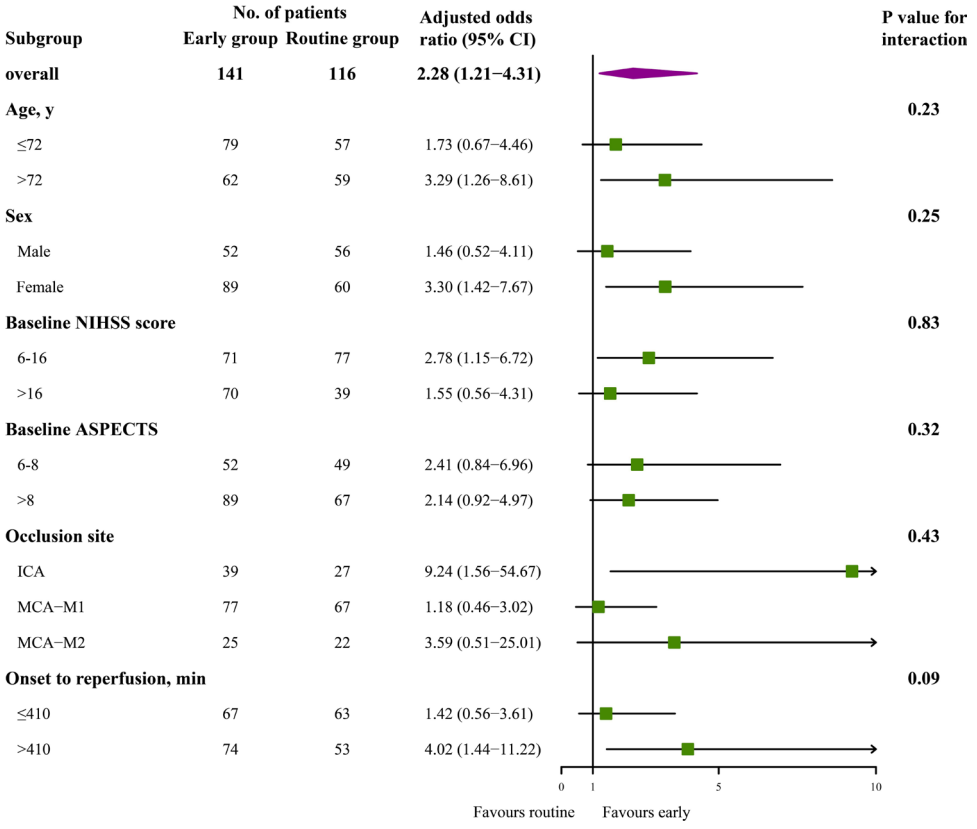

Figure 3 Subgroup analysis. The forest plot displays effect variation across six subgroups for the functional independence at 90 days. The adjusted OR was calculated by using logistic regression and adjusted for age, history of hypertension, baseline NIHSS, baseline glucose level, baseline ASPECTS, treatment with intravenous thrombolysis, heparin during procedure and onset to reperfusion time. The thresholds for age, baseline NIHSS Score, baseline ASPECTS and onset to reperfusion time were chosen at the median. ASPECTS, Alberta Stroke Programme early CT Score; ICA, internal carotid artery; MCA-M1/M2, the first/second segment of middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

outcomes.[27] But recent results from the Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands: the effect of periprocedural MEDication: heparin, antiplatelet agents, both or neithe (MR CLEAN-MED) study showed that periprocedural anticoagulant therapy does not improve patient outcomes and increases the risk of sICH.[28] In the MR CLEAN-MED study, patients treated with moderate dose of UFH after EVT had a significantly increased risk of sICH, and some patients were treated with both UFH and aspirin, which may have contributed to the poor outcome. The study also did not classify the causes of stroke, the use of UFH in patients with large artery atherosclerosis might be inappropriate. For these reasons, the benefit of early anticoagulation may be obscured. In our study, the median dose of UFH was consistent with the low dose in

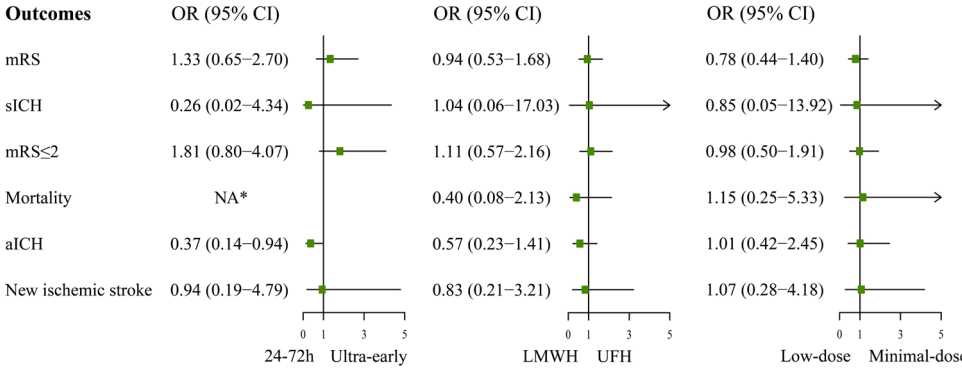

Figure 4 Outcomes in different early anticoagulation regimens. *No patients in the 24–72-hour anticoagulation group died within 90 days, so this OR could not be available. aICH, asymptomatic intracranial haemorrhage; LMWH, low-molecular-weight heparin, mRS, modified Rankin Scale; NA, not available; sICH, symptomatic intracranial haemorrhage, UFH, unfractionated heparin.

the MR CLEAN-MED study, and patients were not treated with aspirin at the same time, which may provide reassurance about safety. And the indication for anticoagulation in AIS patients with atrial fibrillation is more clear, which makes it more likely that the benefit of early anticoagulation will be observed.

After successful recanalisation, inflammation persists in the cerebral ischaemic area. Neutrophils release neutrophil extracellular traps (NETs) during the inflammatory response, which form a scaffold and activate coagulation factors to promote thrombosis,[29] resulting in failure to maintain microvascular reperfusion. In addition to inhibiting the coagulation process, UFH or LMWH can promote the dissolution of NETs or decrease the release of NETs by regulating the complement system, enhancing DNase I digestion of DNA–histone complexes and inhibiting neutrophil autophagy,[13 14] thereby reducing the microthrombi formation and improving no reflow status. Because the no reflow phenomenon mainly occurs in the first 24 hours after recanalisation,[12] it makes more sense to initiate anticoagulation with UFH or LMWH as early as possible after EVT. After 24 hours, the effect of anticoagulation on microcirculation is limited. Due to the prolonged ischaemic time, the damage to the neurovascular unit becomes more severe,[30] so initiation of anticoagulant therapy at 24–72 hours cannot improve patient outcomes and may increase the incidence of intracranial haemorrhage. This may account for our finding that favourable functional outcomes in patients are more significantly associated with ultraearly anticoagulation.

Limitations

First of all, because this was a retrospective observational study, the differences in baseline characteristics between the two groups might have had an impact on the physician's decision to administer heparin as well as the impact of early anticoagulant therapy on patient outcomes. Due to this, we adjusted for the relevant prognostic factors. Second, the early anticoagulant drugs and doses after EVT are not uniform, and their effects on microcirculation may be different. Future randomised controlled trials are needed to develop a uniform anticoagulation protocol. Third, the timing of initiation of anticoagulation therapy and the type of anticoagulant drugs were not uniform in the routine anticoagulation group, which may affect the incidence of new ischaemic stroke and intracranial haemorrhage. Fourth, some patients did not re-examine CT or MRI of the head within 90 days after discharge, because some intracranial haemorrhage and new ischaemic stroke were asymptomatic, which may have led to an underestimation of these outcomes in this study. Finally, early anticoagulation after EVT is still in the exploratory stage, and the number of cases included in this study is limited. The proportion of patients who initiated early anticoagulant therapy after EVT differed between stroke centres, but we did not adjust for heparin preference across centres, this may have had an impact on clinical outcomes.

CONCLUSIONS

In AIS patients with atrial fibrillation, early anticoagulation with UFH or LMWH after successful recanalisation is associated with favourable functional outcomes without increasing the risk of sICH. A randomised controlled trial is needed for further study.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study was approved by the medical ethics committee of Beijing Tiantan Hospital of the Capital Medical University (approval no. KY2018-057-01). Participants gave informed consent to participate in the study before taking part.

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REFERENCES

1 Goyal M, Menon BK, van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
2 Albers GW, Marks MP, Kemp S, *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018;378:708–18.
3 Nogueira RG, Jadhav AP, Haussen DC, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11–21.
4 Yang P, Zhang Y, Zhang L, *et al*. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
5 LeCouffe NE, Kappelhof M, Treurniet KM, *et al*. A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021;385:1833–44.
6 Mitchell PJ, Yan B, Churilov L, *et al*. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular

thrombectomy within 4·5 H of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet* 2022;400:116–25.
7 Benjamin EJ, Muntner P, Alonso A, *et al*. Heart disease and stroke statistics-2019 update: a report from the American heart association. *Circulation* 2019;139:e56–528.
8 Kamel H, Healey JS. Cardioembolic stroke. *Circ Res* 2017;120:514–26.
9 Lamassa M, Di Carlo A, Pracucci G, *et al*. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (the European community stroke project). *Stroke* 2001;32:392–8.
10 Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/american stroke association. *Stroke* 2019;50:e344–418.
11 The international stroke trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International stroke trial collaborative group. *Lancet* 1997;349:1569–81.
12 Ng FC, Churilov L, Yassi N, *et al*. Prevalence and significance of impaired microvascular tissue reperfusion despite macrovascular angiographic reperfusion (no-reflow). *Neurology* 2022;98:e790–801.
13 Sohrabipour S, Muniz VS, Sharma N, *et al*. Mechanistic studies of DNase I activity: impact of heparin variants and PAD4. *Shock* 2021;56:975–87.
14 Manfredi AA, Rovere-Querini P, D'Angelo A, *et al*. Low molecular weight heparins prevent the induction of autophagy of activated neutrophils and the formation of neutrophil extracellular traps. *Pharmacol Res* 2017;123:146–56.
15 Kimura S, Toyoda K, Yoshimura S, *et al*. Practical " 1-2-3-4-day " rule for starting direct oral anticoagulants after ischemic stroke with atrial fibrillation: combined hospital-based cohort study. *Stroke* 2022;53:1540–9.
16 Hacke W, Kaste M, Fieschi C, *et al*. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA* 1995;274:1017.
17 Frontera JA, Claassen J, Schmidt JM, *et al*. Prediction of symptomatic vasospasmafter subarachnoid hemorrhage. *Neurosurgery* 2006;59:21–7.
18 Paciaroni M, Agnelli G, Falocci N, *et al*. Early recurrence and major bleeding in patients with acute ischemic stroke and atrial fibrillation treated with non-vitamin-K oral anticoagulants (RAF-noacs) study. *J Am Heart Assoc* 2017;6:12.
19 Paciaroni M, Agnelli G, Corea F, *et al*. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. *Stroke* 2008;39:2249–56.
20 Kablau M, Kreisel SH, Sauer T, *et al*. Predictors and early outcome of hemorrhagic transformation after acute ischemic stroke. *Cerebrovasc Dis* 2011;32:334–41.
21 Whiteley WN, Adams HP, Bath PMW, *et al*. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. *Lancet Neurol* 2013;12:539–45.
22 Lip GYH, Nieuwlaat R, Pisters R, *et al*. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. *Chest* 2010;137:263–72.
23 Pisters R, Lane DA, Nieuwlaat R, *et al*. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro heart survey. *Chest* 2010;138:1093–100.
24 Lip GYH, Banerjee A, Boriani G, *et al*. Antithrombotic therapy for atrial fibrillation. *CHEST* 2018;154:1121–201.
25 Nahab F, Walker GA, Dion JE, *et al*. Safety of periprocedural heparin in acute ischemic stroke endovascular therapy: the multi MERCI trial. *J Stroke Cerebrovasc Dis* 2012;21:790–3.
26 Winningham MJ, Haussen DC, Nogueira RG, *et al*. Periprocedural heparin use in acute ischemic stroke endovascular therapy: the TREVO 2 trial. *J Neurointerv Surg* 2018;10:611–4.
27 van de Graaf RA, Chalos V, van Es ACGM, *et al*. Periprocedural intravenous heparin during endovascular treatment for ischemic stroke: results from the Mr clean registry. *Stroke* 2019;50:2147–55.
28 van der Steen W, van de Graaf RA, Chalos V, *et al*. Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial. *Lancet* 2022;399:1059–69.
29 Laridan E, Denorme F, Desender L, *et al*. Neutrophil extracellular traps in ischemic stroke thrombi. *Ann Neurol* 2017;82:223–32.
30 Jickling GC, Liu D, Stamova B, *et al*. Hemorrhagic transformation after ischemic stroke in animals and humans. *J Cereb Blood Flow Metab* 2014;34:185–99.