

# Anticoagulant management by low-dose of low molecular weight heparin in patients with nonvalvular atrial fibrillation following hemorrhagic transformation and complicated with venous thrombosis

## Five case reports and literature review

Ling Zhang, MD, Yu-Han Kong, PhD, Da-Wu Wang, PhD, Kai-Ting Li, MD , He-Ping Yu, MD\*

### Abstract

For patients with nonvalvular atrial fibrillation (NVAF) following hemorrhagic infarction (HI)/hemorrhage transformation (HT) and complicated with venous thrombosis, the management of anticoagulation is controversial. Our study intends to explore the safety and effectiveness of using low-dose of low molecular weight heparin (LMWH) to treat NVAF patients with HI (or HT) and complicated with venous thrombosis.

Between January 2018 and January 2019, NVAF related acute ischemic stroke patients with HT/HI, hospitalized in the department of neurology or rehabilitation in our hospital, are enrolled retrospectively. Among them, those who were found to have venous thrombosis and undergo anticoagulation (LMWH) during the treatment were extracted. We investigate the efficacy and safety in those patients who have been treated with anticoagulant of LMWH.

Five cases accepted LMWH within 3 weeks attributed to the appearance of venous thrombosis, and all of them did not display new symptomatic bleeding or recurrent stroke. However, based on the results of a head computed tomography scan, there were 2 cases of slightly increased intracranial hemorrhage, and then we reduced the dose of anticoagulant. In addition, color ultrasound showed that venous thrombosis disappeared or became stable.

Patients with NVAF following HI/HT have a higher risk of thromboembolism. Early acceptance of low-dose LMWH as an anticoagulant is relatively safe and may gain benefit. However, in the process of anticoagulant therapy, we should follow-up head computed tomography/magnetic resonance imaging frequently, as well as D-dimer values, limb vascular ultrasound. Besides, the changes of symptoms and signs should be focused to judge the symptomatic bleeding or recurrent stroke. Furthermore, it is better to adjust anticoagulant drug dosage according to specific conditions.

**Abbreviations:** AIS = acute ischemic stroke, HI = hemorrhagic infarction, HT = hemorrhage transformation, ICH = intracranial hemorrhage, LMWH = low molecular weight heparin, NVAF = nonvalvular atrial fibrillation, RS = recurrent stroke.

**Keywords:** anticoagulation, hemorrhagic infarction, hemorrhagic transformation, ischemic stroke, nonvalvular atrial fibrillation

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K-TL and H-PY contributed equally to this work

This was a retrospective study, passed approval from our hospital ethics committee (Approved number: 2020-084).

The authors got the agreement from the 5 patients for publication.

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The datasets used during the current study are available from the corresponding author on reasonable request.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Department of Rehabilitation, The First Affiliated Hospital of Chongqing Medical University, Yuzhong District, Chongqing City, China.

\* Correspondence: He-Ping Yu, Department of Rehabilitation, The First Affiliated Hospital of Chongqing Medical University, NO.1 of Youyi Road, Yuzhong District, Chongqing City, China (e-mail: lyshqiao@126.com).

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## 1. Introduction

Patients with cardioembolic stroke have a high risk of developing recurrent stroke (RS), while nonvalvular atrial fibrillation (NVAf) is the leading cause of cardioembolic stroke.<sup>[1,2]</sup> For NVAf patients, if there are no contraindications to anticoagulation, early anticoagulation therapy is necessary. However, some previous studies demonstrate that early anticoagulation is associated with an increased risk of intracranial hemorrhage (ICH). Moreover, patients with cardioembolic stroke always suffer large area-cerebral infarct, who are more prone to hemorrhage transformation (HT) within 2 weeks after stroke, especially for the patients with acute cardioembolic stroke, older age, and those receiving anticoagulation therapy.<sup>[1]</sup> Furthermore, for these patients, regardless of whether they have HT or not, they always suffer from more severe symptoms of limb paralysis, prolonged bed rest, changes in prothrombotic activity and the utilization of hemostatic, which lead to a higher risk of Venous Thrombus Embolism (VTE). Therefore, for patients with cardioembolic stroke caused by NVAf, the anticoagulation strategy when HT occurs is very troublesome for clinicians. For patients with NVAf following hemorrhagic infarction (HI)/HT, most physicians will delay anticoagulation or terminate the anticoagulation therapy immediately. However, for these patients, when the venous thrombosis is found during the course of the disease, the treatment contradiction amplifies. As the risk of venous thrombosis is extremely high and the risk of bleeding with anticoagulation therapy is also very high in such patients. It is unclear whether receiving anticoagulation therapy is available or the optimal time to begin treatment or the optimal anticoagulation dose.

For ICH patients, some studies suggest that starting heparin early is not associated with re-bleeding, hematoma enlargement or increased mortality.<sup>[3–5]</sup> Boer study shows that it is safe to use heparin on the second day following ICH and can be recommended.<sup>[5]</sup> Orken study shows that starting low-dose of low molecular weight heparin (LMWH) after 48 hours of ICH is not associated with re-bleeding and hematoma enlargement.<sup>[4]</sup> For patients with NVAf or/and venous thrombosis, anticoagulation therapy is necessary. However, for NVAf patients with HI (or HT) and venous thrombosis, whether using heparin as anticoagulation therapy available and when to start is absence of proof. So, we share our clinical anticoagulant experience of using heparin to treat NVAf patients with HI (or HT) and venous thrombosis through this analysis for these patients.

## 2. Methods

This retrospective study was performed using data from the database of the first Affiliated Hospital of Chongqing Medical University. Between January 2018 and January 2019, NVAf related acute ischemic stroke (AIS) patients with HT/HI, hospitalized in the department of neurology or rehabilitation, were enrolled retrospectively. Among them, those who were found to have venous thrombosis and undergo anticoagulation (LMWH) during the treatment were extracted.

The following data was collected from the electronic filing system: gender, age, weight, history of hypertension, blood pressure at admission, diabetes, heart disease, prior ischemic stroke (IS)/transient ischemic attack (TIA), initial infarction volume, initial infarction location, HT/HI, anticoagulation after stroke, intravenous thrombolysis, estimated glomerular filtration

rate (eGFR), international normalized ratio (INR), liver function, thromboembolism, or bleeding history, NIHSS score, CHA2DS2-VASc score, HAS-BLED score. Besides, we collected the information about the anticoagulant treatment, including the time to start LMWH after HT/HI, LMWH type, and dose. We got the consent of the 5 patients to publish their personal data.

## 3. Results

Twenty-five patients who had been suffering NVAf related AIS coupling with HT/HI were enrolled, 13 of them were found with venous thrombosis during the treatment. Of the 13 patients, 8 of them refused anticoagulation for some reason. The other 5 cases accepted LMWH as an anticoagulant.

Of the 5 patients, 3 had a history of hypertension, 3 had a history of diabetes, 1 had been suffered heart failure, 1 had been suffered IS or TIA. One patient's eGFR was 44.5 mL/min/1.73 m<sup>2</sup>, the other 4 had good performance in eGFR. All of them had a normal liver function and a stable INR. Only 1 patient accepted intravenous thrombolysis after admitted to hospital. All of them had a severe brain damage and got a NIHSS score >16. All the 5 patients had a high risk of RS, and the CHA2DS2-VASc risk score was 3 or higher. Furthermore, they also suffered a high risk of bleeding, and the HAS-BLED score exceeded 4. All the 5 patients were diagnosed with NVAf by electrocardiogram and echocardiography when admitted to hospital. Two of them had been diagnosed with NVAf for many years, 1 was prescribed rivaroxaban for 1 month but ceased 1 year ago because of the black bowel movement. The others did not accept anticoagulation therapy before admitted to our hospital (Table 1).

Head computed tomography (CT) scan showed that 3 of them had acute cerebral infarction onset but HT emerged during the subsequent course of the disease. Another 2 patients were admitted to hospital with head CT scan showing HI. Meanwhile, all of them accepted low-dose of LMWH within 3 weeks due to the occurrence of venous thrombosis. The exact data were showed by Table 2 and the Supplement Materials, <http://links.lww.com/MD/F623>.

Taken as a whole, the dosage of LMWH we used was low. In case 1, the initial dosage of enoxaparin was 56.3 IU/kg once daily, but adjusted doubly (56.3 IU/kg, twice daily) due to the appearance of new left posterior tibial vein thrombosis showed by following-up ultrasound. In case 2, the anticoagulant dosage of enoxaparin was 53.3 IU/kg, twice daily. In case 3, enoxaparin was started at 71.4 IU/kg, once daily. However, we adjusted the anticoagulant to nadroparin calcium at 54.9 IU/kg, once daily, because the following head CT scan showed a slightly increase in ICH in the previous region. And we re-adjusted the nadroparin calcium to 36.6 IU/kg, once daily as the head CT scan showed a slightly increase in hemorrhage. In case 4, enoxaparin (64.5 IU/kg, twice daily) was started before HT to prevent the increase of venous thrombosis but ceased by gastrointestinal bleeding. However, we restarted the usage of enoxaparin (64.5 IU/kg, once daily) because of the increase of venous thrombosis. And we doubled the anticoagulation dosage as the gastrointestinal bleeding tended to be stable. However, we re-adjusted enoxaparin to 64.5 IU/kg once daily because the following head CT scan showed a slight increase in ICH. In case 5, the patient accepted nadroparin calcium (32.5 IU/kg, once daily) on account of the venous thrombosis and the increase of D-dimer value (Table 2).

**Table 1**  
**Characteristics of Patients.**

|                                     | Case 1   | Case 2   | Case 3   | Case 4  | Case 5                                   |
|-------------------------------------|--|--|--|---|--|
| Sex                                 | F  | M  | F  | M   | F  |
| Age (yr)                            | 69   | 76   | 75   | 84  | 63                                       |
| Weight (kg)                         | 71   | 75   | 56   | 62  | 63                                       |
| History of hypertension             | +  | +  | +  | -   | -  |
| Blood pressure on admission (mm Hg) | 140/77   | 170/80   | 177/86   | 164/105   | 93/60                                    |
| Diabetes mellitus                   | +  | +  | -  | +   | -  |
| Heart failure                       | -  | -  | +  | -   | -  |
| Prior IS/TIA                        | -  | -  | -  | +   | -  |
| AIS                                 | +  | +  | +  | +   | +  |
| Initial infarction volume           | Large  | Large  | Large  | Large   | Large                                    |
| Initial infarction location         | Right-side frontal lobe, temporal lobe, insula, and basal ganglia area | Left-side parietal lobe, temporal lobe, occipital lobe border area | Right-side frontal lobe, temporal lobe, insula, and basal ganglia region | Right-side frontal lobe, temporal lobe, parietal lobe, insula, and basal ganglia area | Right-side parietal lobe, occipital lobe |
| NVAF                                | +  | +  | +  | +   | +  |
| Anticoagulants therapy before AIS   | -  | -  | -  | -   | -  |
| Intravenous thrombolysis            | -  | -  | -  | -   | +  |
| eGFR mL/(min/1.73 m <sup>2</sup> )  | >90  | 44.5   | >90  | >90   | >90                                      |
| INR                                 | 0.94   | 1.19   | 1.05   | 1.43  | 0.94                                     |
| Liver function                      | N  | N  | N  | N   | N  |
| NIHSS score                         | 16   | 19   | 17   | 26  | 18                                       |
| CHA2DS2-VASc score                  | 5  | 7  | 5  | 6   | 3  |
| HAS-BLED score                      | 5  | 6  | 5  | 4   | 4  |

CHA2DS2-VASc indicates congestive heart failure, hypertension, age, diabetes mellitus, stroke (doubled), vascular disease, and sex category (female); HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly. + = have or present, - = without, AIS = acute ischemic stroke, eGFR = estimated glomerular filtration rate, F = female, INR = international normalized ratio, IS = ischemic stroke, M = male, N = normal, NIHSS = National Institutes of Health Stroke Scale, NVAF = nonvalvular atrial fibrillation. TIA = transient ischemic.

None of the 5 patients experienced new symptomatic bleeding or RS during the hospitalization. Besides, the color ultrasound showed the venous thrombosis disappeared or became stable and the value of D-dimer remarkably decreased. They obtained a relatively safe and effective treatment.

**4. Discussion**

Stroke patients associated with NVAF have at high risk of RS. There is no denying that anticoagulation therapy is effective in preventing stroke in patients with NVAF in primary and

secondary prevention.<sup>[2]</sup> The optimal time for anticoagulation remains controversial. For patients with NVAF related IS, many experts recommend anticoagulation early. However, some previous researches have shown that early anticoagulation therapy has an increased risk of symptomatic ICH.<sup>[6]</sup> Moreover, HT often occurs within 2 weeks after stroke, especially for the patients with acute cardioembolic stroke, large infarct area, older age, and those receive anticoagulation therapy.<sup>[1,7]</sup> The Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation study shows that the best time of initiating anticoagulant treatment as a secondary

**Table 2**  
**Patients whether have HT/HI/VT and when to find, as well as the anticoagulation therapy.**

|                                      | Case 1  | Case 2  | Case 3   | Case 4  | Case 5   |
|--------------------------------------|---|---|--|---|--|
| Initial HI                           | -   | +   | +  | -   | -  |
| HT                                   | +   | -   | -  | +   | +  |
| Timing to find HT/HI (d)             | 2   | 1   | 1  | 54  | 2  |
| Timing to find VT (d)                | 8   | 12  | 18   | 4   | 27   |
| Timing to start LMWH after HT/HI (d) | 8   | 13  | 18   | 0*  | 9†   |
| LMWH type and dose                   | Enoxaparin<br>4000 IU (56.3 IU/kg),<br>s.c., once daily;<br>4000 IU (56.3 IU/kg),<br>s.c., twice daily;<br>Rivaroxaban (discharged)<br>10 mg per day. | Enoxaparin<br>4000 IU (53.3 IU/kg),<br>s.c., twice daily. | Enoxaparin<br>4000 IU (71.4 IU/kg),<br>s.c., once daily;<br>Nadroparin Calcium<br>3075 IU (54.9 IU/kg),<br>s.c., once daily;<br>2050 IU (36.6 IU/kg),<br>s.c., once daily. | Enoxaparin<br>4000 IU (64.5 IU/kg),<br>s.c., twice daily;<br>4000 IU, s.c., once<br>daily;<br>4000 IU, s.c., twice<br>daily;<br>4000 IU, s.c., once<br>daily. | Nadroparin Calcium<br>2050 IU (32.5 IU/kg),<br>s.c., once daily; Rivarox-<br>aban (discharged) 10 mg<br>per day. |

HI = hemorrhagic infarction, HT = hemorrhagic transformation, s.c. = subcutaneous, VT = venous thrombosis.  
\* The patient use LMWH (enoxaparin) 4000 IU (64.5 IU/kg) twice daily before found HT, we did not stop the anticoagulation, but just adjusted to enoxaparin 4000 IU (64.5 IU/kg) once daily after HT.  
† On day 2 found right-side basal ganglia area ICH, on day 32 found new hemorrhage in sulci, 9d after the second hemorrhage starting nadroparin calcium 2050 IU (32.5 IU/kg) once daily.

prevention of stroke is between 4 and 14 days after the onset of AIS in patients with NVAF.<sup>[11]</sup> An observational study suggests that for NVAF related AIS/TIA patients, it is feasible to start anticoagulation within 14 days after the onset and has a low incidence of major bleeding events and RS for 90 days after the stroke.<sup>[8]</sup> Meanwhile, for small or medium-sized infarction patients, it may be feasible to start anticoagulation within 3 days after the onset of stroke. In the latest European Society of Cardiology guideline on the management of NVAF, the experts suggest starting anticoagulation immediately in patients with NVAF related TIA and 3, 6 to 8, and 12 to 14 days after a mild (NIHSS score <8), moderate (NIHSS score 8–16), or severe (NIHSS score >16) NVAF related AIS respectively, after excluding secondary hemorrhagic transformation by repeating brain imaging.<sup>[9]</sup> Besides, ischemic lesions, older age, the need for surgical procedures, hemorrhagic transformation, neurological instability, and uncontrolled hypertension may delay the start of anticoagulation therapy. Pacaroni study indicated that if the infarct size is large or a hemorrhagic transformation is present, the initiation of anticoagulation should be delayed for 2 to 3 weeks.<sup>[6]</sup>

ICH survivors are at high risk of IS, VTE, ICH recurrence, mortality, and morbidity.<sup>[10–13]</sup> Some observational studies have suggested that early anticoagulation therapy may reduce VTE, IS, and mortality. However, bleeding is one of the serious potential complications of anticoagulation therapy. Above factors make the resumption of anticoagulation a dilemma in this population. Some existing observational data suggest that early anticoagulation does not increase the risk of recurrent ICH and can reduce the incidence of all-cause mortality and IS rates.<sup>[14–16]</sup> A meta-analysis shows that resumption of anticoagulation after ICH is associated with a lower risk of thromboembolic complications and a similar risk of ICH recurrence.<sup>[17]</sup> Nevertheless, some studies demonstrate that anticoagulation may increase bleeding. A retrospective study shows that anticoagulation therapy increases the risk of major bleeding, and recurrent ICH is observed only in patients taking oral anticoagulants.<sup>[18]</sup> Nielsen study suggests that resumption of anticoagulation therapy after spontaneous hemorrhagic stroke in patients with AF is associated with a higher rate of ICH recurrence, but these differences are not statistically significant.<sup>[19]</sup> Besides, some studies have shown that ICH patients with less bleeding and mild functional changes have a lower risk of ICH recurrence after receiving anticoagulation.<sup>[20,21]</sup> All of our cases had NVAF, IS, ICH, venous thrombosis, and high value of D-dimer. Four of them did not accept anticoagulation therapy before finding venous thrombosis during the course of the disease. According to analysis of our cases, we find that these patients have a higher risk of thromboembolism and may gain benefits from receiving anticoagulant treatment.

For ICH patients, the optimal time for starting anticoagulation therapy is unclear. Majeed et al suggests a broad time-window for optimal resumption of 10 to 30 weeks after ICH.<sup>[22]</sup> Pennlert et al suggests that anticoagulation therapy may be restarted between 7 and 8 weeks after ICH in patients with AF to reduce the rate of thrombotic events without increasing the risk of ICH recurrence.<sup>[23]</sup> Some researchers and the latest European Society of Cardiology guideline suggest a time-window for optimal resumption between 4 and 8 weeks depending on individual patient characteristics.<sup>[9,16,24]</sup> Li et al suggests that both early (<2 weeks) and late (>4 weeks) resumption should be reached only after very careful assessment of risks for ICH recurrence and

thromboembolism.<sup>[13]</sup> Some studies take the opinion that starting LMWH within 48 to 72 hours after the onset of ICH is not associated with re-bleeding, hematoma enlargement or an increased mortality rate.<sup>[3–5]</sup> However, there is no guidelines for the management of anticoagulation for NAVF patients with venous thrombosis after HI/HT. In clinical practice, we often use CHA2DS2-VASc score and HAS-BLED score predict the risk of bleeding and thromboembolism. Moreover, advanced age, prior IS, diabetes, and hypertension are common risk factors for both thromboembolism and bleeding. According to the level of VTE risk and recurrent ICH risk, Da Silva et al suggest a possible paradigm for initiating anticoagulation following ICH.<sup>[25]</sup> All of our cases have high VTE risk and high recurrent ICH risk, according to this paradigm, recommending anticoagulation therapy after 4 weeks of HI/HT.

For patients with NVAF following HI/HT, most physicians will delay anticoagulation or terminate the anticoagulation therapy immediately. However, for these patients, when the venous thrombosis is found during the course of the disease, whether receiving anticoagulation therapy and the optimal timing for starting are unclear. We retrospectively analyzed the patients hospitalized in our hospital, who had NVAF with AIS and following HI/HT. Twenty-five patients were enrolled, 13 of them were found with thrombosis in the process of treatment. Of the 13 patients, 5 cases accepted anticoagulation therapy with LMWH within 3 weeks since radiological evidence of hemorrhage (Table 2), because of the presence of venous thrombosis and high D-dimer value in the course of the disease. Following-up brain CT scan showed that hemorrhage in 2 patients (case 1, case 3) slightly increases after LMWH anticoagulant treatment, but there is no emerging of new hemorrhage symptoms. In the process of anticoagulation therapy, follow-up head CT scan did not show new IS. Besides, limb vascular ultrasound revealed that the venous thrombosis decreased or be stable, D-dimer value gradually decreased and patients did not have bleeding symptoms.

Robertson study shows that the LMWH dose of VTE treatment should be adjusted by participant's body weight.<sup>[26]</sup> Enoxaparin conventional subcutaneous injection dose is 100 anti-factor Xa IU per kg of body weight twice daily (100 IU/kg, twice daily),<sup>[27]</sup> and nadroparin calcium conventional subcutaneous injection dose is approximately 90 anti-factor Xa IU per kg of body weight twice daily (90 IU/kg, twice daily).<sup>[28]</sup> All of our cases had high risk of thromboembolism and bleeding, and they accepted LMWH (enoxaparin or nadroparin calcium) in hospitalization (Table 2), but our initial anticoagulant dose was low. Follow-up brain CT scan found that hemorrhage in 2 patients increased slightly after low-dose of LMWH therapy, but patients did not have new symptoms or signs. In short, low-dose of LMWH anticoagulation therapy was relatively safe and effective for patients with high risk of VTE and ICH recurrence, which is consistent with Sprugel study.<sup>[29]</sup> All the 5 cases were asymptomatic bleeding. However, 2 of them appeared with slightly increase in the ICH, according to the result of head CT scan. The other 3 did not appear with changes in the ICH region. Some studies have shown that cerebral microbleed is associated with an increased risk of subsequent ICH, and cerebral microbleed can be detected by gradient-echo magnetic resonance imaging (MRI) or susceptibility weighted imaging.<sup>[30–33]</sup> Hence, except of common bleeding assessment scale, if condition permission, MRI or susceptibility weighted imaging should be considered.

Some studies have shown that the location of ICH/HT, glomerular filtration rate, and INR may affect the management of anticoagulant treatment and dosage selection.<sup>[9,34,35]</sup> It is a pity that our number of cases is too small and retrospective, so it cannot be used to assess this relationship between them. More clinical trials are needed to guide optimal decision making for these patients.

## 5. Conclusions

Patients with NVAF following HI/HT have high thromboembolism risk. It is relatively safe to receive low-dose of LMWH as anticoagulant and may gain benefits. However, in the process of anticoagulation therapy, we should follow-up head CT/MRI frequently, as well as D-dimer values, limb vascular ultrasound. Besides, the changes of symptoms and signs should be focused to judge the symptomatic bleeding or RS. Furthermore, it is better to adjust anticoagulant drug dosage according to specific condition.

## Author contributions

**Conceptualization:** Ling Zhang, Yu-Han Kong, Kai-Ting Li, He-Ping Yu.

**Data curation:** Da-Wu Wang.

**Investigation:** Ling Zhang.

**Methodology:** Kai-Ting Li.

**Supervision:** He-Ping Yu.

**Writing – original draft:** Ling Zhang.

**Writing – review & editing:** Yu-Han Kong, Kai-Ting Li, He-Ping Yu.

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