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Review

Current evidence and future directions for prophylactic anticoagulation therapy after severe spontaneous intracerebral hemorrhage: a narrative review

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ABSTRACT

Patients with spontaneous intracerebral hemorrhage (sICH) are at high risk for venous thromboembolism (VTE), a complication strongly associated with adverse clinical outcomes. While prophylactic anticoagulation has been shown to effectively reduce VTE incidence, significant uncertainty remains regarding its safety and the optimal timing of initiation. This article comprehensively reviews key aspects including anticoagulant selection, patient eligibility, therapeutic time windows, and current clinical challenges. Research gaps persist in defining appropriate anticoagulation strategies according to drug type, initiation timing, and sICH subtypes (e.g., lobar, deep, or amyloid-related hemorrhage). Future efforts should focus on conducting large-scale, multicenter, prospective clinical trials to validate the efficacy and safety of novel anticoagulants. Concurrently, integrating machine learning to develop high-precision risk prediction models, tailoring individualized treatment approaches, and establishing multidisciplinary collaborative research frameworks are essential steps toward advancing the standardization and rationalization of prophylactic anticoagulation in patients with severe sICH.

Introduction

Spontaneous intracerebral hemorrhage (sICH) is a common form of stroke encountered in the intensive care unit, with an annual incidence ranging from approximately 10–30 cases per 100,000 individuals.[1] Patients with severe cerebral hemorrhage frequently present with concurrent coma, hemiplegia, or prolonged immobilization and typically require extended hospital stays. Consequently, venous thromboembolism (VTE) is a common complication among these patients in the intensive care unit.[2–4] VTE can be categorized into deep vein thrombosis (DVT) and pulmonary embolism (PE). The reported incidence of VTE in patients with intracerebral hemorrhage varies considerably across studies, largely due to differences in study design, patient populations, and diagnostic protocols. A synthesis of available evidence indicates that the incidence of DVT ranges from 1% to 40%, while PE occurs at a lower rate, with reported incidences between 0.5% and 2%.[5–11] Prospective studies have shown that approximately 96% of DVT and 86% of PE cases in the neurological intensive care unit (NICU) are asymptomatic, representing asymptomatic VTE.[4] Therefore, the actual incidence of VTE in the intensive care unit may be even higher. Moreover, patients with hemorrhagic stroke have a 7.35-fold increased risk of DVT compared to those with ischemic stroke, and cerebral hemorrhage itself is an independent predictor of DVT during hospitalization following stroke (P <0.001).[12]

VTE is frequently associated with poor prognosis in patients with intracerebral hemorrhage.[13] In a retrospective cohort study of 2902 such patients, VTE was independently associated with a modified Rankin Scale (mRS) score of ≥4 at discharge and at 3 months.[9] Another study involving 637 patients with intracerebral hemorrhage also demonstrated that VTE was an independent predictor of poor functional outcome, defined as a mRS score of 3–5 at hospital discharge following ICH, and was associated with a 2-fold increase in the risk of disability.[14] Emerging evidence suggests that early initiation of pharmacological DVT prophylaxis in patients with ICH is associated with improvements in neurological status, as reflected by increased Glasgow Coma Scale (GCS) scores.[15] This supports the potential benefit of preventing thrombotic complications in severe

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sICH, which may play a meaningful role in enhancing overall clinical outcomes.

Prophylactic anticoagulation is effective in reducing the incidence of VTE.[16,17] The guideline recommendation for anticoagulant drugs in the prevention of VTE is classified as a low level of evidence, and there remains no consensus regarding the optimal timing and safety of anticoagulation initiation. Therefore, we performed a structured literature search in the PubMed database for publications from the past 5 years using a combination of MeSH terms and free-text keywords, including: Cerebral Hemorrhage, Intracerebral Hemorrhage, Cerebrum Hemorrhage, Cerebral Brain Hemorrhage, Cerebral Parenchymal Hemorrhage, Venous Thromboembolism, Pulmonary Embolism, Deep Vein Thrombosis, Anticoagulation, and Direct Oral Anticoagulants. A comprehensive evaluation was conducted on various types of relevant literature, such as clinical trials, observational studies, systematic reviews, meta-analyses, editorials, expert consensus statements, and clinical practice guidelines, to assess their relevance to the research question. We further extended our analysis by examining the citation chains of key articles. This review is based entirely on previously published studies and does not involve any original research conducted by the authors involving human participants or animals. To enhance the clarity and visual accessibility of the study's content and key findings, we include a graphical abstract in Figure 1 that summarizes the research design and principal outcomes.

Types and Selection of Anticoagulant Drugs

Currently, there remains controversy regarding the use of anticoagulant drugs for the prevention of DVT following sICH. The 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association recommends that low-dose unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) may be used in bedridden patients with sICH to reduce the risk of PE.[18] Currently, the primary anticoagulant agents used in clinical practice include UFH, LMWH, vitamin K antagonists (VKAs) (e.g., warfarin), and direct oral anticoagulants (DOACs). The characteristics of commonly used anticoagulants are summarized in Table 1.

UFH exerts its anticoagulant effect by enhancing the ability of antithrombin III to inhibit coagulation factors Xa and IIa. The efficacy of prophylactic heparin in reducing VTE risk among patients with sICH has been well documented. A study by Khripun et al. demonstrated that initiating prophylaxis within 48 h of hemorrhage onset significantly reduced the incidence of PE from 11.1% to 2.9%, suggesting that earlier intervention may be more effective in preventing fatal PE.[19] Similarly, a large meta-analysis by Chi et al.[20] reported that prophylactic-dose heparin was associated with approximately 73%–76% lower risk of DVT and 63–67% lower risk of PE, without increasing mortality. With regard to safety, multiple studies indicate that when appropriate indications and timing are carefully observed, the risks of hematoma expansion and major bleeding do not increase significantly. A meta-analysis by Pan et al.,[21] which included nine studies involving 4055 sICH patients, found no statistically significant association between prophylactic use of heparin (including LMWH or UFH) and increased risks of intracranial hematoma expansion or mortality. However, this analysis has limitations: eight of the nine included studies were assessed as having a moderate risk of bias, potentially affecting the reliability of the pooled findings. UFH has several clinical advantages, including rapid onset of action, flexible administration via intravenous or subcutaneous routes, ease of dose titration, and the availability of protamine sulfate as a specific reversal agent. Nevertheless, it is associated with a relatively high bleeding risk, necessitates frequent monitoring of coagulation parameters, and may lead to adverse effects such as osteoporosis with prolonged use. Therefore, while current evidence supports cautious use of heparin for thromboprophylaxis in sICH patients, further high-quality randomized controlled trials are needed to definitively establish its safety and efficacy.

LMWH exerts its anticoagulant effect primarily by binding to antithrombin III, thereby markedly enhancing its affinity for factor Xa. This selective inhibition of factor Xa suppresses the conversion of prothrombin to thrombin and subsequently prevents fibrinogen from forming fibrin, effectively interrupting the coagulation cascade and thrombus formation. In recent years, evidence supporting the prophylactic use of LMWH in patients with sICH has grown, yet debate persists regarding the optimal timing of initiation and long-term safety. A randomized controlled trial by Qian et al. demonstrated that initiating enoxa-

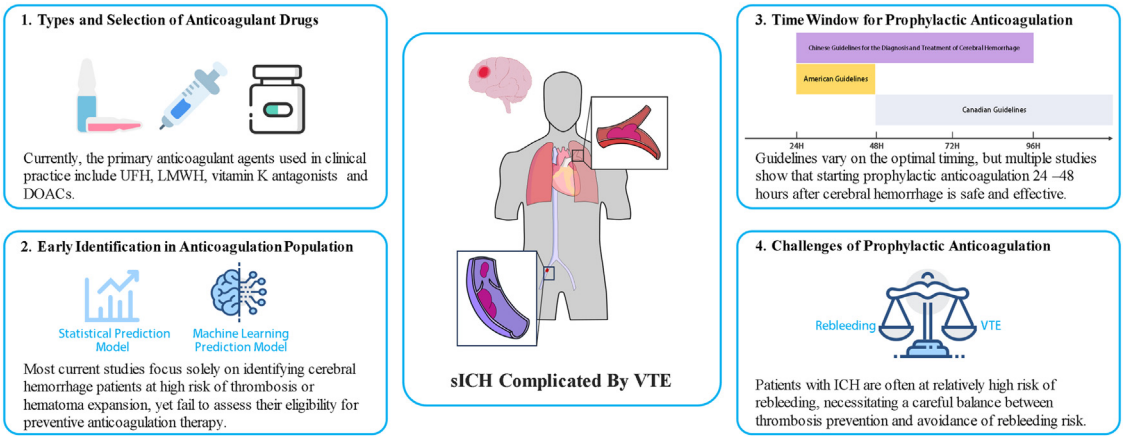

Figure 1. Current evidence for prophylactic anticoagulation therapy after severe spontaneous intracerebral hemorrhage.
DOACs: Direct oral anticoagulants; LMWH: Lowmolecular-weight heparin; sICH: UFH: Unfractionated heparin; VTE: Venous thromboembolism

Table 1
The characteristics of commonly used anticoagulants.

Medicine		Molecular target	Administration route	Prophylactic dose	Characteristics	Adverse effect	Half-life	Antagonist
UFH		Enhances antithrombin III–mediated inhibition of coagulation factors Xa and IIa.	Subcutaneous/Intravenous administration	5000 U every 8 h 5000 U every 12 h	No dose adjustment required in renal insufficiency.	Bleeding risk, thrombocytopenia, allergic reactions, and other adverse effects.	100 U/kg-1 h; 400 U/kg-2.5 h; 800 U/kg-5 h;	Protamine
LMWH								
	Calcium LMWH	Binds antithrombin III to inhibit coagulation factor Xa.	Subcutaneous injection	2000–6000 AXa IU/d	Lower risk of bleeding and thrombocytopenia than unfractionated heparin; dose adjustment required in renal insufficiency.	Bleeding risk, thrombocytopenia, allergic reactions, and injection site hematoma.	3.5 h	Protamine
	Sodium LMWH Tinzaparin Enoxaparin			2500 IU/d 2850 IU/d 2000–4000 AXa IU/d			3.5 h 3.5 h 4–7 h	
Warfarin		Inhibits vitamin K-dependent coagulation factors II, VII, IX, and X.	Oral administration	1–5 mg once a day INR-guided adjustment	INR monitoring required; high interindividual variability.	Bleeding risk, limb gangrene, osteoporosis.	40 h	Vitamin K, prothrombin complex concentrate, fresh frozen plasma
DOACs								
	Dabigatran etexilate	Directly inhibits thrombin.	Oral administration	150 mg twice a day No dose adjustment based on body weight	Contraindicated in severe renal impairment (CrCL <30 mL/min) and in Child-Pugh class B or C liver cirrhosis.	Bleeding risk, gastrointestinal symptoms, anemia.	Normal renal function: 12–14 h; renal failure: up to 28 h.	Idarucizumab
	Rivaroxaban	Inhibits factor Xa.		10 mg once a day No dose adjustment based on body weight	Contraindicated in severe renal impairment (CrCL <15 mL/min), hepatic disease with bleeding risk, or Child-Pugh class B or C liver cirrhosis.	Bleeding risk, gastrointestinal symptoms, abnormal liver function.	Adults: 5–9 h; elderly: 11–13 h.	Andexanet Alfa
	Apixaban			2.5 mg twice a day No dose adjustment based on body weight	Contraindicated in severe renal impairment (CrCL <15 mL/min) or hepatic disease with bleeding risk.	Bleeding risk, anemia.	12 h	
	Edoxaban			Weight >60 kg: 60 mg once a day Weight ≤60 kg: 30 mg once a day CrCL 15–50 mL/min:30 mg once a day	Contraindicated in severe renal impairment (CrCL <15 mL/min) or Child-Pugh class C.	Bleeding risk, anemia.	Adults: 10–14 h; CrCL 15–30 mL/min:17 h	

AXa: Anti-factor Xa activity; CrCL: Creatinine clearance; DOACs: Direct oral anticoagulants; LMWH: Lowmolecular-weight heparin; sICH: Spontaneous intracerebral hemorrhage; UFH: Unfractionated heparin; VTE: Venous thromboembolism

parin at either 24 h or 72 h after symptom onset yielded no significant differences in rates of DVT, hematoma expansion, or 3-month functional outcomes, suggesting that early anticoagulation does not substantially increase rebleeding risk.[22] Similarly, a meta-analysis by Li et al.[17] confirmed that starting low-dose LMWH 3–4 days after ICH significantly reduces the incidence of both DVT and PE without elevating mortality. Despite accumulating evidence, clinical practice remains cautious about post-ICH anticoagulation. A survey by Mendel et al. revealed that many clinicians perceive current data as insufficient—particularly concerning differential risks associated with hemorrhage location (lobar *vs.* deep)—and the majority advocate for additional randomized controlled trials.[23] Furthermore, a study by Li et al.[24] indicated that in patients with ICH complicated by DVT, rivaroxaban may be associated with lower long-term mortality compared to LMWH, although these findings require confirmation through prospective, well-designed studies. LMWH offers several clinical advantages, including high bioavailability, prolonged half-life, reduced bleeding risk relative to UFH, and no requirement for routine laboratory monitoring, making it a suitable option for sICH patients with hypercoagulable states, prolonged immobilization, or elevated thrombotic risk. Nonetheless, potential adverse effects such as injection-site bleeding and heparin-induced thrombocytopenia must be carefully monitored. Clinical decision-making should be individualized, with careful weighing of thromboprophylaxis benefits against the risk of hemorrhagic complications. Large-scale, high-quality randomized controlled trials are still needed to definitively establish the optimal anticoagulation strategy following sICH.

VKAs, such as warfarin, exert anticoagulant effects by inhibiting the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X, thereby reducing the hepatic production of functional clotting factors. To avoid ambiguity, this section summarizes the current evidence on prophylactic-dose VKAs use for VTE prevention following sICH. This indication is distinct from the resumption of therapeutic-intensity anticoagulation in patients with established cardiovascular indications—including atrial fibrillation and mechanical heart valves. In patients with atrial fibrillation who have experienced sICH, VKAs demonstrate efficacy in preventing secondary embolic events; however, their safety profile—particularly the risk of recurrent hemorrhage—remains a central concern in clinical decision-making. A network meta-analysis by Wang et al.[25] showed that compared with no anticoagulation, warfarin reduces the risk of thromboembolic events (RR=0.83), but significantly increases the risk of recurrent intracerebral hemorrhage (RR=1.84), with a higher rebleeding risk than that associated with DOACs (RR=1.92). Imaging evidence further supports this differential safety: the “black hole sign,” a radiological marker of hematoma expansion, is more frequently observed in warfarin-treated patients than in those receiving DOACs, and demonstrates greater predictive value for hematoma progression among warfarin users.[26] Warfarin is orally administered, cost-effective, and supported by decades of clinical experience. Nevertheless, it carries a relatively high bleeding risk, requires frequent monitoring of the international normalized ratio (INR), and is prone to interactions with multiple medications and dietary components, all of which compromise anticoagulant stability. It may be considered in sICH survivors requiring long-term anticoagulation—such as those with mechanical heart valves or selected atrial fibrillation patients—provided they can adhere to INR monitoring and tolerate the associated risks. Despite its established role, research on the preventive use of VKAs in sICH remains limited. While DOACs are increasingly replacing VKAs in non-valvular atrial fibrillation due to their favorable safety and convenience, VKAs remain a cornerstone therapy for patients with valvular heart disease or mechanical prostheses.

DOACs exert anticoagulant effects by directly inhibiting thrombin (e.g., dabigatran etexilate) or factor Xa (e.g., rivaroxaban, apixaban, edoxaban), thereby blocking critical downstream steps in the coagulation cascade. Like the VKAs section, this summarizes current evidence on using prophylactic-dose DOACs to prevent VTE after sICH. This differs from resuming therapeutic-intensity anticoagulation for established indications—such as atrial fibrillation or mechanical heart valves. Currently, evidence on the use of DOACs for prophylactic anticoagulation following sICH remains limited. While some studies suggest that DOACs reduce thrombotic event risk with a relatively favorable bleeding profile, findings vary across agents and dosing regimens, and their long-term efficacy and safety in sICH patients require further investigation. A meta-analysis by Wang et al.,[25] which included 12 studies involving 23,265 patients, demonstrated that compared with warfarin, DOACs significantly reduced the risk of recurrent ICH (RR=0.52) and all-cause mortality (RR=0.51) in patients with atrial fibrillation and prior ICH, while also offering greater protection against thromboembolic events (RR=0.70). Ivany et al.’s meta-analysis indicates that non-vitamin K antagonist oral anticoagulants are more effective in reducing the risk of thromboembolic events and are associated with a lower risk of recurrent intracerebral hemorrhage.[27] Giustozzi et al.’s meta-analysis demonstrated that, compared with LMWH, the use of DOACs in patients with brain metastases confers certain clinical advantages.[28] Uchiyama et al.[29] found that DOACs may be superior to VKAs in reducing the recurrence of ICH, although their long-term safety remains to be confirmed. DOACs offer several clinical advantages, including convenient oral administration, high bioavailability, consistent drug absorption, no requirement for routine coagulation monitoring, fewer drug–drug interactions, short half-life, and dose adjustability based on renal function, enabling flexible and individualized treatment strategies. However, their use is contraindicated or requires caution in patients with severe renal impairment. They are generally suitable for long-term anticoagulation in stable sICH patients who require ongoing thromboprophylaxis—such as those with atrial fibrillation, DVT, or PE—with agent and dose selection tailored to individual patient characteristics. Despite growing evidence supporting their benefits, data specifically on the preventive application of DOACs in sICH populations remain sparse, and current findings may not be directly generalizable to prophylactic anticoagulation protocols.

In addition, the development of novel anticoagulants may provide new therapeutic options for anticoagulation in patients with cerebral hemorrhage. Abelacimab, a specific factor XI inhibitor, prevents thrombosis without increasing the risk of bleeding. Furthermore, compared with patients receiving LMWH, those treated with this drug have a lower incidence of VTE.[30]

Currently, research on prophylactic anticoagulation in patients with sICH is predominantly centered on the use of UFH and LMWH. Nevertheless, the overall body of evidence remains limited, and high-quality studies are urgently needed to generate robust data supporting prophylactic anticoagulation strategies in patients with severe sICH.

High-risk Factors and Early Identification in Anticoagulation Population

To identify the patient population suitable for anticoagulation, previous studies have established high-risk factors for thrombotic events in individuals with intracerebral hemorrhage. Malignant tumors, coagulation disorders, age over 60 years, hospital stay exceeding 16 days, and pulmonary circulation diseases are considered independent risk factors for VTE in ICU patients with intracerebral hemorrhage.[2] Elevated basophil counts in peripheral blood, increased white blood cell counts, and elevated D-dimer levels are also recognized as risk factors associated with a high risk of thrombosis in patients with cerebral hemorrhage.[3,31,32]

Some researchers have developed statistical models to identify patients with sICH who are at high risk of thrombosis. Ji et al.[33] constructed a 31-point ICH-DVT scoring system using multivariate logistic regression, based on six independent predictors: age, hematoma volume, subarachnoid hemorrhage extension, concurrent pneumonia, gastrointestinal bleeding, and length of hospital stay. Each predictor is assigned a score proportional to its regression coefficient (β), and the total score is calculated by summing the individual item scores (range: 0–31 points). Higher scores indicate greater risk of DVT. The scoring system stratifies patients into five risk categories, with corresponding prevention strategies recommended according to each level. Moreover, this scoring system demonstrated good discriminative performance in both internal validation (AUROC=0.83) and external validation cohorts (AUROC=0.88).

With the advancement of artificial intelligence, researchers have also attempted to identify patients with a high risk of thrombosis following cerebral hemorrhage using machine learning approaches. Tang et al.[34] developed a prediction model for early DVT risk in patients with sICH after surgery, which demonstrated good predictive performance in the validation cohort (AUC=0.82, sensitivity: 78%, specificity: 85%). By incorporating SHAP values, the model's interpretability was enhanced, revealing that D-dimer levels are nonlinearly and positively associated with thrombosis risk. Qiu et al.'s study employed a dual-track feature selection approach using LASSO and Boruta to identify six key predictive factors: age, white blood cell count, systolic blood pressure at admission, surgical status, blood loss, and midline shift. Five machine learning algorithms were subsequently developed and compared on a 30% independent test set. Ultimately, the LGBM model demonstrated superior predictive performance with an AUC of 0.998, a Brier score of 0.043, and an F1-score of 0.9504, along with the best calibration and clinical net benefit. Furthermore, SHAP interpretability analysis revealed that blood loss, systolic blood pressure, and age are positively associated with increased risk of DVT.[35]

In addition, previous studies have identified several risk factors associated with hematoma expansion in patients with intracerebral hemorrhage. Hypertension (defined as systolic blood pressure >160 mmHg), hyperglycemia, and elevated levels of inflammatory markers are consistently recognized as independent predictors of hematoma expansion.[36] Meanwhile, imaging findings, including the Spot Sign on computed tomography angiography (CTA), the Swirl Sign and Blend Sign on non-contrast CT, and irregular hematoma shape, are also widely recognized as imaging predictors of hematoma expansion.[37–40] Furthermore, emerging evidence suggests that lobar and deep intracerebral hemorrhage are associated with distinct risk profiles for hematoma expansion. Irregular hematoma shape and reduced fibrinogen levels have been consistently identified as independent predictors of hematoma expansion in lobar ICH, whereas a low GCS score is recognized as a significant risk factor in deep brain hemorrhage.[41] In parallel with thrombosis risk prediction, several studies have developed machine learning models to predict hematoma expansion in sICH. Notably, Satoru Tanioka and colleagues proposed a multimodal neural network model that integrates convolutional neural network (CNN) analysis of CT imaging with neural network–based assessment of clinical variables for predicting hematoma expansion in sICH patients. The model demonstrated strong predictive performance in external validation, achieving a sensitivity of 1.000 (95% CI: 0.768–1.000) and an AUC of 0.799 (95% CI: 0.749–0.849).[42] In the same year, another study integrating deep learning with radiomics for the prediction of hematoma expansion demonstrated strong predictive performance, with an AUC of 0.95 (95% CI: 0.92–0.97), precision of 0.90, recall of 0.79, and mean average precision of 0.87.[43] Despite these advances, a 2024 meta-analysis of 11 predictive model studies involving 12,087 patients with sICH found that although current models exhibit modest predictive capacity for hematoma expansion, their overall performance remains limited, with a pooled C-statistic of 0.74 (95% CI: 0.69–0.78).[44]

However, the aforementioned studies were limited to unidimensional identification of patients at high risk of thrombosis or those prone to hematoma expansion following cerebral hemorrhage, and did not address the critical clinical question of whether these patients are suitable candidates for prophylactic anticoagulation therapy. In 2019, Lioutas et al.[45] developed a "net risk" model (Net Risk Estimation) by integrating the CHA_2DS_2-VASc score with the HAS-BLED score to simultaneously quantify the risks of ischemic events and recurrent hemorrhage. The results showed that when CHA_2DS_2-VASc $\geq$4 and HAS-BLED $\leq$2, anticoagulation therapy was associated with a significant net clinical benefit (HR=0.62, 95% CI 0.48–0.79). This study performed a "net risk" analysis by balancing thrombosis risk against bleeding risk, which is of significant value for identifying the appropriate population for prophylactic anticoagulation in patients with cerebral hemorrhage. Currently, research on the integrated "net risk" assessment of thrombosis and bleeding remains limited.

Time Window for Prophylactic Anticoagulation

The timing of prophylactic anticoagulation represents a central challenge in the management of patients with intracerebral hemorrhage. The primary goal of prophylactic anticoagulation following intracerebral hemorrhage is to identify the optimal timing that maximizes protection against VTE while minimiz-

ing the risk of anticoagulation-associated complications, such as hematoma expansion or secondary bleeding. Early initiation may precipitate rebleeding, whereas delayed administration increases the likelihood of thromboembolic events. In patients with sICH, both VTE and hematoma expansion are well-established contributors to adverse outcomes.[13,46]

Hematoma expansion is defined as an increase in hematoma volume exceeding 33% of the initial volume or an absolute growth of >6 mL within 24 h following intracerebral hemorrhage.[47,48] Current evidence indicates that 30% of patients with cerebral hemorrhage experience hematoma expansion within 3 h, and 73% within 24 h.[49,50] Furthermore, the risk of thrombosis begins to rise immediately after hemorrhage onset and is further elevated in the context of activity restriction and prolonged immobilization. VTE in patients with cerebral hemorrhage may occur as early as 48 h after hemorrhage onset.[51] Recommendations regarding the timing of pharmacologic prophylaxis initiation vary across institutions, ranging from 24 h to 7 days after hemorrhage onset.[52] Therefore, the time window for prophylactic anticoagulation partially overlaps with the high-risk period for hematoma expansion in patients with intracerebral hemorrhage, which raises concerns regarding the safety of such prophylaxis.

Currently, there is no international consensus on the optimal timing of anticoagulation. The American Stroke Association recommends that in nonambulatory patients with sICH, initiating low-dose UFH or LMWH prophylaxis at 24–48 h from sICH onset may be reasonable to optimize the benefits of preventing thrombosis relative to the risk of HE.[18] The Chinese Guidelines for the Management of Severe Stroke recommend individualized pharmacological therapy for patients with cerebral hemorrhage following careful assessment of the risks of DVT, PE, and rebleeding. The Canadian Stroke Best Practice Recommendations: Secondary Prevention of Stroke Update 2020 recommends initiating LMWH after hematoma stabilization, which typically occurs 48 h after symptom onset, provided that neuroimaging confirms no hematoma expansion and that at least 24 h have elapsed since the baseline scan.[53] Current guidelines indicate that there is insufficient evidence to establish the safety of LMWH administration within 48 h of sICH onset. Furthermore, whether repeated neuroimaging to confirm hematoma stability can inform safe initiation of pharmacologic prophylaxis between 24 and 48 h after onset remains uncertain and requires additional supporting evidence. The 2022 AHA/ASA intracranial hemorrhage guidelines recommend earlier pharmacologic prophylaxis, while the Canadian guidelines advise anticoagulation only after hematoma stability is confirmed. In contrast, the Chinese guidelines emphasize individualized risk assessment and tailored decisions based on clinical profile and thromboembolic *vs.* bleeding risk balance. We summarize the key recommendations of the guidelines from various countries in Table 2.

Existing studies have conducted targeted investigations using time windows of >48 h, 24–48 h, and within 24 h after onset—particularly focusing on ultra-early prevention—to provide evidence for the efficacy and safety of prophylactic anticoagulation therapy in patients with sICH.

In a prospective randomized trial conducted in 2009, researchers compared pharmacologic prophylaxis with mechanical prophylaxis using elastic stockings in 75 patients with ICH. The results demonstrated that initiating LMWH 48 h after sICH onset did not increase the risk of hematoma expansion and was not associated with systemic bleeding complications.[54] However, the study had a small sample size and limited statistical power. Moreover, only asymptomatic DVT and PE were captured, with no assessment of long-term outcomes related to symptomatic events. Additionally, the 48-h initiation window for anticoagulation may be relatively late, potentially missing the critical period for early thromboprophylaxis.

The initiation of prophylactic anticoagulation within 24–48 h after intracerebral hemorrhage has been supported by multiple studies as safe and potentially beneficial in reducing thromboembolic events. A randomized study by Boeer et al.[55] involving 68 patients demonstrated that early administration of low-dose heparin—initiated on day 2—was associated with a significantly lower incidence of pulmonary embolism and did not increase the risk of rebleeding. However, this study had a limited sample size, lacked detailed reporting of heparin dosing, and excluded critically ill patients, which may limit the generalizability of its findings. A 2024 meta-analysis incorporating 12 studies—7 randomized controlled trials and 5 observational studies—involving a total of 4419 patients with sICH, found no significant differences in key outcomes such as DVT incidence and mortality between early (within 24–48 h) and delayed initiation of heparin prophylaxis. These findings suggest that early administration of heparin may be both effective and safe in this population.[56] Current evidence indicates that initiating UFH or LMWH within the 24- to 48-h time window may represent one of the optimal strategies for prophylactic anticoagulation in patients with sICH; however, further high-quality studies are required to confirm these findings.

Growing evidence suggests that ultra-early initiation of prophylactic anticoagulation within 24 h after intracerebral hemorrhage may be both safe and effective. Qian et al.[22] conducted a double-blind, placebo-controlled, multicenter trial in which 139 patients with ICH and lower limb paralysis were randomly assigned to an early group (initiating enoxaparin 40 mg/day within 24 h of onset) or a late group (initiating treatment within 72 h of onset). The study compared the incidence of VTE, risk of hematoma expansion, and overall prognosis between groups. No significant differences were observed in thrombotic events, hematoma expansion, or clinical outcomes, suggesting that early initiation of enoxaparin for VTE prophylaxis is both safe and effective in this population. In a retrospective cohort study, Kananeh MF and colleagues analyzed 163 patients with sICH who received UFH for VTE prophylaxis. The results demonstrated that initiating UFH during the ultra-early phase (<24 h after onset) was not associated with an increased risk of hematoma expansion compared to standard initiation timing (mean 46.6 h) (P=0.49).[57] In addition, a study on early prophylactic anticoagulation in patients with traumatic intracerebral hemorrhage analyzed 1784 individuals and found that those who initiated anticoagulation beyond 24 h had a higher risk of VTE compared to those who started within 24 h; however, the difference was not statistically significant (OR=1.51; 95% CI 0.69–3.30; P=0.307).[58] However, although the aforementioned studies provide evidence on the use of early prophylactic anticoagulation in patients with sICH, they are limited by relatively small sample sizes, which may compromise the generalizability and reliability of the findings. Furthermore, the third study primarily included patients with traumatic ICH, limiting the applicability of its conclusions to those with sICH. Taken to-

Table 2
The key recommendations of the guidelines from various countries.

Guidelines	Year	Evidence grade	Key recommendations
Chinese guidelines for the management of severe stroke	2024	Level II Class C	Anticoagulant therapy should be considered based on the risks of deep vein thrombosis, pulmonary embolism, and rebleeding. After hematoma stabilization, treatment should be individualized.
Chinese guidelines for the diagnosis and treatment of cerebral hemorrhage	2019	Level II Class B	In nonambulatory patients with spontaneous ICH, initiating low-dose UFH or LMWH prophylaxis at 24–48 h from ICH onset may be reasonable to optimize the benefits of preventing thrombosis relative to the risk of HE.
Guidelines for the management of spontaneous intracerebral hemorrhage	2022	Level II Class C	Optimal timing for initiating prophylactic anticoagulation with UFH or LMWH is within 24–48 h after onset.
The Canadian Best Practice Guidelines for Stroke	2020	Class B	Chemical prophylaxis with low-molecular-weight heparin may be initiated after 48 h, provided that neuroimaging confirms hematoma stabilization.

ICH: Intracerebral hemorrhage; UFH: Unfractionated heparin; LMWH: Low-molecular-weight heparin; HE: Hematoma expansion.

gether, while these studies provide reassuring signals, the current evidence remains insufficient to support routine ultra-early (<24 h) pharmacologic prophylaxis, particularly in ICU patients; decisions should be individualized and ideally guided by repeat imaging and bleeding risk assessment.

However, for ICU patients, the initiation of anticoagulation may present greater challenges. Patients with intracerebral hemorrhage in the ICU often have lower GCS scores, require prolonged mechanical ventilation with tracheal intubation, and may have concomitant infections, these factors collectively may accelerate the onset of VTE in this population.[9,59] Patients in the intensive care unit are particularly susceptible to systemic inflammatory response syndrome (SIRS), largely due to severe infections and other critical illness-related factors. Evidence from existing studies indicates a significant association between SIRS and hematoma expansion following intracerebral hemorrhage (OR=2.549, 95% CI: 1.497–4.342, P=0.0006).[60] In addition, a low GCS score has been consistently associated with an increased risk of hematoma expansion.[41] These complex factors collectively contribute to an increased risk of both thrombosis and hematoma expansion among patients with intracerebral hemorrhage in the intensive care unit, which may limit the direct applicability of existing evidence on prophylactic anticoagulation timing derived from studies of non-critically ill patients to this critically ill population.

Challenges of Prophylactic Anticoagulation

Patients with cerebral hemorrhage are often at relatively high risk of rebleeding, necessitating a careful balance between thrombosis prevention and avoidance of rebleeding risk. Currently, intermittent pneumatic compression devices are widely used for VTE prophylaxis; however, anticoagulant drug utilization remains low, with only 7.9–16.5% of patients receiving pharmacologic prophylaxis for VTE prevention.[61,62] This may be attributable to clinicians' concerns regarding intracranial hematoma progression and the lack of consensus on the optimal timing for initiating anticoagulation.[63]

There is no consensus among researchers regarding whether anticoagulant drugs increase the risk of rebleeding in patients with intracerebral hemorrhage. A small-scale retrospective study indicated that among 26 patients with intracerebral hemorrhage who received therapeutic anticoagulation, 96% maintained stable intracranial hematoma volumes, and only one patient experienced minor hematoma expansion, which did not affect the clinical course.[64] However, another study indicates that patients with hematoma expansion following cerebral hemorrhage often initiate anticoagulant therapy earlier, with a mean onset time of 5.5 days.[65] The study by Brouwers et al.[66] also indicated that the use of anticoagulant drugs is significantly associated with hematoma enlargement. A meta-analysis involving 4055 patients with sICH also indicated that anticoagulation prophylaxis had no significant effect on hematoma enlargement.[21] Current evidence suggests that the use of prophylactic anticoagulation for VTE prevention in patients with sICH does not substantially increase the risk of rebleeding or hematoma expansion. However, as some studies are based on therapeutic anticoagulation regimens and are limited by small sample sizes, more rigorous and well-designed investigations are required to establish stronger and generalizable evidence.

In addition, evidence regarding the safety of prophylactic anticoagulation in patients with intracerebral hemorrhage across different brain regions demonstrates notable heterogeneity and inconsistency across studies. Eckman et al.'s study indicates that anticoagulant therapy may be considered in patients with deep intracerebral hemorrhage who are at high risk of thromboembolism, whereas it is recommended to avoid such therapy in those with lobar hemorrhage.[67] A systematic review published in 2024 indicated that for patients with traumatic intracerebral hemorrhage and subdural hematoma, early initiation of anticoagulant therapy (within 8 days after injury) may increase the risk of rebleeding.[68] However, the study by Wilson et al.[69] indicates that anticoagulation-related intracerebral hemorrhage does not preferentially occur in lobar regions. The location and type of intracerebral hemorrhage appear to influence the selection of anticoagulant therapy; however, this association remains controversial. Moreover, existing research findings cannot be directly extrapolated to guide prophylactic anticoagulation strategies. Further investigations are required to elucidate the underlying mechanisms of hematoma expansion in patients with hemorrhages at different brain sites and to define the appropriate indications for prophylactic anticoagulation.

In addition, cerebral amyloid angiopathy (CAA) is a major cause of intracerebral hemorrhage in the elderly. The deposition of amyloid proteins in cerebral vessel walls predisposes patients to an increased risk of bleeding. Furthermore, the HAS-BLED score has limited applicability in patients with CAA. Consequently, anticoagulant therapy in these patients is generally approached with caution in clinical practice.[70–72] For CAA patients with concurrent atrial fibrillation, clinical guidelines generally recommend prioritizing DOACs for anticoagulation or considering left atrial appendage occlusion as an alter-

native therapeutic option.[72,73] However, current evidence on prophylactic anticoagulant therapy in patients with CAA combined with cerebral hemorrhage remains limited.

Future Research Directions

Currently, decision-making regarding prophylactic anticoagulation after sICH relies predominantly on clinical experience, with a notable absence of precise quantitative tools. Evidence remains limited on key aspects such as the selection of anticoagulant agents, optimal dosing, and timing of initiation in patients with severe sICH. Future research should prioritize large-scale, multicenter, prospective clinical trials conducted in ICU populations to systematically evaluate the efficacy and safety of various anticoagulation strategies—including drug class, timing of initiation, and dose titration. Rigorous randomized controlled trial designs are essential to generate high-quality evidence that can inform updates to clinical guidelines and advance the standardization and rationalization of prophylactic anticoagulation in critically ill sICH patients.

Concurrently, clinical trials evaluating direct anticoagulants—such as DOACs and factor XI inhibitors—should be implemented in ICU settings to assess their safety and efficacy. A critical focus should be whether these agents can effectively prevent VTE without increasing the risk of rebleeding.

With recent advances in artificial intelligence, machine learning models offer promising potential to integrate multimodal data—including clinical features, laboratory parameters, and neuroimaging findings—to develop high-precision risk prediction tools for VTE and rebleeding in sICH patients. However, studies that comprehensively estimate the "net clinical benefit" or balanced risk of thrombosis *vs.* bleeding remain scarce. Future efforts should leverage machine learning techniques to model individualized net risk, thereby enabling precision-guided anticoagulation decisions.

Furthermore, individualized treatment strategies must be emphasized. Tailoring anticoagulation approaches according to each patient's unique profile—including thrombotic and hemorrhagic risk, comorbidities, and sICH subtypes (e.g., lobar hemorrhage, deep intracerebral hemorrhage, cerebral amyloid angiopathy-related hemorrhage)—can enhance prophylactic efficacy while minimizing adverse outcomes.

Finally, establishing a multidisciplinary research framework involving critical care medicine, neurosurgery, hematology, and radiology will facilitate a comprehensive understanding of the mechanisms underlying prophylactic anticoagulation in sICH. Interdisciplinary collaboration is crucial to refining risk stratification and improving the precision of anticoagulation management in this vulnerable population.

Conclusions

Patients with sICH are at high risk for VTE and associated with poor clinical outcomes, underscoring the importance of prophylactic anticoagulation therapy. However, significant controversies persist regarding drug selection, timing of initiation, and safety of anticoagulation in this population, and there remains a lack of consensus and high-quality evidence to guide clinical decisions. Current evidence indicates that traditional anticoagulants—such as LMWH and UFH—are effective in reducing VTE incidence; however, the optimal timing for initiation and long-term safety profile remain uncertain and warrant further investigation. DOACs and emerging agents such as factor XI inhibitors show promising efficacy and improved safety profiles in other populations, but data supporting their use in sICH patients are limited. Large-scale, multicenter, prospective clinical trials are required to validate their role in this high-risk group.

Furthermore, identifying individuals at high thrombotic risk yet low bleeding risk is essential for enabling personalized anticoagulation strategies. Advances in artificial intelligence, particularly machine learning, offer novel opportunities to integrate multimodal clinical data for accurate prediction of both VTE and rebleeding risks. Nevertheless, current research in this domain remains preliminary, and comprehensive models for estimating the "net clinical risk"—balancing thrombosis and hemorrhage—are still underdeveloped.

Future research should prioritize large-scale, multicenter prospective trials to systematically evaluate the efficacy and safety of various anticoagulation approaches, thereby advancing the standardization and rationalization of prophylactic anticoagulation in severe sICH. Concurrently, clinical development of novel anticoagulants must be accelerated. Integrating advanced technologies like machine learning to construct high-precision risk stratification tools, tailoring individualized treatment plans, and establishing multidisciplinary collaborative frameworks—spanning neurology, critical care, hematology, and radiology—are critical steps toward elucidating the mechanisms of anticoagulation in sICH. These efforts will collectively enhance decision-making precision and provide more targeted, evidence-based guidance for clinical practice.

CRediT Authorship Contribution Statement

Qizhang Yang: Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation. **Jinyuan Mei:** Writing – original draft, Validation, Methodology, Investigation. **Weixiao Feng:** Methodology, Investigation. **Shuixiang Deng:** Validation, Supervision, Methodology, Investigation. **Rui Yan:** Methodology, Investigation, Formal analysis. **Ye Gong:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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