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Managing the Black Swan Event of Spontaneous Intracerebral Haemorrhage in Patients with Anti-coagulant & Antiplatelet Medication

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Abstract

This mini-review examines the management of spontaneous intracerebral haemorrhage (ICH) in patients using anticoagulant and antiplatelet medication. Atrial Fibrillation (AF), a significant risk factor for stroke, is often treated with anticoagulants to prevent cardioembolic events. However, ICH is a serious consequence of anticoagulation therapy, and managing patients who experience this "Black Swan" event is complex. While Vitamin K Antagonists (VKAs) like warfarin increase both the risk and severity of ICH, Direct Oral Anti-Coagulants (DOACs) offer a safer alternative with a lower mortality rate. We explore the pathophysiology of ICH, noting that anticoagulants disrupt the normal hemostatic process, potentially leading to excessive bleeding and hematoma expansion. This is particularly concerning as hematoma enlargement is associated with a poor prognosis. We examine the challenges of managing ICH in patients on anticoagulants, addressing aspects such as coagulation monitoring, reversal agents, and the decision to re-initiate anticoagulation therapy. Balancing the risk of recurrent ICH with the need to prevent thromboembolic events is a delicate process. There is need for more robust clinical data from prospective randomized trials to guide optimal management strategies for patients with AF who experience ICH, particularly regarding the timing and safety of resuming anticoagulation therapy.

Keywords: Intracerebral Hemorrhage; Atrial Fibrillation; Direct Oral Anti-Coagulants; Vitamin-K Antagonists

Introduction

In 2010, it was projected that over 34 million people globally suffered from atrial fibrillation (AF). The impact of AF has been increasing over time. For instance, the age-adjusted incidence rates rose from 61 per 100,000 person-years in men and 44 in women in 1990 to 78 in men and 60 in women by 2010. Furthermore, projections from the ATRIA study suggest that the number of adults living with AF in the U.S. will grow from 2.6 million in 2010 to 5.66 million by 2050, nearly doubling [1]. Therapeutic anticoagulation is the cornerstone of cardioembolic stroke prevention in patients with atrial fibrillation and carries an inherent risk of bleeding. Intracerebral hemorrhage (ICH) is the most severe hemorrhagic consequence [2]. In addition to the increasing incidence of bleeding events such as ICH, antithrombotic treatment is also associated with the more severe form of ICH [3]. Warfarin not only increases the risk of ICH but also worsens the severity of hemorrhage when it occurs, approximately doubling its mortality [4]. While VKA (Vitamin K Antagonist)-ICH was linked to a high death rate of 37.5%, the mortality rate of DOAC (Direct Oral Anti-Coagulants)

-ICH was much lower (12%) [5]. DOACs are safer regarding the risk of ICH (Figures 1 & 2).

Pathophysiology and Management

Procoagulant and anticoagulant forces are balanced in hemostasis, which is made up of systems that maintain constant blood flow. This is accomplished via secondary haemostasis, which necessitates the creation of a fibrin clot via a series of enzymatic processes, and primary hemostasis, which generates the platelet plug. Anticoagulants impair the integrity of the artery wall and change the vascular endothelium, causing excessive bleeding and hematoma expansion. They also interfere with the normal hemostatic process. In addition to being common in the brain, microbleeds can also occur in other organs such as the gastrointestinal tract mucosal lining. Cerebral microbleeds, which occur in cerebral amyloid angiopathy and hypertensive vasculopathy, are tiny, asymptomatic, persistent brain hemorrhages caused by structural defects in the small vessels. Increased risk of intracranial bleeding has been linked to cerebral microbleeds. The mucosa of the gastrointestinal system frequently experiences microbleeds, and subclinical bleeding in individuals taking DOACs can manifest as hemorrhage of clinical significance [6]. There are several risk factors proposed for intracerebral hemorrhage in patients taking anticoagulants as summarized in table 1. Hematoma enlargement is a known risk factor for poor prognosis in both primary ICH and OAC-associated ICH. Hematoma enlargement in primary ICH has been demonstrated to be prevented by pharmacological therapies aimed at hemostasis or blood pressure reduction; however, its impact on clinical outcomes is unclear. The pathophysiological mechanism of hematoma expansion in OAC ICH is complicated, long-lasting, and is primarily caused by abnormal coagulation. This distinction from the main ICH makes it a target for vigorous medical intervention to reduce hematoma enlargement, and perhaps impact the results [7,8]. The straightforward formula ABC/2 can be used to reliably estimate intraparenchymal bleeding volume in less than a minute [9]. Figure 3 illustrates general management strategies employed for intracerebral hemorrhage. In RETRACE, an observational study cohort, it was found that patients whose INR values were reversed below 1.3 within 4 hours of arrival, and whose systolic blood pressure was less than 160 mmHg at 4 hours had lower rates of hematoma enlargement [7]. Patients who take oral anticoagulants are more likely than those who do not to experience secondary hematoma enlargement, which increases the risk of death or poor functional results [10]. Several scores have been developed to estimate the risk of bleeding events as summarized in table 2. Among them HAS-BLED score has been studied better than other scores for predicting bleeding risk [6].

Patients related risk factors
Advanced age
Low body mass
Smoking
Associated comorbidities like hypertension, chronic obstructive pulmonary disease, diabetes mellitus, renal failure, liver disease
Previous gastrointestinal or intracranial bleeding
Malignancies—tumor invasion
Hematologic disorders
Collagen vascular disorders Thrombocytopenia
Concomitant use of other medications including steroids, nonsteroidal anti-inflammatory drugs, aspirin or clopidogrel

Table 1: Risk factors for spontaneous hemorrhage in patients receiving Direct Oral Anticoagulants [6].

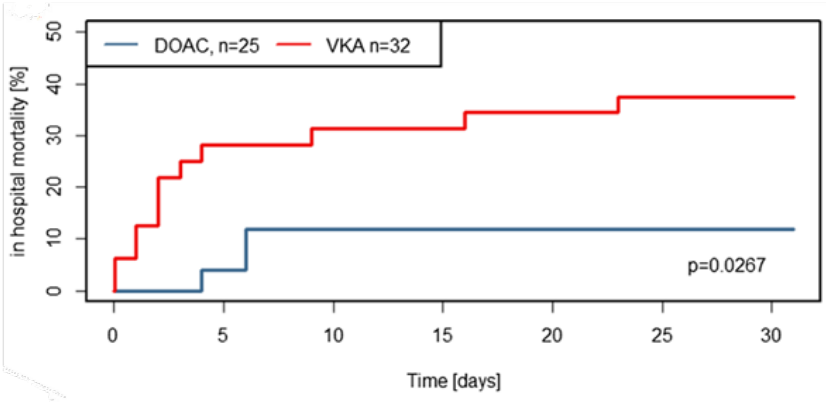

Figure 1: Kaplan Meier curves and p-values from log-rank test for 30 day in-hospital mortality in patients with intracerebral hemorrhage [5].

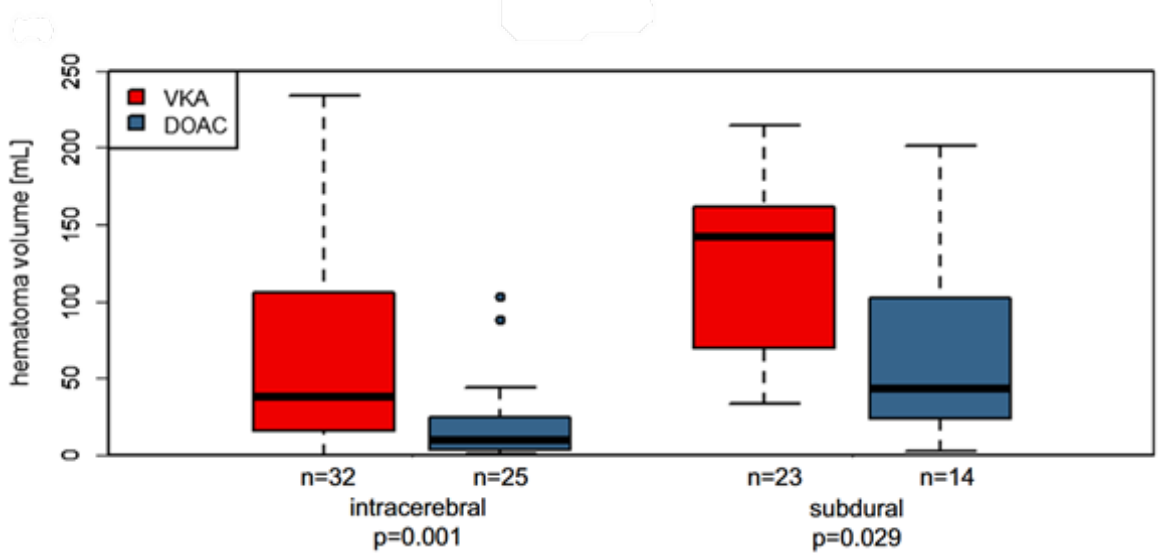

Figure 2: Boxplots comparing hematoma volume in patients with intracerebral and subdural hemorrhage treated with vitamin K antagonist (VKA) and direct oral anticoagulants (DOAC) at hospital admission. Horizontal lines represent the median of the corresponding subgroups. P-values are from a two-sided nonparametric Wilcoxon–Mann–Whitney U-test [5].

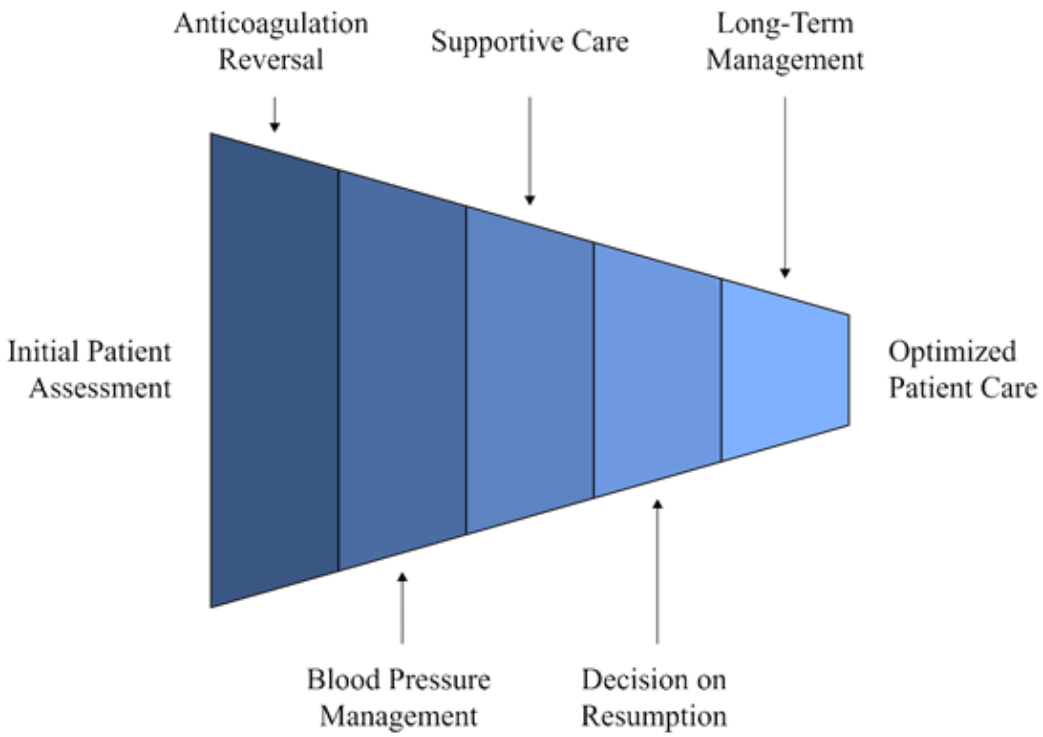

Figure 3: Management of spontaneous ICH in patients who are on anti-coagulants and/or anti-platelet medication.

Common bleeding scores
HAS-BLED score
HEMORR2HAGES score
ATRIA score
ORBIT-AF score
ABC bleeding score

Table 2: Common bleeding scores used in patients receiving anticoagulants [6].

Routine coagulation monitoring is not necessary for non-VKA anticoagulants; for currently approved indications, neither the dosage nor the dosing schedules should be changed in response to variations in laboratory coagulation parameters. Nonetheless, in certain clinical circumstances, such as patients who present with renal or hepatic insufficiency, possible drug-drug interactions, suspected overdosing, or in emergencies, such as severe bleeding and thrombotic events, or in cases requiring immediate surgery, evaluation of drug exposure and anticoagulant effects may be required. DOAC's greatest impact on the clotting test will happen three hours after ingestion when its plasma concentration is at its highest [11].

The anticoagulant effects of all DOACs generally correspond to their plasma concentrations, which can be measured using liquid chromatography-tandem mass spectrometry. However, despite its availability in certain regions, this method is not commonly used in routine clinical practice. Dabigatran has a greater effect on clot-based tests like aPTT and thrombin time than on PT. Thrombin time is typically highly sensitive to dabigatran therapy. Dabigatran may additionally lead to aPTT prolongation, though the level of prolongation differs according on the reagent employed in the test. Factor Xa inhibitors increase PT/INR more than aPTT, but have little clinical effect on thrombin time. However, the degree of PT prolongation is affected by both the drug level and the agent in question. Chromogenic anti-factor Xa testing is frequently used to monitor medications like heparin and low-molecular-weight heparin, but it also has the potential to evaluate DOACs with factor Xa activity [10]. Figure 4 shows the reversal strategies recommended by American Heart Association/American Stroke Association 2022 Guidelines.

Re-initiation of anticoagulant and antiplatelet agents

The majority of patients with intracerebral hemorrhage (ICH) have risk factors for ischemic events, and many have experienced such events. As a result, nearly half of these patients have indications for antithrombotic treatment, either antiplatelet or anticoagulant drugs, or use of such treatment at the time of bleeding [12,13]. In a Swedish population-based study, recurrent ischemic events outpaced recurrent ICH within ICH survivors, and ICH was found to be a standalone predictor of thromboembolic complications among AF patients [14,15].

RESTART, a randomized trial, reveals that antiplatelet treatment after ICH is safe since the potential increase in the risk of recurring ICH is most likely too small to outweigh the advantageous effects of antiplatelet therapy for secondary prevention [16]. The SoSTART randomized study sought to determine whether initiating oral anticoagulation was non-inferior to avoiding oral anticoagulation in victims of intracranial hemorrhage with atrial fibrillation. The incidence of recurrent cerebral bleeding was lower than anticipated, although the results were unclear [17]. The purpose of APACHE-AF was to calculate the nonfatal stroke or vascular mortality rates in atrial fibrillation patients who survived an anticoagulant-associated ICH when apixaban was used as opposed to not using anticoagulation. They discovered that both groups had a high risk of vascular death or nonfatal stroke and emphasized the necessity of conducting large randomized studies [18]. In the one-year follow-up period, the RETRACE multicenter observational trial in Germany examined patients who were admitted acutely with OAC-associated ICH and assessed the incidence of thromboembolic and hemorrhagic events based on treatment exposure (resuming OAC versus not taking OAC). Among all surviving patients (n = 719), crude annual event rates demonstrated that thromboembolic complications significantly decreased with OAC resumption (OAC: 9/172 (5.2%) vs. no OAC: 82/547 (15.0%); p <.001), while hemorrhagic complications did not increase significantly (OAC: 14/172 (8.1%) vs. no OAC: 36/547 (6.6%); p =.48) [7]. These relationships supporting OAC restart during ICH were replicated in several follow-up observational or registry investigations [19-22]. In a meta-analysis of retrospective data undertaken by Murthy et al., 2017, OAC medication was associated with a lowered risk of thromboembolic events and a comparable risk of ICH recurrence [23]. Following full clearance of the CNS hematoma, DOACs can be safely resumed in carefully chosen individuals. The significant recurrence rate of lobar intracerebral hemorrhage in CAA (reported to be over 10% annually), particularly in individuals on antithrombotic medications, makes it a debilitating condition. Generally, re-initiation is not advised in cases of intracerebral hemorrhage associated with CAA [24]. Park, et al. discovered in a retrospective analysis that resuming OAC after inadequate ICH resolution on CT scan resulted in recurrent CNS hemorrhage [19]. After assessing particular patient features to maximize the balance of risks and benefits, starting anticoagulation therapy approximately 7 to 8 weeks after ICH may be suggested.

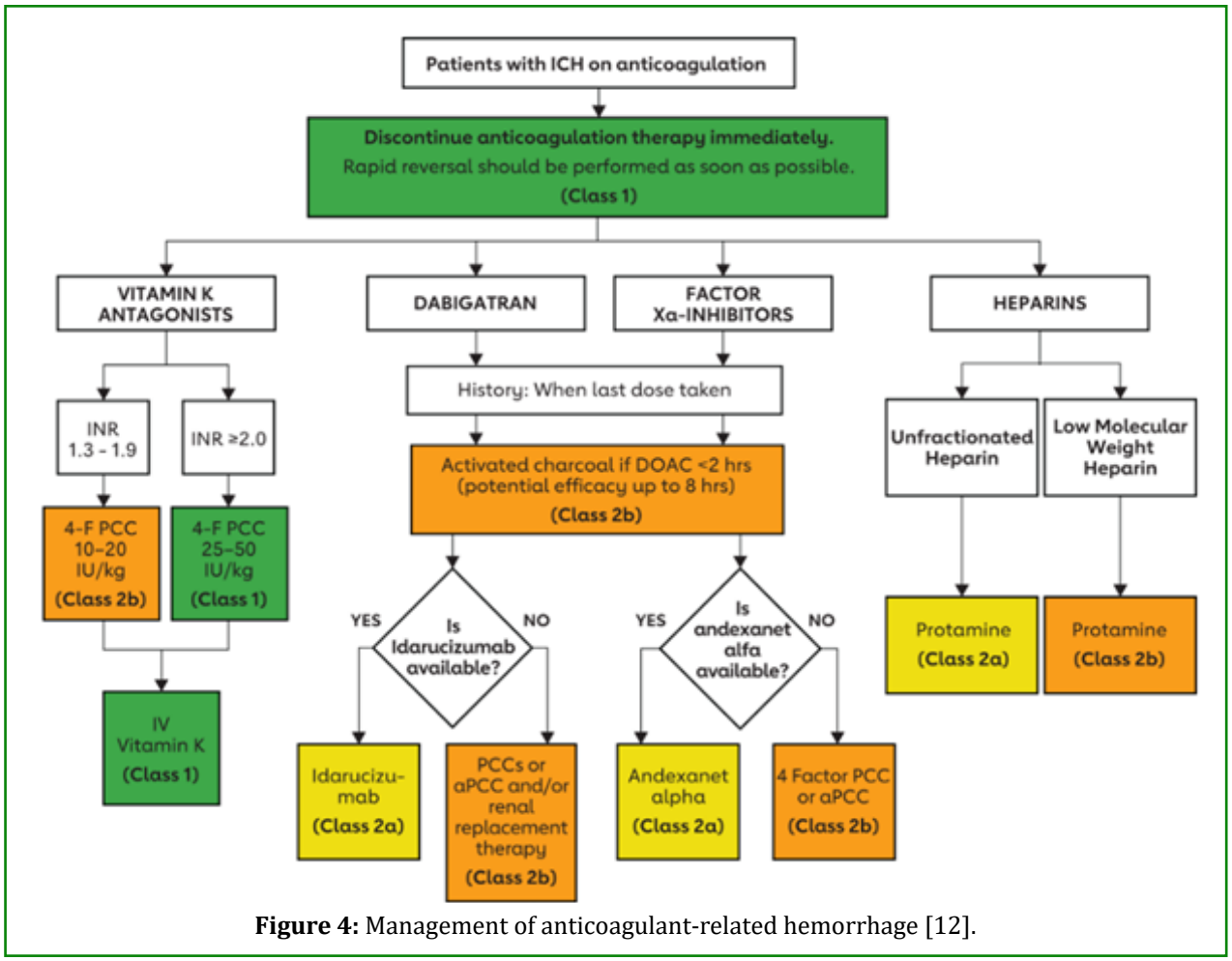

Figure 4: Management of anticoagulant-related hemorrhage [12].

Table abbreviations: aPCC – activated prothrombin complex conentrate, DOAC – Direct Oral Anticoagulant, ICH – Intracerebral Hemorrhage, INR – International Normalized Ratio, PCC – Prothrombin Complex Concentrate

	Preferred reversal agent	Alternate reversal agent	Additional considerations
Oral Direct Thrombin Inhibitors – Dabigatran	Idarucizumab 5-g IV bolus- If dabigatran was administered within past 3-5 half-lives. If renal insufficiency is present has led to exposure beyond 3-5 half-lives	Use if idarucizumab is unavailable Activated PCC (50 U/kg)	Activated charcoal (50 g) Within 2 hours of dabigatran ingestion Activated charcoal (50 g)
Oral factor Xa inhibitors Apixaban Rivaroxaban Edoxaban	4-factor PCC (50 U/kg) If ICH occurred within 3-5 half-lives of drug exposure Andexanet alfa Low dose: 400 mg IV bolus at rate of 30 mg/min followed by infusion of 4 mg/min for up to 2 hours High dose: 800 mg IV bolus at rate of 30 mg/min followed by infusion of 8 mg/min for up to 2 hours	Activated PCC (50 U/kg) If ICH occurred within 3-5 half-lives of drug exposure and 4- factor PCC is unavailable	Within 2 hours of dabigatran ingestion

Table 3: Anticoagulant reversal recommendations for patients with critical bleeding [10].

Table abbreviations: PCC – Prothrombin Complex Concentrate

Recommendations
PCC (30 IU/kg) in adults with ICH occurring during use of vitamin K antagonists (with an INR above normal) over no treatment to decrease mortality and normalise INR.
PCC (30 IU/kg) in patients with ICH occurring during use of vitamin K antagonists (with an INR above normal) over FFP (20 mL/kg) to decrease mortality and normalise INR.
Vitamin K (10 mg IV) in addition to fast reversal strategies including PCC to prevent re-increase of INR to decrease haematoma expansion and decrease mortality in adult patients with ICH occurring during use of vitamin K antagonists (with an INR above normal)
In patients with ICH occurring during use of vitamin K antagonists, we recommend against using rFVlla to improve outcome, decrease haematoma expansion or increase normalisation of INR
In adult patients with ICH occurring during use of vitamin K antagonists (with an INR above normal) we recommend against use of tranexamic acid
In patients with ICH occurring during use of DOAC (fXa inhibitors), we recommend to consider the use of 4-factor PCC (37.5—50 IU/kg) to reverse the anticoagulant effect.
In patients with ICH occurring during use of DOAC, we recommend against using FFP to improve outcome, reduce mortality, decrease haematoma expansion or reverse the effects of NOAC
In adult patients with ICH occurring during use of dabigatran, idarucizumab is recommended to reverse effects of dabigatran
In adult patients with ICH occurring during use of rivaroxaban or apixaban, andexanet alfa may be considered to reverse the anticoagulant effect.
We recommend against the administration of ciraparantag outside of clinical trials

Table 4: Summary of Recommendations by European Stroke Organization Guidelines [1].

Table abbreviations: PCC – Prothrombin Complex Concentrate, ICH – Intracerebral Hemorrhage, INR-International Normalized Ratio, IV – intravenously, DOAC-Direct Oral Anticoagulants, FFP – Fresh Frozen Plasma, IU – International Units

Evidence-Based Clinical Pathways and Risk Stratification Tools:

Bleeding Risk Assessment

HAS-BLED Score: This widely used scoring system predicts major bleeding in patients with atrial fibrillation. A score of ≥3 indicates a high bleeding risk [25-28].
Hypertension (1 point)
Abnormal renal/liver function (1 point each)
Stroke (1 point)
Bleeding history or predisposition (1 point)
Labile INR (1 point)
Elderly (age ≥65 years) (1 point)
Drugs/alcohol concomitantly (1 point each)

Stroke Risk Assessment

CHA2DS2-VASc Score: This score estimates the risk of stroke in patients with atrial fibrillation. A score of ≥2 in men or ≥3 in women warrants consideration for anticoagulation.
Congestive heart failure (1 point)
Hypertension (1 point)
Age ≥75 years (2 points)
Diabetes mellitus (1 point)
Stroke/TIA/thromboembolism (2 points)
Vascular disease (1 point)
Age 65–74 years (1 point)
Sc female sex (1 point)

ICH Characteristics

Location: Patients with lobar ICH tend to have a higher risk of recurrence.
Size: Larger haematoma volumes are associated with poorer outcomes.
Presence of cerebral microbleeds: Multiple microbleeds on MRI suggest an increased risk of recurrent ICH.
Underlying cause: Identifying and addressing underlying causes like hypertension, amyloid angiopathy, or vascular malformations can mitigate future risks.

Patient-Specific Factors

Age: Elderly patients may have a higher bleeding risk.
Comorbidities: Conditions like liver or renal impairment can influence both bleeding and stroke risks.
Medication compliance: Patients with a history of poor adherence to medication regimens may be less suitable for anticoagulant re-initiation.

Life expectancy: Anticoagulant re-initiation may be less beneficial in patients with limited life expectancy.

Type of Anticoagulant

DOACs: Generally considered safer than VKAs regarding ICH risk.

Practical Recommendations

Prioritise patients with a high stroke risk (CHA2DS2-VASc score ≥2 in men or ≥3 in women) and a low bleeding risk (HAS-BLED score <3) [16,19,26-28].

Favour DOACs over VKAs when resuming anticoagulation, considering their lower ICH risk profile.

Delay re-initiation for at least 4–8 weeks after ICH, allowing time for haematoma stabilisation.

Individualise the timing based on specific patient factors, potentially considering earlier resumption in those with very high stroke risk and low bleeding risk, or later resumption in those with higher bleeding risk.

Closely monitor patients after re-initiation, watching for signs of recurrent bleeding or thromboembolic events.

Optimise modifiable risk factors such as hypertension, diabetes, and medication adherence.

Engage patients in shared decision-making, ensuring they understand the risks and benefits of anticoagulation re-initiation.

Alternative therapies

According to the current AHA guidelines(2022), patients with AF who are contraindicated for long-term OAC and have a high risk of bleeding from chronic OAC (Class IIb recommendation) should consider Left Atrial Appendage Occlusion (LAAO) as a stroke prevention strategy [12]. LAAO offers a non-pharmacological alternative for stroke prevention in patients with non-valvular AF who are deemed unsuitable for long-term OAC therapy [28]. It directly addresses the source of most thromboembolic events in AF patients by excluding the LAA, where thrombus formation is prevalent [26]. Compared to long-term anticoagulation, LAAO may offer a lower risk of bleeding, particularly in patients with a history of ICH or high bleeding risk. While LAAO shows promise for stroke prevention in AF patients, robust evidence specifically supporting its use in those with a prior ICH is still limited. Ongoing research is crucial to establish clear recommendations for this population.

Re-initiation in traumatic ICH

Anticoagulation-induced bleeding is caused by intrinsic vascular alterations that are broad and irreversible, such as cerebral amyloid angiopathy or microvascular damage from hypertension. Accordingly, the initial cerebral hemorrhage foreshadows a subsequent one. Traumatic intracranial bleeding, on the other hand, results from a head injury. At a specific location, the shockwave shears the arteries or overcomes vascular resistance. Most of the time, it is a singular incident that indicates a lower danger in the future [16]. An observational cohort study was conducted to assess the risk of recurrent ICH in incident traumatic ICH and was found that risk of ischemic stroke was low after resumption of warfarin treatment [29].

Challenges in Developing Countries

Access to rapid neuroimaging modalities (CT, MRI) is often limited, leading to potential delays in diagnosis and treatment. Scarcity of specialized intensive care units for effective monitoring, potentially compromising the ability to detect and manage complications. High cost of newer anticoagulants and reversal agents, this cost barrier could significantly limit access to these treatments in developing countries, even if they are clinically indicated. Variable availability and affordability of PCCs for VKA reversal. Fixed-dosing strategy for 4F-PCC could be more practical in resource-limited settings compared to weight-based dosing [30].

Potential Adaptations and Considerations: Adapting clinical guidelines to local resource constraints. Implementing task-shifting and training for non-physician providers. Utilizing telemedicine for remote consultations and timely management decisions.

Conclusion

Recently, there's been a growing focus on preventing further vascular events in patients who have survived an intracranial hemorrhage (ICH). A major challenge in caring for these patients is managing atrial fibrillation (AF). While observational studies can help identify trends and potential areas for improvement, they cannot provide definitive answers. To truly understand the best course of treatment, we need large-scale, randomized clinical trials. These trials will provide high-quality evidence to guide patient care and help us make more informed decisions about treatment strategies, especially for different subgroups of patients.

Conflict of Interest

No conflict of interests to report.

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