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Perioperative Management of Coagulation in Nontraumatic Intracerebral Hemorrhage

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APPROXIMATELY 70,000 new cases of spontaneous, nontraumatic intracerebral hemorrhage (ICH) occur annually in the United States.[1] ICH is a significant cause of mortality throughout the Western world, with an estimated 30-day fatality rate of 30–50%. Surgical treatment is indicated for patients meeting specific criteria,[2] and coagulation management is a crucial aspect of perioperative strategy.

Antithrombotic therapies are split into three categories such as antiplatelet agents (*e.g.,* aspirin, clopidogrel), anticoagulant agents (*e.g.,* warfarin, heparins), and fibrinolytic agents (*e.g.,* recombinant tissue plasminogen activator). ICH can occur in the absence or the presence of any antithrombotic treatments. All antithrombotic agents have been associated with an increased risk of ICH in specific settings. Even though antiplatelet agents are the most commonly prescribed agents in the population, oral vitamin-K antagonists (VKAs) are a predominant cause of antithrombotic-associated ICH. With the increased use of antithrombotic therapies, the incidence of antithrombotic-associated ICH appears to be increasing.[3] Moreover, the use of new antithrombotic agents, such as the direct thrombin inhibitors and the oral factor Xa antagonists, is increasing.[4] Specific strategies are recommended to reverse most antithrombotic treatments in the context of ICH.[2,5] Disagreements regarding the use of these reversal strategies will be discussed in this article. Intracranial hemorrhage, in the presence of underlying antithrombotic treatment, is thought to have a worse prognosis due to prolonged bleeding.[6] Thus, anticoagulation reversal may provide a therapeutic opportunity. Although evidence for anticoagulation reversal directly impacting outcomes is scarce,[7,8] this approach, a common element of care in neurological intensive care units, is known to have improved outcomes and is a part of the current ICH guidelines from the American Heart Association and the American Stroke Association with a Class I (level of evidence C).[2]

Even without any antithrombotic agent, it is now clearly established that intracerebral hematoma volume frequently increases during the initial phase of bleeding, contributing to neurological deterioration.[9] The ICH Score identifies independent risk factors for poor neurological outcome,[10] including hematoma volume. Consequently, there has been interest in the use of hemostatic agents to potentially limit hematoma expansion.

The high prevalence of antithrombotic-associated ICH and the potentially protective strategy for improving hemostasis in ICH highlight the pivotal role of coagulation in perioperative management. The critical nature of this disease demands complex management and close collaboration among intensivists, hematologists, neurologists, neurosurgeons, and anesthesiologists. In this nonsystematic review

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article, we will summarize and clarify therapeutic recommendations for intracranial hemorrhage in the presence or absence of antithrombotic treatments, and highlight the debate about new therapeutic strategies in perioperative coagulation management in ICH.

Unique Considerations in Intracranial Bleeding

Because of the distinct architecture and physiology of the brain and cranium, the consequences of intracranial hemorrhage are unique in many ways. Pressure exerted by the hematoma can inflict rapid and direct mechanical injury to the parenchyma. The rigidity of the cranial vault makes a noncompliant receptacle of hemorrhaged blood, meaning that even a small bleed can rapidly increase intracranial pressure. Herniation of brain tissue, past the free edges of the dural reflections or through the foramen magnum, is a feared complication of increased intracranial pressure. Local neuronal death and ischemia cause the release of additional excitotoxic and inflammatory mediators, thus causing decreased blood flow and further neuronal death. In addition, coagulation factors and other constituents of plasma, which are activated by contact with the neuropil (*e.g.,* tissue factor [TF]), can cause cell injury and demise. This indirect form of injury may explain why surgical hematoma evacuation is insufficient to prevent major neurological damage.

The ICH Score is commonly used to stratify patients regarding the risk of early mortality and long-term functional outcome in ICH.[10] Specific factors are present across studies, including the larger hematoma volume (estimated from measurements on an axial imaging scan and the formula for an ellipsoid: length × width × height/2), the presence of intraventricular hemorrhage, impaired consciousness, and increased age.

It is now clearly established that hematoma volume is often unstable during the early phases of bleeding and may continue to increase within hours after the initial hemorrhage, even in the absence of antithrombotic treatments. Within 3 h of symptom onset, approximately 38% of patients experienced volume increases of more than 33%.[11] Hematoma volume is generally stable after the first 24 h. Underlying mechanisms explaining the early increase in hematoma size are not clearly established, but local and systemic factors involved in the coagulation are possibly involved. Although closed cranial head trauma can initiate systemic coagulopathy (*i.e.,* disseminated intravascular coagulation), which depends on the severity of the cortical injury, there is little evidence that disseminated intravascular coagulation is initiated by brain hemorrhage. In the context of surgery, it is postulated that local and systemic coagulation pathways are activated. TF is the primary physiological initiator of the coagulation cascade.[12,13] The cerebral cortex is the major source of TF, which is found in microvessel-rich beds, with less TF abundance in white matter in part due to the lower vascular density.[14] Phospholipids contribute to normal hemostasis *via* several mechanisms. Anionic phospholipid moieties can activate TF and facilitate the generation of thrombin. Although the phospholipid environment affects TF activity,[14] platelet activating factor stimulates platelet degranulation and aggregation, and sphingolipids can promote cerebral vasospasm in animal models.[15,16] Acute brain injury is also known to alter the concentrations of these active phospholipids.[17,18] Moreover, tissue hypoperfusion and activation of the protein C pathway have been implicated in the early coagulation modulation seen in brain injuries.[19] Increased inflammation is also thought to lead to up-regulation of TF in circulating cells of the monocyte or macrophage lineage. These inflammation-related coagulation processes may affect the brain more globally, as imaging studies have shown evidence of diffuse blood–brain barrier breakdown.[20]

Attention has turned to the possibility of continued arterial bleeding as a potential cause of hematoma expansion. The administration of intravenous contrast during an initial computed tomography scan may identify contrast extravasation.[21,22] The presence of this extravasation, called the "spot sign," correlates with the likelihood of hematoma expansion.

Antithrombotic Therapies in the Context of ICH

Antiplatelet Agents

The first responses to vascular injury are contraction of the smooth muscular components of the vessel wall and platelet adhesion to the vessel wall. Hence, strategies that inhibit platelet activation, adhesion, and aggregation are expected to limit vascular occlusion. Aspirin, the most commonly used antiplatelet agent, irreversibly acetylates platelet cyclooxygenase-1 and inhibits thromboxane release, preventing platelet activation (fig. 1). Low-dose aspirin is commonly prescribed to prevent ischemic stroke and myocardial infarction. However, despite the good risk-to-benefit ratio, aspirin alone increases the risk of ICH.[23] Combining aspirin with other antithrombotic agents seems to amplify the risk of ICH.[24]

The active metabolites of the thienopyridines (ticlopidine, clopidogrel, and prasugrel), products of cytochrome P450 metabolism, covalently and irreversibly bind to the P_2Y_{12} receptor for the entire lifespan of the platelet. Newer direct-acting P_2Y_{12} inhibitors (cangrelor and ticagrelor) change the conformation of the P_2Y_{12} receptor. This results in reversible inhibition. All P_2Y_{12} receptor inhibitors block adenosine diphosphate-induced platelet activation (fig. 1) and thus increase ICH risk.[17]

Platelet activation leads to a conformational change in their glycoprotein IIb/IIIa receptors. This change promotes the binding to fibrinogen and platelet aggregation. glycoprotein IIb/IIIa receptor antagonists, such as abciximab, prevent binding of fibrinogen and platelet aggregation (fig. 1), thus increasing the risk of ICH.[25]

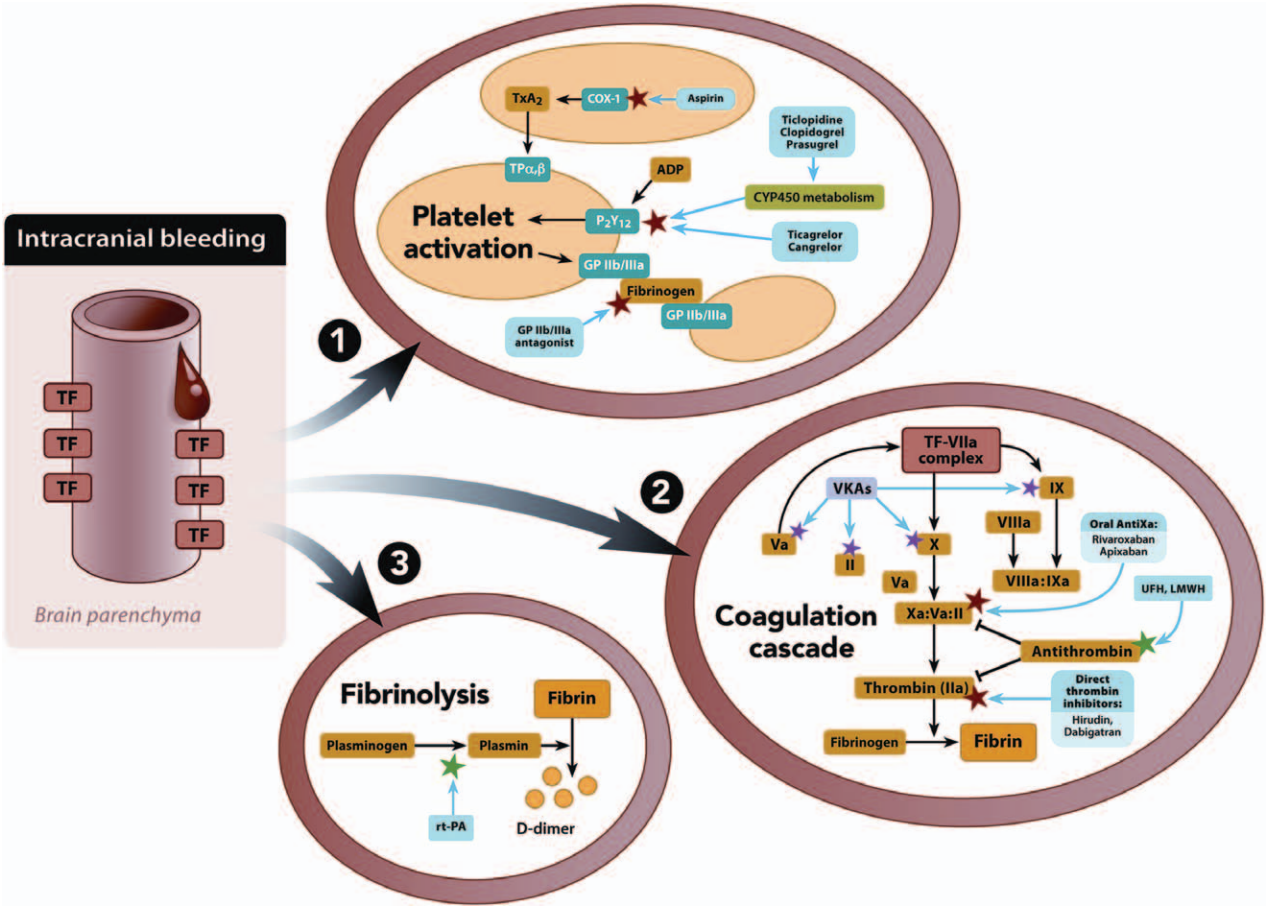

Fig. 1. Schematic sites of action of the major antithrombotic therapies. In the context of intracranial bleeding, the primary antithrombotic therapies modulate three major thrombotic pathways. *Red* and *purple stars* show inhibition, and *green stars* show activation, of the target. 1. Antiplatelet agents: aspirin inhibits platelet cyclooxygenase-1 (COX-1) production of thromboxane, decreasing thromboxane receptor α and β activation and thus inhibiting platelet activation. Platelet activation through stimulation of P_2Y_{12} by adenosine diphosphate (ADP) is inhibited by the metabolites of ticlodipine, clopidogrel, and prasugrel (after CYP450 action), as well as ticagrelor and cangrelor (non CYP450-dependant metabolism). Platelet aggregation through fibrinogen and glycoprotein IIb/IIIa interaction is inhibited by glycoprotein IIb/IIIa antagonists. 2. Anticoagulant agents: vitamin-K antagonists (VKAs) reduce the activity of vitamin K–dependent coagulation factors (II, VII, IX, and X; *purple stars*), blocking the coagulation cascade. Unfractioned heparins (UFH) and low-molecular-weight heparins (LMWH) both activate antithrombin; UFH activation of antithrombin inactivates thrombin (IIa) and Xa, whereas LMWH have relatively less anti-IIa activity. Direct thrombin inhibitors bind the active site of the thrombin molecule. The oral factor Xa inhibitors bind to both free factor Xa and factor Xa bound to the prothrombinase complex. 3. Fibrinolytic agents: recombinant tissue plasminogen activator (rt-PA) cleaves plasminogen into plasmin, increasing enzymatic activity and inducing hyperfibrinolysis, degrading fibrin clot into fibrin degradation products, such as D-dimers. INR = International Normalized Ratio; TF = tissue factor.

Anticoagulant Agents

An initiating event for the coagulation cascade is the exposure of TF from the microvessel-rich beds of the neuropil leading to formation of the TF:VIIa complex with activated factor VII. This "extrinsic" interaction promotes the initiation, amplification, and propagation phases of coagulation.[12,13] The coagulation factors II, VII, IX, and X require a γ-carboxylation step in the liver for biological activity; this process is dependent on the reduced form of vitamin K. VKAs inhibit the enzyme vitamin K epoxide reductase, blocking the formation of reduced vitamin K. VKAs lead to the production of coagulation factors with reduced activity (fig. 1).[26] The response to VKAs is influenced by several factors, including metabolism-altering polymorphisms in the cytochrome P450 system (*e.g.,* sequence variants in CYP2C9 and Vitamin K epoxide reductase complex subunit 1), other drugs, diet, and other disease states.[26] VKAs are the most commonly prescribed oral anticoagulants, currently with approximately 3 million patients in the United States.[26] Aging populations display an increased prevalence of patients treated with VKAs. Unfortunately, this has also led to an increase in the hemorrhagic complications of these agents.[3] ICH is one of the most serious complications of oral anticoagulation, corresponding to 10% of bleeding complications of these drugs and virtually all fatal complications. The excess mortality generated by taking VKAs is strongly dose-dependent.

Unfractionated heparins (UFHs) and low-molecular-weight heparins are commonly used to prevent deep venous thrombosis and pulmonary emboli. Heparin binding accelerates the effects of the inhibitor antithrombin. The heparin:antithrombin complex inactivates thrombin (IIa) and other proteases involved in blood clotting, most notably factor Xa, but also IXa, XIa, and XIIa. Because of their size, low-molecular-weight heparins have lower antifactor IIa activity than UFH and are anticoagulant through antifactor Xa activity, whereas UFHs act on both targets and other sites. With extensive perioperative use of low-molecular-weight heparins in neurosurgery, rare cases of ICH have been reported.[27]

Direct thrombin inhibitors interact directly with the thrombin molecule and bivalent direct thrombin inhibitors (*e.g.*, bivalirudin or hirulog) bind to the active site and exosite 1, whereas the univalent direct thrombin inhibitors (argatroban, melagatran, and dabigatran) bind only to the active site. Dabigatran has the advantage of being an oral prodrug, which makes it convenient to use. New factor Xa antagonists (rivaroxaban, apixaban, and endoxaban) have also the advantage of being an oral formulation. Even if the risk of antithrombotic-associated ICH seems to be lower with these agents,[28,29] dabigatran,[24] apixaban,[29] and rivaroxaban[30] have been associated with increased risk of hemorrhage. Unlike VKAs, however, there are yet no recognized reversal strategies.[31]

Fibrinolytic Agents

Fibrinolysis is the enzymatic process leading to solubilization of fibrin clot by plasmin. Plasmin is generated from its zymogen, plasminogen, through the action of a plasminogen activator. One naturally occurring plasminogen activator, tissue-type-plasminogen activator (tissue plasminogen activator), is synthesized by endothelial cells and secreted locally after stimulation of the endothelium. Tissue plasminogen activator is co-secreted with its principal inhibitor plasminogen activator inhibitor-1. Recombinant tissue plasminogen activator can also decrease *in vitro* fibrinogen concentrations. It is licensed for use in the context of acute ischemic stroke and myocardial infarct. Its most feared complication is parenchymal hemorrhage. The incidence of symptomatic ICH, in the context of recombinant tissue plasminogen activator treatment for acute ischemic stroke, varies from 6 to 11 *versus* 0.6 to 3% in the placebo group in one study.[32] Secondary analysis of recombinant tissue plasminogen activator trials has identified extended hypodensity on initial computed tomography scan as a risk factor for severe hemorrhagic transformation.[33] Furthermore, combination of heparin and fibrinolytic agent increases the risk of hemorrhage in patients with acute middle cerebral artery stroke.[34] ICH is a serious, but rare, complication of intravenous thrombolysis combined with heparin after myocardial infarction. The incidence of ICH after myocardial infarction is estimated to be between 0.4 and 1.3% after administration of recombinant tissue plasminogen activator, with two-thirds of cases occurring within the first 6 h after recombinant tissue plasminogen activator delivery.

General Recommendations for Treatment of ICH

The decision to surgically evacuate ICH is controversial. Clinical trials examining this question have often been underpowered. The surgical treatment of ICH trial has recently influenced the American Heart Association guidelines for the surgical management of ICH.[2] The American Heart Association currently suggests that patients with cerebellar hemorrhage, who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction, should undergo surgical removal of the hemorrhage as soon as possible (Class I). These patients should not be treated by ventricular drain alone (Class III). For patients presenting with lobar hemorrhages of more than 30 ml and within 1 cm of the surface, evacuation of the supratentorial ICH by standard craniotomy may be considered (Class IIb). Importantly, at present, no clear evidence indicates that ultra-early removal of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to the increased risk of recurrent bleeding (Class III). Although theoretically attractive, minimally invasive endoscopic coagulum evacuation awaits further trials, and its utility is still unknown (Class IIb).

The American Heart Association guidelines recommend rapid computed tomography or magnetic resonance imaging to distinguish ischemic and hemorrhagic strokes (Class I). Patients should be managed in an intensive care setting, preferably a neurological intensive care unit (Class I). Normoglycemia (Class I), blood pressure (Class I), and seizure control (Class I) should be maintained. Patients with cerebellar hemorrhage and neurological deterioration, or who have brain stem compression and/or hydrocephalus from ventricular obstruction, should immediately undergo surgical coagulum removal (Class I). Intermittent pneumatic compression stockings should be applied to prevent venous thromboembolism (Class I).

When intracranial hemorrhage occurs in the absence of antithrombotic therapy, the objective is to bring the patient to surgery with normal ranges of fibrinogen, coagulation factors, and platelets. Factor-replacement therapy or platelet transfusions are currently recommended only for patients with severe coagulation factor deficiency or thrombocytopenia, respectively (Class I). In this setting, although activated recombinant FVII (rFVIIa) has been shown to reduce hematoma expansion (80 μg/kg within 4 h after the onset of the ICH) in patients without antithrombotic therapy,[35] it did not improve patient outcomes and was associated with increased risk of arterial thromboembolic events in unselected patients.[36] rFVIIa is, therefore, not recommended for this indication (Class III; for further details about the pharmacologic prevention of hematoma expansion, see below).

Specific Recommendations for Management of Bleeding in the Setting of Antithrombotic Therapies

The American Heart Association recommendations for coagulation management in ICH in the setting of antithrombotic therapies provide no explicit instruction for perioperative care. It is crucial, for perioperative management and preparation of patients for surgery, to have guidelines for their management. The goal of treatment is the specific reversal of the effects of particular antithrombotic agent to restore efficient hemostasis before any surgery (table 1). In this context, reversal of antiplatelet, anticoagulant, and fibrinolytic agents will be presented. The recommendations regarding the management of antithrombotic-associated ICH are summarized in figure 2.

Antiplatelet Agents

Although no strict guidelines exist for antiplatelet agents, such as aspirin and clopidogrel, platelet transfusion before surgical hematoma evacuation for patients taking antiplatelet drugs is proposed. For patients undergoing antiplatelet treatment, platelet transfusions are still considered investigational (Class IIb).

The antiplatelet agent presugrel, a thienopyridine adenosine diphosphate-receptor inhibitor, and the adenosine-like molecule ticagrelor have been developed for the management of acute coronary syndrome and for use with stents. Their potency and risk of ICH have not been fully assessed, and there are as yet no guidelines for their management in this setting.

Anticoagulant Therapies

VKAs. ICH guidelines from different countries for patients taking VKAs are summarized in table 2. The consensus for managing ICH patients on VKAs is that the anticoagulant should be withheld, vitamin K delivered intravenously, vitamin K–dependent factors replaced, and the International Normalized Ratio corrected (Class I). With regard to vitamin K–dependent factor replacement, the guidelines vary by country. European guidelines advocate the use of prothrombin complex concentrates (PCCs) for factor replacement. The current American Heart Association and American Stroke Association guidelines state that PCCs have not been shown to improve outcome compared with fresh frozen plasma (FFP), but are reasonable to consider because they may have fewer complications (Class IIa), primarily related to a lower volume of delivery.[2] rFVIIa acutely normalizes prothrombin time, but its effect lasts only a few hours. In addition, it does not replace all clotting factors. It can thus lower the International Normalized Ratio without restoring coagulation ability *in vivo* (Class III). Therefore, it is not recommended as the sole agent for VKA reversal in ICH management.

Heparins. For patients receiving UFH with an activated partial thromboplastin time of more than two times longer than reference, the American Heart Association recommends slow intravenous infusion of protamine sulfate (Class I). The recommended dose must be adjusted for UFH load and elapsed time since the last heparin dose.[5] In the case of low-molecular-weight heparins, full reversal with protamine sulfate is not possible. Protamine sulfate will inhibit only 50% of the anti-Xa activity, and may need to be redelivered.

Table 1. Characteristics of Anticoagulant Agents Associated with Intracranial Hemorrhage

Agents	Route	Site of Action	Plasma Half-life	Duration of Effect	Metabolism	Antidote
Antiplatelet agents						
Aspirin	Oral	COX-1	20 min	7 d	Hepatic	None
Ticlodipine	Oral	P2Y12 receptor	4 d	10 d	Hepatic	None
Clopidogrel	Oral	P2Y12 receptor	7 h	5 d	Hepatic	None
Prasugrel	Oral	P2Y12 receptor	4 h	5–9 d	Hepatic	None
Ticagrelor	Oral	P2Y12 receptor	7 h	12 h	Hepatic	None
Abciximab	IV	Glycoprotein IIb-IIIa	30 min	72 h	Renal	None
Anticoagulant agents						
VKAs	Oral	Vitamin K epoxide reductase	2–4 d	2–4 d	Hepatic	Vitamin K PCCs FFP
UFHs	IV/SC	Antithrombin III	1.5 h	6 h	Hepatic	Protamine
LMWHs	SC	Antithrombin III	4–6 h	12–24 h	Renal	Protamine (partial)
Dabigatran	Oral	Direct thrombin inhibitor	12 h	1–2 d	Renal	None
Apixaban	Oral	Factor Xa antagonist	8–12 h	24 h	Hepatic	None
Rivaroxaban	Oral	Factor Xa antagonist	9–12 h	24 h	Hepatic	None
Fibrinolytic agents						
Recombinant t-PA	IV	Plasminogen	5 min	1 h	Hepatic	None

Adapted from the review of Roberts *et al*.[13] Aspirin, ticlodipine, clopidogrel, and prasugrel irreversibly block platelet aggregation.

COX = cyclooxygenase; FFP = fresh frozen plasma; IV = intravenous; LMWHs = low-molecular-weight heparins; PPCs = prothrombin complex concentrates; SC = subcutaneous; t-PA = tissue-type-plasminogen activator; UFHs = Unfractioned heparins; VKAs = vitamin-K antagonists.

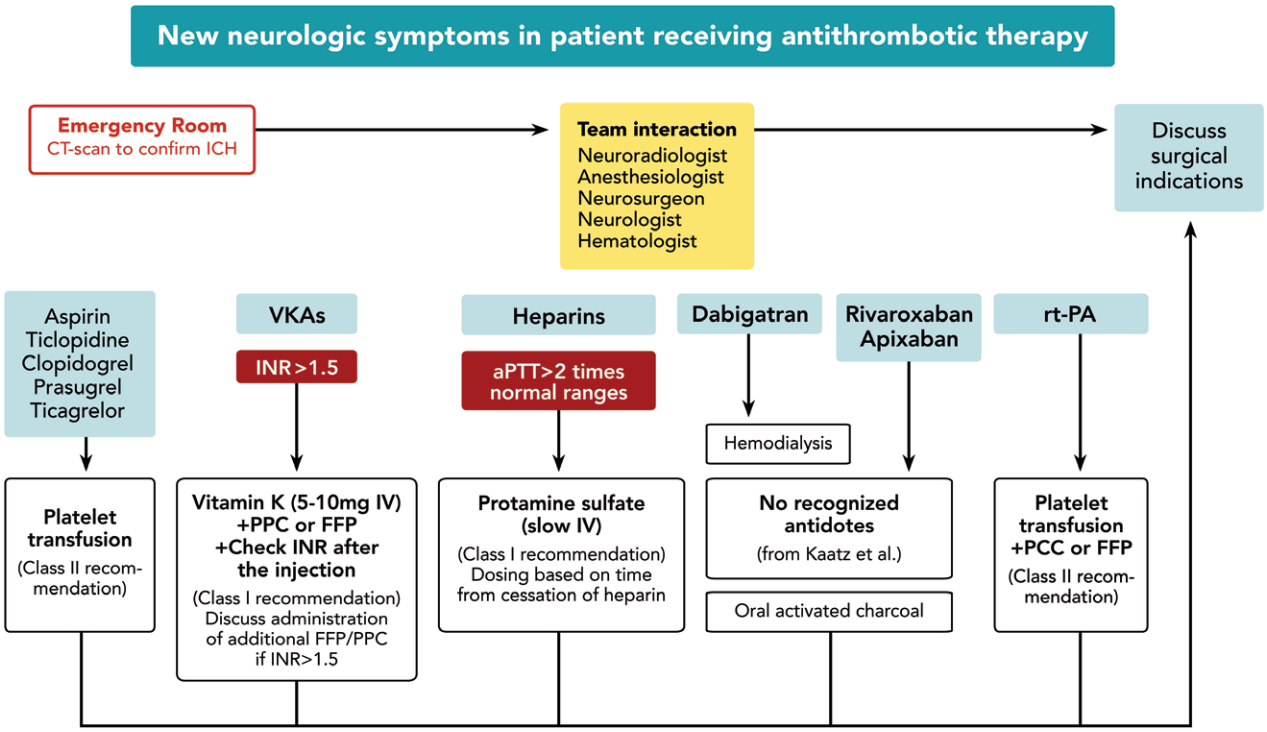

Fig. 2. Clinical algorithms for patients presenting with acute neurological symptoms receiving antithrombotic therapies. Class level recommendations were extracted from the American Heart Association guidelines.[2,6] Recommendation for prasugrel and ticagrelor were not explicitly expressed in the recommendations. Current strategies regarding new oral anticoagulants (dabigatran, rivaroxaban, and apixaban) were extracted from Kaatz *et al.*[31] Dabigatran can be dialyzed, whereas rivaroxaban and apixaban cannot (protein bound). aPTT = activated partial thromboplastin time; CT = computed tomography; FFP = fresh frozen plasma; ICH = intracerebral hemorrhage; INR = International Normalized Ratio; IV = intravenous; PCC = prothrombin complex concentrates; rt-PA: recombinant tissue plasminogen activator; VKAs = vitamin-K antagonists.

New Oral Anticoagulants. The new oral anticoagulants, dabigatran and rivaroxaban, have been associated with a risk of hemorrhage.[31] There is no dedicated standard for these agents in the context of surgical ICH as yet. Unlike VKAs, there are no recognized reversal strategies available. Specific pharmacological reversal strategies for dabigatran and rivaroxaban are currently in progress and are likely to develop for apixaban. Because half-lives of these drugs are short (table 1), delays between the last intake and the hemorrhage will help to determine the reversal needs. Evaluation of the coagulation status with blood test (activated partial thromboplastin time and blood anticoagulant

Table 2. Guideline Recommendations for Coagulation Management in ICH in the Presence of VKAs

Name	Year	Country	VKA	Vitamin K	FFP	PCC	rFVIIa	Access to 4-PCCs
ACCP	2012	USA	Stop	IV (5–10 mg)	Recommended	Recommended and preferred	Possible	No#
AHA	2010	USA	Stop	IV (NS)	Recommended	Recommended	No	No
BCSH	2006	UK	Stop	IV (5–10 mg)	Recommended	Recommended and preferred	No	Yes
EUSI	2006	EU	Stop	IV (5–10 mg)	Recommended	Recommended	No	Yes
NAH	2010	France	Stop	Oral or IV (10 mg)	Recommended*	Recommended and preferred	No	Yes

* Use of FFP only when PCCs are not available. # Recent approval by the American Food and Drug Administration of the 4-PCC Behring preparation for warfarin reversal in the U.S. as of April 30, 2013).

ACCP = American College of Chest Physicians; AHA = American Heart Association; BCSH = British Committee for Standards in Haematology; EU = European Union; EUSI = European Stroke Initiative; FFP = fresh frozen plasma; ICH = intracerebral hemorrhage; IV = intravenous; NAH = National Authority for Health; NS = not specified; 4-PCCs = prothrombin complex concentrates with similar amounts of FII, FVII, FIX, and FX; rFVIIa = activated recombinant FVII; UK = United Kingdom; USA = United States of America; VKA = vitamin-K antagonist.

direct or indirect concentrations measures) should also be part of the therapeutic strategy before introducing reversal therapies.[37] In the case of dabigatran, oral activated charcoal should be used if the agent was ingested less than 2 h before presentation. Because of its renal clearance, dabigatran can be removed by hemodialysis. The use of oral activated charcoal is also suggested for rivaroxaban.[31] Animal studies suggest that factor VIII inhibitor bypass activity (table 3) and rFVIIa present *in vitro* reversal effects, but further studies are needed before any recommendations can be made.[31]

Fibrinolytic Agents. Fibrinogen levels can be depleted in patients who have received a plasminogen activator. To manage this situation, replacement of fibrinogen, coagulation factors, and platelets (Class IIb) has been proposed. Plasminogen activator inhibitors (ε-aminocaproic acid and tranexamic acid) have not been shown to be effective in reducing hematoma expansion or improving survival, but have potentially harmful effects.[38,39] Well-controlled randomized trials, however, are lacking. Further studies are needed for firm recommendations.

Current Debates Regarding Coagulation Treatment in ICH Management

Surgical Treatment of Intracranial Bleeding in the Presence of Antithrombotic Therapies: Indications for Surgery and Preoperative Coagulation Requirements

Indications for evacuating an intracerebral hematoma are controversial.[2] Intraparenchymal hemorrhage is a destructive event that injures brain tissue directly and by compression. Hematoma evacuation is intended to alleviate secondary effects such as mass effect and edema. Therefore, the neurosurgeon must evaluate whether the neurological deficits and overall condition of the patient are due to primary tissue damage or secondary effects of the hematoma. In cases with underlying lesions such as aneurysms or arteriovenous malformations, surgery treats the cause of the hemorrhage while also evacuating the hematoma. Surgery can do nothing to address the devastating effects of primary tissue damage from the mechanical injury to the parenchyma.

Anticoagulation is an important consideration in the surgical care of patients with ICH. If surgery is indicated, patients must be corrected before proceeding to the operating room with International Normalized Ratio less than 1.5, platelet counts preferably greater than 100 K, and an activated partial thromboplastin time in the normal range. A hematoma that is evacuated in an uncorrected patient will likely recur, eliminating the benefits of surgery. Therefore, reversal of anticoagulation must be managed immediately, swiftly, and completely (fig. 2).

Intracranial Bleeding in the Presence of VKAs: FFP or PCC as Adjunct to Intravenous Vitamin K?

Despite the preference given to PCCs and FFP over rFVIIa in most guidelines, implementation of this treatment option has been less uniform in Western countries. For example, in a survey of North American physicians, only 10% chose to treat intracranial bleeding in the presence of antithrombotic therapies with PCCs, and 70% chose to treat with rFVIIa.[40] Differences in prescriptions are in part due to local availability, expense, and unproven efficacy.

Table 3. Factor Composition of Major PCCs Available to Reverse Vitamin-K Antagonists Action in ICH

			Vitamin K–Dependent Factor Levels (Expressed as % of Factor IX)			
Product	Country	Heparin	II	VII	IX	X
Three factors PCCs						
Profilnine-SD (Grifols)	USA	–	≈150	≈35	100	≈100
Bebulin (Baxter)	USA	+	≈100	≈20	100	≈100
Prothromplex HT (Baxter)	Australia	+	100	—	100	400
Four factors PCCs						
Octaplex (Octapharma)	UK, Canada, EU	+	60–150	30–80	100	70–150
Beriplex (CLS Behring)	UK, EU	+	70–100	70–100	100	100–200
Cofact (Sanquin)	EU	–	70–150	80	100	70–150
Other combinations						
FEIBA (Baxter)	USA, UK, Canada, EU	–	90–124	68–134 activated	100	79–93

The relative abundance of the four factors is expressed as a percentage of factor IX concentration (the concentration of factor IX is normalized at 100% for each product). According to the American Heart Association recommendation,[2] the suggested dosing of PCCs should be adapted to restore factor IX activity. It is generally accepted that restoring 50% factor IX activity will correct the INR to 1.2. With a good approximation, 1 unit of factor IX per kilogram increases factor IX activity of 1%. The classic recommended dose of 4-PCCs in this indication is similar to 3-PCCs with 25–50 units of factor IX per kilogram. The use of FEIBA, an active PCC containing nonactivated factors II, IX, X, and activated factor VII, is indicated for treatment of hemorrhage in hemophilia with factor VIII and IX inhibitors, but is not yet indicated in the context of antithrombotic-associated ICH. FEIBA contains activated factor VII and 1–6 units of factor VIII coagulation antigen (FVIII C:Ag) per vial.

EU = European Union; FEIBA = factor VIII inhibitor bypass activity; ICH = intracerebral hemorrhage; INR = International Normalized Ratio; PCCs = prothrombin complex concentrates; UK = United Kingdom; USA = United States of America.

Most guidelines recommend PCCs over FFP as an adjunct to intravenous vitamin K (table 1). The disadvantages of FFP transfusion compared with PCC injection are manifold and include: (1) the time needed for ABO blood-typing, thawing large volumes of FFP, and transfusion time; (2) delayed onset of the therapeutic effect; (3) potential circulatory overload from large transfusion volumes, especially in patients with cardiac disease; (4) possible allergic reactions; (5) risk of infection from exposure to multiple donors; and (6) the risk of transfusion-related acute lung injury. Delays in effect are likely detrimental to the acute disease.

In contrast, PCCs are reconstituted within minutes in a small volume (20–40 ml/dose) and can be infused rapidly (10 ml/min) for partial or complete replacement of vitamin K coagulation factors. Importantly, there is minimal risk of transfusion-related acute lung injury. PCCs also carry a negligible risk for viral transmission. For all these reasons, PCCs are potentially superior to FFP for urgent reversal of the VKA effect. One notable issue, however, is that PCCs often contain low doses of heparin, so patients can theoretically be subject to heparin-induced thrombocytopenia.

PCCs were first designed for hemophilic patients with high concentrations of factor VIII and IX inhibitors. Their indication was extended to patients taking VKAs who were in need of replacement of factors II, VII, IX, and X. Although the argument and evidence for the adoption of PCC treatment as standard practice are compelling, they are not unanimously supported. Intriguingly, other studies were unable to prove the superiority of PCCs[41] in the context of VKA-associated intracranial bleeding. This lack of consensus, compared with PCC use in hemorrhage elsewhere in the body, could be due to the immediate functional impairments caused by central nervous system bleeding, or could simply be a result of small sample size and heterogeneity in research methods and clinical practice. Furthermore, although both American and European guidelines are supportive of PCCs, marked geographical differences exist in PCC composition and usage.

The clear discrepancy between guidelines and practice in North America could be due to three factors. First, comprehensive recommendations for the management of stroke came recently and may not have been well distributed among American physicians. Second, current American guidelines may not accurately reflect the reality of treatment options available in the United States. Third, there are strikingly different FVII concentrations among PCCs distributed in Europe compared with the United States.[42] Before April 2013, PCCs available in the United States (table 3) contain low amounts of FVII relative to FII, FIX, and FX levels and are thus called "3-factor PCCs." PCCs available in countries outside the United States are called "4-factor PCCs" because they contain relatively the same amounts of FII, FVII, FIX, and FX. This difference in factor ratio motivated a recent American study that supplemented an available 3-PCC (Profilnine-SD; Grifols, Los Angeles, CA) with rFVIIa.[42] In other American institutions, local guidance proposed to add FFP to 3-PCC treatments. Moreover, a four-component PCC has very recently been approved for warfarin reversal by the American Food and Drug Administration (tables 2 and 3). If the importance of FVII can be demonstrated in a randomized trial, then these behavioral discrepancies will likely disappear.

Intracranial Bleeding in the Absence of Antithrombotic Therapies: Treatments to Prevent Hematoma Extension

One-third of ICH patients present with expanding hematomas. Because hematoma volume is a major risk factor for poor outcome, the hypothesis naturally developed that decreasing hematoma expansion with procoagulant treatments could improve patient outcomes. The potential benefits of procoagulant treatments are balanced with the thrombosis risks of these treatments.

Using rFVIIa, a prospective, randomized trial tested the hypothesis that the administration of rFVIIa could limit the extent of cerebral hemorrhage in patients not receiving anticoagulant therapy.[35] The administration of rFVIIa halved this increase in volume compared with placebo (29% of volume increase for placebo *versus* 14% for the group treated with 80 μg/kg of rFVIIa). A subsequent larger phase III trial failed to show any effect of rFVIIa on mortality or functional outcomes, whereas demonstrating an association between rFVIIa use and arterial thrombosis.[36] Continuing this paradigm, Levi *et al.*[36] recently pooled 35 studies in a safety analysis and showed that treatment with high doses of rFVIIa on an off-label basis (31% of the recruited patients had ICH) increased the risk of arterial thromboembolic events, especially among the elder patients. Even if a subgroup of patients with less risk of thrombosis could be a target population for treatment designed to reduce hematoma expansion,[43] independent replications are required before rFVIIa can be recommended for this indication.

Other agents to prevent hematoma expansion have been proposed. For example, antifibrinolytic agents, such as tranexamic acid, have already been demonstrated to reduce the hematoma size in traumatic ICH and could be of interest in this indication.[44] However, their contraindication in the setting of disseminated intravascular coagulation limits the interest of the antifibrinolytic agents for patients with ICH.

Finally, the possibility of treating patients who have intracranial hemorrhage in the absence of antithrombotic therapies, and who have a spot sign[21,22] with hemostatic agents, is enticing, but unstudied.

Conclusions

ICH is a disease associated with high morbidity and mortality. The literature demonstrates that anticoagulant agents and perioperative coagulation management strategies have a profound impact on outcomes. The use of powerful new anticoagulant agents is increasing. Increased understanding and knowledge of the mechanisms of each anticoagulant agent are necessary to adapt perioperative therapeutic strategies. Although treatment

strategies would ideally be evidence-based, the increase in the use of new anticoagulant agents, local availability, and expense explain why, in normal practice, not all guidelines are completely adhered to. Further complicating the matter are the differences in therapeutic tools in various countries. Many important questions in the field are still unanswered and require further scrutiny and investigation.

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