Anticoagulation in Acute Neurological Disease

Cina Sasannejad, MD[1] Kevin N. Sheth, MD[1]

[1] Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Yale School of Medicine, New Haven, Connecticut

Address for correspondence Kevin N. Sheth, MD, Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510 (e-mail: kevin.sheth@yale.edu).

Semin Neurol 2021;41:530–540.

Abstract

While anticoagulation and its reversal have been of clinical relevance for decades, recent academic and technological advances have expanded the repertoire of its application in neurological disease. The advent of direct oral anticoagulants provides effective, mechanistically elegant, and relatively safer therapeutic options than warfarin for eligible patients at risk for neurological sequelae of prothrombotic states, particularly given the recent availability of corresponding reversal agents. In this review, we examine the provenance, indications, safety, and reversal tools for anticoagulant medications in the context of neurological disease, with specific attention to acute ischemic stroke, cerebral venous sinus thrombosis, and intracerebral hemorrhage. We will use specific clinical scenarios to illustrate the complex factors that must be considered in the use of anticoagulation, including intracranial pathology such as intracerebral hemorrhage, traumatic brain injury, or malignancy; metabolic complications such as chronic kidney disease; pregnancy; and advanced age.

Keywords

- atrial fibrillation
- intracerebral hemorrhage
- reversal agents
- oral anticoagulant

Anticoagulation has been used for stroke prevention for 80 years. Clinical applications of unfractionated heparin (UFH), which promotes the inactivation of thrombin and factor Xa by binding antithrombin, and its depolymerized variant, low-molecular-weight heparin (LMWH), have been documented as early as the 1940s and 1980s, respectively.[1] Likewise, warfarin, an oral vitamin K antagonist (VKA) that prevents posttranslational modification of vitamin K–dependent coagulation factors II, VII, IX, and X, has been used since the 1950s.[1] Despite preclinical literature in the 1960s, and clinical literature in the 1970s and 1980s documenting the usage of long-term anticoagulation—chiefly warfarin—in stroke prevention, controversy regarding the benefits versus the risk of hemorrhage remained until the 1980s.[2] Large-scale randomized clinical trials investigating the use of anticoagulants specifically for stroke prevention began enrolling patients in the mid to late 1980s and were published in the early 1990s. The 1991 SPAF trial established the use of warfarin rather than aspirin for stroke prevention in atrial fibrillation (AF), and subsequent trials through the 1990s and early 2000s[3] established warfarin dosing and INR goals for stroke prevention. Recently, the variety of available anticoagulation agents has expanded to include direct oral anticoagulants (DOACs), otherwise known as non–vitamin K antagonist oral anticoagulants (NOACs). These medications mechanistically comprise direct factor Xa inhibitors—such as apixaban, rivaroxaban, and edoxaban—and direct thrombin inhibitors, most notably dabigatran.

While anticoagulation is one of the most powerful and reliable tools for ischemic stroke prevention on both acute and longitudinal timescales, it has the potential to cause, or worsen, hemorrhagic strokes. The incidence of intracerebral hemorrhage (ICH) is 24.6 per 100,000 person years, with a 40% 1-month case fatality rate.[4] Decision-making regarding initiation of anticoagulation is particularly complicated in patients who have underlying conditions that may predispose to ICH, including cerebral amyloid angiopathy (CAA) and cerebral venous sinus thrombosis (CVST). The risk of anticoagulation-associated ICH highlights the necessity to weigh risks and benefits when determining whether and when to initiate anticoagulation and the importance of effective reversal agents.

Issue Theme Inpatient Consultations in Neurology; Guest Editors: Pria Anand, MD, and Joshua P. Klein, MD, PhD

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0041-1733793.
ISSN 0271-8235.

Here, we address the indications, safety, reversal, and special considerations associated with the use of anticoagulation in patients with acute neurological disease.

Accepted and Investigated Indications for Initiation of Anticoagulation

Arterial Stroke Prevention in Patients with Nonvalvular Atrial Fibrillation

In the United States, the prevalence of AF is estimated at 5.2 million cases, and is projected to increase nearly threefold by 2030.[5] AF has long been recognized as a risk factor for ischemic stroke, with risk increasing concomitantly with age, hypertension, prior stroke, and diabetes. Data from multiple studies in the early-to-mid 1990s established warfarin as the treatment of choice in reducing the risk of ischemic stroke in patients with AF.[6] Later, a 2007 meta-analysis of 29 clinical trials, encompassing 28,000 patients with nonvalvular AF (AF in the absence of a mechanical heart valve or moderate-to-severe mitral stenosis), demonstrated a 40% relative risk reduction in stroke among patients treated with warfarin versus those treated with antiplatelet therapy.[3] However, the requirement for frequent monitoring, questions of how and when to bridge therapy, and the prolonged half-life and hemorrhage risk associated with warfarin collectively invited further investigation into the use of DOAC in stroke prevention in AF.

While eventually limited in usage by concerns for hepatotoxicity, the direct thrombin inhibitor ximelagatran was one of the earliest DOACs to show noninferiority to warfarin in stroke prevention in patients with nonvalvular AF.[7] The RE-LY trial in 2009 established the efficacy of the direct thrombin inhibitor dabigatran versus warfarin in patients with nonvalvular AF, finding lower rates of both stroke and major hemorrhage.[8] A series of landmark trials in 2011 established the relevance of factor Xa inhibitors as viable anticoagulation agents in patients with nonvalvular AF. Apixaban demonstrated reduced stroke risk without increased risk of intracranial hemorrhage in AVERROES, and direct benefit compared with warfarin in stroke prevention, diminished bleeding risk, and lower mortality in ARISTOTLE.[9,10] Rivaroxaban showed noninferiority to warfarin in stroke prevention in ROCKET AF.[11] A third oral factor Xa inhibitor, edoxaban, demonstrated noninferiority to warfarin in stroke prevention, in addition to lower rates of bleeding and cardiovascular causes of death, in ENGAGE AF-TIMI 48 in 2013.[12] In a retrospective observational study of patients with nonvalvular AF taking DOACs, ARISTOPHANES corroborated the reduction in stroke rate in apixaban, dabigatran, and rivaroxaban in comparison to warfarin in a large, well-powered, pooled dataset.[13] ►**Table 1** summarizes the major clinical trials establishing the efficacies of individual oral anticoagulants.

While patients taking DOACs do not require routine monitoring, low plasma levels of DOACs—measured using anti-Xa or direct thrombin inhibitor assays, depending on the anticoagulant—are associated with worse stroke severity and higher risk of large vessel occlusion.[14]

Due to noninferiority of DOACs compared with warfarin in stroke prevention and reduction in hemorrhage risk, DOACs have now become the first-line agents recommended for stroke prevention in eligible patients with nonvalvular AF.[15]

Arterial Stroke Prevention in Patients with Embolic Stroke of Undetermined Source

The potential role for anticoagulation as an alternative to antiplatelet therapy in noncardioembolic acute ischemic stroke and embolic stroke of undetermined source (ESUS) remains a frequently investigated and as-yet elusive area of research. The WARSS trial found no difference in recurrent ischemic stroke, death, or major hemorrhage over 2 years among patients with ischemic stroke taking warfarin versus aspirin.[16] In RE-SPECT ESUS, dabigatran did not demonstrate superiority to aspirin in preventing stroke recurrence.[17] Similarly, in NAVIGATE ESUS, rivaroxaban not only failed to demonstrate superiority to aspirin, but also was found to be associated with higher rates of major bleeding; of note, however, subsequent subgroup analysis found that rivaroxaban may have efficacy in patients with left atrial enlargement.[18]

Arterial Stroke Prevention in Patients with Intracranial Arterial Stenosis

Intracranial arterial stenosis reflects a third mechanism of ischemic stroke in which anticoagulation has been investigated in comparison to antiplatelet therapy. The WASID trial was one of the first to investigate this question in the form of a randomized clinical trial, ultimately finding increased rates of hemorrhage and death in patients taking warfarin rather than aspirin.[19] This has not been studied in patients taking DOACs. Additionally, advancements in endovascular treatment of intracranial arterial stenosis may impact the risk/benefit analysis of the use of anticoagulation in this patient population.

Arterial Stroke Prevention in Patients with Intracranial Arterial Dissection

In a study of patients with intracranial artery dissections, a Finnish group found that of 81 patients with nonaneurysmal dissections, 79% achieved favorable 3-month outcomes after treatment with anticoagulation, while those with aneurysmal dissections had significantly worse 3-month outcomes.[20] Notably, the majority of dissections observed occurred in the posterior circulation.[20]

Venous Stroke Prevention in Patients with Cerebral Venous Sinus Thrombosis

In addition to arterial infarct prevention, anticoagulation may also be indicated for the prevention of venous infarcts. Decision-making about initiation of anticoagulation in CVST requires balanced consideration of the need to prevent clot propagation, rises in intracranial pressure, and venous infarcts, while mitigating the risk of ICH. Although a Cochrane review of randomized controlled trials found reduced relative risk of death or dependency (95% CI: 0.16–1.31) in patients with CVST who were treated with anticoagulation, this effect was not statistically significant, and only two studies met criteria for inclusion in the meta-

Table 1 Key trials of oral anticoagulants

Trial	Enrollment (*n*)	Duration	Patient population	Anticoagulant	Comparator	Mean follow-up	Primary endpoint	Result	Interpretation	Complications
SPAF	1,330	1987–1989	Age ≥18 with nonvalvular AF	Warfarin	Aspirin	1.3 y	Ischemic stroke or systemic embolism	RR: 0.67, 95% CI: 0.27–0.85, $p = 0.01$	Warfarin superior to aspirin	1–2% CNS bleeding (no significant difference between groups)
RE-LY	18,113	2005–2007	Age ≥75 or 65–74 with stroke risk factors, with nonvalvular AF	Dabigatran	Warfarin	2 y	Ischemic stroke or systemic embolism	High-dose (150 mg): RR: 0.66, 95% CI: 0.53–0.82, $p < 0.001$ for superiority Low-dose (110 mg): RR: 0.91, 95% CI: 0.74–1.11, $p < 0.001$ for noninferiority	High-dose dabigatran superior to warfarin	3.1% major bleeding ($p = 0.31$), 0.74% MI (HR: 1.38, 95% CI: 1.00–1.91, $p = 0.048$)
ROCKET-AF	14,264	2006–2009	Age ≥18 with nonvalvular AF and CHADS2 score ≥2	Rivaroxaban	Warfarin	2 y	Ischemic stroke or systemic embolism	HR: 0.88, 95% CI: 0.75–1.03, $p < 0.001$ for noninferiority, $p = 0.12$ for superiority	Rivaroxaban noninferior to warfarin	3.6% major bleeding ($p = 0.58$), MI ($p = 0.12$); ICH: 0.5% (compared with 0.7% in warfarin group, $p = 0.02$), fatal bleeding: 0.2% (compared with 0.5% in warfarin group, $p = 0.003$)
ARISTOTLE	18,201	2006–2010	Age ≥75 with nonvalvular AF and ≥1 stroke risk factor	Apixaban	Warfarin	1.8 y	Ischemic stroke or systemic embolism	HR: 0.79, 95% CI: 0.66–0.96, $p = 0.01$ for superiority and <0.001 for noninferiority	Apixaban superior to warfarin	2.13% major bleeding (compared with 3.09% in warfarin group, HR: 0.69, 95% CI: 0.60–0.80, $p < 0.001$)
AVERROES	5,599	2007–2009	Age ≥50 with ≥1 stroke risk factor and nonvalvular AF, unsuitable to receive VKA	Apixaban	Aspirin	1.1 y	Ischemic stroke or systemic embolism	HR: 0.45, 95% CI: 0.32–0.62, $p < 0.001$	Apixaban superior to aspirin	1.4% major bleeding ($p = 0.57$)
ENGAGE AF-TIMI 48	21,105	2008–2010	Age ≥21 with nonvalvular AF and CHADS2 score ≥2	Edoxaban	Warfarin	2.8 y	Ischemic stroke or systemic embolism	RR: 0.79, 95% CI: 0.63–0.99, $p < 0.001$ for noninferiority and $p = 0.02$ for superiority	Edoxaban superior to warfarin	2.75% major bleeding (compared with 3.43% in warfarin group, HR: 0.80, 95% CI: 0.71–0.91, $p < 0.001$), 2.74% cardiovascular death (compared with 3.17% in warfarin group, HR: 0.86, 95% CI: 0.77–0.97, $p = 0.01$)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; MI, myocardial infarction; RR, relative risk.

Seminars in Neurology Vol. 41 No. 5/2021

analysis, both of which had sample sizes less than 100 patients.[21] Differences between anticoagulation agents and treatment timing impart further challenges in direct comparisons between trials; both UFH and LMWH have shown efficacy without definitive evidence supporting the usage of one versus another.[21] Guidelines from the European Federation of Neurological Societies provide Level B recommendations supporting the usage of LMWH or intravenous (IV) heparin, regardless of the presence of ICH.[22] With respect to newer agents, however, a recent randomized clinical trial of 120 patients found dabigatran to be noninferior to warfarin in efficacy and safety in the treatment of CVST with similarly low recurrence rates over 6 months.[23]

Safety

Risk of Intracerebral Hemorrhage

An early retrospective study of patients older than 50 found a 10-fold increased risk of ICH in patients taking oral anticoagulants compared with those in the general population, with risk potentiated by anticoagulation intensity and the presence of hypertension.[24] Furthermore, a 2004 study of 435 patients older than 55 found that risk of death from ICH doubled within 3 months in patients taking warfarin, and that risk was higher in patients with increased international normalized ratio (INR).[25] Since then, the development of DOACs has allowed for more favorable safety profiles. A meta-analysis found that, compared with patients taking warfarin, patients taking DOACs had a 47% reduction in the relative risk for fatal bleeding (case-fatality rate of 7.57%, 0.1% per 100 patient-years vs. 11.04%, 0.3% per 100 patient-years).[26] However, an observational cohort study of over 1,000 patients with ICH secondary to DOAC or VKA use found no differences in hematoma enlargement, hematoma characteristics, or 3-month functional outcome depending on anticoagulant mechanism.[27]

Decision-Making about Initiating or Restarting Anticoagulation for Ischemic Stroke Prevention after ICH

Balancing the risk of recurrent ICH after restarting anticoagulation with the risk of ischemic stroke off anticoagulation can be challenging. A longitudinal cohort study of patients with ICH secondary to CAA found that a quarter of CAA patients concurrently suffered from AF,[28] introducing a clinical challenge of balancing the risk of stroke against that of recurrent cerebral hemorrhage. Indeed, a recent study found significantly increased risk for arterial ischemic events, including ischemic stroke, among elderly patients in the first 6 months following ICH (hazard ratio [HR]: 6.1, 95% confidence interval [CI]: 3.5–9.3).[29] Analysis of data from three independent observational trials—RETRACE, MGH, and ERICH—in OAT-ICH (oral anticoagulation treatment—ICH) also demonstrated that ICH survivors with AF who are maintained off anticoagulation experience a higher risk of cardioembolic stroke within a year and a lower likelihood of functional recovery.[30] A 2017 meta-analysis of eight studies investigating resumption of anticoagulation following nonlobar ICH found a significantly reduced relative risk of thromboembolic complications (0.34, 95% CI: 0.25–0.45) without any associated increase in the risk of ICH recurrence (1.01, 95% CI: 0.58–1.77).[31] Despite the absence of a randomized controlled trial investigating the risk of repeat hemorrhage following lobar versus nonlobar ICH among patients with AF taking oral anticoagulants, a joint analysis of OAT-ICH data found decreased risk of ischemic stroke without increased risk of ICH in patients with AF who had resumed oral anticoagulation, contrary to guidelines recommending deferring resumption in lobar ICH.[32] This bears particular impact on patients with spontaneous lobar hemorrhage secondary to CAA (►**Fig. 1**), which has historically been considered a contraindication to anticoagulation, despite limited data.[33] Indeed, subgroup analysis of 190 lobar ICH patients with possible or probable CAA by Biffi et al found resumption of oral anticoagulation after ICH was associated with a decrease in mortality (HR: 0.27, 95% CI: 0.08–0.86) and an increase in favorable outcome (HR: 3.40, 95% CI: 1.22–9.46).[32]

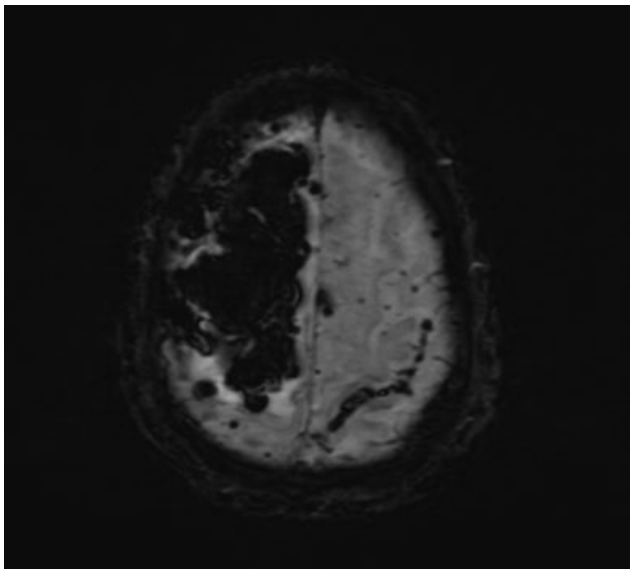

Fig. 1 Susceptibility-weighted magnetic resonance imaging of the brain, showing spontaneous lobar hemorrhage in a patient with cerebral amyloid angiopathy.

There are no definitive guidelines on resumption or initiation of anticoagulation in patients with AF and ICH. However, a longitudinal observational study of more than 2,000 patients in the Swedish Stroke Registry found 7 to 8 weeks after the index hemorrhage was the ideal time point to do so. The authors noted that in a 3-year follow-up period, restarting anticoagulation at this time (as compared with not restarting anticoagulation at all) was associated with significant reductions in the risk of thrombotic events without an increase in hemorrhagic events.[34]

Because of the discrepancy between the prevalence of CAA in elderly patients who develop ICH and those who have asymptomatic CAA, clinicians should consider obtaining a magnetic resonance imaging (MRI) prior to initiation of anticoagulation or resumption after ICH to assist in determining the safety of anticoagulation.[33] The presence of

cortical superficial siderosis embodies a distinct risk factor for bleeding in patients with CAA: in a recent meta-analysis, both focal and disseminated superficial siderosis, diagnosed on MRI, significantly increased the HR for ICH, to 2.11 (95% CI: 1.31–2.41) and 4.28 (95% CI: 2.91–6.30), respectively.[35] In another recent study, MRI was used to identify specific patterns of advanced cerebral small vessel disease predicting greater susceptibility to oral anticoagulant-associated ICH, finding the rates of anticoagulant-associated ICH was highest in patients with a combination of cerebral microbleeds and moderate-to-severe white matter hyperintensities (HR: 2.7, 95% CI: 1.1–7 and HR: 5.7, 95% CI: 1.6–20, respectively).[36] Given the requirement of MRI to draw conclusions in both these circumstances, however, cost considerations limit the generalizability of these findings to centers with limited access to imaging resources.

Decision-Making about Initiating or Restarting Anticoagulation for Ischemic Stroke Prevention after ICH in Elderly Patients

In elderly patients with AF, age increases the risk of ischemic stroke within the first 6 months following ICH, providing compelling evidence supporting the use of anticoagulation.[29] A Canadian study of 683 ICH survivors with nonvalvular AF, with an average age of 83 years, found that initiation of oral anticoagulation—VKAs and DOACs both included—following ICH was associated with significant reductions in ischemic stroke (0.1, 95% CI: 0.05–0.21) and death (0.43, 95% CI: 0.19–0.97), though the authors did note a nonsignificant trend toward higher rates of ICH recurrence.[37] Anticoagulant use in elderly patients with AF is also associated with reduction in the risk of dementia, though there is no specific data on this in patients who had ICH.[38]

Decision-Making about Initiating or Restarting Anticoagulation for Ischemic Stroke Prevention after Ischemic Stroke

Determination of when to resume or initiate anticoagulation following an ischemic stroke, and what agent to use, remains an area of controversy, with limited reliable guiding data. A prospective cohort study of 1,000 patients with acute stroke and AF found high rates of recurrent ischemic stroke or hemorrhagic stroke within 90 days of the incident event, with improved outcomes among patients treated with oral anticoagulants—VKAs or DOACs, at a 3:1 ratio—rather than with LMWH.[39] Furthermore, statistical regression analysis of the data from this investigation determined adverse events principally occurred on days 4 to 14 following acute ischemic stroke.[39] A large European study comparing initiation of a DOAC versus VKA in patients with nonvalvular AF at a median of 5 days after ischemic stroke found that risk of ICH and poor clinical outcome were reduced with initiation of a DOAC.[40] Recent data suggest that bridging with LMWH to oral anticoagulation after ischemic stroke is associated with increased rates of hemorrhagic conversion and ischemic recurrence, without significant differences between VKAs and DOACs or among DOAC types.[41]

A 2018 meta-analysis comparing apixaban to warfarin, dabigatran, and rivaroxaban found apixaban to have the best safety profile among these—comprising lower rates of ICH and gastrointestinal bleeding.[42] However, DOAC selection largely reflects provider preference and considerations of other medical morbidities that could affect metabolism or side effects.

The Relationship between Anticoagulation Use and Outcome in Patients with Traumatic Brain Injury

Anticoagulation use is related to outcome in patients with TBI. A retrospective analysis of nearly 1,500 TBI patients, among whom 159 were anticoagulated with warfarin prior to injury (to INR 2.40 ± 1), found mortality was six times higher among patients taking warfarin as compared with those who were not on anticoagulation. In patients with INR greater than 4.0, there was a 50% risk of mortality and a 75% risk of ICH.[43]

The relative impact of warfarin versus DOACs on outcome after TBI is unclear. A recent study evaluating the impact of preinjury DOAC to warfarin use in patients with TBI found significantly more adverse outcomes, and increased rate of progression, neurosurgical intervention, mortality, and ICU length of stay in patients on DOACs.[44] This contrasts with a similar analysis conducted by the American Association for the Surgery of Trauma, which found DOACs, as compared with warfarin, were not associated with higher risk for ICH, hemorrhage progression, or death. Both studies had nearly similar numbers of patients enrolled (1,459 in the former vs. 1,847 in the latter),[44,45] but the prevalence of ICH differed (30 vs. 100%, respectively).

The Impact of Central Nervous System Malignancies on Selection of Anticoagulant

In patients with central nervous system malignancies, the elevated risk of venous thromboembolism (VTE) must be weighed against that of hemorrhage from a brain mass. Although LMWH carries a threefold increase in the risk of ICH in patients with primary brain tumors, it is safer in subsets of patients with metastatic tumors; DOACs have been found to demonstrate a favorable safety profile in patients with VTE and both primary and metastatic tumors.[46]

The Impact of Unruptured Intracranial Aneurysms on Selection of Anticoagulant

A retrospective study investigating the risk of aneurysm rupture in patients taking systemic anticoagulant medications found no increase in the rate of aneurysm rupture associated with anticoagulation, though, of note, this study did not include patients taking DOACs.[47]

The Impact of Impaired Renal Clearance on Selection of Anticoagulant

Potential impairments in pharmacokinetic clearance constitute a relevant consideration in anticoagulant selection, as randomized controlled trials investigating DOACs have largely excluded patients with advanced chronic kidney disease or on dialysis due to renal metabolism of DOACs. While VKAs would intuitively represent a superior option in the setting of isolated renal failure, their use is limited in patients with

chronic hepatic impairment and concomitant coagulopathies. Surprisingly, a meta-analysis of patients with chronic kidney disease requiring oral anticoagulants found more favorable safety and efficacy when using DOACs versus warfarin[48]; patients treated with factor Xa inhibitors showed reductions in the risks for stroke, mortality, ICH, and major bleeding.[48] This was corroborated by another study finding significantly lower rates of bleeding and stroke in patients taking DOACs versus warfarin at all stages of chronic kidney disease.[49]

Decision-Making about Anticoagulation in Pregnancy

Pregnancy is a prothrombotic state characterized by elevated levels of fibrinogen, factor VII, factor VIII, factor X, von Willebrand factor, plasminogen activator inhibitor, and decreased levels of free protein S.[50] Although population studies show increased rates of thrombotic events in the third trimester,[51] the risk of thrombosis is elevated through all trimesters of pregnancy, and levels of prothrombotic factors do not normalize until 8 weeks postpartum.[50,52] Additional risk factors for stroke during pregnancy include preeclampsia, eclampsia, increased maternal age, and hypertension.[52] Epidemiologic differences also exist in types of pregnancy-associated stroke, as ischemic stroke secondary to arterial occlusion accounts for a larger proportion of stroke among pregnant women in the United States and Canada, while studies from Japan and Taiwan demonstrate a relatively larger proportion of hemorrhagic stroke secondary to venous thrombosis and vascular malformations.[53] The risk for thrombosis can even persist following delivery up to 12 weeks, despite a general standard of care of continuation of anticoagulation for 6 weeks following delivery in women who have experienced thrombotic events during pregnancy.[54] Because VKA anticoagulants have been associated with fetal malformation in the first trimester, LMWH is the anticoagulant of choice among pregnant patients with AF or thromboembolic disease, as it does not cross the placenta. This therapy should be administered with concomitant monitoring of factor Xa levels.[55] While the initial landmark DOAC studies excluded pregnant women, the enhanced safety profiles and conveniences of eliminating monitoring or injections make these medications a subject of future study in the setting of pregnancy. The limited data available thus far, however, do not support their usage in this setting. A meta-analysis of 236 cases of DOAC use during pregnancy, including both factor Xa and factor II inhibitors used predominantly for VTE, found increased rates of miscarriage (31%) and skeletal fetal malformations (4%), the latter reflecting the use of rivaroxaban in the first semester.[55] Furthermore, in two studies investigating the use of rivaroxaban in nonpregnant patients with antiphospholipid antibody syndrome, a common cause of miscarriage, rivaroxaban failed to show noninferiority to warfarin.[56,57]

Reversal

Heparin

Unfractionated heparin and LMWH can be reversed by IV protamine sulfate at 1 mg per 100 units of heparin up to 50 mg.[58] For patients with contraindications to protamine, IV recombinant factor VIIa, at doses ranging from 40 to 160 μg/kg given within 4 hours of hemorrhage, can be used for reversal in ICH.[59]

VKAs

Phytonadione is an accepted, effective, versatile reversal agent in patients taking VKAs with INR $\geq$1.4. It is available in oral, IV, and subcutaneous formulations and does not carry a risk of prothrombotic adverse effects. Vitamin K is typically administered as a 10 mg IV dose, with faster reversal from IV versus oral dosing. However, as it may take up to 24 hours to resynthesize vitamin K–dependent factors, the simultaneous administration of other reversal agents is necessary.[60,61]

Fresh frozen plasma (FFP) and prothrombin complex concentrates (PCCs) constitute the mainstays of adjunct therapies used with vitamin K in patients requiring VKA reversal. FFP is given at 10 to 15 mL/kg IV, while PCC is given at 50 units/kg IV.[61] As a blood product, FFP requires time-consuming preparation including blood typing and thawing, and it carries the risk of infusion reaction and possible infection in addition to the risk of volume overload. By contrast, PCC can achieve rapid delivery of factors II, IX, X, +/− VII with relatively lower volumes and faster infusion times.[58,62,63] Furthermore, in a retrospective study of FFP in patients with warfarin-associated hemorrhage, although each 30-minute delay in FFP administration decreased the probability of 24-hour INR reversal by 20%, even patients who survived 90 days had not received FFP until an average of 110 minutes after CT imaging.[64] Among patients taking VKAs, PCC has been shown to be associated with lower 90-day risk of death or severe disability compared with FFP, with similar time to INR correction,[65] and patients taking VKAs who experience anticoagulation-associated ICH achieve faster reversal with PCC than with FFP.[66]

Direct Oral Anticoagulants

While the absence of direct reversal agents initially posed limitations on widespread DOAC use, recent years has seen the emergence of therapeutic options for both direct thrombin inhibitors and factor Xa inhibitors. Idarucizumab, a humanized monoclonal antibody fragment binding directly to dabigatran, became the first commercially available DOAC reversal agent in 2015, achieving reversal within minutes and intraoperative hemostasis in 92% of patients requiring urgent surgery.[67] Recommended idarucizumab dosing in ICH is 5 g IV in two 2.5 g/50 mL vials.[61]

In 2018, specific reversal became available for factor Xa inhibitors with the advent of andexanet alfa, a modified factor Xa decoy protein that binds factor Xa inhibitors to prevent these agents from inhibiting prothrombin activation.[68] Cost remains a barrier to the availability of andexanet alfa in hospitals outside major tertiary care centers, as 9 to 18 vials of 100 mg could be necessary depending on the required dosage, with an average cost of $2,750 USD per vial.[68] ►**Fig. 2(A–D)** shows a DOAC-associated hemorrhage treated with andexanet alfa.

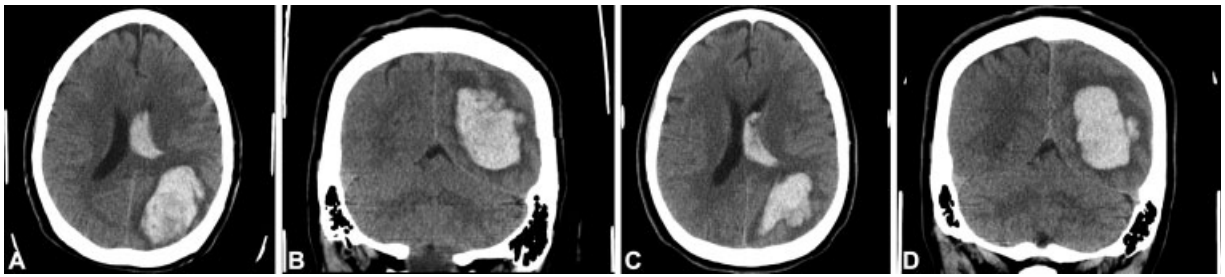

Fig. 2 (**A**) Axial and (**B**) coronal views of computed tomography of the head, showing anticoagulation-associated hemorrhage in a patient taking rivaroxaban. (**C**) Axial and (**D**) coronal views are shown after reversal with andexanet alfa.

Table 2 Key trials of novel reversal agents

Agent	Mechanism	Reversal target(s)	Onset time	Cost/Dose	Trial(s)	Clinical question	Enrollment (*n*)	Duration
Idarucizumab	Humanized monoclonal antibody fragment that binds to factor II inhibitors	Direct thrombin inhibitors	< 5 min	$3,500–$4,200	RE-VERSE AD	Reversal of dabigatran	503	2014–2015
Andexanet alfa	Recombinant modified factor Xa decoy that binds to factor Xa inhibitors	Direct factor Xa inhibitors	2–5 min	$27,500–$49,500	ANNEXA (ANNEXA-A and ANNEXA-R)	Reversal of apixaban, rivaroxaban	145	2014–2015
					ANNEXA-4	Hemostatic efficiency in patients taking apixaban, rivaroxaban, edoxaban, LMWH	500	2015–2022
Ciraparantag	Small molecule directly binding targets with noncovalent hydrogen bonds to block anticoagulant binding targets	Direct thrombin inhibitors, direct factor Xa inhibitors, UFH, LMWH	10–30 min	N/A	NCT01826266	Phase I evaluation, reversal of edoxaban	83	2013
					NCT03172910	Phase II evaluation, reversal of rivaroxaban	48	2017–2019
					NCT03288454	Phase II evaluation, reversal of apixaban	48	2017–2019

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Table 3 Relevant ongoing and future trials

Trial	Duration	Planned enrollment (*n*)	Clinical question	Country
APACHE-AF	2014–2021	100	Apixaban vs. antiplatelet drugs or no antithrombotic drugs after anticoagulation-related ICH in patients with AF	The Netherlands
BRAIN-AF	2015–2022	3,250	Rivaroxaban vs. standard of care in reducing stroke, transient ischemic attack, and neurocognitive decline	Canada
ATTICUS	2015–2023	500	Apixaban vs. aspirin for treatment of embolic stroke of undetermined source	Germany
DANNOAC-AF	2017–2021	11,000	Comparison of safety and efficacy of edoxaban, apixaban, rivaroxaban, and dabigatran in patients with AF	Denmark
ELAN	2017–2021	2,000	Early (< 2 d) vs. late (3–14 d depending on stroke severity) initiation of DOAC following ischemic stroke	Switzerland
START	2017–2021	1,000	Optimal time to resume anticoagulation after acute ischemic stroke in patients with AF	US
TIMING	2017–2021	3,000	Early (< 4 d) vs. late (5–10 d) initiation of anticoagulation (DOAC) after acute ischemic stroke in patients with AF	Sweden
ERSAF	2018–2021	1,000	Early (< 14 d) rivaroxaban after acute ischemic stroke or transient ischemic attack in patients with AF	China
ARISTA	2018–2022	280	Apixaban vs. warfarin in reducing the rates of cognitive decline, new cerebral infarction, and cerebral microbleeds in patients with AF	US
NVAF	2019–2021	400	Predictive value of infarct volume on hemorrhagic transformation in newly diagnosed ischemic stroke or transient ischemic attack in patients with nonvalvular AF	China
RIG-ICH	2019–2021	380	Safety and efficacy of idarucizumab in patients on dabigatran admitted with intracranial hemorrhage, vs. standard of care in patients on VKA admitted with intracranial hemorrhage	Germany
SECRET	2019–2021	50	Safety of rivaroxaban vs. standard of care for treatment of symptomatic cerebral venous thrombosis	Canada
ENRICH-AF	2019–2022	1,200	Risks of hemorrhagic or ischemic stroke in treatment of AF with edoxaban (30 or 60 mg) vs. no anticoagulation in patients with history of ICH	Canada
OPTIMAS	2019–2022	3,478	Optimal time to initiate anticoagulation (DOAC) after acute ischemic stroke	UK
PRESTIGE-AF	2019–2022	654	Hemorrhage risk for DOAC vs. no anticoagulation in patients with recent ICH and comorbid AF	UK
A3ICH	2019–2023	300	Apixaban vs. left atrial appendage closure vs. avoidance of anticoagulation to optimize composite risk of hemorrhagic vs. ischemic stroke in patients with history of ICH and comorbid AF	France
RISAPS	2020–2023	140	Rivaroxaban vs. warfarin in stroke patients with antiphospholipid syndrome, with or without systemic lupus erythematosus	UK
ASPIRE	2020–2024	700	Comparison of safety and efficacy of apixaban vs. aspirin in patients with recent ICH and high-risk nonvalvular AF	US
RESTART tICrH	2021–2027	1,100	Optimal time to resume anticoagulation (DOAC) after traumatic ICH	US

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; VKA, vitamin K antagonist.

In scenarios in which such reversal agents are unavailable, four-factor PCC—containing factors II, VII, IX, and X—may be used to reverse bleeding in patients taking factor Xa inhibitors. However, mechanistic incongruity prevents full reversal by PCC in comparison to andexanet alfa.[61,69] In addition to idarucizumab and PCC, activated charcoal (50 g within 2 hours of DOAC ingestion) may also help reverse factor Xa inhibitors and dabigatran, but must be administered within 2 hours of ingestion.[61] ►**Table 2** summarizes clinical trials investigating novel reversal agents.

Recent Developments

Basic Science

Preclinical models on which to test the effects of anticoagulation and its reversal predominantly encompass rodent studies in which stereotactic injection of collagenase induces hemorrhage by disrupting the extracellular matrix; transgenic mouse models also exist of other conditions, including CAA.[70] Current technical limitations in accurately replicating human application scenarios include resolving differences in vascular pathophysiology, achieving greater consistency in the occurrence and size of ICH in models, and better accounting for comorbid conditions that may impart physiological interaction.[70] Ciraparantag, a reversal agent under current investigation, could provide a novel reversal mechanism by binding to—and removing—anticoagulants from their targets through ionic charge interactions, potentially representing a reversal agent against multiple mechanisms of anticoagulants.[68] MAA868, a novel human antibody binding both the factor XI zymogen and active factor XIa, has also shown promise in achieving anticoagulation without bleeding in

murine models (tested by thromboelastography) and primate models (tested by prolongation of activated partial thromboplastin time), and was found to be safe when administered subcutaneously in a small cohort of human adults between ages 18 and 60.[71]

Translational/Clinical Trials

ARCADIA, which is presently underway, is investigating atrial cardiopathy—a thrombogenic atrial substrate independent of AF, defined by electrocardiographic, echocardiographic, or laboratory test (probrain natriuretic peptide elevation) criteria suggestive of left atrial enlargement—as a therapeutic target for apixaban versus aspirin in stroke prevention in patients with a history of cryptogenic stroke.[72]

While DOACs have been studied in multiple trials of ischemic stroke management in patients with nonvalvular AF or cryptogenic stroke, several studies are presently underway to investigate the role of DOACs in patients with nonvalvular AF recovering from ICH. Among these, APACHE-AF, ASPIRE, and A3ICH seek to compare apixaban versus antiplatelet monotherapy, and ENRICH-AF seeks to compare edoxaban versus standard of care, whereas others, such as PRESTIGE-AF, do not specify a specific DOAC to compare against standard therapy.[73]

With respect to the timing of when to initiate oral anticoagulation following ischemic stroke, multiple trials investigating early DOAC initiation are set to complete in 2021–2022, encompassing a range of 2 to 4 days following stroke in ELAN, OPTIMAS, and TIMING, and 3 to 14 versus 6 to 21 days in START depending on stroke severity. ►**Table 3** summarizes ongoing and future clinical trials and their respective clinical questions.

Conclusion

The confluence of prothrombotic risk factors, interactions between underlying medical conditions, and risk of bleeding demands a nuanced, individualized approach to selecting the ideal anticoagulant—or none—in each patient's clinical scenario. The recent availability of a newer, safer, and more direct generation of oral anticoagulant options—in addition to the more recent development of effective corresponding reversal agents—grant greater flexibility and control in devising safe and effective strategies for minimizing the risk of stroke and other thromboembolic disease. More favorable safety profiles of DOACs versus warfarin and other anticoagulants, in addition to emerging pathophysiological information guiding prediction and risk stratification of bleeding complications, invite reconsideration of traditionally regarded contraindications to anticoagulation, including subtypes of CAA. Current studies may provide more evidence regarding the timing of when to start or resume anticoagulation following ischemic stroke or ICH. As new reversal agents continue to enter the market, practical considerations of cost and availability will be expected to present less and less of an obstacle to more widespread usage of these medications.

Conflict of Interest
None declared.

References

1 Franchini M, Liumbruno GM, Bonfanti C, Lippi G. The evolution of anticoagulant therapy. Blood Transfus 2016;14(02):175–184
2 Levine M, Hirsh J. Hemorrhagic complications of long-term anticoagulant therapy for ischemic cerebral vascular disease. Stroke 1986;17(01):111–116
3 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857–867
4 van Asch CJJ, Luitse MJA, Rinkel GJE, van der Tweel I, Algra A, Klijn CJM. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 2010;9(02):167–176
5 Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol 2013;112(08): 1142–1147
6 Investigators AF. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154 (13):1449–1457
7 Albers GW, Diener H-C, Frison L, et al; SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293(06):690–698
8 Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–1151
9 Connolly SJ, Eikelboom J, Joyner C, et al; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364(09):806–817
10 Granger CB, Alexander JH, McMurray JJV, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981–992
11 Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883–891
12 Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22):2093–2104
13 Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients. Stroke 2018;49(12):2933–2944
14 Macha K, Marsch A, Siedler G, et al. Cerebral ischemia in patients on direct oral anticoagulants. Stroke 2019;50(04):873–879
15 January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74(01):104–132
16 Mohr JP, Thompson JL, Lazar RM, et al; Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001; 345(20):1444–1451
17 Diener H-C, Sacco RL, Easton JD, et al; RE-SPECT ESUS Steering Committee and Investigators. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019; 380(20):1906–1917
18 Hart RG, Sharma M, Mundl H, et al; NAVIGATE ESUS Investigators. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378(23):2191–2201

19 Chimowitz MI, Lynn MJ, Howlett-Smith H, et al; Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352(13):1305–1316

20 Metso TM, Metso AJ, Helenius J, et al. Prognosis and safety of anticoagulation in intracranial artery dissections in adults. Stroke 2007;38(06):1837–1842

21 Coutinho J, de Bruijn SF, Deveber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. Cochrane Database Syst Rev 2011;30(08):CD002005

22 Einhäupl K, Stam J, Bousser MG, et al; European Federation of Neurological Societies. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. Eur J Neurol 2010;17(10):1229–1235

23 Ferro JM, Coutinho JM, Dentali F, et al; RE-SPECT CVT Study Group. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. JAMA Neurol 2019

24 Wintzen AR, de Jonge H, Loeliger EA, Bots GT. The risk of intracerebral hemorrhage during oral anticoagulant treatment: a population study. Ann Neurol 1984;16(05):553–558

25 Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med 2004;164(08): 880–884

26 Chai-Adisaksopha C, Hillis C, Isayama T, Lim W, Iorio A, Crowther M. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost 2015;13(11):2012–2020

27 Gerner ST, Kuramatsu JB, Sembill JA, et al. Characteristics in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. Stroke 2019;50(06):1392–1402

28 Kaiser J, Schebesch KM, Brawanski A, Linker RA, Schlachetzki F, Wagner A. Long-term follow-up of cerebral amyloid angiopathy-associated intracranial hemorrhage reveals a high prevalence of atrial fibrillation. J Stroke Cerebrovasc Dis 2019;28(11):104342

29 Murthy SB, Díaz I, Wu X, et al. Risk of arterial ischemic events after intracerebral hemorrhage. Stroke 2020;51(01):137–142

30 Murphy MP, Kuramatsu JB, Leasure A, et al. Cardioembolic stroke risk and recovery after anticoagulation-related intracerebral hemorrhage. Stroke 2018;49(11):2652–2658

31 Murthy SB, Gupta A, Merkler AE, et al. Restarting anticoagulant therapy after intracranial hemorrhage: a systematic review and meta-analysis. Stroke 2017;48(06):1594–1600

32 Biffi A, Kuramatsu JB, Leasure A, et al. Oral anticoagulation and functional outcome after intracerebral hemorrhage. Ann Neurol 2017;82(05):755–765

33 Charidimou A, Shoamanesh A, Al-Shahi Salman R, et al. Cerebral amyloid angiopathy, cerebral microbleeds and implications for anticoagulation decisions: the need for a balanced approach. Int J Stroke 2018;13(02):117–120

34 Pennlert J, Overholser R, Asplund K, et al. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. Stroke 2017;48(02):314–320

35 Charidimou A, Boulouis G, Greenberg SM, Viswanathan A. Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy: a meta-analysis. Neurology 2019;93(24):e2192–e2202

36 Martí-Fàbregas J, Medrano-Martorell S, Merino E, et al; HERO Study Investigators. MRI predicts intracranial hemorrhage in patients who receive long-term oral anticoagulation. Neurology 2019;92(21):e2432–e2443

37 Perreault S, Côté R, White-Guay B, Dorais M, Oussaïd E, Schnitzer ME. Anticoagulants in older patients with nonvalvular atrial fibrillation after intracranial hemorrhage. J Stroke 2019;21(02): 195–206

38 Silva RMFLD, Miranda CM, Liu T, Tse G, Roever L. Atrial fibrillation and risk of dementia: epidemiology, mechanisms, and effect of anticoagulation. Front Neurosci 2019;13:18

39 Paciaroni M, Agnelli G, Falocci N, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: effect of anticoagulation and its timing: the RAF study. Stroke 2015;46(08):2175–2182

40 Seiffge DJ, Paciaroni M, Wilson D, et al; CROMIS-2, RAF, RAF-DOAC, SAMURAI, NOACISP LONGTERM, Erlangen and Verona Registry Collaborators. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation. Ann Neurol 2019;85(06):823–834

41 Altavilla R, Caso V, Bandini F, et al. Anticoagulation after stroke in patients with atrial fibrillation. Stroke 2019;50(08):2093–2100

42 Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke 2018;49(01): 98–106

43 Franko J, Kish KJ, O'Connell BG, Subramanian S, Yuschak JV. Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. J Trauma 2006;61(01): 107–110

44 Zeeshan M, Jehan F, O'Keeffe T, et al. The novel oral anticoagulants (NOACs) have worse outcomes compared with warfarin in patients with intracranial hemorrhage after TBI. J Trauma Acute Care Surg 2018;85(05):915–920

45 Kobayashi L, Barmparas G, Bosarge P, et al; AAST Multicenter Prospective Observational Study of Trauma Patients on Novel Oral Anticoagulants Study Group. Novel oral anticoagulants and trauma: the results of a prospective American Association for the Surgery of Trauma Multi-Institutional Trial. J Trauma Acute Care Surg 2017;82(05):827–835

46 Carney BJ, Uhlmann EJ, Puligandla M, et al. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. J Thromb Haemost 2019;17(01):72–76

47 Tarlov N, Norbash AM, Nguyen TN. The safety of anticoagulation in patients with intracranial aneurysms. J Neurointerv Surg 2013;5 (05):405–409

48 Malhotra K, Ishfaq MF, Goyal N, et al. Oral anticoagulation in patients with chronic kidney disease: a systematic review and meta-analysis. Neurology 2019;92(21):e2421–e2431

49 Makani A, Saba S, Jain SK, et al. Safety and efficacy of direct oral anticoagulants versus warfarin in patients with chronic kidney disease and atrial fibrillation. Am J Cardiol 2020;125(02): 210–214

50 James AH. Pregnancy and thrombotic risk. Crit Care Med 2010;38 (2, Suppl):S57–S63

51 Scott CA, Bewley S, Rudd A, et al. Incidence, risk factors, management, and outcomes of stroke in pregnancy. Obstet Gynecol 2012; 120(2, Pt 1):318–324

52 James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol 2005;106(03):509–516

53 Yoshida K, Takahashi JC, Takenobu Y, Suzuki N, Ogawa A, Miyamoto S. Strokes associated with pregnancy and puerperium: a nationwide study by the Japan Stroke Society. Stroke 2017;48 (02):276–282

54 Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a thrombotic event after the 6-week postpartum period. N Engl J Med 2014;370(14):1307–1315

55 Lameijer H, Aalberts JJJ, van Veldhuisen DJ, Meijer K, Pieper PG. Efficacy and safety of direct oral anticoagulants during pregnancy; a systematic literature review. Thromb Res 2018; 169:123–127

56 Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, et al. Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial. Ann Intern Med 2019;171(10): 685–694

57 Cohen H, Hunt BJ, Efthymiou M, et al; RAPS Trial Investigators. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus

erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Lancet Haematol 2016;3(09): e426–e436
58 Hemphill JC III, Greenberg SM, Anderson CS, et al; American Heart Association Stroke Council Council on Cardiovascular and Stroke Nursing Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46(07): 2032–2060
59 Mayer SA, Brun NC, Begtrup K, et al; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2005;352(08):777–785
60 Shields RC, McBane RD, Kuiper JD, Li H, Heit JA. Efficacy and safety of intravenous phytonadione (vitamin K1) in patients on long-term oral anticoagulant therapy. Mayo Clin Proc 2001;76(03):260–266
61 Frontera JA, Lewin JJ III, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: executive summary. a statement for healthcare professionals from the Neurocritical Care Society and the Society of Critical Care Medicine. Crit Care Med 2016;44(12):2251–2257
62 Sarode R, Milling TJJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128(11): 1234–1243
63 Yasaka M, Sakata T, Minematsu K, Naritomi H. Correction of INR by prothrombin complex concentrate and vitamin K in patients with warfarin related hemorrhagic complication. Thromb Res 2002;108(01):25–30
64 Goldstein JN, Thomas SH, Frontiero V, et al. Timing of fresh frozen plasma administration and rapid correction of coagulopathy in warfarin-related intracerebral hemorrhage. Stroke 2006;37(01): 151–155
65 Frontera JA, Gordon E, Zach V, et al. Reversal of coagulopathy using prothrombin complex concentrates is associated with improved outcome compared to fresh frozen plasma in warfarin-associated intracranial hemorrhage. Neurocrit Care 2014;21(03):397–406
66 Fredriksson K, Norrving B, Strömblad LG. Emergency reversal of anticoagulation after intracerebral hemorrhage. Stroke 1992;23 (07):972–977
67 Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373(06):511–520
68 Rogers KC, Finks SW. A new option for reversing the anticoagulant effect of factor Xa inhibitors: andexanet alfa (ANDEXXA). Am J Med 2019;132(01):38–41
69 Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the Anticoagulation Forum. Am J Hematol 2019;94(06):697–709
70 Hemorrhagic Stroke Academia Industry (HEADS) Roundtable Participants. Basic and translational research in intracerebral hemorrhage: limitations, priorities, and recommendations. Stroke 2018;49(05):1308–1314
71 Koch AW, Schiering N, Melkko S, et al. MAA868, a novel FXI antibody with a unique binding mode, shows durable effects on markers of anticoagulation in humans. Blood 2019;133(13): 1507–1516
72 Kamel H, Longstreth WT Jr, Tirschwell DL, et al. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: rationale and methods. Int J Stroke 2019;14(02):207–214
73 Shoamanesh A, Charidimou A, Sheth KN. Comorbid atrial fibrillation in cerebral amyloid angiopathy-related intracerebral hemorrhage: between a rock and a hard place. J Stroke Cerebrovasc Dis 2019;28(11):104351