EDITORIAL

FRANKLIN MICHOTA, MD, FHM
Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, and Director of Academic Affairs, Department of Hospital Medicine, Cleveland Clinic

Intracerebral hemorrhage: Pick your poison

Anticoagulants have been helping patients at risk of thrombosis since the late 1930s.[1,2] Although the indications for these agents are many, the development of anticoagulants beyond oral vitamin K antagonists and parenteral heparin has been slow. In the United States, the vitamin K antagonist warfarin (Coumadin) is still the only oral anticoagulant available.

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The major complication of anticoagulant therapy is bleeding, and vitamin K antagonists have proven challenging to use in clinical practice.[1,3] They have a narrow therapeutic window, they vary considerably in dose-response from patient to patient, and they are subject to significant interactions with other drugs and with foods. For these reasons, therapy must be monitored with laboratory testing, and good patient compliance and patient education are essential. Yet even with these measures, life-threatening hemorrhage still can occur.

In this issue of the *Cleveland Clinic Journal of Medicine* (page 791), Goldstein and Greenberg[4] review warfarin-related intracerebral hemorrhage (ICH) and provide a framework for considering whether to resume anticoagulant therapy.

WHAT TO DO IN THE ACUTE PHASE

Goldstein and Greenberg divide the difficult clinical question of what to do after ICH into the acute phase and the chronic phase.

What to do in the acute phase appears straightforward, as the risk of hematoma expansion in the hours immediately after warfarin-related ICH outweighs the risk of arterial or venous thromboembolism. Anticoagulant reversal should be the primary consideration in the first 24 hours, and, assuming the patient does not have acute (< 4-week-old) deep vein thrombosis, intermittent pneumatic compression should be applied to the lower extremities to reduce the risk of venous thromboembolism associated with ICH.[5]

Prophylactic anticoagulation with subcutaneous fixed-dose heparin or low-molecular-weight heparin is recommended starting 72 hours after ICH is diagnosed, provided the patient is not underweight (< 50 kg), has relatively normal renal function (creatinine clearance > 30 mL/minute/1.73 m^2) and normal platelet function, and does not have coagulopathy.[6] If any one of these criteria is not met, the risk of bleeding can be higher, even with only prophylactic doses of anticoagulant drugs. Prophylactic anticoagulation should be continued until hospital and rehabilitation discharge, typically 1 to 2 weeks after ICH, depending on the severity of the patient's neurologic impairment.

Anticoagulant reversal is the primary consideration in the first 24 hours

If a patient with warfarin-related ICH has concomitant acute proximal deep vein thrombosis or pulmonary embolism (ie, < 4 weeks old), then caval interruption therapy would be indicated.[7] Although retrievable inferior vena cava filters are increasingly preferred over permanent filters, it is important to recognize the relative lack of both longitudinal and prospective data on retrievable devices. Given that provoked venous thromboembolism requires a minimum of 3 months of anticoagulation, and retrievable filters gen-

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TABLE 1

Suggested patient risk stratification for arterial or venous thromboembolism

	INDICATION FOR VITAMIN K ANTAGONIST		
	MECHANICAL HEART VALVE	ATRIAL FIBRILLATION	VENOUS THROMBOEMBOLISM
High risk	Any mitral valve prosthesis Older prosthetic aortic valve (caged-ball, tilting-disc) Recent stroke or transient ischemic attack (within 6 months)	$CHADS_2$ score ≥ 5 Recent stroke or transient ischemic attack (within 3 months) Rheumatic valvular heart disease	Recent event (within 3 months) Severe thrombophilia (low protein C, protein S, or antithrombin level; antiphospholipid antibody syndrome; multiple abnormalities)
Moderate risk	Bileaflet aortic valve prosthesis and one of the following: Atrial fibrillation Prior stroke or transient ischemic attack Hypertension Diabetes Congestive heart failure Age over 75	$CHADS_2$ score 3 or 4 Prior stroke or transient ischemic attack	Venous thromboembolic event in the past 3 to 12 months Nonsevere thrombophilic conditions (eg, heterozygous factor II mutation) Recurrent venous thromboembolism Active cancer (treated within 6 months, or palliative treatment)
Low risk	Bileaflet aortic valve prosthesis without atrial fibrillation, and with no other stroke risk factors	$CHADS_2$ score ≤ 2 and no prior stroke or transient ischemic attack	Single venous thromboembolic event > 12 months ago and no other risk factors

$CHADS_2$ = Acronym for scoring system used to assess stroke risk based on key risk factors: congestive heart failure, hypertension, age over 75, diabetes mellitus (1 point for each of these factors present), and prior stroke or transient ischemic attack (2 points)

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erally need to be removed before 3 months, a retrievable filter should be chosen only if the clinician has already decided that oral anticoagulation will be restarted in the next 3 to 4 weeks after filter removal.

WHAT TO DO IN THE CHRONIC PHASE

A more difficult question in patients with warfarin-related ICH arises in the chronic phase: should oral anticoagulation be resumed at all?

Goldstein and Greenberg outline important considerations. Under the principle of primum non nocere, patients who have suffered a warfarin-related ICH should first be evaluated for their risk of thrombosis in light of their original indication for oral anticoagulant therapy. As the authors point out, oral anticoagulation for primary prevention of thrombosis after warfarin-related ICH must be viewed differently than oral anticoagulation for secondary prevention of thrombosis. In addition, Douketis et al[8] have described a method of stratifying a patient's risk of thrombosis as low, moderate, or high (TABLE 1), which is the basis for decisions about perioperative anticoagulation. Based on Goldstein and Greenberg's review, we can similarly categorize these patients as being at low, moderate, or high risk of ICH recurrence (TABLE 2). Patients at low risk of thrombosis should probably not resume taking a vitamin K antagonist, regardless of their ICH risk (TABLE 3). It would be reasonable, however, for patients at moderate or high risk of thrombosis and at low risk of ICH to resume taking their vitamin K antagonist.

Uncertainty remains for patients with a moderate or high risk of thrombosis and a moderate or high risk of ICH. For patients with these combinations of risk, individual-

TABLE 2

Suggested risk stratification for recurrent intracranial hemorrhage

High risk	Cerebral amyloid angiopathy or lobar intracranial hemorrhage Microbleeds on magnetic resonance imaging Apolipoprotein E genotype
Moderate risk	Hypertensive vasculopathy or deep intracranial hemorrhage with any of the following: Normal international normalized ratio at the time the hemorrhage is diagnosed Patient not compliant with the dosing and monitoring of vitamin K antagonist therapy Patient not compliant with antihypertensive therapy
Low risk	Hypertensive vasculopathy or deep intracranial hemorrhage in a compliant patient

ized approaches need to be explored. All attempts should be made to widen the margin of safety of vitamin K antagonist therapy; these include referring the patient to an anticoagulation management service, frequent laboratory monitoring, and ongoing patient education.[1]

Since the risk of ICH is related to the intensity of anticoagulation, a lower target international normalized ratio may be the best compromise, depending on the patient. Alternatively, antiplatelet therapy alone may offer some benefit with less risk of ICH.

THE NEWER ORAL ANTICOAGULANTS

As Goldstein and Greenberg mention, the ongoing development of new and potentially safer oral anticoagulants may affect how we approach these risk-benefit equations.

Three new oral anticoagulants—dabigatran (Pradaxa), apixaban, and rivaroxaban (Xarelto)—are being tested for various anticoagulant indications, and several phase III studies have recently closed or are nearing completion.

Dabigatran is an oral direct thrombin inhibitor currently available in Europe and Canada.

In the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial, the efficacy and safety of two different doses of dabigatran (110 mg twice daily or 150 mg twice daily) relative to warfarin were studied in more than 18,000 patients with atrial fibrillation.[9] The primary outcome measure was stroke or systemic embolism. Dabigatran 110 mg was not inferior to warfarin in terms of the primary outcome, while dabigatran 150 mg was superior. The rate of major bleeding was 3.36% per year in the warfarin group vs 2.71% in the 110-mg group (P = .003) and 3.11% in the 150-mg group (P not significant).

Additional safety data on this drug are available from the 2,500-patient RE-COVER trial.[10] Dabigatran was not inferior to warfarin in the treatment of acute venous thromboembolism, with a similar rate of major bleeding and a lower rate of combined major plus nonmajor bleeding.

Apixaban, an oral direct factor Xa inhibitor, is in a phase III trial in patients with atrial fibrillation—Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[11]—comparing apixaban vs warfarin. Another phase III trial, AVERROES,[12] was stopped early after a predefined interim analysis by the independent data-monitoring committee found clear evidence of benefit in the apixaban group.[13] The AVERROES results were presented at the 2010 European Society of Cardiology Congress, August 28–September 1, Stockholm, Sweden.[14]

Rivaroxaban, another promising oral direct factor Xa inhibitor, is currently available in Europe and Canada for the prevention of thrombosis in orthopedic surgery patients. Rivaroxaban is also in large phase III trials for the treatment of acute venous thromboembolism[15–17] and for the prevention of stroke in atrial fibrillation.[18]

All attempts should be made to widen the margin of safety of vitamin K antagonist therapy

Newer agents have drawbacks, too

These new agents need no laboratory monitoring, and they do not appear to be subject to

TABLE 3

Guidelines for resuming a vitamin K antagonist after warfarin-related intracranial hemorrhage

RISK OF ICH	RISK OF THROMBOSIS		
	High	**Moderate**	**Low**
High	Do not resume	Do not resume	Do not resume
Moderate	Individualized approach	Individualized approach	Do not resume
Low	Resume	Resume	Do not resume

The decision to resume anticoagulation after anticoagulant-associated intracranial hemorrhage should be based on the risk of rebleeding vs the risk of thrombosis. Patients determined to be at high risk of thrombosis and low risk of rebleeding are the best candidates for resuming anticoagulation.

the dose variability and the interactions with drugs and foods seen with vitamin K antagonists. As a result, they may pose less risk of anticoagulant-related ICH.

Still, for patients who suffer an anticoagulant- or warfarin-related ICH, these new anticoagulants are not likely to simplify the issue of restarting anticoagulant therapy. Unlike vitamin K antagonists, dabigatran and the direct factor Xa inhibitors have no known antidote for their anticoagulant effects. Animal data suggest that factor Xa concentrates may help,[19] but for patients at risk of a second anticoagulant-related ICH, this does not provide much reassurance.

As with all clinical decisions in medicine, the potential benefits of any therapy should outweigh the risks. In the case of warfarin-related ICH, resuming anticoagulant therapy requires careful consideration of many factors, including patient preferences and tolerance of different levels of risk. As new and perhaps safer anticoagulants become available, clinicians may face such difficult questions less and less. But in the meantime, doctors and their patients are left to pick their poison. ■

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***ADDRESS**: Franklin Michota, MD, Department of Hospital Medicine, M2 Anx, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail michotf@ccf.org.*