CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will weigh when and how to restart anticoagulation therapy after intracerebral hemorrhage

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Should anticoagulation be resumed after intracerebral hemorrhage?

ABSTRACT

Intracerebral hemorrhage (ICH) is the most feared and the most deadly complication of oral anticoagulant therapy, eg, with warfarin (Coumadin). After such an event, clinicians wonder whether their patients should resume anticoagulant therapy. The authors review the management of anticoagulation during and after anticoagulation-associated ICH.

KEY POINTS

Given the high risk of hematoma expansion in the early phase of acute ICH, most experts recommend reversing anticoagulation immediately.

Many clinicians start subcutaneous heparinoids in low doses 24 to 72 hours after ICH to prevent deep vein thrombosis, and after the first few days or a week, consider either increasing the dose to a full anticoagulation dose or making a transition to oral anticoagulants.

Many patients with lobar hemorrhage or cerebral amyloid angiopathy may remain at higher risk of anticoagulant-related ICH recurrence than thromboembolic events and would therefore be best managed without anticoagulants.

Those with deep hemispheric ICH, hypertension that can be well controlled, and a high risk of disabling thromboembolism may receive net benefit from restarting anticoagulation.

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If a patient taking warfarin (Coumadin) or other anticoagulant drug suffers an intracerebral hemorrhage (ICH) and survives, the physician faces the dilemma of whether to resume the anticoagulant. On one hand, the drug was prescribed because the patient was at risk of a thromboembolic event such as stroke or pulmonary embolism. On the other hand, warfarin use may increase the risk of another ICH.

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Unfortunately, we have little evidence from clinical trials on which to base the decision. Nevertheless, we believe that in selected patients the potential benefit of resuming anticoagulation outweighs the considerable risk.

In the pages that follow, we summarize when and how anticoagulation therapy should be resumed after ICH.

A DEADLY COMPLICATION OF ANTICOAGULANT THERAPY

Intracranial bleeding is the most feared and the most deadly complication of oral anticoagulant therapy.[1] The substantial risks associated with oral anticoagulants likely account for these drugs being underprescribed in patients who have indications for them.[2–4]

While bleeding is the major risk, not all bleeding events are equally damaging. Extracranial bleeding (eg, gastrointestinal bleeding, hematuria, epistaxis) leads to death or disability in only 3% of cases, whereas intracranial bleeding such as ICH leads to death or disability 76% of cases.[5]

Even without anticoagulation, ICH is the deadliest form of stroke,[6–9] and if the patient

TABLE 1

Risk factors for hematoma expansion[a]

Early presentation[26–28,33,34]
"Spot sign" (contrast extravasation on computed tomography)[27,29,30,32,35]
Larger initial hemorrhage[26,27]
Warfarin (Coumadin) use or elevated international normalized ratio[10,34]
Larger intraventricular volume[26]
Heterogeneity of hematoma[31]
Elevated D-dimer[36]
Reduced platelet activity[37] (although not use of antiplatelet agents)[26,38–40]

[a]Factors are shown in approximate order of the number of validating studies.

Urgent reversal of anticoagulation is standard in the acute phase of ICH

has been taking warfarin, the risk of disability and death is substantially higher.[6,10] Warfarin has a striking effect on the incidence and outcomes of ICH. While the overall incidence of ICH in the general population is approximately 25 per 100,000 person-years, the incidence in patients on warfarin is exponentially higher, at 2 to 3 per 100 per year, and appears to be increasing.[11,12] In addition, once ICH occurs, the risk of death is up to twice as high in those on warfarin.[6] The bulk of this effect is likely due to a higher risk of ongoing bleeding after the event.[10,13–16]

Major risk factors for ICH in patients taking oral anticoagulants include a higher international normalized ratio (INR) and older age.[11,17]

TWO KEY QUESTIONS

Once a patient is diagnosed with warfarin-related ICH, clinicians typically take urgent measures to restore normal coagulation, hoping to limit ongoing bleeding and improve outcome.[18,19]

The higher the INR at presentation, the greater the risk of death.[6] In addition, in retrospective studies, some authors have noted that earlier correction of the INR is associated with better outcome.[14,16]

While emergency reversal of warfarin is widely considered standard treatment in the acute phase,[20–24] concern persists about its safety in patients at high risk of thromboembolism.

Until the results of clinical trials are available, decisions about whether to reverse and when to resume anticoagulation hinge on two questions:

- In the acute phase, how does the risk of further bleeding (hematoma expansion) compare with the short-term risk of thromboembolism?
- In the chronic phase, how does the risk of recurrent hemorrhage compare with the excess risk of thromboembolism if the patient does not resume anticoagulation therapy?

ACUTELY, THE RISK OF BLEEDING OUTWEIGHS THAT OF CLOTTING

High risk of hematoma expansion after ICH

Unfortunately, continued bleeding is common after ICH. In patients who present within 3 hours of symptom onset, 26% of hematomas expand more than 33% over the first hour, and another 12% expand this amount over the next 20 hours.[6] In warfarin-associated ICH, up to 50% of patients develop this level of hematoma expansion, but it appears to take place over a more prolonged period of time.[10,13–16] Over 70% of patients presenting acutely develop at least some amount of expansion within 24 hours.[25] Therefore, the risk of hematoma expansion in the first 24 hours is likely so high that patients cannot safely receive anticoagulants during this time frame.

But not all patients are at equal risk of hematoma expansion. Several features are associated with higher risk (TABLE 1)[10,26–40]:

- A large hematoma volume on presentation is a significant predictor of expansion, possibly reflecting a more severe underlying insult.[26,27]
- Early presentation, especially within 3 hours of symptom onset, also appears to mark those at higher risk, presumably because such patients undergo computed tomography (CT) while still bleeding.[26,27]
- For those on warfarin, a higher INR is a significant predictor, not just of higher risk, but also of a more delayed expansion.[10,28]
- Certain radiographic findings indicate higher risk. One is the "spot sign," ie, contrast extravasation after contrast-enhanced

CT[27,29–31] (FIGURE 1). Apparently, the more spots present, and the denser the contrast, the greater the risk, an observation that has led to a proposed "spot-sign score" that may predict both expansion and poor outcome.[32,41]

Given the high risk of hematoma expansion in the early phase, and given our inability to predict hematoma expansion, most authorities recommend immediate reversal of anticoagulation after diagnosis.[42–44] Reversal of anticoagulation typically includes intravenous vitamin K, which begins to act within several hours, and repletion of coagulation factors, which act within minutes (prothrombin complex concentrates and recombinant factor VIIa [NovoSeven]) or a few hours (fresh frozen plasma).[1]

Dosages:

- Vitamin K 5 to 10 mg intravenously
- Prothrombin complex concentrates 10 to 50 U/kg
- Recombinant factor VIIa 40 to 80 µg/kg
- Fresh frozen plasma 10 to 50 U/kg.

Risk of thromboembolism after ICH: Ongoing and cumulative

Thromboembolism after ICH is a major concern, for two main reasons.

First, patients on oral anticoagulation typically have a preexisting risk factor and are thus at higher risk of a thromboembolic event, particularly while they are off anticoagulation. Patients with atrial fibrillation or a mechanical valve are at risk of arterial events such as ischemic stroke, whereas patients with a known venous thromboembolic condition such as deep venous thrombosis or pulmonary embolism are at risk of extension of the thrombosis or recurrence of a venous thrombotic event.

Second, ICH itself increases the risk of arterial and venous thromboembolic events. Including patients not previously on anticoagulation, this risk is as high as 7% during the initial hospitalization and 9% during the first 90 days.[45,46] Worth noting is that patients who previously received anticoagulant drugs (and who are off this therapy in the acute phase) are at no higher risk of thromboembolism compared with those who never received anticoagulants.[45]

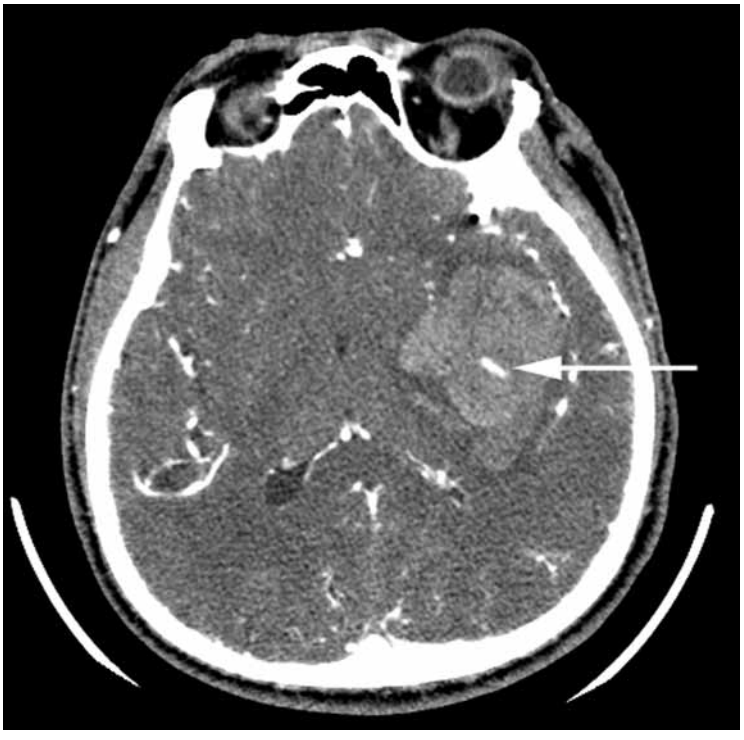

FIGURE 1. The "spot sign" (arrow), contrast extravasation after contrast-enhanced computed tomography, is associated with a high risk of hematoma expansion.

However, while the risk of hematoma expansion is highest at presentation and then decreases with time, the risk of thromboembolism (particularly venous thromboembolism) is ongoing and cumulative. Arterial thromboembolism is more likely to occur early, within the first week, whereas venous thromboembolism can occur later.[45]

The proposed 'spot-sign score' may predict both expansion and poor outcome

Overall, studies have estimated the short-term risk of pulmonary embolism to be 1% to 2%, deep venous thrombosis 1% to 4%, myocardial ischemia about 2%, and cerebral ischemia 2% to 3%.[45,46] However, when patients are actively screened, the incidence of asymptomatic deep venous thrombosis is found to be as high as 16% in the first 10 days,[47] and evidence of myocardial ischemia can be detected in up to 27% of patients.[48]

Therefore, the risk of hematoma expansion appears to be high and the risk of thromboembolism appears to be low during the first day after ICH. Over the next days, as the risk of hematoma expansion recedes, this ratio shifts.

Studies of in-hospital anticoagulation after ICH

The data on restarting oral anticoagulation in the acute phase are sparse. In practice, clinicians typically start heparinoids in low subcutaneous doses to prevent deep venous thrombosis and, after the first few days or a week, consider increasing to a full anticoagulation dose or starting an oral anticoagulant and subsequently discontinuing the heparin when the INR is in the therapeutic range (see discussion below).

ICH patients in general may benefit from starting prophylactic-dose heparin therapy early. One randomized trial found that starting heparin in a low subcutaneous dose the day after an ICH decreased the risk of thromboembolism without increasing the risk of rebleeding.[49] Another study also found no increased risk of rebleeding with early prophylactic-dose subcutaneous heparin.[50]

As the benefit appears to outweigh the risk, national guidelines suggest starting subcutaneous heparin early in all ICH patients, including those not previously on warfarin.[42,43]

Commonly used heparinoid regimens include unfractionated heparin 5,000 units subcutaneously twice a day; enoxaparin (Lovenox) 40 mg once a day; and dalteparin (Fragmin) 5,000 units once a day.[51] In addition, all patients should receive optimal mechanical thromboprophylaxis, including graduated compression stockings or intermittent pneumatic compression stockings, or both.

Antihypertensive therapy likely reduces the risk of recurrence in patients with hypertensive hemorrhage

LONG-TERM MANAGEMENT: ICH RECURRENCE VS THROMBOEMBOLISM

Risk of ICH recurrence on warfarin is not precisely known

Overall, the risk of ICH recurrence is about 1% at 3 months, and warfarin likely increases this risk.[42,52] Unfortunately, the risk of ICH recurrence in patients on anticoagulation therapy after a first ICH is not clear, and no population-based study has clarified this risk. Therefore, the best we can do at present is to try to estimate the risk of recurrent warfarin-related ICH by separately examining two issues:

- The risk of ICH recurrence in general
- The risk of major bleeding (including ICH) in the general population of patients on warfarin.

The risk of ICH recurrence in general is about 2% to 4% per patient-year.[52–54] However, this risk appears to be a function of the underlying vasculopathy. ICH location is often used as a surrogate for underlying cause. Most ICHs in deep hemispheric (basal ganglia, thalamus) or brainstem territories are likely caused by hypertensive vasculopathy, whereas lobar ICH is often associated with cerebral amyloid angiopathy.[52–54] Presumably because of this distinction, ICH in a deep location recurs in about 2% of cases per year, compared with 4% for lobar ICH.[53] The presence and number of microbleeds on T2-weighted gradient-echo magnetic resonance imaging appear to predict ICH recurrence; microbleeds likely are markers of more severe or widespread underlying vasculopathy.[55–57]

A genetic risk factor for the recurrence of lobar ICH is apolipoprotein E genotype[58]; future studies may highlight genetic variations that specifically modify the risk of warfarin-related ICH.[59] Unfortunately, there is currently no way to modify the risk of ICH associated with cerebral amyloid angiopathy. On the other hand, in patients with hypertensive hemorrhage, antihypertensive therapy likely reduces the risk of recurrent ICH. One randomized controlled trial showed that such therapy decreased the risk of ICH by more than half.[60]

The risk of major bleeding in the general population of patients on warfarin may be 2% to 3% per year and is likely higher in the first month.[11] The risk is higher in older patients and if the INR rises above 4.0.[11,17] For some patients, it is possible to estimate the likelihood of major bleeding using validated decision-support tools that include factors such as age, sex, and medical history.[11,61–64]

Given the lack of data specifically addressing the risk of ICH recurrence on warfarin, the clinician is left to try to extrapolate this risk from available data using specific patient characteristics that modify the presumed risk. For example, one can combine factors such as ICH location (or better yet, the underlying cause) with decision-support tools that predict the risk of major bleeding. Close control of both blood pressure and the INR appears

especially critical for patients receiving anticoagulation after ICH.[11,60,65] Still, the risk does not disappear with good INR control, and most patients with anticoagulation-related ICH present with INRs within the therapeutic range.[5,10,65]

Long-term risk of thromboembolism depends on underlying condition

In the long term, the risk of thromboembolism depends on the reason for which the patient was originally given anticoagulation. In addition, many patients with ICH suffer decreased mobility and are therefore at higher risk of venous thromboembolism than before their event.

Nonvalvular atrial fibrillation is the most common indication for anticoagulation. For these patients, the risk of ischemic stroke is 2% to 5% per year.[66,67] The system usually used to stratify this risk is $CHADS_2$, an acronym for five key risk factors:

- Congestive heart failure (1 point)
- Hypertension (1 point)
- Age over 75 (1 point)
- Diabetes mellitus (1 point)
- Prior stroke or transient ischemic attack (2 points).

The annual risk of stroke ranges from 1.9% (score of 0) to 18.2% (score of 6).[68,69] In patients with nonvalvular atrial fibrillation, the excess risk of ischemic stroke without anticoagulation must be weighed against the risk of ICH recurrence.

A mechanical heart valve, another common indication, carries a risk of ischemic stroke of about 4% per year.[70] A mechanical valve is traditionally considered an absolute indication for anticoagulation. However, patients with lobar ICH face a risk of recurrence that is greater than 4% per year, and so the risks of resuming anticoagulation may well outweigh the benefits.

Heart failure may be associated with a risk of ischemic stroke of 1% to 4% per year, and this is likely a function of disease severity.[71]

Venous thromboembolism. The risk of recurrent venous thromboembolism in patients with deep venous thrombosis or pulmonary embolism is around 4% per year.[72] Given that ICH itself confers a 2% to 3% risk of these conditions, the rate of recurrence of deep venous thrombosis may well be much higher in those ICH patients who have also already had deep venous thrombosis.

TABLE 2

Studies of resuming anticoagulation after intracerebral hemorrhage (ICH)

AUTHORS AND TREATMENT	NO. OF PATIENTS	THROMBOEMBOLIC EVENTS	RECURRENT ICH
De Vleeschouwer et al[74]			
Warfarin restarted	25	0 (0%)	1 (4%)
Warfarin not restarted	81	8 (10%)	7 (9%)
Claassen et al[73]			
Warfarin restarted	25	6 (24%)	3 (12%)
Warfarin not restarted	27	13 (48%)	0 (0%)
Butler et al[75]			
Warfarin restarted	13[a]	3 (23%)	1 (8%)
Bertram et al[76]			
Warfarin restarted	15[b]	5 (33%)	3 (20%)

[a] All with prosthetic valves
[b] All at high risk

Data on resuming oral anticoagulation after ICH

Several studies have examined the outcomes when oral anticoagulants were resumed after ICH (TABLE 2),[73–76] but experts differ on when these drugs should be resumed (eg, between 1 and 10 days after onset), or even whether they should be resumed at all.[19]

Notably, an analysis of 52 patients found a high risk of ICH recurrence (and gastrointestinal bleeding) in patients who restarted warfarin, and a high risk of myocardial infarction and ischemic stroke in those who did not restart, with neither strategy demonstrating a clear benefit in the rate of death or disability.[73] All patients with a thromboembolic event were being treated for a previous event, suggesting that secondary prevention is a stronger indication for anticoagulation than primary prevention in this population.[73]

Most patients with anticoagulation-related ICH have a presenting INR within the therapeutic range

IF AND WHEN TO RESTART

Two major questions to consider are whether the benefits of restarting anticoagulation outweigh the risk, and if so, when and how should anticoagulation be restarted?

TABLE 3

Factors arguing for and against resuming anticoagulation after intracerebral hemorrhage

FACTOR[a]	FOR	AGAINST
Etiologic factor		
Hypertension-related hemorrhage, hypertension adequately controlled	X	
Cerebral amyloid angiopathy		X
Microvascular risk		
Microbleeds on gradient-echo magnetic resonance imaging		X
Indication for anticoagulation		
Secondary prevention	X	
Primary prevention		X
Atrial fibrillation, high $CHADS_2$ score	X	
Atrial fibrillation, low $CHADS_2$ score		X
Mechanical heart valve	X	
Hypercoagulable state	X	
Anticipated difficulty controlling the international normalized ratio		X

[a]These features are neither indications nor contraindications, but rather factors to consider.
$CHADS_2$ = Acronym for scoring system used to assess stroke risk based on key risk factors: congestive heart failure, hypertension, age over 75, diabetes mellitus, and prior stroke or transient ischemic attack.

The risks of restarting warfarin are high on the first day, but much lower after several days

Whether to restart anticoagulation

As for the risk-benefit ratio, many think that anticoagulation should be restarted only with extreme caution and possibly only in those with deep ICH or a documented history of thromboembolism.[19]

In one decision analysis examining whether to restart anticoagulation after ICH in patients with atrial fibrillation, the risk of thromboembolism would need to exceed 7% per year to justify restarting anticoagulation after deep ICH,[67] and no risk level was high enough to justify restarting anticoagulation after lobar ICH.

For patients at sufficiently high risk of ICH recurrence, antiplatelet treatment is probably safer, as antiplatelet agents carry a substantially lower risk of bleeding.[54,77–79] The American Heart Association comments that for nonvalvular atrial fibrillation, long-term anticoagulation should be avoided after spontaneous lobar ICH, but that antiplatelet agents may be considered.[42] They note that anticoagulation after nonlobar ICH may be considered depending on the indication.[42]

The decision to restart anticoagulation may also be a function of whether the underlying risk factor is a temporary one. For example, atrial fibrillation or a mechanical heart valve confers a long-term, ongoing risk of arterial thromboembolism, and such patients would not normally be considered for a short course of warfarin therapy. However, isolated deep vein thrombosis may only require anticoagulation for a limited time, such as 3 to 6 months.[80] Perhaps for such patients the long-term outcome is maximized with a narrowly defined, temporary course of anticoagulation.

When to restart anticoagulation

As for when to restart, it is not certain how long after symptom onset the risk of ongoing bleeding continues. Clearly, the risk is high on the first day, but small after the first few days.

The European Stroke Initiative recommends that patients with a strong indication for anticoagulation, such as a history of embolic stroke with atrial fibrillation, should be restarted on warfarin after 10 to 14 days, depending on the risk of thromboembolism and ICH recurrence.[43]

The American Heart Association suggests that, in patients with a very high risk of thromboembolism for whom restarting warfarin is considered, warfarin may be restarted 7 to 10 days after ICH onset.[42]

The American College of Chest Physicians recommends starting prophylactic-dose heparin the day after an ICH, with no clear guidance on restarting warfarin.[81]

ALTERNATIVES TO WARFARIN

Alternatives to warfarin that show promise in reducing bleeding risk include factor Xa and direct thrombin inhibitors, which may reduce the risk of thromboembolism to an extent similar to that of warfarin, but with fewer bleeding complications.[82]

In patients with atrial fibrillation, the direct thrombin inhibitor dabigatran (Pradaxa) was shown to prevent ischemic stroke to a similar or greater degree than warfarin, with fewer bleeding complications.[83] Further patient follow-up is under way to ensure that this drug does not cause liver problems, as did a similarly designed predecessor.[84]

The availability of this and other agents in various stages of development[82] will probably not make warfarin extinct. Rather, they may change the "tipping point," the threshold at which the risk of thromboembolism is high enough to justify the risks associated with restarting warfarin therapy. In addition, clinical decision tools clarifying the individual patient's risk of thromboembolism vs the risk of ICH recurrence will help physicians tailor the therapy to the patient.

For the moment, in situations in which the decision is difficult, maximizing the use of antiplatelet agents offers the best hope.[85]

RECOMMENDATIONS IN LIEU OF GUIDELINES

No guideline can broadly cover every clinical scenario. Many factors go into assessing a patient's risk of hematoma expansion or recurrent hemorrhage (TABLE 3) and the extent to which anticoagulation can reduce the risk of thromboembolism.

In the short term, most patients with ICH will likely benefit from acute reversal of anticoagulation, followed by gradual reinstitution of prophylactic-dose anticoagulation after the first 24 to 72 hours.

In the long term, many patients with lobar hemorrhage, cerebral amyloid angiopathy, or other risk factors may remain at higher risk of anticoagulant-related ICH recurrence than of fatal or disabling thromboembolic events and would therefore be best managed without anticoagulants. Conversely, those with deep hemispheric ICH, hypertension that can be well controlled, and a high risk of disabling thromboembolism may receive a net benefit from restarting anticoagulation.

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