What to do after the bleed: resuming anticoagulation after major bleeding

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Resuming anticoagulation therapy after a potentially life-threatening bleeding complication evokes high anxiety levels among clinicians and patients trying to decide whether resuming oral anticoagulation to prevent devastating and potentially fatal thromboembolic events or discontinuing anticoagulation in hopes of reducing the risk of recurrent bleeding is best. The available evidence favors resumption of anticoagulation therapy for gastrointestinal tract bleeding and intracranial hemorrhage survivors, and it is reasonable to begin postbleeding decision making with resuming anticoagulation therapy as the default plan. After considering factors related to the index bleeding event, the underlying thromboembolic risk, and comorbid conditions, a decision to accept or modify the default plan can be made in collaboration with other care team members, the patient, and their caregivers. Although additional information is needed regarding the optimal timing of anticoagulation resumption, available evidence indicates that waiting ~14 days may best balance the risk of recurrent bleeding, thromboembolism, and mortality after gastrointestinal tract bleeding. When to resume anticoagulation after intracranial hemorrhage is less clear, but most studies indicate that resumption within the first month of discharge is associated with better outcomes.

Learning Objectives

- Distinguish which patients should resume anticoagulation therapy after an episode of anticoagulation therapy–related major bleeding based on patient-specific factors
- Formulate an opinion regarding the optimal timing of anticoagulation therapy resumption after gastrointestinal tract bleeding and intracranial hemorrhage

Introduction

Bleeding commonly complicates oral anticoagulation (OAC) therapy.[1] Annual bleeding rates during OAC range from 2% to 5% for major bleeding, 0.5% to 1% for fatal bleeding, and 0.2% to 0.4% for intracranial bleeding.[2] Common presentations include gastrointestinal tract bleeding (GIB), intracranial hemorrhage (ICH), hematuria, and epistaxis.[1] Case mortality rates associated with anticoagulation-related major bleeding are as high as 13.4%, underscoring the seriousness of this common complication.[3] Resuming a therapy that just contributed to a potentially life-threatening bleeding complication seems risky and evokes high anxiety levels among clinicians and patients trying to decide whether resuming oral anticoagulation to prevent devastating and potentially fatal thromboembolic events or discontinuing anticoagulation in hopes of reducing the risk of recurrent bleeding is best.[4] Consensus guidelines provide limited guidance regarding the optimal timing for patients deemed suitable for anticoagulation resumption after major bleeding. Conducting randomized clinical trials to guide clinical decision making regarding oral anticoagulation after major bleeding is logistically challenging, if not impossible.[4] Therefore, the evidence base pertaining to anticoagulation therapy resumption after major bleeding summarized in this article is derived from observational studies.

Gastrointestinal tract bleeding

Gastrointestinal tract bleeding complicates long-term anticoagulation therapy in 5% to 15% of patients[5] and is probably the most commonly occurring major bleeding complication in patients receiving anticoagulation therapy.[1] Gastrointestinal tract bleeding is rarely acutely fatal but often initiates a cascade of events that contributes to the aforementioned high-case fatality rates associated with major bleeding.[3]

Results from 4 observational studies (N = 5377) assessing outcomes associated with resumption of anticoagulation after GIB have been published since 2012.[5-8] In general, these studies identified patients surviving anticoagulation-related GIB and then compared rates of recurrent GIB, thromboembolism, and all-cause mortality between patients resuming and not resuming anticoagulation therapy over follow-up periods ranging from 90 days to 5 years. Three important observations can be discerned from careful review of these studies: first, the risk that recurrent GIB is not significantly increased in patients resuming anticoagulation (Table 1); second, resuming anticoagulation is associated with a significant reduction in the likelihood of thromboembolic events; and third, overall mortality was significantly lower among patients resuming anticoagulation therapy.

We studied patients from the Kaiser Permanente Colorado Clinical Pharmacy Anticoagulation Service with warfarin-associated GIB (Table 1).[6] Among 442 included patients, 58% continued warfarin after the bleeding event (including 41 patients in whom warfarin therapy was never stopped). The median (interquartile range [IQR]) time to resumption of warfarin was 4 days [2-9]). Warfarin was resumed more often in patients taking warfarin for mechanical heart valves and in patients with bleeding hemorrhoids and less often in older patients and those in whom the GIB source was not identified.

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Table 1. Outcomes after anticoagulation-related gastrointestinal tract bleeding in patients who do and do not resume anticoagulation therapy

Study	Indication for anticoagulation	Anticoagulant	Follow-up period	Adjusted HR-TE (95% CI)	Adjusted HR-recurrent GIB (95% CI)	Adjusted HR all-cause mortality (95% CI)
Witt 2012, N = 442[6]	AF, VTE, MVR, Other	Warfarin	90 d	0.05 (0.01-0.58)	1.32 (0.50-3.57)	0.31 (0.15-0.62)
Qureshi 2014, N = 1329[5]	AF	Warfarin	1-y (TE) 90-d (GIB) 2-y (ACM)	0.71 (0.54-0.93)	1.18 (0.94-1.10)	0.67 (0.56-0.81)
Staerk 2015, N = 3409[7]	AF	Single OAC*	5-y	0.41 (0.31-0.54)	1.22 (0.84-1.77)	0.39 (0.34-0.46)
		Single antiplatelet†		0.76 (0.61-0.95)	1.19 (0.82-1.74)	0.76 (0.68-0.86)
		OAC + antiplatelet*		0.54 (0.36-0.82)	1.34 (0.79-2.28)	0.41 (0.32-0.52)
		Dual antiplatelet‡		0.79 (0.34-1.84)	0.58 (0.08-4.30)	0.88 (0.57-1.36)
Sengupta 2015, N = 197[8]	Various	Warfarin	90 d	0.12 (0.006-0.81)	2.17 (0.86-6.67)	0.63 (0.22-1.89)

ACM, all-cause mortality; AF, atrial fibrillation; HR, hazard ratio; MVR, mechanical valve replacement; TE, thromboembolism; VTE, venous thromboembolism.
*Mainly Vitamin K antagonists.
†Aspirin or $P2Y_{12}$ antagonists.
‡Aspirin and $P2Y_{12}$ antagonists.

Patients who either never interrupted warfarin therapy or resumed therapy within 14 days of GIB experienced no thrombosis, but the rate of recurrent GIB was significantly increased when warfarin therapy was resumed within 7 days. The death rate during follow-up was lowest when warfarin therapy was resumed between 15 and 90 days after the index GIB. The observed higher overall mortality in patients who did not resume warfarin was not readily explained, given that only 3 of the 37 deaths in this group were attributed to thrombosis. Higher mortality persisted after adjusting for possible confounding factors using multivariable and propensity score analyses and modeling that adjusted for intensive care unit admission as well as blood transfusions—interventions indicating more serious initial GIB.

The retrospective cohort study published by Qureshi et al evaluated 1329 patients from the Henry Ford Health System Anticoagulation Management Service diagnosed with major GIB while taking warfarin (Table 1).[5] Important differences from the Witt et al study included the exclusion of patients who died within 72 hours of GIB, were in hospice, had an indication for anticoagulation other than nonvalvular atrial fibrillation, and in whom warfarin was interrupted for <48 hours. There were 653 patients (49%) who resumed taking warfarin after a median duration of 50 days (IQR 21-78) vs 4 days in the study by Witt et al. The risk of recurrent GIB was significantly greater if warfarin was resumed within the first week of major GIB; however, lower mortality and thromboembolism risk was associated with earlier warfarin resumption. Failure to resume anticoagulation was a result of physician refusal because of the previous GIB in 37% of patients.

A Danish nationwide cohort study published by Staerk et al examined recurrent GIB, thromboembolism, and all-cause mortality risks associated with restarting antithrombotic treatment after GIB in patients with atrial fibrillation.[7] This study also evaluated resuming antithrombotic agents other than vitamin K antagonists (VKA), including aspirin, $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, or ticagrelor), direct oral anticoagulants (DOACs), and combinations of these agents (Table 1). Follow up continued for 5 years but did not commence until 90 days after the index GIB. This blanking period was deemed necessary to remove uncertainty regarding the timing of antithrombotic therapy resumption stemming from the use of administrative data without confirmatory chart reviews. Detailed information regarding clinical outcomes was not available. Of 3409 patients available for analysis after the blanking period, 924 (27%) did not resume antithrombotic therapy after GIB. This rate is lower than previous studies, but antiplatelet therapy was counted as resumption, an element unique to this study. Resuming oral anticoagulant monotherapy was associated with the lowest all-cause mortality and thromboembolism rates (Table 1). Resuming or switching treatment to oral anticoagulant monotherapy was associated with the greatest effectiveness and relative safety independent of pre-index GIB antithrombotic treatment. Unfortunately, the number of patients using DOACs was too small to allow conclusions regarding their use in this setting. The use of proton pump inhibitors in groups who resumed antithrombotic therapy ranged from 90.0% to 96.1%.

These results strongly suggest that most patients with anticoagulation-related GIB should probably resume anticoagulation therapy once the acute event has been managed. A similar conclusion was reached by authors of a meta-analysis, including 2 of these studies that showed warfarin resumption was associated with a significant reduction in thromboembolic events (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.52-0.88). There was a significant reduction in mortality (HR 0.76, 95% CI 0.66-0.88) and a small nonsignificant increase in recurrent GIB for patients restarting warfarin compared with those who did not (HR 1.20, 95% CI 0.97-1.48).[9] The optimal time to resume anticoagulation therapy remains unclear, but based on the available information, it appears that around 2 weeks may provide the best balance among GIB recurrence, thromboembolism, and mortality risks. Prescribing proton pump inhibitor therapy—histamine-2 receptor antagonists (eg, ranitidine, cimetidine) provide less protection, at least initially, should be given consideration, especially for patients with GIB related to peptic ulcer disease.[10]

Intracranial hemorrhage

Compared with the general population, anticoagulation therapy increases ICH risk between ten- to 15-fold and anticoagulated patients experiencing ICH also tend to be older and carry a higher burden of comorbid illness.[11] Resuming anticoagulation in patients with recent life-threatening ICH is a difficult proposition, and carefully evaluating competing recurrent ICH and thromboembolic risks is especially challenging.

As is the case for GIB, the evidence for anticoagulation resumption after ICH is derived from observational studies and subject to the confounding and bias inherent in this type of research. Two studies

Table 2. Outcomes after anticoagulation-related intracranial bleeding in patients who do and do not resume anticoagulation therapy

Study	Indication for anticoagulation	Anticoagulant	Follow-up period	HR-TE (95% CI)	HR-recurrent ICH (95% CI)	HR all-cause mortality (95% CI)
Kuramatsu 2015, N = 719[17]	AF, VTE, MVR, Other	VKA	1-y	NR*	NR†	0.26 (0.13-0.53)‡
Witt 2015, N = 160[18]	AF, VTE, MVR, Other	Warfarin	1-y	0.28 (0.06-1.27)§	0.47 (0.10-2.30)§	0.76 (0.30-1.89)¶
Nielsen 2015, N = 1752[19]	AF	VKA, DOAC Antiplatelet therapy	1-y	0.59 (0.33-1.03)¶ 0.98 (0.65-1.49)¶	0.91 (0.56-1.49)¶ 0.60 (0.37- 1.03)¶	0.55 (0.37-0.82)¶ 0.90 (0.67-1.21)¶

NR, not reported.

*Resumed VKA, 9/172 (5.2%) vs did not resume VKA, 82/547 (15.0%); $P < .001$.

†Resumed VKA, 14/172 (8.1%) vs did not resume VKA, 36/547 (6.6%)—also included extracranial bleeding events; $P = 0.48$.

‡Propensity score-matched AF cohort.

§Not adjusted because of small number of events.

¶Adjusted analysis.

published in 2010 reached very different conclusions regarding the timing of anticoagulation resumption after ICH. Hawryluk et al performed a systematic review of studies evaluating anticoagulation resumption in ICH survivors.[12] Data from 63 studies detailing 492 patients with various indications for anticoagulation were pooled for analysis and revealed a significant difference in recurrent ICH and thromboembolic risk based on when anticoagulation was resumed. The authors concluded that a 72-hour cutoff for anticoagulation resumption seemed to separate recurrent ICH from thromboembolic complications, and therefore resuming anticoagulation about 72 hours after initial presentation should be considered. It should be noted that others suggest that >70% of patients with acute ICH develop at least some hematoma expansion within 24 hours. 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.[13] In contrast, Majeed et al reviewed medical records from 234 patients from 3 tertiary centers in Sweden and Canada with warfarin-related ICH surviving at least the first week after discharge.[14] Warfarin indications included atrial fibrillation, mechanical heart valves, left ventricle thrombus, or previous ischemic stroke. Cox modeling was used to estimate combined cumulative 3-year risk of either recurrent ICH or ischemic stroke for a range of warfarin resumption times. The authors concluded that post-ICH warfarin resumption should be delayed at least a month and may be optimal between week 10 and week 30.

Yung et al followed a cohort of consecutive patients with warfarin-related ICH (including intracerebral bleeding, approximately one third of which was lobar, and subarachnoid hemorrhages).[15] Among the 284 patients studied, warfarin was resumed during the index hospitalization in 91 (32%) patients. Mortality rates at 30 days and 1 year were lower in those resuming warfarin during the index hospitalization (32% vs 54%, $P < .001$ and 48% vs 61%, $P = .04$, respectively), with no increase in bleeding risk. Multivariable analysis indicated that resuming anticoagulation during the index ICH admission was protective for mortality (30-day odds ratio [OR] 0.49, 95% CI 0.26-0.93), whereas intraventricular hemorrhages, ICH associated with more severe categorization scores, and international normalized ratios (INRs) >3.0 at ICH presentation all predicted increased mortality risk.

Poli et al evaluated the risk of recurrent ICH in 267 survivors of VKA-related ICH gathered from 27 Italian anticoagulation centers all of whom resumed VKA therapy.[16] Although this study did not include a comparator group of patients not resuming VKA therapy, useful factors that may help identify patients at higher recurrent ICH risk (male sex, hypertension, prosthetic heart valves, previous ischemic stroke, renal failure, cancer, and ICH classified as spontaneous) is provided.

Three recent studies evaluating outcomes associated with resuming anticoagulation therapy after ICH are summarized in Table 2.[17-19] The study by Kuramatsu et al investigated the association between resuming anticoagulation and incidence of hemorrhagic and ischemic complications after VKA-related ICH in 719 patients surviving to discharge from 19 German tertiary care centers.[17] The median time to VKA resumption was 31 days (IQR 18-65) in the 24% of patients resuming anticoagulation. Anticoagulation resumption rates were highest for patients receiving VKA for mechanical heart valves (68.0% resumed therapy compared with 19.4% of patient with atrial fibrillation). Hazard ratios were not calculated for ischemic complications or recurrent ICH, but the incidence of ischemic complications was significantly less in those resuming anticoagulation without increasing recurrent ICH (Table 2). Mortality was significantly lower after anticoagulation resumption in the subgroup of patients with atrial fibrillation in a propensity score matching analysis that included age, ICH volume, intraventricular hemorrhage, hematoma growth, stroke severity, $CHADS_2$ score, and pre- and postdischarge functional capacity (HR 0.26, 95% CI 0.13-0.53). Incident ICH location (lobar vs deep) was similar between patients resuming and not resuming VKA, indicating that this factor did not appear to influence the decision to resume anticoagulation.

We determined incidences of recurrent ICH, thrombosis, and death in 160 patients resuming and not resuming warfarin therapy after surviving incident ICH.[18] The median time from index ICH to warfarin resumption was 14 days (IQR 7-63) in the ~33% resuming anticoagulation. Compared with patients not resuming warfarin, patients with mechanical heart valve replacements resumed warfarin more frequently (1.9% vs 38.9%, respectively). The decision to resume warfarin therapy did not appear to be influenced by whether intracerebral bleeding location was categorized as deep or lobar. Surprisingly, recurrent ICH occurred in a numerically greater, but statistically nonsignificant, proportion of patients who did not resume warfarin therapy (7.6% vs 3.7%, $P = .497$). Patients who did not resume warfarin had a threefold higher (12.3% vs 3.7%, $P = .092$) and approximately twofold higher (31.1% vs 18.5%, $P = .089$) rates of thrombosis and all-cause mortality, respectively. Although the study was likely underpowered to detect significant differences between groups according to warfarin resumption status, the reported outcomes were largely similar to the Kuramatsu study.[17]

Table 3. Clinical characteristics arguing for or against resuming anticoagulation after major bleeding

Clinical characteristic	For	Against
Bleed-related characteristics		
Known, correctable source	+++	
Known, uncorrectable source	+	
Unknown source		+
Deep ICH location, blood pressure–controlled	++	
Lobar ICH location, MRI evidence of microbleeding		+
Indication for anticoagulation		
Mechanical heart valve	+++	
Idiopathic or recurrent VTE	+++	
Provoked VTE, completed 3 mo of therapy		+++
VTE + protein C/S or antithrombin deficiency or APLA syndrome	++	
Atrial fibrillation, prior history of stroke or higher $CHADS_2$ or CHA_2DS_2-VASc score	+++	
Atrial fibrillation, lower $CHADS_2$, or CHA_2DS_2-VASc score	+	
Atrial fibrillation, no additional stroke risk factors		+++
Other characteristics		
History of anticoagulation therapy nonadherence		+
Previously unstable INR control despite adequate adherence		+
Renal failure		+
Poor prognosis, limited life expectancy		+

Adapted from Goldstein and Greenberg.[13]

$CHADS_2$, scoring system used to assess stroke risk based on key risk factors: congestive heart failure, hypertension, age over 75 y, diabetes mellitus, and prior stroke or transient ischemic attack; CHA_2DS_2-VASc, scoring system used to assess stroke risk based on same factors as $CHADS_2$ with the addition of vascular disease age over 65 y, and female sex; MRI, magnetic resonance imaging.

+++, consider very strongly; ++, consider strongly; +, consider.

Nielsen et al used nationwide Danish registries to track outcomes relative to whether antithrombotic therapy was resumed or not among 1752 patients with atrial fibrillation after ICH.[19] A unique aspect of this study was inclusion of a cohort of patients resuming antiplatelet therapy rather than anticoagulation therapy (Table 2). A 6-week blanking period between the index ICH and outcome assessment was used similar to the aforementioned Danish registry GIB study.[7] Median time elapsing between hospital discharge and first anticoagulant prescription was 34 days; however, patients could have resumed anticoagulation therapy sooner using medication they had on hand. As was seen in Kuramatsu[17] and Witt,[18] patients not resuming anticoagulation treatment had higher thromboembolic and all-cause mortality rates without increased risk of recurrent ICH. Outcomes associated with antiplatelet therapy resumption were similar to those in the group not resuming any antithrombotic therapy, casting doubt on whether the common practice of switching patients formerly on anticoagulation therapy to antiplatelet therapy (mainly aspirin) after ICH is best for patients.

Other bleeding

No information is available to guide whether to resume anticoagulation therapy that is interrupted secondary to nongastrointestinal tract or intracranial bleeding (eg, hematuria or severe epistaxis). However, general principles extrapolated from the available evidence form a reasonable framework for clinical decisions regarding anticoagulation resumption after bleeding events (Table 3).

For example, a patient receiving warfarin therapy for a mitral mechanical valve presenting with significant hematuria resulting from pyelonephritis should probably resume anticoagulation therapy once the bleeding complication has been controlled and antimicrobial therapy initiated. In this case, the source of bleeding is known and can be corrected and the underlying thromboembolic risk is high. In contrast, not resuming anticoagulation therapy may be the best option for a patient with a remote history of deep vein thrombosis with poorly controlled INRs who is seen frequently in the emergency department for recurrent severe nosebleeds from a perforated septum that cannot be corrected. The patient's individual preferences and values may well affect the decision to resume anticoagulation therapy if the risk-benefit tradeoffs are relatively well balanced.

Conclusion

The available evidence favors resumption of anticoagulation therapy for GIB and ICH survivors, and it is reasonable to begin postbleeding decision making, with resuming anticoagulation therapy as the default plan. After considering factors related to the index bleeding event, the underlying thromboembolic risk, and comorbid conditions, a decision to accept or modify the default plan can be made in collaboration with other care team members, the patient, and their caregivers. Table 3 summarizes clinical characteristics arguing for or against anticoagulation therapy resumption. Although additional information is needed regarding the optimal timing of anticoagulation resumption, available evidence indicates that waiting ~14 days may best balance the risk of recurrent bleeding, thromboembolism, and mortality after GIB. When to resume anticoagulation after ICH is less clear, with evidence ranging from 72 hours to 30 weeks. One study in high thromboembolic risk patients concluded that 1 to 2 weeks off anticoagulation therapy was relatively safe,[20] and most studies indicate resumption within the first month of discharge is associated with better outcomes.[15,17-19] Comparatively little information regarding DOAC therapy after major bleeding is available to guide decision making, a situation that will hopefully change soon with increasing use of these agents in clinical practice. However, it should be noted that in the recently published REVERSE AD study,[21] all (or nearly all) of the thrombotic events in the 30 days after idarucizumab administration for dabigatran reversal, occurred in patients who had not resumed anticoagulation, reinforcing the message that, although the resumption of anticoagulation will not be appropriate for all patients, the decision to delay or withhold anticoagulation therapy should be reached after careful consideration. It seems reasonable to assume that the risks and benefits of resuming DOAC therapy will be largely similar to those associated with resuming warfarin therapy because these agents have shown similar if not superior efficacy and safety to warfarin in clinical trials.

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