Anticoagulation Holiday: Resumption of Direct Oral Anticoagulants for Atrial Fibrillation in Patients with Index Traumatic Intracranial Hemorrhage

Yohannes Ghenbot¹, John D. Arena¹, Susanna Howard¹, Connor Watthen¹, Monisha A. Kumar², James M. Schuster¹

BACKGROUND: The optimal time to restart direct oral anticoagulants (DOACs) for nonvalvular atrial fibrillation (NVAF) after traumatic intracranial hemorrhage (tICH) is unknown. Physicians must weigh the risk of recurrent hemorrhage against ischemic stroke. We investigated rates of stroke while holding anticoagulation, hemorrhage after anticoagulation resumption, and factors associated with the decision to restart anticoagulation.

METHODS: Patients presenting to our level I trauma center for tICH while on a DOAC for NVAF were retrospectively reviewed over 2 years. Age, sex, DOAC use, antiplatelet use, congestive heart failure, hypertension, age, diabetes, previous stroke, vascular disease, sex score for stroke risk in NVAF, injury mechanism, bleeding pattern, Injury Severity Score, use of a reversal agent, Glasgow Coma Scale at 24 hours, hemorrhage expansion, neurosurgical intervention, Morse Fall Risk, DOAC restart date, rebled events, and ischemic stroke were recorded to study rates of recurrent hemorrhage and stroke, and factors that influenced the decision to restart anticoagulation.

RESULTS: Twenty-eight patients sustained tICH while on a DOAC. Fall was the most common mechanism (89.3%), and subdural hematoma was the predominant bleeding pattern (60.7%). Of the 25 surviving patients, 16 patients (64%) restarted a DOAC a median 29.5 days after tICH. One patient had recurrent hemorrhage after resuming anticoagulation. One patient had an embolic stroke after 118 days off anticoagulation. Age >80, Injury Severity Score ≥16, and expansion of tICH influenced the decision to indefinitely hold anticoagulation.

CONCLUSION: The low stroke rate observed in this study suggests that holding DOACs for NVAF for 1 month is sufficient to reduce the risk of stroke after tICH. Additional data are required to determine optimal restart timing.

INTRODUCTION

Therapeutic anticoagulation is commonly prescribed for primary prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF), as well as in disorders of thrombosis such as deep vein thrombosis (DVT) and pulmonary embolism (PE). Currently, there are 3–6 million Americans with atrial fibrillation, which is projected to increase up to 16 million by the year 2050. Many of these patients will require long-term anticoagulation to prevent embolic stroke. The most devastating complication of anticoagulation is intracranial hemorrhage (ICH).

Clinicians at trauma centers frequently care for patients who sustain traumatic ICH (tICH) while on therapeutic anticoagulation. In the immediate postinjury phase, anticoagulation is universally held, and reversal agents may be given in order to prevent hemorrhagic expansion. After the acute phase of injury, clinicians face a dilemma—when to restart anticoagulation after an...
index tICH to prevent embolic stroke. The benefit of long-term anticoagulation to reduce ischemic stroke in NVAF is well established, and clinicians must weigh the risk of ischemic stroke against recurrent ICH.

Furthermore, NVAF is a disease of the aging population. Traumatic brain injury (TBI) in the elderly is distinct from TBI in younger patients; older patients have poorer outcomes after TBI. However, prior studies often mix these patients together when discussing resumption of anticoagulation after ICH. Elderly patients have more comorbidities compared with younger patients and experience polypharmacy, which make them particularly predisposed to TBI secondary to falls. We retrospectively reviewed rates of stroke in patients with NVAF who had anticoagulation held after tICH and rates of ICH after anticoagulation resumption to inform the decision of when to resume anticoagulation.

**METHODS**

Patients who presented to our level I trauma center with tICH while on an anticoagulant were retrospectively reviewed from January 2018 to January 2020. Patients who were on a non–direct oral anticoagulant (DOAC) (e.g., warfarin, lovenox) or a DOAC for an indication other than NVAF were excluded from the study. This was performed to limit heterogeneity of the patient population. The electronic medical records of selected patients were reviewed including inpatient notes, clinic visits, imaging, telephone call documentation, and prescription data. Demographic data obtained included age and sex. Clinical data before injury were recorded including type of DOAC used, concurrent antiplatelet use, and congestive heart failure, hypertension, age, diabetes, previous stroke, vascular disease, sex (CHA2DS2VASC) score. The CHA2DS2VASC scoring system incorporates clinical variables including congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, and sex that predicts yearly risk of stroke in NVAF. Characteristics of the injury were recorded including the mechanism of injury (e.g., fall, motor vehicle collision, or assault), predominant pattern of bleeding (e.g., subarachnoid, subdural, intraparenchymal, or intraventricular), and Injury Severity Score (ISS). If there was bleeding within more than one intracranial compartment, the bleeding pattern was defined as multicompartimental hemorrhage. Postinjury data while hospitalized included use of a reversal agent, Glasgow Coma Scale at 24 hours after presentation, hemorrhage expansion, need for surgery, and Morse Fall Risk score. Data extracted from post-discharge outpatient clinic records included DOAC restart date, rebleed events, occurrence of embolic stroke, and length of follow-up. A χ² analysis was used to analyze clinical variables associated with the decision to hold anticoagulation indefinitely. Statistical analysis was performed using STATA software (StataCorp, College Station, Texas, USA).

**RESULTS**

**Patient Characteristics**

Summary data for our study population are available in Table 1. A total of 28 patients on a DOAC for NVAF were identified. Anticoagulation was held in all patients after injury. The average age of our cohort was 78 years and predominantly included men (71%). The average CHA2DS2VASC score was 4.4, and patients were mostly at moderate-to-high risk for embolic stroke (CHA2DS2VASC ≥2, 92.9%). The most common mechanism of trauma was fall (89.3%), and the predominant pattern of bleeding...
was subdural hematoma (60.7%). Anticoagulation was universally held at the time of injury, and 17 patients (60.7%) were reversed with either prothrombin complex concentrate or andexanet alfa. Seven patients (25%) required surgical intervention for decompression or clot evacuation after trauma. The procedures included unilateral craniotomy (n = 3, 42.9%), bilateral burr holes (n = 2, 28.5%), bilateral craniotomies (n = 1, 14.3%), and bifrontal decompressive craniectomy (n = 1, 14.3%). At the time of presentation, patients did not show signs of coagulopathy or thrombocytopenia. The average partial thromboplastin time was 31.7 seconds (confidence interval [CI]: 29.4–32.8 seconds), international normalized ratio 1.19 (CI: 1.1–1.2), and platelets 194.6K/μL (CI: 170.6–218K/μL).

Three patients did not survive their injuries. Of the remaining 25 surviving patients, 16 patients were restarted on anticoagulation (64%) after being held for a median 29.5 (interquartile range: 13.6–51.5), while 9 (36%) were held indefinitely. Two patients had initial expansion of hematoma while on apixaban and rivaroxaban, respectively, and the predominant pattern of bleeding was subdural hematoma (SDH). Our follow-up time based on a chart review ranged from 16 days to 3 years, with a mean of 202 ± 280 days.

### Risk of Hemorrhage Is Low After Anticoagulation Resumption

A second tICH occurred in only 1 patient who resumed anticoagulation. The patient had a CHA2DS2-VASC score of 5; given the significant risk of stroke, anticoagulation was restarted on post-bleed day 6. Eighteen days after restarting anticoagulation, the patient experienced a traumatic SDH due to another fall. Surgery was performed in a delayed fashion (6 days after the identification of rebleed), and anticoagulation was held for 38 days after the second event. The patient was taking apixaban, and there was no hematoma expansion after resumption.

### Short-Term Risk of Stroke Is Low During Anticoagulation Holiday

In patients who were restarted on a DOAC, anticoagulation was held for a median time of 29.5 days. At our institution, patients who resume anticoagulation undergo interval noncontrast head computed tomographies before resuming anticoagulation, which helps inform anticoagulation resumption.

Among the 9 patients who were not restarted on anticoagulation, we observed 1 embolic stroke. This resulted in an incidence rate of 1 stroke per 7.8 person-years. The patient’s CHA2DS2-VASC score was 6, and anticoagulation was held for 36 weeks after the patient had another tICH 118 days after index tICH. The patient presented with dysarthria and weakness and was found to have an ischemic left thalamic stroke due to posterior cerebral embolic phenomena. The decision to hold this patient’s anticoagulation was made difficult by recurrent tICH in the presence of cerebral amyloid angiopathy.

Significant clinical variables that were associated with the decision to hold anticoagulation indefinitely included age greater than 80 years (P = 0.011), ISS ≥16 (P = 0.025), and expansion of ICH (P = 0.049, Table 2). Among patients who were restarted on anticoagulation, late resumption (>3 weeks) was associated with

### Table 2. Patient Factors Associated with the Decision to Restart Anticoagulation After tICH

|                              | No Restart | Restart | P Value |
|------------------------------|------------|---------|---------|
| Age (years)                  |            |         |         |
| >80                          | 7          | 4       | 0.011   |
| <80                          | 2          | 12      |         |
| Sex                          |            |         |         |
| Male                         | 7          | 11      | 0.629   |
| Female                       | 2          | 5       |         |
| CHA2DS2-VASC >4              |            |         |         |
| >4                           | 4          | 11      | 0.234   |
| <4                           | 5          | 5       |         |
| Pattern                      |            |         |         |
| SDH                          | 6          | 9       | 0.61    |
| No SDH                       | 3          | 7       |         |
| Mechanism                    |            |         |         |
| Fall                         | 7          | 15      | 0.238   |
| Other                        | 2          | 1       |         |
| GCS ≥13                      |            |         |         |
| 14–15                        | 7          | 15      | 0.238   |
| ≤13                          | 2          | 1       |         |
| ISS >16                      |            |         |         |
| ≥16                          | 7          | 5       | 0.025   |
| <16                          | 2          | 11      |         |
| Expansion                    |            |         |         |
| Expansion                    | 2          | 0       | 0.049   |
| No expansion                 | 7          | 16      |         |
| Fall Risk                    |            |         |         |
| High                         | 6          | 8       | 0.242   |
| Low                          | 2          | 8       |         |
| Antiplatlet use              |            |         |         |
| Yes                          | 2          | 6       | 0.432   |
| No                           | 7          | 10      |         |
| Surgery                      |            |         |         |
| Yes                          | 2          | 4       | 0.876   |
| No                           | 7          | 12      |         |
| Reversal                     |            |         |         |
| Yes                          | 4          | 7       | 0.973   |
| No                           | 5          | 9       |         |

**Notes:**
- CHA2DS2-VASC: congestive heart failure, hypertension, age, diabetes, previous stroke, vascular disease, sex; SDH: subdural hematoma; GCS: Glasgow Coma Scale; ISS: Injury Severity Score.
DISCUSSION

In our study of 28 patients with tICH while on a DOAC for NVAF, ischemic stroke was rare and delayed after holding anticoagulation. The risk of rebleed after resuming anticoagulation was also low and occurred in the setting of recurrent trauma. Older age, severity of injury, and expansion of initial hematoma were associated with the decision to discontinue anticoagulation indefinitely, whereas the need for surgery trended toward later restart timing. The ISS measures the severity of traumatic injury across 9 body regions and has been shown to be associated with mortality in tICH. Several variables such as CHA2DS2VASC score, Glasgow Coma Scale, antiplatelet use, and fall risk had no effect on the decision to restart or when to restart. There was wide variability in restart timing, which reflects the difficulty that clinicians face balancing the risk of rebleed against embolic stroke. A recent survey of neurosurgeons, neurologists, and thrombosis experts found variability in anticoagulation restart timing after ICH in varying clinical scenarios.

Ischemic Stroke Risk

Currently, there are limited data surrounding stroke risk while holding anticoagulation for atrial fibrillation after tICH. Long-term risk assessment tools exist to aid in this decision. The well-validated CHA2DS2VASC scoring system for atrial fibrillation calculates a patient’s annual ischemic stroke risk as a function of modifiable and nonmodifiable risk factors including history of congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, and sex. Anticoagulation is recommended for high-risk patients—CHA2DS2VASC ≥2. Although helpful, short-term ischemic stroke risk cannot be calculated using this tool and is less helpful in the period after tICH. Recent data suggest that stroke risk may have a temporal relationship with an increase in the daily burden of NVAF, which could help inform anticoagulation resumption in the future. In a recent retrospective study that investigated the risk of cardioembolic stroke while holding anticoagulation for atrial fibrillation, 41 of 79 patients with traumatic SDH were restarted on anticoagulation at a median 32 days after injury. Four strokes were observed at 90-day follow-up (5%). We observed a similar median restart timing and stroke percentage, but in a more delayed fashion.

Given the paucity of literature in tICH, the spontaneous ICH (sICH) literature may help inform optimal restart timing after an anticoagulation holiday as patients share risk factors for embolic stroke due to NVAF. In a subanalysis of the ROCKET-AF trial that originally compared rivaroxaban with warfarin for atrial fibrillation, transient interruptions in anticoagulation were studied in 2165 patients who had 3393 interruptions in anticoagulation for a median of 5 days. The average CHA2DS2VASC was 3.4, and stroke occurred at a rate of 0.3% per 30 days. A 3% 30-day risk of stroke was observed in a smaller cohort of patients (n = 53) who had warfarin held for twice as long after ICH (median 10 days).

Table 3. Patient Factors Associated with the Timing of Anticoagulation Resumption

|                  | Late Restart | Early Restart | P Value |
|------------------|--------------|---------------|---------|
| Age (years)      |              |               |         |
| >80              | 7            | 4             | 0.398   |
| <80              | 2            | 12            |         |
| Sex              |              |               |         |
| Male             | 6            | 4             | 1.00    |
| Female           | 3            | 2             |         |
| CHA2DS2VASC >4   |              |               |         |
| >4               | 6            | 4             | 1.00    |
| <4               | 3            | 2             |         |
| Pattern          |              |               |         |
| SDH              | 6            | 3             | 0.519   |
| No SDH           | 3            | 3             |         |
| Mechanism        |              |               |         |
| Fall             | 8            | 6             | 0.398   |
| Other            | 1            | 0             |         |
| GCS >13          |              |               |         |
| 14–15            | 9            | 5             | 0.205   |
| ≤13              | 0            | 1             |         |
| ISS >16          |              |               |         |
| ≥16              | 5            | 1             | 0.132   |
| <16              | 4            | 5             |         |
| Expansion        |              |               |         |
| Expansion        | Na           | Na            | Na      |
| No expansion     | 9            | 6             |         |
| Fall Risk        |              |               |         |
| High             | 6            | 2             | 0.205   |
| Low              | 3            | 4             |         |
| Antiplatelet use |              |               |         |
| Yes              | 3            | 3             | 0.519   |
| No               | 6            | 3             |         |
| Surgery          |              |               |         |
| Yes              | 4            | 0             | 0.057   |
| No               | 5            | 6             |         |
| Reversal         |              |               |         |
| Yes              | 5            | 3             | 0.833   |
| No               | 4            | 3             |         |

Early restart was defined as anticoagulation before 3 weeks after tICH. CHA2DS2VASC, congestive heart failure, hypertension, age, diabetes, previous stroke, vascular disease, sex, SDH, subdural hematoma; GCS, Glasgow Coma Scale; ISS, Injury Severity Score.
Longer anticoagulation holidays were retrospectively reviewed by Claassen et al., who held warfarin indefinitely in 14 patients with sICH. Three thromboembolic strokes were observed, occurring an average 5.7 months after holding anticoagulation (range, 3–7 months). This reflects the cumulative risk of stroke while anticoagulation is held and suggests that holding anticoagulation within the first 1–2 weeks after tICH can be safe.

Current recommendations of optimal timing to restart anticoagulation vary widely in the sICH literature, ranging from 3 days to 30 weeks. This wide variation exists in part due to the heterogeneous populations studied including patients with a wide range of indications for anticoagulation (e.g., NVAF, mechanical heart valve, PE, and DVT), different anticoagulants (e.g., DOACs and warfarin), and different anatomic locations of sICH. Thus, consensus statements give class IIb evidence recommending resumption at 4–8 weeks after an index event following multidisciplinary discussion.

### Risk of Hemorrhage

The risk of recurrent hemorrhage after reinitiating anticoagulation after clinical and radiographic stabilization was low in our study. It was not due to restarting anticoagulation alone but resulted from recurrent trauma. The HAS-BLED bleeding risk tool has limited utility in this clinical scenario, as ICH is defined as hemorrhagic stroke and grouped into “major bleeding” that also includes any pathology requiring hospitalization, resulting in a hemoglobin drop >2 g/L, or needing transfusion. HAS-BLED risk factors include hypertension, impaired renal or liver function, stroke, prior major bleeding, labile international normalized ratio, age >65, and use of medication that increased bleeding risk (e.g., aspirin) or alcohol. It does not include variables such as fall risk that are a major cause of tICH in the elderly. Furthermore, patients with high CHA<sub>2</sub>DS<sub>2</sub>-VASc tend to have comorbidities that also increase their HAS-BLED score, as these scores have been shown to correlate with one another.

DOACs inhibit clot propagation but are not thrombolytics and should not break down clot once hemostasis is achieved after a traumatic event. Weighing the risk of recurrent hemorrhage cannot be generalized from the sICH literature as tICH and sICH are separate clinical entities. The most common locations of sICH are lobar and deep, which results from disparate pathologies such as amyloid angiopathy or lipohyalinosis secondary to hypertension. Unlike sICH, tICH is a provoked event due to mechanical forces. The risk of recurrent hemorrhage after resumption of anticoagulation is lower in tICH compared with sICH as demonstrated in an observational cohort study evaluating recurrent ICH in 2415 patients resuming warfarin for NVAF who suffered spontaneous or traumatic (n = 1090) index hemorrhages. In addition, the type of recurrent ICH (i.e., sICH or tICH) largely matched the mechanism of the index hemorrhage after reinitiation of anticoagulation.

Retrospective studies in the trauma literature have demonstrated that the risk of recurrent hemorrhage after anticoagulation resumption. Divito et al. examined 105 patients with TBI who required anticoagulation for thromboembolic complications after index tICH. Only 3% of patients had expansion of ICH after initiating therapeutic anticoagulation with heparin, lovenox, or warfarin a median 8 days after injury. Byrnes et al. examined 26 patients who were given therapeutic anticoagulation with heparin or lovenox for thrombotic complications after TBI (DVT, PE, blunt cerebrovascular injury) a median 12 days after injury. One patient (4%) had worsened ICH.

Our population was mostly composed of older patients with high risk of recurrent trauma due to falls. Clinicians are often hesitant to restart anticoagulation and may discontinue indefinitely in this population. However, patients who are prone to falling benefit from anticoagulation for NVAF if CHA<sub>2</sub>DS<sub>2</sub>-VASc >2, and this benefit increases with older age. Models have estimated that elderly patients would have to fall hundreds of times within a year for the risk of recurrent hemorrhage to outweigh the benefits of stroke prevention from anticoagulation.

Another important factor in the decision to restart anticoagulation after tICH is the role of surgical intervention. Although a neurosurgical intervention does not change stroke risk, it likely alters the risk profile for subsequent hemorrhage. The added risk of postoperative hemorrhage is balanced against

### Table 4. Direct Oral Anticoagulant and Warfarin Mechanism of Action, Reversal Agents, and 30-Day Thrombotic Risk Associated with Reversal

|                  | Dabigatran | Apixaban | Rivaroxaban | Edoxaban | Warfarin |
|------------------|------------|----------|-------------|----------|----------|
| Mechanism        | Direct Thrombin Inhibitor | Direct Factor Xa Inhibitor | Direct Factor Xa Inhibitor | Direct Factor Xa Inhibitor | Inhibitor of Factors II, VII, IX, X, Protein C and S |
| Half-life (hours)| 12–14      | 8–12     | 5–13        | 10–14    | 20–60    |
| Reversal agent   | Idarucizumab (Praxbind) | Andexanet alfa (Andexxa) | Andexanet alfa (Andexxa) | Andexanet alfa (Andexxa) | PCC |
| Reversal time (minutes) | 15 | 2–5 | 2–5 | 2–5 | 10–15 |
| 30-day thrombotic risk (%) | 4.8 | 10–18 | 10–18 | 10–18 | 9–18 |

PCC, prothrombin complex concentrate.
While on apixaban in ARISTOTLE, ICH needed; however, they may be quickly cleared from the body during this time, the DOACs have rapid onset of action and reach therapeutic effect, which often necessitates heparin therapy as a bridge to guide DOAC resumption after surgical intervention. In our cohort of patients, 25% underwent surgical intervention. It is difficult to determine the effect of surgical intervention on hemorrhage given the low incidence of hemorrhage after DOAC resumption.

When restarting anticoagulation, clinicians may choose from a direct thrombin inhibitor (i.e., dabigatran) or a factor Xa inhibitor (rivaroxaban, apixaban, or edoxaban). Compared with prior anticoagulants like warfarin that require up to 5 days to reach therapeutic effect, which often necessitates heparin therapy as a bridge during this time, the DOACs have rapid onset of action and reach maximal concentration within 4 hours of administration. Like warfarin, they may be rapidly reversed when emergent reversal is needed; however, they may be quickly cleared from the body in patients with normal renal function (Table 4). This is important as reversal of both DOACs and warfarin can increase the risk of surgical intervention on hemorrhage after ICH resumption. Most literature that investigates resumption of anticoagulation after ICH has involved warfarin. DOACs have become increasingly popular. RCTs have shown both superiority and noninferiority in preventing ischemic stroke when comparing DOACs with warfarin, while having reduced risk of sICH for both direct thrombin (dabigatran) and Xa inhibitors (apixaban, rivaroxaban, and edoxaban). Patients with a history of ICH were excluded in these trials; however, a subsequent observational cohort study including patients with prior ICH found a similar reduction in risk of ICH when using DOACs compared with warfarin. If sICH occurs while on anticoagulation, the volume of hemATOMA is smaller for DOAC-treated patients when compared with warfarin, with associated improved functional outcomes. Research is ongoing in tICH; however, some studies have shown reduced hematoma volumes and improved functional outcome at the time of discharge. Proposed mechanisms underlying the difference in clinical behavior include efflux of apixaban and rivaroxaban by P-glycoprotein channels, limited penetration of the blood brain barrier by dabigatran, and selectivity of the DOACs when compared with warfarin. Intraclass variability also exists within the DOAC family. Between the 2 commonly used direct factor Xa inhibitors (i.e., rivaroxaban and apixaban), rivaroxaban has higher levels of anti-Xa activity. Clinically, rivaroxaban has higher rates of ICH when compared with apixaban and dabigatran. In our rebleed event after DOAC resumption, the patients were on apixaban, but it is difficult to make inferences given our sample size. It may be reasonable to choose apixaban based on its pharmacodynamic profile or dabigatran when restarting anticoagulation after tICH.

**Table 5. Randomized Control Trials Investigating Anticoagulation Resumption After Intracranial Hemorrhage While on a Direct Oral Anticoagulant for Nonvalvular Atrial Fibrillation**

| Study        | Population | Treatment | Primary End Point                                      | Follow-Up Time (months) | Sample Size | End Date     |
|--------------|------------|-----------|--------------------------------------------------------|-------------------------|-------------|--------------|
| APACHE-AF    | sICH       | Apixaban vs. no anticoagulation | Nonfatal stroke or vascular death                      | 12—72                   | 101         | January 31, 2021 |
| ENRICH-AF    | sICH       | Edoxaban vs. no anticoagulation | Stroke (ischemic or hemorrhagic) or major hemorrhage   | 48                      | 1200        | July 2023   |
| Restart tICH | tICH       | Initiation of anticoagulation at 1, 2, and 4 weeks after tICH | 60-day thrombotic or bleeding event                     | 2                      | 1100        | February 2027 |

APACHE-AF, apixaban versus no anticoagulation after anticoagulation-associated intracerebral hemorrhage in patients with atrial fibrillation; ENRICH-AF, edoxaban for intracerebral hemorrhage survivors with atrial fibrillation; Restart tICH, restarting anticoagulation after traumatic intracranial hemorrhage; sICH, spontaneous intracerebral hemorrhage; CHA2DS2-VASC, congestive heart failure, hypertension, age, diabetes, previous stroke, vascular disease, sex; VTE, venous thromboembolism.

The benefit of surgically controlling the source of bleeding from tICH. These 2 factors likely act to modulate the risk of recurrent hemorrhage or expansion of initial hemorrhage. Although anticoagulant use has been shown to increase the risk of surgical intervention in the acute period after injury, data are not available to guide DOAC resumption after surgical intervention. In our cohort of patients, 25% underwent surgical intervention. It is difficult to determine the effect of surgical intervention on hemorrhage given the low incidence of hemorrhage after DOAC resumption.
DOAC resumption following traumatic ICH

Our study was primarily limited by its retrospective design. The sample size was also small and may affect the ability to detect differences in variables associated with the decision to restart anticoagulation and timing of resumption. Stroke rate may be underestimated as it was detected by clinical events and screening, and magnetic resonance imaging scans were not performed. However, we provide insight into a specific patient population within the limited tICH literature that is often composed of heterogeneous patient populations who have different risks of thromboembolic complications.

CONCLUSION
In this case series of patients with tICH on a DOAC, risk of recurrent hemorrhage and risk of stroke in the immediate post-injury phase were low. Recurrent hemorrhage after restarting anticoagulation did not require emergency surgery, and thromboembolic complications occurred months after anticoagulation was held. Compared with sICH, tICH is a provoked event and anticoagulation may be able to be resumed earlier. Based on our data and available literature, it may be reasonable to hold anticoagulation for 1 month after index tICH after confirming hemorrhage stability. Ongoing RCTs of tICH in the setting of DOAC use will help establish the optimal evidence-based restart time.

REFERENCES
1. Kornej J, Börschel CS, Benjamin EI, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. Circ Res. 2020;127:430.
2. Lip GY, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. JAMA. 2013;310:1995-1996.
3. Ramanathan DM, Williams N, Schatz P, Hillary FG. Epidemiological shifts in elderly traumatic brain injury: 18-year trends in Pennsylvania. J Neurol. 2012;269:1371-1378.
4. Powers AY, Finto MB, Tang OY, Chen JS, Doberstein C, Asaad WF. Predicting mortality in traumatic intracranial hemorrhage. J Neurosurg. 2019;131:352-359.
5. Xu Y, Shoamanesh A, Schulman S, et al. Oral anticoagulant re-initiation following intracerebral hemorrhage in non-valvular atrial fibrillation: global survey of the practices of neurologists, neurosurgeons and thrombosis experts. PLoS One. 2016;11:e0159737.
6. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rythm Association (EHRA) of the ESC. Eur Heart J. 2021;42:373-407.
7. Singer DE, Ziegler PD, Koehler J, Sarkar S, Passman RS. Temporal association between episodes of atrial fibrillation and risk of ischemic stroke. JAMA Cardiol. 2021;6:1394-1396.
8. Naylor RM, Dodin RE, Henry KA, et al. Timing of restarting anticoagulation and antiplatelet therapies after traumatic subdural hematoma—a single institution experience. World Neurosurg. 2021;150:2303-2308.
9. Sherwood MW, Douketis JD, Patel MR, et al. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonist for prevention of stroke and embolism in atrial fibrillation (ROCKET AF). Circulation. 2014;129:1850-1859.
10. Phan TG, Koh M, Wijdicks EF. Safety of discontinuation of anticoagulation in patients with intracranial hemorrhage at high thromboembolic risk. Arch Neurol. 2006;63:1710-1713.
11. Claassen DO, Kazemi N, Zubkov AY, Wijdicks EFM, Rabinstein AA. Restarting anticoagulation therapy after warfarin-associated intracerebral hemorrhage. Arch Neurol. 2008;65:1313-1318.
12. Hawkes MA, Rabinstein AA. Anticoagulation for treatment following intracerebral hemorrhage: a systematic review. Neuro Crit Care. 2019;20:40-47.
13. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016;49:1034-1059.
14. Pisters R, Lane DA, Nieuwlaat R, de Vos CB. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2017;377:431-441.
15. Pennlert J, Asplund K, Carlberg B, et al. Antithrombotic treatment following intracerebral hemorrhage: a review and summary of ongoing and planned prospective randomized clinical trials. Trauma Surg Acute Care Open. 2020;5: e000685.
16. Psaltis R, Lane DA, Nieuwlaat R, de Vos CB. Crijns HGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chot. 2010;138:1003-1010.
17. Penenent J, Asplund K, Carlberg B, et al. Antithrombotic treatment following intracerebral hemorrhage in patients with and without antithrombotic therapy. Stroke. 2013;44:1315-1320.
18. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2000;355:163-164.
19. Divito A, Kerr R, O’Malley M, Shepherd S, Choi A, Kitagawa KS. Use of anticoagulation agents after traumatic intracranial hemorrhage. World Neurosurg. 2019;123:235-243.
20. Byrnes MC, Irwin E, Roach R, James M, Horst PK, Reicks P. Therapeutic anticoagulation can be safely accomplished in selected patients with traumatic intracranial hemorrhage. World J Emerg Surg. 2017;12:75.
21. Lip GYH, Clements N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged 75-79 years with atrial fibrillation: the Loire Valley atrial fibrillation project. Stroke. 2015;46:143-150.
22. Wei W, Rasu RS, Hernández-Muñoz JJ, et al. Impact of full risk and direct oral anticoagulant treatment on quality-adjusted life-years in older adults with atrial fibrillation: a Markov decision analysis. Drugs Aging. 2021;38:713-733.
23. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med. 1999;159:677.
24. King B, Milling T, Gajewski B, et al. Restarting and timing of oral anticoagulation after traumatic intracranial hemorrhage: a review and summary of ongoing and planned prospective randomized clinical trials. Trauma Surg Acute Care Open. 2020;5:e000685.
25. Proietti R, AlTurki A, Ferri N, Russo V, Bunch TJ. Direct Oral Anticoagulants from Pharmacology to Clinical Practice. Cham, Switzerland: Springer International Publishing; 2021.
26. Pollack CV, Reilly PA, van Ryn J, et al. Idolucizumab for dabigatran reversal—full cohort analysis. N Engl J Med. 2017;377:431-441.
27. Siegl DM, Curnette JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373:2413-2424.
28. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. Circulation. 2011;123:1486-1490.
29. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol. 2013;75:476-487.
30. Mueck W, Stampfl P, Kubitz B, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014;53:1-16.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT
Yohannes Ghenbot: Conceptualization, Data curation, Formal analysis, Writing – original draft. John D. Arena: Writing – review & editing. Susanna Howard: Writing – review & editing. Connor Wathen: Writing – review & editing. Monisha A. Kumar: Writing – review & editing, Supervision. James M. Schuster: Conceptualization, Supervision, Writing – review & editing.
29. Parasrampuria DA, Truitt KE. Pharmacokinetics and pharmacodynamics of edoxaban, a non-vitamin K antagonist oral anticoagulant that inhibits clotting factor Xa. Clin Pharmacokinet. 2016; 55:641-655.

30. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med. 2016; 375:1131-1141.

31. Connolly SJ, Gibson CM, Crowther M. Andexanet alfa for factor Xa inhibitor reversal. N Engl J Med. 2016;375:2499-2500.

32. Felton D, Foley EM, Traub SJ, Vodonos A, Ganetsky M. Risk of venous thromboembolism after receiving prothrombin complex concentrate versus fresh frozen plasma for urgent warfarin reversal in the emergency department. J Emerg Med. 2016;50:1-6.

33. Maguire M, Fuh L, Goldstein JN, et al. Thromboembolic risk of 4-factor prothrombin complex concentrate versus fresh frozen plasma for urgent warfarin reversal in the emergency department. West J Emerg Med. 2019;20:619-625.

34. Hart RG, Diener HC, Yang S, et al. Intracerebral hemorrhage in patients with atrial fibrillation (APACHE-AF). ClinicalTrials.gov identifier NCT0255693. Available at: https://clinicaltrials.gov/ct2/show/NCT0255693; 2021. Accessed April 15, 2022.

35. Hankey GJ, Stevens SR, Piccini JP, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955-962.

36. Ruff CT, Giugliano RP, Braunwald E, et al. Non-vitamin K antagonist oral anticoagulants versus warfarin in atrial fibrillation patients with intracerebral hemorrhage. Stroke. 2015;46:955-962.

37. Wartenberg KE. Are direct anticoagulants safer in atrumatic brain injury compared to warfarin? Neurocrit Care. 2020;32:367-368.

38. Scotti P, Séguin C, Lo BWY, de Guise E, Troquet JM, Marcoux J. Anti thrombotic agents and traumatic brain injury in the elderly population: hemorrhage patterns and outcomes. J Neurosurg. 2020;133:486-495.

39. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955-962.

40. Apixaban after anticoagulation-associated intracranial hemorrhage in patients with atrial fibrillation (APACHE-AF). ClinicalTrials.gov identifier NCT0255693. Available at: https://clinicaltrials.gov/ct2/show/NCT0255693; 2021. Accessed April 15, 2022.

41. Nicolaisen PB, Skjøth F, Segard M, Kjældgaard JN, Lip GYH, Larsen TB. Non-vitamin k antagonist oral anticoagulants versus warfarin in atrial fibrillation patients with intracerebral hemorrhage. Stroke. 2015;46:955-962.

42. Wilson D, Charidimou A, Shakeshaft C, et al. Volume and functional outcome of intracerebral hemorrhage according to oral anticoagulant type. Neurology. 2016;86:606-606.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 30 June 2022; accepted 2 October 2022

Citation: World Neurosurg. X (2023) 17:100148.

Journal homepage: www.journals.elsevier.com/world-neurosurgery-x

Available online: www.sciencedirect.com