



Long-term outcome of resuming anticoagulation after anticoagulation-associated intracerebral hemorrhage



Alireza Sadighi^a, Lisa Wasko^a, Heather DiCristina^a, Thomas Wagner^a, Kathryn Wright^a, Kellie Capone^a, Maureen Monczewski^a, Margaret Kester^a, George Bourdages^a, Christoph Griessenauer^b, Ramin Zand^{a,*}

^a Department of Neurology, Geisinger Medical Center, Danville, PA, USA

^b Department of Neurosurgery, Geisinger Medical Center, Danville, PA, USA

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ABSTRACT

Introduction: The risk and benefit of restarting oral anticoagulation (OAC) therapy among patients with atrial fibrillation or flutter (AF) and an episode of anticoagulation-associated intracerebral hemorrhage (ICH) remain unclear. Whether or not to resume OAC after an OAC-associated ICH will remain an unanswered clinical question until we have sufficient data through randomized clinical trials. Here, we analyzed the long-term outcome of patients with AF who did or did not resume OAC after an OAC-associated ICH.

Patients and methods: We studied consecutive patients with AF who were discharged from our institution after an OAC-associated ICH event between 2010 and 2017. Baseline characteristics of patients, past medical history, and history or OAC use were recorded. Outcome measures in our study included recurrent ICH, ischemic stroke or systemic emboli, and death.

Results: Out of 115 patients with AF and OAC-associated ICH, 93 patients (mean age 76.2 ± 10.3 years [44–91 years old], 54.3% men) were included in this study. Thirty-eight (40.9%) patients resumed OAC after the episode of OAC-associated ICH. More than 70% of patients had resumed OAC within two months of ICH (mean delay 56.0 ± 52.5 days). There was no significant difference between the group who resumed OAC and the group who did not in terms of mean follow-up duration (1.9 vs. 2.4 years), the type of initial ICH, as well as history of hypertension, diabetes, previous ischemic stroke, congestive heart failure, coronary artery disease, and tobacco use. There was no significant difference between the two groups considering the incidence rate of recurrent ICH (relative risk 2.9; 95% CI, 0.3–30.8). There was also no significant difference between the two groups regarding the incidence rate of ischemic stroke or systemic emboli (relative risk 0.9; 95% CI, 0.3–2.7). There was no significant difference between patients who did and did not resume OAC was 96 and 121 per 1000 patient-years, respectively (relative risk 0.8; 95% CI, 0.3–1.9).

Conclusions: We did not observe any significant difference between the group of patients who resumed OAC and the patients who did not in terms of recurrent ICH, ischemic stroke or systemic emboli, and death. However, there was a tendency toward a higher long-term risk of recurrent ICH among patients who resumed OAC.

1. Introduction

Atrial Fibrillation or flutter (AF) is the most common abnormal heart rhythm in the world [1]. Patients with AF are potential candidates for oral anticoagulation (OAC) therapy to prevent the formation of blood clots and ensuing thromboembolic stroke or systemic embolism.

Bleeding in the gastrointestinal tract, genitourinary tract, and intracranial space are the significant complications of OAC therapy. Of them, intracranial hemorrhage (ICH) is the most important cause of morbidity and mortality among patients who are on OAC [2]. Moreover, OAC-associated ICH (OAC-ICH) has been found to have worse clinical prognosis compared to spontaneous ICH [3,4].

* Corresponding author at: Department of Neurology, Division of Cerebrovascular Diseases, Geisinger Medical Center, 100 N Academy Ave, Danville, PA 17822, USA.

E-mail addresses: lawasko@geisinger.edu (L. Wasko), hrdicristina@geisinger.edu (H. DiCristina), twagner@geisinger.edu (T. Wagner), kwwright@geisinger.edu (K. Wright), kacapone@geisinger.edu (K. Capone), mmonczewski@geisinger.edu (M. Monczewski), mckester@geisinger.edu (M. Kester), gbourdages@geisinger.edu (G. Bourdages), cgriessenauer@geisinger.edu (C. Griessenauer), ramin.zand@gmail.com (R. Zand).

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Anticoagulation cessation following OAC-ICH increases the risk of thromboembolic events among patients who require chronic OAC therapy [5]. However, when and whether to resume OAC following OAC-ICH is considered a clinical dilemma due to the risk of recurrent ICH [6]. There are no randomized clinical trials to provide reliable evidence in this circumstance. Randomized clinical trials regarding OAC use in stroke prevention sometimes exclude cases with a high risk of ICH; however, there are a few observational studies available [7–10]. In a systematic review by Murthy et al. [11], anticoagulation resumption after ICH showed to be associated with a lower risk of thromboembolic complications and a similar risk of ICH recurrence; though, there was significant heterogeneity in the follow-up periods and selection criteria in the individual studies [12].

In this study, we aimed to investigate the long-term outcome of patients with AF who either did or did not resume OAC after an OAC-ICH.

2. Methods

We analyzed consecutive patients with AF who were discharged from one of our three tertiary stroke centers after hospitalization for an OAC-ICH event between the years 2010 and 2017. OAC-ICH included patients with clinical diagnosis of AF and a cardinal ICH event while on warfarin with an international normalized ratio (INR) of 1.5 or higher [13] at the time of admission or on a novel oral anticoagulant (NOAC) with the last dose within 48 h from the admission. Patients with ICH secondary to arteriovenous malformation, aneurysmal rupture, amyloid angiopathy, trauma, tumor, hemorrhagic transformation of a cerebral infarction, thrombolysis and other types of coagulopathies were excluded. We manually reviewed all the patients' baseline characteristics including demographics, past medical history, OAC use (warfarin or novel oral anticoagulants) and clinical work-up.

We divided patients into two groups – patients who resumed OAC and patients who did not resume OAC. Patients were assigned into the OAC resumed group if they were put on OAC primarily within 90 days after an OAC-ICH event. None of patients in this group had their OAC resumption more than 110 days after OAC-ICH. We did not have any patient included with ICH recurrences prior to initiation of OAC in the OAC resumed group. The decision to resume or not resume oral anticoagulant therapy was based on physician discretion with patient-centered decision making or involvement.

Outcome measures in our study included rate of recurrent ICH, ischemic stroke or systemic emboli, and death. Patients who were included in this study had at least one confirmatory radiological imaging using either CT Scan or MRI for ICH recurrence and ischemic stroke. The Institutional Review Board of Geisinger approved this study.

2.1. Statistical analysis

We summarized all continuous variables as mean \pm SD (normal distribution) and as median with IQR (skewed distribution). We summarized all categorical variables as percentages with their corresponding 95% CIs. We performed statistical comparisons between two groups using the χ^2 test or, in the case of small expected frequencies, Fisher's exact test. We compared continuous variables using the unpaired two-sample *t*-test. We used SPSS 24.0 (Chicago, Ill., USA) for all our statistical analysis. Incidence rates were calculated using MedCalc software.

3. Results

Out of 115 patients with AF and OAC-ICH, 93 patients (mean age 76.2 ± 10.3 [44–91] years old, 54.3% men, 2 patients with atrial flutter) were included in this study (Table 1). Twenty-two patients (amyloid angiopathy 5, brain mass 2, hemorrhagic transformation of an ischemic stroke 3, unavailability of follow-up information 11,

placement of an arterial appendage closure device 1) were excluded.

Out of 93 patients, 82 (88.2%) were on warfarin before OAC-ICH. The mean INR at the time of ICH among patients who were on warfarin was 2.8 ± 1.0 (range: 1.6–9.6). Of the rest, 3 patients were on apixaban, 2 were on dabigatran, and 6 patients were on rivaroxaban. The mean duration of OAC intake before the hemorrhage was 61.4 ± 54.3 months (range: 1.7–218.5 months). Out of 93 patients, 31 (33.3%) were taking an antiplatelet medication addition to OAC. The average duration of antiplatelet intake before the hemorrhage was 47.0 ± 58.1 months (range: 3.0–219.0 months).

Out of 93 patients, 38 (40.9%) patients resumed OAC after the episode of OAC-ICH. Eight patients (21%) were started on novel oral anticoagulants (apixaban:4, rivaroxaban:3, dabigatran:1), and the rest were taking warfarin. All patients had AF, however, two and three patients had superimposed mechanical heart valve and hypercoagulable state, respectively. More than 70% of patients resumed OAC within two months of ICH (mean delay 1.9 ± 1.8 months). The mean duration of OAC intake recorded in the study among patients who resumed OAC was 28.4 ± 21.5 months (range: 3.0–91.0 months). Out of 38 patients who resumed OAC, 5 (13.5%) patients (mean age 81.5 [74–84] years old) had recurrent ICH. The average wait time to restart OAC among these 5 patients was 50.3 days. The average duration of OAC intake before the recurrent ICH was 7.4 ± 3.9 months (range: 3.0–7.4 months). The average INR at the time of recurrent ICH was 2.4.

Out of 55 patients in the OAC non-resumed group, three patients had initially started OAC, but they were switched to antiplatelet medication in less than three months. More than 83% of patients who did not resume OAC were kept on antiplatelet medication. Three patients in this group were noted to be in a hypercoagulable state in addition to AF.

There was no significant difference among the group who resumed OAC and the patients who did not in terms of mean follow-up duration (1.9 vs. 2.4 years), history of hypertension, diabetes, previous ischemic stroke, congestive heart failure, coronary artery disease, and tobacco use (Table 2). Although the incidence rate of recurrent ICH was higher among patients who resumed OAC compared with those who did not (55 vs. 15 cases per 1000 patient-years), the difference was not significant (relative risk 2.9; 95% CI, 0.3–30.8). There was also no significant difference between the two groups regarding the incidence rate of ischemic stroke or systemic emboli (relative risk 0.9; 95% CI, 0.3–2.7). The mortality rates among patients who did and did not resume OAC were not significantly different; 96 and 121 per 1000 patient-years, respectively (relative risk 0.8; 95% CI, 0.3–1.9) (Table 3).

4. Discussion

We investigated the risk of major clinical outcomes among AF patients with a history of OAC-ICH who resumed OAC. The long-term evaluation of two groups of patients with AF who either did or did not resume OAC after an OAC-ICH did not show any statistically meaningful differences in the risk of recurrent ICH, ischemic stroke or systemic emboli, and death. However, we observed a tendency toward a higher long-term risk of recurrent ICH among patients who resumed OAC.

There are a limited number of studies evaluating the risk of recurrent ICH among AF patients [14]. In a Sweden based study [15], incidences of recurrent ICH among patients on OAC and those with no OAC treatment were 6.9% and 4.4%, respectively. The related thromboembolic events incidences were 6.3% and 13.8%, respectively. In this study, no statistically significant differences for recurrent ICH between two groups were observed. Furthermore, they found an increased relative risk for recurrent ICH following warfarin resumption which was not statistically meaningful. The risk of recurrent ICH was the same (3.9%) among patients who were and were not on OAC in a study performed by Kuramatsu et al. [16] However, the risk of ischemic stroke and vascular death were lower in patients on OAC. Similarly,

Table 1
Demographic characteristics of studied cohort.

	^a OAC resumed (N = 38)	OAC not resumed (N = 55)	Total (N = 93)	P-value
Age, mean ± SD	74.3 ± 10.5	77.2 ± 10.1	89	0.194
Gender, Male, no (%)	25 (65.8%)	25 (46.3%)	50	0.089
INR (warfarin cases) before initial ICH, mean ± SD	2.0 ± 1.1	2.1 ± 1.7	93	0.713
Length of anticoagulants consumption before initial ICH (Months), mean ± SD	68.5 ± 65.5	51.3 ± 47.8	57	0.262
Length of follow-up months, mean ± SD	22.7 ± 22.4	28.8 ± 22.0	93	0.195

^a OAC: Oral Anticoagulation.

Nielsen et al. [17], results that showed a lower rate of cerebral ischemic events after resumption of warfarin compared to AF patients who did not. It was shown by Kuramatsu et al. [16] that the risk of ischemic stroke was significantly lower among patients who resumed OAC (12.7% vs. 3.9%). In our study, there was no significant difference between the two groups regarding the incidence rate of ischemic stroke or systemic emboli.

Our findings suggest that OAC resumption after OAC-ICH might increase the risk of recurrent ICH (5.5% vs. 1.5%), although the difference was not statistically meaningful. This is similar to findings from previous studies [15,18]. Nevertheless, studies suggest that OAC resumption after OAC-ICH can be beneficial in terms of ischemic stroke prevention [19–21]. Furthermore, a joint analysis of different studies by Murphy et al. revealed that patients who had their anticoagulation therapy resumed after ICH have better functional recovery [22]. None of these studies provide enough evidence regarding the selection criteria for patients who resumed OAC.

Majeed et al. [13] reported a five-times increase in recurrent ICH following OAC resumption. This outstanding risk increment of recurrent ICH could be partially related to a higher risk of SDH (subdural hematoma) recurrence in comparison with ICH (16% vs. 8.4%, $p = .07$). In another study, a three times increase in the risk of ICH recurrence has been observed among ICH patients who resumed OAC [23]. Nevertheless, this study had some limitations including a small number of patients in the OAC resumption group and a small number of AF patients (4 patients). Considering the reports of increased risk of recurrent ICH following OAC therapy, there is an ongoing randomized clinical trial studying the effectiveness of Apixaban as an alternative to other anticoagulants or antiplatelets in optimal prevention of ischemic

stroke among patients with AF after OAC-ICH [24]. This trial aims to define a clear estimate of vascular death rate or ischemic stroke in AF patients following an OAC-ICH. The results of this multicenter trial can provide further clinical evidence in support of or against the effectiveness of OAC, in this case Apixaban, among this group of AF patients.

At this time, there is no certainty about the optimal time to resume OAC following OAC-ICH [6,25]. The most recent American Heart Association/American Stroke Association guidelines recommend four weeks after ICH as the optimal time for OAC restart in ICH survivors (patients with prosthetic heart valve are excluded) [26]. There is limited evidence regarding the optimal time for OAC resumption among patients with a prosthetic heart valve following ICH. In a recent survey of field experts, a four to fourteen day delay for OAC resumption following OAC-ICH was preferred [27], however in a systematic review and meta-analysis by AlKherayf et al. [28], four to seven days post-ICH was found to be the optimal time for OAC resumption. More OAC indication-based studies are needed to clarify the optimal time for post-ICH, OAC resumption.

It is difficult to reach a conclusion given the heterogeneity of published studies on this topic and the absence of clinical consensus among physicians. We suggest that OAC resumption be considered based on patients' specific clinical characteristics and neuroimaging findings, for example: comorbidities, age, anatomic location of ICH. We exclude patients who we consider to potentially have amyloid angiopathy as evidenced by multiple cortical cerebral microbleeds on susceptibility MRI sequences. These patients can be at higher risk for developing an ICH [29]. Our study had limitations. This is a retrospective interpretation of data and we had small sample size. OAC resumption was not decided randomly, and risk-benefit of OAC resumption were

Table 2
Medical history and outcome of studied cohort.

	^a OAC resumed (N = 38)	OAC not resumed (N = 55)	Total (N = 93)	P-value
Past medical history				
History of ischemic stroke, no (%)	11 (28.9%)	16 (29.1%)	27	1.000
Congestive heart failure, no (%)	12 (31.6%)	13 (23.6%)	25	0.477
Hypertension, no (%)	31 (81.6%)	46 (83.6%)	77	0.788
Diabetes mellitus, no (%)	14 (36.8%)	12 (21.8%)	26	0.158
Coronary artery disease, no (%)	10 (26.3%)	10 (18.2%)	20	0.443
Transient ischemic attack, no (%)	4 (10.5%)	5 (9.1%)	9	1.000
History of other thromboembolic events, no (%)	4 (10.5%)	1 (1.8%)	5	0.155
Smoking, no (%)	8 (21.1%)	8 (14.5%)	16	0.420
Patients on antiplatelet (Aspirin/Plavix) before ICH, no (%)	15 (39.5%)	16 (29.1%)	31	0.372
Oral Anticoagulant medication before initial ICH				
Warfarin (Coumadin), no (%)	32 (84.2%)	50 (90.9%)	82	0.264
Rivaroxaban (Xarelto), no (%)	2 (5.3%)	4 (7.3%)	6	
Apixaban (Eliquis), no (%)	2 (5.3%)	1 (1.8%)	3	
Dabigatran (Pradaxa), no (%)	2 (5.3%)	0 (0.0%)	2	
Indication for oral anticoagulant before initial ICH				
Atrial fibrillation, no (%)	32 (84.2%)	50 (92.6%)	82	0.195
Atrial fibrillation + prosthetic heart valve, no (%)	2 (5.3%)	0 (0.0%)	2	
Multiple factors, no (%)	4 (10.5%)	4 (7.4%)	8	
Outcomes				
Recurrent ICH, no (%)	5 (13.5%)	3 (5.5%)	8	0.260
Ischemic stroke & systemic embolism, no (%)	7 (18.4%)	10 (18.2%)	17	1.000
Death no (%)	10 (27.0%)	20 (36.4%)	30	0.375

^a OAC: Oral Anticoagulation.

Table 3
Outcome incidence rates for studied cohort.

	Incidence rate in ^a OAC resumed (per 1000 patient-years)	Incidence rate in OAC not resumed (per 1000 patient-years)	Relative risk	95% Confidence interval
Outcome				
Recurrent ICH	55	15	2.9	0.3–30.8
Ischemic stroke & systemic embolism	76	69	0.9	0.3–2.7
Death	96	121	0.8	0.3–1.9

^a OAC: Oral Anticoagulation.

calculated for every single patient independently by the treating physician. The decision to resume or not resume oral anticoagulant therapy was also based on the experience and comfort level of the treating physician as well as the comfort level of the patient and their family. Nevertheless, there was no significant difference between the two groups in terms of common stroke risk factors. We did not have further information about average ICH score between groups. We did not classify our outcome analysis based on the anatomic location of the primary ICH and we did not use any of the risk stratification tools (e.g., CHA₂DS₂-VASc or HAS-BLED score). It has been shown that survivors of deep hemispheric ICH with AF had a lower risk of recurrent ICH after OAC resumption compared to patients with lobar ICH [30]. This difference seems to be related to distinctive underlying pathophysiology in the development of ICH in the deep hemispheric and lobar regions. Hypertensive vasculopathy is the main responsible mechanism for ICH in the deep hemispheric regions which makes risk of recurrent ICH limited by hypertension control. However, cerebral amyloid angiopathy is the responsible mechanism for lobar ICH in studied elderly patients for which there is no known treatment for it [31–33].

In conclusion, the results of our observational study did not show any significant difference between the group of patients who resumed OAC and the patients who did not in terms of recurrent ICH, ischemic stroke or systemic emboli, and death. However, there was a tendency toward a higher long-term risk of recurrent ICH among patients who resumed OAC.

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Informed consent

Written informed consent was obtained from all subjects before the study.

Ethical approval

Institutional Review Board of Geisinger approved this study.

Guarantor

Ramin Zand

Contributorship

Alireza Sadighi: Chart Review, Manuscript Writing, Statistical Analysis.

Lisa Beckett; Heather DiCristina; Thomas Wagner; Kathryn Wright; Kellie Capone; Maureen Monczewski; Margaret Kester; George Bourdages: Data Gathering, Manuscript Review.

Christoph Griessenauer: Manuscript Review.

Ramin Zand: Study Design, Manuscript Writing, Statistical Analysis.

Declaration of Competing Interest

The Authors declare that there is no conflict of interest.

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