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Effectiveness and Safety of Restarting Oral Anticoagulation in Patients with Atrial Fibrillation after an Intracranial Hemorrhage: Analysis of Medicare Part D Claims Data from 2010–2016

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Abstract

Background—In patients with atrial fibrillation (AF) who survive an anticoagulant-related intracranial hemorrhage (ICH), the benefits of restarting oral anticoagulation (OAC) remain unclear.

Objective—In this study we sought to determine the effectiveness and safety associated with resumption of OAC in atrial fibrillation patients who survive an ICH.

Methods—Using 2010–2016 Medicare claims data, we identified patients with non-valvular AF who experienced an OAC-related ICH and survived at least 6 weeks after the ICH (n=1,502). The primary outcomes included the composite of ischemic stroke and transient ischemic attack (TIA), thromboembolism (TE), a composite of ischemic stroke/TIA and TE, recurrent ICH, and all-cause mortality. We constructed Cox proportional hazard models to evaluate the association between post-ICH OAC resumption, which was measured in a time-dependent manner, and the risk of primary outcomes while controlling for a comprehensive list of covariates.

Results—Among patients who survived an ICH, 69% reinitiated OAC within 6 weeks of the event and among those who resumed OAC, 83% restarted warfarin. There was no significant difference in the risk of ischemic stroke/TIA [hazard ratio (HR) 0.87; 95% CI 0.62–1.21], TE (HR 0.85; 95% CI 0.55–1.32), and ischemic stroke/TIA/TE (HR 0.81; 95% CI 0.61–1.07) between post-ICH OAC use and non-use. Post-ICH OAC use was associated with a lower risk of recurrent ICH (HR 0.62; 95% CI 0.41–0.95) and all-cause mortality (HR 0.48; 95% CI 0.37–0.62) compared to non-OAC use.

Conclusions—In AF patients who survived an ICH, restarting OAC was not associated with a greater risk of recurrent ICH. Evidence from randomized controlled studies is needed to further

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clarify the clinical benefit of restarting OAC in this high-risk population. Further evaluation of which individuals benefit from restarting OAC is also needed to provide more clinical guidance.

Keywords

Anticoagulants; Atrial Fibrillation; Hemorrhage; Stroke

Subject terms:

Atrial Fibrillation; Intracranial Hemorrhage; Ischemic Stroke; Quality and Outcomes

INTRODUCTION

The most common cardiac arrhythmia, Atrial Fibrillation (AF), is associated with a five-fold increase in the risk of stroke and accounts for 15–20% of all ischemic strokes [1, 2]. Oral anticoagulation (OAC) is recommended for stroke prevention in patients with an intermediate or high risk of stroke, which is measured as having a CHA₂DS₂-VASc score ≥ 2 [3]. While OAC decreases the risk of stroke and systemic embolism by two thirds, it also increases the risk of bleeding [4–6]. Intracranial hemorrhage (ICH) is the most serious bleeding complication and the leading cause of death and disability associated with OAC use [7]. It has been estimated that 35–52% of patients who suffer a ICH die within 30 days of the event [8].

The clinical benefit of OAC reinitiation in AF patients who survive an ICH is unclear. On one hand, ICH survivors are at increased risk of experiencing a recurrent ICH; and on the other hand, the occurrence of ICH increases the risk for ischemic stroke and systemic embolism [9]. Because most clinical trials evaluating anticoagulants excluded patients with a history of ICH, the effectiveness and safety of OAC in this patient population remains unknown [10]. Using Danish national registries, Nielsen et al. evaluated the resumption of OAC in AF patients who presented with an ICH and found that post-ICH OAC resumption decreases the risk of ischemic stroke and mortality without increasing the risk of ICH recurrence [11]. This study, however, mostly used data that preceded the approval of direct oral anticoagulants (DOACs), and may not be representative of the US population [11, 12].

In this study, we used Medicare Part D claims data from 2010–2016 to clarify effectiveness and safety outcomes associated with the resumption of OAC in AF patients who survived an ICH.

2 METHODS

2.1 Data Source and Study Population

We obtained 2010–2016 pharmacy and medical claims data for beneficiaries enrolled in United States (US) Medicare, provided by the Centers for Medicare and Medicaid Services (CMS). The data that support the findings of this study cannot be made available upon request because it was obtained under a data user agreement that does not allow for data sharing. The most relevant files for this study include a) the Master Beneficiary Summary Files, which contain demographic and enrollment information, b) inpatient and outpatient

medical claims, which contain diagnosis, procedure codes, and dates of service, and c) pharmacy claims, which contain national drug code, generic name, quantity dispensed, date of fill, and days of supply for each prescription.

We selected the study sample in 6 steps (Figure 1): First, using inpatient claims, we identified all patients with a primary diagnosis of ICH in 1/1/2010–10/31/2016, including subarachnoid hemorrhage, intracerebral hemorrhage, and other intracranial hemorrhages (n=34,205, lists of ICD-9 and ICD-10 codes in Supplemental Table 1). Since our data source contained patient data until 12/31/16, the date of 10/31/16 was chosen to ensure all patients had enough follow-up time to ensure a 6-week quarantine period and observe any outcomes. For each patient, the index date was defined as the date of the first inpatient claim with a primary diagnosis of ICH in this time window. Second, we further selected patients who had a diagnosis of AF prior to the index date. AF was defined using CMS Chronic Condition Warehouse definition (n=8,404) [13]. Third, we excluded beneficiaries with a diagnosis of valvular AF (ICD 9: 394.0, V43.3; ICD 10: I05.0, Z95.2) before index date. Fourth, using pharmacy claims, we further constrained for patients who filled a prescription for an OAC, including warfarin, dabigatran, apixaban, rivaroxaban, or edoxaban, within 6 months before the index date (n=2,958). Fifth, because we started to observe patient outcomes 6 weeks after the index ICH, we excluded patients who died within this 6-week time window (n=1,795). Finally, we only included patients who had continuous enrollment in Medicare Part D after the index ICH event for 12 months or until death, whichever occurred first. The final sample included 1,502 patients who were followed from their index ICH event until the occurrence of death or the end of the study period. As previously done in the literature, we started to observe patient outcomes 6 weeks after the index ICH in order to make sure that outcomes observed over the follow-up period were related to the restart of OAC rather than to the ICH index event [11].

2.2 Outcomes

Our study included 5 primary outcomes: the composite of ischemic stroke and transient ischemic attack (TIA), thromboembolism, the composite of ischemic stroke, TIA and thromboembolism, ICH, and all-cause mortality (Supplemental Table 2). Outcomes were collected after a 6-week quarantine period from the date of index ICH.

2.3 Exposure to Oral Anticoagulation Therapy

We extracted all prescriptions for warfarin, apixaban, dabigatran, rivaroxaban and edoxaban filled after the ICH event. Using the dates of fill and days of supply, we constructed a supply diary to track daily OAC possession. We defined a variable for every day of the follow-up period to indicate whether patients possessed any OAC. Then, using these indicator variables, we defined exposure to OAC in a time-dependent manner as follows: on each day of follow-up OAC use was defined as having at least 1 day with possession of an OAC within the previous 7 days. No OAC use was then defined as not having any OAC possession in the previous 7 days. For example, to classify exposure to OAC for a patient on September 14th, we observed daily indicator variables from September 8–14th. If, on any day in that time period, the patient had possession of an OAC, then on September 14th the patient will be coded as having OAC use. This exposure classification was done for all patients for every

day of the follow-up period. All analyses evaluating association between OAC use and primary outcomes were performed using this time-varying OAC exposure.

2.4 Covariates

Covariates included demographics, clinical characteristics, factors capturing severity of index ICH, and prior medication use. Demographic factors included age, gender, and race. Clinical characteristics included congestive heart failure (CHF), hypertension, renal disease, liver disease, diabetes, vascular disease, ischemic stroke/TIA, thromboembolism, bleeding, CHADS2-VASc score, and HAS-BLED score. The HAS-BLED score is a validated prediction tool used to measure the risk of bleeding with OAC [14]. Since Medicare claims data do not contain international normalized ratio (INR) levels, we calculated HAS-BLED scored as the sum of 8 factors excluding labile INR. CHF, hypertension, renal disease, diabetes, and stroke or TIA were defined according to CMS Chronic Condition Warehouse definitions [13]. The remaining clinical covariates were identified using ICD-9 and ICD-10 diagnosis codes from claims in the year prior to the index event (see Supplemental Table 1 for lists of ICD-9 and ICD-10 procedure codes). Covariates capturing the severity of index ICH included the type of ICH (intracerebral bleeding vs. subarachnoid hemorrhage, subdural hemorrhage, or other), length of stay, intensive care unit (ICU) length of stay, quantity of blood transfused during index hospital stay, receipt of surgery, and lifetime reserve days. Prior medication use includes the receipt of beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, loop diuretics, statins, non-steroidal anti-inflammatory agents, antiplatelets, and digoxin in the year prior to index date (Supplemental Table 3).

2.5 Statistical Analysis

We first compared baseline patient characteristics between the OAC restart and non-restart groups, defined on a time-independent manner, using chi-square tests and two-sample t-tests as appropriate. Because it would not be possible to compare baseline patient characteristics according to time-dependent OAC exposure, we classified study participants in a time-invariant manner, according to whether they filled at least one OAC prescription on the first day after a 6-week quarantine period. This time-invariant exposure was only used to compare baseline patient characteristics. To evaluate the association between time-dependent OAC use and time to primary outcomes we constructed Cox proportional hazards models which adjusted for all the covariates listed in Table 1 and included a time-dependent variable for OAC use. Time 0 was the last day of the quarantine period (6-weeks after index date), and time at risk was censored at death or end of the study period (except for the analyses where death was the primary outcome, in which case death was not a censoring event but the outcome of interest). All analyses were performed using statistical software SAS 9.4 (Cary, NC).

2.6 Sensitivity Analyses

In primary analyses, we defined OAC exposure as any possession of an OAC in the previous 7 days. To assess the robustness of our findings we performed sensitivity analyses by observing OAC exposure in the time windows of 14 days and 30 days.

3 RESULTS

3.1 Patient Characteristics

Among patients who survived an ICH, 69% reinitiated OAC within 6 weeks of an ICH. Among those who resumed OAC, 83% restarted on warfarin. The average follow-up time for all patients was 780 days. Table 1 shows patient characteristics across two groups defined by OAC use on the first day following the 6-week quarantine period. Patients who restarted OAC had lower CHADS₂-VASc and HAS-BLED scores and lower prevalence of chronic diseases such as CHF, renal disease, vascular disease, and previous ischemic stroke or TIA. Additionally, patients who restarted OAC experienced shorter lengths of stay in the hospital and were more likely to present with intracerebral hemorrhage as the type of ICH compared to subarachnoid hemorrhage, subdural hemorrhage, and other types of intracranial hemorrhages.

3.2 Restart of Oral Anticoagulation

Figure 2 depicts the proportion of patients who possessed an OAC following an index ICH event starting after a 6-week quarantine period. Our study shows that within the first month after the quarantine period, or between 2 and 3 months from the index ICH, an average of 20% of study participants possessed an OAC. Following the third month post-ICH, OAC possession decreased slightly, and then remained relatively steady throughout the year.

3.3 Unadjusted Rates of Events

Table 2 shows the unadjusted incidence rates for all outcomes. The unadjusted incidence rates of ischemic stroke/TIA did not differ significantly between post-ICH OAC use [6.17 per 100 person-years (p-y); 95% CI, 4.65–8.19] and non-use (7.52; 95% CI, 6.40–8.83). Likewise, unadjusted rates of thromboembolism and the composite of stroke/TIA/thromboembolism did not differ significantly between post-ICH OAC use and non-use. However, no OAC use was associated with a higher incidence rate of recurrent ICH (5.80; 95% CI, 4.83–6.96) and all-cause mortality (28.29; 95% CI, 26.13–30.62) compared to OAC use (3.29; 95% CI, 2.27–4.77), (12.11; 95% CI, 10.01–14.65). Supplemental Figure 1 shows unadjusted hazard ratios for the comparisons of primary outcomes between OAC use and non-use.

3.4 Adjusted Hazard Ratios

After adjusting for covariates listed in Table 1, the hazards of ischemic stroke/TIA did not significantly differ between post-ICH OAC use and non-use, with hazard ratio (HR) 0.87; 95% CI, 0.62–1.21 (Figure 3). Similarly, there was no significant difference between OAC use and non-use in the risks of thromboembolism (HR 0.85; 95% CI, 0.55–1.32) and the composite of ischemic stroke/TIA/thromboembolism (HR 0.81; 95% CI, 0.61–1.07). Although these events did not reach statistical significance, there was a trend towards decreased risk associated with OAC use. Compared to non-use, post-ICH OAC use was associated with lower hazards of ICH (HR 0.62; 95% CI, 0.41–0.95) and all-cause mortality (HR 0.48; 95% CI, 0.37–0.62).

3.5 Sensitivity Analyses

The results from our original analyses were consistent with the results from the sensitivity analysis using a 14-day time window of OAC exposure (Supplemental Figure 2). We also obtained similar findings with a definition of OAC exposure in a 30-day time window, aside from the effect of OAC on ICH, which became non-significant.

4 DISCUSSION

To our knowledge, our study is the first real-world analysis to use a nationally representative sample of the Medicare population to evaluate clinical outcomes associated with the resumption of OAC in AF patients who survive an ICH. We found that 69% of AF patients who survived an ICH restarted OAC within 6 weeks of the event, and among those who did, 83% restarted warfarin. Post-ICH OAC use was not associated with a significantly lower thromboembolic risk than non-use, yet, it was not associated with a higher risk of recurrent ICH either.

Using Danish national registry data, Nielsen et al. found that OAC resumption in AF patients surviving an ICH was associated with a lower risk of ischemic stroke and all-cause mortality without conferring a greater risk of recurrent ICH as compared to no resumption [11]. Additionally, using data collected from patient interviews and medical records from Germany and the US, Biffi and colleagues showed that restarting OAC in AF patients surviving after an intracerebral hemorrhage decreased mortality and increased functional outcomes [15]. Other systematic reviews and meta-analyses included studies from multiple geographic regions and generally concluded that restarting OAC is beneficial in decreasing the risk of thromboembolic events without increasing the risk of a recurrent intracerebral hemorrhage [16–19]. Our results are in part consistent with this existing body of literature, since we found that post-ICH OAC resumption was not associated with a higher risk of recurrent ICH. In fact, our estimates for the comparative risk of recurrent ICH signaled that OAC resumption was associated with a lower risk of recurrent ICH. This finding may reflect residual confounding, since individuals who restarted OAC were generally healthier compared to individuals who did not restart. The lower incidence of ICH events associated with OAC use could also be an artifact of the data, in particular, the difficulty of discerning new ICH events from follow-up care visits for the index ICH in claims data. However, to minimize this problem, we only used inpatient claims to identify recurrent ICH events. With regards to thromboembolic risk, our results failed to confirm prior findings since we did not demonstrate that post-ICH resumption decreases thromboembolic risk. This may have been due to the relatively small sample size and the short follow-up period. Given the established efficacy of OAC for stroke prevention in AF, it is likely that the benefits of post-ICH OAC use in reducing thromboembolic risk would have been observed if patients were followed for longer time periods.

Clinical guidelines provide no clear recommendation on the management of OAC in AF patients who have survived an ICH; therefore, the decision on whether to restart OAC is heterogeneous among clinicians and subject to a large degree of uncertainty [20, 21]. Moreover, since our study did not evaluate OAC adherence on an extended time period, but rather recent exposure to OAC, our results may not capture the long-term benefit of OAC

use. In pondering the benefit/risk ratio of OAC in this high risk subgroup, clinicians should consider known risk factors for recurrent ICH, including hematoma volume, presence of lobar hemorrhage, cerebral amyloid angiopathy, or microbleeds [22]. Future studies evaluating clinical outcomes associated with post-ICH OAC resumption should be conducted with data sources that contain this clinical information. Moreover, due to the difficulty to capture subjective assessments of ICH severity or of clinicians' perceived risks of both recurrent ICH and thromboembolic events, randomized clinical studies would be particularly helpful in the assessment of the benefit/risk ratio of post-ICH OAC resumption. Currently, restarting anticoagulation in AF patients post-ICH is being evaluated in a number of ongoing randomized controlled trials (Table 3) [23–25]. These trials will examine direct oral anticoagulants (DOACs) and warfarin as an intervention arm compared to no antithrombotic therapy or antiplatelet therapy in patients with AF [23–25]. Results from these trials will help to further guide and inform the decision to restart oral anticoagulation after an intracranial hemorrhage.

Our study has limitations. First, in order to capture ICH events related to OAC use, we required that patients had at least one prescription for an OAC six months before the index ICH date. However, claims data only contain information on whether patients refilled prescriptions but not on whether the patient actually took the medication. As a result, it is possible that patients may not have been taking OAC at the time of the index ICH event. Likewise, our time-dependent definition of OAC exposure throughout the study period also assumes that patients were taking OAC as prescribed. Secondly, due to the use of claims data, we did not have information regarding relevant clinical variables such as INR, functional status, or fall risk. Additionally, we were not able to observe results of neuroimaging tests so it was not possible to control for the location of ICH (deep vs. lobar), volume of ICH, and the presence of micro-bleeds. This lack of information could make our findings subject to residual confounding, since it is possible that patients who reinitiated OAC had less severe ICH events. Thirdly, it would have been informative to explore safety and effectiveness data for resumption of DOAC after an ICH event; however, we did not have an adequate sample size to separately study resumption of DOACs. This limits the extent to which we can generalize results to individuals restarting on a DOAC after an ICH. Fourthly, we recognize that our study may be subjected to healthy-user bias where individuals who restart and adhere to OAC may also be more likely to adhere to other healthy behaviors, which can affect the risk of ischemic stroke or ICH. Lastly, in our paper we used a time-dependent study design because patients restarted OAC therapy at different intervals, and this allowed us to correctly categorize patients according to their use of OAC therapy throughout time. However, with the use of time-dependent exposures, it is difficult to assess the balance of patient characteristics across the two treatment groups.

5 CONCLUSIONS

Using claims data from Medicare beneficiaries, we found that restarting OAC in AF patients who survived an ICH is not associated with a greater risk of recurrent ICH. Evidence from randomized controlled studies is needed to further assess the clinical benefit of restarting OAC in this high-risk population. Additionally, evaluation of which individuals benefit from restarting OAC is needed to provide more clinical guidance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- This study used 2010–2016 Medicare Part D claims data to evaluate safety and effectiveness outcomes associated with the restart of oral anticoagulation in patients with atrial fibrillation who survive an intracranial hemorrhage.
- Restarting anticoagulation after an intracranial hemorrhage was not associated with a greater risk of recurrent intracranial hemorrhage compared to not restarting oral anticoagulation.
- Restarting oral anticoagulation was associated with a lower risk of mortality compared to not restarting oral anticoagulation, but the risk of ischemic stroke and thromboembolism did not differ between the two groups.

Figure 1.
Cohort Selection

Notes: Using claims data from a 5% random sample of Medicare part D beneficiaries, we selected patients with an ICH event in 2010–2016. After excluding those with a history of valvular disease and those who died within 6 weeks of an ICH, the final sample included 1,502 continuously enrolled, atrial fibrillation patients who survived an ICH and refilled at least one oral anticoagulant within the past 6 months of an ICH.

Figure 2.

Proportion of Patients with Possession of OAC During the Study Period.

Abbreviations: OAC= Oral Anticoagulation. This figure shows the proportion of patients who possessed OAC during each day of the study period for 1 year, beginning after a 6-week quarantine period.

Adjusted Hazard Ratios for OAC use vs. no OAC use (95% CI)

Figure 3.

Adjusted Hazard Ratios of Primary Outcomes.

Abbreviations: OAC=Oral Anticoagulation; TIA= Transient Ischemic Attack. Hazard ratios were estimated with Cox Proportional Hazard models which included a time-dependent covariate for OAC use and adjusted for all covariates listed in Table 1.

Table 1.

Baseline Characteristics of Study Participants According to the Resumption of Oral Anticoagulation on the First Day after Six-Week Quarantine Period.

Variable—n(%)	Total Population (n=1502)	Restart OAC (n=976)	Non-Restart OAC (n=526)	P-value *	Standardized Difference
Demographics					
Age				0.472	0.074
<65	80 (5.33)	53 (5.43)	27 (5.13)		
65–74	328 (21.84)	222 (22.75)	106 (20.15)		
≥75	1094 (72.84)	701 (71.82)	393 (74.71)		
Female sex	845 (56.26)	549 (56.25)	296 (56.27)	0.993	0.001
Race				0.368	0.087
White	1293 (86.09)	849 (86.99)	444 (84.41)		
Black	117 (7.79)	70 (7.17)	47 (8.94)		
Other	92 (6.13)	57 (5.84)	35 (6.65)		
Clinical Characteristics					
CHA2DS2-VASc score				<0.001	0.249
0–3	110 (7.32)	83 (8.50)	27 (5.13)		
4–5	371 (24.70)	266 (27.25)	105 (19.96)		
6	1021 (67.98)	627 (64.24)	394 (74.90)		
HAS-BLED score ^a				<0.001	0.226
0–1	42 (2.80)	28 (2.87)	14 (2.66)		
2–3	818 (54.46)	569 (58.30)	249 (47.34)		
4	642 (42.74)	379 (38.83)	263 (50.00)		
CHF ^b	1016 (67.64)	636 (65.16)	380 (72.24)	0.005	−0.153
Hypertension ^b	1462 (97.34)	948 (97.13)	514 (97.72)	0.500	−0.037
Renal Disease ^b	749 (49.87)	457 (46.82)	292 (55.51)	0.001	−0.175
Liver Disease ^c	25 (1.66)	13 (1.33)	12 (2.28)	0.170	−0.071
Diabetes ^b	821 (54.66)	524 (53.69)	297 (56.46)	0.303	−0.056
Vascular Disease ^c	375 (24.97)	209 (21.41)	166 (31.56)	<0.001	−0.231
Stroke or TIA ^b	296 (19.71)	421 (43.14)	274 (52.09)	0.001	−0.180
Prior thromboembolism ^c	84 (5.59)	47 (4.82)	37 (7.03)	0.074	−0.094
Prior bleeding ^c	356 (23.70)	219 (22.44)	137 (26.05)	0.117	−0.084
Severity of Index ICH—mean (SD) ^d					
Intracerebral Hemorrhage ^e	753 (50.13)	512 (52.46)	241 (45.82)	0.014	0.133
Quantity of blood (pints) transfused during stay	0.08 (0.64)	0.07 (0.66)	0.08 (0.60)	0.904	−0.033
Hospital/SNF length of stay (days)	11.41 (16.76)	9.93 (11.64)	14.14 (23.23)	<0.001	−0.175
Lifetime reserve days used	0.01 (0.28)	0.01 (0.34)	0.00 (0.00)	0.340	0.064

Variable—n(%)	Total Population (n=1502)	Restart OAC (n=976)	Non-Restart OAC (n=526)	P-value *	Standardized Difference
Intensive care days used by beneficiary for stay	3.49 (5.75)	3.76 (5.99)	2.99 (5.23)	0.013	0.222
Prior medication use—n(%) ^f					
B-Blockers	1149 (76.50)	754 (77.25)	395 (75.10)	0.347	0.051
ACE-I/ARBs	865 (57.59)	579 (59.32)	286 (54.37)	0.064	0.100
Calcium channel blockers	615 (40.95)	398 (40.78)	217 (41.25)	0.858	−0.010
Loop diuretics	728 (48.47)	458 (46.93)	270 (51.33)	0.103	−0.088
Statin	902 (60.05)	606 (62.09)	296 (56.27)	0.028	0.119
NSAIDs	164 (10.92)	108 (11.07)	56 (10.65)	0.804	0.014
Antiplatelets	152 (10.12)	80 (8.20)	72 (13.69)	0.001	−0.177
Digoxin	371 (24.70)	229 (23.46)	142 (27.00)	0.130	−0.081
Amiodarone	170 (11.32)	110 (11.27)	60 (11.41)	0.937	−0.004

Notes:

Abbreviations: OAC=Oral Anticoagulation; CHF= Congestive Heart Failure; TIA= Transient Ischemic Attack; SNF= Skilled Nursing Facility; B-Blockers= Beta Blockers; ACE-I=Angiotensin-Converting Enzyme Inhibitors; ARBs= Angiotensin Receptor Blockers; NSAIDs= Non-Steroidal Anti-inflammatory Drug.

* P-values were derived from chi-squared and Student's t-tests.

^aBecause Medicare claims data do not contain information on INR levels, we calculated a modified HAS-BLED score that did not include labile INR.

^bCHF, hypertension, renal disease, diabetes, and stroke or TIA were defined using the respective CMS Chronic Condition Warehouse definitions of each of these conditions.

^cLiver disease, vascular disease, prior thromboembolism, and prior bleeding were each defined using their respective ICD-9 and ICD-10 codes in the year prior to the index ICH.

^dSeverity of index ICH characteristics were defined using inpatient claims from the hospitalization related to the index ICH event.

^eIntracerebral hemorrhage refers to the anatomical location of the index ICH.

^fMedication use was defined in the year prior to index ICH date.

Table 2.

Number of Events and Unadjusted Incidence Rates of Primary Outcomes.

	OAC Use	Non-OAC Use
Patient-years (% of Total Time-at-Risk)	875.20 (28.83%)	2,160.03 (71.17%)
Stroke/TIA		
No. Events	48	149
Incidence per 100 p-y (CI)	6.17 (4.65, 8.19)	7.52 (6.40, 8.83)
Thromboembolism		
No. Events	27	92
Incidence per 100 p-y (CI)	3.43 (2.35, 5.00)	4.48 (3.65, 5.49)
ICH		
No. Events	28	116
Incidence per 100 p-y (CI)	3.29 (2.27, 4.77)	5.80 (4.83, 6.96)
Stroke/TIA/Thromboembolism		
No. Events	66	230
Incidence per 100 p-y (CI)	9.36 (7.36, 11.92)	12.19 (10.71, 13.87)
All-Cause Mortality		
No. Events	106	611
Incidence per 100 p-y (CI)	12.11 (10.01, 14.65)	28.29 (26.13, 30.62)

Abbreviations: p-y= person-years; OAC= Oral Anticoagulation; TIA=Transient Ischemic Attack; ICH=Intracranial Hemorrhage.

OAC use was defined as having any OAC possession within the previous 7 days of each event. Non-OAC use was defined as having no OAC possession within the previous 7 days of each event. The total time-at-risk accounts for the total time spent in each time-dependent treatment group for all study participants starting after the 6-week quarantine period.

Table 3.
Ongoing Randomized Controlled Trials Evaluating Effectiveness and Safety of Oral Anticoagulants Post-Intracranial Hemorrhage in Atrial Fibrillation Patients

Study Title	NCT Identification Number	Study Population	Intervention	Comparator	Primary Outcomes	Estimated Enrollment Number	Estimated Completion Date
Start or Stop Anticoagulants Randomised Trial (SoSTART) After Spontaneous Intracranial Hemorrhage	NCT03153150	Adults with persistent or paroxysmal atrial fibrillation/flutter who survive a spontaneous symptomatic ICH	VKA or DOAC	Antiplatelet or no antithrombotic drugs	Composite of non-fatal acute coronary syndrome, non-fatal stroke, and death	800 patients	July 2021
Prevention of Stroke in Intracerebral Hemorrhage Survivors with Atrial Fibrillation (PRESTIGE-AF)	NCT03996772	Adults with AF and recent spontaneous intracerebral hemorrhage	DOAC	Antiplatelet or no antithrombotic drugs	Ischemic stroke, intracerebral hemorrhage	654 patients	July 2022
NOACs for Stroke Prevention in Patients With Atrial Fibrillation and Previous ICH (NASPAF-ICH)	NCT02998905	Adults with high-risk AF (CHADS ₂ 2 and previous spontaneous or traumatic ICH)	DOAC	Acetylsalicylic acid	Composite of ischemic stroke and recurrent intracerebral hemorrhage	100 patients	January 2020

Abbreviations: AF=Atrial Fibrillation; DOAC=Direct Oral Anticoagulant; ICH=Intracranial Hemorrhage; NCT=National Clinical Trial; NOAC= New Oral Anticoagulant; VKA= Vitamin K Antagonists.