Title

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Authors

Saeed, Omar
Zhang, Shuaiqi
Patel, Snehal R
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Omar Saeed, MD[a], **Shuaiqi Zhang, MS**[b], **Snehal R. Patel, MD**[a], **Ulrich P. Jorde, MD**[a], **Mario J. Garcia, MD**[a], **Nurilign Bulcha, MD**[c], **Tanush Gupta, MD**[d], **Ying Xian, MD, Ph.D**[b], **Roland Matsouaka, Ph.D.**[b], **Shreyansh Shah, MD**[e], **Eric E. Smith, MD, MPH**[f], **Lee H. Schwamm, MD**[g], **Gregg C. Fonarow, MD**[h]

[a]Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY

[b]Department of Neurology, Duke University School of Medicine, Raleigh, NC

[c]Division of Cardiology, University of Pennsylvania Hospital Center, Philadelphia, PA

[d]Division of Cardiology, Columbia University Medical Center, New York, NY

[e]Duke Clinical Research Institute, Raleigh, NC

[f]Calgary Stroke Program, Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Canada

[g]Department of Neurology, Massachusetts General Hospital, Boston, MA

[h]Division of Cardiology, University of California, Los Angeles, Los Angeles, CA

Abstract

Background: The safety and effectiveness of oral anticoagulation (OAC) after an ischemic stroke in older patients with heart failure (HF) without atrial fibrillation remains uncertain.

Methods: Utilizing Get With The Guidelines Stroke national clinical registry data linked to Medicare claims from 2009–2014, we assessed the outcomes of eligible patients with a history of HF who were initiated on OAC during a hospitalization for an acute ischemic stroke. The cumulative incidences of adverse events were calculated using Kaplan-Meier curves and adjusted Cox proportional hazard ratios were compared between patients discharged on or off OAC.

Results: A total of 8,261 patients from 1,370 sites were discharged alive after an acute ischemic stroke and met eligibility criteria. Of those, 747 (9.0%) were initiated on OAC. Patients on OAC

Address for Correspondence: Omar Saeed, MD, Montefiore Medical Center, Albert Einstein College of Medicine, 3400 Bainbridge Avenue, MAP Building 7th floor, Bronx, N.Y. 10467, Phone: 718 920-2248, Fax: 718 652-1833, osaeed@montefiore.org.

were younger (77.2±8.0 vs. 80.5±8.9 years, p<0.01). After adjustment for clinical covariates, the likelihood of 1 year mortality was higher in those on OAC (aHR: 1.22, 95% CI 1.05–1.41, p<0.01), while no significant differences were noted for ICH (aHR: 1.34, 95% CI 0.69–2.59, p=0.38) and recurrent ischemic stroke (aHR: 0.78, 95% CI 0.54–1.15, p=0.21). The likelihood of all-cause bleeding (aHR: 1.59, 95% CI 1.29–1.96, p<0.01) and all-cause re-hospitalization (aHR: 1.14, 95% CI 1.02–1.27, p=0.02) was higher for those on OAC.

Conclusion: Initiation of OAC after an ischemic stroke in older patients with HF in the absence of atrial fibrillation is associated with death, bleeding and re-hospitalization without an associated reduction in recurrent ischemic stroke. If validated, these findings raise caution for prescribing OAC to such patients.

Keywords

Heart Failure; Oral Anticoagulation; Mortality; Stroke; Hemorrhage

Introduction

Heart failure (HF) invokes a hypercoagulable state through reduced flow, abnormalities in hemostasis and platelet dysregulation and endothelial dysfunction.[1, 2] Activation of these elements from Virchow's triad promotes thrombus formation and increases the risk of cerebral embolism.[1] This risk of ischemic stroke persists in the absence of atrial fibrillation and is reported to be 0.69–1.5% per 100 patient years.[3] Oral anticoagulation (OAC) reduces the burden of ischemic stroke in patients with co-existent atrial fibrillation and HF.[4] However, several randomized clinical trials have failed to show a net benefit of OAC in patients with HF with reduced ejection fraction in sinus rhythm.[5, 6] The risk of ischemic stroke without concurrent atrial fibrillation remains elevated in HF patients with reduced or preserved ejection fraction[7] but the role of OAC in higher risk subgroups remains uncertain.

A prior history of an ischemic stroke is a strong risk factor for recurrence[3], but it remains unknown if initiation of OAC, in these higher risk patients with HF without atrial fibrillation, is beneficial. To address this gap in knowledge, we queried a national registry linked to Medicare claims data to assess the safety and clinical effectiveness of OAC after an ischemic stroke in older patients with HF in the absence of atrial fibrillation.

Methods

Data Source

The data for this investigation was derived from the American Heart Association and American Stroke Association's Get With The Guidelines-Stroke (GTWG-S) registry. This registry is a voluntary, national, performance initiative which utilizes internet-based entry of cases by participating hospitals to improve delivery of care to patients with stroke. Additional details about the registry have been previously described.[8, 9] To track outcomes, the registry data was linked to Medicare claims from the US Centers of Medicare and Medicaid Services (CMS). Patients admitted with a diagnosis of acute ischemic stroke were eligible for inclusion in this study. Ischemic stroke was determined through the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 434.91,

434.11 and 434.01. The registry contains demographics, arrival and admission information, medical history, results of physical examination and laboratory testing and discharge medications. IQVIA serves as the data collection (through their Patient Management Tool™ – PMT™) and coordination center for GWTG. The Duke Clinical Research Institute (DCRI) serves as the data analysis center and has an agreement to analyze the aggregate de-identified data for research purposes. Medicare data consists of 100% Medicare inpatients claims, along with the corresponding denominator files from 2009 through 2014. These inpatient files contain institutional claims with costs covered by Medicare Part A and additional encrypted beneficiary identifiers including demographic information, dates of service, diagnosis related groups (DRGs), and ICD-9-CM codes. The denominator files contain encrypted beneficiary identifiers, demographics, date of death and information pertaining to program enrollment. The linking procedure between the GTWG registry to CMS has been described previously.[10] In brief, the registry data is linked to indirect hospital identifiers, including hospital identifier, admission date, discharge date, and birth date in CMS files.[11, 12] After the data is linked to unique beneficiaries, Medicare identifiers are used to get information for subsequent clinical events. The Duke University Health System institutional review board approved the study.

Study Cohort

Derivation of the study cohort is depicted in figure 1. Overall, 493, 709 patients at 1,864 sites had an index hospitalization for an acute ischemic stroke who survived to discharge from January 1, 2009 through December 31, 2014 and were captured by the GWTG-S registry with linkable claims to CMS. Of these, 440,708 were excluded due to no reported history of HF, and an additional 29,674 were not included due to known history of AF. After further exclusion of patients with prior strokes or transient ischemic attack (TIA), already being on OAC at admission, mechanical heart valves, carotid stenosis, and not being discharged on any antithrombotics, a study cohort of 8,261 patients from 1,370 sites was derived. Patients with a deep vein thrombus (DVT) and / or pulmonary embolism (PE) were not excluded since the registry does not capture clot location and the independent indication for OAC in such cases.

Exposure

OAC at discharge from the index acute ischemic stroke hospitalization was the exposure of interest for this investigation. Patients receiving OAC with either warfarin or Direct Oral Anticoagulants (DOACs) were grouped together, as warfarin was utilized in over 90% of the patients.

Outcomes

The primary outcomes of interest were all-cause mortality, recurrent ischemic stroke and intracranial hemorrhage at 1 year. To evaluate the aggregate safety and effectiveness of OAC, the preceding outcomes were also assessed as a composite outcome at 1 year. Secondary outcomes included all-cause bleeding and all-cause rehospitalization at 1 year. GWTG-Stroke is an established and validated registry for accurately recording and reporting the outcomes of interest.[13] Outcomes were determined from the Medicare denominator files with their corresponding DRGs as described previously.[9] Days to outcomes were calculated

from the date of discharge of the hospitalization with the initial ischemic stroke. For patients that did not have an outcome, the censoring date was the earliest of the following: 1) 1 year after discharge, 2) the end of the period for which the follow-up data was available (December 31, 2015) or 3) the data at which the patient's data were no longer available due to the patient no longer being enrolled in Medicare.

Subgroups

The NIH Stroke Scale (NIHSS)[14] score was only available in a portion (71%) of the cohort. To assess its impact as a covariate, a subgroup analysis was conducted only for those patients with an available NIHSS score.

Statistical Analysis

Continuous data are displayed as mean ± SD or as median with Q1–Q3 interquartile range (IQR), and were compared between the OAC and no OAC groups by the Wilcoxon rank sum test, unless otherwise specified. Categorical data, shown as percent, were compared by the Pearson χ^2 tests. Given the large sample size, it was possible to see significant differences based on p-values, thus an absolute standardized difference was also reported. For clinical characteristics, a percent standardized difference greater than 10 indicates a substantial difference.[15] Cumulative incidence of the outcome was calculated by Kaplan Meier analysis. For rehospitalization and non-fatal outcomes, the cumulative incidence accounts for the competing risk of mortality. Log-rank test was used to assess the difference in all-cause mortality, and the composite of all-cause mortality, intracranial hemorrhage and recurrent ischemic stroke. Gray's test was used to assess the difference in intracranial hemorrhage, recurrent ischemic stroke, and rehospitalization. Cox proportional regression was used to calculate unadjusted and adjusted hazards ratios (aHR). This allowed to appropriately consider censoring and for differential follow-up time. Robust sandwich variance estimators are used in the Cox models to account for correlation among patients from the same hospital and a cause-specific Cox model is used to account for the competing risks of deaths in the assessment of non-mortality outcomes. In the adjusted model, the covariates included were age, sex, race/ethnicity, insurance status, history of coronary artery disease or myocardial infarction (MI), diabetes, peripheral vascular disease, dyslipidemia, smoking status, arrival via EMS, arrival on vs. off hours, hospital region, hospital type (teaching or non-teaching), number of beds, annual ischemic stroke volume, rural location, The Joint Commission (TJC) primary stroke center status, dual or single antiplatelet therapy at discharge. A log-rank or Gray's test p-value less than 0.05 indicate that the cumulative incidences of the given outcome differ significantly between patients on or off OAC. The scaled Schoenfeld residuals curve demonstrated that the proportionality assumption was satisfied. As a falsification analysis to assess for selection bias related to treatment, we compared negative control outcomes of hospital readmission for pneumonia and sepsis between those on and off OAC.[16] A p-value for a HR less than 0.05 indicates a statistically significant difference between groups. SAS version 9.2 (SAS Institute Inc.) was used for all analysis.

Results

Patient Characteristics

The study cohort comprised of 8,261 patients from 1,370 sites who were discharged alive after an admission for an acute ischemic stroke and met the eligibility criteria. They were 80.2±8.8 years old, 61.1% were female, 73.9% were non-Hispanic white, 85.5% had a history of hypertension and 73.5% were admitted to a teaching hospital (table 1). Within the cohort, 747 (9%) were initiated on OAC. Warfarin was utilized as the OAC agent in 678 (90.8%) patients, while the remainder received DOACs. Patients on OAC were younger (77.2±8.0 vs. 80.5±8.9 years, p<0.01), less frequently women (51.1% vs. 62.1%, p<0.01), less commonly placed on either aspirin, clopidogrel or both at discharge and more often admitted to a primary stroke center. In the OAC group, 37 (0.49%) patients had a documented DVT and /or PE.

All-Cause Mortality, Intracranial Hemorrhage and Recurrent Ischemic Stroke

The cumulative incidence rates between patients on OAC and not on OAC for all-cause mortality (33.3% vs. 32.1%, p=0.60), ICH (1.2% vs. 0.8%, p=0.19), recurrent ischemic stroke (5.0% vs. 6.6%, p=0.09) and the composite outcome (36.4% vs. 36.6%, p=0.74) were similar at 1 year and are shown in table 2 and figure 2. However, after adjustment for clinical and hospital covariates, the likelihood of death was higher in those on OAC (aHR: 1.22, 95% CI 1.05–1.41, p<0.01), while no significant differences were noted for ICH (aHR: 1.34, 95% CI 0.69–2.59, p=0.38), recurrent ischemic stroke (aHR: 0.78, 95% CI 0.54–1.15, p=0.21) and the composite outcome (aHR: 1.13, 95% CI 0.98–1.29, p=0.10), as shown in table 2.

All-Cause Bleeding and All-Cause Rehospitalizations

At 1 year, the cumulative incidence rate of all-cause bleeding was higher in patients on OAC (16.3% vs. 11.7%, p<0.01) in comparison to those not on OAC (figure 3). After covariate adjustment, the likelihood of all-cause bleeding (aHR: 1.59, 95% CI 1.29–1.96, p<0.01) remained elevated with OAC (table 2). Similarly, all-cause rehospitalization occurred in more patients on OAC over the follow-up period (60.7% vs. 57.1%, p=0.02, figure 3) and remained more likely to occur after adjustment of clinical characteristics (aHR: 1.14, 95% CI 1.02–1.27, p=0.02, table 2).

Falsification Analysis

The incidence of hospitalizations for pneumonia (OAC: 13.5% vs. no OAC 13.1%) and sepsis (OAC: 12.2% vs. no OAC 11.4%) were numerically higher for patients on OAC. After adjustment with multivariable Cox regression, these differences were not significant for patients on OAC in comparison to those not on OAC (pneumonia: aHR: 1.03, 95% CI 0.79–1.34; sepsis: aHR 0.96, 95% CI 0.71–1.30). These findings suggest that the noted differences in study outcomes between OAC and no OAC groups were less likely due to selection bias related to treatment.

NIHSS Subgroup

NIHSS score was available for 5,858 (71%) patients. Within this group, those on OAC had a higher (5, IQR: 2–11) NIHSS score than patients not discharged on OAC (4, IQR: 2–9, p<0.01). As shown in table 3 and supplemental table 1, after adjustment for clinical covariates including NIHSS score, patients on OAC had a higher likelihood of mortality (aHR: 1.21, 95% CI 1.02– 1.44, p=0.03) and all-cause bleeding (aHR: 1.55, 95% CI 1.21– 2.00, p<0.01). No differences were present in the risk of ICH, recurrent ischemic stroke and all-cause rehospitalization between patients on or off OAC within this subgroup.

Discussion

The principal findings of this study which evaluated the clinical utility of OAC after an ischemic stroke in older HF patients without atrial fibrillation are as follows: First, OAC was associated with greater 1-year all-cause mortality. Second, OAC was also associated with a higher likelihood of all-cause bleeding and all-cause rehospitalization. Lastly, although patients on OAC experienced lower numerical incidence of recurrent ischemic stroke, this did not reach statistical significance. Patients started on OAC were less often on concurrent single and dual anti-platelet medications and had more impairment as evident by a higher NIHSS score; however, even after adjustment for these covariates, the outcomes were nearly unchanged. Two major clinical trials have assessed the effectiveness of OAC in patients with HF with reduced ejection fraction without atrial fibrillation. The Warfarin and Antiplatelet therapy in Chronic Heart Failure (WATCH) trial randomized patients to warfarin, aspirin or clopidogrel and the primary composite of all-cause mortality, nonfatal myocardial infarction (MI) and nonfatal stroke was similar between groups.[6] Major and minor bleeding episodes were noted to be more frequent in patients on warfarin. The Warfarin versus Aspirin in Reduced Cardiac Function (WARCEF) clinical trial found no difference between aspirin and warfarin in the primary composite endpoint of ischemic stroke, ICH and death.[5] The rate of major hemorrhage and gastrointestinal bleeding was over 2 fold higher in comparison to aspirin only.[5] In contrast to these preceding studies, our study population was older, did not distinguish left ventricular ejection fraction (LVEF) and only consisted of patients who had experienced an ischemic stroke. Only a minority of patients in WATCH (5%) and WARCEF (13%) had a prior history of ischemic stroke or a transient ischemic attack. By selecting this subset of HF patients, we did observe a higher burden of ischemic stroke during the 1 year follow up period in those off OAC at 6.6%, in comparison to controls in WATCH (2.3%) and WARCEF (4.7%) with even longer follow up periods.[5] This increased burden of recurrent ischemic stroke was also noted in an exploratory analysis of WARCEF, which showed that patients with a prior history of stroke were at a greater risk of experiencing recurrence at 8.1% (2.37 per 100 patient years), in comparison to those without a prior stroke (3.1%, 0.89 per 100 patient years).[17] Despite focusing on these patients at an elevated risk for incurring a recurrent stroke, we instead noted higher mortality, all-cause bleeding and all-cause rehospitalizations in patients that were initiated on OAC. The safety and maintenance of OAC with coumadin analogues in HF patients has been investigated and these patients are prone to a higher international normalized ratio (INR) and require frequent dose reductions.[18] These effects may be related to liver impairment due to congestion from HF.[18] This risk of HF related over anticoagulation and drug-drug interactions from poly-

pharmacy in older patients with greater comorbidity burden may explain why we observed a higher mortality with OAC in comparison to WATCH and WARCEF studies which enrolled a relatively younger population. Consistent with both WATCH and WARCEF, we did note more bleeding events with OAC. Although these risks of OAC are also present in older HF patients with atrial fibrillation, numerous studies have demonstrated benefits of OAC in such populations, which are further amplified in patients with a prior history of stroke.[19] Thus indicating that even after an ischemic stroke, atrial fibrillation remains a necessary clinical factor to merit initiation of OAC in older HF patients.

This study showed that patients on OAC had an associated numerically lower risk of recurrent stroke (aHR: 0.78, 95% CI 0.54–1.15), but these findings did not reach statistical significance. In contrast, patients in WARCEF experienced a significantly reduced risk of ischemic stroke with an aHR 0.52 (95% CI: 0.33–0.82).[5] The effectiveness of OAC in our population may not be evident due to a type II error from limited sample size. However, lack of benefit is less likely impacted by a mixture of HF patients with either reduced or preserved ejection fraction as even those with preserved LVEF remain at an elevated risk of ischemic stroke (1.0 per 100 patient years) as shown in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Preserved and I-Preserved trials.[7] Nonetheless, the elevated burden of death, bleeding and rehospitalizations underscores that further investigation is needed to validate our findings when considering OAC after an ischemic stroke in older HF patients without atrial fibrillation

Limitations

This investigation has several limitations. Given the observational and registry based study design we could not eliminate selection bias and residual confounding; however, multivariable regression modeling was conducted to adjust for measured confounders.[20] Additional variables that may be associated with OAC and outcomes including socioeconomic status and health literacy were not collected and limit the generalizability of results. Since LVEF was not collected, HF patients were not sub-categorized by preserved or reduced ejection fraction. The association of OAC with DOACs could not be evaluated, as less than 10% of the patients were on these medications. Of note, a recent randomized study, demonstrated no difference in the composite incidence of all-cause mortality, myocardial infarction, stroke and bleeding, in higher risk HF patients with reduced ejection fraction and coronary artery disease with rivaroxaban or placebo in the absence of atrial fibrillation.[21] During the course of the observational period, patients on OAC may have been outside the intended therapeutic INR range, changed their INR target, switched OAC agents or stopped OAC at the discretion of the treating physician, thus our findings can only be framed as the effects of originally intended and not as utilized OAC therapy. Lastly, GWTG-Stroke is voluntary quality improvement registry and may not represent outcomes and practices of all hospitals.

Conclusion

In summary, in this national registry-based observational study, initiation of OAC after an ischemic stroke in older HF patients without atrial fibrillation was independently associated

with a higher risk of death, bleeding and re-hospitalization without an associated reduction in recurrent ischemic stroke. This elevated morbidity and mortality associated with OAC use raises caution and concerns of safety when considering OAC for such patients and warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding

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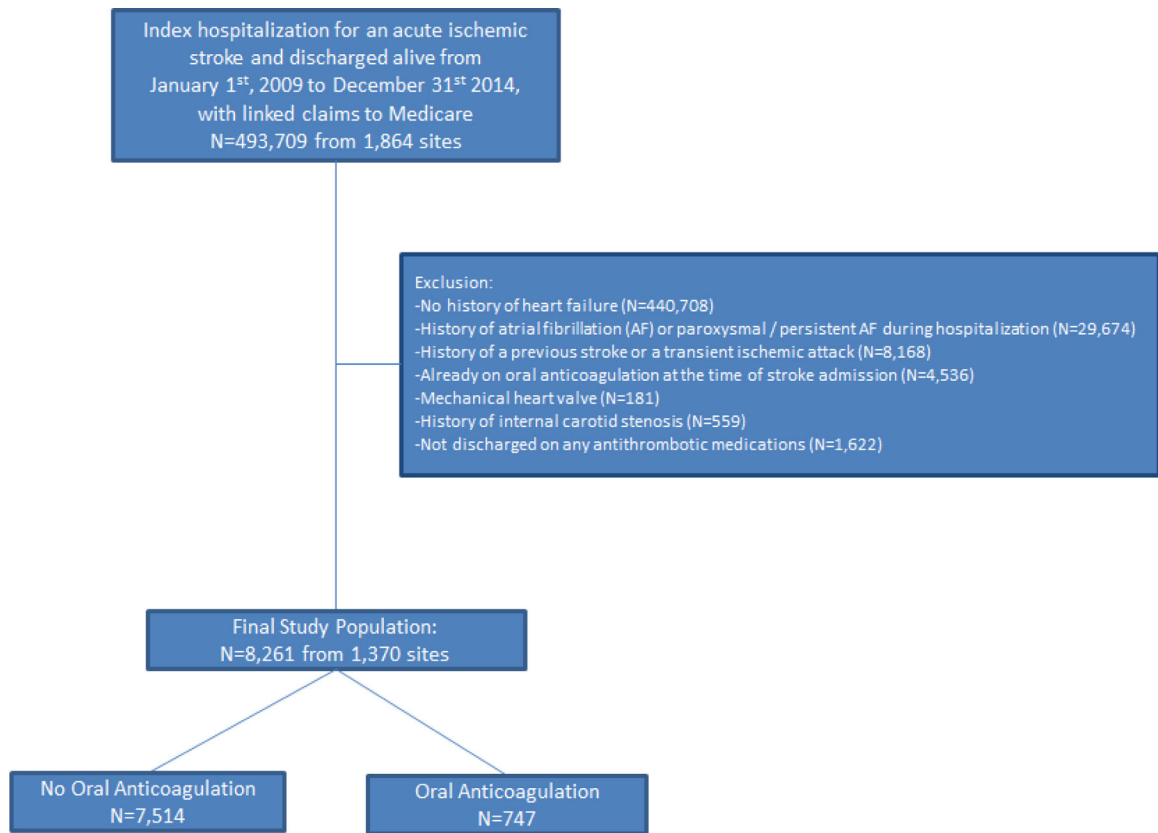
Figure 1:

CONSORT diagram showing derivation of the study population and comparison groups on and off oral anticoagulation.
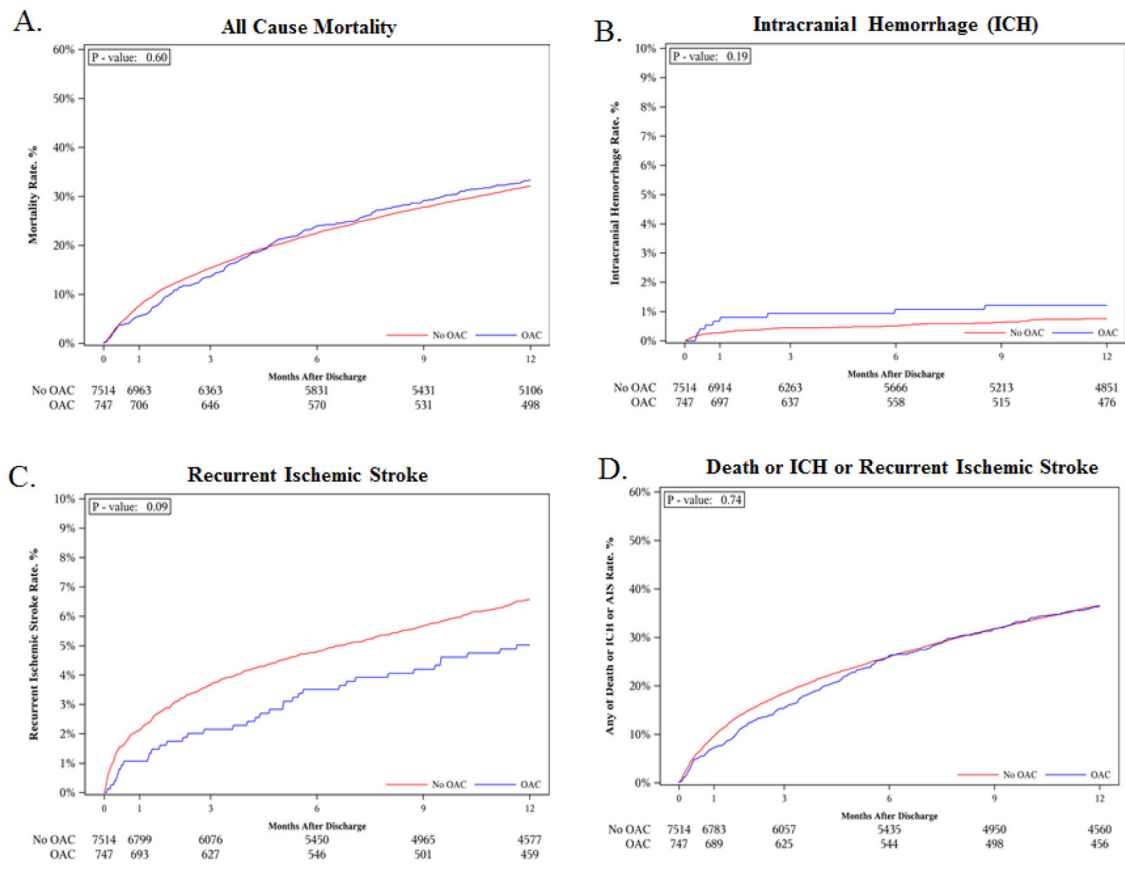
Figure 2:
Cumulative incidence of all-cause mortality (a), intracranial hemorrhage (ICH) (b), recurrent ischemic stroke (c), and composite outcome of death, ICH or recurrent ischemic stroke (d) in patients with heart failure on or off oral anticoagulation.

A.

All Cause Bleeding

B.

All Cause Rehospitalization

OAC: oral anticoagulation

Figure 3:
Cumulative incidence of all-cause bleeding (a) and all-cause rehospitalization (b) in patients with heart failure on or off oral anticoagulation.

Table 1:

Baseline Patient and Hospital Characteristics

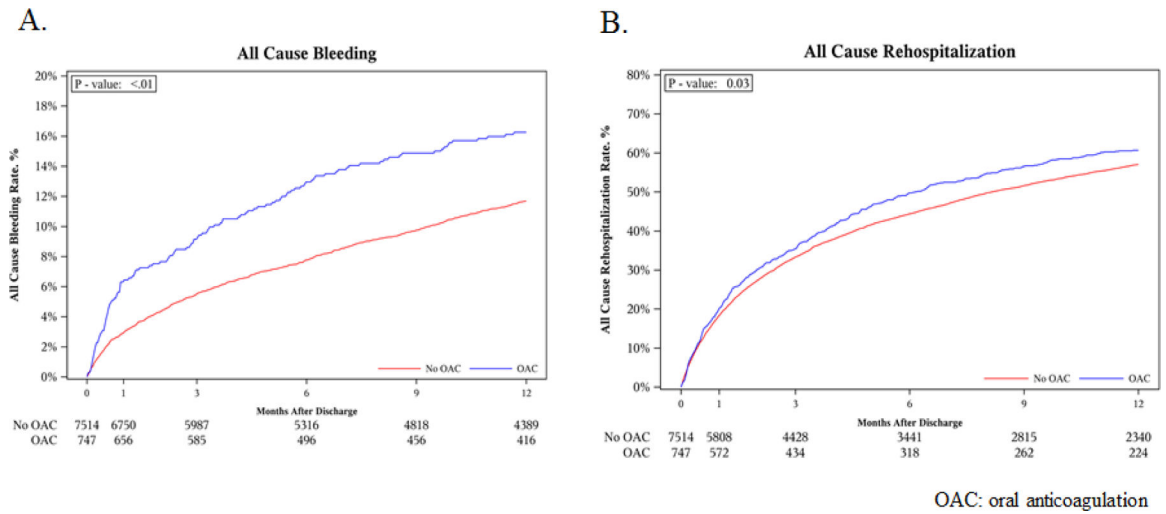| Characteristics	Total (N=8261)	No OAC (N=7514)	OAC (N=747)	p-value	Absolute Std Diff (%)
Age(years)				**<.001**	39.14
Mean(SD)	80.2 (8.8)	80.5 (8.9)	77.2 (8.0)		
Median(IQR)	81.0(73.0, 87.0)	81.0(73.0, 87.0)	76.0(70.0, 84.0)		
Women (n, %)	5049 (61.1%)	4667 (62.1%)	382 (51.1%)	**<.001**	22.28
Race (n, %)				0.641	6.39
Non-Hispanic White	6104 (73.9%)	5553 (73.9%)	551 (73.8%)		
Non-Hispanic Black	1461 (17.7%)	1320 (17.6%)	141 (18.9%)		
Hispanic (any race)	300 (3.6%)	276 (3.7%)	24 (3.2%)		
Asian	132 (1.6%)	124 (1.7%)	8 (1.1%)		
Other (includes UTD)	264 (3.2%)	241 (3.2%)	23 (3.1%)		
Insurance (n, %)				0.225	9.14
Private/VA/Campus/Other Insurance	2451 (29.7%)	2246 (29.9%)	205 (27.4%)		
Medicaid	749 (9.1%)	692 (9.2%)	57 (7.6%)		
Medicare	3926 (47.5%)	3551 (47.3%)	375 (50.2%)		
Self - Pay/No Insurance	29 (0.4%)	25 (0.3%)	4 (0.5%)		
Not Documented	1106 (13.4%)	1000 (13.3%)	106 (14.2%)		
EMS Arrival (n, %)	4363 (52.8%)	3995 (53.2%)	368 (49.3%)	0.415	7.82
Off-Hour Arrival (n, %)	4118 (49.8%)	3731 (49.7%)	387 (51.8%)	0.262	4.31
NIHSS Median(IQR)	4.0(2.0, 10.0)	4.0(2.0, 9.0)	5.0(2.0, 11.0)	**0.003**	14.58
CAD/Prior MI (n, %)	3964 (48.0%)	3567 (47.5%)	397 (53.1%)	**0.003**	11.37
Diabetes Mellitus (n, %)	3571 (43.2%)	3246 (43.2%)	325 (43.5%)	0.871	0.62
PVD (n, %)	631 (7.6%)	571 (7.6%)	60 (8.0%)	0.671	1.61
Hypertension (n, %)	7065 (85.5%)	6449 (85.8%)	616 (82.5%)	**0.013**	9.22
Dyslipidemia (n, %)	4119 (49.9%)	3733 (49.7%)	386 (51.7%)	0.299	3.99
Smoking (n, %)	750 (9.1%)	679 (9.0%)	71 (9.5%)	0.671	1.61
Renal Insufficiency-Chronic [*] (n, %)	840 (14.3%)	779 (14.6%)	61 (11.3%)	**0.038**	9.79
OAC agent (n, %)					
Warfarin			678 (90.76%)		
Apixaban			22 (2.95%)		
Dabigatran			18 (2.42%)		
Rivaroxaban			29 (3.88%)		
Hospital Region (n, %)				0.470	6.10
Northeast	2017 (24.4%)	1839 (24.5%)	178 (23.8%)		
Midwest	1956 (23.7%)	1792 (23.8%)	164 (22.0%)		
South	3284 (39.8%)	2968 (39.5%)	316 (42.3%)		

Characteristics	Total (N=8261)	No OAC (N=7514)	OAC (N=747)	p-value	Absolute Std Diff (%)
West	1004 (12.2%)	915 (12.2%)	89 (11.9%)		
Hospital Location-Rural (n, %)	462 (5.6%)	433 (5.8%)	29 (3.9%)	**0.033**	8.79
Primary Stroke Center (n, %)	4826 (58.4%)	4365 (58.1%)	461 (61.7%)	**0.008**	12.28
Teaching Hospital (n, %)	5958 (73.5%)	5396 (73.1%)	562 (77.0%)	**0.024**	8.95
Number of Beds				**<.001**	8.29
Median(IQR)	362.0(237.0, 548.0)	357.0(235.0, 548.0)	394.0(274.0, 564.0)		
Annual Ischemic Stroke Volume				**<.001**	10.34
Median(IQR)	234.9 (157.9, 363.8)	233.6 (156.3, 363.3)	264.2 (169.9, 390.9)		
Aspirin Only (n,%)	4480 (54.2%)	4125 (54.9%)	355 (47.5%)	**<.001**	14.79
Clopidogrel Only (n,%)	1345 (16.3%)	1296 (17.2%)	49 (6.6%)	**<.001**	33.46
Aspirin + Clopidogrel (n,%)	1582 (19.2%)	1550 (20.6%)	32 (4.3%)	**<.001**	51.08

*
Renal Insufficiency-Chronic was not available until 2012; remaining covariables were available in >99% of the patients. OAC = oral anticoagulation; NIHSS=National Institute of Health Stroke Scale; Absolute Std Diff =absolute standardized difference; UTD=unable to determine; IQR=interquartile range

Table 2:

Unadjusted and adjusted hazard ratios for clinical outcomes associated with oral anticoagulation (OAC).

Outcome	Event rate years per patient 100	Unadjusted		Adjusted	
		HR* (95% CI)	P-value	HR* (95% CI)	P-value
All-Cause Mortality	39.44	1.04 (0.91,1.18)	0.6091	1.22 (1.05,1.41)	0.0081
Intracranial Hemorrhage (ICH)	1.01	1.58 (0.79,3.16)	0.1930	1.34 (0.69,2.59)	0.3822
Recurrent Ischemic stroke (RIS)	8.28	0.75 (0.53,1.06)	0.1004	0.78 (0.54,1.15)	0.2114
Composite of Death/RIS/ICH	46.99	0.98 (0.86,1.11)	0.7490	1.13 (0.98,1.29)	0.0974
All-Cause Bleeding	16.33	1.44 (1.18,1.76)	0.0003	1.59 (1.29,1.96)	<.0001
All-Cause Re-hospitalization	111.49	1.10 (0.99,1.22)	0.0678	1.14 (1.02,1.27)	0.0193

*
Reference: No Oral Anticoagulation; RIS=recurrent ischemic stroke

Table 3:

Adjusted hazard ratios with NIHSS score as an additional covariate for clinical outcomes associated with oral anticoagulation (OAC).

Outcome	Adjusted HR[*] (95% CI)	P-value
All-Cause Mortality	1.21 (1.02,1.44)	0.0280
Intracranial Hemorrhage (ICH)	1.25 (0.55,2.82)	0.5969
Recurrent Ischemic stroke (RIS)	0.74 (0.46,1.19)	0.2115
Composite of Death/RIS/ICH	1.11 (0.95,1.31)	0.1949
All-Cause Bleeding	1.55 (1.21,2.00)	0.0006
All-Cause Re-hospitalization	1.09 (0.96,1.23)	0.1956

[*]Reference: No Oral Anticoagulation