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Acute Ischemic Stroke, Depressed Left Ventricular Ejection Fraction, and Sinus Rhythm: Prevalence and Practice Patterns

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Abstract

Background: There are limited data about the epidemiology and secondary stroke prevention strategies utilized for patients with depressed left ventricular ejection fraction (LVEF) and sinus rhythm following an acute ischemic stroke (AIS). We sought to describe the prevalence of LVEF ≤ 40% and sinus rhythm among AIS patients and anti-thrombotic treatment practice in a multi-center cohort from 2002 to 2018.

Methods: This was a multi-center, retrospective cohort study comprised of AIS patients hospitalized in the Greater Cincinnati Northern Kentucky Stroke Study and 4 academic, hospital-based cohorts in the United States. A 1-stage meta-analysis of proportions was undertaken to calculate a pooled prevalence. Univariate analyses and an adjusted multivariable logistic regression model were performed to identify demographic, clinical, and echocardiographic characteristics associated with being prescribed an anticoagulant (AC) upon AIS hospitalization discharge.

Results: Among 14,338 AIS patients with documented LVEF during the stroke hospitalization, the weighted pooled prevalence of LVEF ≤ 40% and sinus rhythm was 5.0% (95% C.I. 4.1-6.0%; I^2 84.4%). Of 524 patients with no cardiac thrombus and no prior indication for AC who survived post-discharge, 200 (38%) were discharged on AC, 289 (55%) were discharged on anti-platelet (AP) therapy only, and 35 (7%) on neither. There was heterogeneity by site in the proportion discharged with an AC (22% to 45%, p<0.0001). Cohort site and National Institutes of Health Stroke Severity scale (NIHSS) > 8 (odds ratio 2.0; 95% C.I. 1.1-3.8) were significant, independent predictors of being discharged with an AC in an adjusted analysis.

Conclusions: Nearly 5% of AIS patients have a depressed LVEF and are in sinus rhythm. There is significant variation in the clinical practice of anti-thrombotic therapy prescription by site and stroke severity. Given this clinical equipoise, further study is needed to define optimal anti-thrombotic treatment regimens for secondary stroke prevention in this patient population.

INTRODUCTION:

There is a known association between depressed left ventricular ejection fraction (LVEF) and ischemic stroke risk [1, 2, 3, 4]. Despite the increased risk of ischemic stroke in patients with depressed LVEF and sinus rhythm [5], there is uncertainty around optimal anti-thrombotic medication strategy for ischemic stroke prevention. In 2002, the WARIS II trial demonstrated superiority of warfarin to aspirin after a myocardial infarction in preventing a composite outcome that included thromboembolic ischemic stroke [6]. From 2004 to 2014, the WASH [7], HELAS [8], WATCH [9], and WARCEF [10] trials and their meta-analysis demonstrated reduced ischemic stroke risk among anticoagulated patients with depressed LVEF and sinus rhythm (OR 0.49; 95% confidence interval 0.32-0.74), but a higher major bleeding risk (OR 2.01; 95% C.I. 1.40-2.88) [11]. Post-hoc analysis of the COMMANDER HF trial in 2018 showed decreased risk of ischemic stroke (HR 0.66, 95% C.I. 0.47-0.95) with rivaroxaban versus aspirin in patients with an LVEF ≤ 40% and sinus rhythm, and there was no excess significant bleeding [12]. The state of clinical equipoise about anticoagulating these patients was reflected in the 2014 guidelines that assigned a Class IIb recommendation for anticoagulation in patients with LVEF ≤ 35% with a B level of evidence [13].

We aimed to characterize the burden of disease and variability in practice by 1) estimating the prevalence of LVEF ≤ 40% and sinus rhythm among AIS patients, and 2) describing anti-thrombotic prescription patterns for AIS patients with LVEF ≤ 40%, no history of atrial fibrillation (AF), and no other indication for anticoagulation during an era of clinical equipoise for AIS patients from 2002 to 2018.

METHODS:

Study Population and Design:

This was a retrospective, multi-center cohort study. Data of hospitalized, consecutive AIS patients with LVEF ≤ 40% and sinus rhythm were obtained from: (1) Massachusetts General Hospital (MGH; 2002-2016), (2) Rhode Island Hospital (RIH; 2016-2018), (3) Yale-New Haven Hospital (YNHH; 2015-2017), (4) Cornell Acute Stroke Academic Registry (2011-2018), and (5) the Greater Cincinnati Northern Kentucky Stroke Study (GCNKSS; years 2005, 2010, 2015). Reasonable requests for the hospital-affiliated datasets by investigators trained in human subjects' research will be considered by each institution's co-author representative. Access to GCNKSS data requires approval by the GCNKSS principal investigators. Institutional review board approval was obtained from all of the hospitals. The GCNKSS steering committee provided approval for use of their data. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines in the conduct of this multi-center study [14].

GCNKSS is a population-based study of stroke events ascertained in 14 to 17 acute-care hospitals, depending on study year, within a 5-county region of Southern Ohio and Northern Kentucky, inhabited by a population of 1.3 million. Data is collected every 5 years over the course of a full calendar year. While the sampling strategy to derive the GCNKSS population has been demonstrated to be socio-demographically representative of the U.S. [15] and has been utilized to estimate prevalence of various conditions, we pooled the

GCNKSS cohort with 4 other hospital-associated cohorts to capture variations in clinical practice by institution and geography which may impact prevalence and anti-thrombotic treatment. There may be regional differences in ordering of an echocardiogram for AIS etiology evaluation, LVEF measurement methodology, and anti-thrombotic prescription. Patient-level data were analyzed from MGH, RIH, Cornell, and YNHH while aggregate de-identified data were obtained from GCNKSS.

Patient Selection:

In GCNKSS, a study nurse reviewed the medical records of all patients discharged from one of the 14 to 17 acute-care hospitals (depending on study year) in years 2005, 2010, and 2015. AIS patients were identified by International Classification of Diseases, ICD-9 and 10 codes (430 to 436, I63) for either a primary or secondary discharge diagnosis [16]. AIS cases were adjudicated by trained study physicians by medical record review and standardized case report forms. Details about GCNKSS methodology has been previously published [17]. Data from reports of transthoracic echocardiograms (TTE) performed during the stroke admission were retroactively extracted and entered into the study database.

AIS cases were identified at all four hospital-based cohorts using the institutional Get-with-the-Guidelines databases. These databases are curated as a quality improvement initiative collecting clinical, radiographic, and pharmacologic data of all patients hospitalized with a stroke diagnosis [18]. AIS patients were ascertained and logged in the database using discharge ICD-9 and ICD-10 codes (434, 436; I63) and prospectively by daily review of clinical logs. These databases were merged with their respective institutional echocardiogram databases at all four hospitals to determine which AIS patients had an LVEF ≤ 40% visualized by an inpatient TTE interpreted by board-certified echocardiographers.

When estimating the prevalence of LVEF ≤ 40% and sinus rhythm among AIS patients, we analyzed AIS patients in the cohorts who met the following criteria: age ≥ 18 years, LVEF measured during stroke hospitalization, LVEF ≤ 40%, absence of a mechanical heart valve, and no documentation of AF or flutter prior to or by the time of hospital discharge (Figure 1). When characterizing anti-thrombotic practice patterns, we excluded patients if any of the following criteria were met: (1) presence of a mural thrombus by cardiac imaging during the stroke hospitalization, (2) anticoagulant use prior to the stroke hospitalization, and (3) a hospital discharge status of deceased or comfort measures only.

Medications:

Anti-platelets prescribed upon discharge that were studied included aspirin, clopidogrel, dipyridamole, cilostazol, ticlopidine, prasugrel, anagrelide, and eptifibatide. Therapeutically-dosed anticoagulation medications included warfarin, enoxaparin, dalteparin, dabigatran, apixaban, rivaroxaban, or edoxaban. Anti-thrombotic use was categorized as prescription of anti-platelet only or anticoagulation. Patients discharged with both an anticoagulant and an anti-platelet were grouped in the anticoagulation category.

Covariates:

Demographic, clinical, and echocardiographic characteristics during the AIS hospitalization that may associate with anti-thrombotic practice pattern were collected. Demographic information included age, sex, self-reported race, and health insurance status. We recorded prior anti-platelet use, and history of stroke, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, myocardial infarction, heart failure, chronic kidney disease, carotid artery disease, peripheral vascular disease, and cigarette smoking. Echocardiographic parameters included LVEF, the presence of left ventricular hypertrophy, patent foramen ovale, and aortic atheromata. National Institutes of Health Stroke Severity (NIHSS) scale were documented as a proxy of stroke volume and a known independent predictor of hemorrhagic transformation [19]. The NIHSS was dichotomized at the sample median in this study. AIS hospitalization years were categorized as 2002 to 2007, 2008 to 2013, and 2014 to 2018.

Statistical Analysis:

The pooled and patient-level analyses were performed using StataMP software version 16.1 (College Station, Texas). All statistical testing was conducted at a prespecified, 2-tailed significance level of 0.05.

We performed a meta-analysis of the proportions of AIS patients with LVEF ≤ 40% and sinus rhythm who met inclusion criteria at the 5 clinical sites. We utilized the *metaprop* [20] function in StataMP software version 16.1 (College Station, Texas). Anticipating heterogeneity across clinical sites, we selected a random-effects model to calculate a pooled, weighted prevalence estimate and a 95% Wald confidence interval. In order to understand differences in AIS patients who did and did not undergo echocardiography testing that may potentially impact the external validity of the calculated prevalence, we also compared baseline demographic and clinical characteristics of AIS patients in the GCNKSS who did and did not have a documented ejection fraction.

We next studied anti-thrombotic prescription patterns among patients in the pooled cohort (except Cornell) who met eligibility criteria. Demographic, clinical, and echocardiographic characteristics of patients were compared among the 4 sites. Pearson's chi-squared test was used to compare categorical features while a one-way analysis of variance (ANOVA) was used for continuous variables. Next, in a univariate analysis, we explored differences in characteristics of patients discharged with either an anti-platelet only or an anticoagulant. Subsequently, to identify independent predictors of anticoagulation prescription at the time of AIS hospitalization discharge, an adjusted multivariable logistic regression model was generated using patient-level data available from the 3 hospital-based cohorts with the variables significant in the univariate analysis. This was a complete case analysis, and no variables were imputed. In a sub-analysis, we also evaluated additional clinical factors available in the GCNKSS dataset that may be associated with anticoagulation versus antiplatelet only prescription.

Finally, given variability in the years of stroke occurrence among the cohorts, to isolate temporal trends, we examined the MGH cohort in a sub-analysis by modeling the

association of time epoch and antithrombotic treatment prescription by an adjusted logistic regression.

RESULTS:

Among 19,155 AIS patients, 14,338 had a documented LVEF (Figure 1). Of these patients, there were 1,426 patients with an LVEF ≤ 40%. After excluding patients with AF or flutter, there were 805 patients remaining for the prevalence analysis. Next, patients with prior use of anticoagulation, current cardiac thrombus, or discharge status of deceased or comfort measures only were further excluded, yielding a cohort of 524 patients for medication-related analyses.

Prevalence Analysis:

The percentages of AIS patients with LVEF ≤40% and no history of AF or flutter per study site are presented in Figure 2 and ranged from 4% to 6%. In particular, the percentage in the GCNKSS was 6.0% (95% C.I. 5.2-6.6%). The pooled prevalence of AIS patients with LVEF ≤40% and no history of AF or flutter was 5.0% (95% CI 4.1-6.0%) with an I^2 of 84.4%, suggesting heterogeneity in the percentages by site.

When comparing patients who did and did not undergo echocardiography in the GCNKSS study, there were 1,917 patients with no documented EF and 4,824 patients with documented LVEF ($p<0.001$). Notably, stroke patients without a documented EF were underinsured, had strokes in earlier time epochs, and were more likely to be on a prior anticoagulant, to have had a prior stroke, or to have carotid artery disease. There was no difference by hemorrhage status. Only patients with other determined stroke etiology were significantly less likely to have a documented ejection fraction. (Supplemental Table 1).

Description of the Medication Cohort by Site:

Medication-related data were available from MGH, RIH, YNHH, and GCNKSS cohorts (n = 524) and were analyzed by study site (Table 1). These patients were similar in age and sex. More patients in the GCNKSS and YNHH cohorts were Black compared to the MGH and RIH cohorts. There was variability in health insurance payors and pre-existing vascular risk factors and co-morbidities by site. Mean LVEF ranged from 29% to 32% and differences in means were statistically significant across sites ($p=0.03$). There were also differences in presence of various other echocardiographic features by site. There were significant differences in the mean NIHSS by cohort, ranging from 5 in the GCNKSS to 11 in the RIH cohort ($p<0.001$). Percentages of patients discharged with anticoagulation varied significantly by site (MGH 44.6%, RIH 30.0%, YNHH 30.8%, GCNKSS 22.0%, $p<0.0001$).

Factors Associated with Anti-Thrombotic Prescription:

We studied characteristics of 489 patients in the pooled cohort discharged with an anti-platelet versus anticoagulation (Table 2). We excluded patients who were discharged on no anti-thrombotic to understand variations in anti-thrombotic patterns among patients who were eligible for and received standard-of-care antithrombotic therapy for secondary stroke prevention. There were 289 patients (59%) discharged with an anti-platelet only while 200

patients (41%) were discharged with an anticoagulant. Patients discharged on an anti-platelet agent alone were similar to patients discharged with anticoagulation in terms of age, sex, race, and health insurance payor status. There was a difference in the distribution of year of AIS admission and anticoagulation prescription with an increasing proportion of patients anticoagulated in each subsequent time epoch (p=0.006) (Table 2). There was significant variability in the proportion of patients anticoagulated by site. Patients anticoagulated at discharge were significantly less likely to have been prescribed an anti-platelet prior to the AIS admission, less likely to have had a prior stroke, and less likely to have had pre-existing coronary artery disease or heart failure. Anticoagulated patients had significantly lower LVEF during AIS admission (29% versus 32%, p<0.001). Patients discharged with an anticoagulant had a significantly higher initial NIHSS compared to those discharged with an anti-platelet alone (9 versus 6, p<0.001).

A multivariable logistic regression model was built from the 3 hospital cohorts with patient-level data using variables significant in univariate analysis. Study site and presentation NIHSS greater than 8 (OR 2.0; 95% C.I. 1.1-3.8) were significant, independent predictors of being prescribed an anticoagulant upon discharge (Table 3), after adjusting for other covariates. Year of stroke admission, medical comorbidities, and echocardiographic parameters were not associated with anticoagulation prescription upon discharge. In the GCNKSS cohort sub-analysis, AIS patients diagnosed with cardioembolic stroke subtype only were significantly more likely to be anticoagulated. There was no association between hemorrhagic conversion of any degree and anticoagulation upon discharge (Supplemental Table 2). Within the MGH cohort, in an adjusted analysis, there was no association between time epoch and anticoagulation prescription (p=0.08) (Supplemental Table 3).

DISCUSSION:

The prevalence of and optimal treatment strategy for AIS patients with LVEF ≤ 40% and sinus rhythm are uncertain. Our study demonstrates that the prevalence of AIS patients with LVEF ≤ 40% and sinus rhythm at four study sites was 5%. The percentage of these patients prescribed an anticoagulant at these sites range from 22% to 45%. There was no significant temporal variation in prescribing patterns. Institutional site and stroke severity were independent predictors of being prescribed an anticoagulant at the time of stroke hospitalization discharge.

While the global epidemiology of depressed LVEF and sinus rhythm among patients hospitalized with an AIS is not well-known, studies have provided local prevalence estimates. The ATHENS Registry revealed a prevalence of 4.8% [21], comparable to our study's finding. In contrast, the ASTRAL Registry percentage was lower at 2.9% [22]. The Dong-A University prevalence was comparable at 3.2% [23]. Abreu observed a 3.7% prevalence in a single-center study [24]. One study estimated that 8.9% of AIS patients without a history of AF had some degree of impairment of left ventricular function, but the degree of dysfunction is not delineated [10]. Our study uniquely describes the prevalence of depressed LVEF and sinus rhythm in AIS patients at multiple centers in the U.S. The strength of our study estimate was that it represented both the GCNKSS with a sampling strategy reflective of U.S. demographics as well as 4 academic centers with

their respective institutional practice patterns in testing and treatment. Single-center registry studies at academic centers may not represent practice within the community at large, and may suffer from referral and diagnosis biases. While prevalence of multiple conditions has been quantified in the GCKNSS, there may be variability in ordering of diagnostic testing and anti-thrombotic prescription patterns by geography and academic status of hospitals. The confidence interval of the pooled estimate in our study is narrow, suggesting that nearly 1 in 20 AIS patients have at least a moderately reduced LVEF and no history of AF and are subject to the variation in anti-thrombotic therapeutic strategies demonstrated in our study.

There was a higher propensity for anticoagulation upon discharge among patients by stroke severity in our study, even upon adjusting for other factors. The severity of the index AIS and possibility of another such event may be perceived to be concerning enough to the clinician and patient decision-makers to tip the scale towards tolerating the risk of bleeding with anticoagulation in favor of the potential benefit of stroke prevention. Higher NIHSS has been associated with cardioembolic stroke subtype compared to all other stroke subtypes [25], increasing the pre-test probability of a possible cardioembolic etiology. Since dilated cardiomyopathy is considered a high-risk cardioembolic source [26] and an elevated NIHSS points to a cardioembolic etiology, even in the absence of definitive benefit, it is conceivable that the presence of these two datapoints of severe stroke and depressed LVEF prompted initiation of empiric anticoagulation in our pooled cohort. Other factors that may influence the antithrombotic prescription patterns include the pathogenic mechanism of ischemic stroke, infarct volume, large vessel atherosclerotic disease, and bleeding either into the stroke bed or systemically.

In the GCNKSS sub-analysis, we delved further into clinical characteristics associated with anticoagulation prescription. We observed that patients diagnosed with a cardioembolic stroke subtype alone were significantly more likely to be anticoagulated. There was no difference in initial NIHSS score, which can serve as a proxy for infarct volume [27]. Patients with baseline carotid artery disease were significantly less likely to be anticoagulated. However, notably, those who had stroke secondary to a symptomatic large vessel were just as likely to be anticoagulated. We also noted that patients with any, symptomatic, or asymptomatic, hemorrhagic transformation were as likely to be anticoagulated versus those without hemorrhage. Furthermore, there was also no difference in rates of anticoagulation among those who experienced systemic hemorrhage.

The risk-to-benefit ratio of anticoagulation of patients with AIS, depressed LVEF, and sinus rhythm has yet to be definitively established. WARCEF and multiple other similar trials demonstrated stroke risk reduction among patients randomized to warfarin, however this was not the trial's primary outcome and there was a significant degree of major bleeding [7, 9, 8, 11, 28]. A post-hoc analysis of COMMANDER HF demonstrated that patients with LVEF ≤40% randomized to rivaroxaban versus aspirin had fewer composite thromboembolic events (HR 0.83, 95% C.I. 0.72-0.96) [29]. There was no increased risk of major bleeding with rivaroxaban therapy. The only ongoing clinical trial in this arena is a primary prevention trial, APIXBRAIN-HF trial (NCT04696120), with a target enrollment of 200 participants. The uncertainty about the benefits and risks of anticoagulation as a secondary prevention measure in patients with AIS, depressed LVEF, and sinus rhythm is

reflected in the stroke guidelines [13]. Our study spans the era of emerging literature in the field from 2002 to 2018 and notably, there was no significant variation in anticoagulant prescription pattern during the course of this timeframe in our adjusted analysis. The lack of temporal variation likely reflects the persistent scientific equipoise regarding the potential net clinical benefit of anticoagulation. Given the paucity of definitive evidence, a substantial proportion of patients are empirically treated with anticoagulation, likely driven by biologic plausibility [1, 2, 3, 4], the compelling ischemic stroke prevention point estimates in studies to date, and the advent of direct oral anticoagulants with favorable bleeding profiles. Further randomized controlled studies for secondary stroke prevention in this patient population are critical to either substantiate this widespread practice or provide an alternative strategy.

This study has several limitations. It is uncertain whether the results from our pooled cohort are generalizable. Our findings are likely generalizable since we studied a well-phenotyped sample comprised of academic and community hospitals to ensure diversity of case mix, diagnostic testing preferences to mitigate case ascertainment bias, echocardiographic parameter measurement approaches, and anti-thrombotic prescribing behaviors. Nevertheless, our cohort represents only Northeast and Midwest hospitals and may not capture practice patterns in other U.S. regions. Furthermore, our analysis of the GCNKSS cohort revealed that AIS patients who did not undergo echocardiography were, for instance, more likely to be underinsured or already on an anticoagulant, thus the calculated prevalence may be subject to ascertainment bias. Our datasets were cross-sectional and lacked information about potential delayed crossover from antiplatelet to anticoagulation therapy due to initially large stroke volume or hemorrhagic transformation. An effort was made to account for stroke volume and the proclivity to bleed using the proxy of the presenting NIHSS. This observational study of pharmacotherapy practice patterns is subject to confounding due to unmeasured variables. Our data did not include granular treatment information such as the specific type of anti-platelet or anticoagulant or dosing prescribed, which may have variable efficacy and safety profiles that may impact clinical decision-making.

We estimate a 5% prevalence of LVEF ≤ 40% and sinus rhythm among AIS patients. Rates of anticoagulation of these patients upon discharge from stroke hospitalization are high and vary by institution, ranging from 22% to 45%. Notably, from 2002 to 2018, there was no temporal variation in anticoagulation prescription practice. Study site and stroke severity independently predict anticoagulation prescription. Given the appreciable proportion of AIS patients with this cardiac phenotype, further study is needed to determine optimal secondary stroke prevention strategies for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

DISCLOSURES:

Dr. Schwamm reports compensation from mediasphere for other services; and compensation from Medscape for other services. Dr. Furie reports compensation from Janssen Biotech for consultant services. Dr. Flaherty reports compensation from CSL Behring for other services; compensation from Janssen Biotech for other services;

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ABBREVIATIONS:

LVEF	Left ventricular ejection fraction
AIS	Acute ischemic stroke
AF	Atrial fibrillation
MGH	Massachusetts General Hospital
RIH	Rhode Island Hospital
YNHH	Yale-New Haven Hospital
GCNKSS	Greater Cincinnati Northern Kentucky Stroke Study
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
ICD	International Classification of Diseases
NIHSS	National Institutes of Health Stroke Severity

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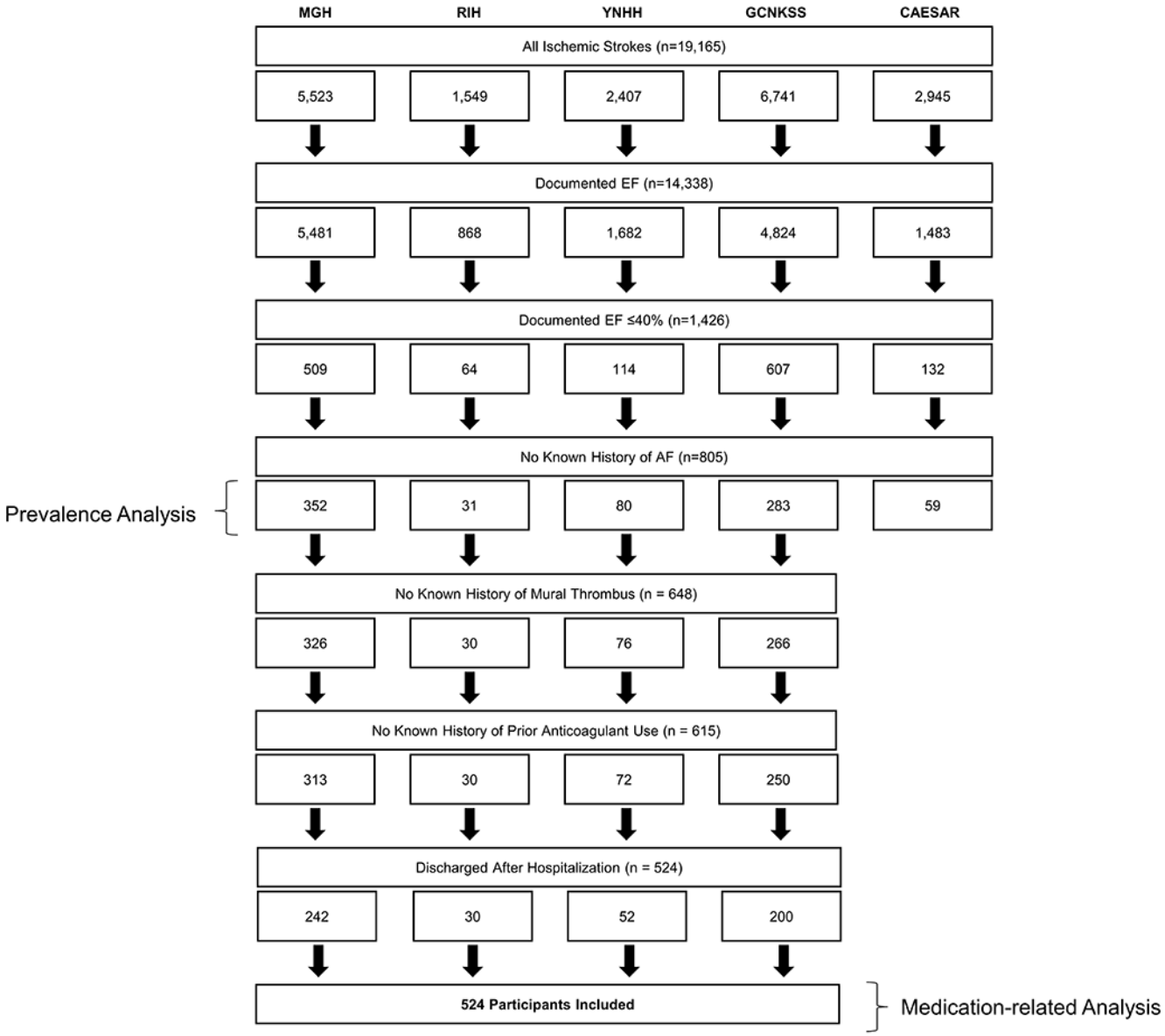
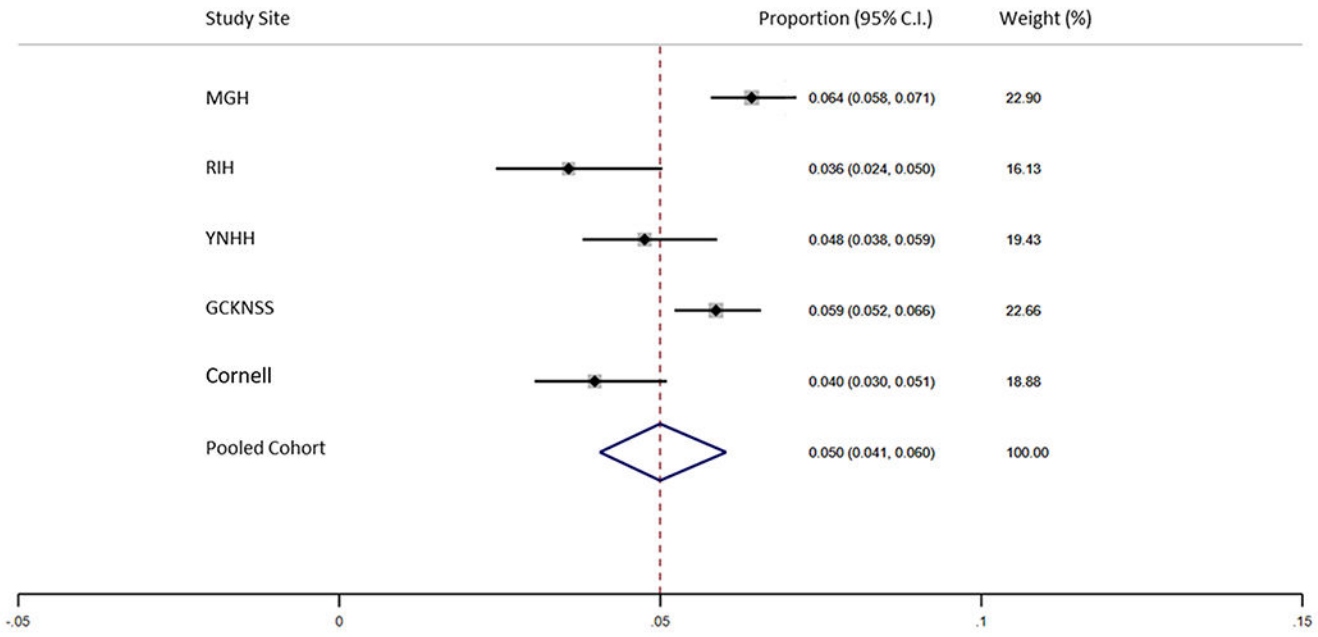


Figure 1.
STROBE flow diagram of study participants



	Total Ischemic Stroke	Ischemic Strokes with LVEF ≤ 40%	Effect Size (95% C.I.)	Weight (%)	p-value
MGH	5481	352	0.06 (0.05, 0.07)	22.90	
RIH	868	31	0.04 (0.02, 0.05)	16.13	
YNHH	1682	80	0.05 (0.04, 0.06)	19.43	
GCNKSS	4824	283	0.06 (0.05, 0.07)	22.66	
Cornell	1483	59	0.04 (0.03, 0.05)	18.88	
Random Pooled Effect Size			0.05 (0.04, 0.06)		<0.001

* *Abbreviations: LVEF, Left Ventricular Ejection Fraction; C.I., Confidence Interval*

Heterogeneity $chi^2 = 25.701$ (d.f. = 4) p = <0.001
I^2 (variation in ES attributable to heterogeneity) = 84.44%
Estimate of between-study variance $Tau^2 = 0.002$
Test of ES = 0: z = 18.635 p = <0.001

Figure 2.

Site-level and pooled proportion of acute ischemic stroke patients with left ventricular ejection fraction ≤ 40% and sinus rhythm. Error bars indicate 95% confidence intervals.

Table 1.

Baseline demographic and clinical characteristics of participants with acute ischemic stroke, no prior history of atrial fibrillation, left ventricular thrombus, or prior anticoagulant use, and LVEF ≤40% by participating site.

Characteristics	MGH (n = 242)	RIH (n = 30)	YNHH (n = 52)	GCNKSS (n = 200)	p-value [a]
DEMOGRAPHICS					
Age, mean (SD)	68 (13.9)	66 (12.8)	67 (14.5)	67 (14.4)	0.82
Gender (female)	84 (34.7)	8 (26.7)	18 (34.6)	60 (30)	0.64
Race (black)	10 (4.1)	4 (13.3)	18 (34.6)	73 (36.5)	<0.001
Insurance Type					
Medicare/ Medicaid	113 (46.7)	0	43 (82.7)	140 (70)	<0.001
Private	75 (31)	0	9 (17.3)	39 (19.5)	<0.001
Self-Pay	10 (4.1)	0	0	14 (7)	0.08
Unknown	44 (18.2)	30 (100)	0	7 (3.5)	<0.001
Year of Stroke					
2002-2007	92 (38)	0	0	67 (33.5)	<0.001
2008-2013	101 (41.7)	0	0	63 (31.5)	<0.001
2014-2018	49 (20.2)	30 (100)	52 (100)	70 (35)	<0.001
MEDICAL HISTORY					
Prior Anti-Platelet Use	70 (28.9)	0	33 (63.5)	110 (55)	<0.001
History of Stroke	21 (8.7)	4 (13.3)	12 (23.1)	45 (22.5)	<0.001
Hypertension	169 (69.8)	25 (83.3)	45 (86.5)	175 (87.5)	<0.001
Diabetes Mellitus	81 (33.5)	10 (33.3)	25 (48.1)	85 (42.5)	0.098
Hyperlipidemia	106 (43.8)	17 (5.7)	24 (46.2)	108 (54)	0.14
Coronary Artery Disease	131 (54.1)	0	25 (48.1)	108 (54)	<0.001
Myocardial Infarction	131 (54.1)	10 (33.3)	25 (48.1)	64 (32)	<0.001
Heart Failure	33 (13.6)	12 (40)	11 (21.2)	96 (48)	<0.001
Chronic Kidney Disease	15 (6.2)	0	6 (11.5)	35 (17.5)	<0.001
Carotid Artery Disease	11 (4.5)	0	3 (5.8)	16 (8)	0.225
Peripheral Vascular Disease	23 (9.5)	0	0	24 (12)	0.015
Smoker Status (Current)	53 (21.9)	0	9 (17.3)	70 (35)	<0.001
ECHOCARDIOGRAPHY					
LVEF, mean (SD)	30 (7.8)	29 (8.5)	31 (6.2)	32 (7.7)	0.03
Left Ventricular Hypertrophy	45 (18.6)	0	0	85 (42.5)	<0.001
Patent Foramen Ovale	31 (12.8)	1 (3.3)	0	7 (3.5)	<0.001
Aortic Atheromata	48 (19.8)	0	1 (1.9)	3 (1.5)	<0.001
CLINICAL COURSE					
Initial NIHSS scale, mean (SD)	9 (7.7)	11 (8.3)	10 (8.7)	5 (5.8)	<0.001
Anticoagulated at Discharge	108 (44.6)	9 (30.0)	16 (30.8)	44 (22.0)	<0.001

[*] Abbreviations: MGH, Massachusetts General Hospital; RIH, Rhode Island Hospital; YNHH, Yale-New Haven Hospital; GCNSS, Greater Cincinnati Northern Kentucky Study; SD, standard deviation; LVEF, left ventricular ejection fraction; NIHSS, National Institutes of Health Stroke Severity

[□] = Pearson's chi square for categorical and Analysis of Variance and Rank sum test for continuous data; Patients with missing datapoints for specific variables were excluded from the corresponding specified p-value analysis.

Table 2.

Pooled baseline demographic and clinical characteristics of participants with acute ischemic stroke, no prior history of atrial fibrillation, left ventricular thrombus, or prior anticoagulant use, and LVEF ≤40% discharged with an anti-platelet only versus an anticoagulant

	All 4 Cohorts (N = 524)		
Characteristics	**AP Only (n = 289)**	**AC (n= 200)**	**p-value** [¤]
DEMOGRAPHICS			
Age, mean (SD)	67.5 (13.6)	66.0 (14.4)	0.24
Gender (female)	100 (35)	65 (33)	0.63
Race (black)	67 (23)	37 (19)	0.21
Insurance Type			
Medicare/ Medicaid	168 (58)	112 (56)	0.64
Private	68 (24)	45 (23)	0.79
Self-Pay	16 (6)	7 (4)	0.3
Unknown	28 (10)	19 (10)	0.95
Year of Stroke			0.006
2002-2007	87 (30)	53 (27)	0.39
2008-2013	91 (31)	63 (32)	1.00
2014-2018	111 (38)	84 (42)	0.43
Site			<0.001
MGH	105 (49.3)	108 (50.7)	<0.001
RIH	17 (65.4)	9 (34.6)	0.503
YNHH	34 (68)	16 (32)	0.18
GCNKSS	156 (78)	44 (22)	<0.001
MEDICAL HISTORY			
Prior Anti-Platelet Use	135 (47)	73 (37)	0.03
History of Stroke	57 (20)	23 (12)	0.02
Hypertension	237 (82)	152 (76)	0.11
Diabetes Mellitus	112 (39)	77 (39)	0.96
Hyperlipidemia	140 (48)	97 (49)	0.99
Coronary Artery Disease	161 (56)	88 (44)	0.01
Myocardial Infarction	125 (43)	90 (45)	0.70
Heart Failure	105 (36)	44 (22)	0.001
Chronic Kidney Disease	30 (10)	15 (8)	0.28
Carotid Artery Disease	17 (6)	11 (6)	0.86
Peripheral Vascular Disease	31 (11)	14 (7)	0.16
Smoker Status (Current)	80 (28)	45 (23)	0.2
ECHOCARDIOGRAPHY			
LVEF, mean (SD)	31.9 (7.02)	28.96 (8.45)	<0.001

	All 4 Cohorts (N = 524)		
Characteristics	**AP Only (n = 289)**	**AC (n= 200)**	**p-value** [¤]
Left Ventricular Hypertrophy	88 (30)	37 (19)	0.003
Patent Foramen Ovale	18 (6)	20 (10)	0.13
Aortic Atheromata	25 (9)	20 (10)	0.61
CLINICAL COURSE			
Initial NIHSS scale, mean (SD)	6.05 (6.55)	8.7 (7.44)	<0.001

[*] Abbreviations: AP, anti-platelet; AC, anticoagulant; SD, standard deviation; LVEF, left ventricular ejection fraction; NIHSS, National Institutes of Health Stroke Severity

[¤] = Pearson's chi square for categorical and Analysis of Variance and Rank sum test for continuous data; Patients with missing datapoints for specific variables were excluded from the corresponding specified p-value analysis.

Table 3.

Predictors of anticoagulant prescription upon acute ischemic stroke hospitalization discharge.

Characteristics	Odds Ratio	95% Confidence Interval	P-value
Site	0.54	0.34-0.84	<0.01
Stroke Time Epoch (reference: 2002-2007)	1.78	0.85-3.79	0.13
Prior Anti-Platelet Use	1.13	0.56-2.29	0.73
History of Stroke	2.02	0.85-4.99	0.12
History of Coronary Artery Disease	0.85	0.42-1.70	0.65
History of Heart Failure	1.24	0.56-2.78	0.59
LVEF < 30%	0.68	0.35-1.30	0.24
Left Ventricular Hypertrophy	0.71	0.26-1.85	0.48
Initial NIHSS scale > 8	2.00	1.06-3.80	0.03

*Abbreviations: LVEF, left ventricular ejection fraction; NIHSS, National Institutes of Health Stroke Severity