HHS Public Access

Author manuscript

J Stroke Cerebrovasc Dis. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

J Stroke Cerebrovasc Dis. 2020 July ; 29(7): 104888. doi:10.1016/j.jstrokecerebrovasdis.2020.104888.

Factors Associated with Therapeutic Anticoagulation Status in Patients with Ischemic Stroke and Atrial Fibrillation

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Abstract

Background and Purpose—Understanding factors associated with ischemic stroke despite therapeutic anticoagulation is an important goal to improve stroke prevention strategies in patients

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Conflict of interest

All authors report no conflict of interest relevant to this manuscript

Compliance with ethical standards

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional board review approval was obtained from each of the participating centers with waiver of informed consent

with atrial fibrillation (AF). We aim to determine factors associated with therapeutic or supratherapeutic anticoagulation status at the time of ischemic stroke in patients with AF.

Methods—The Initiation of Anticoagulation after Cardioembolic stroke (IAC) study is a multicenter study pooling data from stroke registries of eight comprehensive stroke centers across the United States. Consecutive patients hospitalized with acute ischemic stroke in the setting of AF were included in the IAC cohort. For this study, we only included patients who reported taking warfarin at the time of the ischemic stroke. Patients not on anticoagulation and patients who reported use of a direct oral anticoagulant were excluded. Analyses were stratified based on therapeutic (INR ≥2) versus subtherapeutic (INR <2) anticoagulation status. We used binary logistic regression models to determine factors independently associated with anticoagulation status after adjustment for pertinent confounders. In particular, we sought to determine whether atherosclerosis with 50% or more luminal narrowing in an artery supplying the infarct (a marker for a competing atherosclerotic mechanism) and small stroke size (≤ 10 mL; implying a competing small vessel disease mechanism) related to anticoagulant status.

Results—Of the 2084 patients enrolled in the IAC study, 382 patients met the inclusion criteria. The mean age was 77.4 ± 10.9 years and 52.4% (200/382) were men. A total of 222 (58.1%) subjects presented with subtherapeutic INR. In adjusted models, small stroke size (OR 1.74 95% CI 1.10 – 2.76, p = 0.019) and atherosclerosis with 50% or more narrowing in an artery supplying the infarct (OR 1.96 95% CI 1.06 – 3.63, p = 0.031) were independently associated with INR ≥2 at the time of their index stroke.

Conclusion—Small stroke size (≤ 10 ml) and ipsilateral atherosclerosis with 50% or more narrowing may indicate a competing stroke mechanism. There may be important opportunities to improve stroke prevention strategies for patients with AF by targeting additional ischemic stroke mechanisms to improve patient outcomes.

Keywords

Stroke; Atrial Fibrillation; Recurrence; Anticoagulation; Predictors

Introduction

Atrial fibrillation (AF) is a strong risk factor for ischemic stroke in the general population.1 Oral anticoagulation therapy is key to mitigate stroke risk because it confers significantly greater risk reduction for ischemic stroke and systemic embolism as compared to antiplatelet therapy.2–4 Nevertheless, it is well recognized that a significant subset of AF patients develop ischemic strokes despite therapeutic oral anticoagulation.5–7

We previously found an increased CHADS2 score as well as presence of left atrial enlargement may help to identify patients likely to have a stroke while therapeutic on anticoagulation when compared to sub-therapeutic or non-anticoagulated patients.7 Nevertheless, our study was limited by its single center retrospective design, assessment of compliance with direct oral anticoagulants by patient reporting, enrollment of patients not on anticoagulation at the time of admission, and lack of information on the possibility of competing noncardioembolic stroke mechanisms.7

Understanding factors associated with ischemic stroke despite therapeutic anticoagulation may help identify patients to target for additional stroke prevention strategies. We hypothesize that AF patients supra-therapeutic/therapeutic anticoagulation (INR ≥2) at the time of their index stroke were more likely to have a competing non-cardioembolic stroke mechanism than patients with subtherapeutic (INR <2) anticoagulant status.

Methods

Study cohort

Study approval was individually granted by the Institutional Review Board from each of the participating centers. The Initiation of Anticoagulation after Cardioembolic stroke (IAC) study is a multicenter study pooling data from stroke registries of eight Comprehensive Stroke Centers across the United States. Consecutive patients hospitalized with acute ischemic stroke in the setting of AF were included in the IAC cohort. For this study only patients who reported taking warfarin at the time of the ischemic stroke were included. We excluded: 1) Patients not on anticoagulation because they may have a unique clinical profile rendering them ineligible for anticoagulation, which may have confounded our main research question or 2) patients reported being on a direct oral anticoagulant because anti-Xa levels and drug levels were not routinely checked or reported by participating sites.

Study variables

The following study variables were collected:

Demographic factors: Age and Sex

Clinical variables: History of hypertension, history of diabetes, history of hyperlipidemia, history of stroke or TIA, active smoking at the time of the stroke, active cancer at the time of admission, CHA2DS2-Vasc score, NIHSS score, and systolic and diastolic blood pressures on admission.

Medications prior to admission: Antiplatelet use and statin use

Laboratory values on admission: Glucose level and low density lipoprotein level

Neuroimaging and vascular imaging variables: Presence of intracranial or extracranial atherosclerosis with ≥ 50% luminal narrowing in the territory of the stroke, largest ischemic stroke lesion volume (small stroke defined as ≤10 mL), and early hemorrhagic transformation occurring within 48 hours from index event.8, 9

Echocardiographic variables: Left atrial enlargement (determined by left atrial diameter or volume)10, intracranial thrombus, spontaneous echocardiographic contrast, and ejection fraction.

In-hospital treatments: Alteplase and mechanical thrombectomy

Hemorrhagic and Ischemic Complications: Hemorrhagic transformation and recurrent ischemic events within 90 days (recurrent ischemic stroke, TIA, or symptomatic systemic embolism)

Variables of interest

The predictors of interest were: 1) Ipsilateral intracranial or extracranial atherosclerosis with 50% or more luminal narrowing based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria11 and 2) Small stroke size (≤ 10 mL) measured on brain imaging (CT or MRI) using the “ABC/2” method.12

Outcome

The study outcome was therapeutic anticoagulation status defined as INR level of 2 or more. Sub-therapeutic anticoagulation status was defined as being on warfarin with an INR level of less than 2.

Analytical plan

Data from sites was pooled and queries were sent to ensure accuracy of data. We stratified patients based on therapeutic vs. sub-therapeutic anticoagulation status. We then compared baseline characteristics and the above mentioned variables between the two groups. We used chi square tests for categorical variables and t-tests or non-parametric tests for continuous variables.

To determine whether the presence of small stroke size and atherosclerosis with ≥ 50% luminal narrowing in the territory of the stroke were independently associated with oral anticoagulant status we created the following pre-specified binary logistic regression models: model 1 adjusted for CHA2DS2Vasc, model 2 adjusted for important variables on univariate analyses ($p < 0.1$, Table 1). We additionally created a sensitivity analysis adjusted for the CHA2DS2Vasc score and presence of severe left atrial enlargement (model 3). Analyses were done using SPSS version 25.0 (Chicago, IL).

Results

Of the 2084 patients enrolled in the IAC study, 382 met the inclusion criteria. The mean age was 77.4 ± 10.9 years and 52.4% (200/382) were men. Therapeutic or supratherapeutic INR on admission was found in 41.9% (160/382) of patients.

Univariate analyses

Table 1 summarizes the baseline characteristics of patients stratified according to anticoagulation status. Overall, patients with INR ≥2 were more likely to have a competing small vessel disease stroke mechanism as indicated by more frequent presence of an ischemic lesion ≤ 10 mL (52.2% vs. 37.6%, $p = 0.009$) as well as a competing large artery atherosclerotic mechanism as indicated by the presence of ipsilateral atherosclerosis with ≥ 50% luminal narrowing in the territory of the stroke (19.9% vs. 11.9%, $p = 0.039$). In addition, the mean diastolic blood pressure was higher in patients with sub-therapeutic on anticoagulation (81.6 ± 19.4 mm Hg vs. 77.6 ± 32.1 mm Hg, $p = 0.040$) and a higher

proportion of patients in the therapeutic/supratherapeutic group were on concomitant antiplatelet therapy (44.4% vs. 24.3%, p < 0.001). There was trend for more frequent history of prior stroke or TIA among subjects with therapeutic/supratherapeutic anticoagulation (45.0% vs. 35.6%, p = 0.063).

Lastly, patients who were therapeutic/supra-therapeutic (vs. sub-therapeutic) were less likely to have hemorrhagic transformation (10.6% vs. 18.0%, p = 0.045) and less likely to be switched to a direct oral anticoagulant at the time of their ischemic event (19.5% vs. 28.4%, p = 0.015). The rates of recurrent ischemic events within 90 days were not significantly different between those therapeutic/supra-therapeutic vs. sub-therapeutic (6.3% vs. 6%, p = 1.000).

Association between primary predictors (stroke size and significant ipsilateral atherosclerosis) and anticoagulation status

In unadjusted models, there was an association between small stroke size and therapeutic/supratherapeutic anticoagulation status (OR 1.81 95% 1.16 – 2.84, p = 0.010). This association persisted in fully adjusted models (OR 1.74 95% CI 1.10 – 2.76, p = 0.019) (model 2, Table 2).

Moreover, in unadjusted models, there was an association between atherosclerosis with 50% or more narrowing ipsilateral to the infarct and therapeutic/supratherapeutic anticoagulation status (OR 1.84 95% CI 1.03 – 3.30, p = 0.041). This association persisted in a fully adjusted model (OR 1.96 95% CI 1.09 – 3.63, p = 0.031) (Model 2, Table 2).

Additional analyses

To determine whether the association between therapeutic anticoagulation and hemorrhagic transformation is independent of infarct volume, we performed binary logistic regressions models. In these models, there was an association between therapeutic anticoagulation and absence of hemorrhagic transformation (OR 0.54 95% CI 0.29 – 0.99, p = 0.048) in the unadjusted model, but this association was no longer significant after adjusting for ischemic lesion size (OR 0.62 95% CI 0.33 – 1.17, p = 0.138).

Sensitivity analyses

Out of 382 patients included in the study, 268 patients (70.2%) had left atrial dimensions measured on echocardiography. In sensitivity analyses adjusted for CHA2DS2Vasc score and presence of severe left atrial enlargement (model 3), the effect size for ipsilateral atherosclerosis was attenuated and the association no longer significant (OR 1.66 95% CI 0.82 – 3.37, p = 0.161) (table 2). Conversely, the effect size for ischemic lesion ≤ 10 mL was slightly accentuated and the association remained significant (OR 1.95 95% CI 1.14 – 3.35, p = 0.015) (table 2). Anticoagulation status was not independently associated with hemorrhagic transformation.

Discussion

Our study indicates that ischemic stroke patients with AF who present with therapeutic/supratherapeutic INR were significantly more likely to have a competing large artery atherosclerotic and small ischemic lesion than subjects with subtherapeutic INR. These may constitute stroke mechanisms that are not mitigated by treatment with oral anticoagulation and drive stroke risk in this subset of AF patients.

Mechanisms of association

The association between therapeutic anticoagulation status and ipsilateral atherosclerosis causing 50% or more luminal narrowing suggests that patients with AF who have an ischemic event while therapeutic on anticoagulation are more likely to have a competing atherosclerotic mechanism. While anticoagulation is hypothesized to be the most effective strategy to reduce stroke risk in patients with AF, it may not be effective in patients with symptomatic atherosclerotic disease. Other strategies such as carotid revascularization,13 statin use, aggressive risk factor control, and lifestyle changes14 have been shown to be more effective than antithrombotic treatment. Antiplatelet therapy remains the mainstay of treatment in the absence of any other indication for anticoagulation.15–17

The association between small stroke size and therapeutic anticoagulation is noteworthy and consistent with previous studies.18 Since larger infarct size predicts hemorrhagic transformation risk, this finding likely explains the lower rates of hemorrhagic transformation in patients on home anticoagulation.8 The association between stroke size and therapeutic anticoagulation could be explained by at least two potential mechanisms. First, it is possible that patients who are therapeutic on anticoagulation had smaller clots leading to smaller ischemic lesions and this has been suggested in previous studies.18 Second, it is also possible that some of the patients with small stroke size may have had subcortical infarcts in the setting of small vessel disease. In fact, this would constitute competing mechanism where risk factor control19 may be a more effective in stroke prevention than the choice of antithrombotic therapy. In such patients, antiplatelet agents remain the drug of choice in the absence of indications for anticoagulation therapy.20, 21 For instance, an analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial showed that lower blood pressure targets (< 130 mm Hg vs. 130–149 mm Hg) had a trend towards lower risk of stroke and major vascular events.22

Our study is different from a previous study where we found no association between therapeutic anticoagulation status, CHA2DS2Vasc scores, and left atrial enlargement. The subtherapeutic arm included patients not on anticoagulation (possibly due to being in a low risk CHA2DS2Vasc score category or low-burden AF) which is associated with lower likelihood of left atrial enlargement when compared to high-burden AF.23 This is different from our study where the sub-therapeutic anticoagulation group only included patients with known AF on warfarin, who are likely to have similar AF burden and risk categorization. This may have contributed to the disparate findings between our study and the previous study.

Therapeutic implications

Our work should serve to caution future investigators from analyzing all patients with an acute ischemic stroke and confirmed AF in the same mechanistic category. Based on our results, patients with AF who are supratherapeutic/therapeutic on anticoagulation at the time of stroke, may have non-cardioembolic stroke mechanisms. Attention to these alternative mechanisms is important to avoid misclassification in future stroke research.24 Prior authors have noted that information loss is inevitable when ischemic stroke subtypes are determined using a causative classification approach, such as the TOAST subtyping system,11 as opposed to using phenotypic classification. Phenotypic subtyping is determined based on the organization of abnormal test findings into major etiological groups thereby avoiding information loss. For example, a patient with carotid stenosis ipsilateral to their stroke and AF would be classified as having large artery atherosclerosis plus cardiac embolism in a phenotypic system such as the A-S-C-O-D classification system25 as opposed to TOAST11 or CCS26 which assigns patients with more than one etiology to a distinct category (two or more causes or unclassified category). However, phenotypic subtyping has limited use in clinical practice due to the large number of subtypes generated.24

In addition to encouraging future researchers to fully identify and categorize all potential stroke mechanisms in patients with AF to improve the generalizability and reliability of research findings, appropriate stroke subtype classification has important predictive and therapeutic implications. 24, 27 For example, patients with AF and symptomatic carotid stenosis may benefit from surgical revascularization to prevent stroke recurrence.28 We also noted that more patients with a prior stroke or TIA had their included ischemic event while therapeutic/supratherapeutic on anticoagulation (45.0% vs. 35.6%, $p = 0.063$) suggesting that there are AF patients who may have benefited from improved secondary stroke prevention strategies on top of therapeutic anticoagulation after their first stroke/TIA. It is also possible that these patients may have a labile INR and should be switched to a direct oral anticoagulant or have their INR levels more frequently monitored. In our study, patients in the therapeutic/supratherapeutic group were more likely to be on concomitant antiplatelet therapy at the time of admission and therefore, the addition of antiplatelet therapy may not necessarily be the best approach to reduce their stroke risk. Although home statin use was not significantly different between both groups, we lack information on the dose of statin used and thus it remains unknown whether high intensity statin therapy may have mitigated the odds of having an ischemic event while therapeutic on anticoagulation.

Finally, our findings highlight the importance of performing a complete diagnostic evaluation in patients with AF and ischemic stroke to look for competing mechanisms, particularly if they are therapeutic on anticoagulation at the time of the stroke. This includes vessel imaging to determine the presence or absence of a competing atherosclerotic mechanism and brain imaging to visualize the infarct and determine a potential competing small vessel disease mechanism which may inform secondary stroke prevention strategies.

Strengths and Limitations

In addition to limitations inherent to our retrospective study design, not all patients underwent echocardiography, for which reason data on left atrial dimensions was only

available in approximately 70% of patients. We had no data on the infarct location. Thus, we were unable to determine whether patients with small infarcts had subcortical lesions related to small vessel disease or cortical lesions originating from a distant embolic source.

Notable strengths of our study relate to the inclusion of real world data from multiple comprehensive stroke centers across the United States allowing for better generalization to clinical cohorts. In addition, we accounted for several clinical, laboratory, and imaging variables which adds strength to our study.

Conclusion

Small ischemic lesion (≤ 10 ml) and ipsilateral atherosclerosis with 50% or more narrowing are associated with therapeutic anticoagulation status in patients with AF and ischemic stroke. These factors may be suggestive of a competing mechanism requiring tailored stroke prevention strategies thereby reducing the risk of recurrent stroke.

Funding

Dr. Liberman is funded by NIH grant K23NS107643. Dr. Henninger is supported by K08NS091499 from the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) and R44NS076272 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health.

Dr. Mistry is funded by NIH/NINDS grant K23NS113858. Dr. de Havenon is supported by K23NS105924 from the NIH/NINDS. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1.

Baseline characteristics of patients based on anticoagulation status (therapeutic/supra-therapeutic vs. sub-therapeutic).

	Therapeutic INR (n = 160)	**Sub-therapeutic INR (n = 222)**	**p-value**
Age (years, mean ± SD)	77.6 ± 11.6	77.3 ± 10.5	0.769
Male sex (n, %)	87, 54.4%	113, 50.9%	0.502
Hypertension (n, %)	138, 86.3%	181, 81.5%	0.220
Diabetes (n, %)	57, 35.6%	85, 38.3%	0.595
Hyperlipidemia (n, %)	93, 58.1%	126, 56.8%	0.790
Prior Stroke or TIA (n, %)	72, 45.0%	79, 35.6%	**0.063**
Known active cancer (n, %) (n = 366)	14, 9.2%	13, 6.1%	0.271
CHA_2DS_2-Vasc listed as median (IQR)	5 (3)	5 (2)	0.450
Antiplatelet therapy (n, %)	71, 44.4%	54, 24.3%	**<0.001**
Statin therapy (n, %)	94, 58.8%	138, 62.2%	0.525
Systolic blood pressure (mm Hg, mean ± SD)	147.1 ± 29.1	147.6 ± 30.0	0.892
Diastolic blood pressure (mm Hg, mean ± SD)	77.6 ± 17.7	81.6 ± 19.4	**0.040**
Glucose level on admission (mg/dL, mean ± SD)	135.6 ± 52.6	138.9 ± 57.8	0.573
Low density lipoprotein level (md/dL, mean ± SD)	78.5 ± 32.1	81.9 ± 31.9	0.318
NIHSS score listed as median (IQR)	8 (16)	11 (16)	0.196
Troponin positive (n, %) (n=290)	16, 12.4%	19, 11.8%	0.876
Ipsilateral Atherosclerosis ≥50% (n, %) (n=353)	30, 19.9%	24, 11.9%	**0.039**
Ischemic lesion < 10 mL (n, %) (n=322)	71, 52.2%	70, 37.6%	**0.009**
Severe left atrial enlargement (n, %) (n=268)	55, 51.4%	75, 46.6%	0.440
Spontaneous echocardiographic contrast/thrombus (n, %) (n=327)	3, 2.2%	9, 4.7%	0.535

Table 2.

Multivariable binary regression models fit to the outcome of therapeutic anticoagulation (INR ≥2).

	Ipsilateral atherosclerosis	Ischemic lesion ≤ 10 mL
Unadjusted	1.84 (1.03 – 3.30), p = 0.041, n=353	1.81 (1.16 – 2.84), p = 0.010, n=322
Model 1	1.81 (1.01 – 3.25), p = 0.047, n=353	1.84 (1.17 – 2.89), p = 0.008, n=322
Model 2	1.96 (1.06 – 3.63), p = 0.031, n=351	1.74 (1.10 – 2.76), p = 0.019, n=322
Model 3	1.66 (0.82 – 3.37), p = 0.161, n=250	1.95 (1.14 – 3.35), p = 0.015, n=235

Model 1: adjusted for CHADS2Vasc, model 2: adjusted for diastolic blood pressure, home antiplatelet therapy, and prior stroke/TIA, and model 3: adjusted for CHADS2Vasc and prior stroke/TIA, and model 3: adjusted for CHADS2Vasc and severe LAE