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Original Article

Relationship Between Atrial Fibrillation Burden and Ischemic Stroke Risk in Patients with Cardiovascular Disease

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ABSTRACT

Background: Prevention of stroke in atrial fibrillation (AF) has been mainly based on clinical risk factors, and AF burden has emerged as an important prognostic factor.
Objective: To explore the association between AF burden measured by the device and ischemic stroke in patients with cardiovascular disease.
Methods: 396 adults who had paroxysmal AF or device-detected AF were followed for a median of 24 months. AF burden was determined as the percentage of monitored time spent in AF over a prespecified baseline period of 30 days, and was classified as low (<5%), intermediate (5–20%) or high (>20%). The primary outcome was ischemic stroke. Multivariable Cox models were adjusted for age, hypertension, diabetes, previous stroke/transient ischemic attack, heart failure, vascular disease, LVEF, and oral anticoagulant use.
Results: Mean age was 68.4 ± 9.7 years, 62.9% were men, and median AF burden was 8.6% (IQR 2.4–22.1). 6.8% (27 patients) had ischemic stroke. Incidence of stroke rose with increasing AF burden: 2.2% in low burden group, 6.2% in intermediate burden group and 13.2% in high burden group (p<0.001). High AF burden was independently associated with ischemic stroke after adjustment compared with low burden (adjusted HR 3.08, 95% CI 1.37–6.92; p=0.006) as were prior stroke/TIA, age ≥75 years and lack of oral anticoagulation. For every 10-percentage point increase in AF burden, there was a 21% rise in the adjusted risk of stroke.
Conclusions: There was an association between increased AF burden and increased risk of ischemic stroke independent of traditional clinical risk factors. Quantitative rhythm information can be used to supplement, but not supplant, existing decisions regarding thromboembolic risk assessment and anticoagulation.

Keywords: atrial fibrillation; atrial fibrillation burden; ischemic stroke; cardiovascular disease; anticoagulation; device-detected atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is a significant risk factor for ischemic stroke, systemic embolism, heart failure, hospitalization, and cardiovascular mortality. Structured evaluation of the risk of thromboembolism and the use of oral anticoagulation in patients for whom clinical risk warrants treatment are recommended at present [1]. The 2023 ACC/AHA/ACCP/HRS guideline also acknowledges the growing importance of rhythm monitoring technologies and the clinical problem of device-detected atrial high-rate episodes and subclinical AF [2].

AF has been traditionally viewed as a dichotomous exposure, either present or absent. This is a clinically convenient approach, but does not account for the large inter-individual variability in the number, duration, and total time spent in AF. The American Heart Association has pointed out that AF burden is a potentially important dimension of disease that could help to better characterize risk and response to treatment [3]. The burden of AF can now be determined with much greater accuracy than intermittent electrocardiography, using continuous or prolonged rhythm monitoring.

There are several landmark studies that support a relationship between device-detected AF and thromboembolism. ASSERT showed that subclinical atrial tachyarrhythmias were associated with an increased risk of stroke or systemic embolism [4]. Later analysis revealed that episodes lasting longer than 24 hours had a special high risk [5]. Patients with a high daily atrial tachyarrhythmia burden had a numerically higher rate of thromboembolic events than those with no or low burden in TRENDS [6]. The KP-RHYTHM study also found that there was a higher ischemic stroke risk among adults with paroxysmal AF, even after adjusting for traditional clinical scores, when more time was spent in AF during monitoring [7].

Even with this evidence, the clinical implications of AF burden are complex. AF is not always associated with stroke, and sometimes the AF is only a marker of atrial cardiomyopathy rather than the direct cause of all embolic events. Randomized trials have also demonstrated that the duration of the rhythm is not sufficient to guide decisions on anticoagulation in device-detected AF. NOAH-AFNET 6 did not show any significant improvement in its primary efficacy composite score with edoxaban in patients with atrial high-rate episodes, and bleeding was higher [8]. In subclinical AF, ARTESiA showed apixaban to be more effective than aspirin for stroke or systemic embolism, with an increased risk of major bleeding [9].

The results indicate that AF burden could be most useful when used in combination with known clinical risk factors, and not as a standalone treatment threshold. The present study assessed the relationship between the AF burden measured quantitatively and the risk of ischemic stroke in patients with cardiovascular disease and extended device-based rhythm monitoring. We assumed that a greater AF burden would be correlated with a higher stroke risk, after adjusting for traditional thromboembolic risk factors and anticoagulant use.

MATERIALS AND METHODS

Study design and participants

The prospective observational cohort consisted of 396 adults with cardiovascular disease (CVD) with paroxysmal AF or device-detected AF and an implanted pacemaker, defibrillator, cardiac resynchronization device (CRT) or an insertable cardiac monitor (ICM) with the ability to store atrial rhythm information. Eligible participants were those who had at least 30 days of analyzable rhythm data prior to the onset of outcome follow-up, and were 18 years or older. Patients with permanent AF, mechanical prosthetic valves, moderate to severe rheumatic mitral stenosis, recent cardiac surgery, stroke within 30 days, or who could not determine the exposure to anticoagulants were excluded.

AF burden measurement

Electrogram confirmation was used to reduce the risk of misclassification due to oversensing or other atrial tachyarrhythmias when reviewing stored rhythm data. AF burden was calculated as the proportion of time spent in confirmed AF of the total time monitored during a prespecified 30-day baseline period. Patients were classified as low burden (<5%), intermediate burden (5-20%) or high burden (>20%). The longest single AF episode during the window was also recorded. Device interrogation and remote-monitoring records were used to verify rhythm exposure.

Clinical parameters and outcome

Baseline variables were age, sex, hypertension, diabetes, heart failure, prior stroke or transient ischemic attack (TIA), vascular disease, LVEF, chronic kidney disease, smoking and oral anticoagulant therapy. For descriptive purposes, a CHA2DS2-VASc score was computed. The main outcome was ischemic stroke, which was defined as a new focal neurologic deficit of vascular origin confirmed by imaging if available. Secondary outcomes included TIA or systemic embolism and the composite of ischemic stroke/systemic embolism. The participants were followed for a median of 24 months using clinical records, remote-monitoring databases, and structured contact.

Statistical analysis

Continuous variables were expressed in mean ± SD or median (interquartile range) and categorical variables were presented as n (%). Chi-square testing and Kaplan-Meier time-to-event analysis were used to compare the incidence of stroke between AF burden categories. Independent predictors of ischemic stroke were determined using Cox proportional-hazards regression. The burden of AF was assessed both categorically and continuously (per 10 percentage points increase). Multivariable models were adjusted for age, hypertension, diabetes, prior stroke/TIA, heart failure, vascular disease, LVEF, chronic kidney disease, and oral anticoagulant use. Longest AF episode duration and exclusion of patients with treatment changes in the baseline rhythm window were analyzed. A p value of <0.05 on both sides was deemed significant.

RESULTS

The cohort had a mean age of 68.4 ± 9.7 years and included 249 men (62.9%). Hypertension was present in 300 patients (75.8%), diabetes in 126 (31.8%), heart failure in 158 (39.9%), and prior stroke/TIA in 57 (14.4%). Mean CHA2DS2-VASc score was 3.4 ± 1.5. Oral anticoagulation was used by 291 patients (73.5%) at baseline. Median AF burden was 8.6% (IQR 2.4–22.1). Low AF burden was present in 137 patients, intermediate burden in 145, and high burden in 114.

Patients with high AF burden were older, more frequently had heart failure, and were more likely to have reduced LVEF than those with low burden. Prior stroke/TIA and hypertension were common across all categories. Anticoagulant use increased modestly with AF burden, but a clinically relevant proportion of high-burden patients were not receiving anticoagulation at baseline.

Table 1. Baseline characteristics by AF-burden category

Characteristic	<5% (n=137)	5–20% (n=145)	>20% (n=114)	p value
Age, years	66.4 ± 9.5	68.2 ± 9.6	71.0 ± 9.4	0.001
Male sex, n (%)	83 (60.6)	91 (62.8)	75 (65.8)	0.69
Hypertension, n (%)	101 (73.7)	111 (76.6)	88 (77.2)	0.79
Diabetes mellitus, n (%)	40 (29.2)	46 (31.7)	40 (35.1)	0.60
Heart failure, n (%)	42 (30.7)	57 (39.3)	59 (51.8)	0.003
Prior stroke/TIA, n (%)	17 (12.4)	21 (14.5)	19 (16.7)	0.63
LVEF, %	52.1 ± 10.7	49.6 ± 11.2	45.8 ± 12.0	<0.001
Oral anticoagulation, n (%)	92 (67.2)	108 (74.5)	91 (79.8)	0.075

AF: atrial fibrillation; TIA: transient ischemic attack; LVEF: left ventricular ejection fraction.

Table 2. Thromboembolic outcomes according to AF burden

Outcome	<5%	5–20%	>20%	Overall	p value
Ischemic stroke, n (%)	3 (2.2)	9 (6.2)	15 (13.2)	27 (6.8)	<0.001
TIA, n (%)	4 (2.9)	7 (4.8)	8 (7.0)	19 (4.8)	0.31
Systemic embolism, n (%)	1 (0.7)	2 (1.4)	3 (2.6)	6 (1.5)	0.45
Stroke/systemic embolism, n (%)	4 (2.9)	11 (7.6)	18 (15.8)	33 (8.3)	<0.001
All-cause death, n (%)	7 (5.1)	11 (7.6)	14 (12.3)	32 (8.1)	0.11

Individual secondary outcomes may overlap. Percentages are within AF-burden category.

Table 3. Multivariable predictors of ischemic stroke

Predictor	Adjusted HR	95% CI	p value
High AF burden >20% vs <5%	3.08	1.37–6.92	0.006
Intermediate AF burden 5–20% vs <5%	1.72	0.72–4.12	0.22

Predictor	Adjusted HR	95% CI	p value
AF burden, per 10% increase	1.21	1.07–1.37	0.003
Prior stroke/TIA	2.76	1.42–5.38	0.003
Age ≥75 years	1.93	1.02–3.65	0.043
Oral anticoagulant use	0.47	0.25–0.89	0.020
Diabetes mellitus	1.35	0.72–2.52	0.35

HR: hazard ratio; CI: confidence interval. Model additionally adjusted for hypertension, heart failure, vascular disease, chronic kidney disease, and LVEF.

During a median follow-up of 24 months, ischemic stroke occurred in 27 patients (6.8%). Stroke risk showed a stepwise increase with AF burden, from 2.2% in the low-burden group to 6.2% in the intermediate group and 13.2% in the high-burden group. The composite of stroke or systemic embolism showed a similar gradient. Kaplan-Meier analysis demonstrated early and sustained separation of event curves for the high-burden group.

After multivariable adjustment, high AF burden remained independently associated with ischemic stroke compared with low burden. When AF burden was analyzed as a continuous variable, each 10-percentage-point increase was associated with a 21% higher adjusted stroke hazard. Prior stroke/TIA and age ≥75 years were also independent predictors, while oral anticoagulant use was associated with lower risk. Intermediate AF burden showed a higher point estimate than low burden but did not reach statistical significance after adjustment.

DISCUSSION

The key result of this study is that the AF burden was associated with ischemic stroke in a graded fashion in patients with cardiovascular disease who were undergoing prolonged rhythm monitoring. Patients with a burden of AF >20% of monitored time had a significantly higher stroke rate compared to those with a burden <5%, even after adjustment for conventional clinical risk factors and oral anticoagulant use. This pattern was confirmed by the continuous analysis, with an increasing number of monitored time periods in AF corresponding to a greater stroke hazard.

These findings help to confirm the notion that AF is not a dichotomous disease. The AHA scientific statement on AF burden highlighted that there could be clinically relevant information in the duration, frequency, density and total time spent in AF [3]. As more and more devices are implanted and longer ambulatory monitoring is performed, quantitative characterization is becoming more possible. For patients with similar clinical risk profiles, burden may help to account for the wide variation in thromboembolic risk among patients.

Our results are in the same direction as ASSERT. In that study, the risk of stroke or systemic embolism was increased with device-detected subclinical atrial tachyarrhythmias [4]. A subsequent ASSERT analysis narrowed the association to episodes that were longer than 24 hours, as shorter episodes did not have the same level of association with thromboembolic events [5]. This implies that the dose of AF exposure is important, and that a threshold for AF exposure that relies only on the presence of any short exposure is too low to distinguish clinically relevant risk.

TRENDS also correlated increased device-detected atrial tachyarrhythmia burden with increased thromboembolic risk [6]. The absolute annual event rate was relatively small, but the study was significant because burden was not considered a diagnostic category but rather a time-varying physiologic exposure. The KP-RHYTHM study then showed that higher AF burden (as determined by continuous ambulatory monitoring) was linked to ischemic stroke in paroxysmal AF, even after adjusting for known risk scores [7]. Our results corroborate this evidence in a cohort of patients with cardiac rhythm monitoring and adjustment for anticoagulant use who had cardiovascular disease.

However, the AF burden should not be used as a stand-alone treatment threshold. Current guidelines focus on known clinical thromboembolic risk factors, and suggest a case-by-case approach to episodes detected by the device [1,2]. This is why the randomized evidence is so important. NOAH-AFNET 6 did not show a significant decrease in its primary efficacy composite in patients with atrial high-rate episodes, and it showed an increase in major bleeding or death [8]. ARTESiA demonstrated apixaban's superiority over aspirin for stroke or systemic embolism in patients with subclinical AF, with more major bleeding [9]. Therefore, the benefits of anticoagulation remain to be determined depending on the patient's preexisting stroke and bleeding risk, despite the increased risk of emboli with increased arrhythmia burden.

It is not surprising that prior stroke/TIA was associated with recurrent stroke in our analysis, and highlights the ongoing importance of existing risk factor schemes. The CHA2DS2-VASc score was created to better identify clinically relevant stroke risk in addition to older, less detailed scores [10]. The 2024 ESC guideline focuses on a new clinical strategy for stroke prevention, and acknowledges the uncertainties of subclinical AF and device-detected atrial high-rate episodes [1]. The quantitative burden should be considered as complementary information which can be used to inform discussion and follow-up, but should not be used to replace the use of guidelines to assess risk.

There are multiple pathways that could connect the increased AF burden to stroke. Atrial activity that is disorganized for longer periods of time can decrease contractility of the left atrial appendage and lead to blood stasis. More advanced atrial structural remodeling, fibrosis, inflammation, endothelial dysfunction and dilation could also be responsible for the greater burden. These abnormalities of the substrate may continue even when in sinus rhythm, and may account for the incomplete temporal relationship between a particular AF episode and stroke that is often observed. In this context, AF may also be a causal factor in the formation of a thrombus, and it may also be a sign of an underlying atrial cardiomyopathy.

The association between use of anticoagulants and reduced risk of stroke was clinically plausible but is not causal as therapy was not randomized. Patients included in the anticoagulation group were not necessarily similar to those who were not treated with anticoagulants in several aspects, and temporary interruption and dose changes during follow-up were not fully accounted for. However, the association underscores the need to check anticoagulation status if a high AF burden is identified, especially in those who have had a stroke, have vascular disease, older age or heart failure.

There are some limitations to the study. It is observational and so does not establish a burden threshold for starting anticoagulation. The AF burden was assessed over a baseline period and can vary over time. There are different algorithms for the various devices, but electrogram confirmation was used to minimize false detection. The number of stroke events was low, which precluded precision and sub-group analysis. There is potential for residual confounding due to atrial size, left-atrial appendage function, renal function trajectory, medication adherence and competing vascular mechanisms of stroke. Lastly, the cohort needed to have the monitoring devices implanted and thus may have a higher proportion of cardiovascular disease than the general community AF cohort.

Nevertheless, the study contributes to the growing body of evidence that there is prognostic information in quantitative AF exposure. Future studies should assess dynamic burden trajectories, interaction with atrial imaging and biomarkers, and the addition of AF burden to clinical risk to better calibrate absolute stroke risk. Importantly, these models should be evaluated on clinically relevant outcomes and on net treatment benefit, not just on discrimination.

Subgroup analysis of device-detected AHEs also demonstrates that the duration of the AHE cannot be used without considering the baseline thromboembolic risk. NOAH-AFNET 6 studies were conducted on long episodes, where the risk of thromboembolic complications and bleeding were still clinically complex [11]. The findings from large datasets of device-detected AF from the SOS AF project also showed that the amount of AF detected on the device was a quantitative risk marker for stroke, not just a diagnostic label [12].

The timing of the exposure to AF may also be important. A case-crossover study of continuously recorded data from implanted devices revealed that short-term stroke risk increased during multihour AF episodes [13]. The same length of AF was also found to have a different absolute risk for different clinical-risk profiles, as shown by an interaction between AF duration and CHA2DS2-VASc score by Kaplan and colleagues [14]. A systematic review and meta-analysis of subclinical AF detected by devices also showed an overall association with stroke, but with some heterogeneity depending on the duration of the AF episode and patient characteristics [15].

Previous continuous-monitoring studies confirmed this finding, demonstrating that the addition of AF duration to clinical risk factors enhanced thromboembolic risk stratification beyond the clinical risk factors alone [16]. Temporal analyses more recently revealed that the excess risk of ischemic stroke was highest immediately after longer AF episodes, and decreased thereafter [17]. These observations support a model in which the risk is determined by the burden of AF, the duration of the AF episode, temporal proximity, and underlying atrial and vascular disease. The use of quantitative burden should be used in addition to, not instead of, the clinical assessment and shared decision making about anticoagulation.

CONCLUSION

In those with cardiovascular disease, a greater device-measured AF burden was associated with an increased risk of ischemic stroke. In addition to established risk factors and prior stroke/TIA, high burden was independently associated

with stroke after adjustment, and advanced age was further associated with stroke. AF burden can thus be a helpful adjunct to the complete clinical assessment of thromboembolism, but should not be considered as an endpoint of anticoagulation.

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