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Research Article

Prevalence and clinical characteristics of atrial fibrillation in acute ischemic stroke: A prospective cross-sectional single-center study

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ABSTRACT

Background: Atrial fibrillation (AF) is a leading cause of ischemic stroke, often underdiagnosed in acute settings.

Objective: To determine the prevalence of AF in hospitalized ischemic stroke patients and analyze associated clinical characteristics.

Methods: A prospective cross-sectional study was conducted on 99 patients with acute ischemic stroke admitted to Thong Nhat Hospital from January 2024 to March 2025. AF was diagnosed using a 12-lead ECG and 24-hour Holter monitoring. Clinical and paraclinical data were analyzed to compare AF vs. non-AF groups.

Results: AF was present in 15.2% of patients. The AF group was significantly older (81.7 vs. 64.8 years, $p < 0.001$), had higher stroke severity (NIHSS 12.9 vs. 6.2, $p < 0.001$), and more frequent impaired consciousness. Comorbidities, including hypertension, diabetes, and heart failure, were more prevalent. Echocardiography revealed larger left atrial diameters and reduced ejection fraction. Neuroimaging showed a higher rate of large infarcts (> 30 mm), lower ASPECT scores, and more extensive brain damage. Biochemical abnormalities included higher glucose, triglycerides, LDL-c, and cholesterol, and lower HDL-c and eGFR levels in AF patients.

Conclusion: The study confirms the high prevalence of AF in ischemic stroke patients, especially in older individuals with cardiovascular comorbidities. Early rhythm monitoring is critical for diagnosis and secondary prevention.

Key words: acute ischemic stroke, atrial fibrillation, 24-hour Holter monitoring

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INTRODUCTION

Stroke is one of the leading causes of death and long-term disability globally, with a high incidence in Vietnam[1–3]. Strokes are pathologically classified as either ischemic or hemorrhagic, with ischemic stroke accounting for up to 87% of all cases, according to the current report of the American Heart Association (AHA). Based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of ischemic strokes, cardioembolism is a leading etiology, accounting for 20–25% of all cases[4,5]. Cardioembolic stroke results from thrombus formation within the atria—most commonly the left atrial appendage—in patients with atrial fibrillation (AF). These emboli tend to occlude major cerebral arteries, leading to large, sudden-onset infarcts. In contrast, atherosclerotic mechanisms involve progressive plaque buildup and arterial stenosis, usually producing smaller or borderzone infarcts with different clinical patterns. Understanding these distinctions clarifies why AF is associated with more severe stroke presentations and underscores the importance of accurate rhythm monitoring.

AF is an independent risk factor for the formation of cardiac thrombi and is associated with a 4- to 5-fold increased risk of stroke[6,7]. It is also the most common arrhythmia in adults, affecting approximately 46.3 million people worldwide[8,9]. Studies in Western countries have reported AF prevalence rates ranging from 20.4% to 33.4% among patients with ischemic stroke[10]. In contrast, studies in Southeast Asia have shown lower AF prevalence rates, ranging from 5.8% to 23.4%[10–14]. Early diagnosis of AF is critical and allows for the timely initiation of oral anticoagulants (OACs), which can significantly reduce the risk of stroke[15]. It is evident that, beyond merely diagnosing stroke, identifying underlying causes—such as AF—plays an essential role in controlling stroke incidence. To enhance the effectiveness of secondary stroke prevention, it is crucial to determine the prevalence of AF and to evaluate the clinical and paraclinical characteristics of patients with ischemic stroke and AF.

Accurate diagnosis of AF can be challenging in patients with paroxysmal AF, a transient or intermittent form of AF. Therefore, relying solely on surface electrocardiograms (ECGs) may lead to underdiag-

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nosis of AF in stroke patients. According to recommendations from the European Society of Cardiology (ESC), AF screening using 24- to 48-hour Holter ECG monitoring should be performed in all stroke patients. Currently, in Vietnam, studies on the prevalence of AF in acute ischemic stroke patients using 24- to 48-hour Holter monitoring remain limited. Considering these clinical realities, we conducted this study with two primary objectives: to determine the prevalence of AF in patients with acute ischemic stroke and to investigate the clinical and paraclinical characteristics of patients with ischemic stroke and AF.

MATERIALS AND METHODS

Patient Selection

We conducted a prospective, cross-sectional study at a single center involving 99 patients with acute ischemic stroke from January 2024 to March 2025. All patients were diagnosed with acute ischemic stroke confirmed by brain magnetic resonance imaging (MRI) or computed tomography (CT). In accordance with hospital protocol, all stroke patients were examined by experienced neurologists upon admission. Routine 24-hour Holter ECG monitoring was performed to detect potential arrhythmias, including AF; however, 26 out of 99 patients were discharged while awaiting monitoring. Therefore, only 73 of 99 patients underwent 24-hour Holter ECG monitoring. Transthoracic echocardiography was performed in all patients to evaluate cardiac structure and function. Clinical data were collected from the hospital's electronic database. The study was approved by the Ethics Committee in Biomedical Research of Thong Nhat Hospital.

Statistical Analysis

All statistical analyses were performed using IBM SPSS software, version 22.0. The Kolmogorov–Smirnov test was used to assess the normality of the distribution of the variables. Continuous quantitative variables are presented as mean $\pm$ standard deviation or median, while qualitative variables are expressed as frequency (n) and percentage (%). Given the small number of AF cases in the cohort, non-parametric tests such as the Mann–Whitney U test and Fisher's exact test were applied where appropriate to ensure valid interpretation of the data. These updates provide a clearer methodological framework and strengthen the robustness of the comparative analyses presented in the study.

RESULTS

Prevalence of AF

Of the 99 patients with acute ischemic stroke, AF was identified in 15 cases, representing a prevalence of 15.2%. Among these, AF was newly detected in 2 patients through 24-hour Holter ECG monitoring and in 3 patients via standard 12-lead electrocardiography, while 10 patients had a documented history of AF prior to admission. In our study, the CHA_2DS_2-VASc score was calculated based on each patient's clinical profile prior to the occurrence of the index ischemic stroke. Four AF patients did not meet the anticoagulation threshold and had not accumulated sufficient risk factors prior to their stroke—such as hypertension, diabetes, prior stroke/TIA, vascular disease, or advanced age—to warrant the initiation of OACs according to guideline recommendations. As a result, these patients were not on preventive OACs prior to the stroke event. This distinction is important because it clarifies that the absence of anticoagulation therapy was not due to clinical oversight but rather reflected their lower pre-stroke risk categorization under the CHA_2DS_2-VASc scoring system.

A clear distinction between previously diagnosed and newly detected AF is essential for interpreting our findings and for informing clinical pathways. Newly detected AF represents patients whose arrhythmia had not been recognized in routine outpatient care and would likely have remained undiagnosed without systematic post-stroke rhythm assessment. This distinction has important implications: known AF reflects established disease burden requiring long-term anticoagulation management, while newly detected AF highlights gaps in early detection and underscores the need for structured AF screening strategies, extended rhythm monitoring, and improved health system capacity to prevent avoidable cardioembolic stroke.

Comparison of Clinical and Paraclinical Characteristics Between Ischemic Stroke Patients With and Without AF

Table 1 illustrates the differences in clinical characteristics between ischemic stroke patients with AF and those without. Statistically significant differences were observed for the following variables: age ($p < 0.001$), National Institutes of Health Stroke Scale (NIHSS) score at admission ($p < 0.001$), level of consciousness at admission ($p = 0.031$), history of hypertension ($p < 0.001$), diabetes mellitus ($p = 0.005$), heart failure ($p < 0.001$), and prior use of antihypertensive

Table 1: Comparison ofclinical characteristics between patients with and without AF.

Characteristics	No AF (n = 84)	With AF (n = 15)	-value
Age, years	64.8 ± 11.5	81.7 ± 5.9	< 0.001
Male, n (%)	44 (52.4)	8 (53.3)	1.0
BMI, kg/m2	21.8 ± 3.4	22.3 ± 2.7	0.534
Systolic blood pressure (mmHg)	160.3 ± 26.7	146.7 ± 33.7	0.16
NIHSS	6.2 ± 3.8	12.9 ± 4.1	< 0.001
Total GCS score	14.2 ± 1.9	12.1 ± 3.3	0.031
Medical history			
Hypertension, n (%)	41 (48.8)	15 (100.0)	< 0.001
Dyslipidemia, n (%)	30 (35.7)	9 (60.0)	0.137
Diabetes mellitus, n (%)	18 (21.4)	9 (60.0)	0.005
Heart failure, n (%)	7 (8.3)	9 (60.0)	< 0.001
Ischemic heart disease, n (%)	10 (11.9)	4 (26.7)	0.352
Medications			
Antihypertensive drugs, n (%)	41 (48.8)	15 (100.0)	< 0.001
Statins, n (%)	30 (35.7)	5 (33.3)	1.000
OACs, n (%)	6 (7.1)	9 (60.0)	< 0.001
Symptoms			
Hemiparesis, n (%)	46 (54.8)	12 (80.0)	0.090
Language disorder, n (%)	34 (40.5)	10 (66.7)	0.090
Dysphagia, n (%)	8 (9.5)	3 (20.0)	0.365
Consciousness disturbance, n (%)	7 (8.3)	7 (46.7)	0.001
Headache, n (%)	6 (7.1)	1 (6.7)	1.000

AF: Atrialfibrillation, BMI: Body Mass Index, NIHSS: National Institutes of Health Stroke Scale, GCS: Glasgow Coma Scale, OACs: Oral anticoagulants.

and anticoagulant medications ($p < 0.001$). In contrast, variables such as sex, body mass index (BMI), systolic blood pressure, history of dyslipidemia, history of ischemic heart disease, and clinical symptoms, including hemiparesis, speech disturbances, dysphagia, and headache, did not differ significantly between the two groups.

Table 2 compares the paraclinical characteristics between ischemic stroke patients with and without AF. Statistically significant differences were observed for the following parameters: left atrial diameter on echocardiography ($p < 0.001$), size of ischemic stroke lesions greater than 30 mm ($p < 0.001$), estimated glomerular filtration rate (eGFR) < 60 mL/min ($p = 0.019$), blood lipid profile, and blood glucose levels ($p = 0.037$). No statistically significant differences were found between the two groups in terms of complete blood count, number of ischemic stroke lesions, cerebral hemisphere involvement, affected cerebral artery, ischemic stroke location, or left ventricular end-diastolic diameter (LVEDD) on echocardiography.

DISCUSSION

Prevalence of AF in Patients with Ischemic Stroke

Currently, numerous tools are available for AF screening, including both ECG-based and non-ECG-based modalities. In clinical practice, the standard 12-lead ECG remains a widely used diagnostic tool due to its convenience and accessibility. Compared with routine ECG, 24-hour Holter monitoring enhances the detection of paroxysmal AF, thereby contributing to secondary stroke prevention.

Table 2: Comparison of paraclinical characteristics between patients with and without AF.

Characteristics	No AF (n = 84)	With AF (n = 15)	*p*-value
Echocardiography			
LA diameter, mm	31.7 ± 3.4	38.5 ± 4.5	< 0.001
LVEDD, mm	46.7 ± 6.0	45.6 ± 11.1	0.713
EF ≤ 40%, n (%)	4 (4.8)	5 (33.3)	0.004
Ischemic stroke lesion			
Deep, n (%)	23 (27.4)	7 (46.7)	0.233
Subcortical, n (%)	65 (77.4)	11 (73.3)	0.745
Brainstem, n (%)	2 (2.4)	1 (6.7)	0.393
Affected cerebral artery			
Anterior cerebral artery, n (%)	9 (10.7)	2 (13.1)	0.688
Middle cerebral artery, n (%)	71 (84.5)	14 (93.3)	
Posterior cerebral artery, n (%)	4 (4.8)	1 (6.6)	
Affected hemisphere			
Left, n (%)	45 (53.6)	9 (60.0)	0.951
Right, n (%)	32 (38.1)	5 (33.3)	
Bilateral, n (%)	7 (8.3)	1 (6.7)	
Number of ischemic stroke lesions			
Single, n (%)	28 (33.3)	4 (26.7)	0.768
Multiple, n (%)	56 (66.7)	11 (73.3)	
ASPECT			
< 8, n (%)	15 (17.9)	11 (73.3)	0.001
8–10, n (%)	69 (82.1)	4 (26.7)	
Size of ischemic stroke lesions			
< 15 mm	62 (73.8)	0	< 0.001
15–30 mm	10 (11.9)	4 (26.7)	
> 30 mm	12 (14.3)	11 (73.3)	
Blood biochemistry			
Triglyceride, mmol/L	2.0 ± 1.2	3.0 ± 1.1	0.004
Cholesterol, mmol/L	4.8 ± 1.6	7.0 ± 1.9	0.001
HDL-c, mmol/L	1.8 ± 0.7	1.1 ± 0.4	0.009
LDL-c, mmol/L	2.7 ± 1.2	3.4 ± 0.9	0.002
Glucose, mmol/L	6.7 ± 2.2	8.5 ± 3.0	0.037
EF, %	66.5 ± 6.5	65.6 ± 7.7	0.689
Urea, mmol/L	5.8 ± 3.4	6.0 ± 1.9	0.832
PLT, K/μL	257.1 ± 78.6	246.6 ± 90.3	0.677
WBC, K/μL	8.5 ± 2.6	8.3 ± 3.5	0.837
Hgb, g/dL	13.2 ± 1.9	13.5 ± 2.1	0.541
eGFR < 60 ml/min/1.73m^2, n (%)	10 (11.9)	6 (40.0)	0.019

AF: Atrialfibrillation, LA: Leftatrial, LVEDD: Left ventricular end-diastolic dimension, EF: Ejection fraction, ASPECT: Alberta Stroke Program Early CT score, PLT: Platelet count, WBC: White bloodcell, Hgb: Hemoglobin, eGFR: Estimated glomerular filtration rate.

In our study, the prevalence of AF among patients with acute ischemic stroke was 15.2%, corresponding to 15 of 99 patients, irrespective of whether AF was newly diagnosed or pre-existing. As only 73 of 99 patients completed 24-hour Holter monitoring, the true prevalence—especially of paroxysmal AF—was likely underestimated. This finding indicates that approximately one in six patients admitted with ischemic stroke had concomitant AF and is consistent with results reported by Kishore et al. [16], who found a prevalence of 15.9% in patients with cryptogenic stroke. This further reinforces the established association between AF and ischemic stroke within the TOAST classification system.

Our findings are most comparable to those of Phong et al. [17] and Goel et al. [18]. Phong et al. reported an overall AF prevalence of 18.1% in Vietnam, while Goel et al. reported a higher prevalence of 25.2% in an Indian cohort. Although our study also used 12-lead ECG and 24-hour Holter ECG for AF detection, the observed prevalence of AF was lower than in these studies. This discrepancy may be attributable to several factors, such as differences in sample size and study population characteristics. From an epidemiological and demographic standpoint, Phong et al.'s study shares greater similarity with ours because it is set in Vietnam. However, while Phong et al.'s study included 2,038 hospitalized patients with both transient ischemic attacks and ischemic strokes in a cross-sectional design [17], our study focused exclusively on ischemic stroke patients with a smaller sample size (n = 99), potentially contributing to the lower AF prevalence observed.

Additionally, differences in average age and the proportion of comorbidities such as hypertension and diabetes may also influence prevalence rates. In our study, 2 of 73 patients undergoing 24-hour Holter ECG and 3 of 99 patients receiving a 12-lead ECG were diagnosed with AF, yielding detection rates of 2.7% and 3%, respectively. These findings align with prior research on AF detection rates in stroke patients, which reported rates ranging from 2% to 5% with standard ECG [16,19] and 2% to 6% with 24-hour Holter monitoring [20,21]. This underscores the pivotal role of screening method selection in determining AF detection rates.

Studies that used only 12-lead ECG for AF screening, such as those by Khan et al. (2025) and Aslam et al. (2025), reported lower AF prevalence among ischemic stroke patients than our findings. In fact, several investigations have demonstrated that extending the monitoring period significantly increases AF detection in this patient population. Grond et al. [22] reported that prolonging monitoring from 24 to 72 hours raised detection rates from 2.6% to 4.3%. Furthermore, 14-day Holter ECG monitoring has been shown to increase AF detection rates to 14.6% [23 24,25].

Clinical Characteristics Associated with AF in Ischemic Stroke Patients

Patients with AF in our cohort demonstrated significantly worse neurological severity, as evidenced by higher NIHSS scores, lower GCS levels, and substantially larger infarct sizes compared with those without AF. These findings reaffirm that AF-related strokes are typically more severe, a pattern consistently reported in international literature. The observed differences underscore important clinical implications for risk stratification, emphasizing that patients with AF constitute a higher-risk subgroup who may benefit from more intensive diagnostic evaluation. They also highlight the need for resource prioritization toward prolonged rhythm monitoring to avoid missed diagnoses of paroxysmal AF, as well as the importance of initiating timely OACs once AF is identified to reduce the risk of recurrent cardioembolic stroke.

Neurological Severity Assessed by NIHSS

In our study, the distribution of NIHSS scores at admission revealed that most patients (55.6%) had moderate stroke severity (NIHSS score 5–15), followed by mild stroke (35.4%, NIHSS score 1–4), and severe stroke (9.1%, NIHSS score 16–20). Notably, no patients were classified as having very severe stroke (NIHSS score 21–42). These findings provide insight into the spectrum of stroke severity within our study population. The NIHSS is not only a measure of initial stroke severity but also a well-established prognostic indicator. Numerous studies have demonstrated that higher NIHSS scores at admission are strongly associated with worse outcomes, including poor functional recovery [26,27] and increased mortality [28,29].

When comparing the two groups, we found that the mean NIHSS score in the AF group (12.9 $\pm$ 4.1) was significantly higher than that in the non-AF group (6.2 $\pm$ 3.8), with a highly significant -value of $<$ 0.0001. This observation aligns closely with both international and local literature. For instance, Kimura et al. [29] reported mean NIHSS scores of 13.7 in the AF group versus 6.9 in the non-AF group (< 0.001), closely matching our findings. Similarly, Gabet et al. [30] in France found higher median NIHSS scores in the AF group compared to the non-AF group (7 vs. 3, < 0.001). In Vietnam, Lien [31] also observed higher mean NIHSS scores in the AF group (15 vs. 12, <

0.001). The consistency of our results with previous studies reinforces the notion that AF is a significant risk factor for more severe ischemic strokes.

The widely accepted pathophysiological explanation is that AF predisposes patients to the formation of large atrial thrombi. When these embolize to the cerebral circulation, they tend to occlude major cerebral arteries, resulting in large infarct areas and more severe neurological deficits, as reflected by higher NIHSS scores[29 30,31].

GCS

Our findings indicate that a substantial majority of patients (92.9%) had GCS scores ranging from 13 to 15, corresponding to mild or no impairment of consciousness. Only a small proportion of patients exhibited moderate (GCS 9–12) or severe (GCS 3–8) levels of impaired consciousness. Interestingly, the mean GCS score was significantly lower in the AF group (12.1 ± 3.3) compared to the non-AF group (14.2 ± 1.9), with a p-value of 0.031.

Similar to our findings, the study by Nathan et al.[32] showed that the GCS score was significantly lower in the AF group than in the non-AF group ($p = 0.003$). Nathan further reviewed previous studies and proposed that ischemic stroke patients with decreased consciousness (lower GCS scores) often have additional underlying comorbidities. AF is frequently associated with heart failure or coronary artery disease, which may present with symptoms such as dyspnea and reduced oxygen saturation. Hypoxia, in turn, can affect the level of consciousness, thereby contributing to lower GCS scores[32].

Imaging Characteristics of Cerebral Infarcts

Regarding infarct size, we classified patients into three groups based on the largest infarct diameter: <15 mm, 15–30 mm, and > 30 mm. The distribution of infarct sizes is presented in Table 3.7, with the majority falling in the 15–30 mm range (45.5%), followed by lesions > 30 mm (31.3%), and < 15 mm (23.2%). The prevalence of larger infarcts was significantly higher in the AF group: 40% of patients had infarcts sized 15–30 mm (compared to 11.9% in the non-AF group, $p = 0.019$), and 73.3% had infarcts > 30 mm (compared to 14.3%, $p < 0.001$) (Table 3.10). These findings are consistent with those of Lambert et al.[33–36], who reported that 86.4% of stroke patients with AF had infarcts $\geq$ 10 mm, compared to 64.9% in the non-AF group—supporting prior studies describing characteristic imaging features of AF-related infarcts.

Infarct patterns in our cohort were reviewed to evaluate their consistency with cardioembolic versus atherosclerotic mechanisms. Patients with AF more frequently exhibited large territorial infarcts involving major arterial distributions, a pattern characteristic of cardioembolism and consistent with the abrupt occlusion of proximal cerebral vessels by atrial thrombi. In contrast, patients without AF more commonly demonstrated smaller, subcortical, or borderzone infarcts that align with underlying large-artery atherosclerosis or small-vessel disease. These observations suggest that while cardioembolism was the predominant mechanism among AF patients, mixed mechanisms may coexist in individuals with concurrent vascular risk factors, emphasizing the need for individualized etiological assessment when determining secondary prevention strategies.

LIMITATIONS OF THE STUDY

This study has several limitations that warrant consideration. First, it was conducted at a single center with a relatively small sample size (n = 99), which may limit the generalizability of the findings to broader patient populations. Moreover, only 73 of 99 patients underwent 24-hour Holter ECG monitoring due to logistical and clinical constraints. This partial implementation may have resulted in the underdiagnosis of paroxysmal AF, thus underestimating its true prevalence among ischemic stroke patients.

Second, the study did not include long-term follow-up data on functional outcomes, recurrence rates, and mortality, precluding assessment of AF's prognostic impact over time. Furthermore, no stratification by AF subtype (paroxysmal vs. persistent) was performed, which may have exhibited distinct clinical profiles and outcomes.

Third, biochemical parameters such as lipid profiles and glucose levels were measured during the acute phase of stroke, which may reflect stress-related metabolic responses rather than baseline metabolic status. This could potentially confound the interpretation of associations between AF and metabolic abnormalities.

Finally, genetic predispositions, inflammatory markers, and other cardiovascular risk predictors were not evaluated, which may have provided further insight into the pathophysiological mechanisms linking AF and ischemic stroke. Future studies should consider multicenter designs, larger and more diverse patient cohorts, extended cardiac monitoring, and long-term outcome evaluations to validate and expand upon these findings.

CONCLUSION

This study demonstrates that AF is a common risk factor among patients with ischemic stroke, with a relatively high detection rate when both 12-lead ECG and 24-hour Holter monitoring are employed. Patients with AF tend to be older, have larger left atrial diameters, and more frequently present with chronic comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and heart failure. These results underscore the importance of AF screening in the acute ischemic stroke population. Early detection and timely intervention with preventive measures, such as OAC therapy, can significantly reduce the risk of recurrent stroke. Therefore, wider implementation of diagnostic tools—especially 24-hour Holter ECG—is strongly recommended in clinical practice, particularly at facilities equipped with the necessary technical capabilities.

ABBREVIATIONS

AF: Atrial Fibrillation
ECG: Electrocardiogram
MRI: Magnetic Resonance Imaging
CT: Computed Tomography
OAC: Oral Anticoagulants
ESC: European Society of Cardiology
SPSS: Statistical Package for the Social Sciences
BMI: Body Mass Index
NIHSS: National Institutes of Health Stroke Scale
GCS: Glasgow Coma Score
LAA: Left Atrial Appendage
LA: Left Atrium
LVEDD: Left Ventricular End Diastolic Dimension
EF: Ejection Fraction
ASPECT: Alberta Stroke Program Early CT Score
PLT: Platelet Count
WBC: White Blood Cell
Hgb: Hemoglobin
eGFR: Estimated Glomerular Filtration Rate
TOAST: Trial of Org 10172 in Acute Stroke Treatment

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INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Thong Nhat Hospital, Ho Chi Minh City.

INFORMED CONSENT STATEMENT

All patients participating in the study were fully informed about the purpose, benefits, and associated risks before signing the informed consent form.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

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A. APPENDIX

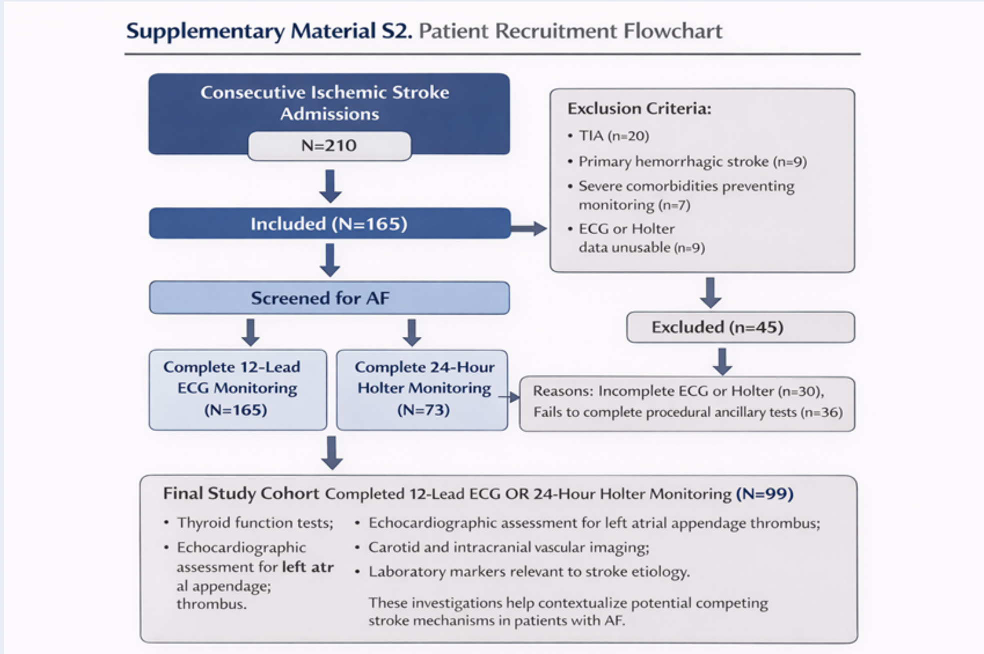

Figure 1: Supplementary Material S2. Patient recruitment flowchart.

A description of the classification criteria used to distinguish AF types:

- **Known AF:** Confirmed from prior medical records, previous ECGs, or documented medical diagnosis before admission.
- **Newly Detected AF:** Identified during hospitalization using 12-lead ECG OR 24-hour Holter monitoring in patients without prior AF diagnosis.

Figure 2: **Supplementary Material S3.** Diagnosticcriteria for known vs. newly detected AF.

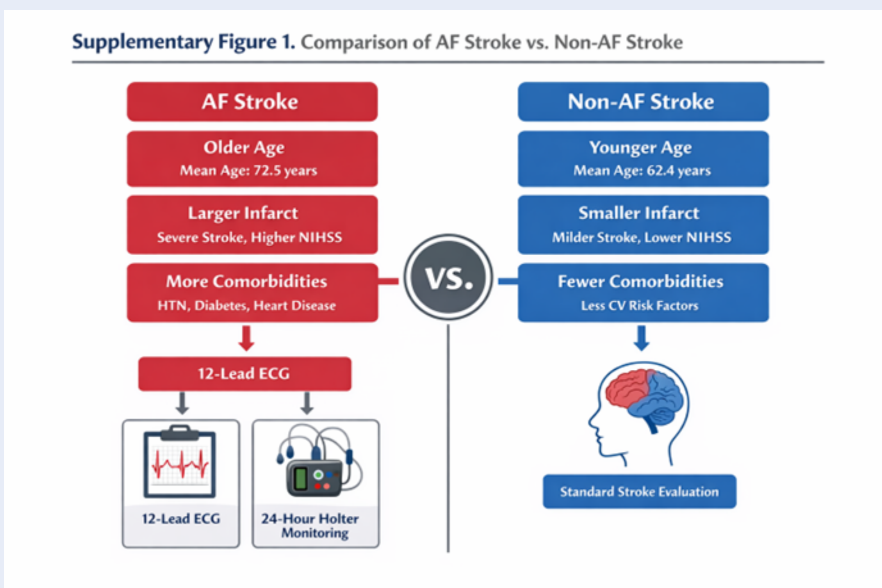

Figure 3: Supplementary Material S4. Supplementary Figure 1: Conceptual diagram.