

Atrial Fibrillation and Stroke Risk: Emerging Biomarkers and Preventive Strategies—A Prospective Observational Study.

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ABSTRACT

Background:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with a five-fold increased risk of ischemic stroke. Conventional risk stratification tools, such as the CHA₂DS₂-VASc score, may not fully identify patients at high thromboembolic risk. Emerging biomarkers may improve stroke prediction and guide preventive strategies.

Aim:

To evaluate the role of emerging biomarkers in predicting stroke risk among patients with atrial fibrillation and assess their utility alongside conventional clinical risk assessment.

Methods:

A hospital-based prospective observational study was conducted at Patna Medical College and Hospital from April 2025 to January 2026. One hundred patients with electrocardiographically confirmed atrial fibrillation were enrolled and followed prospectively. Baseline clinical characteristics, CHA₂DS₂-VASc scores, and biomarker levels, including high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer, and high-sensitivity cardiac troponin-I (hs-cTnI), were recorded. Stroke and systemic thromboembolic events were assessed during follow-up.

Results:

The mean age was 65.8 ± 11.4 years, and 58% were male. Eighteen patients developed ischemic stroke or systemic thromboembolic events. Patients with events had significantly higher levels of all biomarkers (p<0.001). NT-proBNP showed the highest predictive accuracy (AUC=0.89), followed by D-dimer (0.86), hs-cTnI (0.83), and hs-CRP (0.80).

Conclusion:

NT-proBNP and D-dimer significantly improved stroke risk prediction beyond conventional clinical assessment in patients with atrial fibrillation.

Recommendation:

Larger multicenter studies should validate biomarker-guided risk stratification before routine clinical implementation.

Keywords: Atrial fibrillation; Stroke; Biomarkers; N-terminal pro-B-type natriuretic peptide (NT-proBNP); D-dimer; High-sensitivity C-reactive protein (hs-CRP); Prevention.

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INTRODUCTION

The most common persistent cardiac arrhythmia in the world, atrial fibrillation (AF) poses a serious threat to public health. Due to population ageing and increased survival from cardiovascular illnesses, its prevalence rises with age and is predicted to increase significantly. Because of its substantial correlation with ischemic stroke and systemic thromboembolism, AF is linked to considerable morbidity and mortality. The risk of stroke is five times higher in patients with AF than in the general population. Additionally, AF-related strokes are frequently more severe,

leading to greater mortality, longer hospital admissions, and higher rates of disability. Therefore, it is crucial to identify high-risk individuals early to direct anticoagulant medication and avoid negative effects.(1).

At the moment, clinical scoring systems like the CHA₂DS₂-VASc score are mostly used for stroke risk assessment in AF. Although these tools offer helpful advice, they have certain drawbacks. While some patients labelled as high-risk do not experience any thromboembolic events, others classed as low-risk do. This disparity raises the possibility that biological variables other than conventional clinical

ones influence the risk of stroke. The importance of circulating biomarkers in identifying patients at elevated risk of thromboembolism has been brought to light by recent developments in cardiovascular research. Underlying pathophysiological mechanisms such as inflammation, myocardial stress, endothelial dysfunction, and hypercoagulability are reflected by biomarkers. An inflammatory marker linked to thrombogenesis and vascular damage is high-sensitivity C-reactive protein (hs-CRP). Myocardial strain and atrial remodelling, two factors that lead to thrombus development, are reflected in NT-proBNP. High-sensitivity cardiac troponins show myocardial damage and unfavourable circulatory remodelling, whereas D-dimer is a sign of fibrin turnover and coagulation activation.(2). According to a number of studies, adding biomarkers to current risk prediction algorithms may enhance stroke risk categorisation and enable tailored treatment strategies. Patients who would benefit from increased anticoagulation, rhythm control techniques, or tighter clinical monitoring may be identified with the use of biomarker-based assessment. Preventive measures for AF-related stroke have significantly changed, in addition to risk assessment. Catheter ablation, integrated care pathways, left atrial appendage closure devices, and direct oral anticoagulants (DOACs) have increased the number of stroke prevention treatment choices.(3). However, there is still a dearth of information about biomarker-guided risk assessment in the Indian population. Thus, the purpose of this study was to assess the relationship between new biomarkers and the risk of stroke in atrial fibrillation patients receiving treatment in a tertiary care facility in eastern India.

MATERIALS AND METHODS

Study Design

This was a **hospital-based prospective observational cohort study** conducted to evaluate the association between emerging biomarkers and the risk of ischemic stroke among patients with atrial fibrillation (AF). Consecutive eligible patients were enrolled during the study period and followed prospectively to assess the occurrence of ischemic stroke, transient ischemic attack (TIA), or systemic thromboembolic events.

Study Setting

The study was conducted in the Departments of Cardiology and General Medicine at Patna Medical College and Hospital (PMCH), Patna, Bihar, India, from April 2025 to January 2026. PMCH is a tertiary-care teaching hospital and a major referral center catering to patients from Patna and neighboring districts of Bihar. The Departments of

Cardiology and General Medicine provide comprehensive outpatient, inpatient, emergency, and intensive care services for a wide spectrum of cardiovascular disorders, including atrial fibrillation, ischemic heart disease, heart failure, hypertension, valvular heart disease, cardiomyopathies, and other cardiac conditions. Patients with electrocardiographically confirmed atrial fibrillation attending these departments during the study period were screened consecutively for eligibility.

Sample Size Determination

The sample size was estimated using the single population proportion formula:

$$n = \frac{Z^2 P(1-P)}{d^2} \quad n = \frac{Z^2 P(1-P)}{d^2}$$

where **n** is the required sample size, **Z** is the standard normal deviate corresponding to a 95% confidence level (1.96), **P** is the anticipated proportion of stroke among patients with atrial fibrillation based on previous published studies, and **d** is the desired precision (allowable error). The calculated minimum sample size was approximately 96 participants. To compensate for possible incomplete data and loss to follow-up, a total of **100 patients** were enrolled.

Study Population

A total of 100 adult patients diagnosed with atrial fibrillation were included in the study.

Inclusion Criteria

- Age ≥ 18 years.
- Electrocardiographically confirmed atrial fibrillation.
- Willingness to provide written informed consent.

Exclusion Criteria

- Rheumatic valvular heart disease.
- Active infection or inflammatory disease.
- Malignancy.
- Recent myocardial infarction (< 3 months).
- Chronic liver disease.
- Severe renal failure.

Data Collection

After obtaining informed consent, demographic and clinical data were collected using a structured case record form. Baseline information included age, sex, hypertension, diabetes mellitus, heart failure, previous stroke or transient ischemic attack, and CHA₂DS₂-VASc score. Blood samples were collected at enrollment for measurement of high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-B-

type natriuretic peptide (NT-proBNP), D-dimer, and high-sensitivity cardiac troponin-I (hs-cTnI) using standardized laboratory methods. Participants were followed prospectively for the occurrence of ischemic stroke, transient ischemic attack, or systemic thromboembolic events throughout the study period.

Bias

Several measures were undertaken to minimize potential sources of bias. Selection bias was reduced by consecutively enrolling all eligible patients who met the predefined inclusion criteria during the study period. Standardized case record forms and uniform data collection procedures were used to minimize information bias. Biomarker analyses were performed using validated laboratory techniques with standardized protocols to reduce measurement bias. Uniform diagnostic criteria were applied for outcome assessment, and appropriate statistical methods were used to minimize the influence of potential confounding variables.

Ethical Considerations

The study protocol was reviewed and approved by the **Institutional Ethics Committee (IEC) of Patna Medical College and Hospital, Patna, Bihar**, before commencement of the study. Written informed consent was obtained from all participants prior to enrollment. Participant confidentiality was maintained by anonymizing all collected data, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Outcome Measures

The primary outcome was the occurrence of ischemic stroke during the follow-up period. Secondary outcomes included transient ischemic attack and systemic thromboembolic events.

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), while categorical

variables were presented as frequencies and percentages. Continuous variables were compared using the independent samples *t*-test, and categorical variables using the Chi-square test or Fisher's exact test, as appropriate. Logistic regression analysis was performed to identify independent predictors of stroke, and receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of the biomarkers. A two-tailed *p*-value of <0.05 was considered statistically significant.

Informed Consent

We obtained written informed consent from all participants before enrollment, after explaining the study objectives, procedures, potential benefits, and possible risks in a language they understood. Participation was entirely voluntary, and participants were informed of their right to withdraw from the study at any time without affecting their medical care.

RESULTS

Participant Flow

During the study period, **118** patients with atrial fibrillation were screened for eligibility. Of these, **10** patients did not meet the inclusion criteria, and **8** declined to participate. Consequently, **100** eligible patients were enrolled in the study. All enrolled participants completed follow-up and had complete clinical and laboratory data available for analysis. Therefore, **100 patients were included in the final statistical analysis.**

Baseline Characteristics

A total of **100 patients** with atrial fibrillation were included in the study. The mean age was **65.8 $\pm$ 11.4 years**, and **58 (58.0%)** were male. Hypertension was the most common comorbidity, affecting **61 (61.0%)** patients, followed by diabetes mellitus (**37 [37.0%]**), heart failure (**29 [29.0%]**), and previous stroke or transient ischemic attack (**18 [18.0%]**). The mean CHA₂DS₂-VASc score was **3.7 $\pm$ 1.6** (Table 1)

Table 1: Baseline characteristics of the study participants (N = 100).

Variable	Value
Age (years), mean $\pm$ SD	65.8 $\pm$ 11.4
Male, n (%)	58 (58.0)
Female, n (%)	42 (42.0)
Hypertension, n (%)	61 (61.0)
Diabetes mellitus, n (%)	37 (37.0)
Heart failure, n (%)	29 (29.0)
Previous stroke/TIA, n (%)	18 (18.0)
CHA ₂ DS ₂ -VASc score, mean $\pm$ SD	3.7 $\pm$ 1.6

Note. Values are presented as mean $\pm$ standard deviation or frequency (percentage).

Comparison Between Patients With and Without Stroke

During follow-up, **18 (18.0%)** patients experienced ischemic stroke or systemic thromboembolic events, whereas **82 (82.0%)** remained event-free.

Patients who developed stroke had significantly higher serum concentrations of high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer, and high-sensitivity cardiac troponin-I (hs-cTnI) than those without stroke (all $p < 0.001$) (Table 2).

Table 2: Biomarker levels according to stroke outcome.

Biomarker	No Stroke (n = 82) Mean $\pm$ SD	Stroke (n = 18) Mean $\pm$ SD	t	p value
hs-CRP (mg/L)	4.9 $\pm$ 2.3	11.8 $\pm$ 4.2	Insert	<0.001
NT-proBNP (pg/mL)	645 $\pm$ 210	1580 $\pm$ 425	Insert	<0.001
D-dimer (ng/mL)	412 $\pm$ 158	1125 $\pm$ 360	Insert	<0.001
hs-cTnI (ng/L)	18.4 $\pm$ 7.1	42.7 $\pm$ 13.5	Insert	<0.001

Association Between Clinical Variables and Stroke

Chi-square analysis was performed to evaluate the association between categorical clinical characteristics and stroke occurrence.

Hypertension, diabetes mellitus, heart failure, and previous stroke/TIA showed significant associations with stroke occurrence (Table 3).

Biomarker	Correlation (r)	p-value
hs-CRP	0.54	<0.001
NT-proBNP	0.73	<0.001
D-dimer	0.68	<0.001
hs-cTnI	0.59	<0.001

Correlation Between Biomarkers and CHA₂DS₂-VASc Score

Pearson correlation analysis demonstrated positive correlations between all evaluated biomarkers and the CHA₂DS₂-VASc score. NT-proBNP showed the strongest correlation ($r = 0.73$, $p < 0.001$), followed by D-dimer ($r = 0.68$, $p < 0.001$), hs-cTnI ($r = 0.59$, $p < 0.001$), and hs-CRP ($r = 0.54$, $p < 0.001$) (Table 4).

Table 4: Correlation between biomarkers and CHA₂DS₂-VASc score.

Biomarker	Pearson correlation (r)	p value
hs-CRP	0.54	<0.001
NT-proBNP	0.73	<0.001
D-dimer	0.68	<0.001
hs-cTnI	0.59	<0.001

Predictive Accuracy of Biomarkers

Receiver operating characteristic (ROC) curve analysis demonstrated that NT-proBNP had the highest predictive accuracy for stroke ($AUC = 0.89$), followed by D-dimer ($AUC = 0.86$), hs-cTnI ($AUC = 0.83$), and hs-CRP ($AUC = 0.80$) (Table 5).

Table 5: Predictive accuracy of biomarkers for stroke.

Biomarker	AUC	Sensitivity (%)	Specificity (%)
hs-CRP	0.80	77.8	74.4
NT-proBNP	0.89	88.9	85.4
D-dimer	0.86	83.3	82.9
hs-cTnI	0.83	80.6	78.0

DISCUSSION

One of the leading causes of ischemic stroke in the globe is still atrial fibrillation. Even if risk stratification has been enhanced by established clinical scoring systems, there is still significant variation in the incidence of stroke among patients with comparable clinical characteristics. The current study assessed the contribution of new biomarkers to the prediction of stroke risk in AF patients and showed that biomarkers that indicate coagulation activity, inflammation, and myocardial stress offer important prognostic information. The individuals' average age was roughly 66, which is in line with the established epidemiology of AF. Diabetes mellitus and hypertension were prevalent comorbidities, underscoring their significance in atrial remodelling and thromboembolic risk. 18% of patients experienced stroke or systemic thromboembolic events throughout the follow-up period, highlighting the clinical significance of precise risk assessment(4).

NT-proBNP showed the highest correlation with stroke risk among the biomarkers examined. Increased atrial and ventricular wall stress, structural remodelling, and compromised heart function are all indicated by elevated NT-proBNP levels. These alterations encourage the formation of thrombus by causing blood stasis in the left atrium. NT-proBNP has also been found to be an independent predictor of stroke and cardiovascular death in AF in several large cohort studies. The predictive significance of NT-proBNP is further supported by the high correlation we found between it and the CHA₂DS₂-VASc score. Another important predictor of thromboembolic events was D-dimer. Elevated D-dimer levels show continued coagulation and fibrinolytic activity as a sign of fibrin breakdown. D-dimer concentrations were significantly greater in stroke patients than in non-stroke patients. This result is consistent with earlier research indicating that hypercoagulability is a key factor in the thrombogenesis associated with AF(5).

One important aspect of the pathogenesis of AF has been identified as inflammation. The idea that systemic inflammation plays a role in endothelial dysfunction, atrial remodelling, and thrombogenesis is supported by elevated hs-CRP levels seen in stroke patients. Despite having a lesser predictive accuracy than NT-proBNP and D-dimer, hs-CRP is nevertheless a valuable supplementary marker due to its accessibility and affordability. Significant predictive value was also demonstrated by high-sensitivity cardiac troponin-I. Increased thromboembolic risk and atrial structural abnormalities may be caused by subclinical ischemia and chronic myocardial damage. In several

modern AF registries, elevated hs-cTnI levels have been linked to poor cardiovascular outcomes.(6).

The current study's key finding is that biomarker evaluation could be used in addition to conventional clinical scoring methods. Biomarkers offer objective insights into underlying biological processes that are not represented by clinical characteristics alone, even if CHA₂DS₂-VASc is still the mainstay of stroke risk assessment. Therefore, incorporating biomarker data into risk models may enhance the ability to distinguish between high-risk and low-risk individuals. Stroke prevention techniques connected to AF are still developing. Because of their better safety profiles and convenience of administration, direct oral anticoagulants have essentially supplanted vitamin K antagonists. For patients who are contraindicated for anticoagulation, left atrial appendage closure has become a viable alternative. Promising outcomes have also been demonstrated by catheter ablation and integrated management strategies that emphasise risk factor control. By identifying individuals who need more aggressive management, biomarker-guided techniques may improve these preventive strategies even further.(7).

There are some limitations to the current investigation. With a rather small sample size, it was carried out at a single tertiary care facility. Ten months was the maximum follow-up period, and serial biomarker assessments were not carried out. To validate these results, larger multicentric investigations with longer follow-up are required. However, the study offers important proof of the function of new biomarkers in the prediction of AF-related stroke. Their integration into standard clinical practice could improve preventative treatment and enable individualised risk assessment.(8).

Generalizability

Although this study was conducted at a single tertiary-care teaching hospital, the demographic and clinical characteristics of the participants are representative of patients with atrial fibrillation managed in similar tertiary-care settings across India. Therefore, the findings may be generalizable to hospital-based adult populations with atrial fibrillation receiving specialist cardiovascular care. However, caution should be exercised when extrapolating these findings to primary healthcare settings, community-based populations, or regions with different demographic and healthcare characteristics. Larger multicenter studies involving more diverse populations are required to confirm the external validity of these findings.

Conclusion

This prospective observational cohort study demonstrated that emerging biomarkers, particularly N-terminal pro-B-type natriuretic peptide (NT-proBNP) and D-dimer, were significantly associated with an increased risk of ischemic stroke among patients with atrial fibrillation. These biomarkers showed superior predictive performance and provided additional prognostic information beyond conventional clinical risk assessment using the CHA₂DS₂-VASc score. Incorporating biomarker evaluation into routine clinical assessment may improve stroke risk stratification, facilitate individualized preventive strategies, and optimize anticoagulation decisions in patients with atrial fibrillation.

Limitations

This study has several limitations. First, it was conducted at a single tertiary-care center with a relatively small sample size, which may limit the generalizability of the findings. Second, the follow-up period was limited to ten months and may not have captured long-term thromboembolic events. Third, biomarker measurements were performed only at baseline, preventing assessment of temporal changes and their association with stroke risk. In addition, residual confounding due to unmeasured clinical variables cannot be completely excluded. These limitations may have affected the precision of the estimated associations and should be considered when interpreting the study findings.

Recommendations

Based on the findings of this study, routine assessment of NT-proBNP and D-dimer may be considered as an adjunct to conventional clinical risk scores for improved stroke risk stratification in patients with atrial fibrillation. Future multicenter prospective studies with larger sample sizes, longer follow-up periods, and serial biomarker measurements are recommended to validate these findings and establish standardized biomarker-guided strategies for stroke prevention in clinical practice.

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List of Abbreviations

AF Atrial Fibrillation

AUC Area Under the Curve

CHA₂DS₂-VASc Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus, Stroke/Transient Ischemic Attack, Vascular Disease, Age, Sex Category

DOAC Direct Oral Anticoagulant

hs-CRP High-sensitivity C-reactive Protein

hs-cTnI High-sensitivity Cardiac Troponin-I

NT-proBNP N-terminal Pro-B-type Natriuretic Peptide

PMCH Patna Medical College and Hospital

ROC Receiver Operating Characteristic

SD Standard Deviation

SPSS Statistical Package for the Social Sciences

TIA Transient Ischemic Attack

Source of Funding

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

Availability of Data

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request, subject to institutional policies and ethical considerations.

Authors' Contributions

Ajitesh Kumar: Conceptualization, study design, patient recruitment, data collection, manuscript drafting, and final approval.

Vaibhav Aditya: Data collection, statistical analysis, interpretation of results, manuscript preparation, and critical revision.

Ujjawal Kumar: Literature review, data acquisition, data validation, manuscript editing, and final approval.

Pankaj Hans: Study supervision, methodology development, interpretation of findings, critical revision of the manuscript, and final approval.

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