

openheart Phenotypic determinants of atrial fibrillation in ischaemic stroke: a retrospective study

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ABSTRACT

Background Atrial fibrillation (AF) is a common cause of ischaemic stroke and a major global health burden, but is often undetected in routine clinical practice. Detection of AF is essential for secondary stroke prevention, but it remains unclear which patients who had a stroke are at highest risk of previously unrecognised or newly detected AF, limiting targeted detection strategies. The aim of this study was to determine the prevalence of AF and risk factors that are associated with AF among patients who had an ischaemic stroke.

Methods In this retrospective cohort study, all patients who had an ischaemic stroke at the Radboud University Medical Center (Nijmegen, the Netherlands) from January 2019 to October 2024 were included. We applied descriptive statistics, logistic regression analyses and generative topographic mapping (GTM), a probabilistic machine learning method for clustering and data visualisation.

Results Of 1836 patients (median age 73 years (IQR 64–80), 44.1% female), 30.5% had AF, of which 19.7% were previously known and 10.8% were newly detected after stroke. The most significant factors associated with AF were older age, increased stroke severity, history of ischaemic stroke and heart failure, mitral regurgitation, increased left atrial volume and elevated peak E wave velocity. GTM identified a phenotype characterised by older age, severe strokes, high prevalence of history of ischaemic stroke, hypertension, diabetes, high cardiac burden with history of myocardial infarction, heart valve abnormalities and heart failure, impaired kidney function, high premature atrial and ventricular contraction burden, and signs of severe left atrial remodelling to be most associated with AF (prevalence 47.9%).

Conclusions The prevalence of AF and stroke severity among AF patients in this study highlights the relevance of optimising monitoring strategies. Stroke severity, history of ischaemic stroke, high cardiac burden and left atrial remodelling signs were most strongly associated with AF. These findings suggest potential areas for targeted screening in high-risk clinical phenotypes.

INTRODUCTION

Ischaemic stroke is one of the leading causes of long-term disability and mortality worldwide,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial fibrillation (AF) is a major cause of ischaemic stroke and is frequently underdiagnosed, limiting opportunities for effective secondary prevention; however, it remains unclear which patients who had a stroke are at highest risk of undetected AF.

WHAT THIS STUDY ADDS

⇒ This study shows that nearly one-third of patients who had an ischaemic stroke have AF, and identifies key associated factors including older age, greater stroke severity, prior stroke, cardiac comorbidity and markers of left atrial remodelling. Additionally, a distinct high-risk clinical phenotype was identified using machine learning.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings identify additional risk factors and clinical phenotypes that provide important leads for more targeted AF detection strategies in patients who had an ischaemic stroke.

and its global burden continues to rise across all age groups.^{1 2} Epidemiological data indicate that the incidence and prevalence of ischaemic stroke are increasing worldwide.³ Atrial fibrillation (AF) is a well-established cause of ischaemic stroke and represents the most common source of cardioembolic stroke.⁴ Between 2010 and 2019, the global prevalence of AF increased from approximately 33.5 million to nearly 59 million individuals, reflecting a substantial rise in disease burden and associated comorbidities.⁵

Identifying underlying AF in patients presenting with ischaemic stroke is essential for several reasons. AF-related strokes are associated with more severe neurological deficits, higher mortality and increased risk of recurrence compared with those with non-AF-related stroke.^{2 6} Hence, early identification of AF is vital for adequate secondary stroke prevention, including prompt initiation of



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oral anticoagulation, use of rate or rhythm control when indicated and targeted management of cardiovascular risk factors embedded in integrated care patient management and care pathways.^{7–9} Indeed, AF management is more than anticoagulation alone, given the high residual risk of adverse outcomes despite oral anticoagulation.¹⁰

AF is often difficult to detect because it may present with paroxysmal and asymptomatic episodes, which increases the likelihood of missed diagnoses.¹¹ As a result, the true prevalence of AF among patients with ischaemic stroke is likely underestimated. The optimal duration and timing of cardiac monitoring after an ischaemic stroke remains the subject of ongoing debate.¹² Although several general demographic and clinical risk factors for AF have been identified, including advanced age, hypertension and heart failure, uncertainty remains about which subgroups of patients with ischaemic stroke are at highest risk of having previously unrecognised or newly detected AF.¹³ Many comorbid risk factors do not occur in isolation, but cluster together creating patient clinical phenotypes of heterogeneous complexity, with different prognostic implications.^{14 15}

In response to this challenge, there is increasing interest in artificial intelligence (AI)-driven approaches to support more personalised and data-driven management of AF and stroke across the care continuum.¹⁶ In this context, advanced data-driven approaches such as generative topographic mapping (GTM) may offer new opportunities to identify patient subgroups with distinct AF-risk profiles.¹⁷ Such approaches align with broader efforts to enable more personalised, data-driven stroke care, including initiatives such as the European TARGET project,¹⁸ which aims to develop virtual twin technologies for personalised management of AF-related stroke across the care pathway.

The aim of this study was to determine the prevalence of AF among patients who had an ischaemic stroke and to identify factors associated with AF in this population, which we complemented by exploring patient clinical phenotypes using a machine learning clustering method with solid probabilistic foundations.

METHODS

Study design

In this single-centre retrospective cohort study, data were collected from all consecutive patients who had an ischaemic stroke or transient ischaemic attack (TIA) between January 2019 and October 2024, admitted to the emergency department, neurology ward or outpatient neurology clinic of the Radboud University Medical Centre (Nijmegen, the Netherlands). Patients were included based on a clinical diagnosis of ischaemic stroke or TIA, established by the treating physician within the neurology department. Data collection was conducted between December 2024 and February 2026.

This study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting

guideline,¹⁹ of which the checklist is provided in the online supplemental material. Anonymised data supporting the results of this study may be obtained from the corresponding author on reasonable request.

Baseline measures

Information regarding demographics, medical history, lifestyle factors and acute stroke interventions was extracted from the electronic medical records. Stroke severity scores at admission as documented by the treating physician, measured using the National Institutes of Health Stroke Scale (NIHSS) scores,²⁰ were reviewed and recalculated for each patient by trained researchers to ensure consistency and accuracy.

Demographic data concerned age and sex. Collected data regarding medical history concerned: previously known AF, ischaemic stroke, haemorrhagic stroke, hypertension (consisting of a medical history of hypertension and/or use of antihypertensive medication), diabetes (consisting of a medical history of diabetes, use of anti-diabetic medication, use of insulin and/or HbA1c-value >7.0%), dyslipidaemia (consisting of a medical history of dyslipidaemia, use of statins, total cholesterol ≥ 193 mg/dL and/or low-density lipoprotein cholesterol ≥ 116 mg/dL), myocardial infarction, heart valve abnormalities, peripheral artery disease, congenital heart disease, heart failure, current body mass index and family history positive for cardiovascular diseases below the age of 65 years. Collected data on lifestyle factors included smoking status and alcohol consumption. Acute stroke interventions included intravenous thrombolysis and mechanical thrombectomy.

Diagnostic measures

Diagnostic information was collected for each patient from the time of the index event up to the date of data extraction. Diagnostic data included laboratory values, ECG recordings, Holter monitoring results and echocardiography (either transthoracic echocardiography (TTE) or transoesophageal echocardiography (TEE)) findings.

Newly detected AF was defined as AF first identified after the index stroke during follow-up. AF was defined as a documented episode of AF on ECG, Holter monitoring or clinical telemetry, as recorded in the medical records. Cardiac monitoring was performed as part of routine clinical care. A single 12-lead ECG was routinely obtained at admission, and additional rhythm monitoring consisted of in-hospital telemetry during admission and ambulatory Holter monitoring ranging from 24 hours to 7 days. Prolonged monitoring strategies such as implantable cardiac monitors were not performed. Self-reported AF episodes, including those detected by devices such as smartwatches, were not included unless confirmed by ECG, Holter monitoring or clinical telemetry.

Statistical analyses

Baseline characteristics were compared across three groups: patients without AF, those with previously known

AF and those in whom AF was newly detected after stroke. Continuous variables were analysed using a Kruskal-Wallis test for non-normally distributed across more than two independent groups. Post-hoc Dunn tests were applied after a significant Kruskal-Wallis result to identify which specific groups differ from each other. Categorical variables were assessed with the χ^2 test or Fisher's exact test when expected cell counts were low. Post-hoc Bonferroni corrections were used to test pairwise group differences, while controlling for multiple comparisons. Descriptive data are presented as percentages for categorical variables and as median with IQR for continuous variables.

Additionally, to assess potential bias, baseline characteristics were compared between patients who underwent echocardiography and Holter monitoring and those who did not, using the same statistical methods as described above.

Logistic regression analyses were applied to identify potential factors associated with AF. First, a binary logistic regression was performed comparing patients without AF to those with AF, in which previously known and newly detected AF after stroke were combined into a single category. Using univariable logistic regression, potential factors associated with AF were examined by calculating ORs with corresponding 95% CIs. Subsequently, a multivariable logistic regression was performed, including all variables that showed a univariable association with AF at a significance level of $p < 0.1$. Additional multivariable logistic regression analysis was conducted excluding echocardiography variables, as only a limited proportion of the included patients underwent echocardiography.

After this, a multinomial multivariable logistic regression analysis was performed, comparing the group without AF to the group with previously known AF and to the group with newly detected AF after stroke. To not exceed the recommended one-per-ten-events ratio for included variables, only the variables with lowest univariable p values were included. Multicollinearity was assessed by calculating variance inflation factors (VIF) for all selected variables. In cases of $VIF > 5$, a variable would be removed from the model to reduce collinearity. Model performances were evaluated by calculating the area under the receiver operating characteristic curve (AUC) together with the corresponding 95% CIs.

Univariable logistic regression analyses were performed on complete cases. For the multivariable analyses, multiple imputation by chained equations was applied to address missing data.²¹ This approach was chosen because a substantial proportion of the cardiac diagnostic variables were missing. Multiple imputation was applied to reduce bias and improve the precision of the estimated associations.^{22–23} Multiple imputation was performed including all variables used in the regression analyses, and model estimates from the imputed datasets were subsequently pooled using Rubin's rules. As a sensitivity analysis, the binary multivariable model was repeated in patients with a complete cardiac diagnostic work-up, without applying multiple imputation.

GTM, a probabilistic machine learning approach, which is robust to noise, was applied to identify data-driven phenotypes.¹⁷ GTM inherently integrates clustering and visualisation into a single model. Unlike traditional clustering algorithms such as k-means and hierarchical clustering, GTM is grounded in a probabilistic framework allowing for soft assignments of data observations to clusters with associated probabilities.²⁴ GTM projected all input variables into a two-dimensional latent space and clustered patients according to multivariable similarity. Input variables included all baseline and diagnostic measurements. Differences in patient characteristics across phenotypes were evaluated using previously described comparative tests. The association between phenotype and presence of AF was assessed using univariable logistic regression.

All statistical analyses were performed in RStudio (V.4.6.0) and Python (V.3.12.7) between February 2026 and September 2026. All tests were performed two-sided, with p values < 0.05 considered statistically significant. Continuous variables with skewed distributions were log-transformed.

RESULTS

A total of 1836 patients were included in this study (median age, 73 years (IQR, 64–80); 44.1% female). The median follow-up was 23.8 months (IQR, 6.4–45.8). The overall prevalence of AF in this study cohort was 30.5%. Of all patients, 361 (19.7%) had a previously known AF. During follow-up, new AF after stroke was detected in 199 patients (10.8%), of which 81.4%, 7.0%, 7.6% and 4.0% were detected by ECG, Holter monitoring, clinical telemetry and other documented cardiac rhythm assessments (including periprocedural monitoring and pacemaker interrogations), respectively. Patient characteristics, comparing individuals without AF, with previously known AF and with newly detected AF, are presented in [table 1](#).

Of all patients, 1608 (87.6%) underwent ECG, 422 (23.0%) underwent Holter monitoring (median duration 1.5 days (IQR, 1–7)) and 446 (24.3%) received an echocardiogram (TTE or TEE) during follow-up. Patients with AF, both previously known and newly detected, were older and had more severe stroke at admission, as measured by higher NIHSS scores, compared with patients without AF (both p value < 0.001) ([table 1](#)). A comparison of patients who underwent echocardiography and those who did not is presented in online supplemental table 1. A similar comparison of patients with and without Holter monitoring is presented in online supplemental table 2.

Univariable logistic regression

Among demographic variables, age was significantly associated with AF. Clinical factors associated with AF included NIHSS at admission, the presence of vessel occlusion, history of ischaemic stroke, hypertension, myocardial infarction, heart valve abnormalities and heart failure. Among behavioural factors, active smoking and alcohol consumption

Table 1 Baseline characteristics of the study population

Characteristic	Patients				p value
	All patients (N=1836)	Without AF (N=1276)	Previously known AF (N=361)	Newly detected AF (N=199)	
Age, years, median (IQR)	73 (64–80)	71 (61–78)	78 (71–83)	77 (71–82)	<0.001
Sex, female, n (%)	810 (44.1)	559 (43.8)	153 (42.4)	98 (49.2)	0.271
NIHSS at admission, median (IQR)	5 (2–13)	4 (2–11)	7 (3–15)	9 (3–17)	<0.001
CHA ₂ DS ₂ VASc score, median (IQR)	NA	NA	4 (2–4)	3 (2–4)	–
Treatment with IVT, n (%)	598 (32.6)	441 (34.6)	59 (16.3)	98 (49.2)	<0.001
Treatment with EVT, n (%)	647 (35.2)	409 (32.1)	137 (38.0)	101 (50.8)	<0.001
TOAST classification, n (%)					<0.001
Large artery disease	317 (17.3)	303 (23.7)	10 (2.8)	4 (2.0)	
Likely large artery disease	366 (19.9)	345 (27.0)	9 (2.5)	12 (6.0)	
Cardioembolic	479 (26.1)	56 (4.4)	269 (74.5)	154 (77.4)	
Small vessel disease	359 (19.6)	316 (24.8)	30 (8.3)	13 (6.5)	
Other aetiology	136 (7.4)	125 (9.8)	7 (1.9)	4 (2.0)	
Multiple aetiologies	60 (3.3)	15 (1.2)	34 (9.4)	11 (5.5)	
Undetermined aetiology	119 (6.5)	116 (9.1)	2 (0.6)	1 (0.5)	
Medical history of, n (%)					
Ischaemic stroke	313 (17.0)	181 (14.2)	103 (28.5)	29 (14.6)	<0.001
Haemorrhagic stroke	33 (1.8)	21 (1.6)	9 (2.5)	3 (1.5)	0.502
Hypertension	1171 (63.8)	732 (57.4)	310 (85.9)	129 (64.8)	<0.001
Diabetes	351 (19.1)	233 (18.3)	82 (22.7)	36 (18.1)	0.152
Dyslipidaemia	1082 (58.9)	744 (58.3)	220 (60.9)	118 (59.3)	0.664
Myocardial infarction	323 (17.6)	178 (13.9)	105 (29.1)	40 (20.1)	<0.001
Heart valve abnormalities	180 (9.8)	75 (5.9)	89 (24.7)	16 (8.0)	<0.001
Peripheral artery disease	213 (11.6)	136 (10.7)	57 (15.8)	20 (10.1)	0.021
Congenital heart disease	21 (1.1)	16 (1.3)	4 (1.1)	1 (0.5)	0.832
Heart failure	89 (4.8)	30 (2.4)	54 (15.0)	5 (2.5)	<0.001
BMI*, kg/m ² , median (IQR)	25.8 (23.2–28.8) (N=1397)	25.7 (23.2–28.7) (N=957)	26.3 (23.3–29.2) (N=280)	26.3 (23.9–28.9) (N=160)	0.135
Smoking†, n (%)	(N=1581)	(N=1104)	(N=314)	(N=163)	<0.001
Current	328 (20.7)	268 (24.3)	37 (11.8)	23 (14.1)	
Previous	613 (38.8)	398 (36.0)	146 (46.5)	69 (42.3)	
Never	640 (40.5)	438 (39.7)	131 (41.7)	71 (43.6)	
Alcohol consumption‡, n (%)	(N=1534)	(N=1060)	(N=312)	(N=162)	0.021
>1 unit/day	197 (12.8)	149 (14.1)	27 (8.7)	21 (12.9)	
≤1 unit/day	731 (47.7)	513 (48.4)	139 (44.5)	79 (48.8)	
Never	606 (39.5)	398 (37.5)	146 (46.8)	62 (38.3)	
Family history of cardiovascular disease, n (%)	371 (20.2)	262 (20.5)	67 (18.6)	42 (21.1)	0.673

Bold values indicate statistically significant results (p<0.05).

*Missing data for BMI: all patients 439, no AF 319, previously known AF 81, newly detected AF 39.

†Missing data for smoking: all patients 255, no AF 172, previously known AF 47, newly detected AF 36.

‡Missing data for alcohol consumption: all patients 302, no AF 216, previously known AF 49, newly detected AF 37.

AF, atrial fibrillation; BMI, body mass index; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale.

>1 unit per day were significantly inversely associated with AF. Diagnostic factors associated with AF included serum C reactive protein value, serum glomerular filtration rate (inversely), serum low-density lipoprotein (LDL)-cholesterol (inversely), heart rate frequency (inversely), premature ventricular contraction (PVC) burden per day, premature atrial contraction (PAC) burden per day, atrial run burden

per day, mitral regurgitation, left atrial volume and peak E wave velocity (table 2).

Multivariable logistic regression

Factors associated with AF included NIHSS at admission (OR, 1.32 (95% CI 1.12 to 1.55)), history of ischaemic stroke (OR, 2.18 (95% CI 1.28 to 3.70)), history of heart

Table 2 Univariable and multivariable logistic regression between patients with and without AF

Factor	Univariable logistic regression			Multivariable logistic regression		
	OR	95% CI	Wald-test p value	OR	95% CI	Wald-test p value
Age per year	1.06	1.05 to 1.07	<0.001	1.02	1.00 to 1.05	0.100
Sex (female)	1.04	0.85 to 1.27	0.687	0.72	0.51 to 1.03	0.075
NIHSS at admission*	1.39	1.29 to 1.51	<0.001	1.32	1.12 to 1.55	0.001
Vascular occlusion	1.65	1.35 to 2.02	<0.001	1.16	0.75 to 1.81	0.500
Medical history						
Ischaemic stroke	1.87	1.45 to 2.40	<0.001	2.18	1.28 to 3.70	0.005
Haemorrhagic stroke	1.31	0.62 to 2.64	0.462			
Hypertension	2.70	2.15 to 3.40	<0.001	1.23	0.79 to 1.90	0.357
Diabetes	1.20	0.93 to 1.53	0.159			
Dyslipidaemia	1.09	0.89 to 1.33	0.411			
Myocardial infarction	2.16	1.68 to 2.76	<0.001	1.49	0.92 to 2.40	0.104
Heart valve abnormalities	3.70	2.70 to 5.08	<0.001	1.20	0.66 to 2.19	0.547
Peripheral artery disease	1.34	0.99 to 1.80	0.057	1.03	0.62 to 1.73	0.903
Congenital heart disease	0.71	0.23 to 1.82	0.505			
Heart failure	4.89	3.14 to 7.77	<0.001	3.18	1.37 to 7.41	0.008
BMI*	1.71	0.92 to 3.22	0.095	1.80	0.63 to 5.15	0.274
Active smoking	0.45	0.33 to 0.61	<0.001	0.62	0.37 to 1.04	0.069
Alcohol consumption >1 unit/day	0.71	0.50 to 0.99	0.049	1.07	0.61 to 1.90	0.811
Family history of cardiovascular disease	0.94	0.73 to 1.20	0.600			
Laboratory serum values						
CRP*	1.10	1.02 to 1.19	0.015	1.02	0.89 to 1.18	0.774
GFR*	0.37	0.27 to 0.51	<0.001	0.81	0.42 to 1.54	0.518
TSH*	0.96	0.70 to 1.33	0.812			
LDL-cholesterol*	0.58	0.43 to 0.76	<0.001	0.99	0.56 to 1.76	0.968
Heart rate frequency*	0.40	0.18 to 0.86	0.020	0.95	0.33 to 2.69	0.921
Holter characteristics						
PVC/day*	1.23	1.12 to 1.34	<0.001	1.07	0.94 to 1.23	0.314
PAC/day*	1.40	1.22 to 1.61	<0.001	1.20	0.94 to 1.52	0.154
Atrial run/day*	1.47	1.17 to 1.86	0.001	1.11	0.71 to 1.74	0.645
TTE and TEE characteristics						
Mitral regurgitation	4.15	2.98 to 5.83	<0.001	2.34	1.40 to 3.91	0.001
Left atrial volume*	19.08	9.88 to 39.07	<0.001	5.58	2.25 to 13.82	<0.001
Peak E wave velocity*	10.68	5.19 to 23.08	<0.001	6.41	2.20 to 18.70	0.001

Bold values indicate statistically significant results ($p < 0.1$ for univariable analysis and $p < 0.05$ for multivariable analysis).

*Log-transformed.

AF, atrial fibrillation; BMI, body mass index; CRP, C reactive protein; GFR, glomerular filtration rate; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PAC, premature atrial contraction; PVC, premature ventricular contraction; TEE, transoesophageal echocardiogram; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram.

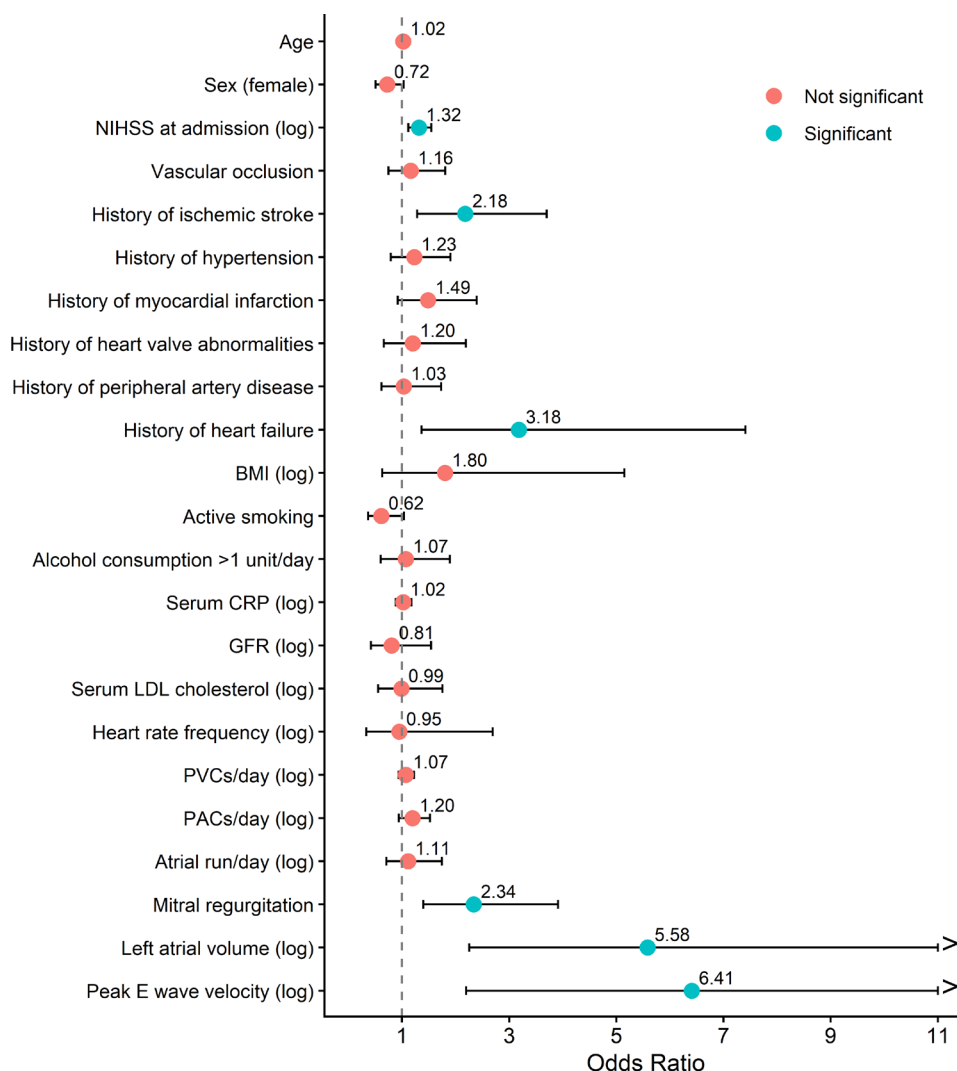


Figure 1 Forest plot from multivariable logistic regression between patients with and without AF. AF, atrial fibrillation; BMI, body mass index; CRP, C reactive protein; GFR, glomerular filtration rate; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PAC, premature atrial contraction; PVC, premature ventricular contraction.

failure (OR, 3.18 (95% CI 1.37 to 7.41)), mitral regurgitation (OR, 2.34 (95% CI 1.40 to 3.91)), left atrial volume (OR, 5.58 (95% CI 2.25 to 13.82)) and peak E wave velocity (OR, 6.41 (95% CI 2.20 to 18.70)) (table 2, figure 1). AUC of the model was 0.86 (95% CI 0.84 to 0.88).

When excluding echocardiography factors from the regression models, five additional factors were significantly associated with AF: history of hypertension (OR, 1.41 (95% CI 1.01 to 1.97)), history of myocardial infarction (OR, 1.57 (95% CI 1.05 to 2.34)), history of heart valve abnormalities (OR, 2.79 (95% CI 1.74 to 4.50)), active smoking (OR, 0.63 (95% CI 0.42 to 0.95)) and PAC burden per day (OR, 1.25 (95% CI 1.01 to 1.55)) (online supplemental table 3). AUC of this model was 0.81 (95% CI 0.78 to 0.84).

Results of the sensitivity analysis restricted to patients with a complete cardiac diagnostic work-up available (N=217, AUC of the model 0.94 (95% CI 0.89 to 0.99))

are presented in online supplemental table 4. These results showed that the factors associated with AF were similar to those observed in the multiple imputation analysis, although with wider CIs, less stable estimates and lower statistical significance due to substantially smaller sample size.

Multinomial logistic regression

The following factors were significantly associated with previously known AF compared with no AF: female sex, NIHSS at admission, history of ischaemic stroke, history of hypertension, history of heart failure, left atrial volume and peak E wave velocity. The AUC for this model was 0.85 (95% CI 0.83 to 0.88).

Multinomial logistic regression comparing newly detected AF with no AF identified four associated factors, including NIHSS at admission, presence of vessel occlusion, mitral regurgitation and peak E wave velocity. AUC

Table 3 Multinomial multivariable logistic regression between patients without AF, previously known AF and newly detected AF

Factor	Previously known AF vs no AF			Newly detected AF vs no AF		
	OR	95% CI	Wald-test p value	OR	95% CI	Wald-test p value
Age per year	1.02	0.98 to 1.05	0.356	1.03	1.00 to 1.06	0.081
Sex (female)	0.64	0.42 to 0.97	0.038	0.81	0.53 to 1.24	0.335
NIHSS at admission*	1.31	1.08 to 1.59	0.007	1.32	1.08 to 1.62	0.008
Vascular occlusion	0.88	0.54 to 1.46	0.628	1.73	1.00 to 2.98	0.049
Medical history						
Ischaemic stroke	2.72	1.48 to 4.98	0.002	1.37	0.71 to 2.61	0.347
Hypertension	2.04	1.18 to 3.51	0.011	0.80	0.50 to 1.29	0.359
Myocardial infarction	1.58	0.93 to 2.69	0.091	1.35	0.77 to 2.37	0.292
Heart valve abnormalities	1.77	0.92 to 3.42	0.089	0.49	0.22 to 1.11	0.088
Heart failure	4.71	1.66 to 13.38	0.004	0.88	0.26 to 3.00	0.840
Active smoking	0.58	0.32 to 1.07	0.082	0.64	0.35 to 1.18	0.152
Laboratory serum values						
CRP*	1.02	0.85 to 1.22	0.850	1.03	0.88 to 1.21	0.690
GFR*	0.74	0.35 to 1.59	0.440	0.88	0.37 to 2.05	0.761
LDL-cholesterol*	1.14	0.59 to 2.20	0.699	0.86	0.46 to 1.61	0.641
Holter characteristics						
PVC/day*	1.08	0.92 to 1.27	0.339	1.06	0.90 to 1.25	0.472
PAC/day*	1.35	0.99 to 1.85	0.067	1.03	0.74 to 1.42	0.878
Atrial run/day*	0.99	0.56 to 1.77	0.983	1.27	0.75 to 2.16	0.383
TTE and TEE characteristics						
Mitral regurgitation	1.65	0.90 to 3.03	0.108	3.79	2.10 to 6.84	<0.001
Left atrial volume*	8.26	2.97 to 22.98	<0.001	3.07	0.98 to 9.58	0.058
Peak E wave velocity*	5.44	1.49 to 19.93	0.013	8.51	2.70 to 26.86	<0.001

Bold values indicate statistically significant results (p<0.05).
 *Log-transformed.
 AF, atrial fibrillation; CRP, C reactive protein; GFR, glomerular filtration rate; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PAC, premature atrial contraction; PVC, premature ventricular contraction; TEE, transoesophageal echocardiogram; TTE, transthoracic echocardiogram.

for comparing newly detected AF with no AF was 0.79 (95% CI 0.76 to 0.81).

Results of multinomial logistic regression, including ORs and CIs, are shown in [table 3](#) and [figure 2](#).

GTM analysis

GTM identified four distinct data-driven phenotypes with marked differences in clinical profiles and AF prevalence ([table 4](#)). Phenotype 3 showed the highest AF prevalence (OR, 7.71 (95% CI 5.39 to 11.25)), representing the oldest, clinically most severely affected group. Phenotype 1 also demonstrated high AF prevalence (OR, 5.26 (95% CI 3.74 to 7.56)), and shared several similarities to phenotype 3, although patients were younger and less clinically severe. Both phenotypes shared a substantial burden of vascular risk factors, high PVC and PAC burden and signs of left atrial remodelling.

In phenotype 3, history of heart valve abnormalities and heart failure, and impaired kidney function

were most prevalent, whereas in phenotype 1 history of myocardial infarction and peripheral artery disease, and mitral regurgitation were most common, respectively. Phenotype 4 included the youngest patients, with relatively high stroke severity and proximal occlusions, with low to moderate AF prevalence (OR, 1.32 (95% CI 0.84 to 2.08)). Phenotype 2, a relatively young and least comorbid group, had the lowest AF prevalence and served as the reference group. Phenotypes 2 and 4 had high prevalence of lifestyle risk factors, such as active smoking and high alcohol consumption, and low overall cardiac burden.

A more detailed table comparing clinical characteristics across all four phenotypes is available as online supplemental table 5, and the corresponding latent space representation of the GTM model is provided as online supplemental figure 1.

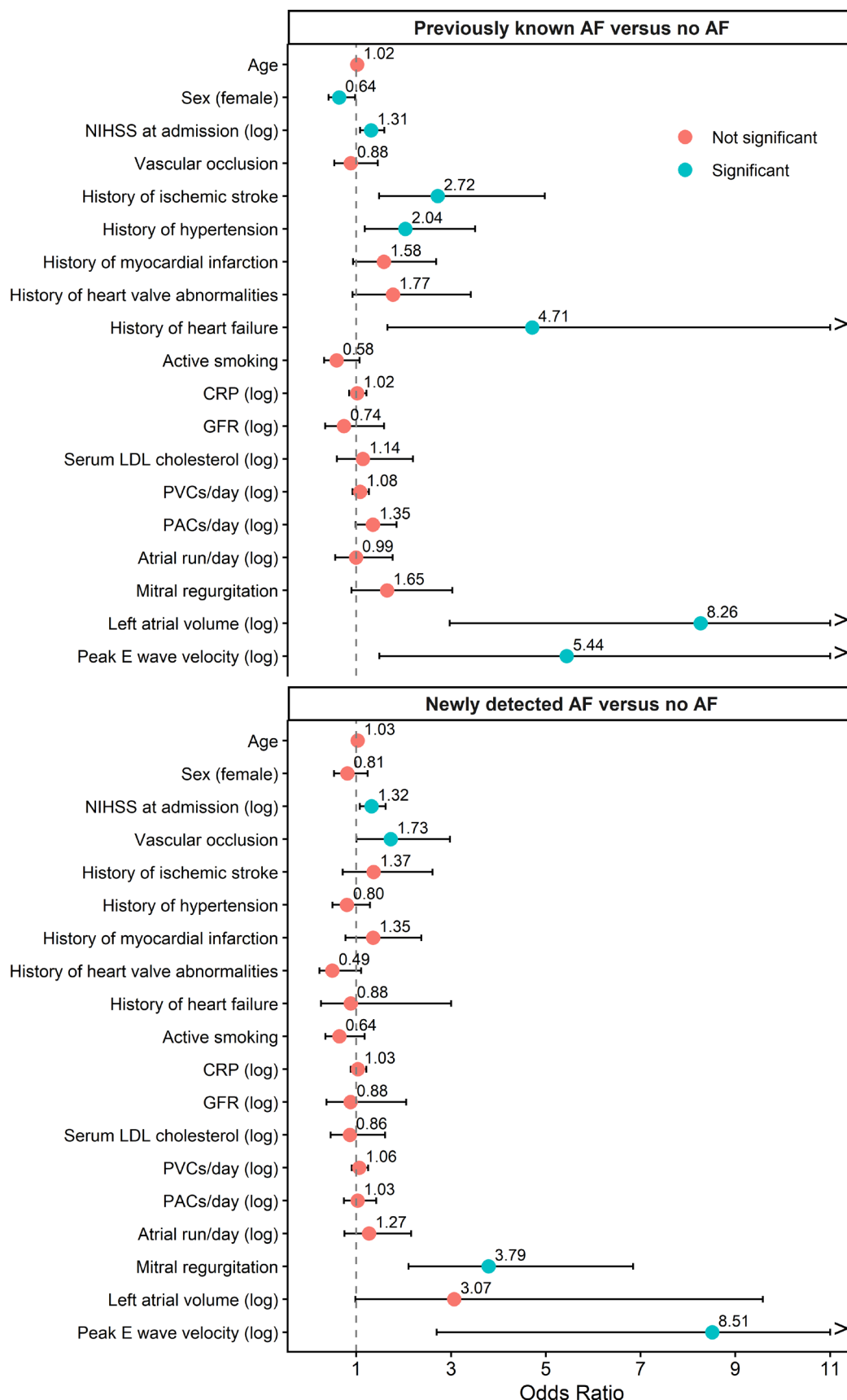


Figure 2 Forest plot from multinomial multivariable logistic regression between patients without AF, previously known AF and newly detected AF. AF, atrial fibrillation; CRP, C reactive protein; GFR, glomerular filtration rate; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PAC, premature atrial contraction; PVC, premature ventricular contraction.

Table 4 Phenotypes from GTM phenotype analysis

	Phenotype 1 (N=687)	Phenotype 2 (N=403)	Phenotype 3 (N=438)	Phenotype 4 (N=308)
Description	▶ Older, mostly male ▶ High AF prevalence ▶ Moderate stroke severity ▶ High prevalence of history of ischaemic stroke, hypertension and diabetes ▶ Highest prevalence of history of myocardial infarction and peripheral artery disease ▶ High PAC, PVC and atrial run burden ▶ Frequent mitral regurgitation ▶ Moderate-severe left atrial remodelling	▶ Younger, mostly male ▶ Lowest AF prevalence ▶ Mildest stroke severity ▶ Lowest rate of proximal occlusions ▶ High lifestyle risk factors (smoking, alcohol) ▶ Highest LDL-cholesterol ▶ Low cardiac burden	▶ Oldest ▶ Highest AF prevalence ▶ Highest stroke severity ▶ High rate of proximal occlusions ▶ High prevalence of history of ischaemic stroke, hypertension and diabetes ▶ Highest prevalence of history of heart valve disease and heart failure ▶ Impaired kidney function ▶ High PAC and PVC burden ▶ Moderate-severe left atrial remodelling	▶ Youngest ▶ Low-medium AF prevalence ▶ High stroke severity ▶ High rate of proximal occlusions ▶ High lifestyle risk factors (smoking, alcohol) ▶ Low cardiac burden
Total prevalence of AF (%)	38.6% (24.3% previously known AF, 14.3% newly detected AF)	10.7% (7.2% previously known AF, 3.5% newly detected AF)	47.9% (33.1% previously known AF, 14.8% newly detected AF)	13.6% (6.5% previously known AF, 7.1% newly detected AF)
OR (95% CI) for AF	5.26 (3.74 to 7.56)	<i>Reference phenotype</i>	7.71 (5.39 to 11.25)	1.32 (0.84 to 2.08)

AF, atrial fibrillation; GTM, generative topographic mapping; LDL, low-density lipoprotein; PAC, premature atrial contraction; PVC, premature ventricular contraction.

DISCUSSION

In this cohort, the overall prevalence of AF was 30.5%, consisting of both previously known AF (19.7%) and newly detected AF during follow-up (10.8%). Second, several factors were independently associated with AF, including stroke severity, history of ischaemic stroke and heart failure, mitral regurgitation, increased left atrial volume and elevated peak E wave velocity. Third, GTM analysis, a machine-learning approach, revealed four distinct phenotypes with markedly different AF prevalence, highlighting heterogeneity in clinical presentation, cardiovascular burden and atrial remodelling across patient subgroups. The GTM phenotype with the highest AF prevalence was characterised by advanced age, increased stroke severity at admission, history of ischaemic stroke, hypertension, diabetes, myocardial infarction, heart valve abnormalities and heart failure, impaired kidney function, high PAC and PVC burden, and severe left atrial remodelling.

The prevalence of AF in this cohort aligns with prior studies showing that up to one-third of all ischaemic strokes may be attributed to AF.²⁵ However, this AF prevalence may be underestimated in this study, as extended cardiac monitoring was not standardised due to the retrospective design, and only 23.0% underwent extended rhythm monitoring via Holter monitoring. Still, the proportion of newly detected AF in this study is consistent with other studies using non-invasive monitoring after ischaemic stroke.²⁶

Multivariable logistic regression and GTM analyses identified vascular risk factors and cardiac-specific markers associated with AF. Older age, increased stroke severity and history of hypertension, ischaemic

stroke, myocardial infarction and heart failure are well-established risk factors for AF among patients who had a stroke and were confirmed in our models.^{13–27} The association between impaired kidney function and AF, besides sharing traditional risk factors, may be explained by chronic systemic inflammation, volume overload and electrolyte disturbances, potentially contributing to structural atrial remodelling and electrical instability.^{28–29} Indeed, several cardiac markers, including increased left atrial volume, mitral regurgitation, elevated peak E wave velocity and PAC burden, were strongly associated with AF. These findings support the central role of atrial remodelling and diastolic dysfunction in AF pathophysiology, highlighting the importance of cardiac monitoring for patients with a suspected cardioembolic stroke. Most existing prediction models for post-stroke AF rely primarily on clinical variables, while models incorporating structural cardiac markers, such as left atrial volume, have demonstrated improved predictive accuracy.^{30–31} This suggests that adding cardiac markers such as those identified in our study, including mitral regurgitation, elevated peak E wave velocity and PAC burden, may further enhance future AF prediction models. Note that mitral regurgitation was defined as any degree of regurgitation reported by a cardiologist on echocardiography. As such, detailed echocardiographic characterisation of mitral regurgitation, including severity grading and mechanism, was not consistently available and therefore could not be analysed reliably in our study. Finally, active smoking and alcohol consumption showed inverse associations with AF. This finding may be explained by the higher prevalence of smoking and alcohol consumption among patients with large artery disease or likely large

artery disease compared with those with a cardioembolic source (22.4% vs 10.4% and 12.7% vs 8.3%, respectively; both $p < 0.05$). However, although vascular imaging was routinely performed, detailed data regarding the extent of atherosclerotic disease (eg, presence and severity of carotid stenosis) were not systematically available for analysis.

In this study, AF detection relied primarily on ECG and Holter monitoring, reflecting routine clinical practice but also highlighting the ongoing debate regarding the optimal strategy for identifying occult AF after ischaemic stroke. Prior literature demonstrates that a meaningful proportion of patients, particularly those with cryptogenic stroke, harbour previously unrecognised AF that is only detected through continuous monitoring, such as with implantable cardiac monitors.¹¹ Indeed, recent studies report AF detection rates ranging from approximately 21% to 49% during 6–24 months of monitoring, although the clinical relevance of subclinical AF episodes remains a matter of debate.^{32–34} In this context, GTM-based phenotyping provides an additional perspective by offering a probabilistic, non-linear latent-variable framework that can uncover complex structures in high-dimensional data and enable stable pattern recognition in heterogeneous clinical datasets, thereby capturing relationships that are not well detected by traditional regression models. These data-driven clustering analyses are highly promising tools, with the potential to more precisely identify risk profiles and to help identify patients who may benefit from extended cardiac monitoring.^{17 35} Recent literature suggests that patients with a high-risk atrial cardiopathy profile, despite the absence of documented AF, may be candidates for intensified surveillance or, in selected cases, anticoagulation.^{36 37}

Strengths and limitations

This study holds several strengths. First, the large study cohort enhances the generalisability of the findings, increases statistical power and improves precision of estimates. Second, the retrospective design reduces selection bias. In addition, the extensive phenotyping of patients and relatively long follow-up period, facilitated by systematic documentation in the electronic medical records, allowed for a detailed assessment of AF-related characteristics. Fourth, the single-centre setting of this study ensured homogeneous assessment of clinical and diagnostic evaluation. Finally, the combined use of traditional multivariable regression and advanced GTM phenotyping adds a complementary perspective and reinforces the robustness of the findings. While not designed as a predictive tool, GTM facilitates the identification of multidimensional patient profiles characterised by co-occurring AF-associated features, providing a complementary perspective on patient heterogeneity beyond the assessment of individual predictors alone. These phenotypes should be regarded as hypothesis-generating and require prospective validation before their potential value for AF

risk stratification or selection for extended rhythm monitoring can be established.

However, several limitations should be acknowledged. First, due to the retrospective design of this study, there was no standardised cardiological diagnostic work-up after the ischaemic stroke, resulting in considerable missing data and possible underestimation of AF prevalence. In line with routine clinical practice at our institution, extended cardiac monitoring, including prolonged Holter monitoring or implantable cardiac monitors, was not routinely performed. This reflects national guideline-based practice, in which additional cardiac investigations are selectively applied according to their expected diagnostic yield, while implantable cardiac monitors are not routinely used. As a result, some patients classified as not having AF may have had undetected paroxysmal AF, and ascertainment bias due to differences in monitoring intensity cannot be excluded.

Furthermore, echocardiographic evaluation was performed as part of routine clinical care based on the national stroke guideline rather than systematically in all patients. In accordance with national guidelines, echocardiography was primarily performed when a cardiac embolic source was suspected, for example, in patients with cerebral ischaemia in multiple vascular territories, previous ischaemic stroke or in ischaemic stroke of undetermined source and in younger patients. As such, patients who underwent echocardiography may represent a subgroup with a higher chance of having a cardioembolic source of stroke, introducing potential selection bias. Therefore, associations involving echocardiographic parameters should be interpreted with caution. Nevertheless, a sensitivity analysis restricted to patients who underwent complete cardiac work-up yielded associations that were directionally consistent with the primary multiple imputation analysis, supporting the overall robustness of the findings.

Moreover, some patients were transferred to other centres, resulting in potential loss to follow-up. Additionally, we were unable to draw conclusions on the presence of subclinical AF, as the necessary data were not available in this study. Finally, as this was a single-centre university hospital-based study, the findings may not fully represent the broader regional population, potentially reflecting more complex cases, although the distribution of aetiologies aligns with that reported in comparable studies. Our results should be regarded as hypothesis-generating and demonstrate associations, rather than causality.³⁸ Finally, our data reflect a predominantly European population, and additional studies in other ethnic populations are needed, given the recognised ethnic differences in stroke.³⁹

CONCLUSION

The prevalence of AF and stroke severity among AF patients in this study highlights the relevance of optimising monitoring strategies. Stroke severity, history of

ischaemic stroke, high cardiac burden and left atrial remodelling signs were most strongly associated with AF. These findings suggest potential areas for targeted screening in high-risk clinical phenotypes. Our results emphasise the need for more personalised approaches to AF detection and secondary prevention in stroke care.

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