



Association of non-invasive atrial cardiomyopathy markers with cerebral stroke lesions: a population-based analysis from the Hamburg City Health Study

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Aims

Atrial fibrillation (AF) is a well-known risk factor for ischaemic stroke. Emerging evidence suggests that atrial cardiomyopathy (AtCM), independent of AF, may be a key contributor to stroke risk. We aimed to evaluate whether non-invasive AtCM markers assessed by electrocardiography (ECG), transthoracic echocardiography (TTE), and blood-based biomarkers provide incremental diagnostic value beyond established clinical risk factors for identifying cerebral stroke lesions on magnetic resonance imaging (MRI).

Methods and results

We analysed 1794 Hamburg City Health Study participants who underwent cerebral MRI with available baseline 12-lead ECG and TTE in sinus rhythm. Logistic regression analyses were performed to identify associations between non-invasive AtCM markers and stroke lesions. The incremental discriminatory performance of these markers beyond clinical risk factors was assessed. Stroke lesions were present in 152 participants (8.5%). Male sex, history of prior AF, and higher CHA₂DS₂-VA score were significantly associated with stroke lesions. Among AtCM markers, amplified P-wave duration (APWD), P-wave area in lead II, PR interval, left atrial volume index, left atrial ejection fraction, and NT-proBNP were also significant. Combining both clinical and AtCM markers, only CHA₂DS₂-VA score (OR: 1.95 per point, 95% CI: 1.49–2.55, $P < 0.001$) and P-wave area in lead II (OR: 0.99 per 100 $\mu\text{V}\cdot\text{ms}$, 95% CI: 0.98–1.00, $P = 0.031$) remained independent predictors. However, this resulted in only marginal improvement in discrimination (ΔAUC : 0.03, 95% CI: 0.0001–0.0594) compared with the clinical risk factor model alone.

Conclusion

The incremental diagnostic value of AtCM markers beyond clinical risk factors for MRI-defined cerebral lesions is limited, likely reflecting the heterogeneous aetiology of stroke lesions in a general population cohort.

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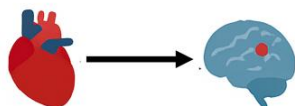
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Graphical Abstract

Association of non-invasive atrial cardiomyopathy markers with cerebral stroke lesions: a population-based analysis from the Hamburg City Health Study

Background

- Atrial cardiomyopathy (AtCM) may be a key contributor to stroke risk independent of atrial fibrillation



- Can non-invasive AtCM markers from ECG, TTE, and blood-based biomarkers improve the discriminatory performance of clinical risk factors for detecting stroke lesions on MRI?

**Methods**

- 1794 participants of the epidemiological Hamburg City Health Study



- Tests:

- Clinical risk factors



- ECG



- TTE



- Blood-based biomarkers



- Outcome:

- Stroke lesions on cerebral MRI

**Key Findings**

- Stroke lesions in 8.5% of participants
- Clinical risk factors (CHA₂DS₂-VA score, male sex, history of prior atrial fibrillation) are predictors for stroke lesions. Among non-invasive AtCM markers, only P-wave area in lead II remained an independent predictor when added to the clinical risk factor model, resulting in only a minimal improvement in discrimination (Δ AUC: 0.03)



Non-invasive markers of atrial cardiomyopathy add only limited diagnostic value for identification of individuals with stroke lesions over established clinical risk factors, possibly due to the heterogeneous etiology of strokes in a general population cohort.

Keywords

Stroke • Atrial fibrillation • Non-invasive screening • ECG • TTE • Biomarkers

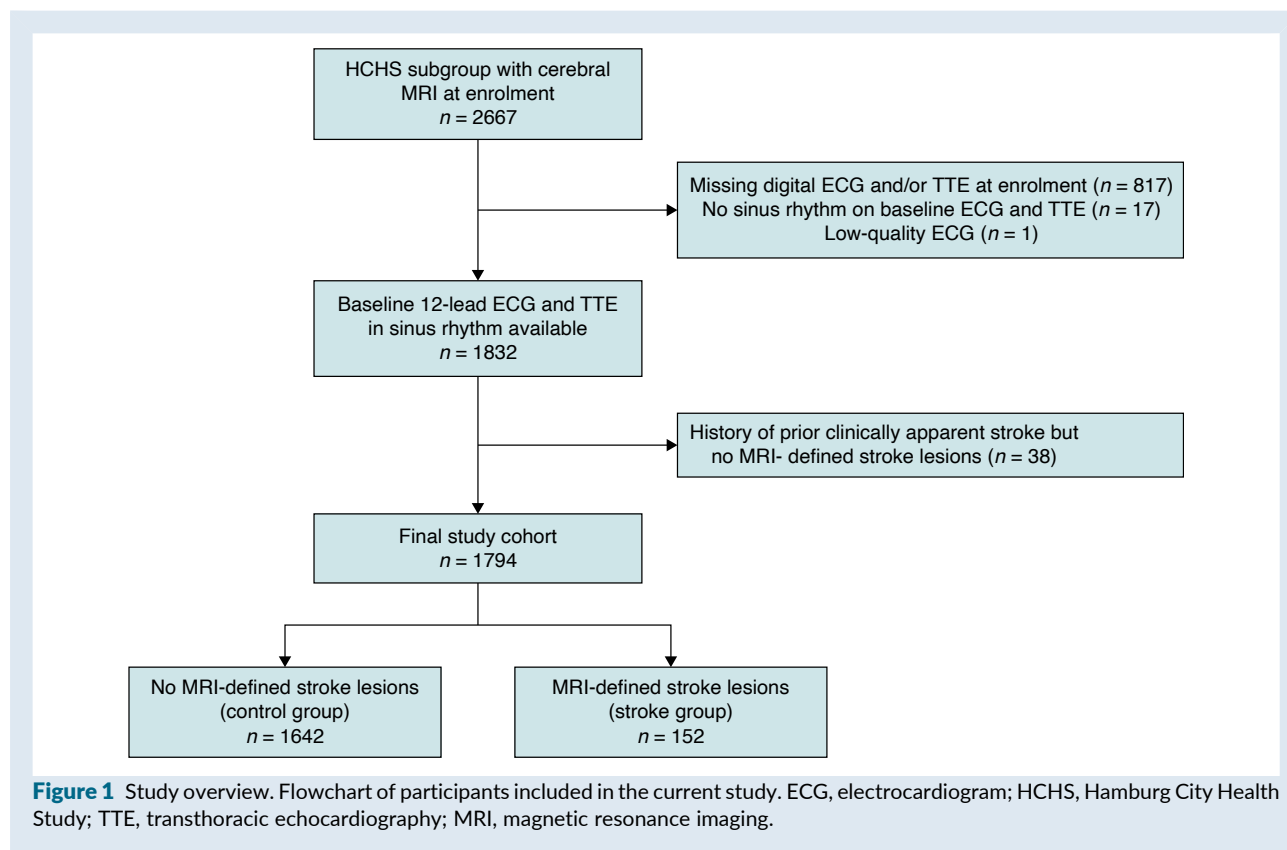
What's new?

- This study provides a population-based evaluation of non-invasive atrial cardiomyopathy markers in relation to magnetic resonance imaging-defined cerebral stroke lesions.
- Among electrocardiographic, echocardiographic, and blood-based markers of atrial cardiomyopathy, amplified P-wave duration, P-wave area in lead II, PR interval, left atrial volume index, left atrial ejection fraction, and NT-proBNP were significantly associated with cerebral stroke lesions.
- When added to established clinical risk stratification including CHA₂DS₂-VA score, gender and history of prior atrial fibrillation non-invasive atrial cardiomyopathy markers provided marginal incremental discriminatory value, highlighting important limitations of their application in unselected populations with heterogeneous stroke mechanisms.

Introduction

Atrial fibrillation (AF) is a common disease in older individuals and is associated with a significantly elevated risk of ischaemic stroke, which has a substantial impact on morbidity, mortality and quality of life.^{1–3} Strokes affect about 1.1 million people each year, and the mean global lifetime risk has increased to 24.9% over the past years.^{4,5} Approximately one-third of all ischaemic strokes are caused by AF, and as the Framingham study revealed, patients with AF have a three- to five-fold increased risk of stroke.^{6,7}

Atrial fibrillation-related strokes are often more severe than non-AF-related strokes underlining the importance of adequate risk stratification.⁶ The clinical CHA₂DS₂-VA score, though widely used for stroke risk stratification in AF, has only moderate predictive accuracy.⁸ Moreover, increasing evidence suggests that atrial structural, functional, and electrophysiological abnormalities present in atrial cardiomyopathy (AtCM) may lead to atrial blood stasis and thromboembolism even in sinus rhythm.^{9,10} This hypothesis is supported by device-based studies that found no temporal association between AF episodes and acute ischaemic stroke, indicating that AtCM itself, rather than AF, may be the critical driver of embolic stroke risk.^{11,12} Consequently, both the latest European Society of Cardiology and American College of Cardiology guidelines for AF as well as two recently published AtCM consensus statements emphasize the importance of AtCM diagnosis for stroke risk assessment.^{1–3,9,10} The currently most established diagnostic methods for AtCM include invasive electroanatomical mapping and late gadolinium enhancement cardiac magnetic resonance imaging (MRI) both of which have been linked to increased rates of prior ischaemic strokes.^{13,14} However, these methods are time-consuming, expensive, and only suitable for certain patient groups. On the other hand, non-invasive, widely available, and cost-effective tools for AtCM diagnosis using electrocardiography (ECG), transthoracic echocardiography (TTE), or blood-based biomarkers have not been established as routine screening modalities for the general population due to limited clinical validation. Moreover, most population-based MRI cohorts comprise heterogeneous lesion mechanisms (small-vessel disease, large-artery atherosclerosis, and cardioembolism), and it remains unclear whether non-invasive



AtCM surrogate markers retain incremental value beyond established vascular risk profiles in such real-world settings.

Therefore, we investigated (i) the association of non-invasive ECG-, TTE-, and blood biomarker-derived AtCM surrogate markers with cerebral stroke lesions on MRI and (ii) whether these markers improve discrimination beyond established clinical risk factors in a mixed-aetiology, population-based cohort of the Hamburg City Health Study (HCHS).

Methods

Study design and participants

The HCHS is an ongoing large, prospective, long-term, population-based cohort study with the aim to obtain knowledge on important risk and prognostic factors in major chronic diseases.¹⁵ Since spring 2016, more than 45 000 individuals have been contacted via Hamburg's residents' registration office, and until now, 45 000 participants have been registered in the study. The HCHS includes a representative distribution across sex and age strata with participants aged 45–74 years and equal numbers of men and women. As part of the baseline examinations, a predefined subgroup with cardiovascular risk factors (European Society of Cardiology EuroSCORE > 4%) underwent standardized cerebral MRI for the assessment of stroke lesions at enrolment. To enable standardized ECG and TTE phenotyping of AtCM markers, we required availability of a digital 12-lead ECG and TTE performed at enrolment in sinus rhythm. Participants were excluded if digital ECG and/or TTE were missing at enrolment ($n = 817$), if sinus rhythm was not present on baseline ECG and TTE ($n = 17$), or if ECG quality did not allow reliable P-wave assessment ($n = 1$). This yielded 1832 participants with baseline 12-lead ECG and TTE in sinus rhythm available.

Participants with self-reported history of clinically apparent stroke but without MRI-defined stroke lesions were excluded ($n = 38$) to reduce potential outcome misclassification in the control group. The final study cohort comprised 1794 participants. Within this cohort, individuals with MRI-defined stroke lesions constituted the stroke lesion group ($n = 152$), and those without MRI-defined stroke lesions constituted the control group ($n = 1642$). History of cardiovascular diagnoses was defined as documented diagnoses in medical records and/or participant self-report. An overview of the study population of our subgroup analysis is illustrated in Figure 1.

The study was approved by the local ethics committee of the Hamburg Chamber of Medical Practitioners (PV5131), and all participants provided written informed consent prior to study inclusion (identifier: NCT03934957 on clinicaltrials.gov).

Magnetic resonance imaging diagnostics

A cerebral MRI was performed using a 3 Tesla Skyra MRI scanner (Siemens, Erlangen, Germany) as described previously.¹⁶ In brief, single-shell diffusion weighted imaging sequence was obtained using 75 axial slices covering the whole brain with gradients ($b = 1000 \text{ s/mm}^2$) applied along 64 non-collinear directions with the following parameters: repetition time = 8500 ms, echo time = 75 ms, slice thickness = 2 mm, in-plane resolution = $2 \times 2 \text{ mm}$, and anterior-posterior phase-encoding direction. For 3D T1-weighted anatomical images, rapid acquisition gradient-echo sequence was used with the following sequence parameters: repetition time = 2500 ms, echo time = 2.12 ms, 256 axial slices, slice thickness = 0.94 mm, and in-plane resolution = $0.83 \times 0.83 \text{ mm}$. 3D T2-weighted fluid attenuated inversion recovery images were measured with the following sequence parameters: repetition time = 4700 ms, echo time = 392 ms, 192 axial slices, slice thickness = 0.9 mm, and in-plane resolution = $0.75 \times 0.75 \text{ mm}$.

The MRI findings were subsequently examined by two blinded neuroradiologists. Stroke lesions were defined as hyperintense lesions on T2-weighted fluid attenuated inversion recovery and a markedly hypointense signal intensity on T1-weighted images in a vascular distribution without mass effect or oedema.¹⁷ To better approximate potential stroke mechanisms, MRI-defined stroke lesions were further categorized according to lesion morphology and vascular imaging findings into likely cardioembolic (territorial infarcts or bilateral microembolic lesions), unlikely cardioembolic (lacunar or watershed infarcts, or any lesions associated with high-grade extra- or intracranial stenosis in the supplying vessel), and unclassified (ambiguous patterns).

Non-invasive atrial cardiomyopathy diagnosis

Atrial cardiomyopathy was quantified using the currently most promising non-invasive tools in ECG, TTE, and blood biomarkers as stated in the current AtCM consensus documents.^{9,10}

A standard digital 12-lead ECG (1 CS-200 Excellence, Schiller GmbH, Baar, Switzerland) in sinus rhythm was recorded. Conventional non-amplified P-wave duration (non-APWD), PR interval, P-wave terminal force in lead V1 (PTFV1), and P-wave area in lead II were analysed automatically by Schiller software (SEMA 3, Schiller GmbH, Baar, Switzerland). Amplified P-wave duration (APWD) and presence of advanced interatrial block were investigated manually by experts after digital ECG signal amplification to 80 mm/mV and a sweep speed of 175 mm/s using an automatically generated averaged beat, derived from all ECG single beats. Amplified P-wave duration was measured from the earliest initial deflection of any lead to latest end in any lead as described previously by our group.^{18–21} Subsequently, three AtCM stages depending on APWD were defined (<150 ms no relevant AtCM, 150–180 ms moderate AtCM, >180 ms severe AtCM).¹⁸ Advanced interatrial block was defined as occurrence of biphasic (positive-negative) P-waves in inferior leads II, III, and aVF.²²

Transthoracic echocardiography (Acuson SC2000 Prime, Siemens, Erlangen, Germany) was performed in sinus rhythm in accordance with current guidelines from the European Association of Cardiovascular Imaging and the American Society of Echocardiography.²³ Transthoracic echocardiography parameters were quantified by specially trained cardiologists and sonographers of the HCHS study group following standard operating procedures with regular internal quality controls.²⁴ Left atrial and left ventricular ejection fraction were calculated using the disk summation technique based on biplane measurements (apical four- and two-chamber views).²³ Left atrial global peak strain analysis was analysed using 2D speckle tracking.²⁵

For blood-based biomarkers, high-sensitivity C-reactive protein (hsCRP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were measured from the initial blood sample.

All investigators were blinded to participant's characteristics and clinical outcome.

Objectives

The primary objective was to quantify the association of non-invasive ECG-, TTE-, and blood biomarker-derived AtCM surrogate markers with MRI-defined cerebral stroke lesions in participants with baseline sinus rhythm. The secondary objective was to evaluate whether these markers improve model discrimination beyond established clinical risk factors.

Statistical analysis

Statistical analysis was performed using R v4.3.

Continuous variables are expressed as means $\pm$ standard deviation. Categorical variables are expressed with their absolute (in numbers) and relative frequency (in %). Student's *t*-test and χ^2 test were used to compare the two groups.

Univariable and multivariable logistic regression analyses were performed to identify both clinical parameters and AtCM markers significantly associated with stroke lesions on MRI. Multivariable regression

analysis was performed including significant risk factors from clinical parameters, ECG, TTE, and blood-based biomarkers identified in univariable regression analyses. Results are reported as odds ratios and 95% confidence intervals (CIs). To assess the incremental discriminatory performance of the extended model (clinical risk factors plus non-invasive AtCM markers) compared with the clinical model alone, areas under the receiver operating characteristics curve (ROC-AUCs) were compared using DeLong's test for correlated ROC curves. The difference in AUC (Δ AUC) was calculated with corresponding 95% CIs. To ensure comparability between models, these analyses were restricted to individuals with complete data available for all variables included in both the clinical and the extended model. In addition, decision curve analysis was performed to evaluate the net clinical benefit of both models across a range of clinically relevant threshold probabilities. Decision curve analysis was conducted using the same complete-case dataset as applied for the Δ AUC analysis.

All statistical analyses used a two-sided hypothesis and test significance was defined as $P < 0.05$.

Results

A total of 1794 participants of the HCHS with cerebral MRI and corresponding digital ECG and TTE in sinus rhythm were included in the current study. Mean age of the total study cohort was 63.8 ± 8.4 years with the majority of participants being male (58.3%). Magnetic resonance imaging confirmed stroke lesions in a total of 152 (8.5%) participants who were included in the stroke group and compared to 1642 (91.5%) controls without stroke lesions in cerebral MRI.

Clinical parameters and stroke risk

Compared to the control group, participants in the stroke group were significantly older (68.3 ± 6.4 vs. 63.4 ± 8.4 years, $P < 0.001$) and more often male (69.7% vs. 57.3%, $P = 0.004$). Additionally, a significant difference between the two groups was demonstrated in history of coronary artery disease (9.9% in the stroke group vs. 5.2% in controls, $P = 0.022$), prior myocardial infarction (7.9% vs. 3.5%, $P = 0.013$), and prior AF (10.5% vs. 3.6%, $P < 0.001$). Moreover, stenosis of cerebral vessels was significantly more present in the stroke group (10.5% vs. 2.1%, $P < 0.001$). Prior clinically apparent stroke was diagnosed in 19 (12.5%) participants of the stroke group. The remaining lesions represented clinically silent infarctions detected incidentally on MRI. The CHA₂DS₂-VA score was also statistically significantly different with 1.3 ± 0.9 in the stroke and 0.7 ± 0.8 in the control group ($P < 0.001$). Detailed clinical data of both the stroke and the control group are displayed in Table 1.

Electrocardiography-based atrial cardiomyopathy markers and stroke risk

Amplified P-wave duration was significantly different in both groups with a length of 128 ± 17 ms in the stroke group and 125 ± 16 ms in controls ($P = 0.015$; Figure 2A). Participants in the stroke group were slightly more frequently classified into higher AtCM stages based on APWD without reaching statistical significance ($P = 0.065$). There was no relevant difference in the appearance of advanced interatrial block (3.9% vs. 2.6%, $P = 0.451$).

Conventional non-APWD was not statistically significant between both groups (117 ± 24 ms vs. 116 ± 17 ms, $P = 0.570$) underlining the importance of amplification. Moreover, P-wave area in lead II was significantly lower in participants of the stroke group compared to controls (4516 ± 3034 vs. 5339 ± 2541 μ V $\cdot$ ms, $P = 0.002$; Figure 2B). PR interval was significantly longer in the stroke group (173 ± 32 ms vs. 165 ± 26 ms, $P < 0.001$; Figure 2C). All analysed ECG markers for AtCM are listed in Table 2.

Table 1 Participant clinical characteristics

Variables	Total (n = 1794)	Control group (n = 1642)	Stroke group (n = 152)	P value
Age, years	63.8 ± 8.4	63.4 ± 8.4	68.3 ± 6.4	<0.001
Male sex, n (%)	1046 (58.3%)	940 (57.3%)	106 (69.7%)	0.004
Body mass index, kg/m ²	26.8 ± 4.4	26.7 ± 4.3	27.4 ± 4.3	0.057
Smoking history, n (%)	1157 (64.5%)	1057 (64.4%)	100 (65.8%)	0.839
Coronary artery disease, n (%)	100 (5.6%)	85 (5.2%)	15 (9.9%)	0.022
History of myocardial infarction, n (%)	69 (3.9%)	57 (3.5%)	12 (7.9%)	0.013
History of atrial fibrillation, n (%)	75 (4.2%)	59 (3.6%)	16 (10.5%)	<0.001
Heart failure, n (%)	54 (3.0%)	50 (3.1%)	4 (2.6%)	0.970
Stenosis of cerebral vessels, n (%)	50 (2.8%)	34 (2.1%)	16 (10.5%)	<0.001
History of clinically apparent stroke, n (%)	19 (1.1%)	0 (0%)	19 (12.5%)	<0.001
CHA ₂ DS ₂ -VA score	0.8 ± 0.8	0.7 ± 0.8	1.3 ± 0.9	<0.001
Left ventricular ejection fraction, %	59 ± 5	59 ± 5	58 ± 5	0.770

In univariable regression analysis including all ECG parameters, APWD, P-wave area in lead II, and PR interval were statistically significant risk factors of stroke lesions (Table 3).

Transthoracic echocardiography-based atrial cardiomyopathy markers and stroke risk

Left atrial volume index was significantly higher in the stroke cohort compared to controls (31 ± 12 mL/m² vs. 28 ± 8 mL/m², $P = 0.038$; Figure 2D and Table 2), and left atrial ejection fraction was significantly lower in the stroke group ($45 \pm 11\%$ vs. $48 \pm 10\%$, $P = 0.032$, Figure 2E and Table 2). Left atrial global peak strain however was not significantly different between the two groups ($37.8 \pm 12.5\%$ vs. $40.0 \pm 14.6\%$, $P = 0.168$; Table 2).

In univariable regression analysis, left atrial volume index and left atrial ejection fraction were statistically significant risk factors for stroke lesions (Table 3).

Blood-based atrial cardiomyopathy biomarkers and stroke risk

Considering the blood-based parameters, NT-proBNP was significantly different between the stroke group and controls (183.7 ± 212.6 ng/L in the stroke group vs. 117.1 ± 156.2 ng/L in controls, $P < 0.001$; Figure 2F and Table 2) whereas hsCRP was not significantly different (0.31 ± 0.75 mg/dL vs. 0.23 ± 0.40 mg/dL, $P = 0.220$; Table 2). In univariable regression analysis, NT-proBNP was also a significant risk factor for stroke lesions (Table 3).

Best risk prediction model for stroke including clinical parameters and non-invasive atrial cardiomyopathy markers

In univariable regression analysis, several clinical parameters were significantly associated with the presence of stroke lesions on cerebral MRI (Table 3). To avoid collinearity, only the composite CHA₂DS₂-VA score, rather than its individual components, was included in the multivariable clinical model in addition to history of prior AF and male sex (Table 4 and Figure 3A).

When significant risk factors identified from ECG-, TTE-, and blood-based AtCM markers in the univariable analyses were added to the extended model, only the CHA₂DS₂-VA score

and P-wave area in lead II remained independently associated with stroke lesions (Table 5 and Figure 3B). A total of 970 participants had complete data available for all variables included in both models and were therefore analysed in the model comparison. In this complete-case dataset, the ROC-AUC of the clinical parameter model was 0.680. Addition of non-invasive AtCM markers increased the ROC-AUC of the extended model to 0.710 (Δ AUC 0.030, 95% CI: 0.0001–0.0594, $P = 0.049$). Although statistically significant, the absolute improvement in discrimination was modest. Decision curve analysis also did not demonstrate a consistent or clinically meaningful improvement in net benefit of the extended model compared with the clinical model (see Supplementary material online, Figure S1).

To evaluate the association of AtCM surrogate markers with MRI-defined stroke lesions independent of diagnosed AF, we additionally performed a sensitivity analysis excluding all participants with history of prior AF. This AF-excluded cohort comprised 1719 participants, of whom 136 (7.9%) had MRI-defined stroke lesions and 1583 (92.1%) served as controls and yielded findings consistent with those observed in the cohort including participants with history of prior AF (see Supplementary material online, Table S1). In univariable analyses, age, CHA₂DS₂-VA score, male sex, APWD, P-wave area in lead II, PR interval, left atrial volume index, left atrial ejection fraction, and NT-proBNP remained significantly associated with MRI-defined stroke lesions (see Supplementary material online, Table S1a). In the multivariable clinical model, CHA₂DS₂-VA score and male sex remained independent predictors (see Supplementary material online, Table S1b). After adding AtCM surrogate markers (APWD, P-wave area in lead II, PR interval, left atrial volume index, left atrial ejection fraction, and NT-proBNP), only CHA₂DS₂-VA score and P-wave area in lead II remained independently associated with stroke lesions (see Supplementary material online, Table S1c).

Stroke lesion pattern subgroup and sex-stratified analyses

Among participants with MRI-defined stroke lesions ($n = 152$), 37 were classified as likely cardioembolic, 84 as unlikely cardioembolic, and 31 as unclassified.

In a two-group comparison between likely and unlikely cardioembolic lesions, neither clinical risk factors nor ECG-, TTE-, or

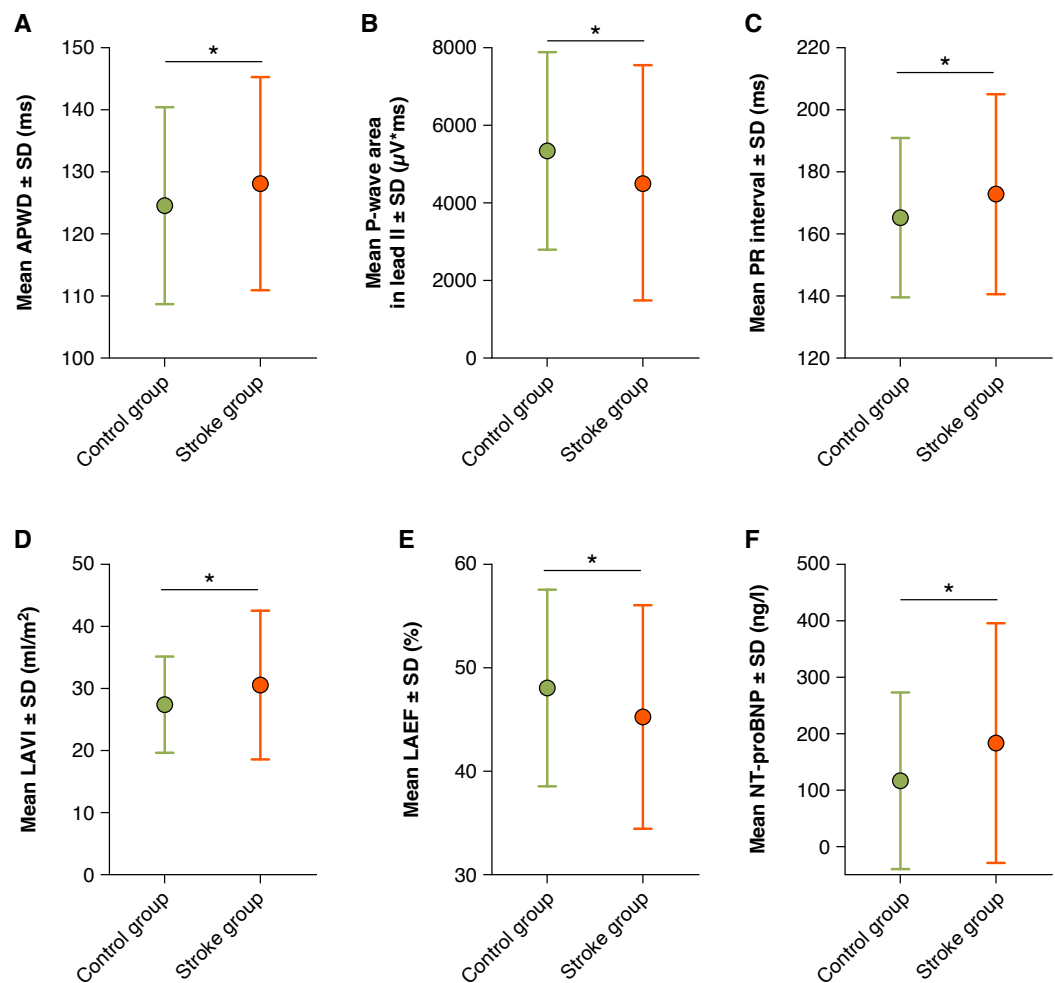


Figure 2 Non-invasive AtCM markers in participants with and without cerebral stroke lesions. Comparison of non-invasive markers of AtCM between participants of control group (in green) and stroke group (in red). Bar plots show the group-wise means $\pm$ standard deviation (SD) for APWD (A), P-wave area in lead II (B), PR interval (C), left atrial volume index (D), left atrial ejection fraction (E), and NT-proBNP (F). Participants with stroke lesions (stroke group) showed significantly different values across all six AtCM markers compared to the control group (* $P < 0.05$ for all comparisons).

blood-based AtCM surrogate markers differed significantly between the groups (see [Supplementary material online, Table S2](#)). Significant sex-related differences were observed for several AtCM parameters including amplified and non-APWD, P-wave terminal force in V1, P-wave area in lead II, PR interval, left atrial volume index, left atrial global peak strain, and NT-proBNP (see [Supplementary material online, Table S3](#)). Using ROC-AUC analysis with the Youden index, exploratory sex-specific optimal cut-off values were determined for the endpoint of MRI-defined stroke lesions (see [Supplementary material online, Table S3](#)).

Discussion

This analysis was designed to test the incremental value of widely available, non-invasive AtCM surrogate markers for the detection of MRI-defined stroke lesions in a population-based cohort with

heterogeneous lesion mechanisms. In this real-world setting, established clinical risk burden, as reflected by the CHA₂DS₂-VA score, male sex, and history of prior AF accounted for most of the discriminatory performance, whereas AtCM surrogate markers provided only marginal incremental value.

- Specifically, we report three main findings:
- (1) Stroke lesions detected by cerebral MRI were present in almost 10% of participants (mean age 63.8 years) within a subgroup of the prospective, population-based HCHS.
 - (2) Higher CHA₂DS₂-VA score, history of prior AF, and male sex, as established clinical risk factors, were independently associated with the presence of stroke lesions.
 - (3) Among non-invasive AtCM markers, only P-wave area in lead II remained an independent predictor when added to the clinical risk factor model, resulting in only a marginal improvement in discrimination for identifying individuals with stroke lesions (Δ AUC: 0.03, 95% CI: 0.0001–0.0594).

Table 2 Non-invasive AtCM parameters

Variables	Total (n = 1794)	Control group (n = 1642)	Stroke group (n = 152)	P value
ECG-based parameters				
Manual amplified P-wave analysis				
APWD, ms	125 ± 16	125 ± 16	128 ± 17	0.015
Advanced interatrial block, n (%)	48 (2.7%)	42 (2.6%)	6 (3.9%)	0.451
AtCM stages, n (%)				0.065
AtCM stage I (APWD < 150 ms)	1688 (94.1%)	1551 (94.5%)	137 (90.1%)	
AtCM stage II (APWD 150–180 ms)	91 (5.1%)	79 (4.8%)	12 (7.9%)	
AtCM stage III (APWD > 180 ms)	15 (0.8%)	12 (0.7%)	3 (2.0%)	
Automatic ECG-analysis				
Non-APWD, ms	116 ± 18	116 ± 17	117 ± 24	0.570
P-wave terminal force in V1, $\mu\text{V}\cdot\text{ms}$	2376 ± 2050	2347 ± 2038	2686 ± 2166	0.073
P-wave area in lead II, $\mu\text{V}\cdot\text{ms}$	5268 ± 2596	5339 ± 2541	4516 ± 3034	0.002
PR interval, ms	166 ± 26	165 ± 26	173 ± 32	<0.001
TTE-based parameters				
Left atrial volume index, mL/m ²	28 ± 8	28 ± 8	31 ± 12	0.038
Left atrial ejection fraction, %	48 ± 10	48 ± 10	45 ± 11	0.032
Left atrial global peak strain, %	39.9 ± 14.4	40.0 ± 14.6	37.8 ± 12.5	0.168
Blood-based biomarkers				
hsCRP, mg/dL	0.24 ± 0.44	0.23 ± 0.40	0.31 ± 0.75	0.220
NT-proBNP, ng/L	122.9 ± 162.8	117.1 ± 156.2	183.7 ± 212.6	<0.001

APWD, amplified P-wave duration; AtCM, atrial cardiomyopathy; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide. Bold values indicate statistical significance.

Table 3 Univariable regression analyses of significant clinical parameters and AtCM markers for stroke lesions

Variable	Univariable regression analyses		
	OR	95% CI	P value
Age per year	1.08	1.06–1.11	<0.001
Male sex	1.72	1.20–2.44	0.003
History of prior atrial fibrillation	3.17	1.72–5.53	<0.001
CHA ₂ DS ₂ -VA score per point	2.00	1.67–2.40	<0.001
APWD per 10 ms	1.13	1.03–1.24	0.009
P-wave area in lead II per 100 $\mu\text{V}\cdot\text{ms}$	0.99	0.98–1.00	<0.001
PR interval per 10 ms	1.10	1.01–1.22	<0.001
Left atrial volume index per mL/m ²	1.04	1.02–1.06	<0.001
Left atrial ejection fraction per %	0.97	0.95–0.99	0.010
NT-proBNP per 10 ng/L	1.02	1.01–1.02	<0.001

APWD, amplified P-wave duration; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; OR, odds ratio; CI, confidence interval. Bold values indicate statistical significance.

Table 4 Multivariable regression analysis including significant clinical parameters for stroke lesions

Variable	Multivariable regression analysis		
	OR	95% CI	P value
CHA ₂ DS ₂ -VA score per point	1.89	1.57–2.27	<0.001
History of prior atrial fibrillation	2.12	1.12–3.80	0.014
Male sex	1.61	1.14–2.38	0.010

OR, odds ratio; CI, confidence interval. Bold values indicate statistical significance.

Considering the growing and aging population, stroke events and their long-term consequences, including health care costs, are expected to increase exceptionally.⁴ In the current study, cerebral stroke lesions were identified on MRI in 8.5% of participants enrolled in the prospective epidemiological HCHS, which is in line with previous population-based studies reporting a prevalence of stroke lesions of 10–20%.²⁶ Among these individuals, 12.5% had a documented history of clinically apparent stroke underlining the clinical relevance. The remaining 87.5% of individuals in the stroke group had clinically silent cerebral lesions that were incidentally detected on brain MRI. Despite the absence of acute neurological symptoms, silent infarctions represent clinically relevant cerebrovascular injury

Clinical relevance of stroke

Stroke is one of the leading causes of death in the European Union and the USA and a leading cause of disability in adults.^{4,5}

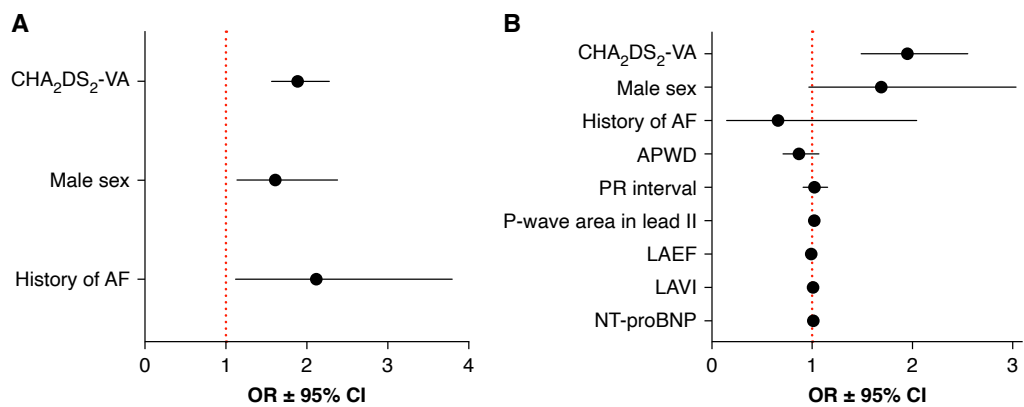


Figure 3 Association of clinical risk factors and non-invasive AtCM markers with cerebral stroke lesions. Forest plots display ORs and 95% CIs from two logistic regression models including statistically significant clinical risk factors as well as significant AtCM markers from ECG-, TTE-, and blood-based biomarkers (A: clinical model including CHA₂DS₂-VA score, male sex, and history of prior AF); B: extended model including CHA₂DS₂-VA score, male sex, history of prior AF, APWD, PR interval, P-wave area in lead II, left atrial ejection fraction, left atrial volume index, and NT-proBNP. All markers were standardized prior to analysis.

Table 5 Multivariable regression analysis including significant clinical parameters and AtCM markers for stroke lesions

Variable	Multivariable regression analysis		
	OR	95% CI	P value
CHA ₂ DS ₂ -VA score per point	1.95	1.49–2.55	<0.001
History of prior atrial fibrillation	0.66	0.15–2.04	0.524
Male sex	1.69	0.97–3.03	0.067
APWD per 10 ms	0.90	0.82–1.11	0.486
P-wave area in lead II per 100 μ V $\cdot$ ms	0.99	0.98–1.00	0.031
PR interval per 10 ms	1.01	0.92–1.11	0.827
Left atrial volume index per mL/m ²	1.02	0.99–1.05	0.257
Left atrial ejection fraction per %	0.99	0.97–1.02	0.485
NT-proBNP per 10 ng/L	1.00	1.00–1.01	0.420

APWD, amplified P-wave duration; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; OR, odds ratio; CI, confidence interval. Bold values indicate statistical significance.

and have been consistently associated with adverse outcomes, including increased risk of future symptomatic stroke and mortality, cognitive decline, and accelerated neurobehavioral disturbances.²⁷

Risk factors for stroke

In the present study, established clinical risk factors including CHA₂DS₂-VA score, male sex, and history of prior AF were confirmed as strong predictors of stroke lesions on cerebral MRI. These findings are consistent with the well-documented role of AF and vascular comorbidities in the pathogenesis of ischaemic stroke.²⁸

The concept of AtCM has gained attention in recent years as a potential contributor to stroke risk, independent of AF.^{9,10,29} In our study, we evaluated multiple electrical, structural, functional, and blood-based biomarker-derived parameters as surrogates of AtCM, but only the ECG-derived parameter P-wave area in lead II was significantly associated with stroke lesions in addition to the CHA₂DS₂-VA score after multivariable adjustment. This finding suggests that electrical remodelling may capture aspects of AtCM relevant to stroke lesions more robustly than structural or biochemical surrogates in this setting and was consistent after exclusion of participants with a prior AF diagnosis, suggesting that the observed findings are not merely driven by known AF. According to the recent European Heart Rhythm Association consensus framework, AtCM can be conceptualized in stages.⁹ In our cohort, predominantly comprising individuals without known AF, most detectable alterations were confined to electrical parameters, consistent with a mild or sub-clinical stage of AtCM. The inverse association between P-wave area in lead II and stroke lesions likely reflects reduced atrial electrical mass secondary to fibrotic remodelling, which represents a hallmark of AtCM. These findings align with prior studies linking P-wave morphology to atrial fibrosis and thromboembolic risk.^{9,10} In contrast, more advanced structural or functional markers such as left atrial volume index, left atrial ejection fraction, left atrial strain, and blood-based biomarkers such as NT-proBNP did not remain independently associated after multivariable adjustment, suggesting that in a population-based setting without overt atrial disease, early electrical changes may precede clinically manifest structural remodelling. However, when added to a model containing only clinical risk factors, the non-invasive AtCM markers increased the model's diagnostic performance only marginally (Δ AUC of 0.03). It should be acknowledged that this model comparison was restricted to 970 of the 1794 participants with complete data available for all variables included in both models. While this approach ensured comparability between both models, it substantially reduced the effective sample size. Moreover, the requirement for complete multimodal phenotyping highlights a potential challenge for real-world implementation of comprehensive AtCM

assessment in population-based settings, where availability of all modalities may be limited. Nevertheless, the modest gain after inclusion of AtCM markers in the clinical risk factor model suggests that, in a heterogeneous cohort with multiple stroke mechanisms, the clinical relevance of AtCM might be diluted by other prevalent risk factors such as large-artery atherosclerosis and small-vessel disease. In our study, individuals in the stroke group more frequently had coronary artery disease, prior myocardial infarction, and cerebral vessel stenosis, all of which are known contributors to atherosclerotic brain injury.²⁸ Given that only 10.5% of stroke patients had documented history of prior AF and the mean CHA₂DS₂-VA score was relatively low, many lesions likely arose from non-cardioembolic causes. This heterogeneity may explain why AtCM markers, although significant, were not strong discriminators in our population demonstrating important limitations for the clinical translation of AtCM surrogate markers in unselected populations. These findings complement recently published large-scale outcome studies investigating AtCM in AF cohorts. In the EAST-AFNET 4 trial, AtCM severity (defined by left atrial enlargement, prolonged PR interval, and elevated NT-proBNP) was associated with adverse cardiovascular outcomes, including stroke, in patients with recently diagnosed AF.²⁹ Relander *et al.* demonstrated that various P-wave abnormalities were able to predict future stroke in patients with AF undergoing electrical cardioversion.³⁰ In such populations, electrical, structural, and blood-biomarker-based AtCM surrogates likely play a more prominent role, as manifest atrial pathology is already present and the probability of a cardioembolic stroke mechanism is consequently higher compared with our predominantly community-based cohort without known AF. However, even after stroke lesion pattern stratification aiming to enrich for likely cardioembolic infarcts, AtCM surrogate markers did not demonstrate stronger separation between mechanistic subgroups in our study. It must be noted that these subgroup analyses were limited by small sample sizes and should be interpreted with caution. In addition, lesion morphology alone does not allow definitive determination of stroke aetiology, particularly in a population-based cohort largely consisting of individuals without previously diagnosed AF and without formal aetiological adjudication. Nevertheless, our findings may provide a possible explanation for the negative results of the ARCADIA trial, in which anticoagulation did not reduce recurrent stroke compared with aspirin in patients with evidence for AtCM.³¹

Another important finding of our study was that gender impacts multiple non-invasive AtCM parameters. We could demonstrate that not only structural remodelling parameters are influenced but also electrical, functional, and blood-based biomarkers of AtCM. Currently available consensus documents emphasize that no universally established diagnostic cut-offs for AtCM exist.^{9,10} Our findings further highlight that uniform thresholds may be biologically inappropriate. The proposed sex-specific thresholds should be considered exploratory and hypothesis-generating, as external validation in independent cohorts is required before incorporation into risk stratification algorithms.

Moreover, advanced artificial intelligence-based multimodal phenotyping approaches may further improve risk stratification in large imaging cohorts. Future studies integrating explainable artificial intelligence techniques with mechanistically grounded AtCM markers may provide complementary insights.

Limitations

First, this is an observational cross-sectional analysis. Therefore, causality cannot be inferred. Second, although the participants

included in the present study exhibited cardiovascular risk factors, they nevertheless represented a relatively young and healthy sample from a prospective population-based cohort. Consequently, the proportion of individuals with stroke lesions and the generalizability of these findings to a potentially older and more severely ill population are limited. Third, while we performed a subgroup analysis based on stroke lesion morphology and vascular imaging findings to approximate potential cardioembolic mechanisms, definitive aetiological adjudication was not available. Therefore, the true aetiology of the diagnosed strokes remains uncertain in the analysis, precluding a definitive assessment of whether they were cardioembolic in origin and thus potentially attributable to an underlying AtCM, particularly in a general population-based cohort largely comprising individuals without previously diagnosed AF. Fourth, restricting ECG and TTE phenotyping to participants in sinus rhythm at enrolment enables standardized AtCM marker measurements but preferentially captures participants with paroxysmal (rather than persistent) AF among those with a history of prior AF. However, this approach was necessary to allow mechanistic assessment of AtCM and likely biases the results towards underestimation rather than overestimation of diagnostic performance. Additionally, according to the study design, it was not possible to assess AF burden, a metric of growing interest beyond the dichotomous analysis based on presence/absence of AF.³²

Conclusion

In this population-based cohort, multiple non-invasive AtCM surrogate markers were associated with stroke lesions on MRI in univariable analyses. However, beyond established clinical risk factors, their incremental diagnostic value was modest. These findings highlight limitations of current non-invasive AtCM surrogate markers for stroke lesion detection in unselected populations with heterogeneous lesion mechanisms.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding authors.

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