SVN Stroke & Vascular Neurology

Distribution of atrial cardiomyopathy markers and association with atrial fibrillation detected after ischaemic stroke in the SAFAS study

Romain Didier ,[1] Lucie Garnier,[2] Gauthier Duloquin,[2] Alexandre Meloux,[3] Audrey Sagnard,[1] Mathilde Graber,[2] Geoffrey Dogon,[3] Karim Benali,[4] Thibaut Pommier,[1,3] Gabriel Laurent,[1,3] Catherine Vergely,[3] Yannick Bejot ,[2,3] Charles Guenancia[1,3]

To cite: Didier R, Garnier L, Duloquin G, *et al*. Distribution of atrial cardiomyopathy markers and association with atrial fibrillation detected after ischaemic stroke in the SAFAS study. *Stroke & Vascular Neurology* 2023;**0**. doi:10.1136/svn-2023-002447

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2023-002447).

Journées Européennes de la Société Française de Cardiologie 2023

Received 6 March 2023
Accepted 27 June 2023

[1]Cardiology, CHU Dijon Bourgogne, Dijon, France
[2]Dijon Stroke Registry, Department of Neurology, University Hospital Centre Dijon, Dijon, France
[3]PEC 2, Université de Bourgogne, Dijon, France
[4]Cardiology, CHU Saint Etienne, Saint Etienne, France

Correspondence to
Professor Charles Guenancia; charles.guenancia@chu-dijon.fr

ABSTRACT

Background Atrial cardiomyopathy (AC) is an emerging concept explaining the pathophysiology of cardioembolic strokes in absence of atrial fibrillation (AF). A definition based on the presence of electrical abnormality (P-wave terminal force in lead V1 (PTFV1) >5000 µV×ms), N-Terminal pro-B-type natriuretic peptide (NT pro BNP) >250 pg/mL and/or indexed left atrial diameter (LADI) >3 cm/m² is currently tested in the ARCADIA (AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke) trial. We set out to estimate the prevalence of AC as defined in the ARCADIA trial, its determinants and its association with AF detected after stroke (AFDAS).

Methods Stepwise screening for silent Atrial Fibrillation After Stroke (SAFAS) study prospectively included 240 ischaemic stroke patients. AC markers were complete for 192 of them and 9 were not included in this analysis because AF had been diagnosed on admission.

Results A total of 183 patients were analysed, of whom 57% (104 patients) met the AC criteria (79 NT-proBNP, 47 PTFV1, 4 LADI). In the multivariate logistic regression, C reactive protein >3 mg/L (OR (95% CI) 2.60 (1.30 to 5.21), p=0.007) and age (OR (95% CI) 1.07 (1.04 to 1.10), p<0.001) were found to be independently associated with AC. After 6 months of follow-up, AFDAS was detected in 33% of AC patients and in 14% of the remaining ones (p=0.003). However, AC was not independently associated with AFDAS, contrary to left atrial volume index (>34 mL/m², OR 2.35 (CI 1.09 to 5.06) p=0029).

Conclusion AC as defined in ARCADIA is mostly based on NT pro BNP elevation (76% of patients) and is associated with age and inflammation. Moreover, AC was not independently associated with AFDAS at follow-up. The ARCADIA trial, which compares aspirin to apixaban in patients with embolic strokes of undetermined source with AC markers and must, therefore be analysed in the light of these limitations.

Trial registration number NCT03570060.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial cardiomyopathy may explain cardioembolic stroke without atrial fibrillation, but its definition is still a matter of debate.

WHAT THIS STUDY ADDS

⇒ Atrial cardiomyopathy as defined in ARCADIA is mostly based on N-Terminal pro-B-type natriuretic peptide elevation and is not an independent predictor of atrial fibrillation diagnosed after stroke at follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of ARCADIA trial should be analysed in the light of these limitations.

INTRODUCTION

Twenty to thirty percent of ischaemic strokes are of cardioembolic aetiology while up to 25% of them do not have an identifiable cause.[1 2] The embolic strokes of undetermined source (ESUS) may be explained by distant cardiac embolism, artery lesions, patent foramen ovale and incompletely elucidated risk factors.[2]

In the main analysis of the Stepwise screening for silent Atrial Fibrillation After Stroke study (SAFAS), AF detected after stroke (AFDAS) accounted for 32% of stroke without obvious aetiology. Moreover, we found that AFDAS was related to an underlying left atrial substrate, also known as atrial cardiomyopathy (AC).[3] AC is an emerging concept that could explain the mechanisms of ESUS and may lead to a thrombogenic substrate even in the absence of supraventricular arrhythmia.[4–6]

The key issue in relation to this newly proposed definition is to identify a population of ESUS that may benefit from secondary stroke prevention with anticoagulation therapy in the absence of AF. So far, anticoagulation in non-selected or selected patients with ESUS has failed to demonstrate a clinical benefit compared with aspirin (NAVIGATE-ESUS,

RESPECT-ESUS and ATTICUS trials).[7–10] The ARCADIA trial, currently ongoing, aims to compare aspirin to apixaban in patients with ESUS and at least one AC marker.[11] AC is defined in the ARCADIA by the presence of one of the following criteria: electrical abnormality (P-wave terminal force in lead V1 (PTFV1)>5000 µV×ms), biological abnormality (N-Terminal pro-B-type natriuretic peptide (NT-proBNP >250 pg/mL) and/or structural abnormality (indexed left atrial diameter (LADI) >3 cm/m^2).[11]

However, the current definition of AC is based on epidemiological cohorts, and on three markers only. Thus, we aimed to estimate the prevalence of AC as defined in the ARCADIA trial, its determinants and its association with AFDAS in a prospective cohort of ischaemic stroke patients.

METHODS

Population

SAFAS was a prospective cohort using a stepwise diagnostic approach to detect AFDAS at 6 months (ECG, continuous electrocardiographic monitoring, long-lasting Holter monitoring during the stay in neurology department and implantable cardiac monitor at discharge if needed). The study was conducted in adult patients hospitalised from 31 March 2018, to 18 January 2020, in Dijon Bourgogne University Hospital stroke unit.

We included patients with ischaemic stroke as defined by the WHO.[12] Exclusion criteria were previous AF or atrial flutter, presence of a pacemaker/cardioverter defibrillator with an atrial lead, under guardianship patients, pregnant/breastfeeding women, refusal to participate and patients transferred outside of the primary care area of the Dijon Bourgogne University Hospital after stroke unit stay.

Oral consent was obtained from all patients or their representative.

Clinical, biological and imaging data during hospital stay

We collected previous medical history and clinical data within 48 hours of stroke hospitalisation as well as clinical outcomes and complementary exams during the hospital stay.

Veinous blood samples were taken immediately after the admission of the patient in the stroke unit. Biological samples were stored at 3°C in a Stroke unit refrigerator for up to 24 hours. The blood samples were then centrifuged for 5 min at 4°C and the plasma was frozen immediately in liquid nitrogen and then stored at –80°C until analysis. Assays were performed on thawed biologic serum. Plasma Nt-proBNP was measured using immunoassay on a Vista analyzer (SIEMENS). The C reactive protein (CRP) levels were assessed using an enzymatic method on Xpand (Dade Behring, Deerfield, Illinois).

The following data were collected on echocardiography (transthoracic with bubble study for patent foramen ovale±transesophageal): left atrial parameters (diameter, area, volume, indexed volume calculated using the biplane method), left ventricular ejection fraction and patent foramen ovale (large with more than 30 microbubbles associated with an atrial septal aneurysm). Left atrial dilatation was defined according to international guidelines as left atrial volume index (LAVI)>34 mL/m.[2 13]

The following electrocardiographic data were collected: P-wave duration (ms), P-wave terminal force (PTF) (amplitude of P-wave in V1 terminal negative portion x duration of the P-wave in V1 terminal negative portion).

The modalities for the detection of AFDAS are described in the SAFAS study.[3]

Analysis

Medians (25th to 75th percentiles) were used of continuous data expression whereas numbers (percentages) were used for dichotomous data. The Mann-Whitney test or Student's t-test was used for comparisons of continuous data, and the χ^2 test or Fisher's test was used for dichotomous data. Collinearity was excluded before the construction of the multivariate models (r-coefficient did not exceed ±0.25). Variables included in the multivariate model were chosen according to their univariate relationship, with an inclusion cut-off at 10% and exclusion cut-off at 5%. Multicollinearity was tested before multivariate analysis. We used two multivariate backward stepwise logistic regression models, one for AC-associated factors and the second one focusing on AFDAS-associated factors. A p value <0.05 was considered statistically significant. Statistics were performed using SPSS software (26.0, IBM).

RESULTS

AC markers prevalence and distribution

Of the 265 patients of the SAFAS cohort, 25 were excluded for finally not matching inclusion criteria. Among 240 patients analysed in the SAFAS study, 16 were not included of the analysis due to AF on admission ECG. Among the remaining 224, 41 were finally excluded for missing at least one data regarding AC definition (figure 1). Out of these 41 patients, 3 had missing data for both NT pro BNP and echocardiography or ECG, and the remaining 38 patients had missing data for either NT pro BNP, echocardiography or ECG.

Among the 183 patients included in this study, 104 (57%) presented at least one criterion for AC. Most of the patients diagnosed with AC had the positive NT-proBNP criterion (76%), less than half of them had the ECG criterion (45%) and only 4% had the left atrial dilatation criterion (figure 2). Twenty-six patients had more than one AC criterion.

Among the excluded patients, 17 (41%) would have been characterised as having an AC if not excluded from the analysis. The distribution of AC criteria in the excluded patients was similar to that in the main analysis, with no positive LADI criteria and a major impact of NT-proBNP criteria (14 patients, 81% of AC) on AC definition and

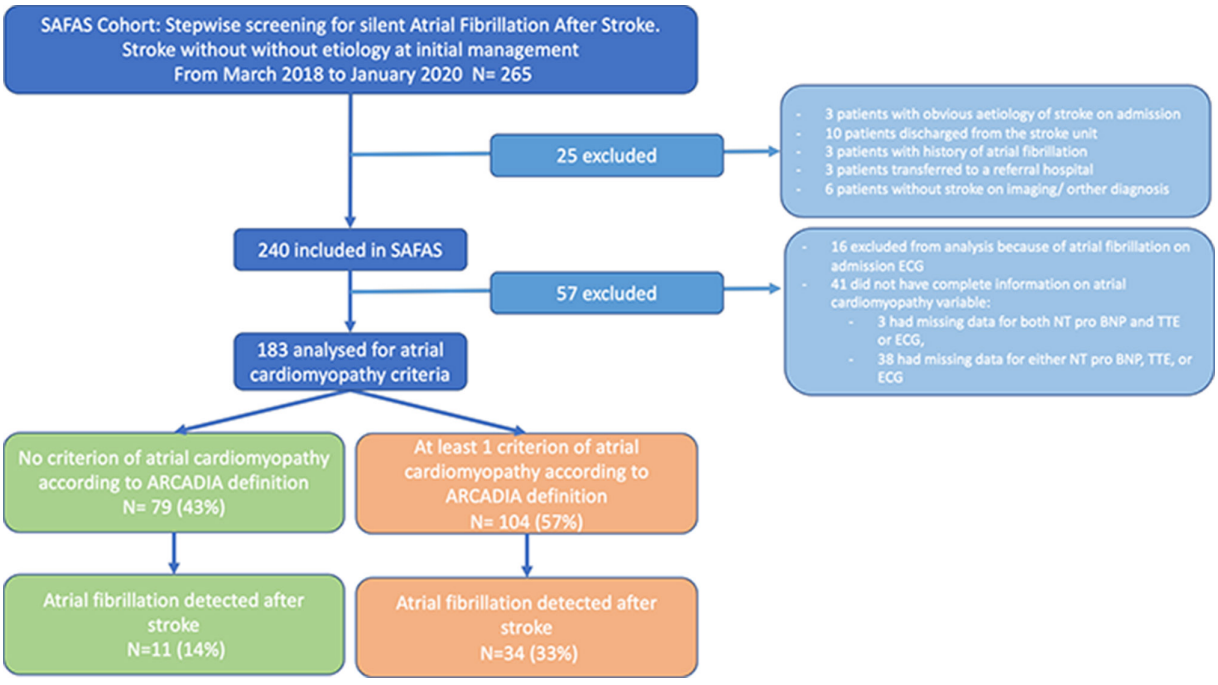

Figure 1 Flowchart. NT-proBNP, N-Terminal pro-B-type natriuretic peptide; SAFAS, Stepwise screening for silent Atrial Fibrillation After Stroke; ARCIDIA, AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke.

8 patients (47% of AC) having PTFV1 criteria (5 (29%) having both) (online supplemental figure 1).

Compared with the included patients, the non-included patients had similar baseline clinical, biological, imaging and ECG data, except for a higher rate of superficial sylvian MCA stroke in the excluded group (68% vs 47%, p=0.014) (online supplemental table 1).

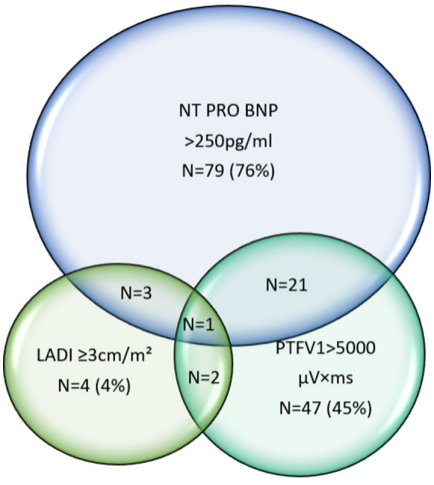

Figure 2 Distribution of the criteria for atrial cardiomyopathy (AC) according to ARCADIA definition in the SAFAS cohort. 104 patients had at least 1 AC criteria, and these were distributed as shown in the figure below. LADI, left atrial diameter index; NT-proBNP, N-Terminal pro-B-type natriuretic peptide; PTFV1, P-wave terminal force in lead V1; SAFAS, Stepwise screening for silent Atrial Fibrillation After Stroke; ARCIDIA, AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke.

AC-associated factors

Compared with the patients who did not fit any of the criteria for AC, AC patients were significantly older (75 vs 63, p<0.001) and had higher rates of hypertension (66.3% vs 44.3%, p=0.003), previous coronary artery disease (12% vs 2%, p=0.023) and valvular heart disease (35.6% vs 13.9%, p=0.001) (table 1).

At hospital admission for stroke, median CHA^2DS^2-Vasc score was higher in the AC group (3 (CI 2 to 4) vs 2 (CI 0 to 3), p<0.001) (table 1). Moreover, at admission, the NT-pro-BNP levels were significantly higher in AC group (NT-pro-BNP 515.5 pg/mL (252.5 to 1266.0) vs 83 pg/mL (44.0 to 128.0), p<0.001). CRP >3 and troponin >0.02 ng/L at admission were significantly associated with the AC group (CRP >3, 48 (46.2%) vs 23 (29.1%), p=0.019; troponin >0.02 ng/L, 20 (19.4%) vs 3 (3.8%), p=0.002) (table 2). On brain imaging, insular and superficial middle cerebral artery lesion were more often found in AC patients than in the other group (23 (22.1%) vs 8 (10.1%), p=0.003 and 62 (59.60%) vs 24 (30.40%), p<0.001, respectively). Moreover, AC patients presented significantly higher LAVI and left atrial surface than non-AC patients (32.02 mL/m² (22.21 to 42.57) vs 25.45 mL/m² (18.71 to 31.07) and 19.7 cm² (16.35 to 25.10) vs 16.90 cm² (15.00 to 21.00) p=0.001, respectively) (table 2).

Stroke aetiology and follow-up

After initial stroke workup, there was similar rate of ESUS in both groups. No difference was observed between the groups for stroke recurrence, vascular events, haemorrhage or death. At 6 months of follow-up, AFDAS

Table 1 Clinical characteristics of patients (n (%) or median (IQR))

	No atrial cardiomyopathy (n=79 (44%))	Atrial cardiomyopathy (n=104 (56%))	P
Risk factors			
Age, years	62.89 (54.94–71.33)	75.21 (64.97–81.87)	**<0.001**
Female sex	31 (39.20)	48 (46.20)	0.350
BMI, kg/m^2	26.49 (23.84–29.39)	26.24 (23.13–29.25)	0.500
Obesity (BMI>30 kg/m^2)	16 (20.30)	22 (21.20)	0.882
High blood pressure	35 (44.30)	69 (66.30)	**0.003**
Hypercholesterolaemia	23 (29.10)	34 (32.70)	0.605
Diabetes	23 (29.10)	27 (26.00)	**0.047**
Active smoking	20 (25.30)	20 (19.20)	0.324
Alcohol consumption	9 (11.40)	8 (7.70)	0.393
Obstructive sleep apnoea	6 (7.60)	12 (11.50)	0.375
Previous kidney failure	1 (1.30)	1 (1.00)	1
Previous cancer	12 (15.20)	15 (14.40)	0.885
Recent infection (<1 month)	2 (2.50)	7 (6.70)	0.303
Cardiovascular history			
Stroke or TIA	13 (16.50)	20 (19.20)	0.629
Peripheral artery disease	0 (0.00)	3 (2.90)	0.260
Heart failure	0 (0.00)	5 (4.80)	0.071
Cardiac valve disease	11 (13.90)	37 (35.60)	**0.001**
Coronary artery disease	2 (2.50)	12 (11.50)	**0.023**
Clinical data at admission			
Systolic pressure, mm Hg	155 (140–173.00)	161 (139–181)	0.453
Diastolic pressure, mm Hg	90 (78.00–97.00)	84 (74.00–92.00)	0.013
Heart rate, bpm	80 (67.75–90.50)	75 (67.00–83.25)	0.099
NIHSS score	4 (1.00–7.00)	4 (3.00–7.00)	**0.040**
CHA_2DS_2VASc *score*	2 (0.00–3.00)	3 (2.00–4.00)	**<0.001**
CHA_2DS_2VASc score≥2	41 (51.90)	86 (82.70)	**<0.001**
Revascularisation			
IV thrombolysis or mechanical thrombectomy	4 (5.10)	12 (11.50)	0.125

Bold face values signfies p<0.05
BMI, body mass index; bpm, beat per minute; IQR, interquartile range; IV, intravenous; NIHSS, National Institute of Health Stroke Scale; SR, sinus rhythm; TIA, transient ischaemic attack.

was more often found in the AC group than in non-AC patients (32.7% vs 13.9%, p=0.003) (table 3).

Multivariate statistical analysis for associated factors of AC

After multivariate backward stepwise logistic regression, CRP >3 mg/L (OR (95% CI) 2.60 (1.30 to 5.21), p=0.007) and age (OR (95% CI) 1.07 (1.04 to 1.1), p<0.001) were found to be independently associated with AC (table 4).

Multivariate analysis for associated factors of AFDAS

The characteristics significantly associated with AFDAS after univariate analysis were age (OR 1.08 (CI 1.04 to 1.12) p<0.001) female sex (OR 2.19 (CI 1.11 to 4.35) p=0.024), diastolic blood pressure (OR 0.97 (CI 0.95 to 0.99) p=0.022), AC (OR 3.01 (CI 1.41 to 6.40) p=0.004), LAVI >34 mL/m² (OR 2.96 (CI 1.48 to 5.95) p=0.002), admission NIHSS (OR 1.05 (CI 1.002 to 1.118) p=0.041) and superficial middle cerebral artery stroke (OR 2.27 (CI 1.14 to 4.53) p=0.020) (table 5).

In the multivariate model 1 (LAVI >34 mL/m² not included because of the presence of left atrial diameter in AC definition), age and NIHSS were independently associated with AFDAS (OR 1.08 (CI 1.48 to 1.13) p<0.001 and OR 1.07 (1.005 to 1.13) p=0.035, respectively), but AC was not. In the multivariate model 2 without AC but including the guidelines recommended left atrial dilatation definition (LAVI >34 mL/m²), age and LAVI >34 mL/m² were

Table 2 Biological, imaging and electrocardiographic characteristics of patients at admission (n(%) or median (IQR))

	No atrial cardiomyopathy (n=79 (44%))	Atrial cardiomyopathy (n=104 (56%))	P
Biological data			
CRP>3, mg/mL	23 (29.10)	48 (46.20)	**0.019**
Creatinine, µmol/L	72 (61.00–86.00)	76.50 (63.50–91.75)	0.174
Troponin>0.02 ng/L	3 (3.80)	20 (19.40)	**0.002**
NT-pro-BNP, pg/mL	83 (44.00–128.00)	515.50 (252.50–1266.00)	**<0.001**
NT-pro-BNP≥250 pg/mL	0 (0.00)	79 (76.00)	**<0.001**
Hba1c, %	5.80 (5.50–6.10)	5.80 (5.60–6.10)	0.350
LDL cholesterol, mmol/l	3.09 (2.41–3.86)	2.70 (1.95–3.44)	0.017
Haemoglobin, g/dl	14.60 (13.40–15.40)	13.80 (12.60–14.70)	**0.006**
Leukocytes, g/dl	8.00 (6.60–10.40)	8.55 (6.83–10.50)	0.419
Platelets, g/dl	252 (215–295)	227 (188–282)	0.069
TSH (UI/l)	1.56 (0.80–2.14)	1.29 (0.77–2.05)	0.299
Imaging data			
Multi-territory stroke	6 (7.6)	14 (13.5)	0.208
Vertebrobasilar stroke	27 (34.2)	35 (33.70)	0.941
Bilateral stroke	6 (7.60)	13 (12.50)	0.281
Insular stroke	8 (10.10)	23 (22.10)	**0.003**
Cerebellar stroke	6 (7.60)	13 (12.50)	0.281
Thalamic stroke	5 (6.30)	6 (5.80)	0.875
Anterior choroidal stroke	5 (6.30)	4 (3.80)	0.503
Posterior fossa stroke	15 (19.00)	25 (24.00)	0.413
Superficial MCA stroke	24 (30.40)	62 (59.60)	**<0.001**
Deep MCA stroke	27 (34.20)	21 (20.20)	**0.033**
ACA stroke	2 (2.50)	7 (6.70)	0.696
Superior PCA stroke	9 (11.40)	10 (9.6)	0.808
Choroidal stroke	5 (6.30)	4 (3.80)	0.503
Mesencephalic stroke	3 (3.80)	2 (1.90)	0.653
Pontine stroke	6 (7.60)	12 (11.50)	0.375
Bulbar stroke	2 (2.50)	2 (1.90)	1
Other	4 (5.10)	0 (0.00)	**0.033**
ECG data			
P-wave duration downwards, ms	40 (40.00–40.00)	60 (40.00–60.00)	**<0.001**
P-wave duration, ms	85 (80.00–100.00)	90 (80.00–110.00)	0.160
P-wave maximum duration, ms	100 (100.00–120.00)	120 (100.00–120.00)	0.059
PTFV1, mV.ms	0 (0–4)	4 (0–6)	**<0.001**
PTF≥5 mv.ms	0 (0.00)	47 (45.2)	**<0.001**
PR duration, ms	170 (149.00–186.50)	170 (151.00–194.00)	0.574
QRS duration, ms	90 (84.00–98.00)	92 (82.00–107.00)	0.286
Corrected QTc duration, ms	424.50 (411.25–443.50)	433.00 (412.50–447.50)	0.358
Echocardiographic data			
LA volume, mL	45.00 (35.00–59.00)	56.65 (41.07–76.32)	**0.001**
LAVI, mL/m²	25.45 (18.71–31.07)	32.02 (22.21–42.57)	**<0.001**
LAVI>34 mL/m²	12 (6.5)	47 (25.7)	**<0.001**
LA diameter, cm	3.60 (3.20–3.90)	3.80 (3.30–4.20)	**0.041**

Continued

Table 2 Continued

	No atrial cardiomyopathy (n=79 (44%))	Atrial cardiomyopathy (n=104 (56%))	P
LADI, cm/m²	1.88 (1.69–2.05)	2.03 (1.81–2.28)	**0.002**
LA surface, cm²	16.90 (15.00–21.00)	19.70 (16.35–25.10)	**0.001**
LVEF	60 (58.00–66.00)	60 (55.00–65.00)	**0.016**
PFO	10 (12.70)	9 (8.70)	0.465

ACA, anterior cerebral artery; AF, atrial fibrillation; CRP, C reactive protein; ECG, electrocardiogram; IQR, interquartile range; LA, left atria; LADI, left atrial diameter indexed; LAVI, left atrial volume indexed; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCA, middle cerebral artery; NT-pro-BNP, N-Terminal pro-B-type natriuretic peptide; PCA, posterior cerebral artery; PFO, patent foramen ovale; PTF, P-wave terminal force; RBBB, right bundle branch block; SR, sinus rhythm.

independently associated with AFDAS (OR 1.07 (CI 1.04 to 1.11) p <0.001 and OR 2.35 (CI 1.09 to 5.06) p=0.029, respectively) (table 5).

Multivariate analysis for associated factors of AC and AFDAS in cryptogenic patients of SAFAS

When restricting the multivariate analysis to cryptogenic patients of SAFAS (n=106), age and hypertension remained significantly associated to AC (OR 1.061 CI (1.02 to 1.10) p=0.002 and OR 2.59 CI (1.06 to 6.35) p=0.038 respectively). However, age was the only associated with AFDAS in the multivariate models 1 and 2 (OR 1.11 CI (1.04 to 1.19) p=0.002 and OR 1.11 CI (1.04 to 1.19) p=0.002 respectively).

DISCUSSION

AC definition: an unsolved issue

AC is frequent in ischaemic stroke patients when using the ARCADIA trial definition. Indeed, 57% of stroke patients in our study presented at least 1 criterion of ARCADIA AC definition.

AC may lead to a thrombogenic substrate even in the absence of AF and is an emerging concept that could explain the pathophysiology of ESUS. Kamel proposed a multimodal definition of AC based on three criteria. $PTFV_1$ (>5000 µV×ms) may be an electrical marker of atrial remodelling such as fibrosis and chronic elevated filling pressure and is associated with ischaemic stroke independently of AF.[14–17] NT-pro-BNP is a major independent risk marker for stroke, and especially of cardioembolic origin. The cut-off value of NT-proBNP >265.5 pg/mL had a specificity of 61.9% and a sensitivity of 88.2%.[18–21] Left atrial enlargement is associated with an increased risk of ischaemic stroke, and recurrent cardioembolic or ESUS.[22 23]

This study showed that the NT-pro-BNP >250 pg/mL criterion seems to be the leading one for identifying AC using ARCADIA definition (79% of the patients while only 4% of them had LADI >3 cm/m^2). We can, therefore, question how appropriate it is to establish the definition of AC mainly on a single parameter, especially as acute clinical settings (such as stroke) may increase the NT pro BNP serum concentration.[24] Thus, the role of the timing of NT-proBNP measurement on AC and AFDAS prediction should be carefully assessed and tested.

Left atrial dilatation is a major marker of AC. Given that 4% of AC patients had left atrial dilatation according to ARCADIA criteria, the choice of the LADI threshold used is questionable. In a congress communication on the preliminary results of ARCADIA, among 924 ESUS patients who met the inclusion criteria as of 16 July 2019, 251 met >1 AC criterion (164 NT-pro-BNP, 114 PTFV1, 4 echo).[25] Our results are, therefore, consistent with the criteria distribution found in this interim analysis of the

Table 3 Stroke aetiology and follow-up (n (%) or median (IQR))

	No atrial cardiomyopathy (n=79 (44%))	Atrial cardiomyopathy (n=104 (56%))	P
Aetiology and management			
Cryptogenic	47 (59.50)	59 (56.7)	0.708
Implantable loop recorder	29 (36.70)	41 (39.40)	0.760
Follow-up			
Atrial fibrillation at 6 months	11 (13.99)	34 (32.7)	**0.003**
Recurrent stroke/TIA at 6 months	1 (1.30)	5 (5.10)	0.229
Vascular event at 6 months	0 (0.00)	1 (1.00)	1
Haemorrhage at 6 months	1 (1.00)	1 (1.00)	0.694
Death	1 (1.30)	7 (6.70)	0.072

TIA, transient ischaemic attack.

Table 4 Univariate and multivariate backward stepwise analysis of atrial cardiomyopathy-associated factors

	Univariate			Multivariate		
Variable	OR	95% CI	p	OR	95% CI	p
Age	1.07	1.04 to 1.10	<0.001	1.073	1.04 to 1.10	<0.001
Hypertension	2.48	1.36 to 4.52	0.003			
Coronary artery disease	5.02	1.09 to 23.2	0.038			
Haemoglobin	0.79	0.66 to 0.94	0.009			
CRP>3 mg/mL	2.09	1.12 to 3.88	0.020	2.60	1.30 to 5.21	0.007
Troponin>0.02 ng/L	6.10	1.74 to 21.36	0.005			
Diabetes	2.17	1.00 to 4.70	0.050			

CRP, C reactive protein.

ARCADIA trial. While our results suggest that the major crossover between elevated NT-proBNP and atrial cardiopathy is a limitation of the ARCADIA trial, this remains to be determined based on final results of this study. LADI may be replaced with LAVI as it has been suggested that increased LAVI may be associated with stroke independently of the onset of AF.[24 26 27] Moreover, in a cohort of 538 cryptogenic cerebrovascular accidents, the left atrial reservoir strain <21.4% was found to add an incremental value to detect AFDAS. Further external study is required to validate the use of this strain threshold.[28 29] Assessment of atrial fibrosis burden by MRI may be another valid avenue to pursue in the identification of AC.[24]

AC-associated factors

After univariate regression analysis, age, hypertension, coronary artery disease, haemoglobin, CRP >3 mg/mL, troponin >0.02 ng/mL and diabetes mellitus were associated with AC definition. For statistic reason (collinearity), NT pro BNP, LAVI and LADI were not included in this analysis. The multivariate analysis identified age and CRP >3 mg/mL as independently associated with AC. In a recent meta-analysis based on 11 observational studies with 2009 ESUS patients, the prevalence of NT-pro-BNP>250 pg/mL did not differ among ESUS versus non-cardioembolic stroke patients (OR=0.73, 95% CI 0.39 to 1.35). Unfortunately, the design of the study did not permit a comparison of the prevalence of AC markers in ESUS and embolic stroke.[24] The elevation of NT-proBNP in non-embolic strokes raises the question of the association of inflammation and acute cardiac damage markers at the acute phase of stroke. It may also suggest that identification of AC by measuring NT-proBNP may be preferable remote from stroke. Inflammation plays a major role in the genesis of AF and may involve chronic remodelling (AC).[30 31]

Age was identified as an independently associated with AC in this study, but age is also associated with increased NT pro BNP blood concentration.[32] Thus, this may explain why NT pro BNP drives ARCADIA AC definition.

The marked association of AC with cardiovascular risk factors and cardiovascular history raises the hypothesis that the relationship between AC and recurrent stroke may be related to associated comorbidities rather than a causal relationship.[5 6] Further analysis of temporality

Table 5 Univariate and multivariate backward stepwise analysis of AFDAS-associated factors

	Univariate			Multivariate model 1			Multivariate model 2		
Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age	1.087	1.049 to 1.126	<0.001	1.088	1.048 to 1.130	<0.001	1.079	1.040 to 1.119	<0.001
Female sex	2.19	1.11 to 4.35	0.024						
Diastolic BP	0.97	0.95 to 0.99	0.022						
Superficial MCA stroke	2.27	1.14 to 4.53	0.020						
NIHSS	1.059	1.002 to 1.118	0.041	1.070	1.005 to 1.139	0.035			
AC	3.01	1.41 to 6.40	0.004				Not included		
LAVI>34 mL/m^2	2.96	1.48 to 5.95	0.002	Not included			2.351	1.090 to 5.067	0.029

Multivariate model 1 includes age, female sex, diastolic BP, sup MCA stroke, NIHSS and AC. Multivariate model 2 includes age, female sex, diastolic BP, sup MCA stroke, NIHSS and LAVI>34 mL/m^2.
AC, atrial cardiomyopathy as defined in ARCADIA; BP, blood pressure; LAVI, indexed left atrial volume; MCA, middle cerebral artery; NIHSS, National Institute of Health Stroke Scale.

and experimental trials are needed to better explain the pathophysiological significance of AC parameters.

AFDAS incidence and association with AC as defined in ARCADIA

AFDAS incidence at 6 months of follow-up in our population (24.6%) was in touch with the incidence described in a recent article that found an overall AFDAS detection rate of 23.7% after all external loop monitoring phases.[33] This diagnostics of AFDAS could be increased with use of implantable cardiac monitors. In this study, 32.7% of AC patients had AFDAS at follow-up. However, AC as defined in ARCADIA was not associated with AFDAS in the multivariate analysis, contrary to LAVI as defined by current guidelines (LAVI >34 mL/m^2). The predictive value of left atrial dilatation has already been demonstrated in our previous work on the role of cardiac CT angiography in the acute stroke imaging protocol.[34] These results taken together suggest that AC as defined in ARCADIA trial may lack sensitivity and specificity to target the patients who will benefit from an anticoagulant therapy.

Limitations

This study has certain limitations. First, it was a single-centre study which limited the number of inclusions. Second, contrary to ARCADIA trial, the SAFAS study was not limited to ESUS patients but included ischaemic stroke patients with no previous AF and without obvious aetiology at admission. Either way, when restricting the analysis to cryptogenic patients of SAFAS, AC as defined in ARCADIA trial was still not associated with AFDAS. Thus, AC-associated features and AFDAS rate may differ in a trial dedicated to ESUS patients. Third, we cannot exclude that this post hoc analysis on a predefined number of subjects (SAFAS study population) may have led to a lack of power to investigate the new hypothesis. However, this design also ensures the quality of the data that were collected prospectively during the original study. The sensitivity analysis did not reveal any difference in baseline characteristics between included and excluded patients, except for stroke location in superficial middle cerebral artery stroke. Moreover, the distribution of AC criteria (when available) was similar to that observed in the included patients. Finally, elevation of NT pro-BNP and CRP may be linked to blood samples taken during acute stroke admission.

CONCLUSION

AC as defined in ARCADIA is mostly based on NT pro BNP elevation (79% of patients) and is associated with age and inflammation. Moreover, these data suggest that AC based on this definition may be a suboptimal predictor of the risk of AFDAS. The ARCADIA trial, which aims to compare aspirin versus apixaban in ESUS patients with markers of AC, must, therefore, be interpreted in the light of these limitations.

Twitter Karim Benali @KarimBenali42, Thibaut Pommier @ThibautPommier and Charles Guenancia @GuenanciaC

Contributors Conceptualisation: RD, CG; data curation: LG, AS; formal analysis: RD CG; funding acquisition: CG; investigation: GDu, GDo; methodology: RD, AM; project administration: TP; resources: GDo, AM, CV; supervision: YBn CV, CG, GL; validation: MG, KB; visualisation: GL; writing—original draft preparation: RD; writing—review and editing: RD, CG; guarantor: CG.

Funding The SAFAS study was funded by an unrestricted grant from Microport CRM.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval The study was validated by a national ethics committee and was performed in accordance with the ethical principles of the Declaration of Helsinki and the recommendations of Good Clinical Practice (CPP Sud Méditerranée I n°2018-A00345-50). This study involves human participants and was approved by not applicable. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data available on request from the authors.

ORCID iDs

Romain Didier http://orcid.org/0000-0003-3735-9204
Yannick Bejot http://orcid.org/0000-0001-7848-7072

REFERENCES

1 Sanna T, Diener H-C, Passman RS, *et al*. Cryptogenic stroke and atrial fibrillation. *N Engl J Med* 2014;371:1261.
2 Hart RG, Catanese L, Perera KS, *et al*. Embolic stroke of undetermined source: a systematic review and clinical update. *Stroke* 2017;48:867–72.
3 Garnier L, Duloquin G, Meloux A, *et al*. Multimodal approach for the prediction of atrial fibrillation detected after stroke: SAFAS study. *Front Cardiovasc Med* 2022;9:949213.
4 Goette A, Kalman JM, Aguinaga L, *et al*. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Heart Rhythm* 2017;14:e3–40.
5 Kamel H. Does left atrial mechanical dysfunction contribute to a thrombogenic atrial myopathy? *JACC Cardiovasc Imaging* 2019;12:2428–30.
6 Kamel H, Okin PM, Longstreth WT, *et al*. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. *Future Cardiol* 2015;11:323–31.
7 Hart RG, Connolly SJ, Mundl H. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;379:987.
8 Diener H-C, Sacco RL, Easton JD, *et al*. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;380:1906–17.
9 Poli S, Meissner C, Baezner HJ, *et al*. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS) randomized trial – update of patient characteristics and study timeline after interim analysis. *Eur Heart J* 2021;42:ehab724.
10 Poli S, Keller T, Martus P, *et al*. Abstract 31: the ATTICUS randomized controlled trial - subgroup analyses. *Stroke* 2023;54:A31.

11 Kamel H, Longstreth WT Jr, Tirschwell DL, *et al*. The atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke (ARCADIA) randomized trial: rationale and methods. *Int J Stroke* 2019;14:207–14.
12 Sacco RL, Kasner SE, Broderick JP, *et al*. An updated definition of stroke for the 21st century. *Stroke* 2013;44:2064–89.
13 Lang RM, Badano LP, Mor-Avi V, *et al*. Recommendations for cardiac chamber Quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–70.
14 Kamel H, Soliman EZ, Heckbert SR, *et al*. P-wave morphology and the risk of incident ischemic stroke in the multi-ethnic study of atherosclerosis. *Stroke* 2014;45:2786–8.
15 Kohsaka S, Sciacca RR, Sugioka K, *et al*. Electrocardiographic left atrial abnormalities and risk of ischemic stroke. *Stroke* 2005;36:2481–3.
16 Kamel H, Hunter M, Moon YP, *et al*. Electrocardiographic left atrial abnormality and risk of stroke: the Northern Manhattan study. *Stroke* 2015;46:3208–12.
17 Kamel H, O'Neal WT, Okin PM, *et al*. Electrocardiographic left atrial abnormality and stroke subtype in ARIC. *Ann Neurol* 2015;78:670–8.
18 Folsom AR, Nambi V, Bell EJ, *et al*. Troponin T, NT-pro BNP, and incidence of stroke: the Atherosclerosis Risk in Communities (ARIC) Sudy. *Stroke J Cereb Circ* 2013;44:961–7.
19 Cushman M, Judd SE, Howard VJ, *et al*. N-terminal pro-B-type natriuretic peptide and stroke risk: the reasons for geographic and racial differences in stroke cohort. *Stroke* 2014;45:1646–50.
20 Longstreth WT Jr, Kronmal RA, Thompson JLP, *et al*. Amino terminal pro–B-type natriuretic peptide, secondary stroke prevention, and choice of Antithrombotic therapy. *Stroke* 2013;44:714–9.
21 Fonseca AC, Brito D, Pinho e Melo T, *et al*. N-terminal pro-brain natriuretic peptide shows diagnostic accuracy for detecting atrial fibrillation in cryptogenic stroke patients. *Int J Stroke* 2014;9:419–25.
22 Yaghi S, Moon YP, Mora-McLaughlin C, *et al*. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. *Stroke* 2015;46:1488–93.
23 Barnes ME, Miyasaka Y, Seward JB, *et al*. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. *Mayo Clin Proc* 2004;79:1008–14.
24 Stalikas N, Doundoulakis I, Karagiannidis E, *et al*. Prevalence of markers of atrial cardiomyopathy in embolic stroke of undetermined source: a systematic review. *Eur J Intern Med* 2022;99:38–44.
25 Elkind M, Longstreth W, Tirschwell D, *et al*. Abstract 26: predictors of atrial cardiopathy among patients in the Arcadia trial: an analysis of the first 924 patients. *Stroke* 2020;51:A26.
26 Tsang TS, Barnes ME, Bailey KR, *et al*. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc* 2001;76:467–75.
27 Tan BYQ, Ho JSY, Sia C-H, *et al*. Left atrial volume index predicts new-onset atrial fibrillation and stroke recurrence in patients with embolic stroke of undetermined source. *Cerebrovasc Dis* 2020;49:285–91.
28 Pathan F, Sivaraj E, Negishi K, *et al*. Use of atrial strain to predict atrial fibrillation after cerebral ischemia. *JACC Cardiovasc Imaging* 2018;11:1557–65.
29 Bhat A, Chen HHL, Khanna S, *et al*. Diagnostic and prognostic value of left atrial function in identification of cardioembolism and prediction of outcomes in patients with cryptogenic stroke. *J Am Soc Echocardiogr* 2022;35:1064–76.
30 Rochette L, Meloux A, Rigal E, *et al*. The role of osteoprotegerin in the crosstalk between vessels and bone: its potential utility as a marker of cardiometabolic diseases. *Pharmacol Ther* 2018;182:115–32.
31 Cao H, Li Q, Li M, *et al*. Osteoprotegerin/RANK/RANKL axis and atrial remodeling in mitral valvular patients with atrial fibrillation. *Int J Cardiol* 2013;166:702–8.
32 Hogenhuis J, Voors AA, Jaarsma T, *et al*. Influence of age on natriuretic peptides in patients with chronic heart failure: a comparison between ANP/NT-ANP and BNP/NT-proBNP. *Eur J Heart Fail* 2005;7:81–6.
33 Sposato LA, Chaturvedi S, Hsieh C-Y, *et al*. Atrial fibrillation detected after stroke and transient ischemic attack: a novel clinical concept challenging current views. *Stroke* 2022;53:e94–103.
34 Braillon A, Bernard A, Leclercq T, *et al*. Incremental value of the combined brain-cardiac CT protocol on prediction of atrial fibrillation after stroke. *Eur Stroke J* 2023;8:175–82.