



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}

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¹Cardiology, CHU Dijon Bourgogne, Dijon, France

²Dijon Stroke Registry, Department of Neurology, University Hospital Centre Dijon, Dijon, France

³PEC 2, Université de Bourgogne, Dijon, France

⁴Cardiology, 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 $\mu\text{V}\times\text{ms}$), 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 Cardiomyopathy 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=0.029).

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.

INTRODUCTION

Twenty to thirty percent of ischaemic strokes are of cardioembolic aetiology while up to 25% of them do not have an identifiable

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.

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 $\mu\text{V}\times\text{ms}$), 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/m²).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 \times 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

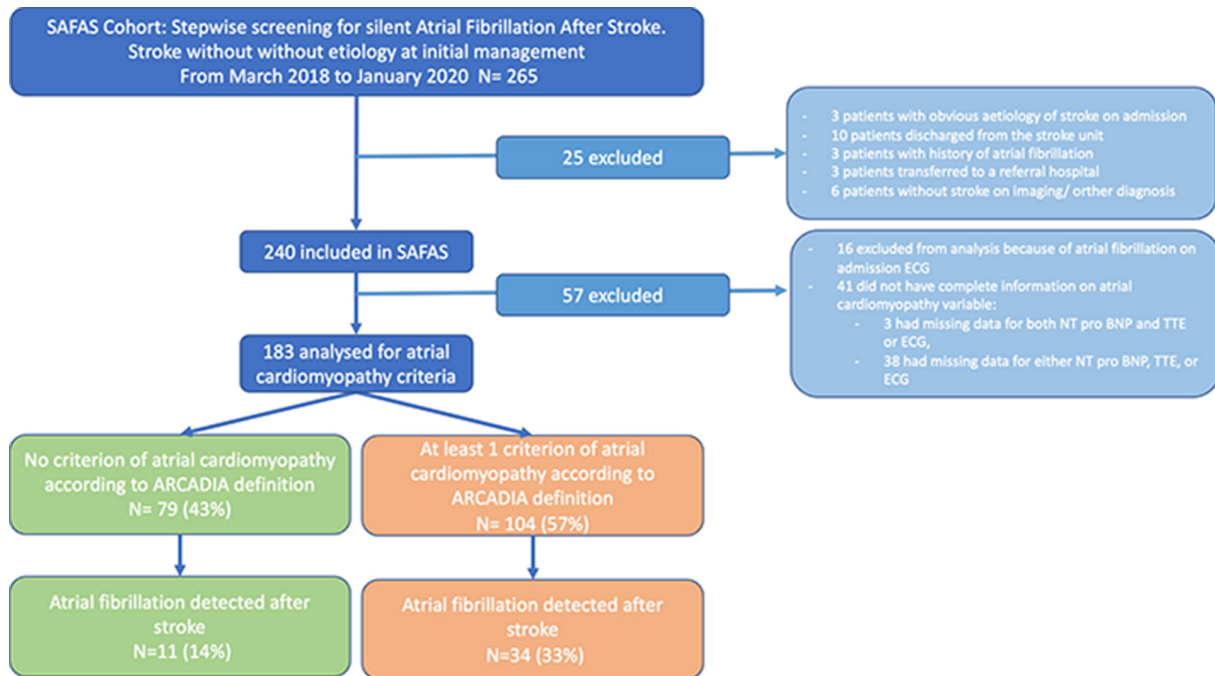


Figure 1 Flowchart. NT-proBNP, N-Terminal pro-B-type natriuretic peptide; SAFAS, Stepwise screening for silent Atrial Fibrillation After Stroke; ARCADIA, AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke.

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).

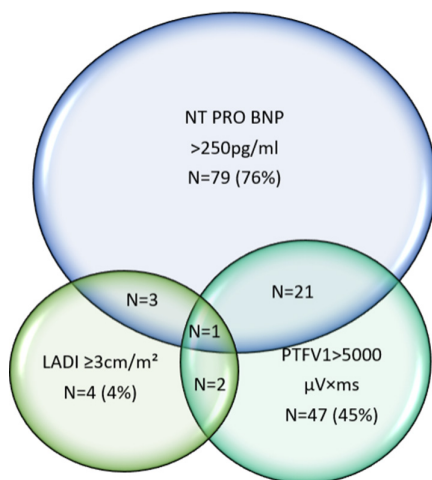


Figure 2 Distribution of the criteria for atrial cardiomyopathy (AC) according to ARCADIA definition in the SAFAS cohort. 104 patients had at least 1 AC criteria, and these were distributed as shown in the figure below. LADI, left atrial diameter index; NT-proBNP, N-Terminal pro-B-type natriuretic peptide; PTFV1, P-wave terminal force in lead V1; SAFAS, Stepwise screening for silent Atrial Fibrillation After Stroke; ARCADIA, 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 $\text{CHA}^2\text{DS}^2\text{-Vasc}$ 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 515.5pg/mL (252.5 to 1266.0) vs 83pg/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 (32.02mL/m² (22.21 to 42.57) vs 25.45mL/m² (18.71 to 31.07) and 19.7cm² (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 ₂ DS ₂ VASc score	2 (0.00–3.00)	3 (2.00–4.00)	<0.001
CHA ₂ DS ₂ VASc 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 signifies 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≥5mv.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/m ²	25.45 (18.71–31.07)	32.02 (22.21–42.57)	<0.001
LAVI>34 mL/m ²	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/m ²	1.88 (1.69–2.05)	2.03 (1.81–2.28)	0.002
LA surface, cm ²	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. PTFV₁ (>5000 $\mu V \times ms$) 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/m²). 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

Variable	Univariate			Multivariate		
	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 cardiomyopathy 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

Variable	Univariate			Multivariate model 1			Multivariate model 2		
	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	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/m². 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/m²). 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.

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

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ORCID iDs

Romain Didier <http://orcid.org/0000-0003-3735-9204>

Yannick Bejot <http://orcid.org/0000-0001-7848-7072>

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Supplementary data

Figure 1:

Distribution of the criteria for atrial cardiomyopathy (AC) according to ARCADIA definition in the excluded patients of the SAFAS cohort. 17 patients had at least 1 AC criteria (41%), and these were distributed as shown in the figure below. Abbreviations: NT-proBNP: N-Terminal pro-B-type natriuretic peptide. PTFV1: P-wave terminal force in lead V1. LADI: left atrial diameter index.

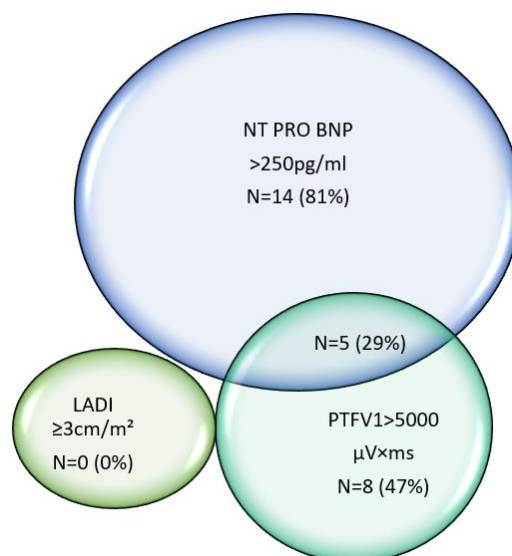


Figure 2:

Distribution of the criteria for atrial cardiomyopathy (AC) according to ARCADIA definition in the cryptogenic strokes of the SAFAS cohort. Abbreviations: NT-proBNP: N-Terminal pro-B-type natriuretic peptide. PTFV1: P-wave terminal force in lead V1. LADI: left atrial diameter index.

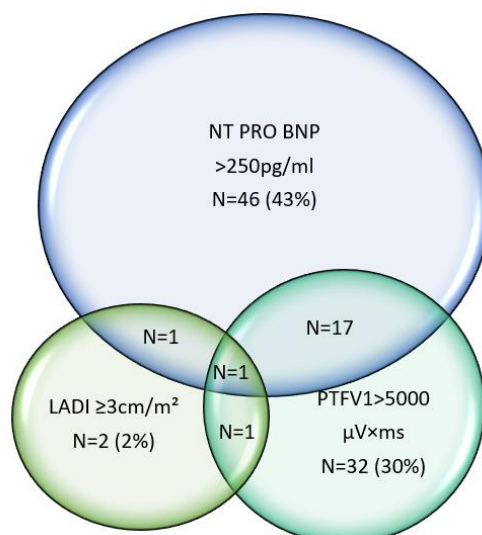


Table 1 :

Clinical characteristics of the excluded patients compared to the included population (n (%), mean \pm SD or median (IQR))			
	Included population (n=183)	Excluded population (n=41)	p
Risk factors			
Age, years	69.7 (58.2-78.9)	69.3 (59.2-77.9)	0.887
Female sex	80 (43.7)	22 (53.7)	0.248
Obesity (BMI>30kg/m ²)	37 (20.2)	11 (26.8)	0.351
High blood pressure	103 (56.3)	21 (51.2)	0.555
Hypercholesterolemia	56 (30.6)	10 (24.4)	0.430
Diabetes	37 (20.2)	6 (14.6)	0.412
Active smoking	40 (21.9)	7 (17.1)	0.496
Obstructive sleep apnea	17 (9.3)	4 (9.8)	0.926
Cardiovascular history			
Heart failure	5 (2.7)	3 (7.3)	0.164
Coronary artery disease	14 (7.7)	5 (12.2)	0.345
Clinical data at admission			
CHA ₂ DS ₂ VASc score	3 (1-4)	2 (1-4)	0.622
Imaging data			
MCA stroke	112 (61.2%)	29 (70.7%)	0.253
Superficial MCA stroke	86 (47%)	28 (68.3%)	0.014
Deep MCA stroke	48 (26.2)	12 (29.3)	0.691
ECG data			
P-wave duration downwards, ms	40 (40-60)	60 (40-60)	0.813
PTF \geq 5mv.ms	48 (98)	8 (100)	0.684
Biologic data			
NT pro BNP, pg/ml	918.5 \pm 826.5	856.3 \pm 921.3	0.938
Echocardiographic data			
LAVI, ml/m ²	27.7 (20.9-36.1)	27.1 (19.4-33.5)	0.569
LVEF, %	60 (55-66)	60 (56-65)	0.745
Abbreviations: IQR: interquartile range; NT-pro-BNP: N-Terminal pro-B-type natriuretic peptide; MCA: middle cerebral artery; ECG: electrocardiogram; LAVI: left atrial volume indexed; LVEF: left ventricular ejection fraction, PTF: P-wave terminal force; SD: standard deviation			