Early Midregional pro-Atrial Natriuretic Peptide predicts the occurrence of atrial fibrillation in stroke patients: Data from the BIOSIGNAL Study

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Background

- The use of rapidly measurable blood biomarkers may advance the identification of patients with underlying atrial cardiopathy, who may benefit more from direct oral anticoagulants compared to antiplatelets for secondary prevention.
- The objective of this study was to assess the incremental value of midregional pro-Atrial Natriuretic Peptide (MR-proANP) in identifying cardio-embolic stroke (CE stroke according to the TOAST criteria), newly diagnosed atrial fibrillation (AF) during hospitalization and on follow-up as well as recurrent vascular events after ischemic stroke.

Methods

- In this prospective, multicenter cohort study (2014-2017) we measured MR-pro ANP in ischemic stroke patients within 24h of symptoms onset. (By a sandwich immunoassay (BRAHMS AG, Berlin).
- Univariate and multivariate logistic regression models were fitted to estimate odds ratios for the magnitude and independence of the association of MR-proANP with each outcome measure.

Outcome measures

- CE stroke defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.
- AF was assessed– during hospitalization (at least 48 hours ECG) and 3 & 12 months after stroke (at least 7 days of ECG monitoring). AF was defined as at least 30 seconds of atrial arrhythmia.
- Composite outcome of recurrent stroke (including fatal stroke) and other cardiovascular death within 365 days after the index stroke.

Results

Baseline		
N (%)	1767	
Demographic data		
Age, median (IQR),	74.4	(63.8 – 82)
Women, <i>n</i> (%)	739	(42)
Medical history, <i>n</i> (%)		
Hypertension	1287	(73)
Diabetes mellitus	299	(17)
Smoking	398	(23)
Dyslipidemia	1206	(68)
History of atrial fibrillation	325	(18)
Chronic heart failure	111	(6)
Myocardial infarction	173	(10)
Previous stroke	304	(17)
Modified Charlson Index (comorbidity score points)	1	(0 – 2)
Clinical data, median (IQR)		
NIHSS on admission (points)	5	(2 – 11)
Treatment of stroke, <i>n</i> (%)		
IV thrombolysis	708	(40)
IA thrombolysis	142	(8)
Thrombectomy	335	(19)
Laboratory values, median (IQR)		
MR-proANP (pmol/l)	145.1	(83.8 – 248.9)
Creatinine (umol/l)	83	(69 –99)
Stroke etiology (TOAST) , <i>n</i> (%)^a		
Large vessel stroke	259	(15)
Cardioembolic stroke	587	(33)
Microangiopathic stroke	183	(10)
Other known	94	(5)
Unknown /cryptogenic stroke	648	(37)

Abbreviations: N= number, IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale; IA = intra-arterial; IV intravenous; MR = Magnetic Resonance; DWI = diffusion-weighted imaging; TOAST = Trial of Org 10172 in Acute Stroke Treatment; MR-proANP = midregional proatrial natriuretic peptide. Statistics: values are median (IQR) or percent (number). ^aBecause of rounding, percentages may not total 100.

Table 2 Multivariable Logistic and Cox Regression Models						
	Predictors	OR ^a	95% CI		P-Value	
Cardio - embolic stroke	Age	0.96	0.95	– 0.98	<0.01	
	Women	0.83	0.57	– 1.21	0.35	
	History of AF	10.84	6.35	– 18.5	<0.01	
	Smoking	0.67	0.43	– 1.03	0.07	
	Chronic Heart failure	1.87	0.83	– 4.22	0.13	
	Hyperlipidemia	0.62	0.43	– 0.90	0.01	
	NIHSS	1.01	0.98	– 1.04	0.40	
	MR-proANP	4.06	2.85	– 5.79	<0.01	
	Creatinine	0.73	0.42	– 1.29	0.28	
	Antihypertensive drugs	0.92	0.61	– 1.36	0.66	
	Small lesion size	0.83	0.57	– 1.22	0.35	
Newly detected AF	Age	1.00	0.99	– 1.02	0.66	
	Women	1.18	0.79	– 1.76	0.43	
	NIHSS	1.01	0.98	– 1.04	0.60	
	MR-proANP	3.28	2.28	– 4.73	<0.01	
	Creatinine	0.77	0.43	– 1.38	0.38	
	Small lesion size	0.60	0.39	– 0.94	0.03	
		HR ^a	95% CI		P-Value	
Recurrent ischemic event	Age	1.02	1.00	– 1.03	<0.01	
	Women	1.15	0.90	– 1.46	0.26	
	Previous cerebrovascular event	1.53	1.16	– 2.01	<0.01	
	NIHSS	1.07	1.06	– 1.09	<0.01	
	MR-proANP	1.28	1.02	– 1.54	0.03	
	Charlson- Index	1.07	1.00	– 1.14	0.04	
	Abbreviations: Af = Atrial fibrillation CI = confidence interval; resonance; MR-proANP = midregional proatrial natriuretic peptide; NA = not applicable; NIHSS on admission= NIH Stroke Scale; OR = odds ratio, HR = hatard ratio; AS5F score to detect paroxysmal atrial fibrillation after stroke including: age x 0.76 points/year, stroke Severity NIH-SS≤5 = 9 points, NIHSS>5 = 21 points					
^a ORs and hazard ratio refer to a 1-unit increase in the explanatory variable and to any 10-fold increase in MR-proANP and Creatinine (log transformed with a base of 10).						

Adding MR-proANP to the full regression model, the discriminatory accuracy improved significantly for

- CE stroke (AUC change from 0.85 [95% CI 0.83–0.88] to 0.86 [95% CI 0.83–0.88], *p* < 0.0071);
- newly detected atrial fibrillation** (AUC change from 0.62 [95% CI 0.59–0.65] to 0.72 [95%CI 0.69–0.75], *p* < 0.01);
- but not for recurrent ischemic event

LogMR-proANP improved the validated AS5F score for the prediction of AF after stroke.

MR-proANP levels ≥255 pmol/L had a specificity of 86% for the diagnosis CE stroke and 79% for newly detected AF

Conclusions

MR-proANP is an independent marker for cardio-embolic stroke etiology according to the TOAST criteria, newly detected atrial fibrillation and cardiovascular events up to one year after the index stroke. Therefore MR-proANP seems to be a good candidate to select patients for prolonged rhythm monitoring in clinical routine or even for oral anticoagulation in a randomized controlled trial.