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Original paper

Clinical and echocardiographic predictors of silent cerebral infarctions in patients with persistent atrial fibrillation

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Summary

Aim. The aims of the study were to evaluate prevalence of silent cerebral infarctions (SCI) and determine their clinical and echocardiographic predictors in patients with atrial fibrillation (AF).
Patients and methods. In prospective cross sectional study we examined 134 patients with non-valvular AF. Clinical examination, laboratory tests, transoesophageal, transthoracic echocardiography and multislice computed tomography of the brain were performed for all patients. According to current guidelines, SCI was defined as imaging ($\geq$3 mm) or neuropathological evidence of central nervous system infarction, without a history of acute neurological dysfunction attributable to the lesion.
Results. Silent cerebral infarctions were detected in 34.3% ($n = 46$) of patients, and infarctions $\geq$ 15 mm (mean diameter 31.3 mm) were detected in 11.2% ($n = 15$) of patients. Superficial SCI were found in 12.7% and basal SCI in 21.6% of cases. In multivariate analysis low creatinine clearance < 90 ml/min was independently associated with small basal SCI ($p = 0.04$). In univariate analysis age $\geq$ 65 years was significantly associated with basal SCI, $p = 0.004$, but not with SCI $\geq$ 15 mm or superficial SCI. The results of multivariate analysis showed that CHA_2DS_2VASc score was an independent predictor of superficial SCI; low left atrial appendage velocity (LAAV) < 30 cm/s was independently associated both with SCI $\geq$ 15 mm ($p = 0.03$) and superficial SCI ($p = 0.02$).
Conclusions. Large and superficial SCI were significantly and independently associated with low LAAV < 30 cm/s and other echocardiographic embolic risk factors and in case of absence of significant large arteries atherosclerosis may be considered as those of cardiac origin. Small basal SCI were associated with age and low creatinine clearance < 90 ml/min which was their independent predictor. CHA_2DS_2VASc score is useful for assessment of risk of cerebral infarctions even those without history of acute symptoms.

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Keywords: atrial fibrillation, silent cerebral infarction, computed tomography, left atrial appendage

Introduction

With the advent of highly sensitive techniques for brain imaging such as computed tomography (CT) or magnetic resonance imaging (MRI), a wide range of potentially abnormal findings such as asymptomatic lesions of different size and localization has been reported [1]. Although ubiquitous, their reported prevalence is variable, and their clinical significance has not been defined [2]. But the development of the concept of silent cerebral infarction (SCI) reflects the recognition that brain abnormalities, consistent with ischemic injury, can be identified pathologically or by neuroimaging in patients without a history of stroke or transient ischemic attack [3]. The strong connection of these findings with age and other stroke risk factors suggests that they may themselves be risk factors, manifestations of clinically important cerebrovascular disease and have some neuropathological consequences. The relationship of atrial fibrillation (AF) to SCI is still uncertain and reviewed in the limited number of studies [4–6]. The aims of this study were to try

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to differentiate potentially cardioembolic origin of silent cerebral infarctions from those that are caused by small vessel disease and to find out predictors of these groups of SCI.

Patients and methods

In prospective cross sectional study we examined 134 patients with non-valvular atrial fibrillation. The investigation conforms to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee, and all patients provided written informed consent. The mean age was 60.6 ± 0.8 years, mean left ventricular ejection fraction (LV EF) $55.3 \pm 0.9\%$, mean left atrial appendage emptying velocity (LAAV) 35.6 ± 1.5 cm/s, mean LV mass index 108.6 g/m^2, mean duration of AF history 3.7 ± 0.4 years, mean duration of arrhythmia episode 6.8 ± 1.4 months, mean CHA_2DS_2VASc score 2.2 ± 0.1, international normalized ratio (INR) 1.8 ± 0.6. There were 94 males (70.2%) and 40 (29.9%) females in the study. Diabetes was found in 31 (23.1%) of patients. All patients were without history of prior stroke. Overall 22.4% ($n = 30$) of patients had concomitant atrial flutter. Only 8.2% ($n = 11$) of patients had previous myocardial infarction. Arterial hypertension was present in 82.1% ($n = 110$) of patients. First episode of arrhythmia was registered in 26.5% ($n = 35$) of patients. In total, 15.7% ($n = 21$) of patients were with paroxysmal, 76.9% ($n = 103$) with persistent and 7.5% ($n = 10$) with permanent form of AF. All patients underwent 12-lead ECG, 24-hour ECG monitoring, and echocardiography.

CT scan acquisition and analysis

Noncontrast CT scans were obtained in all patients of the study before cardioversion attempt. Each scan was read by neurologists and radiologists who had no knowledge of the physical condition or clinical course of the patient, and their consensus interpretation was recorded. According to current recommendations silent cerebral infarction was defined as imaging ($\geq$3 mm) or neuropathological evidence of central nervous system infarction, without a history of acute neurological dysfunction attributable to the lesion [3]. SCIs were divided into large $\geq$15 mm (from the maximal lesion dimension in millimeters) and small <15 mm [7]; superficial (including infarctions in the cortex, centrum semiovale, and also multiple infarctions in superficial and deep regions) and deep or basal (the striatocapsular infarction in the basal ganglia, corona radiate, thalamus, cerebellum, pons).

Carotid duplex ultrasound

To rule out patients with carotid stenosis $\geq$ 50% we performed carotid duplex ultrasound studies in all cases. Intima-media thickness in millimeters and degree of stenosis was determined according to the North American Symptomatic Carotid Endarterectomy Trial [8].

Echocardiography

All patients underwent transthoracic and transoesophageal (TEE) echocardiography. The indication for TEE in all cases involved ruling out intracardiac thrombi before the cardioversion attempt. TEE was performed with multiplane probe with a 2–7 MHz transducer. During the TEE examination, special attention was paid to assess the presence of LA thrombi, severity of spontaneous echo contrast (SEC) and mean (average in six consecutive cardiac cycles) LAAV. A thrombus was considered to be present if a mass detected in the appendage or body of the atrium appeared to be distinct from the underlying endocardium, was not caused by pectinate muscles, and was detected in more than one imaging plane. SEC was defined as dynamic smoke-like echoes within the atrial cavity with the characteristic swirling motion that could not be eliminated by changes in the gain settings. The degree of SEC was characterized independently as absent 0, mild 1+, mild to moderate 2+, moderate 3+ or severe 4+ (sludge). The definition of mild, moderate, and severe SEC is reported elsewhere [9,10]. The following transthoracic echocardiographic measurements were taken by apical and parasternal views from 2-D mode tracings according to the recommendations of the American Society of Echocardiography [11]: left atrial volume index (ml/m^2), left atrial diameter (cm), bi-plane left ventricular end-diastolic volume index (ml/m^2), end-systolic volume index (ml/m^2) and LV EF (%). Volume indices were obtained by dividing the above-mentioned chamber volumes by body surface area. Left ventricular mass index (g/m^2) was calculated by the area–length method. End diastolic thickness of LV septal and inferior walls was measured in short-axis views. To assess LV filling pulsed-wave (PW) Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocity (cm/s) and in the apical views to obtain early diastolic velocity on the lateral and medial segment of the mitral annulus PW tissue Doppler imaging (TDI) was performed. TDI lateral mitral systolic velocity was also obtained to additionally assess LV systolic function [12].

Data analysis

Data are expressed as the mean ± standard deviation (SD). Differences between groups of patients with and without silent cerebral infarctions were analyzed with Pearson χ^2 for noncontinuous variables. Nonlinear logit stepwise regression was computed to establish relationship between a set of independent variables and silent cerebral infarctions. Odds ratio and ninety-five percent confidence intervals were calculated for the variance of the risk ratio [13]. All statistical analyses were performed using Statistica 10 statistical software for Windows (StatSoft Inc., Oklahoma, USA). Values of $p < 0.05$ were considered statistically significant.

Results

Characteristics of the patients

Silent cerebral infarctions were detected in 34.3% (n = 46) of patients, and in total infarctions ≥ 15 mm (mean diameter 31.3 mm) were detected in 11.2% (n = 15) of patients. Among patients with SCI 68.9% of patients had lesions in one hemisphere and 31.1% in both hemispheres. One-sided SCI were located more frequently in the right hemisphere 40% (n = 18) than in the left 28.9% (n = 13). One lesion was detected in 44.4% (n = 20) of patients, two lesions in 42.2% (n = 19) and four or more lesions in 13.3% (n = 6). The majority, 41.3% (n = 19) of SCI were found in striatopallidum and/or capsula interna or externa, 19.6% (n = 9) were cortical or located in centrum semiovale, 13.0% (n = 6) in corona radiate, 8.7% (n = 4) in cerebellum, thalamus, pons and 17.4% (n = 8) had multiple lesions in cortex, centrum semiovale and all mentioned regions. To reveal factors that were significantly associated with silent cerebral infarctions we divided them into groups. At first, we wanted to differentiate large non-lacunar SCI ≥ 15mm. Then, according to localization we divided all SCI into superficial 12.7% (n = 17), including cortical and/or located in centrum semiovale, and basal 21.6% (n = 29), including corona radiate, striatopallidum and/or capsula interna or externa, cerebellum, thalamus and pons. Relationship between those groups is significant and is shown in the Table 1.

Nevertheless the absence of history of acute symptoms some neurological deficit attributable to lesion was found during more detailed neurological examination in all patients with superficial SCI and SCI ≥ 15 mm. Baseline characteristics of the patients with different types of SCI are summarized in Table 2. There were no significant differences among the three groups comparing INR levels, age, CHA_2DS_2VASc score, duration of arrhythmia episode, clinical characteristics, echocardiographic parameters and such biochemical measurements as glucose and total cholesterol levels as well as creatinine clearance (CrCl). Diameter of the lesion was significantly larger in the groups of SCI ≥ 15 mm and superficial SCI compared to basal SCI, $p < 0.001$.

Table 3 shows that although patients with SCI were free from LAA thrombi, measurements that predispose to embolic origin of lesions (LAAV < 30 cm/s, LV thrombus, Sm < 7 cm/s, LV wall akinesis/hypokinesis, aortic arc plaque > 5 mm) were identified more frequently in the groups of SCI ≥ 15 mm and superficial SCI, that eventually will be continued in the estimation of predictors.

Risk factors for large silent cerebral infarction

Based on baseline results univariate analysis was performed, and the main predictors for all mentioned groups of SCI are summarized in Table 4. The main predictors of SCI ≥ 15 mm were LAAV < 30 cm/s, CHA_2DS_2VASc score ≥ 2, CrCl < 90 ml/min, Sm < 7 cm/s, LV wall akinesis/hypokinesis and aortic arc plaque > 5 mm. The main predictors of superficial SCI were LAAV < 30 cm/s, CHA_2DS_2VASc score ≥ 2 and fasting glucose ≥ 7 mmol/l. Interestingly age was not a predictor of SCI ≥ 15 mm and superficial SCI. Low renal function, Sm < 7 cm/s, LV wall akinesis/hypokinesis and aortic arc plaque were not predictors of superficial SCI.

On the other hand we found, that predictors for basal SCI were age ≥ 65 years, CrCl < 90 ml/min, aortic arc plaques > 5 mm, which in sum lead to non-embolic lesions, associated with artery disease. Analysis showed that age as a factor was significantly correlated with aortic arc plaques (r = 0.44, p = 0.0001), CrCl (r = –0.65, p = 0.0001) and systolic arterial pressure (r = 0.26,

Table 1.
Associations between different groups of silent cerebral infarctions

	SCI ≥ 15 mm	Pearson χ^2	p value
Superficial SCI (row %)	64.7	56.1	<0.0001
Basal SCI (row %)	26.7	0.25	0.6

SCI – silent cerebral infarctions.

Table 2.
Baseline characteristics of the patients with SCI ≥ 15 mm, superficial SCI and basal SCI

	Mean ≥ 15 mm ± SD (n = 15)	Mean superficial SCI ± SD (n = 17)	Mean basal SCI ± SD (n = 29)
Lesion diameter, mm	31.3 ± 18.5	26.2 ± 20.2	7.8 ± 6.0
INR	1.6 ± 0.7	1.6 ± 0.7	1.4 ± 0.3
CHA_2DS_2VASc	3.1 ± 1.6	3.0 ± 1.6	2.9 ± 1.6
Episode duration, months	9.6 ± 18	4.05 ± 6.6	5.4 ± 12.8
History of atrial fibrillation, years	3.1 ± 2.8	2.5 ± 2.3	5 ± 5.3
Age, years	63.9 ± 27.8	62.1 ± 8.6	66.0 ± 7.2
LV EDVind, ml/m^2	48.7 ± 6.7	52.5 ± 15.7	47.4 ± 12.0
LV ESVind, ml/m^2	22.9 ± 6.4	24.2 ± 9.2	21.4 ± 7.6
LV EF, %	53.9 ± 8.8	54.9 ± 8.7	55.4 ± 8.1
Em, cm/s	11.6 ± 3.8	10.9 ± 3.7	11.4 ± 2.8
Sm, cm/s	6.8 ± 1.75	7.03 ± 1.7	7.6 ± 1.7
E/Em	9.8 ± 3.8	10.5 ± 3.6	9.9 ± 4.5
LAind, ml/m^2	38.8 ± 5.8	39.5 ± 8.5	38.4 ± 7.2
LAD, cm	4.9 ± 0.49	4.9 ± 0.5	4.7 ± 0.5
MMI, g/m^2	106.7 ± 22.4	114.3 ± 29.8	107.6 ± 27.5
LAAV, cm/s	27.7 ± 6.6	27.4 ± 6.2	32.8 ± 13.1
Fasting glucose, mmol/l	6.5 ± 1.9	6.5 ± 1.9	6.1 ± 1.7
Total cholesterol, mmol/l	5.2 ± 1.13	4.9 ± 1.0	5.5 ± 1.2
SAP, mmHg	135 ± 24.8	138 ± 17.5	135.9 ± 20.2
DAP, mmHg	84.2 ± 414.5	83.7 ± 9.5	86.7 ± 14.0
IMT, mm	0.11 ± 0.02	0.11 ± 0.02	0.1 ± 0.02
CrCl, ml/min	76.6 ± 14.3	88.8 ± 32.1	72.3 ± 24.4
BMI, m^2	30.8 ± 4.4	30.9 ± 4.4	31 ± 7.5

LAind – left atrial volume index; LAD – left atrial diameter; INR – international normalized ratio; LV – left ventricular; EDVind – left ventricular end-diastolic volume index; ESVind – left ventricular end-systolic volume index; EF – ejection fraction; Em – tissue Doppler early diastolic velocity on the lateral segment of mitral annulus; Sm – tissue Doppler systolic velocity on the lateral segment of mitral annulus; MMI – myocardial mass index; LAAV – left atrial appendage velocity; SAP – systolic artery pressure; DAP – diastolic artery pressure; IMT – intima media thickness; CrCl – creatinine clearance; BMI – body mass index.

Table 3.
Representation in percentage of some characteristics of the patients with SCI ≥ 15 mm, superficial SCI and basal SCI

	SCI ≥ 15 (n = 15)	Superficial SCI (n = 17)	Basal SCI (n = 29)
Age ≥ 65, years	40%	35.3%	58.6%
Females	46.7%	35.3%	37.9%
Diabetes	13.3%	23.5%	27.6%
Arterial hypertension	86.7%	94.1%	86.2%
First episode	20%	23.5%	17.9%
LAA thrombus	0%	0%	0%
SEC 4+	8.3%	7.7%	14.8%
LAAV < 30 cm/s	76.9%	78.6%	37.0%
LV thrombus	6.7%	5.9%	3.5%
CHA_2DS_2VASc score ≥ 2	93.3%	88.2%	82.8%
LV EF < 45%	20%	17.7%	13.8%
Sm < 7 cm/s	73.3%	58.8%	37.9%
Aortic arc plaques > 5 mm	53.9%	42.9%	44.4%
CrCl < 90 ml/min	84.6%	66.7%	82.1%
LV wall akinesis/hypokinesis	53.3%	47.6%	31.0%

LAA – left atrial appendage; LAAV – left atrial appendage velocity; SEC – spontaneous echo contrast; LV – left ventricular; EF – ejection fraction; Sm – tissue Doppler systolic velocity on the lateral segment of mitral annulus; CrCl – creatinine clearance.

Table 4.
Odds ratios and 95% confidence intervals for factors associated with each CT group of SCI

	SCI ≥ 15 mm		Superficial SCI		Basal SCI	
	OR	*p* value	OR	*p* value	OR	*p* value
Age ≥ 65 years	1.2 (0.15–2.3)	0.7	0.97 (–0.006–2)	0.98	3.4 (2.6–4.2)	0.004
LAAV < 30 cm/s	4.9 (3.6–6.2)	0.01	5.5 (4.2–6.8)	0.006	0.7 (–0.2–1.5)	0.4
CrCl < 90 ml/min	4.8 (3.3–6.4)	0.03	1.63 (0.5–2.8)	0.4	4.8 (3.8–5.8)	0.002
Fasting glucose ≥ 7 mmol/l	1.9 (0.6–3.2)	0.3	3.8 (2.6–4.9)	0.03	0.42 (–1–1.9)	0.3
Aortic arc plaques > 5 mm	3.34 (2.2–4.5)	0.035	2 (0.9–3.1)	0.2	2.5 (1.7–3.3)	0.04
Sm < 7 cm/s	3.5 (2.3–4.7)	0.032	1.7 (0.7–2.7)	0.3	0.6 (–0.2–1.4)	0.2
CHA_2DS_2VASc score ≥ 2	8.8 (6.8–10.9)	0.01	4.7 (3.2–6.2)	0.03	3.2 (2.2–4.2)	0.02
LV wall akinesis/hypokinesis	2.9 (1.9–4)	0.045	2.2 (1.2–3.2)	0.12	1 (0.17–1.85)	0.98

CrCl – creatinine clearance; LAAV – left atrial appendage velocity; LV – left ventricular; OR – odds ratio; Sm – tissue Doppler systolic velocity, on the lateral segment of mitral annulus.

Table 5.
Logistic multivariate regression models for the different groups of SCI

	SCI ≥ 15 mm		Superficial SCI		Basal SCI	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
CHA_2DS_2VASc score	1.5 (0.9–2.5)	0.1	1.68 (1.1–2.7)	0.03	1.1 (0.8–1.6)	0.57
Age ≥ 65 years	0.3 (0.1–1.6)	0.16	0.36 (0.1–1.7)	0.19	1.5 (0.5–4.6)	0.51
LV EF < 45%	0.5 (0.1–2.4)	0.38	0.48 (0.1–2.1)	0.33	0.7 (0.2–2.6)	0.55
LAind ≥ 45 ml/m^2	0.3 (0.04–1.6)	0.14	0.4 (0.1–1.85)	0.24	1.1 (0.3–3.5)	0.94
LAAV < 30 cm/s	5.1 (1.2–22)	0.03	5.2 (1.35–20)	0.02	0.57 (0.2–1.7)	0.31
AAP > 5 mm	1.6 (0.4–7)	0.53	1.1 (0.3–4.4)	0.92	1.4 (0.5–4.2)	0.56
CrCl < 90 ml/min	4 (0.73–21.8)	0.11	1.4 (0.3–5.7)	0.66	3.6 (1.0–12.8)	0.04

AAP – aortic arc plaques; CI – confidence interval; CrCl – creatinine clearance; EF – ejection fraction; LAind – left atrial index; LAAV – left atrial appendage velocity; OR – odds ratio.

$p = 0.008$) – all factors that may be associated with lacunar non-embolic infarctions [14].

We performed logistic regression multivariate analysis using model that included clinical and echocardiographic parameters to evaluate independent predictors that were associated with different groups of silent cerebral infarctions (Table 5). The aim was to figure out balanced model which includes factors with potentially different mechanism of the action. The results of this analysis showed that CHA_2DS_2VASc score was an independent predictor of superficial SCI; low LAAV < 30 cm/s was an independently associated both with SCI ≥ 15 mm ($p = 0.03$) and superficial SCI ($p = 0.02$). In a case of basal SCI creatinine clearance was only independent predictor ($p = 0.04$).

Discussion

Prevalence of silent cerebral infarctions and role of different risk factors in their prediction

The prevalence of SCI in our study was 34.3%, almost the same as in the CT study of a Brott et al., Ezekowitz et al., MRI study of Hara et al. [4–6]. Many authors studied predictors of all infarctions, but we concentrated on predictors of each group. In our study different types of silent cerebral infarctions were associated with different predictors. As shown in Table 1, opposed to basal SCI, superficial SCI and SCI ≥ 15 mm significantly correlated with each other and statistical analysis revealed the same predictors in these two groups. We found that large SCI ≥ 15 mm and superficial SCI (including cortical and/or located in centrum semiovale except corona radiate) were significantly associated with impaired LAA contractility (LAAV < 30 cm/s) in multivariate analysis and additionally with LV wall motion abnormalities, LV systolic disfunction (Sm < 7 cm/s), aortic arc plaques > 5 mm for SCI ≥ 15 mm in univariate analysis. These results go in accordance with hypothesis that microemboli from the heart or atherosclerotic plaques in major arteries may preferentially propagate to cortical, subcortical and external border zones, which have lower perfusion than other areas of the vasculature and thus, a limited ability to wash out these emboli [15–18]. The CHA_2DS_2VASc score does not imple-

ment echocardiographic data into the decision algorithm for antithrombotic therapy, but low LAA velocity is widely accepted as an independent predictor of stroke [19]. SPAF III investigators do consider LAA velocity $\leq$ 20 cm/s as a risk factor for thromboembolism [20]. The present study underlines these findings, demonstrating that less severe LAA dysfunction with velocity < 30 cm/s can be counted as an independent risk factor for large and superficial brain lesions. This is in accordance with studies performed by Thambidorai et al., where TEE provided significant incremental value in predicting thromboembolism compared with clinical characteristics [10,21].

On the other hand, basal SCI were significantly associated with impaired renal function CrCl < 90 ml/min in multivariate analysis and additionally with advanced age $\geq$ 65 years and plaques in the aortic arc > 5 mm in univariate analysis. Vermeer et al. in the analysis of the Rotterdam Scan Study made a conclusion that SCI are 5 times as prevalent as symptomatic brain infarctions in the general population and their prevalence increases with age [14]. In our study age $\geq$ 65 years was moderately associated with CrCl < 90 ml/min ($r = 0.4$). Vogels et al. in large review showed that glomerular filtration rate (GFR) was associated with SCI (odds ratio GFR, continuous variable: 0.96–0.99 per ml/min/1.73 m^2) [22]. Ikram et al. also showed on 483 patients of the Rotterdam study that persons with lower GFR more often had lacunar infarctions, although the association was not significant [23]. In cross-sectional study of 625 community-based Japanese elderly Wada et al. demonstrated that the association between the presence of chronic kidney disease and lacunar infarction was statistically significant (odds ratio 1.86) and independent from hypertension and diabetes [24]. These findings and that the group of basal SCI was not associated with low LAA velocity, LV systolic dysfunction and LV wall motion abnormalities suggest that small, basal infarctions in patients with AF are caused mostly by small arterial stenosis or occlusion, or haemodynamic compromise, because arteries that supply deep regions have the lowest perfusion pressure and little collateral supply [15].

The role of CHA_2DS_2VASc score in assessment of the risk of overt stroke in patients with AF is indispensable. However, there is very scant data concerning association of CHA_2DS_2VASc score and SCI. In one small study of 71 patients with AF Kobayashi et al. showed that the number of cortical and subcortical SCI significantly correlated with $CHADS_2$ score [25].

In the Framingham study stroke risk profile was strongly associated with white matter hyperintensity volume [26]. In our study we also found that CHA_2DS_2VASc score $\geq$ 2 was significantly correlated with all groups of SCI, which reflects the impact of the sum of each risk factors on the burden of disease and its outcome.

State of anticoagulation therapy in the study patients

Although in the aims of the study we did not intend to reveal the association between anticoagulation therapy and SCI, one interesting question is why mean INR in our patients was below the therapeutic window? By questionnaires, all patients were asked few questions concerning their anticoagulant or antithrombotic therapy. 1. What medication they use for this purpose and how long? 2. Those patients who were on warfarin therapy were asked about rate of INR measurements and about what they usually do if INR is not in the therapeutic window.

We found that at the time of investigation 37.8% of patients never used neither warfarin nor aspirin; 40.7% were on warfarin therapy; 6.7% used novel anticoagulants and 14.8% used aspirin. Moreover, 48.2% of the patients (with mean arrhythmia history of 3.4 years and mean duration of episode 6.6 months) in this study did not know anything about warfarin. Among those who used warfarin mean duration of therapy was 8.3 ± 16 months but the mean INR was 1.76 ± 0.6. We found that only 12.7% of patients measured INR every week, 21.8% every month, 30.9% measured INR irregularly, 11% did not perform INR measurement at all and 23.6% of patients who were on warfarin did not know what is INR. On the question "What do you do if INR measurement is not satisfactory?" 46% of the patients on warfarin answered that they do nothing; 2.7% answered that they adjusted the dose by themselves and 51.3% of patients answered that they ask physician's advice about dosage adjustment. Totally, only 30.8% of patients who were on warfarin had INR $\geq$ 2 on the moment of inclusion in the study. That is why we think we had not enough data concerning influence of anticoagulant therapy on the end points of the study. The other limitations of the study were that since we had searched for lesions without history of acute symptoms, we cannot definitely know the age of SCI, and that influence of therapy better to assess in the longitudinal, not in the transversal study.

Clinical application

In his editorial Pisters et al. consider the possibility of performing a cerebral MRI in patients with "score 0 or 1" to reveal clinically silent cerebral infarctions or small vessel disease, and

thereby re-classifying them from low- to high-stroke-risk patients [27]. But role of SCI as a risk factor of subsequent symptomatic stroke in patients without history overt stroke is controversial. In SPINAF study only angina on exertion was significant predictor of stroke ($p = 0.017$), whereas SCI contributed very little $p = 0.47$ [5]. But population-based studies showed different results. Rotterdam Scan Study – population-based prospective cohort study among 1,077 elderly people showed that the presence of silent brain infarctions increased the risk of stroke more than 3-fold, independently of other stroke risk factors [4]. 3,324 participants in the Cardiovascular Health Study without a history of stroke showed that those 28% of patients with silent infarctions, adjusted relative risk of incident stroke increased with multiple (more than one) silent infarctions, hazard ratio 1.9 (1.2–2.8) [28]. But should we seek for risk stratification for primary prevention of overt stroke in case of "silent" infarction with presumably cardioembolic origin? May be the fact that these lesions are associated with neuropathological consequences, an adverse prognosis for cognitive and functional decline provides the rationale for their inclusion with frank symptomatic stroke as one important measure of health in populations [3]. Maybe future efforts have to be focused to prove that treatment with anticoagulants can significantly decrease incidence of SCI with presumably embolic origin. Nevertheless, having little data which is available to assess all pro and cons it seems to be rational to consider anticoagulation in case of large and superficial "silent" brain lesions, which in detailed neurological examination become symptomatic too often.

Conclusions

Large and superficial SCI were significantly and independently associated with low LAA velocity < 30 cm/s and other echocardiographic embolic risk factors and in case of absence of significant large arteries atherosclerosis may be considered as those of cardiac origin. Small basal SCI were associated with age and low creatinine clearance < 90 ml/min which was their independent predictor. CHA_2DS_2VASc score is useful for assessment of risk of cerebral infarctions even those without history of acute symptoms.

Conflict of interest

None declared.

References

[1] Brant-Zawadzki M, Fein G, Van Dyke C, Keirman R, Davenport L, De Groot J. MR imaging of the aging brain. *Am J Neuroradiol* 1985;6:675–82.

[2] Price T, Manolio T, Kronmal R, Kittner S, Yue N, Robbins J, Anton-Culver H. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults: the Cardiovascular Health Study: CHS Collaborative Research Group. *Stroke* 1997;28:1158–64.

[3] Sacco R, Kasner S, Broderic J, Caplan L, Connors J, Culebras A, et al. An updated definition of stroke for the 21st century. A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:2064–89.

[4] Brott T, Tomsick T, Feinberg W, Johnson C, Biller J, Broderick J, et al. Baseline silent cerebral infarction in the Asymptomatic Carotid Atherosclerosis Study. *Stroke* 1994;25:1122–9.

[5] Ezekowitz M, James K, Davenport J, Broderick J, Gupta S, Thadani V, et al. Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *Circulation* 1995;92:2178–82.

[6] Hara M, Ooie T, Yufu K, Tsunematsu Y, Kusakabe T, Ooga M, et al. Silent cortical strokes associated with atrial fibrillation. *Clin Cardiol* 1995;18:573–4.

[7] Russmann H, Vingerhoets F, Ghika J, Maeder P, Bogousslavsky J. Acute infarction limited to the lenticular nucleus: clinical, etiologic, and topographic features. *Arch Neurol* 2003;60(3):351–5.

[8] Ferguson G, Eliasziw M, Barr H, Clagett G, Barnes R, Wallace M, et al. Symptomatic carotid endarterectomy trial surgical results in 1415 patients for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators. *Stroke* 1999;30:1751–8.

[9] Vincelj J, Sokol I, Jaksic O. Prevalence and clinical significance of left atrial spontaneous echo contrast detected by transesophageal echocardiography. *Echocardiography* 2002;19:319–24.

[10] Kleemann T, Becker T, Strauss M, Schneider S, Seidl K. Prevalence and clinical impact of left atrial thrombus and dense spontaneous echo contrast in patients with atrial fibrillation and low $CHADS_2$ score. *Eur J Echocardiogr* 2009;10(3):383–8.

[11] Lang R, Bierig M, Devereux R, Flachskampf F, Foster E, Pellikka P, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–63.

[12] Nagueh S, Appleton C, Gillebert T, Marino P, Oh J, Smiseth O, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22(2):107–33.

[13] Kutner M, Nachtsheim C, Neter J. *Applied Linear Regression Models*, 4th ed. 2004.

[14] Vermeer S, Hollander M, van Dijk E, Hofman A, Koudstaal P, Breteler M, Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke* 2003;34:1126–9.

[15] Mangla R, Kolar B, Almast J, Ekholm S. Border zone infarcts: pathophysiologic and imaging characteristics. *RadioGraphics* 2011;31:1201–14.

[16] Pollanen M, Deck J. The mechanism of embolic watershed infarction: experimental studies. *Can J Neurol Sci* 1990;17(4):395–8.

[17] Mauro P, Evangelista A, Nihoyannopoulos P, Flachskampf F, Athanassopoulos G, Colonna P, et al. Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr* 2010;11:461–76.

[18] Yonemura K, Kimura K, Minematsu K, Uchino M, Yamaguchi T. Small centrum ovale infarcts on diffusion-weighted magnetic resonance imaging. *Stroke* 2002;33:1541–4.

[19] Camm J, Kirchhof P, Lip G, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31(19):2369–429.

[20] Zabalgoitia M, Halperin J, Pearce L, Blackshear J, Asinger R, Hart R. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. *J Am Coll Cardiol* 1998;31(7):1622–6.

[21] Thambidorai S, Murray R, Parakh K, Shah T, Black I, Jasper S, et al. Utility of transesophageal echocardiography in identification of thrombogenic milieu in patients with atrial fibrillation (an ACUTE ancillary study). *Am J Cardiol* 2005;96:935–41.

[22] Vogels S, Emmelot-Vonk M, Verhaar H, Koek H. The association of chronic kidney disease with brain lesions on MRI or CT: a systematic review. *Maturitas* 2012;71(4):331–6.

[23] Ikram M, Vernooij M, Hofman A, Niessen W, van der Lugt A, Breteler M. Kidney function is related to cerebral small vessel disease. *Stroke* 2008;39(1):55–61.

[24] Wada M, Nagasawa H, Iseki C, Takahashi Y, Sato H, Arawaka S, et al. Cerebral small vessel disease and chronic kidney disease (CKD): results of a cross-sectional study in community-based Japanese elderly. *J Neurol Sci* 2008;272(1–2):36–42.

[25] Kobayashi A, Iguchi M, Shimizu S, Uchiyama S. Silent cerebral infarcts and cerebral white matter lesions in patients with nonvalvular atrial fibrillation. *J Stroke Cerebrovasc Dis* 2012;21(4):310–7.

[26] Jeerakathil T, Wolf P, Beiser A, Massaro J, Seshadri S, D'Agostino R, DeCarli C. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke* 2004;35(8):1857–61.

[27] Pisters R, Olesen J, Lip G. The role of echocardiography in stroke risk assessment in patients with atrial fibrillation: is it additive or does it simply echo clinical risk factors? *Europace* 2012;14(1):1–2.

[28] Bernick C, Kuller L, Dulberg C, Longstreth WT Jr, Manolio T, Beauchamp N, et al. Cardiovascular Health Study Collaborative Reseach Group. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology* 2001;57(7):1222–9.