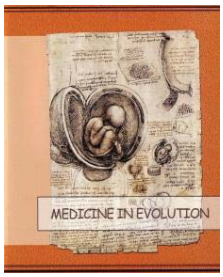
Correlations between echocardiographic parameters and cardiovascular risk factors for stroke incidence in non-valvular AF



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Abstract

Our retrospective, cross-sectional study was aimed to determine a general profile of non-valvular atrial fibrillation (NVAF) ambulatory patients, by identifying echocardiographic parameters and risk factors associated with cardioembolic stroke. 156 patients with previously diagnosed NVAF were selected from an Ambulatory Cardiology Praxis database. We applied the CHA_2SDS_2_VASC and HASBLED scores and analyzed 3 echocardiographic parameters (LAV, LVEDV and LVEF%), the presence of carotid atheromatosis and coronary artery disease and evaluated the lipidic profile and HbA1c. LAV, LVEDV and LVEF% were associated with cardioembolic stroke in NVAF (especially LVEDV), and also with ischemic heart failure (LAV in particular). Altered lipidic profile, presence of coronary artery disease and diabetes were also important indicators for incident stroke in NVAF. Further large cohort studies are necessary to develop a risk stratification chart for cardioembolic stroke based on these parameters in patients with NVAF.

Keywords: atrial fibrillation, cardioembolic stroke, echocardiographic parameters, CHA_2DS_2_VASC, lipidic profile

INTRODUCTION

Atrial fibrillation is the most frequent form of cardiac arrhythmia [1]. With the ageing population of today`s civilized countries the prevalence of this cardiac condition is estimated to double in the next ten years.[2] From the age of 40 years on the risk for developing AF is 1 in 4 for both genders.[3] AF can be triggered by common cardiovascular risk factors such as obesity, dyslipidemia and habits like smoking or alcohol abuse.[4] Heart failure followed by stroke are the main consequences of AF [5], while sudden cardiac death is the leading cause of cardiovascular death for this disease. [6]

Cardioembolic stroke is the most common complication of AF and one of the main causes of death in patients with AF. The prevalence of CE stroke is 14-30% from all stroke types with the highest mortality, especially the in-hospital mortality in patients with early embolic recurrences.[7] The Framingham Heart Study already studied the impact on mortality of AF alone, with differences on sex (1.9 in women vs.1.5 in men) but with no significant differences regarding age.[8] Due to the severe outcome of CE stroke it is very important to detect and diagnose patients with potential cardioembolic risk. For this matter CHA_2DS_2_VASC score is a potent diagnostic tool for determining which patients are eligible for oral anticoagulation therapy in stroke prevention [9], but also has some limitations linked to lack of information about cardiac structure or function that lead to thromboembolism. [10] Primary and secondary prevention measures for cardioembolic stroke could be reanalyzed by correlating CHA_2DS_2_VASC scores with certain echocardiographic parameters. These could predict the functional outcome and clinical evolution of NVAF patients, and thus help prevent cerebral cardioembolic events.

Echocardiography plays a crucial role in evaluating of certain parameters associated with thromboembolism in AF, TEE being 100% sensitive in detecting cardiac embolic sources.[11] The Framingham Heart Study published in 1994 detected echocardiographic parameters that predicted the risk for NVAF development, such as LA enlargement, increased LV wall thickness and reduced LV fractional shortening. [12] LV diastolic dysfunction determines LA enlargement, a common cause for AF. [13] LA enlargement is considered an independent predictor of heart failure and of other cardiovascular diseases [14] and together with an E/A ratio>=1,5 represent novel echocardiographic indicators of potential CE stroke.[15] While the mitral inflow velocity is variable with every RR cycle for AF patients[13], a vector velocity imaging echocardiography study in 2012 demonstrated that LA dysfunction was already present before LA enlargement in paroxysmal AF [16].

Objectives

This retrospective, cross-sectional study was aimed to determine a general profile of NVAF ambulatory patients regarding incident stroke by analyzing certain echocardiographic parameters and applying the CHA_2DS_2_VASC and HASBLED scores, evaluation of lipidic profile and HbA1c and presence of carotid and/or coronary artery disease. We analyzed the types of NVAF and the presence of chronic stroke lesions associated with cardioembolic risk factors and echocardiographic parameters to describe the general profile of NVAF patients.

MATERIAL AND METHODS

We selected 156 patients from an Ambulatory Cardiology Praxis database between October 2018-2019 with the following inclusion criteria: previously diagnosed NVAF (paroxysmal, persistent or permanent) treated with anticoagulation therapy (dicoumarin vs. NOACs). In order to establish the risk for cardioembolism we applied the CHA_2SDS_2_VASC and HASBLED scores and we analyzed 3 echocardiographic parameters (LAV –left atrial

volume, LVEDV- left ventricle end-diastolic volume and LVEF%- left ventricle ejection fraction) which were performed for every patient at their medical visit.

Patients with valvular AF and patients with other comorbidities such as systemic diseases with cardiac dysfunction, oncologic pathology, patients with renal failure and hyperthyroidism were excluded from the study. We also excluded patients with incomplete clinical data (the absence of CT, laboratory test and Doppler carotid echography). From the patients who had a history of cardioembolic stroke with hospitalization, none have received thrombolysis therapy.

The CHA_2DS_2_VASC score was calculated using the associated risk factors involved, with the following formula: Congestive Heart Failure/ LV dysfunction (1 point), Hypertension (1 point), Age >=75 years (2 points), Diabetes mellitus (1point), Stroke/ Transient Ischemic Attack/Thromboembolic events (2 points), Vascular Disease (1 point), Age 65-75 years (1 point), Sex category (female) (1 point) with a total of 9 points.[17] The HASBLED score was calculated with the following parameters: Hypertension (1 point), Abnormal renal/liver function (1 point), Stroke (1 point), Bleeding (1 point), Labile INR (1 point), Elderly age >65 years (1 point), Drug/alcohol abuse/medication with bleeding predisposition (1 point).

Echocardiographic parameters were selected according to the hypothesis that AF leads to the primary dysfunction of the left heart, which further leads to heart failure ultimately affecting ejection fraction. Paroxysmal and persistent AF were previously diagnosed in other Cardiology Ambulatory services or during hospitalization (patients had medical history attesting the diagnosis and ECG/ Holter ECG). Echocardiography was performed with Sonoscope SS1-6000 Series. Using apical 4-chamber view we calculated LVEF according to Simpson's formula as percentage of change in volumes between diastole and systole: EDV-ESV / EDV × 100. LAV was also measured from standard apical 4-chamber view at end-systole just before mitral valve opening. LA borders were determined using planimetry respecting the walls of the left atrium, excluding pulmonary veins and left atrial appendage. The following parameters were selected for the study: LAV with normal values of 18-58 ml for men and 22-52 ml for women, LVEDV 96-157ml for male subjects and 59-138ml for feminine subjects and LVEF% considered normal with values of >50% and higher, >=40% intermediate and < 40% reduced.[18] We chose the end-diastolic function of LV on the premise that AF can determine heart failure with preserved EF, in which case the systolic function of the left ventricle and the ejection fraction remain normal.[19]

Doppler carotid echography was performed in all patients included in the study prior to their medical visit at Rubio Medical Center. We used data regarding intima-media thickness (IMT) with the normal value of <0.9 and the absence/ presence of carotid plaques.

Laboratory tests were performed at specialized centers such as Medinvest Rubio Arad or Bioclinica Arad. We selected from the data available the lipidic profile with the following ranging values: total cholesterol (TC) with values of <200 mg/dl optimal;200-240 mg/dl borderline high and >240 mg/dl high, low density lipoprotein cholesterol (LDLc)= <100 optimal mg/dl,100-129mg/dl borderline optimal,130-159mg/dl borderline high;160-180 mg/dl high and ≥190 mg/dl very high, high density lipoprotein cholesterol (HDLc)= <40 mg/dl low and ≥60mg/dl high, triglycerides (TG)=<150mg/dl optimal, 150-190mg/dl borderline high, 200-499mg/dl high and ≥500mg/dl very high. Glycosylated hemoglobin (HbA1c) with normal values of 4.8-5,6%, ranging values from 5.7% to 6.4% were considered as a high risk for diabetes mellitus and from >=6.5% as diabetes.

The calculation of the ankle-brahial index (ABI) was performed with the following formula: ankle systolic pressure/ brachial systolic pressure and it was performed during the medical visit at Rubio Medical Center Arad. We considered normal values 1.0-1.4; 0.91-0.99 as borderline and <0.90 as peripheral arterial disease.

Computed tomography/ MRI of the brain were performed at specialized imaging centers during hospitalization in the Neurology Department at the Arad County Emergency Hospital or in private imaging centers such as Affidea Medical Center or Hiperdia Medical Center in Arad. We used the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of stroke for patient inclusion.

All patients included have signed an informed consent for personal data processing at the Cardiology Ambulatory Praxis at Rubio Medical Center. The local ethics committee of the County Hospital Arad and the director of RubioMed Medical Center Arad approved the study.

Data processing was done using SPSS v17 software.

RESULTS

From 156 patients included in our study 76,3% were diagnosed with permanent AF, 15,4% patients had persistent AF and 8,3% were with paroxysmal AF.[Fig1] The echocardiographic parameters of the study group were: mean LAV 87,79ml (±33,73), mean LVEDV 136,36ml (±44,28) and mean LVEF% 45,12% (±8,15). The mean CHA_2DS_2_VASC score was 4,67(±1,68), median HbA1c was 5,75%(±0,73) and mean IMT value was 0,83(±0,33). [Table I].

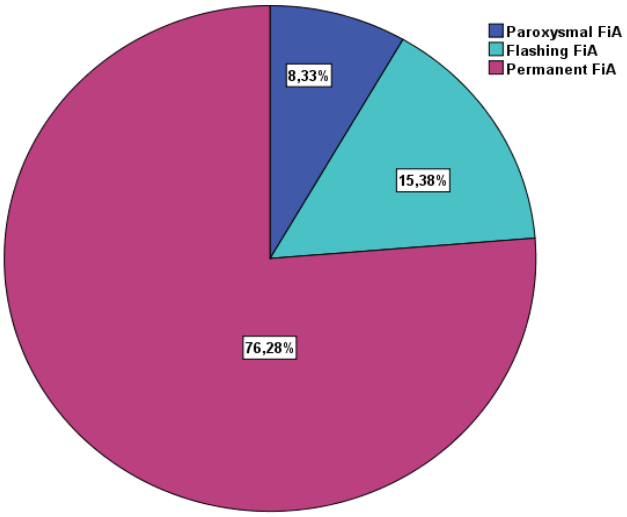


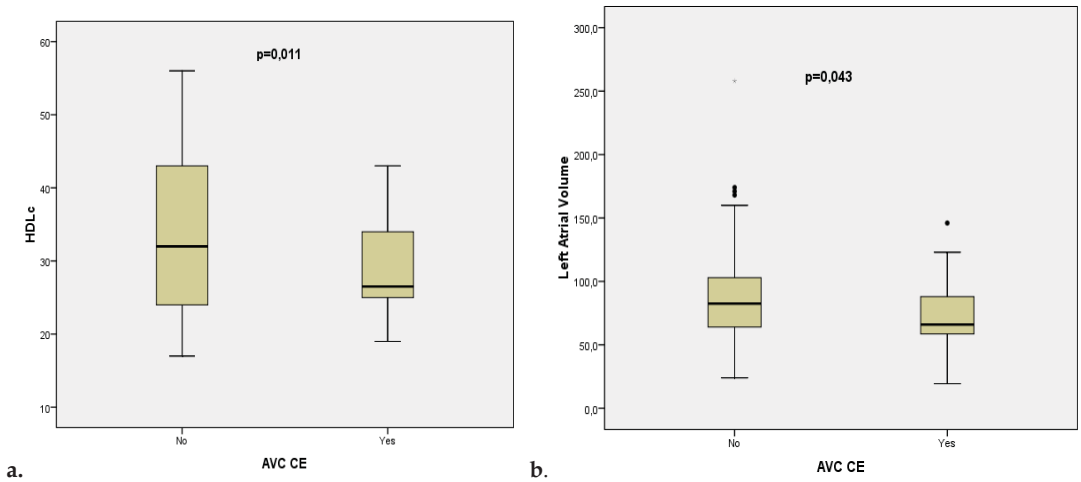
Figure 1. Percentage distribution of Atrial Fibrillation subtypes

Table I. Descriptive statistics (mean± std. deviation) for numerical variables by AF clinical subtypes (n=156)

Variable	Atrial Fibrillation			Psign Kruskal-Wallis test
	Paroxysmal (n=13)	Persistent (n=24)	Permanent (n=119)	
Age	68±10.98	68.8±10.77	72±9.19	0.084
BMI	31.9±4.55	31.3±3.28	31.3±3.55	0.718
HbA1c	6±0.75	6.2±0.72	6.2±0.55	0.474
TC	291.2±47.38	281.3±43.6	277.5±48.69	0.655
LDLc	206.6±26.3	206.5±26.01	202.7±25.98	0.856
HDLc	32.8±8.65	31.8±10.4	33.8±10.25	0.613
TGL	347.5±63.15	357.8±88.03	342.7±97.25	0.827
ABI	0.8±0.16	0.9±0.2	0.9±0.19	0.468
CHA2DS2_VASC	3.7±1.32	4.7±2.37	4.8±1.53	***0.049***^{s}
HASBLED	2.5±1.05	2.8±1.34	2.9±1.03	0.321
LAV	69±14.7	84.8±34	90.6±34.57	***0.045***^{s}
LVEDV	144.5±73.05	136.6±47.11	135.5±39.9	0.929
LVEF (%)	47±5.94	44±9.29	45.1±8.15	0.551
IMT	0.8±0.36	0.7±0.38	0.9±0.33	0.316

There were no significant differences between AF groups regarding age, BMI, HbA1c, TC, LDLc, HDLc, TGL, ABI, HASBLED score, LVEDV, LVEF and IMT. Only LAV (p=0.045) and CHA_2DS_2_VASC (p=0.049) scores varied significantly between AF clinical subtypes (nonparametric Kruskal-Wallis test). [Table I]. LAV values and CHA_2DS_2_VASC scores were significantly increased in patients with permanent NVAF vs. paroxysmal NVAF (p=0.016 in the case of LAV, p=0.017 for CHA_2DS_2_VASC, Mann-Whitney U non-parametric test).

From the total of 156 patients included in the study, 24 patients were diagnosed with cardioembolic stroke, 55 patients had lacunar strokes and 77 patients were without stroke history. When considering CE stroke as an independent variable, the study group characteristics were: mean TC 297.18 mg/dl (±44.46), mean LDLc 203.77 mg/dl (±25.57), mean HDLc 29.45 mg/dl (±6.68) and mean TGL 377.41 mg/dl (±80.26). Also median LAV was 75.94ml (±27.85), mean LVEDV was 124.88 ml (±36.70), mean LVEF% was 46.14(±6.67) and median HbA1c was 6.25%(±0.49). Significantly decreased values of HDLc (p=0.011) and increased LAV values (p=0.043) were found for patients with cardioembolic stroke compared to non-stroke (Mann-Whitney non-parametric test).[Fig.2]



a. **b.**

Figure 2. **a**. Boxplot for HDLc by comparing patients with CE stroke (n=24) vs patients without stroke (n=77) **b**. Boxplot for LAV by comparing patients with CE stroke (n=24) vs. without stroke (n=77)

The patients with lacunar stroke (n=55) had the following group characteristics: the lipidic profile with a mean TC of 283.26 mg/dl (±44.61), mean LDLc of 206.53 mg/dl (±23.56), mean HDLc of 33.42 mg/dl (±9.74) and mean TGL of 357.03 mg/dl (±90.14). The echocardiographic parameters presented following values: mean LAV 86.83ml (±38.07), median LVEDV 132.59 ml (±45.52) and mean LVEF% 44.40%(± 8.32). Median HbA1c was 6.24%(±0.61) in the lacunar stroke group. Significantly increased values of LDLc were found for patients with lacunar stroke vs. non-stroke (p=0.039, Mann-Whitney non-parametric test). [Fig.3]

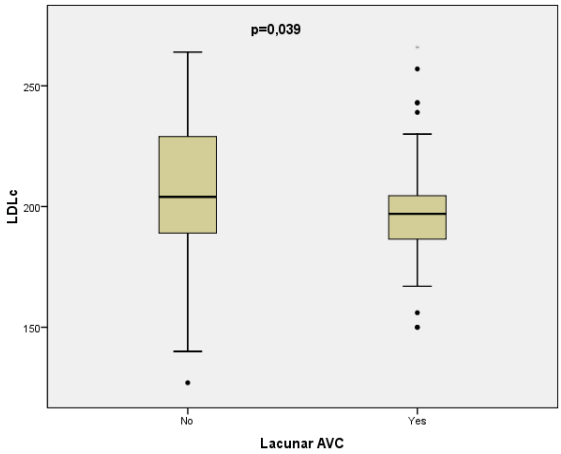
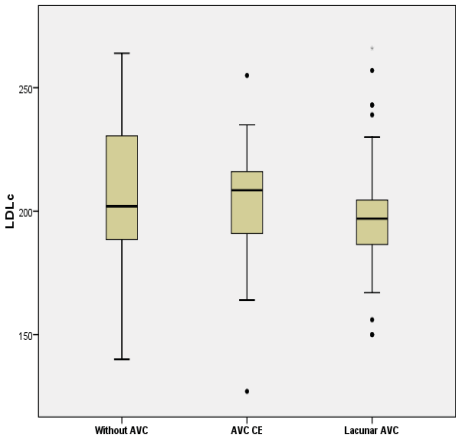


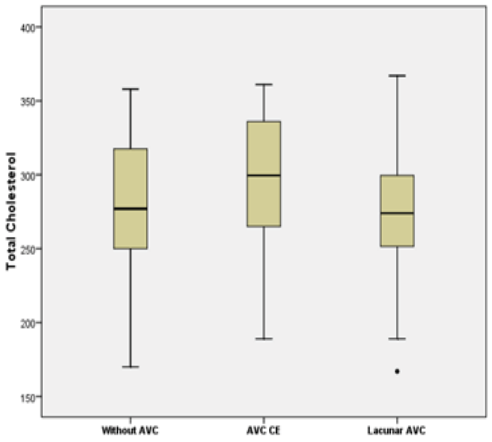
Figure 3. Boxplot for LDLc values comparing patients with lacunar stroke (n=55) vs. patients without stroke (n=77)

By comparing the 3 stroke subgroups by the Mann-Whitney non-parametric test, significantly increased values of TC (mean 297.18±44.46 mg/dl, p=0.041), LDLc (mean 203.77±25.57 mg/dl, p=0.035)[Fig.4] and TGL (mean 377.41±80.26 mg/dl,p=0.045) were present in the CE stroke group.[Fig 5a] Although both stroke groups had increased LAV, the CE group had significantly decreased LAV(mean 75.94±27.85) compared to the lacunar stroke group (mean 89.78±38.07) (p=0.032).[Fig.5b]. Regarding HbA1c there were no significant differences between stroke subgrups. (Kruskal-Wallis test, p=0.668).



p=0.041

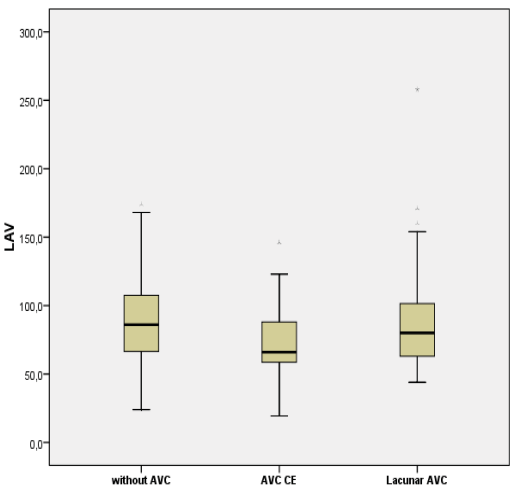
Fig.4a



p=0.035

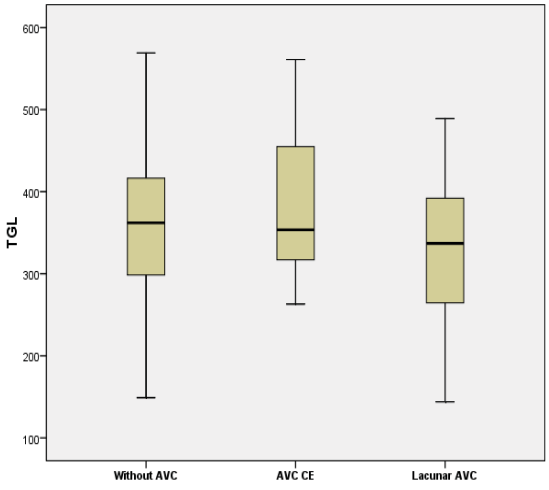
Fig.4b

Figure 4. **a**. Comparison of TC values in stroke subgroups (CE stroke n=24, lacunar stroke n=55) vs. non-stroke (n=77) **b.** Comparison of LDLc values in stroke subgroups (CE stroke n=24, lacunar stroke n=55) vs. non-stroke (n=77)



p=0.045

Fig.5**a**



p=0.032

Fig.5**b**

Figure 5. **a**.Comparison of TGL values in the stroke subgroups (CE stroke n=24, lacunar stroke n=55) vs. non-stroke (n=77) **b.** Comparison of LAV values in the stroke subgroups (CE stroke n=24, lacunar stroke n=55) vs. non-stroke (n=77)

A multivariate regression data analysis was made using stroke as an independent variable related to LAV, LVEDV, LVEF%, IMT and HbA1c. The results showed a statistically significant direct correlation with LAV (rho=0.274, p=0.015). HbA1c and IMT were significantly and directly correlated with CHA_2DS_2_VASC scores (rho = 0.246, p = 0.001 for HbA1c, and rho = 0.196, p = 0.007 for IMT). There was a positive correlation between LAV and LVEDV (rho = 0.269, p <0.001), while LAV and LVEF% were inversely correlated (rho=-0,421, p<0,001). LVEDV and LVFE% were negatively correlated (r=-0,285, p<0,001). The correlation between IMT and LVEF% was positive (r=-0,312, p=0,005). In both cases the correlations between CHA_2DS_2_VASC scores and LVEDV, respectively LVEF%, were negative (rho = -0.134 with p = 0.038 in the case of LVEDV and p <0.001, rho = -0.266 in the case of LVEF%). [Fig 6,7]

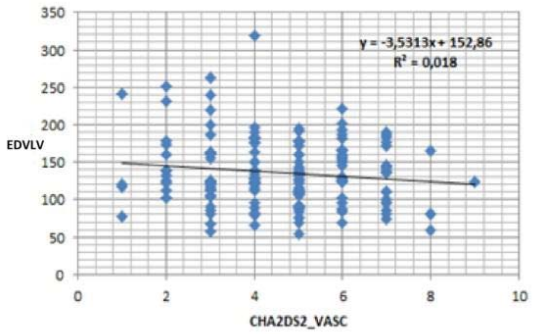


Figure 6. The correlation between CHA2DS2_VASC scores and LVEDV (n=156)

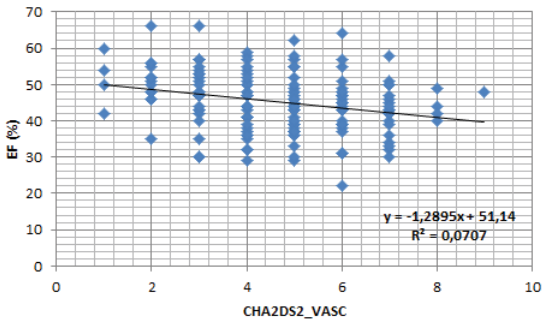


Figure 7. The correlation between CHA2DS2_VASC scores and LVEF% (n=156)

In this study we tried to analyze which parameters represented the most important risk factors for stroke in NVAF. By using Chi2 tests in the comparison of stroke vs. non-stroke patients, high values of TC (p=0.014; OR=2.51 with confidence interval of 95% 1.19;5.27), LDLc (p=0.026, OR=4.22 with confidence interval of 95% 1.13;15.78), TGL (p=0.020; OR=3.45 with 95% confidence interval 1.28; 9.29) and low values of HDLc (p=0.022; OR=2.18 with 95% confidence interval 1.12; 4.28) were found to be important risk factors for stroke incidence in NVAF. Regarding echocardiographic parameters, patients with increased LVEDV had a higher stroke incidence (Chi2 test, p=0.031; OR=2.05 with confidence interval of 95% 1.06;

3.94). Another important risk factor for developing stroke in patients with NVAF was HbA1c with values over 6,5% (Chi2 test, p=0.019; OR=2.2 with confidence interval of 95% 1.13;4.27). Stroke incidence was significantly higher for patients with coronary artery disease (Chi2 test, p=0.004).

DISCUSSIONS

Echocardiography has proven to be a very potent diagnostic tool in detecting thromboembolism in AF and some echocardiographic parameters can be strongly associated with the incidence or increased risk of cardioembolic stroke. The size of LA alone can predict the risk for developing AF by an increase of 5mm in LA diameter. The volume of the left atrium is of superior value when it comes to predicting the outcomes in AF.[20] Echocardiographic parameters related to stroke risk are increased diastolic and systolic diameters of LV, increased LA size, increased E/A ratio and reduced LVEF%.[20] It is also important to note that only 60% of all AF patients develop stroke of cardioembolic origin and that sometimes AF is clinically detected after stroke onset.[21] In this matter the correct evaluation of the embolic source is crucial, for even cryptogenic strokes can occur (7-25% of all strokes) and that covert AF and AHRE (atrial high rate episodes) are the most common causes.[22]

The ENGAGE AF-TIMI trial 48 highlighted that paroxysmal AF was associated with fewer thromboembolic events than permanent AF and that high CHA_2DS_2_VASC scores were found in NVAF patients with important impairment of the diastolic functions of the left heart [23]. In our study patients with permanent AF were more likely to develop increased left atrium volumes and have higher CHA_2DS_2_VASC scores. Also increased LA volumes were correlated with increased LVEDV and lower LVEF% values and significantly higher CHA_2DS_2_VASC scores. With these results we can conclude that AF patients with heart failure are the ones more predisposed to develop stroke. A cross-sectional study in 2018 comparing structural and functional changes of the left heart with CHA_2DS_2_VASC scores revealed that diastolic dysfunction of the left ventricular chamber could play a key role for stroke incidence. Compared to lone NVAF, patients with high CHA_2DS_2_VASC scores and more comorbidities had increased LV size and diastolic dysfunction.[24] Our results pointed towards significantly increased LAV in patients with CE stroke vs. non-stroke, but also revealed that the left atrial volume was significantly decreased for CE patients compared to the lacunar stroke group. Regarding the risk factors we analysed, patients with increased LVEDV had a higher stroke incidence.

Increased intima media thickness can be associated with cardioembolism in AF, highlighted by the direct correlation between HbA1c and IMT to CHA_2DS_2_VASC scores. Also higher IMT values were associated with lower LVEF% values. It has been previously studied that the presence of carotid atheromatosis is an important risk factor involved in the negative outcome of non-valvular AF [25]. Other studies have revealed that an increased IMT can independently predict the risk for cardio and cerebrovascular events and is associated with subclinical organ damage[26].

Studies have shown associations between a modified lipidic profile and different types of stroke, for instance large artery atherosclerotic stroke is associated with dyslipidemia, while lacunar and embolic stroke seem to present low or almost no association. [27] Both stroke groups showed a modified lipidic profile, which can be explained by a low compliance of our study population to lipid lowering therapy. CE stroke patients had significantly lower HDLc, while significantly increased LDLc was found for lacunar stroke patients. The comparison between the 3 stroke groups also revealed significantly increased TC, LDLc and TGL for patients with CE stroke. The modifications of the lipidic profile (high TC, LDLc, TGL with low HDLc) in NVAF can be considered important risk factors for stroke incidence in NVAF.

Coronary artery disease can be very common in patients with AF (17% to 46,5%) and studies have predicted that future stenting could be required to 5%-15% of patients with AF[28].Yang PS et al. studied the effect of non-CE risk factors of ischemic stroke in AF, concluding that high CHA_2DS_2_VASC scores were associated with atherosclerotic intracranial arterial stenosis, significant carotid stenosis, complex aortic plaque and a high coronary artery calcium score[29]. In the light of those clinical findings, our study detected that patients with coronary artery disease had a higher risk to develop stroke. Regarding other comorbidities, a metanalysis performed in 2018 demonstrated an important association between chronic hyperglycemia with high HbA1c levels (even for pre–diabetes mellitus) and stroke risk.[30] Another cohort study demonstrated that patients with AF and type 2 diabetes mellitus who had high levels of HbA1c were associated with a higher risk of thromboembolic events.[31] High values of HbA1c are found to be an important risk factor for stroke in NVAF patients in our study. Comorbidities such as coronary artery disease and diabetes (with high HbA1c) can be considered as important risk factors for stroke incidence in NVAF.

CONCLUSIONS

While non-valvular atrial fibrillation is still associated with a high mortality rate (especially due to sudden cardiac death and cardioembolic stroke) and is strongly associated with high cardiovascular risk[32], recent findings in clinical studies were able to determine a panel of echocardiographic parameters associated to CE stroke, some of which are also confirmed by our small retrospective study. Parameters such as LAV, LVEDV and LVEF% are associated with cardioembolic risk in NVAF (especially LVEDV), but are also useful in detecting patients more prone to develop ischemic heart failure (LAV in particular), as confirmed by the present study.

A modified lipidic profile, the presence of coronary artery disease and diabetes are important indicators for the possible outcome of stroke in NVAF. Further large cohort studies are necessary to develop a risk stratification chart for cardioembolic stroke based on these parameters in patients with NVAF.

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