

# Coronary artery disease, left ventricular hypertrophy and diastolic dysfunction are associated with stroke in patients affected by persistent non-valvular atrial fibrillation: a case-control study

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## Abstract

Persistent non-valvular atrial fibrillation (NVAF) is associated with an increased risk of cardiovascular events such as stroke, and its rate is expected to rise because of the ageing population. The absolute rate of stroke depends on age and comorbidity. Risk stratification for stroke in patients with NVAF derives from populations enrolled in randomized clinical trials. However, participants in clinical trials are often not representative of the general population. Many stroke risk stratification scores have been used, but they do not include transthoracic echocardiogram (TTE), pulsed wave Doppler (PWD) and tissue Doppler imaging (TDI), simple and non-invasive diagnostic tools. The role of TTE, PWD and TDI findings has not been previously determined. Our study goal was to determine the association between TTE and PWD findings and stroke prevalence in a population of NVAF prone outpatients.

Patients were divided into two groups: P for stroke prone and F for stroke free. There were no statistically significant differences

between the two groups concerning cardiovascular risk factors, age ( $p=0.2$ ), sex ( $p=0.2$ ), smoking ( $p=0.3$ ), diabetes ( $p=0.1$ ) and hypercholesterolemia ( $p=0.2$ ); hypertension was statistically significant ( $p<0.001$ ). There were statistically significant differences concerning coronary artery disease, previous acute myocardial infarction (AMI) ( $p<0.05$ ) and non-AMI coronaropathy ( $p<0.04$ ), a higher rate being in the P group. Concerning echo-Doppler findings, a higher statistically significant rate of left ventricular hypertrophy (LVH) ( $p<0.05$ ) and left ventricular diastolic dysfunction ( $p<0.001$ ) was found in the P group and dilated left atrium ( $p<0.04$ ) in the F group, the difference was not significant for mitral regurgitation ( $p=0.7$ ). Stroke prone NVAF patients have a higher rate of hypertension, coronary artery disease, with and without AMI, LVH and left ventricular diastolic dysfunction, but not left atrial dilatation. M-B mode echocardiography and PWD examination help to identify high-risk stroke patients among NVAF subjects; therefore, they may help in the selection of appropriate therapy for each patient.

ple seen in the "real world" of clinical practice.<sup>10</sup> AF prone patients, <65 yrs, without a history of hypertension, previous stroke or transient ischemic attack, or diabetes, are classified as a low-risk population.<sup>3</sup> Many stroke risk stratification scores have been used, but interestingly, available risk scores do not include any variable derived from transthoracic echocardiogram (TTE), pulsed wave Doppler (PWD) and tissue Doppler imaging (TDI), simple and non-invasive diagnostic tools. Transesophageal echocardiographic examination (TEE) is also very useful,<sup>11,12</sup> but it is partially invasive and expensive. Furthermore, in NVAF outpatients with no recent history of embolism, TEE is of limited value in assessing stroke risk<sup>13</sup> and its role in detecting cardiac sources of embolism in elderly stroke patients needs to be better clarified.<sup>14</sup> 3D echo is useful in these patients, but it is not available everywhere and its outcome needs to be validated.<sup>15</sup> A new generation echo system allows transthoracic detection of left atrial appendage thrombi and accurate determination of left atrial appendage function in most patients with a neurological deficit.<sup>16</sup> In addition, the prognostic implications of spontaneous contrast in NVAF patients are unknown.<sup>17</sup> Routine management of NVAF includes the primary stroke-preventive measures; echocardiogram has been an important adjunctive tool in the evaluation of AF.<sup>18</sup> Left ventricular systolic dysfunction impairs left atrial function parameters and it is supposed to increase left atrial thrombus rate in patients with chronic NVAF<sup>19</sup> and in elderly patients, E/A <0.5 and a low atrial filling fraction were markers of increased AF risk, suggesting that impaired atrial filling may, over time, precede AF onset.<sup>20-22</sup> Specifically, the role of TTE, PWD and TDI findings has not been previously determined. Our study goal was to determine the association between TTE, PWD, TDI findings and stroke prevalence in a population of NVAF prone outpatients.

## Introduction

Persistent non-valvular atrial fibrillation (NVAF), the most common cardiac arrhythmia, is associated with an increased risk of heart failure and cardiovascular events such as stroke: its rate is expected to rise<sup>1</sup> because of the ageing population. The absolute rate of stroke depends on age and comorbidity.<sup>2-4</sup> Many studies have attempted to define clinical criteria that can be used to classify patients affected by AF as being at low or high risk,<sup>2,5</sup> in order to choose the therapy with the best risk/effectiveness profile.<sup>1,6-9</sup> Risk stratification for stroke in patients with AF derives from studying populations enrolled in randomized clinical trials.<sup>5,6</sup> However, participants in clinical trials are slightly younger, more likely to be male, and generally have fewer comorbidities than pop-

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## Patients and Methods

### Patients

We studied 230 consecutive patients affected by NVAF referred to our outpatient unit for cardiological examination. All patients gave informed consent to be enrolled in our study. Recruitment started in January 2003 and lasted one year. All patients underwent full cardiological examination, clinical history collection, electrocardiogram, M-B mode echocardiogram and PWD examination. Exclusion criteria were: valvular AF, smoking or left atrial thrombi and bad thoracic view. Persistent AF diagnosis was performed when the arrhythmia was detected by positive electrocardiogram at enrolment and the time-standing of NVAF was over one year. Two hundred and thirty patients were included. Table 1 reports the clinical characteristics of the study population. Patients were classified as prone to stroke from a documented history of stroke with assessment by cerebral contrast tomography scan. All patients enrolled in our study underwent anticoagulation therapy twice monthly monitored by INR.

### Electrocardiographic evaluation

Electrocardiograms were performed by Esaote-Biomedica Archimed 4210 12 lead electrocardiography, the criteria for AF diagnosis are replacement of P waves by rapid oscillations of fibrillatory waves that vary in size, shapes and timing, associated with an irregular ventricular response.

TTE was performed by GE Vivid 3 expert, a phased-array echo-Doppler system equipped with a 2.5 Hz probe. All patients were examined in the left lateral recumbent position using standard parasternal, long-axis, short-axis, and apical views. M-mode recordings were obtained, and left ventricular diastolic diameter, as well as septal and posterior wall thickness were measured. Left ventricular mass index (LVMI) was obtained by dividing the left ventricular mass by body surface area. Left ventricular hypertrophy (LVH) was defined as an LVMI >110 g/m<sup>2</sup> for females and >134 g/m<sup>2</sup> for males.

The left atrial (LA) size was determined as the diameter in parasternal long-axis and short-axis view, directly on B-mode then checked on M-mode, at end systole, from leading edge to leading edge. Diameters and volumes of left atrium and ventricle determined by single beam echocardiography demonstrated a good correlation with hemodynamic findings.<sup>23,24</sup> Echocardiographic measurements were obtained at end-expiration. All analyses were based on the average obtained by five beat measurements. Intra- and inter-observer variability was determined: two study investigators repeated each

**Table 1. Study population: clinical characteristics.**

	P group	F group	p value
Age (years)	76±6	77±3	p=0.2
Male	20/39 (51%)	86/191 (45%)	p=0.2
On smoke	7/39 (17.9%)	31/191 (16.2%)	p=0.3
On diabetes	6/39 (15.4%)	26/191 (13.6%)	p=0.1
On hypercholesterolemia	9/39 (23.1%)	37/191 (19.4%)	p=0.2
On hypertension	28/39 (71.7%)	95/191 (49.7%)	p<0.001

P: atrial fibrillation prone; F: atrial fibrillation free.

**Table 2. Study population: coronary artery diseases.**

	P group	F group	p value
AMI CAD	9/39 (20.5%)	20/191 (10.4%)	p<0.05
nonAMI CAD	18/39 (46.1%)	56/191 (29.3%)	p<0.04

P: atrial fibrillation prone; F: atrial fibrillation free; CAD: coronary artery disease; AMI: acute myocardial infarction.

measurement in 10 randomly chosen patients to ensure that a correlation coefficient of 0.9 was obtained by linear regression analysis. Mitral inflow characteristics were analyzed using Doppler echocardiography. Mitral inflow velocities were measured at end-expiration at the level of the tips of the mitral leaflets on the four-chamber view, using pulsed Doppler, performed at end-expiration. The Doppler beam was aligned to produce the narrowest possible angle between the beam and the blood flow vector.

The peak velocity during early filling (*E*), the deceleration time from peak early filling and isovolumic relaxation time, extrapolated to the baseline were measured. Diastolic dysfunction was assessed when the following two parameters were checked together: mitral flow, E wave DT >220 m.sec and IVRT >105 m.sec. Myocardial tissue characteristics were analyzed using pulsed Doppler echocardiography. Tissue velocities were measured at end-expiration at the ventricular lateral mitral annulus level, on four-chamber view.<sup>25</sup> The peak velocity during early filling (*E<sub>m</sub>*) extrapolated to the baseline was measured.

Mitral regurgitation was assessed by Doppler color flow jet area inside the left atrium. Clinical predictors evaluated included patient demographic data such as age, gender and body surface area; co-existent risk factors were hypertension, diabetes, hypercholesterolemia and smoking. Coronary artery diseases were assessed by medical history of acute myocardial infarction (AMI) or non-AMI coronaropathy only if supported by cardiological records.

### Statistical analysis

The relationship between stroke prone patients (P group) and stroke free patients (F group) for all above-mentioned echo findings

was assessed using the  $\chi^2$  test for non-parametric analysis and the Student's t-test for parametric analysis.  $p<0.05$  was considered significant. Multivariate analysis was performed.

## Results

Thirty-nine of the 230 patients studied had a history of stroke. Stroke prone patients were included in the P group, and stroke free patients in the F group. Mean age was 76±6 yrs in the P group and 77±3 yrs in the F group, 20/39 patients (51%) were males in the P group, and 86/191 were males (45%) in the F group, 7/39 patients (17.9%) in the P group and 31/191 patients (16.2%) in the F group were smokers, 6/39 patients (15.4%) in the P group and 26/191 patients (13.6%) in the F group were affected by diabetes, 9/39 patients (23.1%) in the P group and 37/191 patients (19.4%) in the F group were affected by hypercholesterolemia, 28/39 patients (71.7%) were hypertensive in the P group and 95/191 patients (49.7%) in the F group. Differences between the two groups for age ( $p=0.2$ ), sex ( $p=0.2$ ), smoking ( $p=0.3$ ), diabetes ( $p=0.1$ ) and hypercholesterolemia ( $p=0.2$ ) were not statistically significant. There was a statistically significant difference for the hypertension rate between the P group (71.7%) and the F group (49.7%) ( $p<0.001$ ). Previous AMI was detected in 29/230 patients (12.6%); 9/39 patients (20.5%) in the P group and 20/191 patients (10.4%) in the F group and the difference was statistically significant ( $p<0.05$ ). Non-AMI coronary artery disease was detected in 74/230 patients (32.2%), 18/39 (46.1%) in the P group and 56/191 patients (29.3%) in the F group and the difference was statistically sig-

nificant ( $p < 0.04$ ) (Table 2). LVH was diagnosed in 87/230 patients (37.8%); 10/39 patients (40.3%) in the P group and 77/191 patients (25.6%) in the F group, and the difference was statistically significant ( $p < 0.05$ ) and not dependent on the hypertension rate. Left ventricular diastolic dysfunction occurred in 62/230 patients (26.9%), 16/39 patients (41%) in the P group and 46/191 patients (24%) in the F group and the difference was statistically significant ( $p < 0.001$ ) and not dependent on the hypertension rate. Left atrium diameter was  $>40$  mm in 80/230 patients (34.7%), 8/39 patients (20.5%) in the P group and in 72/191 patients (37.6%) in the F group and the difference was statistically significant ( $p < 0.04$ ). Mitral regurgitation was detected in 75/230 patients (32.6%), 12/39 patients (30.7%) in the P group and 63/191 patients (33%) in the F group but the difference was not statistically significant ( $p = 0.7$ ) (Table 3). Significant statistical differences were preserved also after correction for sex and age.

## Discussion

The most important finding of this study is that coronary artery disease, LVH and diastolic dysfunction evaluated by TTE are associated with a higher prevalence of stroke among NVAf patients.<sup>22</sup>

A previous risk stratifier had been identified in large randomized clinical trials; however, the population enrolled in these studies is often not representative of the general population. If the AF rate is expected to rise<sup>1</sup> it is useful to evaluate the impact of simple and non-invasive diagnostic tools such as TTE, PWD and TDI, in predicting stroke in persistent NVAf. Risk stratification helps in the prognosis and in the selection of appropriate candidates for different therapies such as aspirin, warfarin, direct thrombin inhibitors or electric therapy.<sup>7,9,26</sup> Our patients were a sample of the general population affected by PNVAf, while participants in trials are slightly younger, more likely to be male, and generally have fewer comorbidities than those in our study population.<sup>1,3,5,6,12,13,26</sup> Our two patient groups were similar for age and sex, so the absolute rate of stroke depends only on comorbidity. All risk scores we considered are affected by a selection bias; therefore, risk factors previously used for scoring, such as systolic blood pressure, diabetes, smoking, prior myocardial infarction need to be validated. In our patients, common risk factors such as diabetes, hypercholesterolemia<sup>27</sup> and smoking were similar between the two groups; therefore, in our study of an outpatient population, they seemed not to be so relevant. On the other hand, an important cardiovascular risk factor such as

**Table 3. Study population: echocardiographic characteristics.**

	P group	F group	p value
LV hypertrophy	10/39 (40.3%)	77/191 (25.6%)	$p < 0.05$
LV diastolic dysfunction	6/39 (15.3%)	46/191 (24%)	$p < 0.001$
LA diameter $>40$ mm	8/39 (20.5%)	72/191 (37.6%)	$p < 0.04$
Mitral regurgitation	12/39 (30.7%)	63/191 (33%)	$p = 0.7$

L: left; V: ventricular; A: atrial.

hypertension is more frequent, in a statistically significant way, among our stroke prone patients. Concerning comorbidity, a positive clinical history for previous AMI, associated with a diagnostic tool confirmation, was detected more often, in a statistically significant way, among stroke prone patients. The same occurred for non-AMI coronary artery disease. Therefore, it is clear that previous coronary artery disease, regardless of clinical presentation, is a strong predictor of stroke. Concerning the echocardiographic contribution to stroke prognostic stratification, we considered four parameters. First, LVH is more frequent in a statistically significant way among stroke prone patients, as in the LIFE study which assessed a lower stroke death and acute myocardial infarction rate, in a composite endpoint, in patients affected by LVH.<sup>28</sup> Secondly, left atrium diameter  $>40$  mm is more frequent, in a statistically significant way, among stroke free patients: we know that a dilated left atrium is an important cardiac source of embolism, but this seems not to be important in NVAf patients.<sup>18,19</sup> Thirdly, mitral regurgitation assessment may have proved to be protective against stroke in many studies, but our study does not support this. We observed all mild mitral regurgitations and we can determine that this kind of mitral regurgitation does not play a role in preventing stroke.<sup>29,30</sup>

Fourthly, the rate of LV diastolic dysfunction was higher among stroke prone patients, in a statistically significant way. LV diastolic dysfunction impairs left atrial function parameters and is supposed to increase the frequency of LA thrombus in patients with chronic NVAf.<sup>19,21</sup> We think that TEE is a very useful tool,<sup>12</sup> but it is partially invasive and expensive, although TEE is considered the gold standard for excluding left atrial (LA) thrombi,<sup>31</sup> perhaps in non-rheumatic AF outpatients, with no recent history of embolism, TEE is of limited value in assessing stroke risk<sup>13</sup> and the role of TEE in detecting cardiac sources of embolism in elderly stroke patients needs to be better clarified.<sup>14</sup> In addition, the prognostic implications of spontaneous contrast in patients with NVAf are unknown.<sup>17</sup>

All available risk scores must include some diagnostic tools; therefore, it is correct to analyze every single tool's prognostic power, to predict stroke and to improve primary stroke prevention measures.

## Conclusions

Stroke prone NVAf patients have a higher rate of hypertension, coronary artery disease, with and without AMI, LVH and left ventricular diastolic dysfunction, but not left atrial dilatation. M-B mode echocardiography and PWD examination help to identify high-risk stroke patients among NVAf subjects; therefore, they may help the selection of appropriate therapy for each patient.<sup>12,32</sup>

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