Frequency of Left Ventricular Hypertrophy in Non-Valvular Atrial Fibrillation

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Left ventricular hypertrophy (LVH) is significantly related to adverse clinical outcomes in patients at high risk of cardiovascular events. In patients with atrial fibrillation (AF), data on LVH, that is, prevalence and determinants, are inconsistent mainly because of different definitions and heterogeneity of study populations. We determined echocardiographic-based LVH prevalence and clinical factors independently associated with its development in a prospective cohort of patients with non-valvular (NV) AF. From the "Atrial Fibrillation Registry for Ankle-brachial Index Prevalence Assessment: Collaborative Italian Study" (ARAPACIS) population, 1,184 patients with NVAF (mean age 72 ± 11 years; 56% men) with complete data to define LVH were selected. ARAPACIS is a multicenter, observational, prospective, longitudinal on-going study designed to estimate prevalence of peripheral artery disease in patients with NVAF. We found a high prevalence of LVH (52%) in patients with NVAF. Compared to those without LVH, patients with AF with LVH were older and had a higher prevalence of hypertension, diabetes, and previous myocardial infarction (MI). A higher prevalence of ankle-brachial index ≤ 0.90 was seen in patients with LVH (22 vs 17%, p = 0.0392). Patients with LVH were at significantly higher thromboembolic risk, with $CHA_2DS_2-VASc \geq 2$ seen in 93% of LVH and in 73% of patients without LVH (p <0.05). Women with LVH had a higher prevalence of concentric hypertrophy than men (46% vs 29%, p = 0.0003). Logistic regression analysis demonstrated that female gender (odds ratio [OR] 2.80, p <0.0001), age (OR 1.03 per year, p <0.001), hypertension (OR 2.30, p <0.001), diabetes (OR 1.62, p = 0.004), and previous MI (OR 1.96, p = 0.001) were independently associated with LVH. In conclusion, patients with NVAF have a high prevalence of LVH, which is related to female gender, older age, hypertension, and previous MI. These patients are at high thromboembolic risk and deserve a holistic approach to cardiovascular prevention. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;116:877−882)

Atrial fibrillation (AF) is the most prevalent supraventricular tachyarrhythmia [1,2] associated with high risk of death and stroke.[3] Hypertension is the most frequent cardiovascular risk factor in AF and recognized as a predictor of new onset AF.[4−6] One of the hypertension-related target organ damage is left ventricular hypertrophy (LVH).[7−10] Data on gender differences in development of LVH have been reported in hypertensive patients with[11] or without concomitant heart failure.[10] Notwithstanding different definitions and threshold criteria, LVH prevalence ranges widely in the general population.[10] Nonetheless, LVH is an independent risk factor for major cardiovascular events and all cause death.[12−15] Also, left ventricular remodeling has been identified as an independent risk factor for stroke and mortality in patients with AF.[16] The aim of our study was to determine LVH prevalence, using well-defined echocardiographic criteria based on left ventricular mass (LVM) indexed by body surface area (BSA) in a cohort of patients with non-valvular (NV) AF. Second, we aimed to identify the clinical factors independently associated with LVH in our patients with NVAF. Third, we conducted a gender-stratified analysis to investigate relevant gender differences in LVH in patients with NVAF.

Methods

We performed a cross-sectional analysis on the "Atrial Fibrillation Registry for Ankle-brachial Index Prevalence

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See page 881 for disclosure information.

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[1] Listed in Appendix.

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│ 2,027 NVAF patients enrolled in │
│ ARAPACIS                    │
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┌─────────────────────────────┐
│ 1,184 NVAF patients with complete │
│ echocardiographic data      │
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            │
            │          ┌──────────────────────────────┐
            ├─────────▶│ 97 NVAF patients excluded    │
            │          │ • unreliable or inconsistent data │
            ▼          └──────────────────────────────┘
┌─────────────────────────────┐
│ 1,087 NVAF patients eligible for │
│ analysis about presence or absence │
│ of LVH                      │
└─────────────────────────────┘
        │          │
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┌──────────────┐ ┌──────────────────┐
│ 576 LVH patients │ │ 511 Non-LVH patients │
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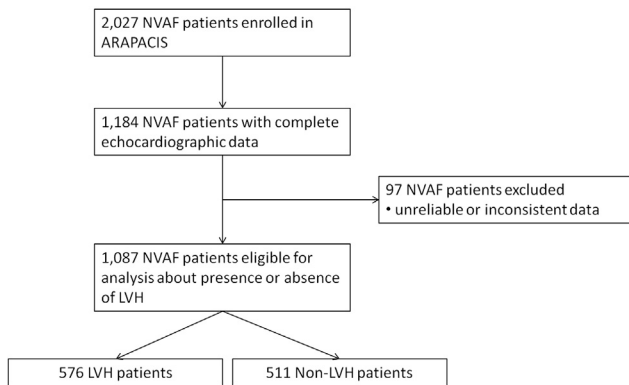
Figure 1. Flow diagram of NVAF patient selection.

Assessment: Collaborative Italian Study" (ARAPACIS), a multicenter, observational, prospective on-going study designed to estimate prevalence of ankle-brachial index (ABI) ≤0.90 in patients with NVAF and its influence on cardiovascular and cerebrovascular events incidence over a 3-year follow-up.[17,18]

Details on standard study procedures have been previously reported.[18] In addition, a standard transthoracic echocardiography[19] was performed where feasible. Even if a central analysis of echocardiographic images was not performed, an experienced cardiologist in echocardiography performed a blinded evaluation of measurements for consistency and reliability.

Patients were consecutively recruited, both as inpatients or outpatients, if they were aged ≥18 years and had NVAF diagnosis recorded in the preceding 12 months. Enrollment was performed in 136 facilities belonging to the Italian Internal Medicine Society network from October 2010 and continued until 30 October 2012. All patients signed a written informed consent. The study was conducted in accordance with the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

LVM estimation was calculated according to American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) joint recommendations.[19] LVM values have been indexed by BSA, calculated with the Dubois and Dubois formula (BSA = 0.007184 × weight [Kg]$^{0.425}$ × height [cm]$^{0.725}$). Thus, we defined the presence of LVH for an LVM indexed by BSA (LVMI-BSA) >95 g/m^2 for women and an LVMI-BSA >115 g/m^2 for men.[19]

The definition of LV remodeling was assessed calculating the relative wall thickness (RWT). In accordance to ASE/EAE recommendations,[19] RWT ≥0.42 defined a concentric remodeling, otherwise an RWT <0.42 defined an eccentric remodeling. All patients were then categorized into 4 categories of cardiac remodeling: (1) no remodeling, that is, patients without LVH and with an RWT <0.42; (2) concentric remodeling, that is, patients without LVH and with an RWT ≥0.42; (3) eccentric hypertrophy, that is, patients with LVH and an RWT <0.42; and (4) concentric hypertrophy, that is, patients with LVH and an RWT ≥0.42.

According to Shapiro−Wilk normality test, variables with a normal distribution were tested for differences by the Student *t* test and reported as mean ± standard deviation. Variables with nonhomogeneous variances were tested by the Mann−Whitney *U* test and reported as median and interquartile range. Categorical variables, expressed as counts and percentages, were analyzed by a chi-square test. A gender-stratified analysis was also conducted. Finally, a multivariate regression analysis was performed to establish LVH determinants in patients with NVAF. To reduce interobserver variability, the regression analysis was corrected for enrolling centers. The probability values were 2 sided; a p value <0.05 was considered statistically significant. All analyses were carried out with SPSS version 20 (IBM, NY, USA).

Results

Among a total of 2,027 patients enrolled in ARAPACIS, echocardiographic data were available for 1,184 subjects (59%). After data revision, 1,087 patients (72 ± 11 years; 56% men) were eligible for analysis (Figure 1). Clinical and demographic variables in nonincluded patients were similar to those analyzed (Table 1).

Previous cardiovascular disease was recorded for about 1/4 of patients. Among classic cardiovascular risk factors, hypertension was the most prevalent (82%). The mean LVMI-BSA was 112 ± 31 g/m^2. Values of LVMI-BSA were greater in permanent NVAF compared to those with persistent AF (p = 0.0107) or paroxysmal AF (p = 0.0023). LVMI-BSA progressively increased with higher CHA$_2$DS$_2$-VASc risk classes (p <0.0001; Figure 2).

LVH was recorded in 52% of patients. Clinical and demographic characteristics in the groups are reported in Table 1. Patients with LVH were older, had a higher prevalence of hypertension, diabetes, and previous myocardial infarction (MI) compared to those without. ABI ≤0.90 was prevalent in patients with LVH. CHA$_2$DS$_2$-VASc ≥2 class was recorded more frequently in patients with LVH.

Table 2 summarizes echocardiographic characteristics of the 2 groups. Patients with LVH had poorer ventricular function compared to those without LVH. In 59% of patients with LVH, there was a concentric hypertrophy pattern.

Pharmacologic treatments distribution in the 2 groups are reported in Table 3. Patients with LVH were more likely treated with oral anticoagulants (OAC) and angiotensin-converting enzyme inhibitors than those without LVH.

Final forward logistic model showed that female gender (odds ratio [OR] 2.808, 95% confidence interval [CI] 2.152 to 3.664, p <0.001), age (OR per year 1.035, 95% CI 1.021 to 1.048, p <0.001), hypertension (OR 2.302, 95% CI 1.606 to 3.299, p <0.001), diabetes (OR 1.623, 95% CI 1.169 to 2.253, p = 0.004), and previous MI (OR 1.964, 95% CI 1.328 to 2.903, p = 0.001) were independently associated with LVH. No influence of enrolling centers was evident.

LVH was detected in 67% of NVAF women compared to 42% in men. Number of atherosclerotic risk factors was greater in male patients with LVH compared to those without (2.04 ± 1.20 vs 1.76 ± 1.02, p = 0.0041). Similar data were recorded in female patients with LVH compared to those without (1.92 ± 1.12 vs 1.70 ± 1.10, p = 0.0434). Concentric hypertrophy was more common in female

Table 1
Clinical and demographic characteristics according to the presence of left ventricular hypertrophy

Variable	Excluded Patients N= 940	Left Ventricular Hypertrophy		P value Yes vs. No
		Yes N=576	No N=511	
Age (years.), mean±SD	74±9	75±9	70±12	<0.0001*
Age Classes				<0.0001[†]
<65 years	263 (28%)	123 (21%)	191 (37%)	
65-74 years	209 (22%)	141 (25%)	142 (28%)	
≥75 years	468 (50%)	312 (54%)	178 (35%)	
Women	439 (47%)	353 (56%)	158 (31%)	<0.0001[†]
Body Mass Index (Kg/m^2), mean±SD	28±5	28±5	28±5	0.4876*
Type of Atrial Fibrillation				0.0866[†]
Paroxysmal	425 (45%)	233 (41%)	221 (43%)	
Persistent	120 (13%)	82 (14%)	90 (18%)	
Permanent	395 (42%)	261 (45%)	200 (39%)	
Hypertension[‡]	785 (84%)	515 (89%)	374 (73%)	<0.0001[†]
Diabetes Mellitus	237 (25%)	152 (26%)	77 (15%)	<0.0001[†]
Smoker	138 (15%)	77 (13%)	100 (20%)	0.0057[†]
Hypercholesterolemia[§]	353 (38%)	231 (40%)	205 (40%)	0.9964[†]
Metabolic Syndrome	282 (31%)	164 (30%)	141 (29%)	0.6767[†]
Previous Transient Ischemic Attack/Stroke	116 (12%)	67 (12%)	52 (10%)	0.4429[†]
Previous Myocardial Infarction	159 (17%)	105 (18%)	49 (9.6%)	<0.0001[†]
Previous Peripheral Artery Disease	13 (1.4%)	9 (1.4%)	10 (1.9%)	0.5624[†]
Heart Failure	189 (20%)	102 (18%)	87 (17%)	0.7668[†]
Ankle-Brachial Index ≤0.90[¶]	212 (23%)	128 (22%)	88 (17%)	0.0391[†]
CHA$_2$DS$_2$-VASc, median [IQR]	3 [2-4]	4 [3-5]	2 [1-4]	<0.0001[‖]
CHA$_2$DS$_2$-VASc Classes				<0.0001[†]
Score 0	25 (2.7%)	8 (1.4%)	46 (9.0%)	
Score 1	108 (11.5%)	35 (6.1%)	94 (18.4%)	
Score≥2	807 (85.8%)	533 (92.5%)	371 (72.6%)	

IQR = Interquartile Range; SD = Standard Deviation.

* Student t test.

[†] Chi-square test.

[‡] Blood Pressure>140/90 mm Hg or treated with anti-hypertensive drugs.

[§] Total Cholesterol≥ 240 mg/dl or treated with lipid lowering drugs.

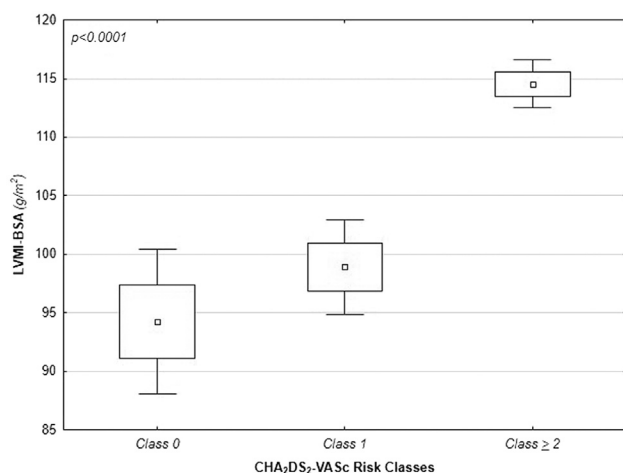[¶] Data referred to 1,084 patients.

[‖] Mann Whitney U test.

Figure 2. LVMI-BSA values distribution according to CHA$_2$DS$_2$-VASc score.

patients (F = 46% vs M = 29%, p = 0.0003). Women with LVH, compared with men, were less treated with OAC (65% vs 69%, p = 0.0318).

Discussion

The present analysis of a selected cohort from the ARAPACIS study provides, for the first time, data on the high prevalence of LVH, defined as LVM indexed by BSA. Second, we identified female gender, age, hypertension, diabetes, and previous MI as clinical factors associated with the presence of LVH in patients with NVAF. Third, we observed that concentric hypertrophy was the most common remodeling pattern in female patients with NVAF.

These findings could contribute to a better understanding of ventricular remodeling in patients with NVAF. In fact, previous clinical studies reported a huge range (from 23% to 68%) of LVH prevalence in AF,[15,16] probably because of heterogeneity of patients enrolled or to different LVH evaluations.[15,16] Using a standard recommended method for LVH definition, we have now provided more reliable data on LVH prevalence in patients with NVAF. Second, taking in account that LVMI-BSA seems to be one of the most reliable method to determine the cardiovascular risk associated with left ventricular remodeling,[20] our work could represent a premise for evaluating clinical usefulness of LVH detection in cardiovascular risk assessment also in

Table 2

Echocardiographic characteristics according to the presence of left ventricular hypertrophy

Variable	Left Ventricular Hypertrophy		P
	Yes N=576	No N=511	
Left Ventricular Ejection Fraction (%), mean±SD	54±10	57±8	<0.0001*
Left Ventricular Ejection Fraction <50%	133 (23%)	62 (12%)	<0.0001[†]
Left Ventricular Mass Indexed by Body Surface Area (g/m^2), mean±SD	132±27	89±15	<0.0001*
Relative Wall Thickness (>0.42)	338 (59%)	215 (42%)	<0.0001[†]
Left Ventricular Internal End-Diastolic Dimension (mm), mean±SD	53±6	48±5	<0.0001*
Interventricular Septum Thickness (mm), mean±SD	12±2	10±2	<0.0001*
Posterior Wall Thickness (mm), mean±SD	11±2	9±1	<0.0001*
Left Atrial Diameter (mm), mean±SD[‡]	45±8	44±9	0.2488*
Cardiac Remodeling			<0.0001[†]
None Remodeling	0 (0)	296 (58%)	
Concentric Remodeling	0 (0)	215 (42%)	
Eccentric Hypertrophy	238 (41%)	0 (0)	
Concentric Hypertrophy	338 (59%)	0 (0)	

SD = Standard Deviation.

* Student t test.

[†] Chi-square test.

[‡] Data referred to 912 patients.

Table 3

Pharmacologic treatments distribution according to the presence of left ventricular hypertrophy

Variable	Left Ventricular Hypertrophy		P*
	Yes N=576	No N=511	
Anti-Thrombotic			0.0134
None	48 (8.3%)	62 (12%)	
Oral Anticoagulant	381 (66%)	309 (61%)	
Antiplatelets	117 (20%)	125 (25%)	
Oral Anticoagulant+Antiplatelets	30 (5.1%)	15 (2.9%)	
Statins	218 (38%)	189 (37%)	0.7697
Beta-Blockers	260 (45%)	213 (42%)	0.2513
Angiotensin-Converting-Enzyme Inhibitors	222 (39%)	155 (30%)	0.0045
Angiotensin II Receptor Blockers	212 (37%)	169 (33%)	0.1979
Calcium Channel Blockers	165 (29%)	127 (25%)	0.1591
Nitrates	83 (14%)	38 (7.4%)	0.0002
Antiarrhythmics	159 (28%)	156 (31%)	0.2888
Digoxin	117 (20%)	64 (13%)	0.0005
Diuretics[†]	293 (60%)	193 (45%)	<0.0001
Oral Hypoglycemic Agents	92 (16%)	52 (10%)	0.0049
Subcutaneous Insulin	44 (7.6%)	11 (2.1%)	<0.0001

* Chi-square test.

[†] Data referred to 859 patients.

patients with NVAF. Indeed, higher prevalence of ABI ≤0.90 could suggest an association between atherosclerosis and LVH,[21,22] which requires further investigations. Moreover, the recognition of LVH may play a pivotal role to correctly stratify cerebrovascular risk of patients with NVAF as reported in hypertensive patients.[23,24] In fact, previous data demonstrated that increased LVM, and abnormal RWT, are associated with increased risk of stroke in hypertensive patients, even higher in patients with a concentric pattern.[24]

A post hoc analysis from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial[16] reported that LVH assessed by LVM was an independent predictor of both all-cause mortality and stroke in patients with AF.[16] Further evaluations of follow-up data of ARAPACIS study will provide a relevant evidence to clarify this poorly explored issue.

Although patients with LVH are at greater thromboembolic risk, we found suboptimal OAC use, as previously reported for the overall ARAPACIS study population.[17] Moreover, female patients with LVH seem to be significantly less treated with OAC. Considering the higher stroke risk in women with LVH compared to men with or without LVH,[25,26] the underuse of OAC could contribute to the higher stroke risk of female patients. The standard evaluation of LVH presence in patients with NVAF could be useful to better define thromboembolic risk, independently by other thromboembolism risk factors. When available, prospective data coming from ARAPACIS study might clarify this aspect.

Our data suggest that different LVH development among sex might be relevant in stratifying thromboembolic risks of patients with NVAF. The prevalence of concentric hypertrophy in our female patients with NVAF was significantly higher compared with men. Indeed, experimental data suggest that cardiac hypertrophy development in response to a pathologic stimulus may be blunted in women compared with men,[27] yet the relative mortality risk, when hypertrophy does occur, is greater in women and is more commonly concentric.[28,29] As stated previously, concentric hypertrophy in hypertensive patients carries the greatest stroke risk.[24] Furthermore, gender differences in LVH distribution and worse cardiac remodeling in patients with NVAF may partly explain why female gender confers additional risk of thromboembolic stroke. Accordingly, the presence of LVH, as defined by electrocardiography, confers a greater stroke risk of in patients with LVH AF.[15]

As with any observational analysis, residual unmeasured confounders may exist and impact the validity of our results. Given the cross-sectional nature of the study, data presented cannot establish a pathophysiological link between NVAF and LVH but provide hypothesis-generating associations. Given that hypertension was highly prevalent in patients with NVAF and because hypertension represents a fundamental risk factor for the developing of LVH, we cannot establish whether LVH was evident before the development of NVAF. Finally, the present analysis is based on the assumption that walls thickness and geometry are homogenous. This assumption could bias the evaluation of LVH prevalence, even if reduced by the use of 3 different measurements to assess LVM.

To summarize, patients with NVAF have a high prevalence of LVH, which is related to female gender, older age, hypertension, and previous MI. Ongoing prospective data from the ARAPACIS study will clarify the potential predictive role of LVH in patients with NVAF.

Disclosures

Professor Lip served as an advisor or consultant for: Astellas Pharma, Inc.; Bayer HealthCare Pharmaceuticals; BIOTRONIK; Boehringer Ingelheim Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Daiichi Sankyo, Inc.; Merck & Co., Inc.; Pfizer Inc; Portola Pharmaceuticals, Inc.; Sanofi. Served as a speaker or a member of a speakers bureau for: Bayer HealthCare Pharmaceuticals; Boehringer Ingelheim Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Pfizer Inc; Sanofi. All other authors have nothing to disclose.

Supplementary Data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2015.05.060.

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