Characteristics and Prognosis of Patients With Nonvalvular Atrial Fibrillation and Significant Valvular Heart Disease Referred for Electrical Cardioversion

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Valvular atrial fibrillation (AF) is defined as AF in the presence of mitral stenosis or mechanical valve prosthesis. However, there are patients with AF who have significant native valvular heart disease (VHD) others than mitral stenosis that are classified as nonvalvular AF. The characteristics and prognostic implications of these entities have not been extensively studied. Of 1,885 AF patients referred for electrical cardioversion (64 ± 13years, 71% male), 171 (9.1%) had valvular AF (any grade of mitral stenosis or mechanical/biological valve prostheses) and 1,714 patients were identified as nonvalvular AF, of whom 329 (17.5%) had significant left-sided VHD. Patients with nonvalvular AF but with significant left-sided VHD were older, more frequently women and had more co-morbidities compared with the other groups. Furthermore, nonvalvular AF patients with significant left-sided VHD showed the worst left ventricular systolic function and largest left atrial volumes. During a median follow-up of 64 months (interquartile range: 33 to 96 months), 488 patients presented with the combined endpoint of all-cause mortality, heart failure hospitalization, and ischemic stroke. Patients with nonvalvular AF and with significant left-sided VHD had more events of heart failure whereas patients with valvular AF had higher all-cause mortality events. There were no differences in ischemic stroke events. Type of AF was not associated with outcomes after correcting for echocardiographic variables. In conclusion, the frequency of AF patients with significant VHD is relatively high. The consequences of VHD and AF on cardiac structure and function are more important determinants of adverse outcome than the type of AF. **(Am J Cardiol 2020;128:84−91)**

Randomized-controlled clinical trials evaluating the efficacy of direct oral anticoagulants (DOACs) have included patients with various types and grades of valvular heart disease (VHD), whereas patients with moderate and severe mitral stenosis and mechanical heart valve prostheses were systematically excluded.[1] Only 1 study showed that dabigatran had no benefit and increased the risk of thromboembolic and bleeding complications in patients with mechanical heart valves.[2] Currently, the European and American guidelines do not recommend the use of DOACs in patients with AF and mechanical heart valve prosthesis or moderate and severe mitral stenosis.[3,4] In patients with AF and significant VHD (other than mitral stenosis and mechanical valve prostheses), the current recommendations consider DOACs as an alternative to vitamin K antagonists (class IIa recommendation). Although the risk of thromboembolism is mainly related to the efficacy of anticoagulation therapy, several clinical, and echocardiographic characteristics have showed to modify this association and may explain the differences in clinical outcomes observed in patients with AF and various types and grades of VHD.[1] We investigated the clinical and echocardiographic characteristics that influence the association between type of AF (valvular vs nonvalvular) and clinical outcomes.

Methods

From a retrospective registry of patients with AF referred for electrical cardioversion to the Leiden University Medical Center from June 2005 until January 2015,[5] 1,885 patients were selected for the present analysis. The first admission with AF for all patients was identified and clinical information was collected based on chart review. Conventional echocardiographic data acquired immediately after the diagnosis of AF were selected for analysis. Patients without clinical or echocardiographic data were excluded. AF was diagnosed in accordance with the European Society of Cardiology guidelines for the management of AF.[3] Patients were divided into 3 groups according to the type of AF: (1) patients with valvular AF, defined as AF in patients

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with any grade of mitral stenosis, or previous valvular replacement (mechanical and biological valve prostheses),[6] (2) nonvalvular AF patients with VHD was defined as AF in patients with moderate to severe left-sided VHD (except mitral stenosis) or previous surgical valve repair,[6] and (3) patients with AF without VHD. The prevalence of each type of AF and the clinical and echocardiographic characteristics of the patients of each group were evaluated. In addition, the association between type of AF and prognosis was evaluated. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent (G16.039).

Clinical characteristics included demographics, cardiovascular risk factors, medication use, and creatinine level. The CHA_2DS_2-VASc-score was additionally calculated for each patient based on a point system in which 2 points were assigned for a history of stroke or transient ischemic attack, or age ≥75 years; and 1 point each was assigned for age 65 to 74 years, a history of hypertension, diabetes, cardiac failure, vascular disease (myocardial infarction, peripheral artery disease, complex aortic plaque), and female gender.[3,7]

Echocardiography was performed with commercially available ultrasound systems (Vivid 7 and E9; General Electric Vingmed, Horten, Norway) with patients in the left lateral decubitus position at rest. Data acquisition was performed with a 3.5-MHz or M5S transducers. Echocardiographic M-mode, 2-dimensional, color, pulsed, and continuous wave Doppler data were obtained and digitally stored for offline analysis (EchoPac BT13; GE Medical Systems, Horten, Norway). Left ventricular (LV) volumes and left atrial (LA) volumes were measured on the apical 2- and 4-chamber views using the Simpson's method and were indexed for body surface area.[8] LV ejection fraction was calculated based on the difference between LV end-diastolic and end-systolic volumes relative to the LV end-diastolic volume.

Presence of left-sided VHD was performed according to prevailing recommendations.[9,10] Mitral stenosis was graded according to the mean transvalvular gradient and mitral valve area calculated according to the pressure half time and/or planimetry (when previous balloon valvuloplasty was performed). Mitral regurgitation grading was based on integrative approach considering the valve morphology, color flow regurgitant jet, continuous wave Doppler of the regurgitant jet, vena contracta width, flow reversal of the pulmonary vein flow, and quantification of the effective regurgitant orifice area and regurgitant volume if feasible as well as the LV and LA dimensions.[9] Aortic stenosis was graded based on peak jet velocity, mean transvalvular gradient, and aortic valve area,[11] whereas aortic regurgitation was graded using an integrative approach that includes width of the regurgitant jet relative to the diameter of the LV outflow tract, the pressure half time of the regurgitant jet, diastolic flow reversal in the descending aorta, as well as the LV dimensions.[9]

Patients were followed up for the occurrence of the combined end point of hospitalization for heart failure, ischemic stroke, and all-cause mortality. Deceased patients were identified from the hospital medical records (EPD-Vision and EZIS; Leiden University Medical Centre, Leiden, the Netherlands). This information system is linked to the national death registry and updated on a monthly basis.

Categorical variables are presented as numbers and percentages. Continuous variables with a normal distribution are presented as mean ± standard deviation. Comparisons of categorical variables between the 3 groups were performed with the chi-square test, whereas continuous data were compared using the 1-way analysis of variance. Post hoc analysis of continuous variables was performed with the Bonferroni test. The time to the combined end point was estimated using the Kaplan-Meier method and the time-to-event rates were compared across groups with the log-rank test. The association between type of AF and outcomes was assessed with Cox regression analysis. The variables with a $p < 0.10$ in the univariable analysis were included in a multivariable Cox regression analysis. A p value <0.05 was considered statistically significant. Analyses were performed using SPSS software (Version 23.0, IBM Corp., Armonk, NY).

Results

Total of 1,885 AF patients were included with a mean age of 64 ± 13 years, 71% male. The prevalence of valvular AF versus nonvalvular AF is displayed in Figure 1: 9.1% (n = 171) had valvular AF and 90.9% (n = 1,385) had

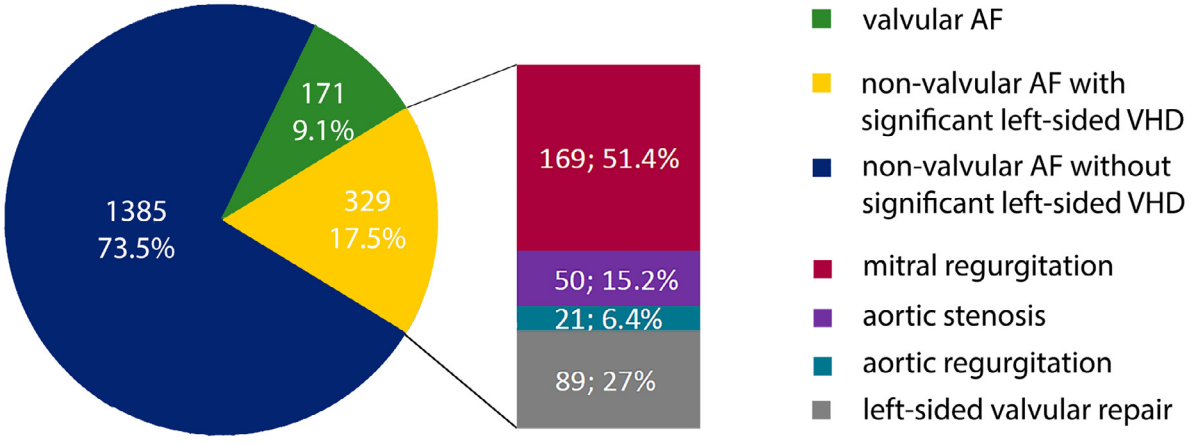

Figure 1. Distribution of valvular versus nonvalvular atrial fibrillation with and without significant valvular heart disease. AF = atrial fibrillation; VHD = valvular heart disease.

Table 1
Clinical characteristics

Variable	Valvular AF (n = 171)	Nonvalvular AF without significant VHD (n = 1,385)	Nonvalvular AF with significant VHD (n = 329)	ANOVA p Value
Age (years)	63.9 ± 12.7	63.0 ± 11.8	67.4 ± 10.9 *	<0.0001
Male	121 (70.8%)	1054 (76.1%)†	211 (64.3%)	<0.0001
Creatinine (μmol/L)	99.7 ± 57.7	93.5 ± 49.4†	101.3 ± 56.1	0.026
Diabetes mellitus	23 (13.5%)	196 (14.2%)	47 (14.3%)	0.972
Hypertension	108 (63.5%)	973 (70.3%)	231 (70.2%)	0.192
Acute myocardial infarction	25 (14.6%)†	303 (21.9%)	85 (25.8%)	0.016
ACE/ARB	105 (61.8%)	752 (54.3%)†	226 (68.9%)	<0.0001
Beta-blocker	120 (70.2%)	941 (67.9%)	239 (72.9%)	0.21
Diuretic	93 (54.4%)	428 (30.9%) *	177 (54.0%)	<0.0001
Statin	75 (43.9%)	613 (44.3%)	161 (49.1%)	0.272
Vitamin K antagonist	135 (78.9%)	956 (69.0%) *	254 (77.4%)	0.001
CHA_2DS_2-VASc	2.94 ± 1.71	2.45 ± 1.67 *	3.27 ± 1.62	<0.0001
CHA_2DS_2-VASc				
Score = 0	9 (5.3%)	166 (12.0%)	17 (5.2%)	
Score = 1	29 (17.0%)	302 (21.8%)	37 (11.2%)	
Score ≥ 2	133 (77.8%)	917 (66.2%)	275 (83.6%)	

AF = atrial fibrillation; ACE/ARB = ace-inhibitors/angiotensin receptor blockers; CHA_2DS_2-VASc = thromboembolic risk score; Acronym for congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and gender category (female); VHD = valvular heart disease.

Valvular AF is defined as AF in patients with any grade of mitral stenosis, or previous valvular replacement (mechanical and biological valve prostheses); nonvalvular AF with significant VHD is defined as AF in patients with moderate to severe left-sided VHD (except mitral stenosis) or previous surgical valve repair.

* p value <0.05 versus all groups.

† p value <0.05 versus nonvalvular AF with significant VHD.

nonvalvular AF. In the nonvalvular AF group, 329 patients (17.5%) had significant left-sided VHD (51.4% mitral regurgitation, 15.2% aortic stenosis, 6.4% aortic regurgitation, and 27% had previous valvular repair). Table 1 summarizes the clinical characteristics of the patients. Nonvalvular AF patients with significant VHD were significantly older, more frequently female and had more comorbidity compared with patients with valvular AF. In addition, patients with nonvalvular AF with significant VHD had the highest CHA_2DS_2-VASc-score.

Echocardiographic characteristics are shown in Table 2. Patients with nonvalvular AF with significant VHD had more severe LV and LA dilatation, and more reduced LV ejection fraction versus the other groups. Patients with nonvalvular AF without significant VHD had the smallest LA dimensions, with the most preserved LV and LA function based on speckle tracking echocardiography analysis.

During a median follow-up of 64 months (interquartile range: 33 to 96), 488 patients presented with the combined

Table 2
Echocardiographic characteristics

	Valvular AF (n = 171)	Nonvalvular AF without significant left-sided VHD (n = 1,385)	Nonvalvular AF with significant left-sided VHD (n = 329)	ANOVA p Value
Left ventricular end-diastolic diameter (mm)	49.5 ± 9.4	48.9 ± 7.9	52.9 ± 10.0*	<0.0001
Left ventricular end-systolic diameter (mm)	34.4 ± 10.7	32.7 ± 8.9	37.9 ± 11.7*	<0.0001
Interventricular septum thickness (mm)	13.2 ± 3.1 *	12.4 ± 2.7	12.6 ± 3.2	0.001
Left ventricular end-diastolic volume (ml)	126.4 ± 59.1	116.1 ± 48.7 *	137.8 ± 63.1	<0.0001
Left ventricular end-systolic volume (ml)	66.4 ± 48.7*	56.6 ± 38.6 *	78.4 ± 53.2*	<0.0001
Left ventricular ejection fraction (%)	50.3 ± 53.4*	53.5 ± 12.8 *	46.3 ± 14.7*	<0.0001
Left atrial diameter (mm)	47.6 ± 9.0	43.9 ± 7.4 *	48.3 ± 7.9	<0.0001
Left atrial volume (ml)	109.7 ± 53.4	87.4 ± 37.3 *	110.8 ± 45.0	<0.0001
Left ventricular global longitudinal strain (%)	−12.4 ± 4.9	−14.7 ± 5.0*	−11.8 ± 5.3	<0.0001
Peak atrial longitudinal strain (%)	16.6 ± 12.1	23.4 ± 15.2*	15.0 ± 10.1	<0.0001

AF = atrial fibrillation; VHD = valvular heart disease.

Valvular AF is defined as AF in patients with any grade of mitral stenosis, or previous valvular replacement (mechanical and biological valve prostheses); nonvalvular AF with significant VHD is defined as AF in patients with moderate to severe left-sided VHD (except mitral stenosis) or previous surgical valve repair.

* p value <0.05 versus all groups.

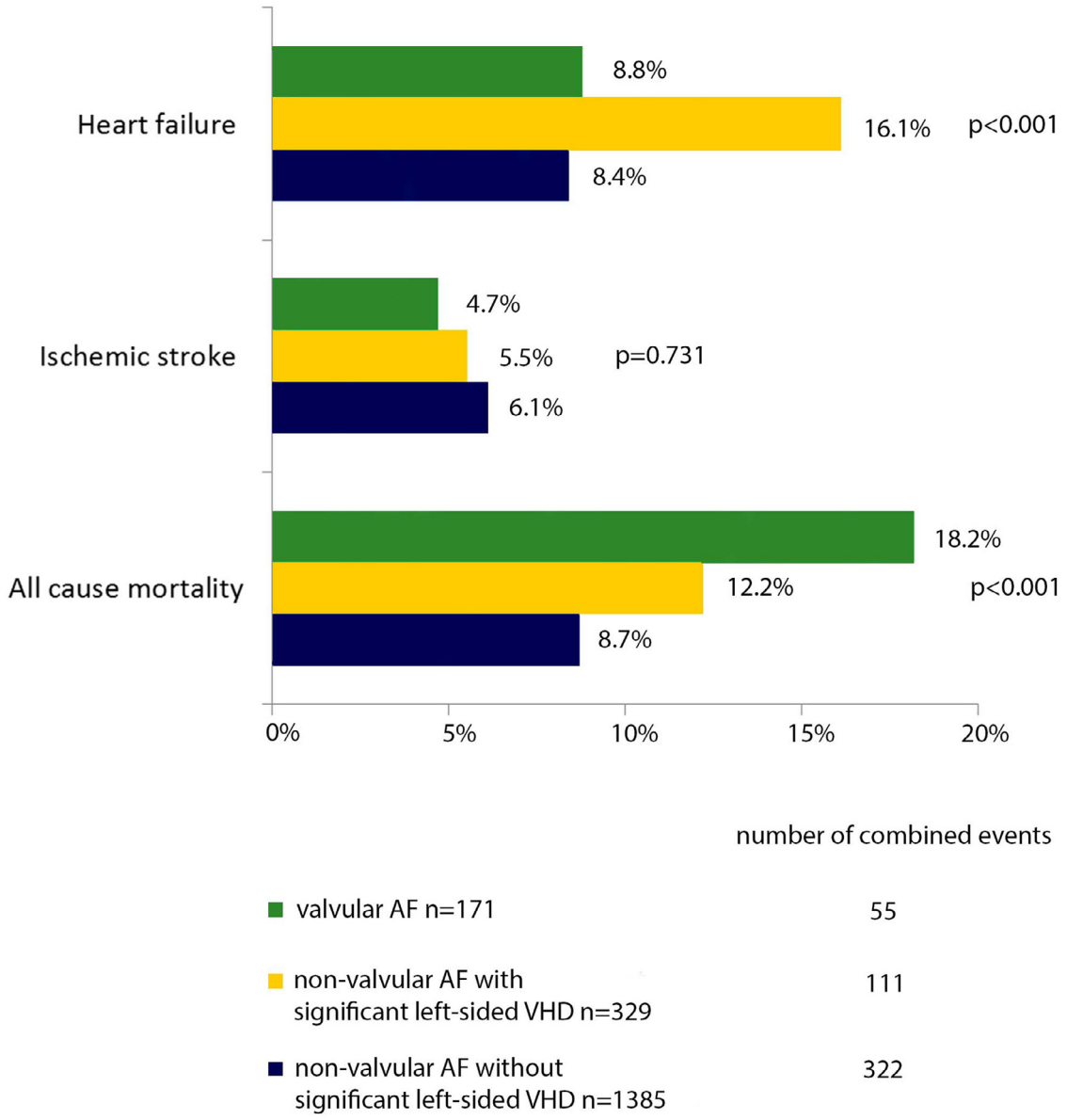

Figure 2. Frequency of the adverse events in AF patients per valvular heart disease status. AF = atrial fibrillation; VHD = valvular heart disease.

end point of all-cause mortality, heart failure hospitalization, and ischemic stroke. Figure 2 shows the event rates for each component of the combined end point for each AF group. All-cause mortality was higher in patients with valvular AF, whereas heart failure hospitalization was more frequent in patients with nonvalvular AF with significant VHD. Ischemic stroke was more frequently recorded in the nonvalvular AF group without significant VHD followed by patients with valvular AF.

The Kaplan-Meier curves for event-free survival of the combined end point for each AF group are displayed in Figure 3. Patients with nonvalvular AF without significant VHD had significantly less events compared with the other groups (log-rank chi-square = 27.616, p <0.001). On univariate Cox regression analysis, valvular AF (HR 1.59, 95% CI 1.19 to 2.13; p = 0.002) and nonvalvular AF with significant VHD (HR 1.70, 95% CI 1.36 to 2.13; p <0.001) were associated with increased risk of the combined end point (Table 3). After correction for clinical variables, valvular AF, and nonvalvular AF with significant VHD remained independently associated with the outcome. However, when introducing the echocardiographic variables that reflect the consequences of VHD and AF, the type of AF was not independently associated with all-cause mortality and cardiovascular events (Table 3).

Discussion

The present study reports a relatively low prevalence of valvular AF but relatively high frequency of AF patients with significant VHD. Both valvular AF and nonvalvular AF with significant VHD were associated with increased all-cause mortality and cardiovascular events. However, when type of AF was corrected for echocardiographic

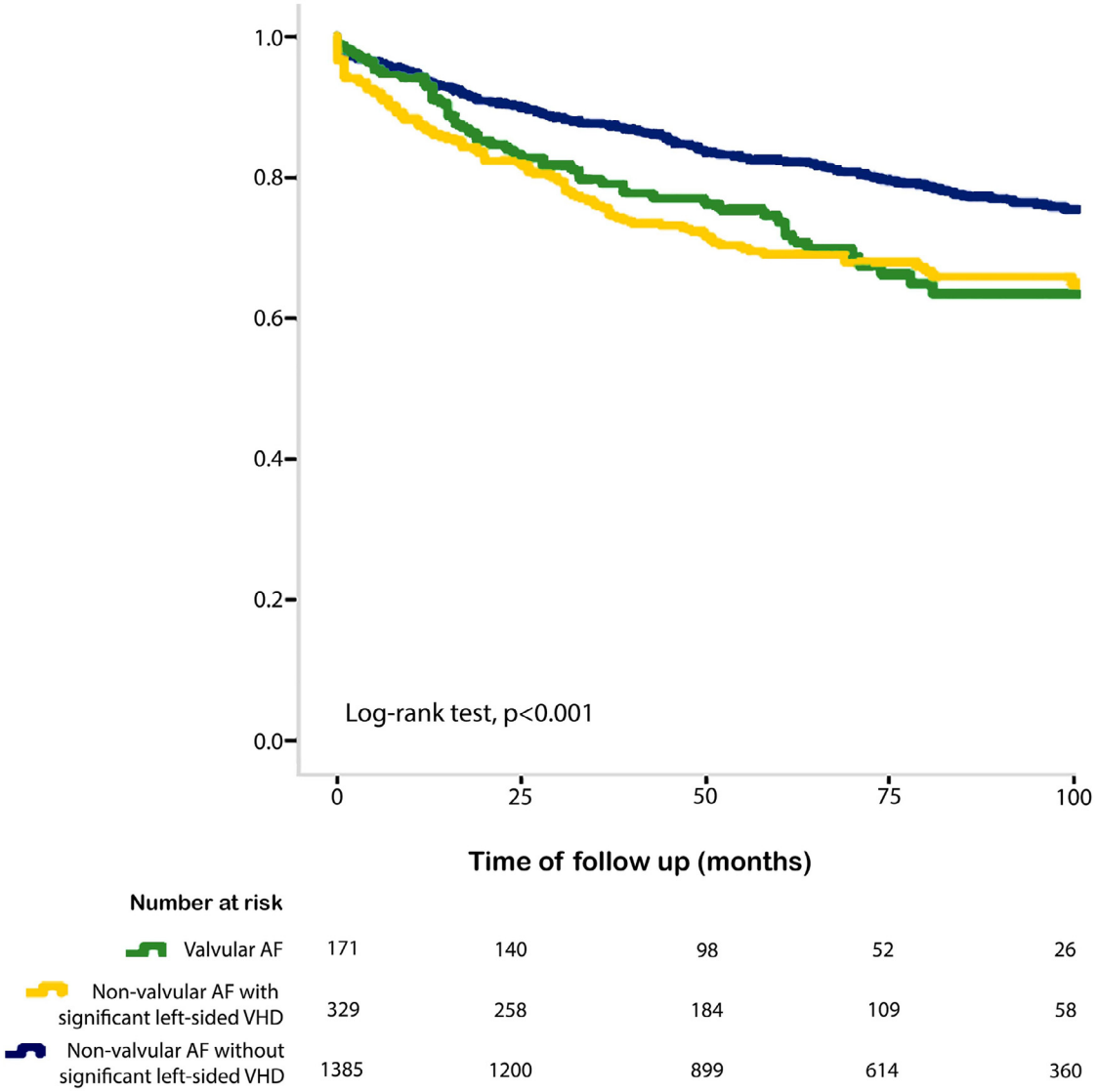

Figure 3. Kaplan-Meier curves for combined adverse events of all-cause mortality, heart failure hospitalization, and ischemic stroke in AF patients per valvular heart disease status. AF = atrial fibrillation; VHD = valvular heart disease.

variables reflecting the consequences of VHD and AF, the association with the outcomes was not significant.

Although the majority of the randomized clinical trials on the efficacy of DOACs in AF patients excluded patients with valvular AF, post hoc analyses have demonstrated that a significant proportion of patients had VHD.[12–15] A meta-analysis of 4 DOAC trials[1,12–15] comparing the prevalence and outcome of 58,095 AF patients without VHD (81%) versus 13,585 (19%) with VHD showed that the most frequent VHD in patients with nonvalvular AF was moderate to severe mitral regurgitation (73.3% to 87.7%) followed by moderate to severe aortic regurgitation (13% to 24.3%) and moderate to severe aortic stenosis (5.8% to 11.9%).[1,12–15] Although the RE-LY trial excluded any valve intervention,[14] the ROCKET-AF study included valve repair (2.1%) and valvuloplasty (3.2%) but excluded bioprosthetic heart valves.[15] In contrast, the ARISTOTLE trial included bioprosthetic valves (1.7%).[12] The present study reported a similar prevalence of nonvalvular AF with significant VHD compared with the pooled data from the meta-analysis by Renda et al (17.5% vs 19%).[1] Among nonvalvular AF patients with significant VHD, mitral regurgitation was the most frequent lesion followed by valvular repair (51.4% vs 27%). These results suggest that the patients included in the DOAC trials differ significantly from patients with AF seen in routine clinical practice (as reported in the current article), particularly for the group of patients with previous valve surgery, a condition known to be associated with increased risk of AF.

The characteristics of patients with and without valvular AF were recently described in a contemporary community-based population, including 9,748 patients, with 19% of them having at least moderate native VHD and 5% having mitral stenosis.[16] Patients with significant native VHD were significantly older compared with patients with mitral stenosis and patients with AF without VHD. Furthermore, patients with mitral stenosis had more frequently cardiovascular risk factors, co-morbidities such as chronic obstructive pulmonary disease, renal dysfunction, heart failure, or

Table 3
Cox regression analysis for combined events of all-cause mortality, heart failure hospitalization, and ischemic stroke

Variable	Univariate analysis		Multivariate analysis clinical model		Multivariate analysis clinical and echocardiographic model	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
AF type:						
Nonvalvular AF without significant VHD	-	<0.001	-	0.001	-	0.273
Nonvalvular AF with significant VHD	1.70 (1.36−2.13)	<0.001	1.44 (1.15−1.81)	0.001	1.28 (0.94−1.74)	0.116
Valvular AF	1.59 (1.19−2.13)	0.002	1.53 (1.13−2.06)	0.005	1.09 (0.86−1.39)	0.460
Age	1.05 (1.04−1.06)	<0.001	1.03 (1.02−1.04)	<0.001	1.03 (1.02−1.04)	<0.001
Male	1.07 (0.87−1.33)	0.527	1.34 (1.07−1.68)	0.010	1.12 (0.89−1.41)	0.335
Diabetes mellitus	2.11 (1.69−2.62)	<0.001	1.57 (1.26−1.96)	<0.001	1.49 (1.18−1.87)	0.001
Hypertension	1.51 (1.21−1.87)	<0.001	0.84 (0.67−1.05)	0.131	0.94 (0.74−1.18)	0.575
Acute myocardial infarction	2.63 (2.17−3.17)	<0.001	1.82 (1.48−2.22)	<0.001	1.41 (1.14−1.75)	0.002
CHA_2DS_2-VASc						
Score = 0	-	<0.001	-	<0.001	-	<0.001
Score = 1	3.74 (1.69−8.30)	0.001	3.63 (1.62−8.13)	0.002	3.02 (1.34−6.78)	0.008
Score ≥ 2	10.89 (5.16−23.00)	<0.001	5.93 (2.67−13.18)	<0.001	4.26 (1.91−9.48)	<0.001
Left ventricular ejection fraction (per each 1% increase)	0.96 (0.95−0.97)	<0.001			0.98 (0.97−0.99)	<0.001
Left ventricular global longitudinal strain (per each 1% impairment)	1.13 (1.10−1.15)	<0.001			1.05 (1.02−1.07)	0.001
Left atrial volume	1.01 (1.00−1.01)	<0.001			1.004 (1.002−1.006)	0.001

AF = atrial fibrillation; CHA_2DS_2-VASc = thromboembolic risk score; Acronym for congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and gender category (female); CI = confidence interval; HR = hazard ratio; VHD = valvular heart disease.

Valvular AF is defined as AF in patients with any grade of mitral stenosis, or previous valvular replacement (mechanical and biological valve prostheses); nonvalvular AF with significant VHD is defined as AF in patients with moderate to severe left-sided VHD (except mitral stenosis) or previous surgical valve repair.

stroke and were more likely to be managed with rate control compared with patients with AF without VHD. The patient population of the present study was similar to that of the randomized trials on DOACs[12−15]: patients with nonvalvular AF but with significant VHD were older, had more frequently heart failure, and other associated co-morbidities compared with patients with AF without VHD. However, the presence of previous stroke was not different between groups.[12,14] Although patients in our study population were 10 years younger than patients included in the abovementioned studies,[12−15] patients with nonvalvular AF but with significant VHD were significantly older and had more frequently comorbidities.[12−15]

Importantly, the present study provides detailed echocardiographic information on 3 different groups of AF patients to better understand the clinical outcomes. In the substudy of the ENGAGE AF—TIMI 48 trial, of 971 patients with nonvalvular AF, 11% had at least moderate mitral regurgitation.[6] Patients with higher values of the $CHADS_2$-score showed more frequently abnormal LV geometry, larger LA dimensions, and higher LV filling pressures.[6] No differences were observed regarding the frequency of moderate and severe mitral regurgitation across the groups. However, comparisons between nonvalvular AF patients with versus without significant mitral regurgitation were not performed. The present study demonstrates that patients with nonvalvular AF with significant VHD showed significantly larger LV volumes, worse LV systolic function, larger LA volumes and higher values of CHA_2DS_2-VASc scores.

The present study showed that both valvular AF and nonvalvular AF with significant VHD were associated with increased risk of the combined end point of all-cause mortality, heart failure hospitalization, and ischemic stroke. However, the crude frequency of each event varied across the groups: heart failure hospitalization was more frequently observed in patients with nonvalvular AF compared with the other groups whereas patients with valvular AF had the highest frequency in all-cause mortality. In contrast, ischemic stroke was similar across the groups. The results of the ROCKET-AF trial showed that patients with aortic stenosis (n = 214) had higher rates of all-cause mortality, stroke, systemic embolism, or vascular death.[15] In the meta-analysis by Renda et al however,[1] there was no difference in safety and efficacy between high doses of DOACs or vitamin K antagonists across the groups of AF patients suggesting that DOACS are as efficacious in nonvalvular AF patients with or without significant VHD. The present study did not compare those treatments, but it does illustrate that under anticoagulant therapy, the groups do not differ in terms of ischemic stroke but they differ in terms of heart failure events and all-cause mortality. Although the type of AF was independently associated with adverse outcomes after correcting for clinical variables, the association did not remain after correcting for echocardiographic variables. These findings suggest that the consequences of VHD and AF on cardiac structure and function may be more important determinants of adverse events than the type of AF per se.

Several limitations should be acknowledged. We performed a retrospective study of a large population of patients with AF referred for first electrical cardioversion and this may have introduced a selection bias. The primary end point was all-cause mortality because these data are available, whereas cardiovascular or other causes of death were not systematically available.

In conclusion, the prevalence of valvular AF is relatively low in a contemporary cohort of patients with AF referred

for electrical cardioversion. The frequency of significant VHD in patients with AF is relatively high. Both valvular AF and nonvalvular AF but with significant VHD were independently associated with increased risk of all-cause mortality and cardiovascular events. When the type of AF was corrected for echocardiographic variables reflecting the consequences of VHD and AF, the significant association with the outcomes was not observed. This suggests that the consequences of VHD and AF on cardiac structure and function are more important determinants of adverse outcome than the type of AF.

Disclosures

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contribution

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