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Impact of valvular heart disease on oral anticoagulant therapy in non-valvular atrial fibrillation: results from the RAMSES study

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Abstract The definition of non-valvular atrial fibrillation (NVAF) is controversial. We aimed to assess the impact of valvular heart disease on stroke prevention strategies in NVAF patients. The RAMSES study was a multicenter and cross-sectional study conducted on NVAF patients (ClinicalTrials.gov identifier NCT02344901). The study population was divided into patients with significant valvular disease (SVD) and non-significant valvular disease (NSVD), whether they had at least one moderate valvular disease or not. Patients with a mechanical prosthetic valve and mitral stenosis were excluded. Baseline characteristics and oral anticoagulant (OAC) therapies were compared. In 5987 patients with NVAF, there were 3929 (66%) NSVD and 2058 (34%) SVD patients. The predominant valvular disease was mitral regurgitation (58.1%), followed by aortic regurgitation (24.1%) and aortic stenosis (17.8%). Patients with SVD had higher CHA_2DS_2VASc [3.0 (2.0; 4.0) vs. 4.0 (2.0; 5.0), $p < 0.001$] and HAS-BLED [2.0 (1.0; 2.0) vs. 2.0 (1.0; 2.0), $p = 0.004$] scores compared to patients with NSVD. Overall, 2763 (71.2%) of NSVD and 1515 (73.8%) of SVD patients were on OAC therapy ($p = 0.035$). When the patients with SVD were analyzed separately, the mean CHA_2DS_2VASc and HAS-BLED scores were higher in patients with mitral regurgitation compared to patients with aortic regurgitation and aortic stenosis [4.0 (3.0; 5.0), 3.0 (2.0; 4.0), 3.0 (2.0; 4.0) $p < 0.001$ and 2.0 (1.0; 3.0), 1.0 (1.0; 2.0), 1.0 (0.0; 2.0) $p < 0.001$, respectively]. In patients with SVD, 65.7% of mitral regurgitation, 82.6% of aortic regurgitation and 88.0% of aortic stenosis patients were on OAC therapy. One out of three NVAF patients had at least one moderate valvular heart disease with the predominance of mitral regurgitation. Patients with SVD were at greater risk of stroke and bleeding compared to patients with

The collaborators of the study are listed in "Acknowledegments".

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NSVD. Although patients with mitral regurgitation should be given more aggressive anticoagulant therapy due to their higher risk of stroke, they are undertreated compared to patients with aortic valve diseases.

Keywords Atrial fibrillation · Valvular heart disease · Non-valvular atrial fibrillation · Oral anticoagulant therapy

Introduction

Atrial fibrillation (AF) is the most common source of cardioembolic stroke, which can be prevented with adequate anticoagulation. Historically, vitamin K antagonists (VKAs) have been the sole oral anticoagulant (OAC) for prevention of stroke in patients with AF. However, the introduction of direct oral anticoagulants (DOACs) into clinical practice have led to a change in the management of AF patients. Although these relatively new agents are superior to VKAs in terms of a stable anticoagulant effect, they have some pitfalls such as their dependence on renal excretion and a contraindication in valvular AF [1]. The definition of non-valvular atrial fibrillation (NVAF) has come into prominence by the widespread use of DOACs; however, no uniform definition of this term exists, as stated in the European atrial fibrillation (AF) guidelines [2]. North American guidelines recommended against the use of DOACs in patients with mitral valve repair, while European guidelines recommended their use [2, 3]. The recent European Heart Rhythm Association (EHRA) practical guide defined NVAF as AF in the absence of moderate to severe mitral stenosis or a mechanical prosthetic valve [4]. However, each phase III trial of DOACs has had its own criteria for inclusion [5–8]. The guideline definitions and inclusion criteria of phase III DOAC trials are summarized in Table 1. These conflicting sources confused cardiologists and internists who participated to a recent survey; 40% of cardiologists and 29% of internists classified AF as NVAF in the presence of valvular heart disease (VHD) other than mitral stenosis [9].

Although VHD other than mitral stenosis is associated with greater comorbidity and higher CHA_2DS_2VASc scores, leading to higher stroke rates compared to no VHD, it is not associated with an increased risk of stroke after adjustment for comorbid situations [10, 11]. As there are conflicting data regarding the definition of NVAF, we sought to investigate the clinical characteristics of patients with and without VHD and the impact of VHD on OAC prescription patterns by analyzing the RAMSES study data.Author: Please check and confirm the inserted doi in the reference [11].The correct journal pages year and doi:J Am Heart Assoc. 2016 Feb 18;5(2). pii:e002776. doi:10.1161/JAHA.115.002776.

Methods

Study design

The RAMSES study (ClinicalTrials.gov identifier NCT02344901) was a multicenter and cross-sectional registry that was conducted in outpatient cardiology clinics in Turkey. The study was conducted from February to May 2015. The details of this study have been described elsewhere [12]. Briefly, patients aged 18 and over and electrocardiographically confirmed AF were included. Major exclusion criteria were the presence of a mechanical heart valve or any degree of mitral stenosis (usually rheumatic in origin). A survey was conducted to evaluate patient characteristics, including demographics, medical history and ongoing pharmacological treatment for stroke prevention (antiplatelet, anticoagulant or none). Antiarrhythmic drug therapies were also recorded. Time in the therapeutic range (TTR) was calculated for patients on VKA using the traditional method (percentage of time in the range of all measured international normalized ratios). To assess the risk of thromboembolic events, the CHA_2DS_2VASc (congestive

Table 1 The guideline definitions and inclusion criteria of phase III DOAC trials for non-valvular atrial fibrillation

Trial	Mechanical heart valve	Moderate-to-severe MS	Bioprosthetic valve	Mitral valve repair	TAVI	Other native valvular disease
RE-LY	X	X	X	X	X	√
ROCKET-AF	X	X	X	√	X	√
ARISTOTLE	X	X	√	√	X	√
ENGAGE AF	X	X	√	√	X	√
Guideline						
ESC	X	X	X	√	X	√
HRS/ACC/AHA	X	X	X	X	X	√
EHRA	X	X	√	√	√	√

heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65–74 years, and sex) score was calculated and bleeding risk was evaluated by the HAS-BLED (hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs, or alcohol) score [13, 14]. A CHA_2DS_2VASc score of ≥2 was accepted to determine high stroke risk patients while a HAS-BLED score of ≥3 was used to specify patients at high risk of bleeding [4]. Patient medical records were used to determine the etiology and severity of VHD.

Analyzing valvular heart disease

The current analysis was focused on patients with and without VHD. Patients with mitral stenosis and prosthetic heart valves were not included in the RAMSES study and the remaining were defined as non-valvular AF. Thus, patients with any degree of mitral regurgitation (MR), aortic regurgitation (AR) or aortic stenosis (AS) were included in the RAMSES study, regardless of disease etiology. Only patients who had an echocardiogram were included. Patients were subsequently divided into the significant valvular disease (SVD) and non-significant valvular disease (NSVD) groups as follows:

- NSVD: Patients without any VHD or non-significant valvular disease according to the recruiting physician's decision (no or mild VHD).
- SVD: Patients with significant VHD (moderate to severe AR, moderate to severe MR, moderate to severe AS) according to recruiting physician's decision by implementing the established criteria [15].

The patient characteristics, comorbid diseases, CHA_2DS_2VASc and HAS-BLED scores, and ongoing medical treatments were compared between the two groups. Subsequently, the SVD group was divided into the MR, AR and AS groups according to the most severe kind of SVD. The patient characteristics were compared among these three groups to assess the impact of VHD on OAC treatment.

Statistical analysis

Mean ± standard deviation (SD) or median and 25th and 75th percentiles were used for continuous variables and categorical variables were expressed as frequencies and percentages. Univariate analysis (Student *t* test, Mann–Whitney U test or Kruskal–Wallis test) was used for continuous variables and the chi-squared or Fisher's exact test was applied to categorical variables. All analyses were performed using the Statistical Package for Social Sciences software (SPSS 21, Chicago, Illinois). A p value <0.05 was considered statistically significant.

Results

Study population

A total number of 6273 patients were enrolled in the RAMSES study; 5987 patients who had a full echocardiogram were included in the present analysis. Of those, 3929 patients (66%) were classified as NSVD and 2058 (34%) patients were classified as SVD. The most predominant VHD was MR (1197 patients, 58.1%), followed by AR (495 patients, 24.1%) and AS (366 patients, 17.8%).

Comparison of patients with SVD and NSVD

Baseline demographics, clinical data and concurrent treatment characteristics of the patients with and without SVD are described in Table 2. Compared with patients without SVD, the 2058 patients with SVD were older (70.4 ± 10.6 vs. 69.1 ± 10.8 years, $p < 0.001$), were more likely to be female (58.9 vs. 54.0%, $p < 0.001$), had a higher prevalence of persistent or permanent AF (88.9 vs. 77.3%, $p < 0.001$), coronary heart disease (32.4 vs. 27.7%, $p < 0.001$), heart failure (32.5 vs. 17.4%, $p < 0.001$), vascular disease (27.6 vs. 22.9%, $p < 0.001$), prior history of stroke (14.7 vs. 12.3%, $p = 0.011$) and minor bleeding (22.0 vs. 14.9%, $p < 0.001$). However, history of major bleeding was less common (41.1 vs. 46.0%, $p < 0.001$) in patients with SVD. The prevalence of hypertension (67.3 vs. 69.2%, $p = 0.120$) and diabetes (22.2 vs. 22.3%, $p = 0.948$) were similar between the two groups. As a consequence of greater comorbidity, the CHA_2DS_2VASc [3.0 (2.0; 4.0) vs. 4.0 (2.0; 5.0), $p < 0.001$] and HAS-BLED [2.0 (1.0; 2.0) vs. 2.0 (1.0; 2.0), $p = 0.004$] scores were higher in patients with SVD. The distribution of SVD patients according to age groups and CHA_2DS_2VASc scores is illustrated in Fig. 1. There were also significant differences in antiarrhythmic and antithrombotic medication usage rates between groups. More patients in the SVD group were prescribed drugs for rate control (beta blocker, calcium channel blocker or digoxin), while the use of drugs for rhythm control (amiodarone, sotalol and propafenone) were less common in SVD patients compared to patients with NSVD. Overall, 2763 (71.2%) of NSVD and 1515 (73.8%) of SVD patients were on OAC therapy ($p = 0.035$). VKA therapy was more prevalent in SVD patients (37.0 vs. 32.9%, $p = 0.002$) than NSVD patients while DOAC therapy was equally chosen for both groups (36.7 vs. 38.0%, $p = 0.324$). When patients on VKA were compared, there was no difference in TTR

Table 2 Baseline demographics of patients with SVD and NSVD

	NSVD (n = 3929)	SVD (n = 2058)	p value
Age, years	69.1 ± 10.8	70.4 ± 10.6	<0.001
Male	1805 (46.0)	846 (41.1)	<0.001
Tobacco	697 (17.8)	297 (14.4)	0.001
COPD	901 (23.1)	474 (23.0)	1.00
Place of residence, urban	2558 (66.1)	1322 (64.4)	0.186
Atrial fibrillation type			
First diagnosis	225 (5.8)	55 (2.7)	<0.001
Paroxysmal	659 (16.9)	171 (8.4)	
Persistent or permanent	3007 (77.3)	1813 (88.9)	
Hypertension	2717 (69.2)	1382 (67.3)	0.120
Coronary heart disease	1086 (27.7)	667 (32.4)	<0.001
Diabetes mellitus	876 (22.3)	457 (22.2)	0.948
Heart failure	685 (17.4)	669 (32.5)	<0.001
Vascular disease	898 (22.9)	567 (27.6)	<0.001
Stroke	483 (12.3)	302 (14.7)	0.011
Minor bleeding	577 (14.9)	446 (22.0)	<0.001
Major bleeding	139 (3.6)	145 (7.1)	<0.001
CHA_2DS_2VASc	3.0 (2.0; 4.0)	4.0 (2.0; 5.0)	<0.001
HAS-BLED	2.0 (1.0; 2.0)	2.0 (1.0; 2.0)	0.004
$CHA_2DS_2VASc \geq 2$	3368 (85.8)	1860 (90.4)	<0.001
HAS-BLED ≥3	655 (16.7)	503 (24.4)	<0.001
Rate control drugs			
Beta blocker	2426 (62.5)	1353 (66.3)	0.004
Digoxin	686 (17.7)	524 (25.7)	<0.001
Calcium blocker	875 (22.6)	522 (25.6)	0.011
Antiarrhythmic agents			
Amiodarone	186 (4.8)	110 (5.4)	0.348
Propafenone	132 (3.4)	43 (2.1)	0.005
Sotalol	39 (1.0)	16 (0.8)	0.477
Antithrombotic drugs			
VKA only	1071 (27.7)	571 (27.9)	0.831
VKA and antiplatelet	199 (5.1)	183 (9.0)	<0.001
DOAC only	1256 (32.4)	602 (29.5)	0.020
Dabigatran	576 (14.9)	331 (16.2)	0.184
Rivaroxaban	557 (14.4)	197 (9.6)	<0.001
Apixaban	123 (3.2)	74 (3.6)	0.362
DOAC and antiplatelet	216 (5.6)	151 (7.4)	0.007
Antiplatelet only	758 (19.6)	392 (19.2)	0.730
No antithrombotic	371 (9.6)	144 (7.0)	0.001

SVD significant valvular disease, *NSVD* non-significant valvular disease, *COPD* chronic obstructive pulmonary disease, *CHA_2DS_2VASc* congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65–74 years, and sex, *HAS-BLED* hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs, or alcohol, *VKA* vitamin K antagonist, *DOAC* direct oral anticoagulant

Values are given as mean ± standard deviation or number (percentage)

between the SVD and NSVD groups (53.60 ± 25.69, 53.03 ± 26.46%, p = 0.664). Of those patients with SVD, 247 (36.7%) had a TTR ≥65% and of those patients with NSVD 381 (37.5%) had a TTR ≥65% (p = 0.740). Antiplatelet drugs were more likely to be added to OAC therapy in SVD compared to NSVD patients (16.3 vs. 10.7%, p < 0.001). Of those patients with SVD, 183 (9.0%) were on antiplatelet and VKA while 151 (7.4%) were on antiplatelet and DOAC and of those patients with NSVD, 199 (5.1%) were on antiplatelet and VKA while 216 (5.6%) were on antiplatelet and DOAC. The antithrombotic therapy use is detailed in Table 2 and Fig. 2.

Characteristics of SVD patients

A comparison of patient characteristics among MR (n = 1197, 19.9%), AR (n = 495, 8.3%) and AS (n = 366, 6.1%) is shown in Table 3. Patients with MR were older than the patients with AR and AS (72.0 ± 10.1, 67.1 ± 11.3, 69.9 ± 10.0, p < 0.001) and they had more comorbidities than the patients with AR and AS. The mean CHA_2DS_2VASc and HAS-BLED scores were also higher in the MR group compared to the AR and AS groups [4.0 (3.0; 5.0), 3.0 (2.0; 4.0), 3.0 (2.0; 4.0), p < 0.001 and 2.0 (1.0; 3.0), 1.0 (1.0; 2.0), 1.0 (0.0; 2.0), p < 0.001, respectively].

Antithrombotic therapy use in SVD

Overall, 784 (65.7%) MR, 409 (82.6%) AR and 322 (88.0%) AS patients were on OAC therapy (Table 3). The rates of VKA use were similar among these three groups (35.6% for MR, 40.4% for AR and 37.2% for AS, p = 0.180). However, DOAC use differed significantly among the three groups (30.1% for MR, 42.2% for AR and 50.8% for AS, p < 0.001 for the MR, AR and AS groups, respectively). Concomitant antiplatelet and OAC use was similar across the three groups (16.9, 14.5 and 16.9%, p = 0.460 for the MR, AR and AS groups, respectively). Detailed OAC use is described in Table 3 and Fig. 3. The mean TTR of patients with MR, AR and AS was 49.19 ± 25.67, 63.42 ± 22.16 and 52.55 ± 26.83%, respectively (p < 0.001). The number of patients with a TTR ≥65% was 111 (30.0%), 95 (53.1%) and 41 (33.1%) for MR, AR and AS patients, respectively (p < 0.001).

Discussion

The RAMSES study showed that nearly one-third of patients with NVAF had at least one moderate VHD in a real-world setting. These patients were older, had more comorbidities and higher CHA_2DS_2VASc and HAS-BLED scores compared to patients with NSVD. Our study also

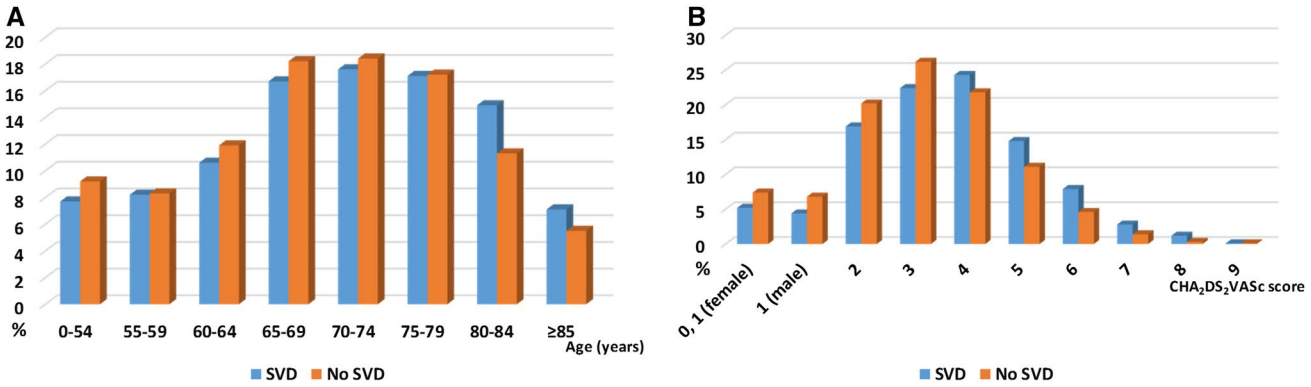

Fig. 1 **a** Distribution of SVD and NSVD according to age. **b** SVD and NSVD patients according to the CHA_2DS_2VASc score

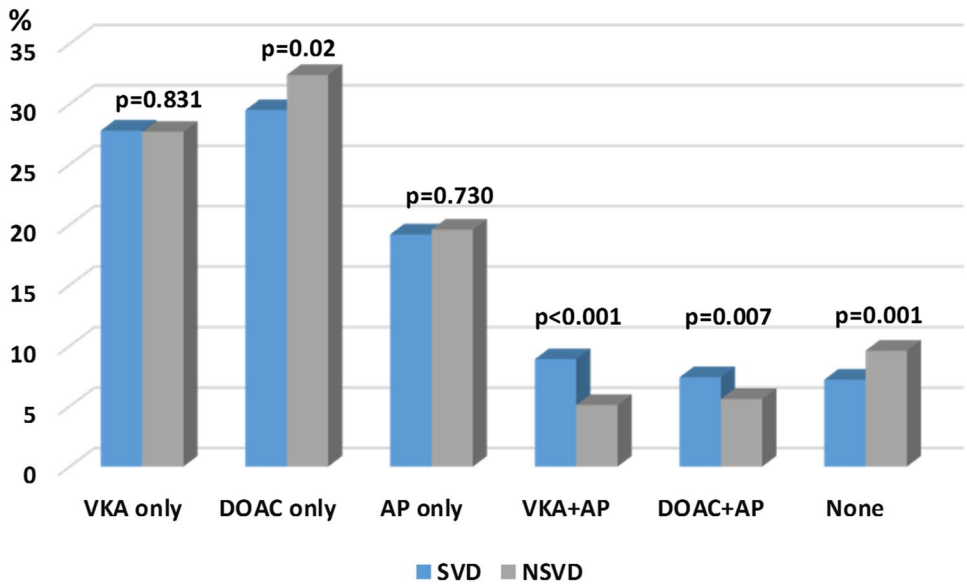

Fig. 2 OAC therapy use in patients with SVD and NSVD

showed that although patients with mitral regurgitation should be given more aggressive anticoagulant therapy due to their higher risk of stroke, they are undertreated compared to patients with aortic valve diseases.

The widespread use of DOACs has led to a discussion regarding DOAC eligible patients with VHD. Some studies have excluded patients with hemodynamically relevant valve disease while others have not. The RE-LY trial excluded patients with severe heart valve disorder, ROCKET AF study excluded patients with hemodynamically significant mitral valve stenosis or prosthetic heart valve, ARISTOTLE and ENGAGE AF TIMI-48 trials excluded patients with moderate or severe mitral stenosis or conditions other than atrial fibrillation that required anticoagulation (e.g. prosthetic heart valve) (Table 1) [5–8]. However, there is a consensus that mitral stenosis (especially of rheumatic origin) should be classified as valvular AF in all trials. The localization of the thrombus differs in valvular AF from that in NVAF. Thrombus formation predominantly occurs in the left atrial appendage in patients with NVAF, whereas about one-half of thrombi are found in the left atrium in patients with rheumatic mitral stenosis [16]. Excluding patients with mitral stenosis, NVAF can be classified as AF with and without native valve disease. A recent European study revealed that 63.5% of patients with AF should be classified as VHD if all patients with any degree of valve disease are counted [17]. Our study showed that 34.0% of RAMSES study patients had SVD, including patients with at least one moderate VHD, excluding patients with mitral stenosis or a mechanical prosthetic valve. The phase III trials on DOACs showed that 21.8% of the RE-LY trial population, 14.1% of the ROCKET AF population and 26.4% of the ARISTOTLE population had at least moderate VHD [18–20]. Boriani et al. showed that 63.6% of AF patients present at least mild valvular disease and 23.2, 12.2 and 8.8% of their study population were classified as bring affected by valvular AF (i.e. would not be included in pivotal DOAC trials)

Table 3 Baseline demographics of patients with MR, AR and AS

	MR (n = 1197)	AR (n = 495)	AS (n = 366)	p value
Age, years	72.0 ± 10.1	67.1 ± 11.3	69.9 ± 10.0	<0.001
Male	477 (39.8)	216 (43.6)	153 (41.8)	0.339
Tobacco	173 (14.5)	89 (18.0)	35 (9.6)	0.002
COPD	338 (28.3)	86 (17.4)	50 (13.7)	<0.001
Place of residence, urban	679 (56.8)	348 (70.6)	295 (80.8)	<0.001
Atrial fibrillation type				
First diagnosis	20 (1.7)	19 (3.9)	16 (4.4)	0.024
Paroxysmal	100 (8.5)	43 (8.7)	28 (8.5)	
Persistent or permanent	1061 (89.8)	430 (87.4)	322 (88.0)	
Hypertension	879 (73.6)	305 (61.6)	198 (54.1)	<0.001
Coronary heart disease	453 (37.9)	128 (25.9)	86 (23.5)	<0.001
Diabetes mellitus	295 (24.6)	83 (16.8)	79 (21.6)	0.002
Heart failure	559 (46.7)	63 (12.7)	47 (12.8)	<0.001
Vascular disease	397 (33.2)	109 (22.0)	61 (16.7)	<0.001
Stroke	191 (16.0)	73 (14.7)	38 (10.4)	0.029
Minor bleeding	260 (22.2)	101 (20.6)	85 (23.3)	0.616
Major bleeding	83 (7.1)	30 (6.1)	32 (8.8)	0.322
CHA_2DS_2VASc	4.0 (3.0; 5.0)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)	<0.001
HAS-BLED	2.0 (1.0; 3.0)	1.0 (1.0; 2.0)	1.0 (0.0; 2.0)	<0.001
Rate control drugs	849 (72.0)	288 (58.2)	216 (59.0)	<0.001
Beta blocker	345 (29.2)	98 (19.8)	81 (22.1)	<0.001
Digoxin	225 (19.1)	165 (33.5)	132 (36.1)	< 0.001
Calcium blocker	80 (6.8)	18 (3.6)	12 (3.3)	0.005
Antiarrhythmic agents	19 (1.6)	20 (4.0)	4 (1.1)	0.002
Amiodarone	7 (0.6)	8 (1.6)	1 (0.3)	0.045
Propafenone	309 (26.1)	159 (32.1)	103 (28.1)	0.045
Sotalol	109 (9.2)	41 (8.3)	33 (9.0)	0.827
Antithrombotic drugs	267 (22.6)	178 (36.0)	157 (42.9)	<0.001
VKA only	116 (9.8)	106 (21.4)	109 (29.8)	<0.001
VKA and antiplatelet	121 (10.2)	47 (9.5)	29 (7.9)	0.420
DOAC only	30 (2.5)	25 (5.1)	19 (5.2)	0.009
Dabigatran	91 (7.7)	31 (6.3)	29 (7.9)	0.539
Rivaroxaban	294 (24.9)	65 (13.1)	33 (9.0)	<0.001
Apixaban	112 (9.5)	21 (4.2)	11 (3.0)	<0.001
DOAC and antiplatelet	91 (7.7)	31 (6.3)	29 (7.9)	0.539
Antiplatelet only	294 (24.9)	65 (13.1)	33 (9.0)	<0.001
No antithrombotic	112 (9.5)	21 (4.2)	11 (3.0)	<0.001

MR mitral regurgitation, *AR* aortic regurgitation, *AS* aortic stenosis, *COPD* chronic obstructive pulmonary disease, *CHA_2DS_2VASc* congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65–74 years, and sex, *HAS-BLED* hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs, or alcohol, *VKA* vitamin K antagonist, *DOAC* direct oral anticoagulant

Values are given as mean ± standard deviation or number (percentage)

if the RE-LY, ROCKET AF and ARISTOTLE-ENGAGE AF criteria were used, respectively [21]. This controversy might prevent physicians from prescribing DOAC to some eligible patients. We propose using the definition in the recent EHRA guidelines for this purpose [3]. However, there is a need for trials comparing the efficacy and safety of DOACs in patients with different types of VHD, such as bioprosthetic heart valves, patients with valve repair and patients who have severe valvular disease.

Our study revealed that the patients with VHD do have more comorbidities and higher CHA_2DS_2VASc and HAS-BLED scores compared to the patients without VHD. Thus, they are at higher risk of stroke and bleeding. The mean CHADS2 score in our cohort (1.8 ± 1.7) was lower than the

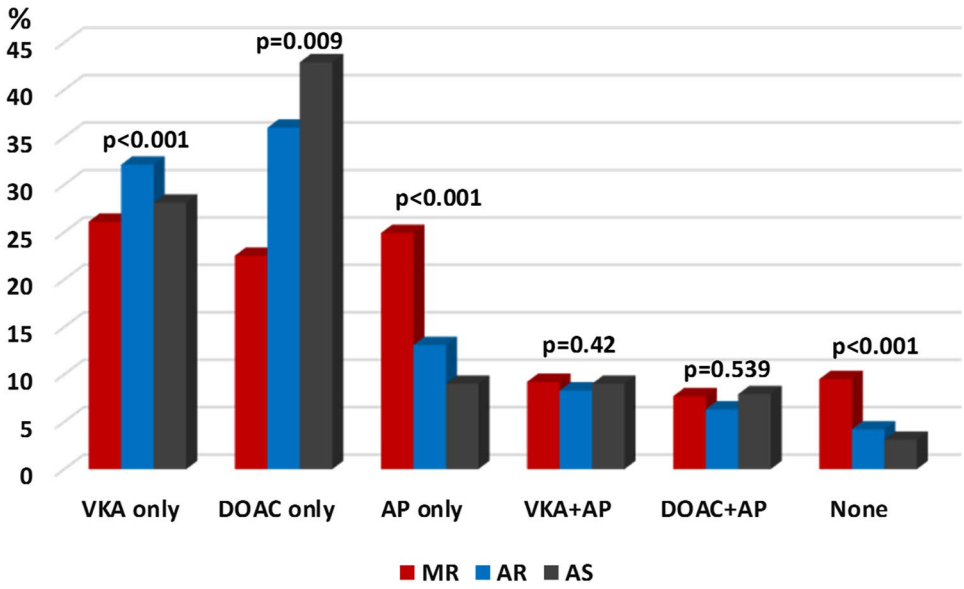

Fig. 3 OAC use among MR, AR and AS patients

randomized controlled trials (2.1 ± 1.1 in RE-LY, 3.5 ± 0.9 in ROCKET-AF, 2.1 ± 1.1 in ARISTOTLE and 2.8 ± 1.0 in ENGAGE AF TIMI-48 trials) reflecting the differences of patient characterics in the real-world [5–8, 22]. Pivotal phase III trials have revealed that the benefits of DOACs are comparable with those of warfarin, in patients both with and without VHD [18–20]. In a subgroup analysis of ROCKET AF and RE-LY patients with VHD, a similar incidence of thromboembolic events and higher rates of clinically relevant bleeding after adjustment for baseline comorbidities was observed [18, 19]. However, a subgroup analysis of the ARISTOTLE trial revealed higher rates of thromboembolic and bleeding events after adjustment for baseline characteristics [20]. Our study showed that patients with SVD are at a higher risk of thromboembolic events, which might be the reason for greater OAC use in these patients. Antiplatelet therapy with OAC was more prevalent and VKAs were preferred over DOACs in patients with SVD.

Mitral regurgitation is the predominant native valve disease, followed by aortic regurgitation and aortic stenosis in both randomized controlled trials and real-world data. Valvular disease might contribute to AF due to volume and pressure overload. AF frequently complicates rheumatic mitral valve disease, developing in at least 30–40% over long-term follow-up [23]. In patients with mitral regurgitation due to flail leaflets, AF has been observed in 18 and 48% of patients at 5- and 10-year follow-up, respectively. Importantly, the development of atrial arrhythmias is independently associated with an increased risk of adverse events in patients with VHD [24]. After adjusting for other comorbidities, VHD was associated with a 1.8- to 3.4-fold increased risk of AF [25]. There are conflicting data regarding mitral regurgitation associated AF and stroke risk. Severe mitral regurgitation might cause to left atrial appendage washing by the regurgitate jet. However, some studies have revealed lower rates of thromboembolic events in patients with MR and AF, while some studies have not [26, 27]. Our study showed that OAC therapy was less utilized and antiplatelet therapy was more prevalent among MR patients that might be associated with this hypothesis. A substudy of the ROCKET AF trial data reported similar rates of thromboembolic events in patients with mitral regurgitation and no SVD. Also, patients with AS were at a higher risk of stroke compared to patients with MR and AR in this study [19]. However, our study showed that patients with mitral regurgitation were older, had more comorbid situations and had a higher risk of stroke and bleeding compared to patients with AR and AS. The RAMSES study included real-world data without strict inclusion criteria, which might explain this difference [22].

Whether AF occurs with or without VHD, OAC therapy is recommended in cases with a moderate or high risk of stroke. Taking into account the fact that patients with VHD are at greater risk of stroke, a comprehensive management strategy should be applied in these patients. Our study showed that OAC and antiplatelet therapy use was significantly higher in patients with SVD and DOAC therapy was slightly less common in patients with SVD. More than one-third of SVD patients were on VKA therapy. The predominant valve disease was MR, and DOAC use was even lower in these patients. Special attention should be paid to patients with MR, as one-third of these patients were not on the appropriate OAC therapy. In addition, only 30% of patients with MR who were on VKA therapy were on target TTR. In a previous study, we showed that OAC therapy is inappropriate and especially VKA therapy is often not on target in NVAF patients [28].

Limitations

The study is limited due to the cross-sectional design. We do not have any results regarding clinical outcomes associated with VHD. However, the design of the study gave us an opportunity to compare the patient characteristics of VHD patients and patients without VHD in a large real-world dataset. This was a hypothesis generating study with well defined criteria and needs to be confirmed in observational cohort studies.

Conclusion

We showed that 34% of NVAF patients had at least moderate VHD in a large real-life dataset. Patients with SVD were older and had a higher risk of stroke and bleeding. In parallel, OAC therapy was more prevalent in these patients. However, when patients with SVD were grouped according to the valve disease type, the most prevalent and high risk group was patients with mitral regurgitation, many of whom were not on target. Nearly one-third of these patients were not on OAC, and only 30% of the VKA group was on target. There is a need for observational studies comparing the efficacy and safety of VKAs and DOACs in NVAF patients with some degree of valvular disease. Our study results should be tested with clinical outcomes in these studies.

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