

# UCLA

## UCLA Previously Published Works

### Title

Prevalence, Characteristics, and Outcomes of Valvular Heart Disease in Patients With Atrial Fibrillation: Insights From the ORBIT-AF (Outcomes Registry for Better Informed Treatment for Atrial Fibrillation)

### Permalink

<https://escholarship.org/uc/item/6g83h5wz>

### Journal

Journal of the American Heart Association, 6(12)

### ISSN

2047-9980

### Authors

Thomas, Kevin L  
Jackson, Larry R  
Shrader, Peter  
[et al.](#)

### Publication Date

2017-12-02

### DOI

10.1161/jaha.117.006475

Peer reviewed

# Prevalence, Characteristics, and Outcomes of Valvular Heart Disease in Patients With Atrial Fibrillation: Insights From the ORBIT-AF (Outcomes Registry for Better Informed Treatment for Atrial Fibrillation)

Kevin L. Thomas, MD; Larry R. Jackson II MD; Peter Shrader, MA; Jack Ansell, MD; Gregg C. Fonarow, MD; Bernard Gersh, MB, ChB, DPhil; Peter R. Kowey, MD; Kenneth W. Mahaffey, MD; Daniel E. Singer, MD; Laine Thomas, PhD; Jonathan P. Piccini, MD, MHS; Eric D. Peterson, MD, MPH

**Background**—The presence of valvular heart disease (VHD) may affect the risk of stroke and mortality in patients with atrial fibrillation (AF). Community-based estimates of prevalence and outcomes of specific forms of VHD in patients with AF are lacking.

**Methods and Results**—We examined the prevalence of VHD, anticoagulation use, mortality, stroke/transient ischemic attack, and bleeding among a community cohort of patients with AF. Significant VHD was defined as follows: (1) moderate/severe mitral stenosis or mechanical valve; (2) bioprosthetic valve, surgical repair, or balloon valvuloplasty; and (3) moderate/severe aortic regurgitation or stenosis, mitral regurgitation, or tricuspid regurgitation. Proportional hazards models were performed to test the association between VHD groups and outcomes. Among 9748 patients with AF, 2705 (27.7%) had significant VHD. Anticoagulation use was highest among patients with mitral stenosis/mechanical valve (91.8%). Compared with individuals with no significant VHD, individuals with aortic regurgitation/aortic stenosis, mitral regurgitation, or tricuspid regurgitation (hazard ratio, 1.23; 95% confidence interval, 1.07–1.42) had the highest risk of death. There were no differences in stroke or transient ischemic attack and major bleeding among individuals with and without significant VHD. Patients with AF and aortic stenosis had the highest risk of death (hazard ratio, 1.32; 95% confidence interval, 1.08–1.62).

**Conclusions**—Significant VHD is common among patients with AF in community practice. In a community cohort of patients with AF and CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ , most were anticoagulated. Individuals with AF and moderate-to-severe biological VHD have more comorbidities and a higher mortality risk; however, stroke and major bleeding are similar among those with and without significant VHD. (*J Am Heart Assoc.* 2017;6:e006475. DOI: 10.1161/JAHA.117.006475.)

**Key Words:** anticoagulant • atrial fibrillation • mortality • stroke • valve

There is a paucity of data on the risk of stroke, transient ischemic attack (TIA), or non-central nervous system (CNS) arterial embolism in a contemporary cohort of patients

with atrial fibrillation (AF) and all forms of valvular heart disease (VHD). Historical data have shown, in small cohorts of individuals with mechanical valves (MVs) and rheumatic mitral stenosis (MS), worse outcomes in patients with these valve disorders in the setting of AF.<sup>1–5</sup> Recent clinical trials of direct oral anticoagulants (DOACs) in patients with AF have varied in their definition of VHD and, consequently, inclusion and exclusion criteria for enrollment.<sup>6–9</sup> DOAC trials largely excluded individuals with hemodynamically significant valve disease, moderate or severe MS, or MVs and had few patients with bioprosthetic valves, prior surgical repair, or balloon valvuloplasty on the basis of the perception of a higher risk for stroke in the setting of AF.

The objectives of this analysis were as follows: (1) to assess the prevalence of VHD in a contemporary community-based population with AF, (2) to describe clinical characteristics among those with significant VHD, (3) to determine oral anticoagulation use and time in therapeutic range (TTR)

From the Duke University Medical Center, Durham, NC (K.L.T., L.R.J., J.P.P., E.D.P.); Duke Clinical Research Institute, Durham, NC (K.L.T., L.R.J., P.S., L.T., J.P.P., E.D.P.); New York University School of Medicine, Lenox Hill Hospital, New York, NY (J.A.); Division of Cardiology, University of California Los Angeles, Los Angeles, CA (G.C.F.); Mayo Clinic, Rochester, MN (B.G.); Lankenau Institute for Medical Research, Wynnewood, PA (P.R.K.); Stanford University School of Medicine, Palo Alto, CA (K.W.M.); and Harvard Medical School and Massachusetts General Hospital, Boston, MA (D.E.S.).

**Correspondence to:** Kevin L. Thomas, MD, Department of Cardiology, Duke University Medical Center, 2400 Pratt St, Durham, NC 27705. E-mail: kevin.thomas@duke.edu

Received July 6, 2017; accepted October 17, 2017.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

## Clinical Perspective

### What Is New?

- Among a community cohort of individuals with atrial fibrillation, valvular heart disease was prevalent and was associated with significant comorbidities.
- Individuals with atrial fibrillation, bioprosthetic valves, prior surgical repair, and balloon valvuloplasty were not associated with higher odds of stroke, death, or bleeding relative to those without significant valvular disease in the setting of high rates of oral anticoagulation.
- The combination of aortic stenosis and atrial fibrillation was associated with a significant increase in mortality.

### What Are the Clinical Implications?

- Treating comorbidities and anticoagulating individuals with atrial fibrillation and valvular heart disease will likely improve outcomes.
- The risk of stroke, transient ischemic attack, and non-central nervous system arterial embolism in individuals with bioprosthetic valves, prior surgical repair, and balloon valvuloplasty appears low; however, additional research is needed to assess the efficacy and safety of direct oral anticoagulants in this population.

among VHD categories, and (4) to evaluate thromboembolic events, major bleeding events, and mortality across a spectrum of VHD categories.

## Methods

### Study Design

The design of the ORBIT-AF (Outcomes Registry for Better Informed Treatment for AF) project has been published and described elsewhere. Briefly, ORBIT-AF is a multicenter, prospective, outpatient registry of patients with incident or prevalent AF that analyzes characteristics, treatment patterns, and outcomes in patients with AF in the United States.<sup>10</sup> The registry enrolled patients managed by a variety of providers that included primary care providers, cardiologists, and electrophysiologists. Sites abstracted data on demographics, comorbidities, medical history, treatment strategy, and provider characteristics and entered information into an interactive web-based data collection form. The Duke Clinical Research Institute (Durham, NC) performed site selection and management. Site investigators enrolled consecutive patients with AF who were >18 years, with electrocardiographic evidence of AF. Patients with AF attributable to a reversible cause (eg, in the setting of cardiac surgery or hyperthyroidism) or life expectancy <6 months were excluded. In addition, patients with atrial flutter were also

excluded from the study. Patients were followed up every 6 months for at least 2 years. A web-based case report form was used to gather data, and primary sources were the patient's medical record and treating physician.

All data on VHD were site reported on the basis of available medical history. All patients provided written informed consent, and approval by the appropriate institutional review boards/ethics committees was obtained at all sites. The primary outcome event in ORBIT-AF was stroke or non-CNS systemic arterial embolism. Consistent with recent clinical trials, stroke was defined as a new, sudden, focal neurologic deficit that persists beyond 24 hours and was not attributable to a readily identifiable nonvascular cause (eg, seizure).<sup>11,12</sup> Primary outcome events were verified by single-source document submission (eg, hospital discharge report) and central review at the data coordinating center. The major safety outcome of interest was major bleeding, as defined by the International Society on Thrombosis and Haemostasis.<sup>13</sup>

For the purposes of this analysis, we categorized registry participants into mutually exclusive categories with a hierarchical structure for nonoverlapping categorization: (1) moderate or severe MS or MV with no other repair or replacement; (2) bioprosthetic valve or prior valve repair or balloon valvuloplasty with no prior MV replacement or existing MS; (3) moderate or severe aortic valve regurgitation or stenosis (AR/AS), mitral regurgitation (MR), or tricuspid regurgitation (TR), no prior valve repair or replacement, and no MS; or (4) mild or no VHD. If an individual had any type of valve intervention, the individual automatically fell into group 1 or 2, regardless of any additional valvular disease.

In addition, we sought to determine the association of all-cause mortality, thromboembolic events (stroke, non-CNS embolism, and TIA), and major bleeding among patients classified by significant individual VHD.

### Statistical Analysis

Baseline characteristics are presented by VHD group. Continuous variables are presented as medians (interquartile ranges [IQRs]), and differences across VHD groups are assessed using the Kruskal-Wallis test. Categorical variables are presented as counts (proportions), and differences across the groups are assessed using the  $\chi^2$  test. To describe the prevalence of VHD by age groups, age is divided into decades (<60, 60–69, 70–79, and  $\geq 80$  years). The prevalence of each VHD category and the individual components is presented in each age group. Cox proportional hazards models with a robust covariance estimate are performed to test the association between VHD groups and outcomes. Multivariable models are adjusted for the following variables: AF type, AF duration, age, anemia, hematocrit, body mass index, cancer history, congestive heart failure, cognitive impairment/

dementia, chronic obstructive pulmonary disease, diabetes mellitus, dialysis dependency, estimated glomerular filtration rate, systolic and diastolic blood pressure levels, history of hypertension, coronary artery disease, percutaneous coronary intervention, myocardial infarction, gastrointestinal tract bleeding, stroke/TIA, hyperlipidemia, frailty, functional status, insurance status, left atrial diameter, level of education, left ventricular ejection fraction, obstructive sleep apnea, peripheral vascular disease, principal investigator/site specialty, rate or rhythm control strategy, geographical region, sex, smoking, and oral anticoagulant use. Frailty was defined as a clinical syndrome in which  $\geq 3$  of the following criteria are present: unintentional weight loss (10 lb in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. These variables were selected on the basis of their clinical relevance to the study outcomes and/or an imbalance in baseline prevalence between groups. Missing covariate data were accounted for using multiple imputation. Final estimates and associated SEs reflect the combined analysis over 5 imputed data sets. Nonlinear associations were accounted for using cubic splines.

## Results

Our analysis included 10 137 patients with baseline data enrolled from 176 US practices from June 29, 2010, through August 9, 2011, over a median follow-up of 2.5 (IQR, 1.8–3.0) years. Patients with missing information on VHD (N=1) or without any follow-up (N=388) were excluded, and the final study population included 9748 patients. Of these patients, 2705 (27.7%) had a history of significant VHD (Table 1). Among individuals with significant VHD, 403 (4.1%) had MS/MV, 455 (4.7%) had bioprosthetic valves or prior surgical repair or balloon valvuloplasty, and 1847 (18.9%) had AR/AS, MR, or TR. The incidence of significant VHD increased with advancing age (Figure). The number of individuals with MS/MV was consistent across age groups.

The clinical characteristics of patients in the overall population and of patients categorized according to the presence or absence of significant VHD by groups are presented in Table 2. The median age for the overall population was 75 years (73 years for those without significant VHD and 79 years for those with AR/AS, MR, or TR). Patients with MS/MV, bioprosthetic valves/surgical repair, or balloon valvuloplasty had the highest rates of hyperlipidemia, anemia, prior stroke or TIA, left ventricle hypertrophy, persistent and permanent AF, and oral anticoagulation and were more likely to be managed with a rate control strategy. Individuals with AR/AS, MR, or TR had the highest rates of hypertension. Those with bioprosthetic valves or surgical

**Table 1.** Prevalence of VHD

Category	Values (N=9748)
No or mild VHD	N=7043 (72.3)
Moderate-to-severe VHD	N=1847*
Aortic regurgitation	N=199 (10.8)
Aortic stenosis	N=210 (11.4)
Mitral regurgitation	N=1165 (63.1)
Tricuspid regurgitation	N=979 (53.0)
Mechanical valve or moderate-to-severe mitral stenosis	N=403
Mechanical valve	N=306 (75.9)
Mitral stenosis	N=137 (34.0)
Other valve replacement or repair	N=455*
Bioprosthetic valve	N=249 (54.7)
Surgical repair	N=225 (49.5)
Balloon valvuloplasty	N=23 (5.1)

Data in parentheses are percentages. VHD indicates valvular heart disease.

\*Patients may have had  $>1$  condition.

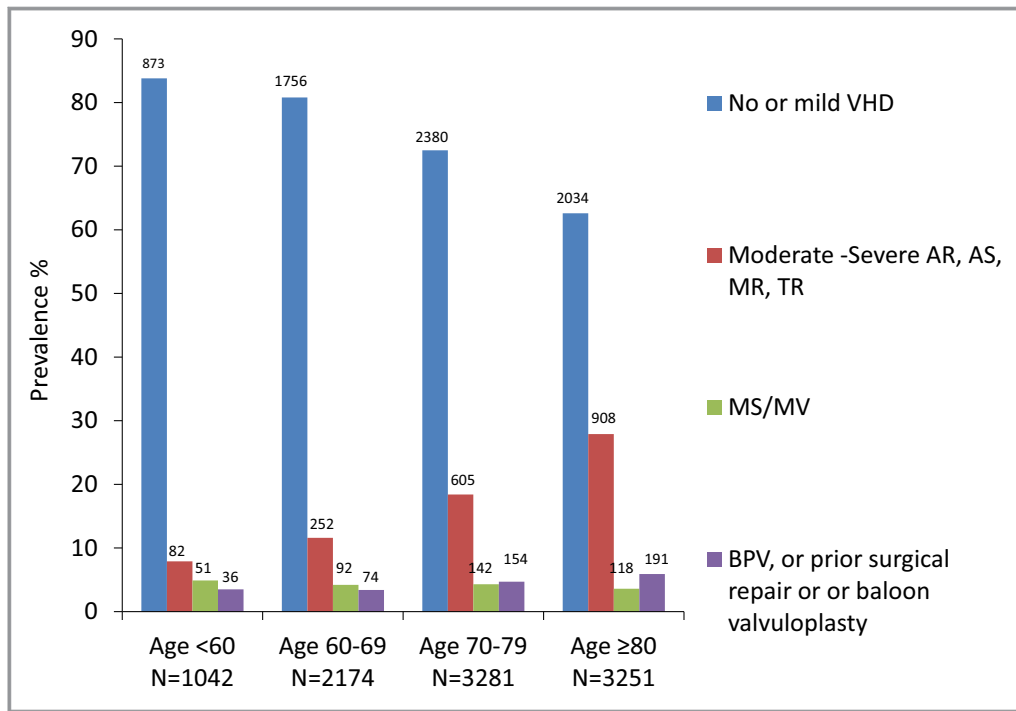
repair/balloon valvuloplasty had the highest rates of chronic obstructive pulmonary disease, diabetes mellitus, prior gastrointestinal tract bleeding, smoking, peripheral vascular disease, congestive heart failure, and coronary artery disease.

## Stroke and Bleeding Risk

The median CHA<sub>2</sub>DS<sub>2</sub>-VASc score for the population was 4.0 (25th–75th IQR, 3–5) and differed across categories of VHD (Table 2). Individuals with a bioprosthetic valve or prior surgical repair had the highest CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk scores (median, 5; IQR, 4–6). In this registry population, 91% of patients had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ , and those with AR/AS, MR, or TR had the highest percentage with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  (97%). Individuals with bioprosthetic valves or prior surgical repair/balloon valvuloplasty had a greater risk for bleeding (median anticoagulation and risk factors in AF bleeding score, 4 [IQR, 3–6]; ORBIT bleeding score, 3 [IQR, 2–4]) and the highest percentage of people with an anticoagulation and risk factors in AF bleeding score  $\geq 5$  (40.2%) and an ORBIT bleeding score  $\geq 4$  (39%).

## Oral Anticoagulation Use and TTR

Oral anticoagulation rates by VHD categories are listed in Table 3. Of the 9748 patients included in our analysis, 76.4% were treated with oral anticoagulation. Approximately 13% (n=1252) had a relative or absolute contraindication to oral anticoagulation (Table 2). The most common relative or absolute contraindications to oral anticoagulation among this



**Figure.** Prevalence of valvular heart disease (VHD) by age (n=9748). AR indicates aortic regurgitation; AS, aortic stenosis; BPV, bioprosthetic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mechanical valve; and TR, tricuspid regurgitation.

population included the following: prior bleeding (28.8%), patient refusal/preference (27.9%), and frequent falls/frailty (17.8%). Of those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ , 78% (n=6941) were prescribed oral anticoagulation. In patients with mild or no VHD, 74% were receiving oral anticoagulation. Anticoagulation use was 92% in patients with MS/MV. Overall, dabigatran was used in 5% of the population and use was highest among individuals with mild or no VHD. Dabigatran was used in 1.5% (N=6) of individuals with MS/MV. The median TTR for the overall population was 65% (IQR, 44%–82%). Individuals with MS/MV had the lowest TTR (56%; IQR, 37%–76%), and those with mild or no VHD the highest TTR (66%; IQR, 45%–83%) (Table 3).

### Outcomes as a Function of VHD

Table 4 shows the incidence of all-cause mortality, stroke, non-CNS embolism or TIA, and major bleeding events across VHD categories. Individuals with AR/AS, MR, or TR had the highest mortality rate (9.2 deaths per 100 patient-years of follow-up [N=373]), and those with mild to no VHD had the lowest mortality rate (4.5 deaths per 100 patient-years of follow-up [N=721]). Stroke, non-CNS embolism, or TIA rates were lowest among individuals with mild to no VHD (1.4 per 100 patient-years of follow-up [N=223]) and similar across all other VHD groups (1.9–2.3 per 100 patient-years of follow-up). Major bleeding events were highest in those with

bioprosthetic valves, surgical valve repair, or balloon valvuloplasty (6.9 per 100 patient-years of follow-up [n=65]) and in those with MS/MV (6.2 per 100 patient-years of follow-up [n=55]) (data not shown). After multivariable adjustment, there were no statistical differences among all VHD disease categories for stroke, non-CNS embolism or TIA, and major bleeding (Table 4). There was higher mortality across the 3 groups of individuals with VHD compared with those without VHD that was driven by a higher mortality risk among those with AR/AS, MR, and TR (hazard ratio [HR], 1.23; 95% confidence interval [CI], 1.07–1.42).

Mortality rates varied across individual moderate-to-severe VHD states but were consistently higher than in individuals without that specific VHD (Tables 5 through 12). The rates of deaths per 100 patient-years were as follows: MS, 9.1 (N=28); MR, 8.6 (N=285); AS, 11.5 (N=104); AR, 8.3 (N=53); TR, 10.1 (N=266); MVs, 6.5 (N=47); bioprosthetic valves, 8.9 (N=59); surgical repair or balloon valvuloplasty, 7.2 (N=47). After multivariable adjustment, only moderate-to-severe AS was significantly associated with a higher risk of death (HR, 1.32; 95% CI, 1.08–1.62;  $P=0.007$ ) (Table 7). The presence of moderate or severe MR, TR, and a bioprosthetic valve was associated with a greater hazard of stroke/non-CNS embolism/TIA, yet after multivariable adjustment, there was no significant difference in this outcome among those with these moderate or severe VHD abnormalities and those without the abnormalities. Last, although many individual

**Table 2.** Baseline Characteristics by VHD Status

Characteristic	Overall (N=9748)	No or Mild VHD (N=7043)	Moderate-Severe AR, AS, MR, or TR (N=1847)	Mechanical Valve or Mitral Stenosis (N=403)	BPV, Surgical Repair, or Balloon Valvuloplasty (N=455)	P Value
Age, y	75 (67–82)	73 (65–81)	79 (72–85)	74 (65–81)	78 (70–83)	<0.001
Male sex	5599 (57.4)	4243 (60.2)	887 (48.0)	208 (51.6)	261 (57.4)	<0.001
Race/ethnicity						
White	8719 (89.6)	6283 (89.4)	1674 (90.8)	348 (86.6)	414 (91.0)	0.194
Black	477 (4.9)	342 (4.9)	91 (4.9)	27 (6.7)	17 (3.7)	
Hispanic	397 (4.1)	302 (4.3)	57 (3.1)	21 (5.2)	17 (3.7)	
Other	139 (1.4)	104 (1.5)	22 (1.2)	6 (1.5)	7 (1.5)	
Body mass index, kg/m <sup>2</sup>	29.1 (25.3–34.0)	29.7 (25.9–34.8)	27.7 (24.2–32.4)	27.6 (24.1–31.3)	27.2 (24.1–31.2)	<0.001
SBP, mm Hg	126 (116–138)	126 (116–138)	124 (115–136)	122 (111–132)	122 (112–132)	<0.001
DBP, mm Hg	72 (66–80)	72 (68–80)	70 (64–80)	70 (62–80)	70 (64–78)	<0.001
Estimated GFR (MDRD)	66.8 (52.7–82.1)	68.8 (55.5–84.3)	61.8 (48.3–76.2)	64.4 (50.8–83.0)	61.5 (48.6–76.4)	<0.001
Type of AF New onset/first detected	438 (4.5)	367 (5.2)	54 (2.9)	9 (2.2)	8 (1.8)	<0.001
Paroxysmal	4939 (50.7)	3852 (54.7)	729 (39.5)	153 (38.0)	205 (45.1)	
Persistent	1635 (16.8)	1104 (15.7)	352 (19.1)	86 (21.3)	93 (20.4)	
Permanent	2736 (28.1)	1720 (24.4)	712 (38.6)	155 (38.5)	149 (32.8)	
EHRA score						0.035
No symptoms	3726 (38.3)	2679 (38.1)	726 (39.4)	144 (35.8)	177 (39.2)	
Mild	4389 (45.2)	3215 (45.8)	786 (42.7)	195 (48.5)	193 (42.7)	
Severe	1430 (14.7)	1003 (14.3)	303 (16.4)	57 (14.2)	67 (14.8)	
Disabling	175 (1.8)	127 (1.8)	27 (1.5)	6 (1.5)	15 (3.3)	
Current AF management strategy						<0.001
Rate	6641 (68.3)	4634 (66.0)	1375 (74.6)	316 (78.4)	316 (69.6)	
Rhythm	3082 (31.7)	2388 (34.0)	469 (25.4)	87 (21.6)	138 (30.4)	
Prior AAD treatment						
Yes	4453 (45.7)	3263 (46.3)	779 (42.2)	180 (44.7)	231 (50.8)	0.002
Prior interventional therapy for AF	1110 (11.4)	727 (10.3)	186 (10.1)	76 (18.9)	121 (26.6)	<0.001
Catheter ablation of AF	543 (5.6)	415 (5.9)	87 (4.7)	13 (3.2)	28 (6.2)	0.037
AV node His bundle ablation	218 (2.2)	127 (1.8)	61 (3.3)	15 (3.7)	15 (3.3)	<0.001
Surgical or hybrid Maze procedure	189 (1.9)	66 (0.9)	10 (0.5)	37 (9.2)	76 (16.7)	<0.001
Cardiac medications						
ACE-I	3465 (35.5)	2470 (35.1)	662 (35.8)	154 (38.2)	179 (39.3)	0.182
ARB	1737 (17.8)	1237 (17.6)	374 (20.3)	62 (15.4)	64 (15.1)	0.003
-Blocker	6267 (64.3)	4425 (62.8)	1240 (67.1)	283 (70.2)	319 (70.1)	<0.001
Digoxin	2296 (23.6)	1492 (21.2)	553 (29.9)	129 (32.0)	122 (26.8)	<0.001
Statin	5401 (55.4)	3877 (55.1)	1019 (55.2)	232 (57.6)	273 (66.0)	0.169
Diuretic	4808 (49.3)	3120 (44.3)	1138 (61.6)	265 (65.8)	285 (62.6)	<0.001
Calcium channel blockers	2964 (30.4)	2181 (31.0)	601 (32.5)	94 (23.3)	88 (19.3)	<0.001
Amiodarone	967 (9.9)	664 (9.4)	200 (10.8)	41 (10.2)	62 (13.6)	0.014

Continued

Table 2. Continued

Characteristic	Overall (N=9748)	No or Mild VHD (N=7043)	Moderate-Severe AR, AS, MR, or TR (N=1847)	Mechanical Valve or Mitral Stenosis (N=403)	BPV, Surgical Repair, or Balloon Valvuloplasty (N=455)	P Value
<b>Antithrombotic medications</b>						
Anticoagulants	7444 (76.4)	5213 (74.0)	1484 (80.4)	370 (91.8)	377 (82.9)	<0.001
Dabigatran	483 (5.0)	396 (5.6)	71 (3.8)	6 (1.5)	10 (2.2)	<0.001
Warfarin	6964 (71.4)	4820 (68.4)	1413 (76.5)	364 (96.3)	367 (80.7)	<0.001
<b>Antiplatelet</b>						
aspirin	4318 (44.3)	3153 (44.8)	757 (41.0)	167 (41.4)	241 (53.0)	<0.001
Clopidogrel	692 (7.1)	504 (7.2)	152 (8.2)	14 (3.5)	22 (4.8)	0.002
CHA2DS2 -VASc	4 (3–5)	4 (3–5)	4 (4–6)	4 (3–5)	5 (4–6)	<0.001
Atria score	3 (1–4)	3 (1–4)	3 (2–6)	3 (1–6)	4 (3–6)	<0.001
<b>Medical history</b>						
Prior stroke or TIA	1479 (15.2)	955 (13.6)	333 (18.0)	90 (22.3)	101 (22.2)	<0.001
CHF	3204 (32.9)	1898 (27.0)	838 (45.4)	218 (54.1)	250 (55.0)	<0.001
Hypertension	8102 (83.1)	5823 (82.7)	1598 (86.5)	312 (77.4)	369 (81.1)	<0.001
Diabetes mellitus	2873 (29.5)	2107 (29.9)	512 (27.7)	114 (28.3)	140 (30.8)	0.258
Prior MI	1562 (16.0)	1070 (15.2)	350 (18.9)	67 (16.6)	75 (16.5)	0.001
PVD	1309 (13.4)	828 (11.8)	335 (18.1)	63 (15.6)	83 (18.2)	<0.001
COPD	1605 (16.5)	1050 (14.9)	371 (20.1)	80 (20.0)	104 (22.9)	<0.001
Smoking	4716 (48.4)	3407 (48.4)	886 (48.0)	197 (48.9)	226 (49.7)	0.926
Cancer	2317 (23.8)	1608 (22.8)	502 (27.2)	94 (23.3)	113 (24.8)	0.001

Values are expressed as numbers (percentages) or medians (25th–75th interquartile ranges). AAD indicates antiarrhythmic drug; ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AR, aortic regurgitation; ARB, angiotensin receptor blocker; AS, aortic stenosis; BPV, bioprosthetic valve; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EHRA, European Heart Rhythm Association; GFR, glomerular filtration rate; MAZE, ; MDRD, modification of diet in renal disease; MI, myocardial infarction; MR, mitral regurgitation; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischemic attack; TR, tricuspid regurgitation; and VHD, valvular heart disease.

valvular heart disorders were associated with major bleeding events, after multivariable adjustment, only moderate or severe AR was associated with significant major bleeding events (HR, 1.38; 95% CI, 1.09–1.76;  $P=0.008$ ) (Table 8).

## Discussion

VHD in the presence of AF greatly magnifies the risk of thromboembolism.<sup>1,14,15</sup> Our study evaluated a large, contemporary, community-based population and is notable for several findings: (1) the prevalence of significant VHD is substantial among patients with AF in community practice; (2) oral anticoagulation was high, with >90% use in patients with MS/MV and >80% use in patients with AR/AS, bioprosthetic valves, and surgical valve repair or balloon valvuloplasty; (3) individuals with significant VHD cluster more comorbidities that, in part, lend themselves to worse outcomes, including mortality, thromboembolism (stroke/non-CNS embolism/TIA), and major bleeding; and (4) moderate or severe AS in

the setting of AF is associated with greater mortality risk, and individuals with moderate or severe AR have a greater risk of major bleeding.

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events), ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF), and ENGAGE AF (Effective Anticoagulation With Factor Xa Next Generation in AF) investigators have published findings on patients with significant biological VHD treated with apixaban, rivaroxaban, and high-dose edoxaban in their respective studies.<sup>1,16,17</sup> In ARISTOTLE, 4808 patients (26.4%) had a history of moderate or severe VHD or prior valve surgery. The ROCKET AF study had 2003 patients (14.1%) with significant VHD; in ENGAGE AF, 2824 patients (13%) had moderate or severe VHD or prior valve surgery. Comparably, ORBIT-AF had 2705 individuals (27.7%) with significant VHD. Across all 4 cohorts, MR was the most prevalent valve disorder. The varying definitions of significant VHD across

**Table 3.** Oral Anticoagulation Rates and TTR Stratified by Valvular Heart Disease Categories

Drug	All Patients (N=9748)	No or Mild VHD (N=7043)	Moderate or Severe AR, AS, MR, or TR (N=1847)	Mechanical Valve or Mitral Stenosis (N=403)	BPV, Surgical Repair, or Balloon Valvuloplasty (N=455)
Warfarin	71.4 (70.5–72.3)	68.4 (67.4–69.5)	76.5 (74.6–78.4)	90.3 (87.4–93.2)	80.7 (77.0–84.3)
Dabigatran	5.0 (4.5–5.4)	5.6 (5.1–6.2)	3.8 (3.0–4.7)	1.5 (0.3–2.7)	2.2 (0.9–3.5)
Any OAC	76.4 (75.5–77.2)	74.0 (73.0–75.0)	80.3 (78.5–82.2)	91.8 (89.1–94.5)	82.9 (79.4–86.3)
TTR	65.0 (44.0–82.0)	66.0 (45.0–83.0)	65.0 (45.0–81.0)	56.0 (37.0–76.0)	61.0 (44.0–80.0)
Relative or absolute contraindication to OAC	12.8 (1252)	12.4 (874)	15.3 (282)	9.2 (37)	13.0 (59)
Need for dual antiplatelet therapy	7.8 (98/1252)	9.0 (79/874)	5.3 (15/282)	5.4 (2/37)	3.4 (2/59)
Unable to adhere/monitor warfarin	6.2 (781/252)	6.3 (55/874)	5.7 (16/282)	2.7 (1/37)	10.2 (6/59)
Occupational risk	0.6 (7/1252)	0.7 (6/874)	0.4 (1/282)	0 (0/37)	0 (0/59)
High bleeding risk	18.1 (226/1252)	15.7 (137/874)	21.6 (61/282)	27.0 (10/37)	30.5 (18/59)
Prior ICH	4.9 (61/1252)	5.0 (44/874)	3.9 (11/282)	10.8 (4/37)	3.4 (2/59)
Comorbid illness	5.3 (66/1252)	4.9 (43/874)	5.3 (15/282)	10.8 (4/37)	6.8 (4/59)
Prior bleeding	28.8 (360/1252)	24.9 (218/874)	37.2 (105/282)	40.5 (15/37)	37.3 (22/59)
Allergy	2.4 (30/1252)	2.5 (22/874)	2.1 (6/282)	2.7 (1/37)	1.7 (1/59)
Patient refusal/preference	27.9 (349/1252)	29.6 (259/874)	23.1 (65/282)	16.2 (6/37)	32.2 (19/59)
Frequent falls/frailty	17.8 (223/1252)	15.2 (133/874)	25.9 (73/282)	27.0 (10/37)	11.9 (7/59)
Pregnancy	0.1 (1/1252)	0.1 (1/874)	0 (0/282)	0 (0/37)	0 (0/59)
Other	12.6 (158/1252)	14.2 (124/874)	10.3 (29/282)	2.7 (1/37)	6.8 (4/59)

Values are expressed as median (25th–75th interquartile range) percentage, percentage (number), or percentage (number/total). AR indicates aortic regurgitation; AS, aortic stenosis; BPV, bioprosthetic valve; ICH, intracranial hemorrhage; MR, mitral regurgitation; OAC, oral anticoagulation; TR, tricuspid regurgitation; TTR, time in therapeutic range; and VHD, valvular heart disease.

these studies likely explain the lower prevalence of significant VHD in ROCKET AF and ENGAGE AF (the latter 2 not including patients with tricuspid valve disease).

Largely on the basis of data from decades ago, VHD, independent of the presence of AF, is thought to be associated with a higher risk of thromboembolic events.<sup>2–5</sup>

**Table 4.** Outcomes Across VHD Categories

Outcome	No or Mild Significant VHD (N=7043)	Moderate or Severe AR, AS, MR, or TR (N=1847)	Mechanical Valve or Mitral Stenosis (N=403)	BPV, Surgical Repair, or Balloon Valvuloplasty (N=455)	P Value*
<b>All-cause mortality</b>					
Unadjusted	Reference	2.08 (1.80–2.39)	1.62 (1.30–2.03)	1.79 (1.44–2.24)	<0.001
Adjusted	Reference	1.23 (1.07–1.42)	1.10 (0.85–1.42)	0.99 (0.76–1.30)	0.025
<b>Stroke, non-CNS embolism, or TIA</b>					
Unadjusted	Reference	1.53 (1.20–1.96)	1.39 (0.86–2.26)	1.70 (1.16–2.49)	<0.001
Adjusted	Reference	0.97 (0.74–1.27)	0.93 (0.58–1.49)	1.07 (0.73–1.57)	0.949
<b>Major bleeding</b>					
Unadjusted	Reference	1.53 (1.26–1.85)	1.91 (1.50–2.44)	2.10 (1.62–2.72)	<0.001
Adjusted	Reference	1.10 (0.91–1.32)	1.22 (0.87–1.71)	1.33 (0.97–1.82)	0.342

Data are given as hazard ratio (95% confidence interval). Multivariable models are adjusted for the following variables: atrial fibrillation (AF) type, AF duration, age, anemia, hematocrit, body mass index, cancer history, congestive heart failure, cognitive impairment/dementia, chronic obstructive pulmonary disease, diabetes mellitus, dialysis dependency, estimated glomerular filtration rate, systolic and diastolic blood pressure levels, history of hypertension, coronary artery disease, percutaneous coronary intervention, myocardial infarction, gastrointestinal tract bleeding, stroke/TIA, hyperlipidemia, frailty, functional status, insurance status, left atrial diameter, level of education, left ventricular ejection fraction, obstructive sleep apnea, peripheral vascular disease, principal investigator/site specialty, rate or rhythm control strategy, geographical region, sex, smoking, and oral anticoagulant use. AR indicates aortic regurgitation; AS, aortic stenosis; BPV, bioprosthetic valve; CNS, central nervous system; MR, mitral regurgitation; TIA, transient ischemic attack; TR, tricuspid regurgitation; and VHD, valvular heart disease. \*P value is the comparison of 3 groups compared with the reference group.



**Table 5.** MS: Incidence Rate and Association With Outcomes

Outcome	Event Rates		Unadjusted		Adjusted	
	No or Mild VHD (N=7043)	MS (N=137)	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause death	721 (4.45)	28 (9.14)	2.07 (1.48–2.89)	<0.001	1.44 (0.98–2.11)	0.061
Stroke, non-CNS embolism, or TIA	223 (1.39)	5 (1.64)	1.18 (0.41–3.39)	0.759	0.79 (0.26–2.42)	0.684
Major bleeding	509 (3.25)	18 (6.27)	1.93 (1.26–2.94)	0.002	1.46 (0.90–2.39)	0.126

Values are expressed as number of events and percentages. CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; MS, mitral stenosis; TIA, transient ischemic attack and VHD, valvular heart disease.

This risk is greatly amplified in the presence of AF.<sup>15</sup> AF in the setting of rheumatic MS and mechanical prosthetic valves is unequivocally associated with a high risk of thromboembolism.<sup>18</sup> On the basis of experience and the high risk of stroke in patients with moderate or severe MS, and concerns for valve thrombosis in patients with mechanical prosthetic valves, contemporary trials of DOACs largely excluded those patients, but included patients with other types of moderate or severe VHD.

Our findings add to available data by including patients with MS/MV, bioprosthetic valve replacement, and other types of valve procedures, including surgical repair and balloon valvuloplasty. Specifically, our registry population differed from ARISTOTLE, ROCKET AF, ENGAGE AF in that it contained patients with MS/MV (n=403). In addition, ARISTOTLE (n=251) and ROCKET AF (n=106) had few patients with bioprosthetic heart valves, surgical repair, or balloon valvuloplasty compared with our ORBIT-AF cohort (n=455). ENGAGE AF had 325 individuals with prior valve surgery; however, the study did not report outcomes specifically for this cohort. Adjusted outcomes differed among the 4 cohorts. Patients with significant VHD in ARISTOTLE had higher rates of stroke or systemic embolism than patients without significant VHD (HR, 1.34; 95% CI, 1.10–1.62;  $P=0.003$ ). In ROCKET AF, ENGAGE AF, and our study population, there were no differences in stroke or systemic embolic events in those with or without significant VHD. In ENGAGE AF and ARISTOTLE, individuals with significant VHD had a greater risk of death than patients without significant VHD (adjusted HR,

1.40 [95% CI, 1.26–1.56] and 1.48 [95% CI, 1.32–1.67], respectively;  $P<0.001$ ). Patients with significant VHD in ARISTOTLE and our cohort did not have higher rates of major bleeding compared with those without significant VHD. Conversely, in ROCKET AF and ENGAGE AF, major bleeding occurred significantly more frequently in patients with significant VHD (HR, 1.32 [95% CI, 1.10–1.57] [ $P=0.0027$ ] and 1.21 [95% CI, 1.03–1.42] [ $P=0.020$ ], respectively). In our community cohort of patients with significant VHD, patients with moderate-to-severe AR, AS, MR, or TR had higher mortality than those without VHD; however, no differences were observed in major bleeding. A recent meta-analysis analyzed 71 683 patients, 13 585 with VHD enrolled in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), ROCKET AF, ARISTOTLE, and ENGAGE AF clinical trials. This represents the largest evaluation of a cohort of patients with AF and VHD. Relative to patients with AF without VHD, those with VHD had higher mortality and major bleeding. There were no differences in the rates of stroke or systemic embolic events.<sup>19</sup>

The use of oral anticoagulation in the ORBIT-AF registry cohort was high, 76.4% (N=7444). However, the use of DOACs was low,  $\approx 5\%$ , and the remainder were treated with warfarin. Anticoagulation use was highest among those with MS/MV. Anticoagulation use was comparable in our cohort of patients to other contemporary registries in which anticoagulation use has ranged from 70% to 80%.<sup>20–23</sup> Notably, there were 6 patients in which DOAC use was reported in the setting of MS/MV. The median TTR (66%) of patients in ORBIT-

**Table 6.** MR: Incidence Rate and Association With Outcomes

Outcome	Event Rates		Unadjusted		Adjusted	
	No or Mild VHD (N=7043)	MR (N=1491)	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause death	721 (4.45)	285 (8.57)	1.93 (1.66–2.26)	<0.001	1.08 (0.92–1.26)	0.360
Stroke, non-CNS embolism, or TIA	223 (1.39)	71 (2.17)	1.56 (1.21–2.02)	<0.001	1.00 (0.75–1.33)	0.999
Major bleeding	509 (3.25)	174 (5.56)	1.71 (1.38–2.11)	<0.001	1.18 (0.92–1.51)	0.188

Values are expressed as number of events and percentages. CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; MR, mitral regurgitation; TIA, transient ischemic attack and VHD, valvular heart disease.

**Table 7.** AS: Incidence Rate and Association With Outcomes

Outcome	Event Rates		Unadjusted		Adjusted	
	No or Mild VHD (N=7043)	AS (N=413)	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause death	721 (4.45)	104 (11.45)	2.58 (2.09–3.19)	<0.001	1.40 (1.13–1.73)	0.002
Stroke, non-CNS embolism, or TIA	223 (1.39)	22 (2.46)	1.76 (1.11–2.79)	0.016	0.97 (0.59–1.60)	0.909
Major bleeding	509 (3.25)	62 (7.31)	2.24 (1.71–2.95)	<0.001	1.38 (1.00–1.92)	0.052

Values are expressed as number of events and percentages. AS indicates aortic stenosis; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; TIA, transient ischemic attack and VHD, valvular heart disease.

AF was higher than in contemporary trials, including warfarin in patients with nonvalvular AF. However, in patients with AF and MS/MV, a known high thromboembolic risk population, the median TTR was 56%.

Despite being one of the most common valvular disorders and frequently coexisting with AF, there are few data on whether AS is an independent risk factor for thromboembolism.<sup>15</sup> Similarly, data are lacking in patients with AR and TR. In our analysis, we examined the risk of thromboembolic events, major bleeding, and all-cause mortality among patients with moderate-to-severe individual valve disorders. Notably, adjusting for comorbidities, only individuals with AS had a greater hazard of death; those with AR had a greater risk of major bleeding events. No individual valvular heart disorder was associated with a larger risk of stroke, TIA, or non-CNS embolism. Patients with AS represent an increasingly older and sicker population; consequently, residual confounders may explain their higher mortality. AF may be a

turning point in the natural history of AS. In a recent analysis of patients with AS and AF, among asymptomatic mild-to-moderate AS, an incidence of new-onset AF of 1.2% per year was associated with a 2-fold increase in the risk of cardiac decompensation. The effect of AF was powerful on patients with AS; after adjustment by age, sex, body surface area, comorbidity index, symptoms, coronary artery disease, and ejection fraction, AF was associated with more than doubling the risk of overall mortality with both medical and surgical management. Although more data on the intersection of these conditions are needed, these data, coupled with our findings, suggest that the management of moderate-to-severe AS should take into account the presence of AF when considering long-term outcomes.

This analysis included 455 patients with bioprosthetic valves, surgical repair, or balloon valvuloplasty. These individuals did not appear to have a greater risk of stroke or non-CNS arterial thromboembolism than those with other valvular

**Table 8.** AR: Incidence Rate and Association With Outcomes

Outcome	Event Rates		Unadjusted		Adjusted	
	No or Mild VHD (N=7043)	AR (N=289)	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause death	721 (4.45)	53 (8.26)	1.87 (1.37–2.53)	<0.001	0.98 (0.75–1.28)	0.893
Stroke, non-CNS embolism, or TIA	223 (1.39)	13 (2.07)	1.49 (0.88–2.53)	0.136	0.83 (0.51–1.35)	0.448
Major bleeding	509 (3.25)	46 (7.79)	2.39 (1.89–3.02)	<0.001	1.41 (1.05–1.89)	0.021

Values are expressed as number of events and percentages. AR indicates aortic regurgitation; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; TIA, transient ischemic attack and VHD, valvular heart disease.

**Table 9.** TR: Incidence Rate and Association With Outcomes

Outcome	Event Rates		Unadjusted		Adjusted	
	No or Mild VHD (N=7043)	TR (N=1199)	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause death	721 (4.45)	266 (10.14)	2.29 (1.93–2.71)	<0.001	1.25 (1.03–1.51)	0.023
Stroke, non-CNS embolism, or TIA	223 (1.39)	54 (2.10)	1.50 (1.11–2.04)	0.009	0.83 (0.60–1.14)	0.250
Major bleeding	509 (3.25)	136 (5.50)	1.69 (1.35–2.10)	<0.001	1.10 (0.86–1.39)	0.449

Values are expressed as number of events and percentages. CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; TIA, transient ischemic attack; TR, tricuspid regurgitation and VHD, valvular heart disease.

**Table 10.** MV: Incidence Rate and Association With Outcomes

Outcome	Event Rates		Unadjusted		Adjusted	
	No or Mild VHD (N=7043)	MV (N=306)	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause death	721 (4.45)	47 (6.49)	1.46 (1.11–1.91)	0.006	1.06 (0.80–1.41)	0.676
Stroke, non-CNS embolism, or TIA	223 (1.39)	14 (1.97)	1.41 (0.86–2.31)	0.171	0.97 (0.56–1.69)	0.918
Major bleeding	509 (3.25)	42 (6.19)	1.90 (1.41–2.56)	<0.001	1.22 (0.78–1.89)	0.385

Values are expressed as number of events and percentages. CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; MV, mechanical valve; TIA, transient ischemic attack and VHD, valvular heart disease.

**Table 11.** Bioprosthetic Valve: Incidence Rate and Association With Outcomes

Outcome	Event Rates		Unadjusted		Adjusted	
	No or Mild VHD (N=7043)	Bioprosthetic Valve (N=288)	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause death	721 (4.45)	59 (8.94)	2.00 (1.57–2.56)	<0.001	1.04 (0.78–1.38)	0.801
Stroke, non-CNS embolism, or TIA	223 (1.39)	19 (2.93)	2.10 (1.33–3.30)	0.001	1.27 (0.85–1.90)	0.246
Major bleeding	509 (3.25)	40 (6.40)	1.96 (1.45–2.66)	<0.001	1.20 (0.86–1.67)	0.277

Values are expressed as number of events and percentages. CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; TIA, transient ischemic attack and VHD, valvular heart disease.

disorders. These patients were largely excluded or underrepresented in recent trials of DOACs. It is, therefore, not clear whether DOACs are effective or safe in patients with bioprosthetic heart valves or prior valve repair/balloon valvuloplasty. A meta-analysis of phase 3 clinical trials of DOACs in patients with AF and VHD suggests that the relative efficacy and safety of DOACs were similar in patients with or without MR, AS, AR, bioprosthetic valves, or valve surgery. However, on the basis of existing American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines and the few patients with bioprosthetic heart valves and prior valve surgery currently evaluated, this VHD subgroup remains an enigmatic area in need of additional studies to specifically address the safety and efficacy of DOACs. Dabigatran has been associated with adverse outcomes in patients with mechanical heart valves and, thus, warfarin remains the standard-of-care oral anticoagulant for this type of VHD.<sup>24</sup>

## Limitations

These data represent observations from a prospective nationwide registry. The participation in the registry is voluntary, and site participation and patient selection may limit generalizability. Detailed echocardiographic information on VHD severity was not collected, and classification of valvular lesion and severity relied on clinical data collected in the case report forms. There was no information on the cause of VHD, and for those with prior valve replacement, surgical repair, or balloon valvuloplasty, the specific valve instrumented was unknown. Individuals with MS/MV and bioprosthetic valves, surgical repair, or balloon valvuloplasty represented smaller subgroups and, thus, yielded HRs with wider CIs; interpretation should be considered in this context. Last, during the follow-up for ORBIT-AF, warfarin was the predominant oral anticoagulant used; thus, our analysis could not address outcomes as a function of DOACs.

**Table 12.** Surgical Repair or Balloon Valvuloplasty: Incidence Rate and Association With Outcomes

Outcome	Event Rates		Unadjusted		Adjusted	
	No or Mild VHD (N=7043)	Surgical Repair or Balloon Valvuloplasty (N=288)	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause death	721 (4.45)	47 (7.17)	1.62 (1.23–2.13)	<0.001	1.05 (0.76–1.46)	0.671
Stroke, non-CNS embolism, or TIA	223 (1.39)	14 (2.17)	1.56 (0.94–2.58)	0.084	1.02 (0.62–1.68)	0.944
Major bleeding	509 (3.25)	41 (6.86)	2.11 (1.59–2.80)	<0.001	1.59 (1.05–2.41)	0.028

Values are expressed as number of events and percentages. CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; TIA, transient ischemic attack and VHD, valvular heart disease.

## Conclusion

In a contemporary registry of individuals with AF, a quarter had significant VHD with prosthetic valve replacements, MS, and prior surgical repairs/balloon valvuloplasty. Anticoagulation use was reasonably high among all individuals but particularly among those with significant VHD. Compared with individuals without significant VHD, those with MS/MV, AR/AS, MR, or TR, and prior bioprosthetic valve replacement, surgical repair, or balloon valvuloplasty had higher mortality, thromboembolic rates, and major bleeding that were attributable to a greater prevalence of comorbidities. Among adjusted analyses of individual valve disorders, AS was associated with a higher mortality risk and AR with a higher risk of major bleeding. Additional studies are needed to better understand the risk of DOAC use in VHD populations not represented in recent trials.

## Sources of Funding

The ORBIT-AF (Outcomes Registry for Better Informed Treatment for Atrial Fibrillation) is sponsored by Janssen Scientific Affairs, LLC (Raritan, NJ).

## Disclosures

Thomas reports being a consultant for Pfizer, Bristol Myers Squibb, and Janssen Pharmaceuticals; and receiving research support from the Patient Centered Research Outcomes Research Institute. Ansell reports consulting activities with Bristol Myers Squibb, Pfizer, Janssen, Daiichi Sankyo, Boehringer Ingelheim, Perosphere Equity, and Perosphere, Inc. Fonarow reports modest consultant/advisory board support from Janssen Pharmaceuticals. Gersh reports being a member of a Data Safety Monitoring Board for Mount Sinai St Lukes, Boston Scientific Corporation, Teva Pharmaceutical Industries, St Jude Medical, Janssen Research and Development, Baxter Healthcare Corporation, and Cardiovascular Research Foundation; doing general consulting for Janssen Scientific Affairs, Cipla Limited, and Armetheon Inc; and being on an advisory board for Medtronic. Kowey reports serving as a consultant to or being on the advisory board of Johnson & Johnson, Daiichi Sankyo, Boehringer Ingelheim, and Bristol Myers Squibb. Financial disclosures for Mahaffey before August 1, 2013, can be viewed at [https://www.dcri.org/ab-out-us/conflict-of-interest/Mahaffey-COI\\_2011-2013.pdf](https://www.dcri.org/ab-out-us/conflict-of-interest/Mahaffey-COI_2011-2013.pdf); disclosures after August 1, 2013, can be viewed at <http://med.stanford.edu/profiles/kenneth-mahaffey>. Singer reports research grants from Boehringer Ingelheim and Bristol Myers Squibb; being a consultant/advisory board member for Boehringer Ingelheim, Bristol Myers Squibb, Merck, Johnson & Johnson, Pfizer, and Medtronic; and being an executive

committee member of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial of rivaroxaban in atrial fibrillation. L. Thomas reports research with Novartis, Boston Scientific, Gilead, and Janssen Scientific. Piccini reports receiving research grants or research support from Johnson & Johnson/Janssen Pharmaceuticals, Boston Scientific Corp, ARCA Biopharma, Gilead, Res Med, and St Jude; and consultant/advisory board fees from Glaxo Smith-Kline, Medtronic Inc, Johnson & Johnson/Janssen Pharmaceuticals, Pfizer, and Spectranetics. Peterson reports consulting and participation in research with Janssen Pharmaceuticals and Bayer Co.

## References

1. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, Pais P, Erol C, Diaz R, Bahit MC, Bartunek J, De Caterina R, Goto S, Ruzyllo W, Zhu J, Granger CB, Alexander JH. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *Circulation*. 2015;132:624–632.
2. Abernathy WS, Willis PW III. Thromboembolic complications of rheumatic heart disease. *Cardiovasc Clin*. 1973;5:131–175.
3. Wood P. An appreciation of mitral stenosis, II: investigations and results. *BMJ*. 1954;1:1113–1124.
4. Wood P. An appreciation of mitral stenosis, I: clinical features. *BMJ*. 1954;1:1051–1063; contd.
5. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. *Br Heart J*. 1962;24:349–357.
6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
8. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Ghalibaf M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
9. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinler J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
10. Piccini JP, Fraulo ES, Ansell JE, Fonarow GC, Gersh BJ, Go AS, Hylek EM, Kowey PR, Mahaffey KW, Thomas LE, Kong MH, Lopes RD, Mills RM, Peterson ED. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. *Am Heart J*. 2011;162:606–612.e1.
11. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J*. 2010;159:340–347.e1.
12. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanaz-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364:806–817.
13. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical

- investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.
14. Halperin JL, Hart RG. Atrial fibrillation and stroke: new ideas, persisting dilemmas. *Stroke*. 1988;19:937–941.
  15. De Caterina R, Camm AJ. What is “valvular” atrial fibrillation? A reappraisal. *Eur Heart J*. 2014;35:3328–3335.
  16. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR, Lohknygina Y, Patel MR, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC, Mahaffey KW, Fox KA, Califf RM; ROCKET AF Steering Committee and Investigators. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. *Eur Heart J*. 2014;35:3377–3385.
  17. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF, Ruff CT, Antman EM, Braunwald E, Giugliano RP. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol*. 2017;69:1372–1382.
  18. Sherman DG, Dyken ML, Fisher M, Harrison MJ, Hart RG. Cerebral embolism. *Chest*. 1986;89:82S–98S.
  19. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol*. 2017;69:1363–1371.
  20. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Lip GY, Mantovani LG, Turpie AG, van Eickels M, Misselwitz F, Rushton-Smith S, Kayani G, Wilkinson P, Verheugt FW; GARFIELD Registry Investigators. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One*. 2013;8:e63479.
  21. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ, Schmitt J, Zamorano JL. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC guidelines on atrial fibrillation: primary results of the PREvention of thromboembolic events—European Registry in Atrial Fibrillation (PREFER in AF). *Europace*. 2014;16:6–14.
  22. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, Oliveira MM, Mairesse G, Crijns HJ, Simantirakis E, Atar D, Kirchhof P, Vardas P, Tavazzi L, Maggioni AP. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2014;16:308–319.
  23. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma C, Zint K, Elsaesser A, Bartels DB, Lip GY; GLORIA-AF Investigators. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: the GLORIA-AF Registry, phase II. *Am J Med*. 2015;128:1306–1313.e1.
  24. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobbmeyer MT, Maas H, Voigt JU, Simoons ML, Van de Werf F; REALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–1214.