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)

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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 CHA2DS2-VASc score ≥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.1–5 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.6–9 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)
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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.

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. 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). 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.

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 ≥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/
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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 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 CHA2DS2-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 CHA2DS2-VASc stroke risk scores (median, 5; IQR, 4–6). In this registry population, 91% of patients had a CHA2DS2-VASc score ≥2, and those with AR/AS, MR, or TR had the highest percentage with a CHA2DS2-VASc score ≥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 ≥5 (40.2%) and an ORBIT bleeding score ≥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

| 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.
population included the following: prior bleeding (28.8%), patient refusal/preference (27.9%), and frequent falls/frailty (17.8%). Of those with a CHA2DS2-VASc score ≥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)                                 | 76 (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/m²                 | 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
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.\(^1\)\(^4\)\(^5\) 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.\(^1\)\(^6\)\(^7\) 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 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 |
|----------------------------------------------------|-----------------|------------------------|-------------------------------------------|---------------------------------------------|--------------------------------------------------------|---------------|
| **Antithrombotic medications**                     |                 |                        |                                           |                                             |                                                        |               |
| 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        |
| **Antiplatelet**                                   |                 |                        |                                           |                                             |                                                        |               |
| 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        |
| **Medical history**                                |                 |                        |                                           |                                             |                                                        |               |
| 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.
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**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  

| 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) |
|-------------------------------|-----------------------|-------------------------|-----------------------------------------------|---------------------------------------------|-------------------------------------------------|
| 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.

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.2–5

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* |
|--------------------------------|-------------------------------------|-----------------------------------------------|---------------------------------------------|-------------------------------------------------|---------|
| All-cause mortality            |                                     |                                               |                                              |                                                 |         |
| 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   |
| Stroke, non-CNS embolism, or TIA |                                    |                                               |                                              |                                                 |         |
| 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   |
| Major bleeding                 |                                     |                                               |                                              |                                                 |         |
| 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.

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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) | <0.001  | 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. In the setting of rheumatic MS and mechanical prosthetic valves is unequivocally associated with a high risk of thromboembolism. 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.

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.

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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. 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 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.

| 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.
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.24

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 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.

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.

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