Aortic valve stenosis provides complementary information to bleeding risk scores in non-valvular atrial fibrillation patients initiating anticoagulation

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Abstract

Background The identification of modifiable bleeding risk factors may be of relevance. The aim is to evaluate if aortic stenosis (AS) provides additional information to bleeding risk scores for predicting major bleeding (MB) in non-valvular atrial fibrillation (AF).

Methods We designed a retrospective multi-center study including 2880 consecutive non-valvular AF patients initiating oral anticoagulation between January 2013 and December 2016. AS was defined as moderate or severe according to European echocardiography guidelines criteria.

HASBLED, ATRIA and ORBIT scores were used to evaluate the bleeding risk. MB was defined according to the International Society on Thrombosis and Haemostasia criteria and registered at 18 months of follow-up.

Results 168 (5.8%) patients had AS. Patients with AS had higher risk for MB compared to those without AS (HR = 2.13, 95% CI: 1.40–3.23, \( P < 0.001 \)). Patients without AS and low-intermediate bleeding risk (0 points) showed the lowest MB rate, whereas the MB rate observed among patients with AS and high bleeding risk (2 points) was the highest one. Discrimination and reclassification analyses showed that AS provided additional information to bleeding risk scores for predicting MB at 18 months of follow-up.

Conclusions In this population, AS was associated with an increased risk for MB at midterm follow-up. The three scoring systems showed a moderate discriminatory ability for MB. Moreover, the addition of AS was associated with a significant improvement in their predictive accuracy. We suggest that the presence of this valvulopathy should be taken into account for bleeding risk assessment.

Keywords: Anticoagulants; Aortic stenosis; Atrial fibrillation; Major bleeding; Valvular disease

1 Introduction

The coexistence of valvular heart disease (VHD) and atrial fibrillation (AF) is common and is associated with a worse prognosis.[1] A significant proportion of patients included in clinical trials with non-vitamin K antagonists (NOAC) had moderate or severe valvular abnormalities. In these studies, patients with VHD showed a worse clinical profile, significantly higher rates of major bleeding (MB) and similar results of NOAC compared to warfarin, irrespective of presence of VHD.[2–6] Recently, our group described a high prevalence of VHD among “real world” patients initiating NOAC (approximately 1 every 5 patients) that was associated with a higher risk of death and MB, especially those with aortic stenosis (AS).[7] Bleeding risk assessment is a cornerstone in AF patient management for a safer use of oral anticoagulants. HAS-BLED, ORBIT and ATRIA scoring systems have demonstrated a moderate ca-
pacity with no significant differences in discriminating bleeding in patients with AF on both vitamin K antagonists (VKA) and NOACs.\(^8\)\(^{-11}\) and HAS-BLED score has been recently validated for the first time in AF patients with VHD.\(^12\) Current clinical practice guidelines recommend identifying modifiable risk factors of MB.\(^13\) However, there are not specific considerations about the potential role of AS in the development of these complications, and this could be due to the lack of evidence supporting the additional information of this valvulopathy. AS is a frequent comorbidity among AF patients and it may represent a modifiable risk factor of bleeding. Therefore, the assessment of its additive value for risk prediction may be of clinical importance and may help improve the management of these patients. The aim of our study was to evaluate if AS was associated with a higher risk of bleeding complications and to assess its complementary value to available risk scores for prediction of MB in a contemporary cohort of non-valvular AF patients initiating oral anticoagulants.

2 Methods

The study was conducted according to the Declaration of Helsinki and the protocol was reviewed and approved by the local Clinical Research Ethics Committee. We designed a retrospective study to evaluate the impact of AS in bleeding event rate and to assess its complementary value to the Hypertension, Age, Stroke, Bleeding tendency/predisposition, Labile international normalized ratios, Elderly age/ frailty, Drugs such as concomitant aspirin/nonsteroidal antiinflammatory drugs or alcohol excess (HAS-BLED)\(^14\), the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA)\(^15\) and Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT)\(^16\) scores (see score definitions in Supplementary Table 1).

We included all non-valvular AF patients initiating oral anticoagulation (VKA or NOAC) for the prevention of stroke or systemic embolism and with an available echocardiogram at two hospitals between January 1, 2013 and December 31, 2016. We excluded patients who received oral anticoagulants for other indications or for cardioversion when long-term anticoagulation was not indicated. Patients with hypertrophic cardiomyopathy, moderate to severe rheumatic mitral stenosis or mechanical prosthetic valves and those with a previous history of oral anticoagulant therapy were also excluded. Patients who underwent aortic valve replacement were censored at the time of intervention. At inclusion, baseline data on demographic and clinical characteristics, complementary test results, as well as medications were recorded in detail by cardiologists trained for this purpose. AS was defined as moderate or severe according to European guidelines criteria.\(^17\) Anemia was defined as hemoglobin < 12 g/dL in women and < 13 g/dL in men. Kidney disease was defined as the presence of an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m\(^2\). Estimated glomerular filtration rate was calculated with the CKD-EPI equation. Abnormal liver function was defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin > 2 × upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3 × upper limit normal). HAS-BLED, ATRIA and ORBIT scores could be calculated in 97.1%, 99.9% and 100% of patients respectively. Bleeding risk categories were defined as low (HAS-BLED: 0–1, ATRIA: 0–3 and ORBIT 0–2 points), intermediate (HAS-BLED = 2, ATRIA = 4 and ORBIT = 3 points) and high (HAS-BLED ≥ 3, ATRIA ≥ 5 and ORBIT ≥ 4 points). Data were obtained from digitized clinical records held at the participating hospitals and associated primary care centers. Data were recorded by specially trained cardiologists in a bespoke data collection file containing all codified study variables.

Patients were followed up from the date they started treatment with oral anticoagulants and all clinical events were recorded in detail at 18 months. All medical records were carefully reviewed, and the patients or their relatives were contacted by telephone to obtain the incidence of bleeding events during the follow-up. Clinical events were recorded in 99.9% of patients. All events recorded during the study were validated by an expert committee of three investigators of the study (SMF, CCM and PJFB). The primary outcome of the study was MB that was defined according to 2005 ISTH (International Society on Thrombosis and Haemostasis bleeding scale) criteria\(^18\) as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells. Major gastrointestinal bleeding was defined as any bleeding from the gastrointestinal tract resulting in death or causing a fall in hemoglobin level of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells.

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± SD and non-normally distributed data as median (interquartile range). Categorical variables are expressed as percentages. Categorical variables were compared with the Chi-square test. Continuous variables were compared with the t-student test. We calculated
Table 1. Baseline characteristics of the study population as a function of the presence of aortic valve stenosis.

| Sociodemographic variables                                      | Whole population | Without aortic stenosis | With aortic stenosis | p    |
|----------------------------------------------------------------|------------------|-------------------------|----------------------|------|
| n = 2880                                                       | n = 2712         | n = 168                 |                      |      |
| **Age, yrs**                                                   | 77 (70–82)       | 76 (69–82)              | 81 (77–86)           | < 0.001 |
| Women                                                         | 1472 (51.1%)     | 1390 (51.3%)            | 82 (48.8%)           | 0.539 |
| Permanent atrial fibrillation                                 | 1388 (49.3%)     | 1290 (48.6%)            | 98 (59.8%)           | 0.016 |
| **Cardiovascular risk factors**                                |                  |                         |                      |      |
| Hypertension                                                  | 2463 (85.5%)     | 2309 (85.1%)            | 154 (91.7%)          | 0.020 |
| Diabetes mellitus                                             | 972 (33.9%)      | 906 (33.4%)             | 69 (41.1%)           | 0.042 |
| Smoking                                                       | 255 (8.9%)       | 245 (9.0%)              | 10 (6.0%)            | 0.200 |
| **Comorbidities**                                             |                  |                         |                      |      |
| Alcohol abuse                                                 | 97 (3.4%)        | 94 (3.5%)               | 3 (1.8%)             | 0.241 |
| COPD/asthma                                                   | 401 (13.9%)      | 370 (13.6%)             | 31 (18.5%)           | 0.081 |
| Previous stroke and/or TIA                                    | 456 (15.8%)      | 432 (15.9%)             | 24 (14.3%)           | 0.571 |
| Previous peripheral embolism                                  | 19 (0.7%)        | 17 (0.6%)               | 2 (1.2%)             | 0.381 |
| Ischemic heart disease                                        | 513 (17.8%)      | 473 (17.4%)             | 40 (23.8%)           | 0.037 |
| Previous stenting                                             | 310 (10.8%)      | 289 (10.7%)             | 21 (12.5%)           | 0.455 |
| Peripheral artery disease                                     | 109 (3.8%)       | 99 (3.7%)               | 10 (6.0%)            | 0.129 |
| Heart failure                                                 | 641 (22.3%)      | 578 (21.3%)             | 63 (47.5%)           | < 0.001 |
| Liver disease                                                 | 82 (2.8%)        | 74 (2.7%)               | 8 (4.8%)             | 0.124 |
| **Risk scores**                                               |                  |                         |                      |      |
| CHA2DS2-VASc, points                                          | 4 (3–5)          | 4 (3–5)                 | 5 (4–5)              | < 0.001 |
| HAS-BLED, points                                              | 2 (2–3)          | 2 (2–3)                 | 3 (2–3)              | < 0.001 |
| ATRIA, points                                                 | 3 (1–4)          | 3 (1–4)                 | 3 (3–6)              | < 0.001 |
| ORBIT, points                                                 | 1 (0–3)          | 1 (0–3)                 | 2 (1–4)              | < 0.001 |
| **Analytical and echocardiography data**                     |                  |                         |                      |      |
| eGFR, mL/min per 1.73 m²                                       | 68 (51–84)       | 69 (52–84)              | 58 (43–75)           | < 0.001 |
| Hemoglobin, g/dL                                              | 13.5 (12.2–14.7) | 13.5 (12.2–14.8)        | 12.8 (11.5–13.9)     | < 0.001 |
| LVEF ≤ 50%                                                    | 556 (19.3%)      | 518 (19.1%)             | 38 (22.6%)           | 0.262 |
| **Pharmacological treatment**                                 |                  |                         |                      |      |
| Acetylsalicylic acid                                          | 425 (14.8%)      | 383 (14.1%)             | 42 (25.1%)           | < 0.001 |
| Antiplatelet therapy                                          | 508 (17.7%)      | 464 (17.1%)             | 44 (26.3%)           | 0.002 |
| Beta-blockers                                                 | 1700 (59.0%)     | 1606 (59.2%)            | 94 (56.0%)           | 0.400 |
| ACEI/ARB                                                      | 1854 (64.4%)     | 1739 (64.1%)            | 115 (68.5%)          | 0.255 |
| Antialdosterone                                                | 210 (7.3%)       | 196 (7.2%)              | 14 (8.3%)            | 0.593 |
| Loop diuretics                                                | 1046 (36.3%)     | 942 (34.7%)             | 104 (61.9%)          | < 0.001 |
| Vitamin K antagonist                                          | 1716 (59.5%)     | 1595 (58.5%)            | 121 (71.4%)          |      |
| Rivaroxaban                                                   | 517 (18.0%)      | 492 (18.1%)             | 25 (14.9%)           |      |
| Dabigatran                                                    | 202 (7.0%)       | 199 (7.3%)              | 3 (1.8%)             | 0.010 |
| Apixaban                                                      | 428 (14.9%)      | 409 (15.1%)             | 19 (11.3%)           |      |
| Edoxaban                                                      | 17 (0.6%)        | 17 (0.6%)               | 0                   |      |

Data are expressed as median (interquartile range) or n (%). ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blockers; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricle ejection fraction; TIA: transient ischemic attack. See article text for expanded versions of score names. *Chronic kidney disease defined as CKD-EPI < 60 mL/min per 1.73 m².
hazard ratios (HR) and 95% confidence intervals (95% CI) derived from the Cox regression analysis to identify predictors of MB during follow-up. The independent effect of AS on MB complications was calculated using Cox multivariate regression analyses with the enter method, incorporating covariates that showed an association with clinical events in the univariate analysis and those judged by the investigators as important for the adjustment. Prior to data collection, a comprehensive literature search was performed to identify the major variables associated with each event. Linearity assumption was tested using Martingale residuals. We performed receiver operating characteristic (ROC) curves and their corresponding areas under the curve (AUC) to assess the discriminatory ability of the different bleeding risk scores for predicting MB.

In order to test the hypothesis that AS would improve risk prediction, patients were categorized on the basis of aortic valve function (AS = 1 point) and their bleeding risk (high bleeding risk = 1 point). A new ordinal variable was built taking into account the presence of none, one or two points. The AS was added to three models containing bleeding risk scores and the improvement in discriminatory ability was evaluated by C indexes (DeLong’s method was used for comparison). Finally, the improvement in predictive accuracy was evaluated by calculating the net reclassification improvement (NRI) and integrated discrimination improvement (IDI), as described by Pencina, et al., where bleeding risk categories were defined as low (<3%), intermediate (3%–8%) and high (>8%). The cumulative incidence of adverse clinical outcomes was estimated according to the Kaplan-Meier method, and the log-rank statistic was used for comparison. Differences were considered statistically significant at \( P < 0.05 \). The statistical analysis was performed with the statistical packages SPSS v21 (SPSS Inc; Chicago, Illinois, United States) and STATA v13.0 (Stata Corp LP.; Texas, United States).

### Results

The study population consisted of 2880 patients with non-valvular AF initiating oral anticoagulants (VKA 59.6% and NOAC 40.4%), among whom 168 (5.8%) patients had moderate or severe AS. Table 1 shows the characteristics of the study population as a function of the presence of AS. Patients with significant AS were older and had a worse clinical profile and higher estimated thromboembolic and bleeding risks. Moreover, these patients were more likely to receive concomitant antiplatelet therapy.

At 18 months of follow-up, there were 185 MB episodes (4.19/100 person-years) and 80 major gastrointestinal bleeding episodes (1.78/100 person-years). Supplementary Table 2 shows patients characteristics as a function of MB events. All risk scores were higher among patients who experienced MB complications vs. those without MB (HAS-BLED: 3 (2–4) vs. 2 (2–3) points, \( P < 0.001 \), ATRIA: 4 (3–6) vs. 3 (1–4) points, \( P < 0.001 \) and ORBIT: 2 (1–4) vs. 1 (0–2) points, \( P < 0.001 \). Risk categories analyses of these bleeding risk scores revealed that there was a graded increase in MB risk with increasing risk categories (Supplementary Table 3S). In addition, all bleeding risk scores showed a moderate discriminatory ability for predicting MB at 18 months (HAS-BLED = 0.66, 95% CI: 0.63–0.67, \( P <

### Table 2.  Univariate and multivariate Cox regression analyses for predicting major bleeding events at 18 months of follow up.

|                  | Univariable HR (95% CI) | Univariable \( P \) | Multivariable HR (95% CI) | Multivariable \( P \) |
|------------------|-------------------------|---------------------|---------------------------|----------------------|
| Age (x 1 year)   | 1.04 (1.03–1.06)         | < 0.001             | 1.03 (1.01–1.05)           | 0.001                |
| Women            | 1.19 (0.89–1.58)         | 0.248               | 1.10 (0.81–1.50)           | 0.526                |
| Permanent atrial fibrillation | 1.28 (0.95–1.72) | 0.105               | -                         | -                    |
| Hypertension     | 1.13 (0.74–1.74)         | 0.573               | 0.88 (0.57–1.37)           | 0.567                |
| Diabetes mellitus| 1.27 (0.94–1.70)         | 0.116               | -                         | -                    |
| History of stroke and/or transient ischemic attack | 1.22 (0.84–1.77) | 0.300               | 1.01 (0.69–1.49)           | 0.952                |
| Ischemic heart disease | 1.79 (1.30–2.45) | < 0.001             | 1.16 (0.80–1.68)           | 0.451                |
| Heart failure    | 1.38 (1.00–1.90)         | 0.051               | 0.94 (0.67–1.31)           | 0.696                |
| Moderate-severe aortic stenosis | 2.90 (1.93–4.36) | < 0.001             | 2.13 (1.40–3.23)           | < 0.001              |
| History of cancer | 2.14 (1.51–3.04) | < 0.001             | 1.57 (1.09–2.26)           | 0.016                |
| History of major bleeding | 2.42 (1.55–3.77) | < 0.001             | 1.65 (1.03–2.64)           | 0.037                |
| Chronic kidney disease* | 1.87 (1.40–2.49) | < 0.001             | 1.20 (0.87–1.64)           | 0.268                |
| Anemia           | 2.60 (1.94–3.48)         | < 0.001             | 1.84 (1.35–2.51)           | < 0.001              |
| Antiplatelet therapy | 2.16 (1.58–2.95) | < 0.001             | 1.52 (1.06–2.19)           | 0.023                |
| Type of anticoagulant (VKA vs. NOAC) | 1.62 (1.18–2.23) | 0.003               | 1.38 (0.99–1.93)           | 0.058                |

NOAC: non-vitamin K antagonist; VKA: vitamin K antagonist. * Chronic kidney disease defined as CKD-EPI < 60 mL/min per 1.73 m².
Table 3. Complementary value of aortic valve stenosis to the bleeding risk scores in major bleeding.

|                          | C-index (95% CI)          | P     | Relative IDI, % | P     | NRI, % | P      | MB events correctly reclassified | Non-MB events correctly reclassified |
|--------------------------|---------------------------|-------|----------------|-------|--------|--------|-------------------------------|---------------------------------------|
| HAS-BLED                 | 0.66 (0.64–0.68)          | 0.041 | 1.83           | 0.005 | 4.81   | 0.034 | 8.94%                         | –4.13%                                |
| HAS-BLED + AS            | 0.68 (0.66–0.70)          | 0.040 | 1.57           | 0.007 | 6.45   | 0.025 | 1.62%                         | 4.83%                                 |
| ATRIA                    | 0.65 (0.64–0.67)          | 0.047 | 1.46           | 0.014 | 2.27   | 0.170 | 4.86%                         | –2.60%                                |
| ATRIA + AS               | 0.67 (0.66–0.69)          | 0.041 | 1.83           | 0.005 | 4.81   | 0.034 | 8.94%                         | –4.13%                                |
| ORBIT                    | 0.67 (0.65–0.68)          | 0.047 | 1.46           | 0.014 | 2.27   | 0.170 | 4.86%                         | –2.60%                                |
| ORBIT + AS               | 0.68 (0.67–0.70)          | 0.047 | 1.46           | 0.014 | 2.27   | 0.170 | 4.86%                         | –2.60%                                |

AS: aortic valve stenosis; IDI: integrated discrimination improvement; MB: major bleeding; NRI: net reclassification improvement. Bleeding risk categories were defined as low (< 3%), intermediate (3%–8%) and high (> 8%). See article text for expanded versions of score names.

The potential enhanced value from the addition of AS to bleeding risk scores for predicting MB is presented in Figure 1A-C, which shows that patients without AS and low-intermediate bleeding risk (0 points) had the lowest MB rate, those with AS and high bleeding risk (2 points) had the highest MB rate, and those with AS or high bleeding risk (1 point) had intermediate rates (log-rank test $P < 0.001$). In adjusted analyses, a significantly higher risk of MB was
observed for each point in the combined score (from 0 to 2), Figure 2A–C).

Table 3 shows the improvement in the predictive discrimination and accuracy conferred by adding aortic valve status to the three bleeding risk scores. The addition of AS was associated with a modest but statistically significant improvement in prediction performance (C index) and showed the highest predictive accuracy (ROC curves are shown in supplementary Figure 1A–C). In reclassification analyses, AS added significant information to bleeding risk scores. The relative integrated discrimination improvement from the addition of AS was 1.83%, 1.57% and 1.46% (all P values < 0.05), whereas the net reclassification improvement was 4.81% (P = 0.034), 6.45% (P = 0.025) and 2.27% (P = 0.17), for HAS-BLED, ATRIA and ORBIT respectively. The probability of correctly predicting MB events when AS was added to the bleeding scales were reflected in the percentage of both MB and non-MB events correctly reclassified.

4 Discussion

In this contemporary cohort of non-valvular AF patients initiating oral anticoagulants, the prevalence of moderate or severe AS was not uncommon. These patients were older and had a worse clinical profile with more comorbidities and higher estimated thromboembolic and bleeding risks. AS was associated with an increased risk of bleeding events at midterm follow-up. The three scoring systems showed a similar moderate discriminatory ability for MB, with the addition of AS being associated with a significant improvement in their predictive accuracy. We suggest that the presence of this valvulopathy should be taken into account for bleeding risk assessment.

The prevalence of valve disease increases with age. Indeed, more than one in eight people aged 75 or older have a moderate or severe valve disease, being mitral regurgitation and AS the most frequent abnormalities. A meta-analysis showed that the prevalence of all AS was 12.4% and the prevalence of severe AS was 3.4% in people older than 75. In the last years, the risk profile of patients with AS has increased, mainly due to older age, accumulation of comorbidities and more advanced disease at presentation. Whilst many patients develop AF as a result of VHD, there are concomitant factors that may contribute to the occurrence and development of AF, such as older age, heart failure, hypertension, coronary artery disease and diabetes. Therefore, coexistence of these two pathologies is common. The prevalence of patients with moderate or severe AS included in clinical trials comparing VKA and NOAC ranged from 5.8% to 11.9% and patients with VHD were on average at higher risk because of their worse clinical profile and comorbidities. These data from randomized trials are in line with our findings from a “real world” non-valvular AF cohort.

In our study, AS was associated with higher rates of MB and AS was found to be an independent predictor with a more than a two-fold increase in the risk for MB, being gastrointestinal the most frequent origin. The association between AS and gastrointestinal bleeding is well known and is linked to a worse quality of life, hospitalization and mortality. This association was first suggested by Heyde E in 1958, who reported 10 cases of AS and massive gastrointestinal bleeding of uncertain origin. Subsequent reports have described angiodysplasia in the gastrointestinal tract as the cause of recurrent bleeding in patients with AS, which...
ranges from 7% to 29%[28] and it is currently termed Heyde syndrome. It has been demonstrated that bleeding is caused by the induction of acquired Von Willebrand disease type 2A caused by a depletion of Von Willebrand factor high molecular weight multimers, which are necessary for an effective platelet-mediated hemostasis, due to proteolysis of Von Willebrand as it passes through the stenotic valve with increased shear forces.[29] This concept is further supported by the demonstration that both biologic abnormalities and bleeding events can be corrected by valve replacement.[30] The association between VHD and bleeding complications has already been described. In the ROCKET AF trial,[3] MB occurred more frequently in AF patients (adjusted HR = 1.61, P < 0.05), and in the four clinical trials comparing VKA and NOAC[3,2,5] and a meta-analysis,[6] patients with VHD had significantly higher rates of MB (HR = 1.34, 95% CI: 1.13–1.59). Recently, our group described that VHD, and especially AS, was associated with a higher risk of MB among “real world” patients initiating NOAC.[7] Current clinical guidelines for the management of AF[13] recommend identifying modifiable and potentially modifiable bleeding risk factors in anticoagulated patients. However, no specific considerations are made about the potential role of AS. In our opinion, in the light of our results and previously commented evidence, AS is an important comorbidity that should be taken into account when initiating anticoagulation and should therefore be included as a risk factor in clinical guidelines.

Balancing safe and effective use of oral anticoagulation is a challenge clinicians have to face in our daily practice. While CHA2DS2VASc score is widely used and recommended for estimating stroke risk in AF patients,[31] the utility and clinical impact of bleeding risk scores is low, and this fact is recognized by the European Society of Cardiology[13] and the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines[32] and more specifically from the AHA/ACC/HRS guideline: “Although these scores may be helpful in defining patients at elevated bleeding risk, their clinical utility is insufficient for use as evidence for the recommendations in this guideline.” Several bleeding risk scores have been developed above all in patients on VKA. In this study, we evaluated the performance of HAS-BLED, ATRIA and ORBIT scores.[14–16] These scores only have modest ability and similar performance to predict bleeding in patients treated with both VKA and NOAC,[8–11] and in a recent study,[12] HAS-BLED score has been validated for the first time in AF patients with VHD, showing again a modest predictive value (C-statistic 0.59 at 1 year). Our results are in consonance with former evidence (all C-statistics < 0.7) and, interestingly, we found that the addition of AS improved the predictive accuracy of the three bleeding risk scores.

This observational and retrospective study includes a real world cohort of non-valvular AF patients initiating oral anticoagulants and suffers from the same limitations as other retrospective studies. Although we adjusted for potential confounders, unmeasured variables cannot be definitively established and there is always a possibility of residual confounding. However, the multi-centric design, the number of events recorded and the low number of patients lost to follow-up are remarkable aspects of this study. Bleeding scores could be calculated in the majority of patients (> 97%) but not in all them. This study includes patients who initiated oral anticoagulants for the first time but does not account for subsequent changes (discontinuation and resumption) during follow-up.

In conclusion, AS is an important comorbidity in AF patients and is associated with a higher risk of MB. Its addition provides complementary information to bleeding risk scores and improves their predictive value. The results of this study are of relevance and may have important clinical implications. We suggest that the presence of this valvulopathy should be taken into account for bleeding risk assessment. On the one hand, AS is a modifiable risk factor and valve replacement could be considered earlier for reducing bleeding events in patients at very high risk or with previous MB complications. On the other hand, patients with AS have a worse clinical profile, with more comorbidities and higher estimated bleeding risk, where bigger efforts to minimize other modifiable factors should be made (i.e., investigation and treatment of anemia, careful re-evaluation of concomitant antiplatelets indication, selection of anticoagulants with better security profile, etc.).

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