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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.

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 NOAC,[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 m². 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.

	Whole population n = 2880	Without aortic stenosis n = 2712	With aortic stenosis n = 168	P
Sociodemographic variables				
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
*Chronic kidney disease	1116 (38.8%)	1019 (37.6%)	97 (57.7%)	< 0.001
Kidney transplant/hemodialysis	26 (0.9%)	22 (0.8%)	4 (2.4%)	0.037
Malignancy	340 (11.8%)	309 (11.4%)	31 (18.5%)	0.006
Previous major bleeding	161 (5.6%)	149 (5.5%)	12 (7.1%)	0.367
Risk scores				
CHA$_2$DS$_2$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 m^2	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
Antiplathelet 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
Antialdosteronic	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 m^2.

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[19] 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*.[20], 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).

3   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		Multivariable	
	HR (95% CI)	P	HR (95% CI)	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 m^2.

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		0.005		0.034		
HAS-BLED + AS	0.68 (0.66–0.70)		1.83		4.81		8.94%	−4.13%
ATRIA	0.65 (0.64–0.67)	0.040		0.007		0.025		
ATRIA + AS	0.67 (0.66–0.69)		1.57		6.45		1.62%	4.83%
ORBIT	0.67 (0.65–0.68)	0.047		0.014		0.170		
ORBIT + AS	0.68 (0.67–0.70)		1.46		2.27		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.

0.001; ATRIA = 0.65, 95% CI: 0.64–0.67, *P* < 0.001 and ORBIT = 0.67, 95% CI: 0.65–0.68, *P* < 0.001). Patients with AS had higher rates of MB at 18 months of follow-up compared to patients without AS (11.02 *vs*. 3.79 events/100 person-years). Table 2 shows univariate and multivariate analyses for predicting MB events. After multivariate adjustment, AS was associated with a higher risk of MB (HR = 2.13, 95% CI: 1.40–3.23, *P* < 0.001).

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

Patients at risk (A)				
No AS and Low/intermediate bleeding risk (score = 0)	1491	1473	1437	1247
AS or high bleeding risk (score = 1)	1209	1165	1116	977
AS and high bleeding risk (score = 2)	97	90	80	77

Patients at risk (B)				
No AS and Low/intermediate bleeding risk (score = 0)	2078	2048	1990	1722
AS or high bleeding risk (score = 1)	732	694	661	592
AS and high bleeding risk (score = 2)	69	63	57	54

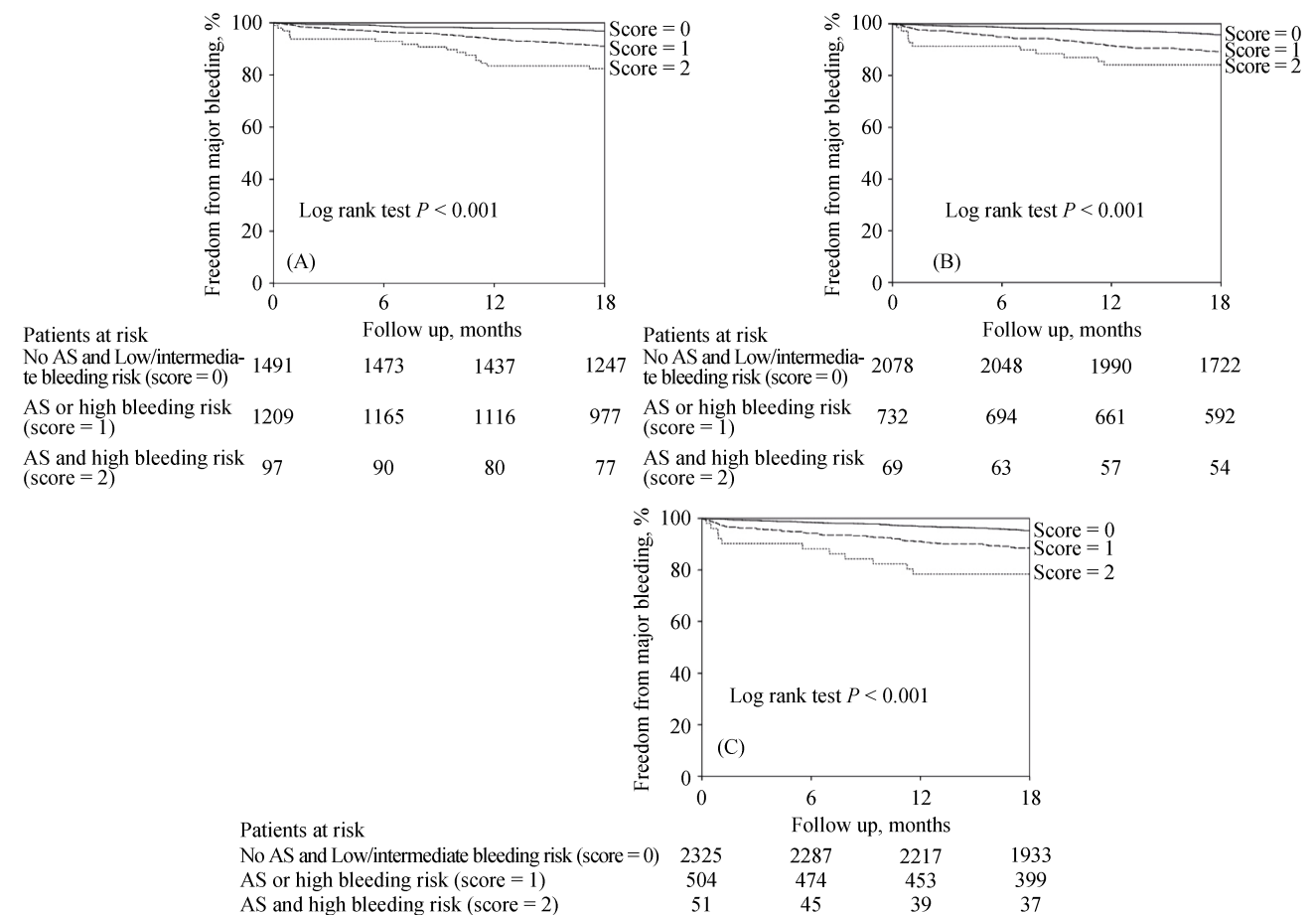| Patients at risk (C)				
No AS and Low/intermediate bleeding risk (score = 0)	2325	2287	2217	1933
AS or high bleeding risk (score = 1)	504	474	453	399
AS and high bleeding risk (score = 2)	51	45	39	37

Figure 1.   Kaplan-Meier survival curves for MB as a function of the combined risk score including aortic valve status and bleeding risk score categories. (A): HASBLED; (B): ATRIA; (C): ORBIT. AS: aortic stenosis; MB: major bleeding.

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 im-

provement 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.[21] 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.[22] 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.[23] 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.[24] 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,[2–6] 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.[25] Subsequent reports have described angiodysplasia in the gastrointestinal tract as the cause of recurrent bleeding in patients with AS,[26,27] which
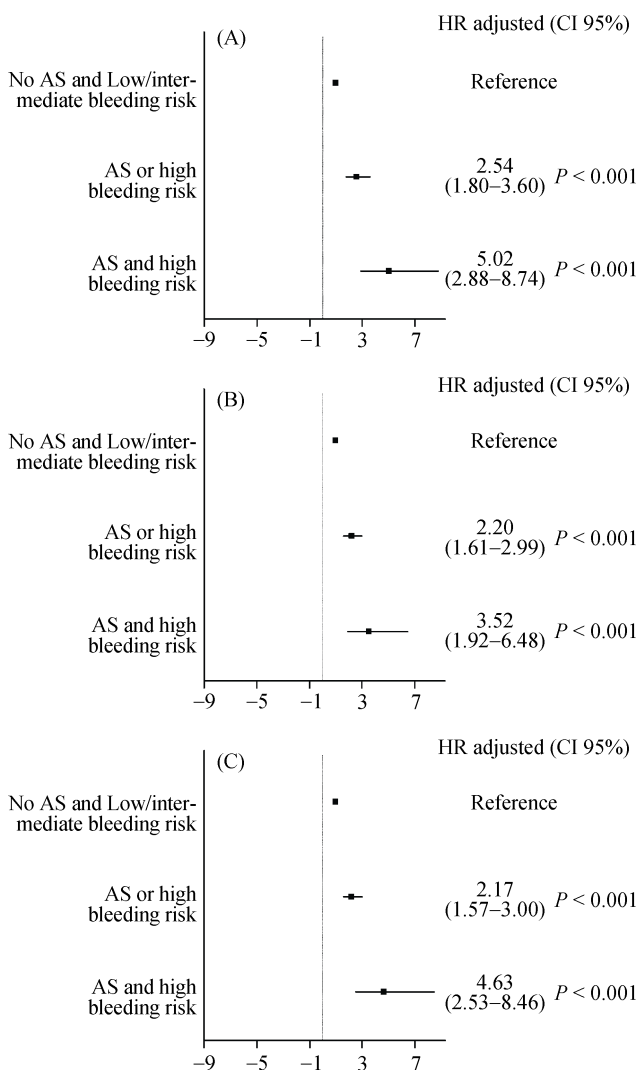

Figure 2. **Multivariate hazard ratios for the association between the combined risk score and MB at 18 months of follow-up.** (A): HASBLED; (B): ATRIA and (C) ORBIT. Combined risk score includes aortic valve status and bleeding risk score categories. AS: aortic stenosis; MB: major bleeding.

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 AS patients (adjusted HR = 1.61, $P < 0.05$), and in the four clinical trials comparing VKA and NOAC[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.).

Acknowledgments

References

1   Petty GW, Khandheria BK, Whisnant JP, *et al*. Predictors of cerebrovascular events and death among patients with valvular heart disease: A population-based study. *Stroke* 2000; 31: 2628–2635.

2   Ezekowitz MD, Nagarakanti R, Noack H, *et al*. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: The RE-LY trial (randomized evaluation of long-term anticoagulant therapy). *Circulation* 2016; 134: 589–598.

3   Breithardt G, Baumgartner H, Berkowitz SD, *et al*. Native valve disease in patients with non-valvular atrial fibrillation on warfarin or rivaroxaban. *Heart* 2016; 102: 1036–1043.

4   Avezum A, Lopes RD, Schulte PJ, *et al*. Apixaban in com-

parison 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.

5   De Caterina R, Renda G, Carnicelli AP, *et al*. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol* 2017; 69: 1372–1382.

6   Renda G, Ricci F, Giugliano RP, *et al*. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol* 2017; 69: 1363–1371.

7   Caro Martinez C, Elvira Ruiz G, Flores Blanco PJ, *et al*. Prevalence and prognostic implications of valve disease in patients with atrial fibrillation initiating direct oral anticoagulants. *Rev Esp Cardiol* (*Engl Ed*) 2019; 72: 935–943.

8   Caro Martinez C, Andreu Cayuelas JM, Flores Blanco PJ, *et al*. Comparison of bleeding risk scores in patients with non-valvular atrial fibrillation starting direct oral anticoagulants. *Rev Esp Cardiol* (*Engl Ed*) 2017; 70: 878–880.

9   Abumuaileq RR, Abu-Assi E, Raposeiras-Roubin S, *et al*. Comparison between 3 bleeding scoring systems in nonvalvular atrial fibrillation patients. What can the new ORBIT score provide? *Rev Esp Cardiol* (*Engl Ed*) 2016; 69: 1112–1114.

10   Donze J, Rodondi N, Waeber G, *et al*. Scores to predict major bleeding risk during oral anticoagulation therapy: a prospective validation study. *Am J Med* 2012; 125: 1095–1102.

11   Yao X, Gersh BJ, Sangaralingham LR, *et al*. Comparison of the CHA2DS2-VASc, CHADS2, HAS-BLED, ORBIT, and ATRIA risk scores in predicting non-vitamin K antagonist oral anticoagulants-associated bleeding in patients with atrial fibrillation. *Am J Cardiol* 2017; 120: 1549–1556.

12   Lip GYH, Jensen M, Melgaard L, *et al*. Stroke and bleeding risk scores in patients with atrial fibrillation and valvular heart disease: evaluating "valvular heart disease" in a nationwide cohort study. *Europace* 2019; 21: 33–40.

13   Kirchhof P, Benussi S, Kotecha D, *et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Rev Esp Cardiol* (*Engl Ed*) 2017; 70: 50.

14   Pisters R, Lane DA, Nieuwlaat R, *et al*. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; 138: 1093–1100.

15   Fang MC, Go AS, Chang Y, *et al*. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011; 58: 395–401.

16   O'Brien EC, Simon DN, Thomas LE, *et al*. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015; 36: 3258–3264.

17   Baumgartner H, Hung J, Bermejo J, *et al*. EAE/ASE. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009; 10: 1–25.

18   Schulman S, Kearon C, Subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. defi-

nition of major bleeding in clinical investigations of anti-hemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–694.

19   DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44: 837–845.

20   Pencina MJ, D'Agostino RB S, D'Agostino RB, *et al*. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008; 27: 157–172.

21   Nkomo VT, Gardin JM, Skelton TN, *et al*. Burden of valvular heart diseases: a population-based study. *Lancet* 2006; 368: 1005–1011.

22   Osnabrugge RL, Mylotte D, Head SJ, *et al*. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013; 62: 1002–1012.

23   Baran J, Podolec J, Tomala MT, *et al*. Increased risk profile in the treatment of patients with symptomatic degenerative aortic valve stenosis over the last 10 years. *Postepy Kardiol Interwencyjnej* 2018; 14: 276–284.

24   Menezes AR, Lavie CJ, DiNicolantonio JJ, *et al*. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. *Mayo Clin Proc* 2013; 88: 394–409.

25   Heyde E. Gastrointestinal bleeding in aortic stenosis. *N Engl J Med*. 1958; 259: 196–196.

26   Weaver GA, Alpern HD, Davis JS, *et al*. Gastrointestinal angiodysplasia associated with aortic valve disease: part of a spectrum of angiodysplasia of the gut. *Gastroenterology* 1979; 77: 1–11.

27   Bourdette D, Greenberg B. Twelve-year history of gastrointestinal bleeding in a patient with calcific aortic stenosis and hemorrhagic telangiectasia. *Dig Dis Sci* 1979; 24: 77–79.

28   Shoenfeld Y, Eldar M, Bedazovsky B, *et al*. Aortic stenosis associated with gastrointestinal bleeding. A survey of 612 patients. *Am Heart J* 1980; 100: 179–182.

29   Warkentin TE, Moore JC, Morgan DG. Aortic stenosis and bleeding gastrointestinal angiodysplasia: is acquired von Willebrand's disease the link? *Lancet* 1992; 340: 35–37.

30   Anderson RP, McGrath K, Street A. Reversal of aortic stenosis, bleeding gastrointestinal angiodysplasia, and von Willebrand syndrome by aortic valve replacement. *Lancet* 1996; 347: 689–690.

31   Lip GY, Nieuwlaat R, Pisters R, *et al*. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; 137: 263–272.

32   January CT, Wann LS, Alpert JS, *et al*, ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014; 130: 2071–2104.