Incidence, source, and prognostic impact of major bleeding across the spectrum of aortic stenosis

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Background Severe aortic stenosis (AS) has been associated with bleeding. However, there is a lack of prospective assessment of bleeding events and their clinical significance in a large population of outpatients with variable degree of AS severity.

Objectives To assess the incidence, source, determinants, and prognostic impact of major bleeding in patients with variable degree of AS severity.

Methods Between May 2016 and December 2017, consecutive outpatients were included. Major bleeding was defined as type ≥3 bleed using the Bleeding Academic Research Consortium definition. Cumulative incidence was calculated with death as the competing event. Data was censored at time of aortic valve replacement.

Results Among 2,830 patients, 46 major bleeding events occurred (0.7%/year) during a median follow-up of 2.1 years (interquartile range: 1.4-2.7). Most frequent sites of bleeding were gastrointestinal (50%) and intracranial (30.4%). Major bleeding was significantly associated with all-cause mortality (hazard ratio: 5.93 (95% confidence interval 3.64-9.65); $P < .001$). AS severity was associated with major bleedings ($P = .041$). By multivariable analysis, severe AS was an independent determinant of major bleeding (hazard ratio vs mild AS: 3.59 [95% confidence interval 1.56-8.29]; $P = .003$). The increased risk of bleeding associated with severe AS was significantly exacerbated in patients using oral anticoagulation.

Conclusion In AS patients, major bleeding is rare but a strong independent predictor of death. AS severity is a determinant of bleeding events. Severe AS and oral anticoagulation should be identified as an association at very high risk of major bleeding. (Am Heart J 2023;262:140–147.)

Background

There has been considerable interest in the recent literature regarding bleeding events occurring in patients with cardiovascular diseases. Previous studies performed in patients with atrial fibrillation,[1] acute coronary syndrome,[2,3] coronary revascularization,[4,5] stable coronary artery disease[6] or heart failure (HF)[7] have identified major bleedings as events associated with important prognostic consequences. Identifying patients at risk of bleeding is thus an integral part of patient management to elaborate preventive strategies in the most appropriate populations.

It has been reported that aortic stenosis (AS) can be complicated by bleeding.[8-10] Bleeding events in patients with AS have been associated with acquired type 2A von Willebrand syndrome and its resultant hemostatic disorders.[11-13] However, most of the literature on AS and bleeding is from retrospective analyses, small series of patients included in tertiary centers, or case-report studies focusing on severe AS. While there have been large studies on the risk of bleeding after aortic valve replacement (AVR),[14-16] a prospective assessment of bleeding events in patients with varying severity of AS, in the pre-AVR state, is still lacking. Such information would be

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Abbreviations: AS, Aortic Stenosis; AVR, Aortic Valve Replacement; BARC, Bleeding Academic Research Consortium; CI, Confidence Interval; HR, Hazard Ratio; IQR, Interquartile Range; LVEF, Left Ventricular Ejection Fraction; SD, Standard Deviation.

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of interest to clinicians managing AS patients, especially when considering the frequent indications of antithrombotic medications in this elderly population with high prevalence of atrial fibrillation and coronary artery disease.[17,18]

We therefore designed the present study to assess the importance of bleedings in patients with AS. We analyzed the data of 2830 AS outpatients included in the VALVENOR (*Suivi d'une cohorte de patients présentant une sténose VALVulaire aortiquE en région NORd-pas-de-Calais*) registry. We report the incidence, source, determinants, and prognostic impact of major bleeding events occurring during the follow-up of the study.

Methods

Study population

The VALVENOR registry was a prospective multicenter study that enrolled 2830 outpatients with native valvular AS.[19] Patients were included between May 2016 and December 2017 by 117 cardiologists from the Nord-Pas-de-Calais region in France during outpatient visits. The cardiologists were selected based on geographic distribution to provide a representative sample of the area's current cardiology practices in university public hospitals, non-university public hospitals, and private centers. This study was approved by the French medical data protection committee and authorized by the Commission Nationale de l'Informatique et des Libertés for the treatment of personal health data. All patients consented to the study after being informed in writing of the study's objectives and treatment of the data, as well as on their rights to object, of access, and of rectification.

Inclusion criteria

Consecutive outpatients with a peak aortic jet velocity ≥2.5m/s were prospectively included in the registry. Transthoracic echocardiography was performed as part of routine clinical practice using commercially available systems. Peak aortic jet velocity was derived from trans aortic flow, recorded with continuous wave Doppler. Patients younger than 18 years or with a documented history of AVR were excluded. To represent the real-life spectrum of AS, patients with other cardiovascular or non-cardiovascular illnesses or comorbidities were not excluded from the study.

Study design and data collection

At the initial visit, the investigators (ie, the cardiologists) prospectively completed a case record form containing information regarding demographic, clinical and echocardiographic details of the patients. During the outpatient visit, the investigators reviewed the patients' current drug treatment and entered all prescribed drugs on the case record form. According to current diagnostic criteria,[20] patients were categorized as follows: mild AS (peak velocity 2.5-2.99 m/s), moderate AS (peak velocity 3-3.99 m/s) and severe AS (peak velocity ≥ 4m/s). Left ventricular ejection fraction (LVEF) was estimated by the Simpson biplane method. Aortic and mitral regurgitation were also assessed as previously described.[21,22]

Objective, follow-up, and end points

The objectives of this analysis were to assess the incidence, source, determinants, and prognostic impact of major bleeding in outpatients with AS. The patients were followed up by their treating cardiologists. The number of outpatient's visits was at the discretion of the cardiologists. Protocol-specified follow-up was scheduled at 2 years and performed using a standardized case record form to report clinical events. General practitioners and/or patients were contacted by a research technician in the case of missing information. The identification of patients with events for adjudication was based on interviews with patients/relatives during outpatient visits, on discharge summaries for hospitalization during follow-up that were sent to treating cardiologists, and on information obtained by the research technician. We collected information on major bleeding events (defined as BARC type 3 events using the Bleeding Academic Research Consortium [BARC] definitions[23]). BARC type 1 and 2 bleeds were not collected in our registry. Bleeding events were adjudicated according to prespecified definitions, by 2 investigators, with a third opinion in cases of disagreement.

Statistical analysis

Statistical analyses were performed with the Stata 14.2 software (Stata Corporation, College Station, TX). Continuous variables were described as the mean ± standard deviation (SD) or as median with interquartile range. Categorical variables were presented as absolute numbers and percentages. Bleeding events were analyzed by censoring data at the time of AVR ($n = 663$ patients). The incidence of major bleeding was estimated with the cumulative incidence function, with death as the competing event. Cumulative incidence and 95% confidence intervals (CIs) were obtained using the stcompet and stcomlist packages. Univariable and multivariable assessments of baseline variables associated with major bleeding were performed with the use of a cause-specific hazard model.[24,25] Hazard ratios (HRs) and 95% CIs were calculated. The proportional hazards assumption was tested visually by examining plots of -ln[-ln(survival time) against the ln(time) and by including time-dependent interaction terms in the regression analysis. Collinearity was excluded by constructing a correlation matrix between variables included into the model. Subgroup analyses were conducted to evaluate the association between AS severity and major bleeding according to the type of antithrombotic regimen at inclusion and according to the

Table I. Baseline characteristics of the study population.

	All patients (n = 2,812)	No major bleeding (n = 2,766)	Major bleeding (n = 46)	P value
Age (y)	75.9 ± 11.1	75.8 ± 11.2	80 ± 9	.005
Women	1,322 (47)	1,292 (46.7)	30 (65.2)	.013
Diabetes mellitus	840 (29.9)	829 (30)	11 (23.9)	.407
History of hypertension	2,139 (76.1)	2,099 (75.9)	40 (87)	.093
Previous myocardial infarction	257 (9.1)	252 (9.1)	5 (10.9)	.674
Previous coronary bypass	127 (4.5)	124 (4.5)	3 (6.5)	.404
Previous percutaneous coronary intervention	360 (12.8)	353 (12.8)	7 (15.2)	.636
Atrial fibrillation	656 (23.3)	636[23]	20 (43.5)	<.001
Previous hospitalization for heart failure	298 (10.6)	290 (10.5)	8 (17.4)	.027
Previous stroke	241 (8.6)	231 (8.4)	10 (21.7)	.001
AS severity:				
- Mild	1,191 (42.4)	1,175 (42.5)	16 (34.8)	
- Moderate	1,165 (41.4)	1,144 (41.3)	21 (45.6)	.041
- Severe	456 (16.2)	447 (16.2)	9 (19.6)	
Left ventricular ejection fraction (%)	63.8 ± 8.9	63.8 ± 8.9	60.1 ± 9.9	.001
Bicuspid aortic valve*	282 (12.7)	279 (12.8)	3 (7.9)	.384
Grade 3-4 aortic regurgitation	27[1]	27[1]	0	1.000
Grade 3-4 mitral regurgitation	27[1]	26[1]	1 (2.2)	.201
Mitral stenosis < 1.5 cm^2	37 (1.3)	37 (1.3)	0	1.000

Data are mean ± SD or n (%).
*Undetermined in 585 patients.

absence/presence of atrial fibrillation at baseline. The association between major bleeding and subsequent mortality was assessed with a Cox analysis, and major bleeding was modeled as a time-dependent variable. HRs and 95% CIs were calculated. Statistical significance was assumed at P <.05.

Results

Baseline characteristics

Among the 2,830 included patients, 2,812 (99.4%) underwent clinical follow-up at a median of 2.1 years (interquartile range: 1.4-2.7). The baseline characteristics of the study population are summarized in Table I. This was an elderly population, with a mean age of 75.9 ± 11.1 years. There was a high prevalence of risk factors and underlying cardiovascular diseases (coronary artery disease, atrial fibrillation and stroke). At inclusion, 1,191 (42.4%) patients had mild AS, 1,165 (41.4%) moderate AS and 456 (16.2%) severe AS. Preventive cardiovascular treatments were widely prescribed (Table II). Of note, 64.6% of the patients received at least one antithrombotic treatment at inclusion (antiplatelet therapy, 44.4%; oral anticoagulant, 22.5% with vitamin K antagonists in 14% and direct oral anticoagulants in 8.5%) (Table II).

Bleeding events

There were 46 major bleeding events and 475 deaths during the follow-up period. Figure 1A illustrates the timing of the bleeding events and shows that the risk of bleeding was constant throughout follow-up. The cumulative incidence of major bleeding (with death as the competing event) was 1.4% (95% CI 1-1.9) at 2 years. As shown in Table III, most events were BARC type 3 bleeds. In most of the cases, the site of bleeding was gastrointestinal (50%) or intracranial (30.4%). The site of the 8 fatal bleeds (type 5) was gastrointestinal in 4 patients, intracranial in 3 patients, and retroperitoneal in 1 patient. During the follow-up, 9 additional deaths (cardiovascular n = 4, non-cardiovascular n = 5) occurred among the patients who experienced major bleeding, giving a total of 17 (37%) deaths. When used as a time-dependent variable, major bleeding was associated with a significant increase in mortality (HR = 5.93 [95% CI 3.64-9.65]; P < .001).

Correlates of major bleeding

The patients who experienced major bleeding were older and more frequently women. The patients who bled also more frequently displayed moderate or severe AS, atrial fibrillation, previous hospitalization for HF, previous stroke, and a lower LVEF (Table I). Regarding medications at inclusion, the patients who bled more frequently received oral anticoagulation. As shown in Table IV, 5 variables were identified as independently associated with major bleeding by multivariable analysis: Severe AS, LVEF (negative association), women, previous stroke, and oral anticoagulation.

Figure 1B illustrates the impact of AS severity on the risk of major bleeding. The 2-year cumulative incidence of major bleeding was 0.8% (95% CI 0.4-1.4) in patients with mild AS, 1.7% (95% CI 1-2.7) in patients with moderate AS and 2.6% (95% CI 1.2-4.9) in patients with severe AS (P = .041). In a subgroup analysis, the impact of AS severity on the risk of major bleeding was further investigated according to the type of antithrombotic treatment at inclusion. There were 569 patients receiving oral anticoagulation alone, 1184 receiving an-

Table II. Medications at inclusion.

	All patients (n = 2,812)	No major bleeding (n = 2,766)	Major bleeding (n = 46)	P value
Antiplatelet drug	1,248 (44.4)	1,227 (44.4)	21 (45.7)	.856
Oral anticoagulant	633 (22.5)	616 (22.3)	17 (37)	.007
Any antithrombotic drug	1,817 (64.6)	1,781 (64.4)	36 (78.3)	.033
Angiotensin-converting enzyme inhibitor or angiotensin 2 receptor antagonist	1,842 (65.5)	1,809 (65.4)	33 (71.7)	.463
Aldosterone antagonist	154 (5.5)	152 (5.5)	2 (4.4)	.728
ß-blocker	1,257 (44.7)	1,233 (44.6)	24 (52.2)	.253
Statin	1,531 (54.5)	1,506 (54.5)	25 (54.4)	.888
Calcium antagonist	915 (32.5)	905 (32.7)	10 (21.7)	.096
Diuretic	1,261 (44.8)	1,238 (44.8)	23 (50)	.312

Data are n (%).

Table III. Major bleeding events during the follow-up period.

BARC type:	
3a	13 (28.3%)
3b	14 (30.4%)
3c	11 (23.9%)
4	-
5	8 (17.4%)
Site of bleeding:	
Gastrointestinal	23 (50%)
Intracranial	14 (30.4%)
Other	9 (19.6%)

BARC, Bleeding Academic research Consortium.[22]
Data are n (%).
Total number of patients = 46. Type 3a: overt bleeding plus hemoglobin drop of 3 to <5 g/dL and/or any transfusion with overt bleeding; Type 3b: overt bleeding plus hemoglobin drop <5 g/dL and/or cardiac tamponade and/or bleeding requiring surgical intervention for control and/or bleeding requiring intravenous vasoactive agents; Type 3c: intracranial hemorrhage and/or intraocular bleed compromising vision; Type 4: coronary bypass-related bleeding; Type 5: fatal bleeding.

Table IV. Multivariable analysis: baseline characteristics independently associated with major bleeding.

	Hazard ratio	95% CI	P value
AS severity:			
- Mild	Reference	-	-
- Moderate	1.82	0.94-3.54	.078
- Severe	3.59	1.56-8.29	.003
LVEF (per %)	0.95	0.92-0.98	<.001
Women	2.39	1.29-4.45	.006
Previous stroke	2.70	1.28-5.66	.009
Oral anticoagulant	1.91	1.03-3.54	.040

The variables considered for inclusion into the model were age, gender, diabetes mellitus, history of hypertension, previous hospitalization for heart failure, previous stroke, aortic stenosis severity, left ventricular ejection fraction (LVEF) antiplatelet therapy, and oral anticoagulation. A stepwise approach was used with forward selection (the P value for entering the stepwise model was set at .05).

tiplatelet therapy alone, and 995 without antithrombotic therapy; 64 further patients who received a combination of oral anticoagulation and antiplatelet therapy were not included in this analysis. As shown in Figure 2A, patients with severe AS receiving oral anticoagulation had a much higher risk of major bleeding than patients with moderate or mild AS also receiving oral anticoagulation (P = .036). By contrast, in patients under antiplatelet therapy (Figure 2B) and in patients without any antithrombotic therapy (Figure 2C), the risk of bleeding was not significantly modulated by AS severity. An additional subgroup analysis according to absence/presence of atrial fibrillation at baseline provided concordant results (Supplemental Figure 1).

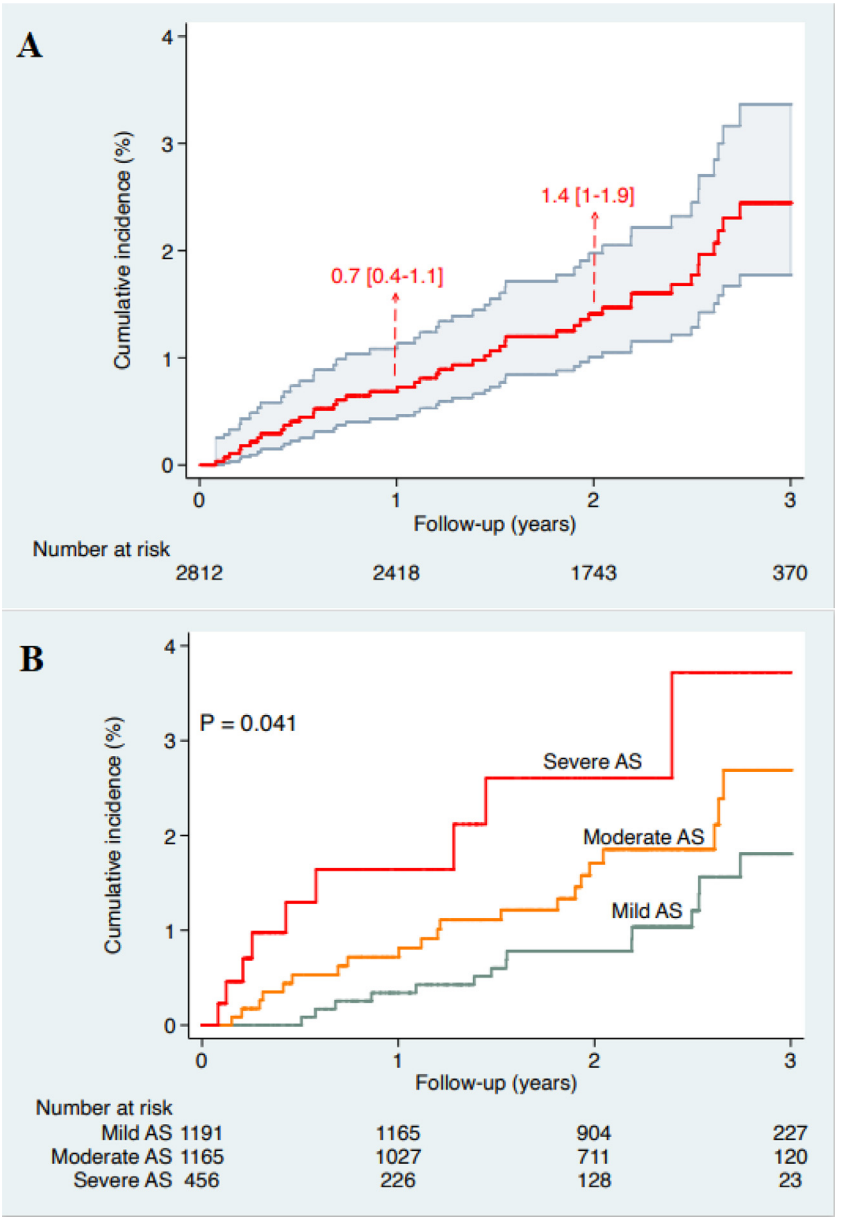
Discussion

The results of the present study can be summarized as follow: (1) in the overall population of AS outpatients with variable degree of severity, the cumulative incidence of major bleeding is relatively low, ie, 0.7%/year; (2) AS severity is independently associated with bleeding events; (3) the increased risk of major bleeding in severe AS is restricted to the subgroup of patients receiving oral anticoagulation.

Bleeding from gastrointestinal angiodysplasia in severe AS patients (Heyde's syndrome) has been recognized for many years.[8,10] Retrospective studies have confirmed a significant association between severe AS and the risk of gastrointestinal bleeding.[9] Subsequently, it has been suggested that the increased bleeding tendency of AS patients may be due to acquired type 2A von Willebrand syndrome as a consequence of shear stress during turbulent passage through the narrowed valve.[11-13] Prospective data on the incidence of major bleeding events in AS patients are however lacking.

It should be noted that the treatment has an impact on bleeding events. In PARTNER I, SAVR was associated with a significantly higher 30-day transfusion rate (17.9%) than either transfemoral-TAVR (7.1%) or transapical-TAVR

Figure 1

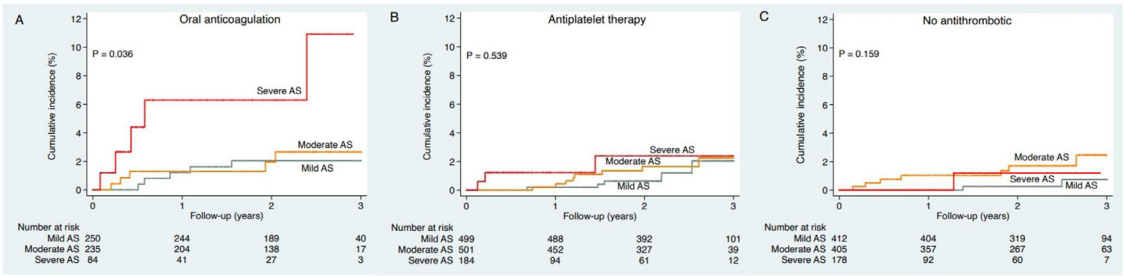


Major bleeding during follow-up. Panel A = Overall population; data are cumulative incidence of BARC ≥3 bleeding (death as competing event) with 95% confidence interval. Pane B = according to aortic stenosis severity; data are cumulative incidence of BARC ≥3 bleeding (death as competing event). *BARC*, Bleeding Academic Research Consortium.

(4.8%; $P < .0001$).[15] Recently, in an observational study of consecutive TAVR procedures, 13.8% of patients had severe gastrointestinal bleeding (defined as abnormal hemoglobin/hematocrit and overt bleeding or a positive fecal occult blood test). Of the 164 TAVRs with severe GIB, 130 (79.3%) had resolution of their bleeding after their TAVR.[26]

In the present study, we demonstrate a limited (0.7%/year) risk of major (BARC ≥3) bleeds in a large cohort of AS outpatients. As a comparison, the incidence of BARC ≥3 bleeds has been reported to be 0.6%/year in stable coronary artery disease[6] and 1.2%/year in chronic HF.[7] Bleeding events were most frequently gastrointestinal, but other sites were also reported with intracranial

Figure 2



Major bleeding according to aortic stenosis (AS) severity and antithrombotic treatment at baseline. Panel A = patients with oral anticoagulation at baseline ($n = 569$). Panel B = patients with antiplatelet therapy at baseline ($n = 1,184$). Pannl C = patients without antithrombotic treatment at baseline ($n = 995$).Data are cumulative incidence of BARC ≥3 bleeding (death as competing event).

bleeding in 30% of the cases. This observation of a relatively low risk of bleeding must however be tempered by the fact that our analysis focused on severe events. Indeed, our study also points to the considerable prognostic implications of these bleeding events which were strongly associated with subsequent mortality. All physicians following AS patients should, therefore, pay special attention to the determinants of bleeding.

A strength of the present study was the recruitment of patients with different stages of AS severity and our data demonstrate that AS severity is a determinant of bleeding. To the best of our knowledge, this information has not been previously reported. The effect size was substantial as the risk of major bleeding in severe AS was more than 3 times higher than that observed in mild AS. Although our study was purely observational and thus did not allow to draw conclusions regarding the mechanism(s) implicated, this finding is consistent with the previously demonstrated relation between von Willebrand factor abnormalities and the mean transvalvular gradient.[12] In addition to AS severity, we identified several patient-related variables (previous stroke, female gender and a low LVEF) that were associated with bleeding by multivariable analysis and may help to identify the high-risk patients. A history of stroke and female gender have previously been associated with a high risk of bleeding in different settings.[1,27]

Finally, antithrombotic medications were widely used in the present cohort. Comorbidities such as atrial fibrillation, coronary artery disease or stroke are highly prevalent in AS outpatients and account for the long-term prescription of antiplatelet drugs and/or oral anticoagulants. Our study documents a higher risk of major bleeding in patients receiving oral anticoagulation (almost a quarter of the study population). By contrast, the risk of major bleeding was not increased in patients receiving antiplatelet therapy. In addition, while the results from subgroup analyses should be interpreted with caution, the impact of AS severity on the risk of major bleedings was restricted to patients with oral anticoagulation. The combination of anticoagulation with the hemostatic abnormalities of severe AS may account for the high risk of these patients.

Clinical implications

Physicians should be aware of the high risk of major bleeding when patients with severe AS are treated with oral anticoagulants. This knowledge may help refine the analysis of the risk-benefit ratio of oral anticoagulation. In addition, whether the patient has an indication of long-term anticoagulation could potentially be considered when assessing the need for AVR in asymptomatic patients with severe AS. In these patients, an early intervention may protect from the devastating consequences of a potential major bleeding; indeed, previous studies have reported that both surgical AVR or transcatheter AVR reverse the hemostatic abnormalities and offer long-term resolution of the risk of bleeding in most patients with severe AS.[28,29]

Limitations

As for all observational registries, biases may have occurred, and our results may have been affected by unmeasured confounders. Our data reflect the practice in a regional area. Although this was not a population-based registry, the patients included were treated at research institutions and smaller community hospitals, as well as in private practice. It will have to be determined whether our findings are generalizable for practices in other parts of the world. By categorizing patients with AS according to peak aortic jet velocity, we acknowledge the imprecision in diagnosing severe low-gradient AS. Our study only focused on BARC ≥3 bleeds; thus, less severe events that could be associated with outcomes were not analyzed.

Further studies are needed to clarify the association of the different BARC classes with prognosis in patients with AS. Finally, we also acknowledge that our study has limited power for subgroup analyses.

Conclusions

In outpatients with AS, major bleeding events occur at a rate of 0.7%/year and are a strong predictor of death. There is a progressive increase in bleeding risk with increased severity of AS. Patients with severe valvular disease (peak aortic jet velocity $\geq$ 4 m/s) receiving oral anticoagulation are at the highest risk of bleeding. This should be kept in mind while managing AS patients, especially when considering the frequent indications of anticoagulation in this elderly population with high prevalence of atrial fibrillation.

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Disclosures

None reported.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.04.011.

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