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ORIGINAL RESEARCH

Aortic Stenosis and Outcomes in Patients With Atrial Fibrillation: A Nationwide Cohort Study

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BACKGROUND: Patients with aortic stenosis (AS) have been underrepresented in the trials evaluating direct oral anticoagulants (DOACs) in atrial fibrillation (AF). We aimed to assess whether AS impacts outcomes in patients with AF and estimate the effects of DOACs versus warfarin in patients with AF and AS.

METHODS AND RESULTS: The registry-based FinACAF (Finnish Anticoagulation in Atrial Fibrillation) study covered all patients with AF diagnosed during 2007 to 2018 in Finland. Hazard ratios (HRs) of first-ever gastrointestinal bleeding, intracranial bleeding, any bleeding, ischemic stroke, and death were estimated with cause-specific hazards regression adjusted for anticoagulant exposure variables. We identified 183 946 patients (50.5% women; mean age, 71.7 [SD, 13.5] years) with incident AF without prior bleeding or ischemic stroke, of whom 5231 (2.8%) had AS. The crude incidence rate of all outcomes was higher in patients with AS than in patients without AS. After propensity score matching, AS was associated with the hazard of any bleeding, gastrointestinal bleeding, and death but not with intracranial bleeding or ischemic stroke (adjusted HRs, 1.36 [95% CI, 1.25–1.48], 1.63 [95% CI, 1.43–1.86], 1.32 [95% CI, 1.26–1.38], 0.96 [95% CI, 0.78–1.17], and 1.11 [95% CI, 0.99–1.25], respectively). Among patients with AS, DOACs were associated with a lower risk of ischemic stroke when compared with warfarin, while bleeding and mortality did not differ between DOACs and warfarin.

CONCLUSIONS: AS is associated with substantially higher risk of gastrointestinal bleeding in patients with AF. DOACs may be more effective in preventing ischemic stroke than warfarin in patients with AF and AS.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04645537.

Key Words: anticoagulation ■ aortic stenosis ■ atrial fibrillation ■ bleeding ■ ischemic stroke ■ outcomes

Atrial fibrillation (AF), the most common sustained arrhythmia with a prevalence as high as 4.1%, is an important cause of ischemic stroke.[1,2] Fortunately, ischemic strokes due to AF are largely preventable with oral anticoagulant (OAC) therapy, which, on the other hand, predisposes patients to adverse bleeding events. Assessment of patients' bleeding risk is essential in the clinical decision-making on OAC therapy.[3,4] A multitude of bleeding risk factors in patients with AF have been identified, and different combinations of these factors are incorporated into the commonly used bleeding risk stratification scores.[5]

Aortic stenosis (AS) is a common valvular disease affecting especially the elderly, and its prevalence, along with that of AF, is expected to further increase due to the aging population.[6–8] AS and AF often

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CLINICAL PERSPECTIVE

What Is New?

- Aortic stenosis was associated with a higher risk of gastrointestinal bleeding in patients with atrial fibrillation.
- In patients with coexisting atrial fibrillation and aortic stenosis, direct oral anticoagulants were associated with a lower risk of ischemic stroke when compared with warfarin, while bleeding and mortality did not differ between direct oral anticoagulants and warfarin.

What Are the Clinical Implications?

- Aortic stenosis should be considered in the bleeding risk assessment of patients with atrial fibrillation.
- Direct oral anticoagulants seem safe and superior to warfarin in stroke prevention among patients with both atrial fibrillation and aortic stenosis.

Nonstandard Abbreviations and Acronyms

ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
AS	aortic stenosis
AvoHILMO	Primary Health Care Outpatient Care Notification registry
DOAC	direct oral anticoagulant
FinACAF	Finnish Anticoagulation in Atrial Fibrillation
HILMO	Hospitalizations and Outpatient Specialist Visits registry
KELA	Social Insurance Institute registry
OAC	oral anticoagulant
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
VKA	vitamin K antagonist

coexist, with AS prevalence estimates of 2% to 5% in patients with AF.[9] Conversely, 20% to 30% of patients with AS have concomitant AF.[10,11] Previous studies have associated AS with an increased risk of gastrointestinal bleeding, as well as ischemic stroke, regardless of the presence of AF.[12,13] Indeed, gastrointestinal bleeding from angiodysplasias in patients with AS is a well-known but uncommon clinical presentation of Heyde syndrome, which in addition to AS and bleeding angiodysplasias is characterized by acquired type IIA von Willebrand syndrome caused by blood flowing through the stenotic aortic valve.[12] Reports on the prevalence of Heyde syndrome in patients undergoing transcatheter aortic valve replacement have ranged between 2% and 3%, but the overall prevalence and impact of Heyde syndrome is unknown.[14–16]

There is little information on the safety and efficacy of OACs in patients with coexisting AF and AS. Patients with AS were underrepresented in the randomized trials evaluating the efficacy and safety of direct oral anticoagulants (DOACs) compared with vitamin K antagonists (VKAs) in patients with AF, and the results in these patients were inconsistent.[17–20] Furthermore, the magnitude of the risks associated with AS in patients with AF is unclear. Therefore, we conducted a nationwide cohort study to evaluate the impact of AS on outcomes in patients with AF and to compare the effect of DOACs and VKAs on outcomes in this fragile patient group.

METHODS

Data Availability Statement

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Finnish national register holders (KELA, Finnish Institute for Health and Welfare, Population Register Center and Tax Register) through Findata (https://findata.fi/en/).

Study Population

The FinACAF (Finnish Anticoagulation in Atrial Fibrillation) study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a retrospective nationwide registry-based cohort study that includes all patients diagnosed with AF in Finland during 2004 to 2018.[2] The inclusion criterion for the cohort was the *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis code I48 (atrial fibrillation and atrial flutter, together referred to as AF), and cohort entry occurred on the date of the first recorded AF diagnosis. Patients with a diagnosis of AF were identified from the following national health care registers: HILMO (Hospitalizations and Outpatient Specialist Visits) registry, AvoHILMO (Primary Health Care Outpatient Care Notification) registry, and the National Reimbursement Register upheld by the KELA (Social Insurance Institute) registry. The general exclusion criteria of the study were age <20 years at AF diagnosis and permanent migration abroad before December 31, 2018. The present substudy was conducted within a cohort of patients diagnosed with incident AF during 2007 to 2018, established in previous studies within the FinACAF cohort.[21,22] For this substudy, patients with any bleeding

event, ischemic stroke, or aortic valve replacement before cohort entry were excluded to definitively distinguish the first-ever outcome event. Follow-up started from the date of the first recorded AF diagnosis, and the study observation period ended on December 31, 2018. Outcomes of OAC therapy were assessed among patients with AS and separately among patients with AS starting OAC therapy without bleeding, ischemic stroke, or aortic valve replacement before OAC initiation. The study flowchart summarizes the patient selection process (Figure S1).

Aortic Stenosis

Patients were classified in the AS group if they had an *ICD-10* code of AS at the time of AF diagnosis, and patients with no AS diagnosis at baseline were used as reference (Table S1). All stages of AS were included because classification of AS severity from the used data was not feasible.

Study Outcomes

The outcomes of interest were first-ever ischemic stroke, gastrointestinal bleeding, intracranial bleeding, or bleeding from any anatomic site, as well as all-cause death. The outcome was considered to occur on the date of the first recorded event of interest. The diagnosis codes and dates were obtained from the aforementioned HILMO hospital care register. Only diagnoses from the hospital register were included to ensure that the event of interest was truly major and clinically relevant. The outcome diagnosis codes used are summarized in Table S1.

Exposure to OACs

VKA and DOAC exposures were treated as time-varying variables. VKA exposure was considered to start from VKA (warfarin) purchase date and continue until 120 days after the last purchase or a purchase of a DOAC. Similarly, DOAC exposure was considered to start from DOAC (dabigatran, apixaban, rivaroxaban, or edoxaban) purchase date and continue until 120 days after the last purchase or a VKA purchase. The 120-day interval was chosen because in Finland it is possible to purchase drugs with reimbursement for a maximum of 90 days, and an additional 30-day grace period was allowed to cover possible stockpiling and differences in warfarin dosing.

Statistical Analysis

The chi-square test was used to analyze differences between categorical variables, and Student's *t* test was used to compare continuous variables. Incidence rates and crude incidence rate ratios were generated for all end points with the Poisson regression. Because baseline characteristics differed significantly between patients with or without AS, we employed 1:5 propensity score matching to adjust for imbalances between the study cohorts. A propensity score was estimated using logistic regression, with diagnosis of AS as the dependent variable considering the following variables: age, sex, year of AF diagnosis, income quartiles, hypertension, heart failure, diabetes, dyslipidemia, mitral regurgitation, kidney failure, liver failure or cirrhosis, prior transient ischemic attack, alcohol use disorder, any vascular disease, cancer, dementia, psychiatric disorder, and the HAS-BLED and CHA_2DS_2-VASc scores. Propensity score matching was performed with the nearest neighbor method using a caliper width of 0.2 of the SD of the logit of the propensity score. Standardized differences <0.1 were considered a nonsignificant imbalance between the matched cohorts.

Subsequently, cause-specific hazards regression adjusted with VKA and DOAC exposures was used to estimate the association between AS and the aforementioned outcomes. Robust standard errors were used to account for clustering in the comparisons within the matched cohort. Follow-up continued until first-ever outcome event of interest, death, transcatheter or surgical aortic valve replacement, or end of the observation period on December 31, 2018. Death was considered as a competing event when assessing hazard ratios (HRs) for bleeding and stroke events. In the mortality analyses, follow-up continued until death or end of the observation period.

We compared the effect of DOACs versus VKAs on outcomes covering only patients with AS using 2 separate approaches. First, we included all patients with AS and assessed the association of the aforementioned time-varying DOAC and VKA exposure variables with outcomes. In this analysis, follow-up started from the first diagnosis of AF and continued until the first-ever outcome event of interest, death, transcatheter or surgical aortic valve replacement, or end of the observation period on December 31, 2018. Thereafter, we emulated intention-to-treat analyses among patients with AS initiating OAC therapy with either a DOAC or a VKA.[23] In this analysis, follow-up began on the date of the first OAC purchase and continued until first-ever outcome event of interest, death, transcatheter or surgical aortic valve replacement, December 31, 2018, or maximum 2 years from OAC initiation. In the intention-to-treat analysis, patients were considered exposed to either initiated DOAC or VKA therapy irrespective of any subsequent treatment changes. In both study approaches, outcome HRs were estimated with the cause-specific hazards regression adjusted for the same above-mentioned variables used in the calculation of the propensity score, except for the HAS-BLED and CHA_2DS_2-VASc risk scores.

Thereafter, to evaluate whether the association between anticoagulant exposures and outcomes is modified by the presence of AS, interaction terms between AS and the time-varying DOAC and VKA exposure variables were fitted into the regression models in the adjusted analyses within the matched cohort.

A *P* value <0.05 was considered statistically significant. Statistical analyses were performed with the IBM SPSS Statistics software version 28.0 (SPSS, Inc., Chicago, IL) and R version 4.0.5 (https://www.R-project.org).

Study Ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (nr. 15/2017) and granted research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018; THL 2101/5.05.00/2018); Population Register Centre (VRK/1291/2019–3 and Tax Register VH/874/07.01.03/2019). The patients' identification numbers were pseudonymized, and the research group received individualized but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2002.

RESULTS

Overall Cohort

We identified 183 946 patients (50.5% women; mean age, 71.7 [SD 13.5] years) with incident AF without prior bleeding or ischemic stroke, of whom 5231 (2.8%) had a diagnosis of AS at cohort entry. In the overall cohort before propensity score matching, patients with AS were older and had higher prevalence of cardiovascular comorbidities and higher bleeding and stroke risk scores than patients without a history of AS (Table 1). Of the patients with AS, 931 (17.8%) underwent a transcatheter or surgical aortic valve replacement during the study period. The mean follow-up time in the all-cause mortality analyses was 4.4 (SD, 3.3) years. The crude incidence rates of all bleeding types, ischemic stroke, and all-cause death were higher in patients with AS than among those without (Figure, Table 2).

Outcomes of Patients With AS in the Propensity Score–Matched Cohort

Propensity score matching yielded a cohort of 5229 patients with AS and 25 625 patients without AS with similar baseline characteristics (Table 1). Among the matched patients, OACs were initiated more often in patients with AS than in those without AS before the end of the observation period (76.6% versus 73.8%; *P*<0.001). Moreover, patients with AS were more likely to receive VKAs and less likely DOACs during follow-up than patients without AS (59.5% versus 51.5% and 26.0% versus 31.8%, respectively; both *P*<0.001). In the matched cohort, after adjusting for VKA and DOAC exposures, AS was associated with higher hazard of any bleeding, gastrointestinal bleeding, and death. However, AS was not significantly associated with the hazard of ischemic stroke or intracranial bleeding (Figure, Table 3). According to the interaction analyses, the presence of AS did not significantly modify the outcome effects of DOAC use compared with VKAs (Table S2).

DOAC Versus VKA in Patients With AS

Of the 5231 patients with AS, 3285 (62.8%) started OAC therapy without bleeding, ischemic stroke, or aortic valve replacement before OAC initiation. The initial anticoagulant was warfarin, rivaroxaban, apixaban, dabigatran, and edoxaban in 73.3%, 9.6%, 12.1%, 4.6%, and 0.4% of these cases, respectively. DOACs were initiated more toward the end of the observation period. Additionally, patients initiating DOACs were more often men and had higher income and mean HAS-BLED score but similar CHA_2DS_2-VASc score when compared with patients starting stroke prevention with VKA (Table S3). Among the patients with AS and AF, DOACs were associated with similar hazard of bleeding and death as VKA both when drug exposures were treated as time-varying variables and in the intention-to-treat analyses based on OAC initiation. However, initiation of DOAC therapy was associated with a lower risk of ischemic stroke than VKA in the intention-to-treat approach. A similar but nonsignificant trend toward lower risk of ischemic stroke for DOACs was observed in the analyses with time-varying OAC exposures (Table 4 and Table S4).

DISCUSSION

This nationwide retrospective cohort study observed that AS is associated with a higher risk of bleeding in patients with AF. In particular, the presence of AS increased the risk of gastrointestinal bleeding, while the risk of intracranial bleeding was similar in patients with and without AS. Additionally, AS was associated with higher all-cause mortality but not with the risk of ischemic stroke. Among patients with AS, DOACs were associated with reduced risk of ischemic stroke compared with VKA, while otherwise no difference was observed between anticoagulant groups with respect to bleeding and death.

Previous research on the association of AS and outcomes in patients with AF is limited. The increased risk of gastrointestinal bleeding in severe AS and the pathophysiology of Heyde syndrome are well documented, but the actual clinical impact of this

Table 1. Baseline Characteristics of the Overall Cohort and the Propensity Score–Matched Cohort

	Overall cohort			Propensity score–matched cohort		
	No aortic stenosis n=178 715	Aortic stenosis n=5231	Standardized mean difference	No aortic stenosis n=25 625	Aortic stenosis n=5229	Standardized mean difference
Age, y	71.5 (13.6)	79.0 (9.8)	0.561	78.9 (10.0)	79.0 (9.8)	0.011
Cohort entry year	2013 (3.5)	2013 (3.4)	0.085	2013 (3.4)	2013 (3.4)	0.014
Female sex	88 773 (49.7)	2265 (43.3)	0.128	11 226 (43.8)	2264 (43.3)	0.010
Income quartiles			0.281			0.007
First (lowest)	41 675 (23.3)	1591 (30.4)		8198 (32.0)	1591 (30.4)	
Second	46 519 (26.0)	1699 (32.5)		7679 (30.0)	1699 (32.5)	
Third	44 509 (24.9)	1142 (21.8)		5473 (21.4)	1140 (21.8)	
Fourth (highest)	46 012 (25.7)	799 (15.3)		4275 (16.7)	799 (15.3)	
Any vascular disease	44 431 (24.9)	2476 (47.3)	0.517	11 791 (46.0)	2474 (47.3)	0.026
Diabetes	35 922 (20.1)	1370 (26.2)	0.152	6756 (26.4)	1370 (26.2)	0.006
Dyslipidemia	78 879 (44.1)	3285 (62.8)	0.376	16 058 (62.7)	3283 (62.8)	0.002
Heart failure	28 102 (15.7)	1857 (35.5)	0.538	8489 (33.1)	1855 (35.5)	0.050
Hypertension	128 087 (71.7)	4405 (84.2)	0.280	21 598 (84.3)	4403 (84.2)	0.002
Mitral regurgitation	4230 (2.4)	668 (12.8)	0.650	2570 (10.0)	666 (12.7)	0.088
Prior TIA	8743 (4.9)	324 (6.2)	0.060	1570 (6.1)	324 (6.2)	0.003
Abnormal liver function	652 (0.4)	26 (0.5)	0.022	144 (0.6)	26 (0.5)	0.009
Abnormal renal function	5702 (3.2)	324 (6.2)	0.169	1476 (5.8)	323 (6.2)	0.018
Alcohol use disorder	6291 (3.5)	95 (1.8)	0.093	470 (1.8)	95 (1.8)	0.001
Cancer	34 197 (19.1)	1288 (24.6)	0.139	6256 (24.4)	1287 (24.6)	0.005
Dementia	7745 (4.3)	301 (5.8)	0.069	1479 (5.8)	301 (5.8)	0.001
Psychiatric disorder	22 234 (12.4)	527 (10.1)	0.072	2583 (10.1)	527 (10.1)	0.001
Modified HAS-BLED score	2.2 (0.9)	2.5 (0.7)	0.389	2.5 (0.7)	2.5 (0.7)	0.009
CHA_2DS_2-VASc score	3.1 (1.7)	4.2 (1.5)	0.675	4.2 (1.5)	4.2 (1.5)	0.027

Values denote n (%) or mean (SD). CHA_2DS_2-VASc: congestive heart failure, hypertension, age≥75 years, diabetes, history of stroke or TIA, vascular disease, age 65 to 74 years, sex category (female); modified HAS-BLED score: hypertension, abnormal renal or liver function, prior stroke, bleeding history, age>65 years, alcohol abuse, concomitant antiplatelet/nonsteroidal anti-inflammatory drugs (no labile international normalized ratio, max score 8). TIA indicates transient ischemic attack.

phenomenon on a population level has been unclear, particularly in interplay with the prothrombotic state in AF.[12,24] Likewise, there has been a paucity of information on the impact of AS on the safety and efficacy profiles of OAC therapies in patients with AF. Few previous observational studies have assessed the relationship between AS and bleeding and stroke outcomes in patients with AF, although the generalizability of their findings has been limited by small or selected sample sizes.[25–27] Substudies of the original DOAC trials have also reported outcomes of patients with valvular heart diseases.[17–20] However, specific outcomes of patients with AS were reported only in the post hoc analyses of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trials.[17,19] Furthermore, the trials covered only individuals meeting strict inclusion criteria and deemed suitable recipients for OAC therapy, with only a limited number of patients with AS. Moreover, in the ROCKET AF trial, patients with severe AS or planned intervention for AS were excluded. Therefore, our nationwide study covering all patients with incident AF in Finland considerably increases our understanding of the impact of AS on outcomes, as well as of the risk–benefit profile of DOACs versus VKAs in this commonly encountered patient group.

AS and Outcomes in Patients With AF

AS was associated with a markedly higher risk of bleeding, especially gastrointestinal bleeding, which was increased by >60%. This finding is concordant with previous reports associating AS with risk of gastrointestinal bleeding, regardless of the presence of AF.[12,25,26] The bleeding risks associated with AS were evident even after controlling for a comprehensive set of patient characteristics, indicating that the high bleeding risks in patients with

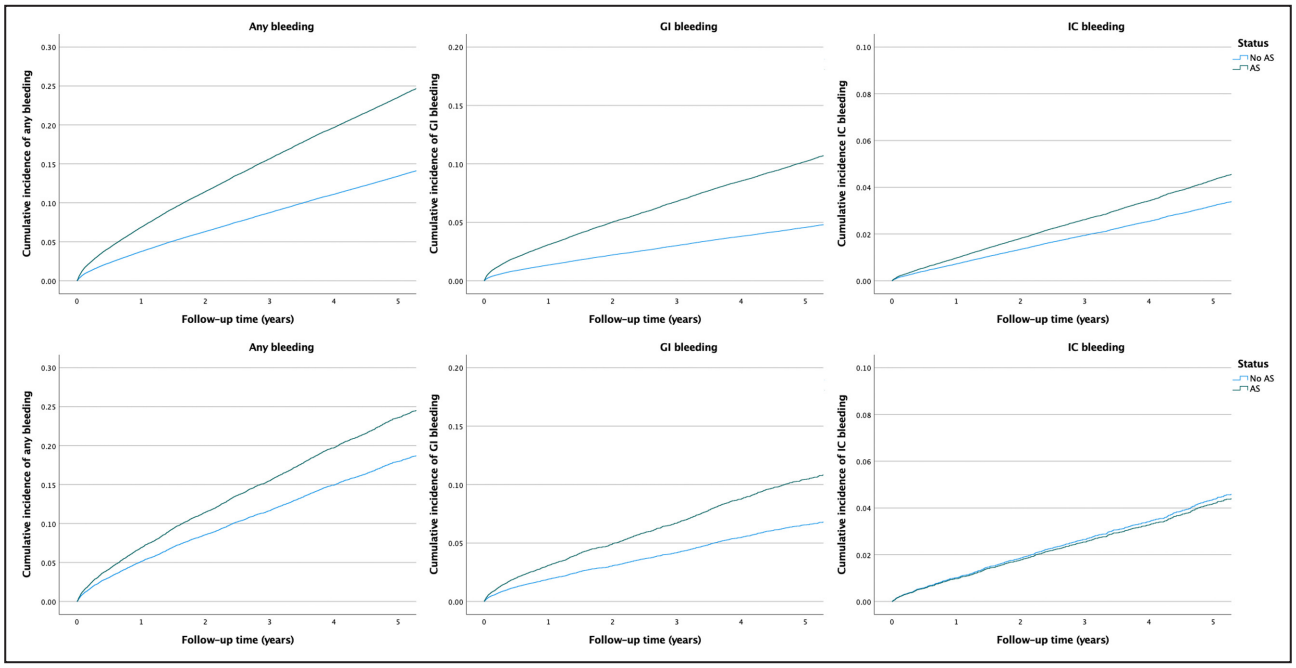

Figure. Cumulative incidence curves of bleeding events in the overall cohort (above) and in the propensity score–matched cohort (below).
AS indicates aortic stenosis; GI, gastrointestinal; and IC, intracranial.

AS are only partially explained by the factors incorporated in the widely used bleeding risk stratification tools. The previously described high prevalence of gastrointestinal tract angiodysplasias and depletion of the von Willebrand factor multimers in patients with AS may partly explain our findings.[28] However, while Heyde syndrome has mainly been observed in patients with severe AS, in the present study, gastrointestinal bleeding risk was elevated in unselected patients, including all stages of AS. Indeed, although the true prevalence of Heyde syndrome in patients with AS is unknown, our findings suggest that AS may increase gastrointestinal bleeding risk in AF beyond the clinical diagnosis of Heyde syndrome.

Previous studies have associated AS with a higher risk of ischemic stroke in both patients with AF and patients without AF.[13,17,19,25] In the present study, we observed only a trend toward a higher risk of ischemic stroke in patients with AS (Table 3). Hence, the higher risk of bleeding seems to predominate in the risk profile of patients with AF and AS. This observation may help in the clinical decision-making of stroke prevention and guide in balancing bleeding and stroke risks in these vulnerable patients.

DOACs Versus VKAs in Patients With AS and AF

Among patients with AS, DOAC therapy was associated with a lower risk of ischemic stroke when compared with VKAs, while bleeding and mortality did not differ between DOACs and VKAs. These findings are discordant with the higher bleeding and similar ischemic stroke rate in patients with AS on rivaroxaban compared with warfarin in the post hoc analysis of the ROCKET AF trial.[19] On the other hand, more in concordance with our results, the post hoc analysis of the ARISTOTLE trial observed similar stroke and bleeding rates in patients with AS on apixaban and warfarin.[17] The variance in the results of these post hoc analyses may partly be explained by their small sample sizes of 214 and 324 patients with AS, respectively. Also, our results are in contrast with the findings of a recent Danish observational study, reporting a higher risk of thromboembolism but a lower risk of major bleeding for treatment with DOACs compared with VKAs in patients with AF and AS.[27] In relation to our work, the Danish study also included patients with prior aortic valve interventions and did not cover patients with AF diagnosed solely in the primary care, which may in part explain the discrepancy in the findings. According to our interaction analyses, the presence of AS did not significantly modify the outcome effects of DOACs compared with VKA, suggesting that in patients with AF, DOACs can be chosen for stroke prevention irrespective of the presence of AS. Importantly, we found no signals of DOAC therapy entailing more risks than VKA therapy in these patients.

Limitations

Our findings must be interpreted bearing in mind the limitations of this study, especially the challenges inherent to observational studies based on real-life

Table 2. Crude Incidence of Outcome Events Before and After Propensity Score Matching

	Overall cohort			Propensity score–matched cohort		
	No aortic stenosis	Aortic stenosis	*P* value	No aortic stenosis	Aortic stenosis	*P* value
Any bleeding						
Events (%)	21 299 (11.9)	640 (12.2)	0.486	3427 (13.4)	640 (12.2)	0.075
Patient-years (100 y)	7319	111		839	111	
Incidence rate (per 100 y)	2.91 (2.87–0.95)	5.74 (5.31–6.20)	<0.001	4.09 (3.95–4.23)	5.74 (5.31–6.20)	<0.001
Incidence rate ratio	(Reference)	1.97 (1.82–2.13)	<0.001	(Reference)	1.41 (1.29–1.53)	<0.001
Gastrointestinal bleeding						
Events (%)	7196 (4.0)	277 (5.3)		1213 (4.7)	277 (5.3)	0.222
Patient-years (100 y)	7674	118		888	118	
Incidence rate (per 100 y)	0.94 (0.92–0.96)	2.35 (2.08–2.64)	<0.001	1.37 (1.29–1.45)	2.34 (2.08–2.63)	<0.001
Incidence rate ratio	(Reference)	2.25 (2.22–2.82)	<0.001	(Reference)	1.71 (1.50–1.95)	<0.001
Intracranial bleeding						
Events (%)	5099 (2.9)	109 (2.1)		847 (3.3)	109 (2.1)	<0.001
Patient-years (100 y)	7753	121		899	121	
Incidence rate (per 100 y)	0.66 (0.64–0.68)	0.90 (0.75–1.09)	<0.001	0.94 (0.88–1.01)	0.90 (0.75–1.09)	0.678
Incidence rate ratio	(Reference)	1.37 (1.14–1.66)	<0.001	(Reference)	0.96 (0.79–1.17)	0.678
Ischemic stroke						
Events (%)	12 483 (7.0)	332 (6.3)		2048 (8.0)	332 (6.3)	<0.001
Patient years (100 y)	7542	118		872	118	
Incidence rate (per 100 y)	1.65 (1.63–1.68)	2.82 (2.53–3.14)	<0.001	2.21 (2.11–2.31)	2.81 (2.41–3.00)	<0.001
Incidence rate ratio	(Reference)	1.70 (1.53–1.90)	<0.001	(Reference)	1.27 (1.18–1.37)	<0.001
Mortality						
Events (%)	53 625 (30.0)	2576 (49.2)		10 980 (42.8)	2574 (49.2)	<0.001
Patient-years (100 y)	7871	172		916	172	
Mortality rate (per 100 y)	6.81 (6.75–6.87)	14.92 (14.36–15.51)	<0.001	11.94 (11.72–12.17)	14.89 (14.33–15.48)	<0.001
Mortality rate ratio	(Reference)	2.19 (2.11–2.28)	<0.001	(Reference)	1.25 (1.19–1.31)	<0.001

Ninety-five percent CIs in parentheses. Incidence rates and incidence rate ratios estimated with Poisson regression accounting for clustering in the comparisons within the matched cohort.

administrative data. Hence, our results represent associations and not necessarily causation between AS and outcomes, nor between OACs and outcomes. Information bias may be present owing to unmeasured or inappropriately recorded data, and due to the nonrandomized study design and clinical patient selection to receive OACs, confounding and selection biases may affect the risk estimates of OACs. Moreover, we were unable to definitively distinguish repeat bleeding or stroke episodes and therefore focused our analyses on the first-ever event of interest, excluding patients with bleedings or ischemic stroke before AF diagnosis, which may impose selection bias on our study. OAC exposures are based on pharmacy purchase dates, and whether patients actually took their medications is unknown. Moreover, because nonsteroidal anti-inflammatory drugs and low-dose acetylsalicylic acid are frequently purchased over the counter without a prescription in Finland, we did not consider their use in the analyses. Finally, we lacked information on the severity of AS. Notwithstanding these limitations, major strengths of our study are the large nationwide study sample, the comprehensive medical data from all levels of care, and coverage of all OAC purchases, because OACs are not sold over the counter without a prescription in Finland. Additionally, the validated national registries used have considerably high diagnostic accuracy, especially regarding cardiovascular diseases.[29,30] Importantly, our analyses focused on AS, compared with previous studies including all types of valvular disease in patients with AF.

Table 3. Adjusted Outcome Hazard Ratios for Aortic Stenosis in the Propensity Score–Matched Cohort

Outcome	Aortic stenosis	*P* value
Any bleeding	1.36 (1.25–1.48)	<0.001
Gastrointestinal bleeding	1.63 (1.43–1.86)	<0.001
Intracranial bleeding	0.96 (0.78–1.17)	0.693
Ischemic stroke	1.11 (0.99–1.25)	0.076
Mortality	1.32 (1.26–1.38)	<0.001

Hazard ratios estimated with the cause-specific hazards regression and adjusted for VKA and DOAC exposures. 95% CIs in parentheses. DOAC indicates direct oral anticoagulant; and VKA, vitamin K antagonist.

Table 4. Hazard Ratios of Outcome Events for DOACs Compared With VKAs Among Patients With Aortic Stenosis

Outcome	Analyses with time-varying OAC variables	*P* value	Intention-to-treat analyses	*P* value
Unadjusted analyses				
Any bleeding	1.09 (0.84–1.40)	0.527	1.07 (0.80–1.42)	0.673
Gastrointestinal bleeding	1.24 (0.83–1.85)	0.340	1.00 (0.66–1.53)	0.998
Intracranial bleeding	1.02 (0.56–1.87)	0.941	1.01 (0.54–1.88)	0.994
Ischemic stroke	0.55 (0.32–0.94)	0.028	0.44 (0.25–0.80)	<0.001
Mortality	1.17 (0.98–1.41)	0.097	0.70 (0.56–0.87)	<0.001
Adjusted analyses				
Any bleeding	0.93 (0.70–1.24)	0.563	0.85 (0.58–1.23)	0.397
Gastrointestinal bleeding	1.10 (0.70–1.72)	0.722	0.84 (0.50–1.43)	0.515
Intracranial bleeding	0.94 (0.48–1.86)	0.850	0.87 (0.40–1.87)	0.723
Ischemic stroke	0.60 (0.34–1.06)	0.074	0.41 (0.21–0.75)	0.004
Mortality	1.20 (0.99–1.45)	0.059	0.89 (0.67–1.18)	0.171

Hazard ratios estimated with the cause-specific hazards regression. Adjusted analyses included the following variables: age, sex, year of atrial fibrillation diagnosis, income quartiles, alcohol use disorder, psychiatric disorder, cancer, dementia, hypertension, heart failure, diabetes, dyslipidemia, mitral regurgitation, kidney failure, liver failure or cirrhosis, prior transient ischemic attack, and any vascular disease. Ninety-five percent CIs in parentheses. DOAC indicates direct oral anticoagulant; and VKA, vitamin K antagonist.

Implications for Future Research

Future studies are needed to explore optimal treatment strategies in the high-risk population of patients with AS and AF. The role of low-dose DOAC therapy and left atrial appendage closure should be evaluated regarding the high bleeding risks associated with AS. Additionally, data on AF outcomes according to the severity of AS are needed. Moreover, possible outcome disparities between different DOACs in the presence of AS require further investigation.

CONCLUSIONS

In conclusion, the present registry-based nationwide cohort study documented that AS is associated with a substantially increased risk of gastrointestinal bleeding in patients with AF, and AS should thus be considered in the bleeding risk assessment in these patients. Compared with VKAs, DOACs had a similar profile in safety outcomes but were associated with a lower risk of ischemic stroke in patients with AS and AF.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figure S1

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Supplemental Material

Table S1. Definitions of the comorbidities, outcomes and exposure.

	ICD-10	ICPC-2	Reimbursement code	ATC code	Other
Exposure					
Aortic stenosis	I35.0, I35.2, I06.0, I06.2				
Outcomes					
Any bleeding	D50.0, D62, D68.3, I60-I62, I85.0, I86.4, J94.2, K22.1, K22.3, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K63.1, K63.3, K92.0-K92.2, N02, R04, R31, R58, S06.3-S06.6, S06.8				
Gastrointestinal bleeding	D50.0, I85.0, I86.4, K22.1, K22.3, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K63.1, K63.3, K92.0-K92.2				
Intracranial bleeding	I60-I62, S06.3-S06.6, S06.8				
Comorbidities					
Hypertension	I10-I15	K85, K86, K87	205	C03A, C03B, C03DB, C03EA, C07A, C08CA, C08D, C09	
Dyslipidemia	E78	T93	206	C10	
Heart failure	I50, I11.0, I13.0, I13.2	K77	201		
Diabetes	E10-E14	T89, T90	103, 215	A10	
Previous stroke	I63, I64, I69.3-I69.8	K90			
Transient ischemic attack	G45	K89			
Bleeding history	D50.0, D62, D68.3, I60-I62, I69.0-I69.2, I85.0, I86.4, J94.2, K22.1, K22.3, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K63.1, K63.3, K92.0-K92.2, N02, R04, R31, R58, S06.2-S06.6, S06.8				
Alcohol abuse	F10				
Renal failure or dialysis	N18, Z49				
Liver cirrhosis or failure	K70.2-K70.4, K71.7, K71.8, K72, K74				
Dementia	F00-F03, G30				
Cancer					Any cancer registered in the Finnish Cancer Registry
Coronary heart disease	I21-I25				
Prior myocardial infarction	I21-I22				
Psychiatric disorder	F04-F99				

ATC, anatomic therapeutic chemical; ICD-10, International Classification of Diseases, Tenth Revision; ICPC-2, International Classification of Primary Care, Second Edition

Table S2. Outcome hazard ratios of interaction terms between AS and anticoagulant exposures.

Outcome	AS x DOAC vs. VKA	p-value
Any bleeding	0.98 (0.74-1.28)	0.885
GI bleeding	0.95 (0.61-1.46)	0.818
IC bleeding	1.43 (0.75-2.72)	0.277
Ischemic stroke	0.62 (0.36-1.10)	0.093
Mortality	1.16 (0.96-1.41)	0.130

Hazard ratios estimated with the cause-specific hazards regression. VKA and DOAC exposures were treated as time-varying variables. 95% confidence intervals in parenthesis. AS, aortic stenosis; DOAC, direct oral anticoagulant; GI, gastrointestinal; IC, intracranial; VKA, vitamin K antagonist

Table S3. Baseline characteristics of patients with AS initiating DOAC or VKA therapy.

	VKA n=2 413	DOAC n=872	p-value
Age, years	78.8 (9.4)	79.1 (8.7)	0.34
Cohort entry year	2012 (2.9)	2016 (1.6)	<0.001
Female sex	1 383 (57.3)	411 (47.1)	0.02
Income quartiles			<0.001
1st (lowest)	644 (26.7)	149 (17.1)	
2nd	614 (25.4)	195 (22.4)	
3rd	615 (25.5)	229 (26.3)	
4th (highest)	540 (22.4)	299 (34.3)	
Any vascular disease	1 075 (44.6)	373 (42.8)	0.37
Diabetes	607 (25.2)	274 (31.4)	<0.001
Dyslipidemia	1 519 (63.0)	601 (68.9)	<0.001
Heart failure	843 (34.9)	236 (27.1)	<0.001
Hypertension	2 044 (84.7)	771 (88.4)	0.01
Mitral regurgitation	321 (13.3)	111 (12.7)	0.67
Prior TIA	119 (4.9)	79 (9.1)	<0.001
Abnormal liver function	5 (0.2)	1 (0.1)	0.58
Abnormal renal function	144 (6.0)	42 (4.8)	0.21
Alcohol use disorder	36 (1.5)	18 (2.1)	0.26
Cancer	551 (22.8)	225 (25.8)	0.08
Dementia	112 (4.6)	46 (5.3)	0.45
Psychiatric disorder	204 (8.5)	116 (13.3)	<0.001
Modified HAS-BLED score	2.5 (0.7)	2.7 (0.6)	<0.001
CHA_2DS_2-VASc score	4.2 (1.5)	4.2 (1.5)	0.21

Values denote n (%) or mean (standard deviation). $ACHA_2DS_2$-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, history of stroke or TIA, vascular disease, age 65-74 years, sex category (female); DOAC, direct oral anticoagulant; modified HAS-BLED score, hypertension, abnormal renal or liver function, prior stroke, bleeding history, age >65 years, alcohol abuse, concomitant antiplatelet/NSAIDs (no labile INR, max score 8); TIA, transient ischemic attack; VKA, vitamin K antagonist.

Table S4. Outcome events within two-year follow-up from initiation of different OACs in patients with AS.

Outcome	Warfarin	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
	n= 2 413	n= 305	n= 409	n= 144	n= 14
Number of events (%)					
Any bleeding	228 (9.4)	18 (5.9)	29 (7.1)	16 (11.1)	0 (0.0)
GI bleeding	89 (3.9)	8 (2.6)	10 (2.4)	7 (4.9)	0 (0.0)
IC bleeding	41 (1.7)	2 (0.7)	7 (1.7)	3 (2.1)	0 (0.0)
Ischemic stroke	105 (4.4)	1 (0.3)	5 (1.2)	4 (2.8)	0 (0.0)
Mortality	564 (23.4)	29 (9.5)	46 (11.2)	23 (16.0)	1 (7.1)
Incidence rate per 100 patient-years					
Any bleeding	5.8 (5.1-6.6)	5.6 (3.7-8.6)	7.5 (5.2-10.8)	9.6 (6.1-15.3)	0
GI bleeding	2.2 (1.8-2.7)	2.1 (1.0-4.2)	2.5 (1.4-4.7)	4.6 (2.4-8.8)	0
IC bleeding	1.0 (0.7-1.4)	1.0 (0.4-2.8)	1.8 (0.8-3.7)	1.5 (0.5-4.7)	0
Ischemic stroke	2.6 (2.1-3.1)	0.3 (0.4-1.8)	1.3 (0.5-3.0)	2.0 (0.8-5.4)	0
Mortality	13.6 (12.6-14.8)	8.8 (6.3-12.3)	11.5 (8.6-15.4)	13.3 (9.1-19.3)	9.3 (1.3-65.7)

AS, aortic stenosis; DOAC, direct oral anticoagulant; GI, gastrointestinal; IC, intracranial. 95% confidence intervals in parenthesis. Incidence rates estimated with Poisson regression.

Figure S1. Flow-chart of the patient selection process.