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Pre-procedural oral anticoagulant use is associated with cardiovascular events in women after transcatheter aortic valve replacement: An analysis from the WIN-TAVI cohort

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ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) has become an accepted treatment for patients with severe aortic stenosis (AS). Predicting which patients are at risk for adverse clinical outcomes after TAVI remains difficult, especially in women.
Aim: To identify predictors of adverse events in the WIN-TAVI cohort.
Methods: The WIN-TAVI study is an observational registry of 1019 women undergoing TAVI for severe symptomatic AS. Follow-up was 1 year. The primary outcome was defined according to VARC-2: a composite of mortality, stroke, myocardial infarction or hospitalization for valve-related symptoms or heart failure. The

Abbreviations and acronyms: AF, Atrial fibrillation; eGFR, Estimated glomerular filtration rate; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; OAC, Oral anticoagulants; PCI, Percutaneous coronary intervention; PVD, Peripheral vascular disease; SAVR, Surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, Transcatheter aortic valve implantation; VARC, Valve academic research consortium.

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secondary outcome was a composite of cardiovascular mortality or hospitalization for valve-related symptoms or heart failure.
Results: We included 1019 women with severe AS (mean age of 82.5 ± 6.3 years). At 1 year, 16.4% of the patients experienced the primary endpoint and 12.6% the secondary endpoint. The use of oral anticoagulants (OAC) was the strongest independent predictor of the primary outcome (adjusted hazard ratio [aHR] 1.51, 95% confidence interval [CI] 1.079–2.106, $p = 0.016$). Independent predictors of the secondary endpoint were age (aHR 1.04 per year, 95% CI 1.01–1.074, p = 0.016) and use of OAC (aHR: 1.79, 95% CI 1.24–2.60, $p = 0.002$). OAC use was not associated with higher bleeding risk.
Conclusion: Pre-procedural use of OAC was the strongest predictor of adverse outcomes during 1-year follow-up, likely reflecting a combination of high-risk factors and comorbidities, but was not related to increased bleeding risk.

1. Introduction

Transcatheter Aortic Valve Implantation (TAVI) has become an accepted treatment of patients with severe aortic stenosis (AS) who are at intermediate or high risk for surgical aortic valve replacement (SAVR) [1–3]. In this elderly TAVI population, a high percentage is female in contrast to patients undergoing SAVR [4].

Clinical characteristics in patients undergoing TAVI differ between men and women, as women are older, have a higher STS (Society of Thoracic Surgeons) score and show differences in echocardiographic parameters, such as higher mean left ventricular ejection fraction (LVEF) and higher aortic valve gradients [5,6]. Different clinical outcomes between sexes have been reported as well, albeit with conflicting results. Kodali et al. showed lower mortality rates in women, but higher vascular and bleeding complications, compared to men [7]. The PARTNER 3 study showed a higher event rate (a composite of death from any cause, stroke, or rehospitalization) in women in the SAVR group compared to men (18.5% versus 13.8%). In contrast, the results in the TAVI group for both women and men were similar (8.1% event rate in women compared to 8.7% in men) [2]. This suggests that women may have better outcomes after TAVI than SAVR, which has been confirmed in other studies [8].

However, accurate risk prediction models for adverse outcomes after both procedures are lacking. The commonly used risk scores for predicting adverse outcomes after TAVI, such as STS-score and the EuroSCORE II, take sex into account, and the EuroSCORE identifies female sex as a predictor for mortality [9–12]. Nevertheless, both risk models mostly focus on short-term periprocedural outcomes and are mainly validated in SAVR patients. More recently, new models for outcome prediction post-TAVI have been created, using machine learning, resulting in a large number of potentially predicting variables [13,14].

Neither the old nor newer scores specifically focus on women. The WIN-TAVI cohort is a registry dedicated specifically to women and as such identified predictors of poor outcomes specific to women 30 days and 1 year after TAVI. Prior revascularization, EuroSCORE I, a history of atrial fibrillation (AF) and prior percutaneous coronary intervention (PCI) were predictors for adverse outcome [15–19]. We extended the previous findings by adding more baseline variables including laboratory values and baseline medications, to create a more comprehensive model. The aim of this analysis is to identify baseline clinical predictors for adverse cardiovascular events specific to women undergoing TAVI.

2. Methods

2.1. Study design

The WIN-TAVI registry is a prospective, international, multicentre, observational registry of women receiving TAVI for severe symptomatic AS. WIN-TAVI included 19 sites from Europe and North America. From January 2013 until December 2015, a total of 1019 women were included in the registry. All participating sites had institutional approval from the local ethical review board, and the study was conducted according to the principles of the Declaration of Helsinki, International Organization for Standardization Guidelines, and Good Clinical Practice Guidelines. Details on the design of the study and results have been published before [18]. In previous reports of this cohort, predictors for clinical outcomes were identified. However, in order to create an easy-to-use risk model which could replace contemporary risk models, all available baseline characteristics were incorporated. Only peri-procedural variables were not incorporated, because we aimed to identify predictors for worse outcome, prior to the procedure. We aimed at creating a prediction model that could be used during the heart team decision making.

2.2. Data collection and management

Patient information on medical history and peri-interventional parameters was collected as per standard of care. The Clinical and Data coordinating center at the Icahn School of Medicine at Mount Sinai (New York, United States) was responsible for the monitoring of electronic data entry, database and data management, and statistical analyses.

2.3. Endpoints

The primary endpoint is defined according to the valve academic research consortium criteria 2 (VARC-2): A composite of mortality, stroke, myocardial infarction (MI) or hospitalization for valve-related symptoms or heart failure. The secondary endpoint is a composite of cardiac mortality or hospitalization for valve-related symptoms or heart failure. All events were adjudicated by an independent Clinical Event Committee using source documents provided by the sites.

2.4. Statistical analysis

Variables were selected based on clinical relevance and excluded when >10% of the values were missing. Continuous variables are reported as mean ± (SD) or median [IQR] and categorical variables are reported as n (%). Univariable predictors with a $p < 0.05$ were included in a multivariable Cox proportional hazards model. To provide a multivariable model, we used backward stepwise selection with a *p*-value cut-off at entry of 0.1 and exit of 0.2.

3. Results

Baseline characteristics of patients with and without the primary and secondary endpoint are presented in Table 1. The mean age of the WIN-TAVI cohort was 82.5 ± 6.3 years, with a mean EuroSCORE of 17.8 ± 11.7% and a mean STS-score 8.3 ± 7.4%.

The primary endpoint (all-cause mortality, stroke, MI or hospitalization) occurred in 167 of 1019 (16.4%) patients and the secondary endpoint (cardiac mortality or hospitalization) in 128 of 1019 (12.6%) patients. Patients that experienced the primary endpoint more often had a history of stroke, prior PCI and atrial fibrillation or flutter, had higher serum creatinine concentrations and more often were on oral anticoagulants (OAC). There was no statistically significant difference in echo parameters between patients with and without a primary endpoint

Table 1
Baseline & procedural characteristics of WIN TAVI subjects, stratified by primary and secondary outcome.

	Primary Outcome (VARC-2)			Secondary Outcome		
Variable	Event ($n = 167$)	No Event ($n = 852$)	p-value	Event ($n = 128$)	No Event ($n = 891$)	p-value
Demographics						
Age - years	83.2 ± 7.0	82.4 ± 6.1	0.204	83.8 ± 6.8	82.4 ± 6.2	0.017
BMI (kg/m^2)	25.3 ± 5.7	26.1 ± 5.5	0.103	25.5 ± 6.2	26.0 ± 5.4	0.374
NYHA classification			0.390			0.435
None	26 (16.0%)	130 (15.4%)		21 (16.9%)	135 (15.3%)	
Class I	0 (0.0%)	8 (0.9%)		0 (0.0%)	8 (0.9%)	
Class II	35 (21.5%)	177 (20.9%)		20 (16.1%)	192 (21.7%)	
Class III	88 (54.0%)	484 (57.3%)		73 (58.9%)	499 (56.4%)	
Class IV	14 (8.6%)	46 (5.4%)		10 (8.1%)	50 (5.7%)	
CCS classification			0.536			0.158
None	26 (16.0%)	130 (15.4%)		121 (96.0%)	802 (90.8%)	
Class I	0 (0.0%)	8 (0.9%)		2 (1.6%)	11 (1.2%)	
Class II	35 (21.5%)	177 (20.9%)		2 (1.6%)	57 (6.5%)	
Class III	88 (54.0%)	484 (57.3%)		1 (0.8%)	12 (1.4%)	
Class IV	14 (8.6%)	46 (5.4%)		0 (0.0%)	1 (0.1%)	
Medical history						
Diabetes	43 (25.7%)	221 (26.2%)	0.913	34 (26.6%)	230 (26.0%)	0.896
Hypertension	139 (83.7%)	680 (81.2%)	0.448	108 (85.0%)	711 (81.2%)	0.292
Hypercholesterolemia	83 (49.7%)	378 (44.7%)	0.234	67 (52.3%)	394 (44.5%)	0.097
Previous stroke	18 (10.8%)	58 (6.9%)	0.075	15 (11.8%)	61 (6.9%)	0.049
Previous TIA	83 (57.6%)	382 (52.1%)	0.225	7 (6.2%)	45 (5.7%)	0.844
Anaemia	20 (12.1%)	72 (8.7%)	0.161	66 (62.3%)	399 (51.8%)	0.042
Peripheral artery disease	116 (69.5%)	622 (73.0%)	0.349	15 (11.9%)	77 (8.9%)	0.268
History of pregnancy	28 (18.5%)	150 (19.8%)	0.719	87 (68.0%)	651 (73.1%)	0.228
History of osteoporosis	43 (25.7%)	221 (26.2%)	0.913	18 (15.5%)	160 (20.2%)	0.235
Cardiac History						
Pre-existent pacemaker	15 (9.0%)	73 (8.6%)	0.865	12 (9.4%)	76 (8.5%)	0.753
Previous ICD	3 (2.0%)	8 (1.0%)	0.396	2 (1.7%)	9 (1.1%)	0.633
Previous CABG	15 (9.0%)	50 (5.9%)	0.138	7 (5.5%)	58 (6.5%)	0.642
Previous PCI	47 (28.1%)	187 (22.1%)	0.088	35 (27.3%)	199 (22.4%)	0.218
Previous MI	21 (12.6%)	77 (9.1%)	0.159	15 (11.7%)	83 (9.3%)	0.393
Congestive heart failure	140 (84.3%)	720 (84.7%)	0.904	106 (83.5%)	754 (84.8%)	0.693
Previous aortic valve procedure	10 (6.0%)	58 (6.9%)	0.680	9 (7.1%)	59 (6.7%)	0.875
Previous non-aortic valve procedures	8 (4.8%)	29 (3.5%)	0.394	7 (5.5%)	30 (3.4%)	0.308
Atrial fibrillation/flutter	41 (25.3%)	159 (19.1%)	0.073	36 (29.3%)	164 (18.9%)	0.007
Laboratory Values						
Haemoglobin (g/dL)	11.6 ± 1.7	11.9 ± 1.7	0.134	11.6 ± 1.7	11.9 ± 1.7	0.144
Creatinine (mg/dL)	1.1 [0.8–1.3]	1.0 [0.8–1.3]	0.023	1.1 [0.9–1.4]	1.0 [0.8–1.3]	0.017
eGFR (ml/min/1.73 m^2)	50.7 ± 20.1	54.4 ± 19.7	0.047	49.7 ± 18.9	54.3 ± 19.8	0.029
Medications at baseline						
Acetylsalicylic acid	93 (56.7%)	505 (60.9%)	0.314	70 (55.6%)	528 (60.9%)	0.252
P2Y12-Inhibitors	49 (29.9%)	211 (25.6%)	0.253	38 (30.2%)	222 (25.7%)	0.291
Oral anticoagulants	49 (29.9%)	174 (21.1%)	0.014	42 (33.3%)	181 (21.0%)	0.002
Low-Molecular weight heparin	14 (8.6%)	53 (6.4%)	0.309	12 (9.7%)	55 (6.4%)	0.174
Echo characteristics at baseline						
LVEF (%)	55.3 ± 11.7	55.7 ± 10.5	0.673	55.1 ± 11.9	55.7 ± 10.5	0.567
Mean aortic valve gradient (mmHg)	48.4 ± 17.0	49.3 ± 15.6	0.523	47.6 ± 17.0	49.4 ± 15.7	0.247
Total aortic regurgitation grade			0.997			0.891
None	49 (33.3%)	261 (33.0%)		38 (33.9%)	272 (32.9%)	
Mild	71 (48.3%)	380 (48.0%)		55 (49.1%)	396 (47.9%)	
Moderate	24 (16.3%)	133 (16.8%)		16 (14.3%)	141 (17.0%)	
Severe	3 (2.0%)	18 (2.3%)		3 (2.7%)	18 (2.2%)	
Mitral regurgitation grade			0.622			0.578
None	18 (12.0%)	114 (14.3%)		15 (13.0%)	117 (14.1%)	
Mild	82 (54.7%)	413 (51.9%)		65 (56.5%)	430 (51.8%)	
Moderate	42 (28.0%)	239 (30.1%)		29 (25.2%)	252 (30.4%)	
Severe	8 (5.3%)	29 (3.6%)		6 (5.2%)	31 (3.7%)	
Tricuspid regurgitation grade			0.960			0.990
None	35 (24.6%)	185 (24.3%)		27 (24.5%)	193 (24.3%)	
Mild	78 (54.9%)	434 (57.0%)		61 (55.5%)	451 (56.9%)	
Moderate	25 (17.6%)	123 (16.2%)		19 (17.3%)	129 (16.3%)	
Severe	4 (2.8%)	19 (2.5%)		3 (2.7%)	20 (2.5%)	

Primary endpoint: composite of all-cause mortality, stroke, myocardial infarction and hospitalizations for valve-related symptoms or heart failure. Secondary endpoint is a composite of cardiac mortality or hospitalization for valve-related symptoms or heart failure.
Continuous variables are reported as mean ± (SD) or median [IQR]. Categorical variables are reported as n (%).
BMI: body mass index, CABG; Coronary Artery Bypass Graft, CCS: Canadian Cardiovascular Society, eGFR: estimated glomerular filtration rate, ICD: implantable cardioverter-defibrillator, LVEF: left ventricular ejection fraction, MI; Myocardial Infarction, NYHA: New York Heart Association, PCI; Percutaneous Coronary Intervention, TIA; Transient Ischemic Attack.

event. Patients that experienced the secondary endpoint were older and were more likely to have hypercholesterolemia, previous stroke, anaemia and a history of atrial fibrillation or flutter. In addition, their creatinine levels were higher, and they were more likely to be on OAC. Echocardiographic parameters were not different in those with or without a secondary endpoint event. In supplementary table 1, the variables excluded due to more than >10% of missing values are shown.

3.1. Univariable and multivariable predictors of outcome

Significant univariable and multivariable predictors of the primary endpoint of mortality, stroke, MI or hospitalization are provided in Table 2. Significant univariable predictors of the primary endpoint were: lower estimated glomerular filtration rate (eGFR) (hazard ratio [HR] 0.99 per unit increase, 95% confidence interval [CI] 0.98–1.00, $p = 0.047$) and use of OAC (HR 1.51, 95% CI 1.08–2.11, $p = 0.016$). In the multivariable analysis, the only predictor of the primary endpoint was use of OAC (HR 1.51, 95% CI 1.06–2.16, $p = 0.024$). Hazard ratios for the primary endpoint for all variables are shown in supplementary table 2.

Significant univariable and multivariable predictors of the secondary endpoint of cardiac mortality or hospitalization are provided in Table 3. A higher age (HR 1.04 per year increase, 95% CI 1.01–1.07, $p = 0.015$), hypercholesterolemia (HR 1.34, 95% CI 0.95–1.90, $p = 0.097$), previous stroke (HR 1.75, 95% CI 1.02–3.00, $p = 0.042$), anaemia (HR: 1.50, 95% CI 1.01–2.22, $p = 0.044$), chronic kidney disease (HR 1.54, 95% CI 1.00–2.38, $p = 0.049$), history of atrial fibrillation or flutter (HR 1.70, 95% CI 1.15–2.51, $p = 0.007$), lower eGFR (HR 0.99 per unit increase, 95% CI 0.98–1.00), $p = 0.027$) and use of OAC (HR 1.76, 95% CI 1.22–2.56), $p = 0.003$) were univariate predictors. In the multivariable analysis, only age (HR 1.04, 95% CI 1.01–1.07, $p = 0.020$), and use of OAC (HR 1.79 95% CI 1.24–2.60), $p = 0.002$) remained significant predictors for the secondary endpoint. Hazard ratios for all variables for the secondary outcome are shown in supplementary table 3.

3.2. Baseline characteristics and outcomes stratified by OAC use

Baseline characteristics stratified by OAC use are presented in supplementary table 4. Patients on OAC had a higher NYHA and CCS classification, more likely a history of stroke, higher prevalence anaemia, peripheral vascular disease and chronic kidney disease, and more history of pacemaker implantation, previous PCI, previous MI, valve procedures and atrial fibrillation or flutter. Patients on OAC also had a lower mean aortic valve gradient and more likely moderate or severe tricuspid regurgitation. The primary and secondary endpoints occurred significantly more often in patients on OAC versus those not on OAC, primarily driven by cardiovascular mortality and hopsitalization

Table 2
Univariate and multivariate predictors of primary endpoint.

Variable	Univariable		Multivariable	
	Hazard Ratio	p-value	Hazard Ratio	p-value
Laboratory Values				
eGFR	0.99 (0.98–1.00)	0.047		
Medications at baseline				
Oral anticoagulants	1.51 (1.08–2.11)	0.016	1.51 (1.08–2.11)	0.016

Only statistically significant variables are shown. * Univariable predictors with a $p < 0.05$ were included in a multivariable Cox proportional hazards model.
Primary endpoint: A composite of mortality, stroke, myocardial infarction (MI) or hospitalization for valve-related symptoms or heart failure (according to the VARC-2 criteria)
eGFR: estimate glomerular filtration rate.

Table 3
Univariate and multivariate predictors of secondary endpoint.

Variable	Univariable		Multivariable	
	Hazard Ratio	p-value	Hazard Ratio	p-value
Demographics				
Age – years	1.04 (1.01–1.07)	0.015	1.04 (1.01–1.07)	0.016
Medical History				
Hypercholesterolemia	1.34 (0.95–1.90)	0.097		
Previous Stroke	1.75 (1.02–3.00)	0.042		
Anaemia	1.51 (1.02–2.24)	0.039		
Chronic kidney disease	1.54 (1.00–2.38)	0.049		
Cardiac History				
Atrial fibrillation/ flutter	1.70 (1.15–2.51)	0.007		
Laboratory Values				
eGFR	0.99 (0.98–1.00)	0.027		
Medications at baseline				
Oral anticoagulants	1.76 (1.22–2.56)	0.003	1.79 (1.24–2.60)	0.002

Only statistically significant variables are shown * Univariable predictors with a $p < 0.05$ were included in a multivariable Cox proportional hazards model.
Secondary endpoint: composite of cardiac mortality or hospitalization for valve-related symptoms or heart failure.
eGFR: estimate glomerular filtration rate.

rates for valve-related symptoms and heart failure. Event rates for the components of the primary and secondary endpoints as well as bleeding events are presented in Table 4. There were no differences in bleeding rates between the two groups. In supplementary fig. 1 and 2 Kaplan-Meier curves are shown for respectively the primary and secondary endpoint, stratified by OAC use. Kaplan-Meier curves for the individual components of the primary and secondary endpoints are shown in supplementary fig. 3, 4 and 5.

4. Discussion

The aim of this study was to identify pre-procedural predictors of 1-year adverse outcomes in women undergoing TAVI. The main finding of the study was that the use of OAC before TAVI was the strongest predictor of 1-year cardiovascular events.

Aortic stenosis is the most common heart valve disease in the Western world and the number of TAVI procedures performed is rapidly increasing [20]. It is thus becoming more important to determine which patients will have unfavourable outcomes after TAVI and which patient characteristics are predictive of these unfavourable outcomes. Accurate predictors are lacking and as TAVI outcomes differ between women and men, sex specific predictors must be determined.

The event rate for the combined primary endpoint of mortality, stroke, MI or hospitalization for valve-related symptoms or heart failure was 16.4% and for the combined secondary endpoint of cardiac mortality or hospitalization for valve-related symptoms or heart failure 12.6% at 1 year post TAVI, which is comparable to other cohorts of intermediate surgical risk [21]. These results are especially encouraging as the WIN-TAVI patients had more comorbidities, were older, had higher STS-scores and EuroSCOREs and higher prevalence of prior MI and atrial fibrillation or flutter than patients in comparable intermediate surgical risk cohorts.

The use of OAC before TAVI was associated with a higher risk of both the primary and secondary endpoint. This association between OAC use and outcomes after TAVI has not been described before. There are several potential explanations for this association. First, indications for

Table 4
Kaplan-Meier estimates & unadjusted hazard ratios for 1-year outcomes in WIN TAVI subjects, stratified by oral anticoagulant use at baseline.

Variable	OAC (n = 223)	No OAC (n = 765)	Log-rank p-value	Hazard Ratio (95% CI)	p-value
Primary composite outcome[1]	49 (22.1%)	115 (15.1%)	0.015	1.51 (1.08–2.11)	0.016
All-cause mortality	36 (16.3%)	88 (11.6%)	0.074	1.42 (0.97–2.10)	0.075
Stroke	6 (2.9%)	16 (2.2%)	0.590	1.29 (0.51–3.30)	0.592
Myocardial infarction	2 (0.9%)	8 (1.1%)	0.865	0.87 (0.19–4.12)	0.865
Hospitalization for valve related symptoms or HF	15 (7.3%)	17 (2.4%)	<0.001	3.12 (1.56–6.24)	0.001
Valve-related dysfunction	1 (0.4%)	2 (0.3%)	0.646	1.74 (0.16–19.22)	0.650
Secondary composite outcome[2]	42 (19.1%)	84 (11.1%)	0.002	1.76 (1.22–2.56)	0.003
Cardiovascular mortality	32 (14.6%)	74 (9.8%)	0.052	1.50 (0.99–2.28)	0.054
Hospitalization for valve related symptoms or HF	15 (7.3%)	17 (2.4%)	<0.001	3.12 (1.56–6.24)	0.001
Bleeding					
VARC life-threatening or disabling bleeding	10 (4.5%)	36 (4.7%)	0.890	0.95 (0.47–1.92)	0.891
VARC major bleeding	21 (9.5%)	63 (8.3%)	0.579	1.15 (0.70–1.89)	0.575
BARC type 3–5 bleeding	31 (14.0%)	99 (13.0%)	0.704	1.08 (0.72–1.62)	0.698

BARC: Bleeding Academic Research Consortium, HF: Heart Failure, OAC: oral anticoagulation, VARC: valve academic research consortium criteria 2

[1] Primary composite outcome comprises of all-cause mortality, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure, or valve-related dysfunctions (clinical presentation with valve thrombosis or endocarditis).

[2] Secondary composite outcome comprises of cardiovascular mortality, or hospitalization for valve-related symptoms or heart failure.

anticoagulants use prior to TAVI are history of stroke, AF and peripheral vascular disease (PVD). In the current analysis, there was a higher incidence of AF in the event group for both endpoints, although only statistically significant for the secondary endpoint of cardiac mortality or hospitalization for valve-related symptoms or heart failure. Atrial fibrillation and stroke were significant predictors in the univariate analysis for the secondary endpoint, as has been shown in previous reports of this cohort [18,19]. Overall, OAC use seems to reflect a combination of high-risk factors and comorbidities associated with increased cardiovascular events.

Another potential explanation might be that it is a common practice in many centres to stop anticoagulation peri-procedurally for transfemoral TAVI exposing patients potentially to a higher risk of stroke. We did not demonstrate a significant difference in stroke rate between OAC treated patients and those without OAC in this study. Unfortunately, in our study there was no data on peri-procedural use of OAC. The ongoing POPULAR Pause trial will investigate the effect of stopping versus continuing anticoagulants peri-procedurally on the risk of ischemic and bleeding complications [22].

Third, we initially hypothesized that use of oral anticoagulants was associated with increased bleeding risks leading to the primary or secondary event. Bleeding is a common complication of oral anticoagulants use, but exact rates vary between studies and medications [23,24]. Bleeding rates after TAVI have been associated with pre-TAVI AF in previous studies. While the exact mechanism of this relationship is not clear, the common thought is that the use of oral anticoagulants for AF might be the reason for these higher bleeding rates [25]. However, we demonstrated no difference in bleeding risk in patients with or without OAC use prior to TAVI, thus not supporting this hypothesis.

Another possible explanation for OAC use as predictor for events, is the possible contribution of Vitamin-K antagonists (VKA) in the formation and even evolution of valvular and vascular calcifications [26,27]. These calcifications independently predict cardiovascular mortality and morbidity. However, as the exact type of OAC used in this study is not known, these explanations remain speculative.

Older age was associated with a higher risk of cardiovascular mortality and hospitalization for valve-related symptoms or heart failure. Some studies have linked older age to adverse outcome post-TAVI [29]. In contrast to this, others stated that age is not a risk factor in the prediction for adverse outcome post-TAVI [30,31]. These studies showed a significantly higher number of women in the older age group but did not stratify for sex and the sample sizes were small. Compared to men, women are older at the time of intervention [32].

Evaluation of predictors for worse clinical outcomes post-TAVI from this registry has been part of a previous analysis [15–19]. In contrast to the previous analysis, we aimed to consider also baseline laboratory values, baseline medication, and echocardiographic characteristics in our models. Most importantly, however, we did not include procedural and post-procedural parameters in order to identify baseline parameters for risk prediction to help in clinical decision making before the procedure at the time of the heart team discussion.

The novelty of this study is that the use of oral anticoagulants pre-TAVI predicts adverse outcome after the procedure, without an increased risk for bleedings, indicating that the use of oral anticoagulants might reflect presence of other risk factors and comorbidities that may not be readily captured.

4.1. Limitations

This study has some limitations. We excluded the variables which had a high number of missing values (10% and above). Because of this, only a few echocardiographic parameters were taken into consideration in the final analysis. The same applies to Computed Tomography Angiography (CTA) characteristics, as an earlier analysis of this cohort showed its important prognostic value in TAVI outcomes [16]. In addition, only a few laboratory values were included, haemoglobin, creatinine and eGFR. This may have led to a selection bias and omission of potentially important factors. Also, this study has a relatively short follow-up duration of 1 year. Extending this follow-up time could allow us to generate a more comprehensive set of predictors. Validation of these predictors in other cohorts is necessary to assess the generalizability of the predictors to other TAVI populations. A comparison with a men-only cohort is also necessary to see if there is a difference between risk factors in men and women.

5. Conclusion

In conclusion, the strongest predictor for adverse outcomes after TAVI specific to women at 1 year was the use of OAC at baseline, which likely reflects a combination of high-risk factors and comorbidities. There was no association of OAC use with bleeding. The findings need to be validated in an external cohort and analyses further broadened to include biomarkers and more extensive echocardiographic parameters.

Declaration of Competing Interest

Dr. Petronio received consultancy fees from Medtronic, Abbott, Boston Scientific, and funds from Boston Scientific and Abbott. Dr. Lefèvre received consultancy fees from Edwards, Boston Scientific and Abbot. Dr. Van Mieghem received research grants from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, Abiomed, PulseCath BV,

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.11.056.

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